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D-1.1/D-1.2 REVIEW OF DIAGNOSTIC MEASURES AND TREATMENT OPTIONS

CaVD-PACE

"Cardiovascular Diseases – Pilots and ATCOs Cardiovascular Evaluation"

New diagnostic measures and treatments

for cardiovascular diseases

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It is emphasised that the present deliverable is a living document that will be regularly reviewed by the contractor. Eventual changes will be included in the quarterly reports and discussed during the project quarterly meetings

Executive Summary

Description of Work

The present document CaVD D 1.1/D 1.2 “Review of diagnostic measures and treatment options” is the combination of the reports CaVD D 1.1 (report on the review of diagnostic measure) and CaVD D 1.2 (report on the review of treatment options). Both reports have been merged into one report because it was considered most practical to describe new diagnostic tools in combination with newly developed treatment options for each cardiological condition.

In line with the EASA technical requirements this document provides the results of the review and interpretation of the main findings concerning current state-of-the-art diagnostic tools to identify cardiovascular risks as well as benefits and risks of currently recommended treatments of the different cardiovascular conditions.

Structure of the document

This deliverable is structured as follows:

- 1. Executive Summary with summaries of each sub-chapter and “Take Away Messages” to provide an overview of important issues emerging from the present literature study. All Take Away messages present findings that warrant consideration for aeromedical risk assessments.
- Chapter 1.1: Introduction with background, aim, and methods of the research
- Chapters 2 - 6 and sub-chapters: Discussion and considerations concerning the state-of-the art diagnostic, monitoring, and treatment options for all cardiovascular conditions mentioned above. Each chapter ends with main conclusions and recommendations and a bibliography relevant for the issue discussed.

Introduction

For the EASA Research and Innovation Committee (RIC), pilot and ATCO medical fitness is one of the prioritised topics in the area of medical requirements to safeguard flight safety. It is generally known that one of the frequently reported medical conditions, that may lead to on-the-job incapacitation, or restriction of license privileges of pilots and ATCOs, is caused by cardiovascular conditions. Therefore, a thorough and effective cardiovascular risk assessment will significantly contribute to optimally safeguard flight safety and personal wellbeing of pilots and ATCOs.

Since the development of the currently prevailing EASA requirements concerning the assessment of cardiological fitness of pilots and ATCOs in the context of medical certification, cardiological diagnostic methods, monitoring, and treatment possibilities have made impressive progress with developments providing opportunities for earlier and more accurate identification of cardiovascular risks and

improved treatment results. In the context of flight safety standards, these recent developments could lead to more accurate detection of cardiovascular risk in pilots and ATCOs. New treatment and monitoring options might also provide opportunities for pilots and ATCOs with cardiovascular conditions to meet the aeromedical safety requirements. The suitability of the new treatment and diagnostic options should be considered taking into account their added value for flight safety and their feasibility in terms of availability, costs, and impact on the risk assessment process.

In this context, EASA has commissioned DLR to perform the present research project addressing the assessment of new medical developments for early diagnosis, monitoring, and treatment of cardiovascular diseases for the benefit of pilots, ATCOs, and flight safety.

The project name CaVD-PACE stands for CardioVascular Diseases - Pilots and ATCOs Cardiovascular Evaluation. To optimise EASA's flight safety standards, the CaVD-PACE research project is aimed at producing evidence-based recommendations for updating the cardiovascular requirements taking the most recent cardiological diagnostic and therapeutical developments into account.

To achieve this aim, a dedicated search of the published peer-reviewed scientific literature and selected "grey" literature concerning state-of-the-art tests, diagnostic and monitoring methods, and new treatment options related to the above-mentioned cardiovascular conditions, comorbidities, and cardiovascular risk factors. The study concerned the literature published after 2017, including older literature if needed. Attention was focused on the level of scientific evidence and their suitability for an aeromedical examination setting. As a primary basis for the scientific review the evaluation and assessment of the most recent guidelines of the European Society of Cardiology (ESC) and guidelines of the EAPC (European Association of Preventive Cardiology), ACA (American College of Cardiology), AHA (American Heart Association), and the ESH (European Society of Hypertension) were taken.

The cardiovascular conditions mentioned in EASA Part MED.B.010 (Cardiovascular system) were taken as a basis to define the cardiovascular issues relevant for all classes of pilots and ATCOs. The review considered the issues mentioned in chapters 2 - 6 as provided in the table of contents. These issues were also used as search terms for the designated literature search.

The present document is to report the results of the first task that has been performed in the context of the CaVD PACE research project and will provide input to tasks 2 and 3. This first task was aimed at making an inventory of new diagnostic methods, new treatments, and monitoring options that may be considered suitable to assess the cardiovascular risks and their consequences for safe task performance of pilots and ATCOs.

Results

This section presents a summary of the findings of the review concerning current state-of-the-art diagnostic tools to identify and manage cardiovascular risks and currently recommended treatments of the different cardiovascular conditions. Besides basic characteristics of the various cardiovascular disorders, the present report discusses the current status of developments of diagnostic and therapeutic options and provides recommendations that may be suitable to consider in the

aeromedical certification setting. The developments are particularly characterised by developments of (AI-assisted) cardiological imaging techniques which currently provide opportunities for more accurate and detailed anatomical and functional non-invasive diagnostic measurements in the context of risk assessment. Together with recent developments of risk prediction this may lead to an update of guidelines which are important for cardiovascular risk assessment in the context of flight safety.

In the description of findings the references to the related sub-chapters, as mentioned in the table of contents, is indicated between parentheses ( ).

Cardiological examination (2.1)

In the procedure of a general cardiological examination, the necessity of careful history taking, physical examination, and basic diagnostics like blood pressure measurements and 12 lead ECG is undisputed. Recently, diagnostic wearables have become increasingly popular and offer new insights into the individual supervision of health. The most popular functions include tracking physical activity, heart rate, heart rhythm, sleep, blood pressure, and peripheral oxygen saturation. Recent studies showed a positive effect of wearables in encouraging people to increase their daily physical activity, and also supported diagnosis of atrial fibrillation. The sub-chapter provides an extensive overview of crucial steps on specific findings in cardiovascular assessment.

Reference chapter #	Take away message
2.1	Recent studies showed a positive effect of physiological wearables in encouraging people to increase their daily physical activity, and also supported diagnosis of atrial fibrillation.

Blood pressure (2.2)

Arterial hypertension represents the most common cardiovascular risk factor worldwide. The 2023 ESH guidelines for the management of arterial hypertension provide an algorithm of appropriate combinations of drug therapy. The central objective of therapy of primary arterial hypertension is to lower blood pressure to <140/80mmHg, although a reduction to <130/80mmHg has been shown to further reduce the risk of stroke.
Pulmonary Hypertension (PH) is in most cases caused by left heart disease, while chronic obstructive pulmonary disease (COPD) is the second most common cause. Current ESC guidelines advise patients with PH to avoid altitudes exceeding 1500 m without supplemental oxygen.

Reference chapter #	Take away message
2.2	The 2023 European Society of Hypertension (ESH) guidelines for the management of arterial hypertension provide an algorithm of appropriate combinations of drug therapy. The objective of therapy is to lower blood pressure to <140/80mmHg, and a reduction to <130/80mmHg has been shown to reduce the risk of stroke.

Peripheral arterial disease and aortic disease (2.3)

Atherosclerotic lesions in PAD are independent risk factors for all atherosclerotic cardiovascular and cerebrovascular conditions. Assessment of medical history should include cardiovascular risk factors, co-morbidities, medication, claudication as well as pain free walking distance and neurological deficiencies. The ankle-brachial index calculated by means of Doppler ultrasound sonography, is considered to be a useful tool to indicate the presence of PAD. In cases with suspected PAD Duplex sonography is the next step to confirm the findings and assess severity as well as planning treatment strategies. Digital subtraction angiography (DSA) is considered to be the gold standard in diagnosis of PAD. Treatment of symptomatic cases includes risk factor management, vasodilating medication and antiplatelet therapy. Patients with lifestyle-limiting claudication despite lifestyle modification and medical therapy and patients with chronic limb ischemia should be considered for revascularization. Pilots and ATCOs should be thoroughly evaluated after surgical intervention before aeromedical license renewal.

Aortic diseases include aortic syndromes (e.g. dissection) and thoracic as well as abdominal aneurysms. In addition to the classic modifiable cardiovascular risk factors, connective tissue disorders, congenital disorders (e.g. bicuspid aortic valve), inflammatory vasculitis, cocaine abuse, and trauma are considered as risk factors. The risk of a rupture increases with the size of the aneurysm. The periodicity of surveillance in thoracic and abdominal aneurysms depends on the diameter. When aortic surgery is considered the choice of procedure is crucial for license renewal of aviation personnel and this should be discussed with the cardiac surgeon.

Reference chapter #	Take away message
2.3	Screening of symptoms of peripheral arterial disease (PAD) should be part of the screening procedure of cardiovascular risk factors.
2.3	The ankle-brachial index calculated by means of Doppler ultrasound sonography, is considered to be a useful first line tool to find evidence for peripheral artery disease.

Valvular Heart Disease (VHD) (2.4)

Calcific aortic valve disease, degenerative mitral valve disease, and rheumatic valvular disease are the most common VHDs. In individuals < 55 years congenital heart diseases such as bicuspid aortic valve (BAV) or partial mitral valve prolapse (PMP) may play a crucial role. VHD may lead to cardiac incompetence to adequately adapt or stabilise cardiac output under exercise, or orthostatic stimulus. VHDs might predispose to various cardiac arrhythmias. Diagnosis is made using detailed medical history, auscultation, and clinical signs of heart failure. As emphasised by the current ESC and AHA-Guidelines, echocardiography, particularly by using 4D Echocardiography (=real-time 3D), Speckle Tracking Echocardiography, and Strain Imaging, has a central place in the assessment of the aetiology of valvular heart disease and the feasibility of potential surgical or interventional approaches. Severity of VHD can be tested using biomarkers, such as natriuretic peptides. Functional evaluation includes stress testing. MRI and CT may provide additional information, although these tools are not suitable

for screening. Serial testing is crucial to determine the dynamics of the disease and to identify the earliest point of time with a relevant risk of impairment and possible intervention.

Reference chapter #	Take away message
2.4	Echocardiography has a central place in diagnosis of Valvular Heart Disease, particularly by using 4D Echocardiography (= 3D spatial + time), Speckle Tracking Echocardiography, and Strain Imaging to assess the aetiology of suspected valvular heart disease and the feasibility of potential surgical or interventional approaches.

Thromboembolic disorders (2.5)

In venous thromboembolism, pulmonary embolism (PE) is the most important clinical manifestation. In some cases, PE is caused by emboli from the heart such as septic embolism with endocarditis of the tricuspid valve or cardiac tumour. The majority of cases of PE result from venous thrombosis related to immobilization, trauma, inflammation, malignancy or postoperative. PE may lead to pressure overload of the right ventricle which is demonstrated by echocardiography (leftwards septal shift) and ECG changes such as right axis deviation, right bundle branch block and atrial fibrillation. Sequelae of PE can vary from total resolution to persistent pulmonary vascular occlusions leading to pulmonary hypertension. In arterial thromboembolism cerebrovascular stroke and peripheral arterial embolization are the main clinical manifestations. Cardiac sources of arterial thromboembolism are related to atrial fibrillation and in a minority of cases atrial septal defect, left-sided endocarditis, and after acute anterior myocardial infarction. Non-cardiac causes may be related to atherosclerotic disease or aortic aneurysm with thrombus formation. The current ESC guidelines recommend to perform systematic cardiovascular risk assessment in all PE patients, using validated scores and risk calculators. When pulmonary hypertension is suspected, it is recommended to perform a cardiological assessment at 3 to 6 months after the acute phase of PE.
In arterial thromboembolism echocardiography and Holter monitoring are indicated to search for atrial fibrillation. CT scan or MRI may be necessary to detect subtle forms of intracardiac thrombosis or tumour and aortic abnormalities. The likelihood of coexisting coronary artery disease has to be estimated. In pilots and ATCOs -even without cardiac complaints- a coronary calcium score and coronary CT angiography should be advised in order to mitigate the risk of incapacitation.

Reference chapter #	Take away message
2.5	In pilots and ATCOs suffering from VTE a thorough cardiovascular risk-assessment should be performed with use of applicable risk-calculators. Whether the coronary arteries should be investigated will be based on the cardiovascular risk-profile.
2.5	In pilots or ATCOs suffering from arterial thromboembolism consultation of a cardiologist is mandatory. Cardiac evaluation should consist of echocardiography and Holter monitoring. The presence of coronary atherosclerosis should be investigated with a coronary calcium score and subsequently, CT-coronary angiography.

Congenital heart disease (CHD) (2.6)

There is a multitude of different CHD pathologies. The present report discusses the following aeromedically relevant CHD conditions: 1) Cyanotic CHD, 2) Eisenmenger syndrome (ES), 3) Conditions with increased thromboembolic risk, and 4) Arrhythmias and sudden cardiac death (SCD). The term cyanotic CHD comprises the types of CHD that are characterized by a right-to-left cardiac shunt, which leads to deoxygenated blood entering the systemic circulation. Patients with CHD have a high prevalence of atrial arrhythmias, such as atrial fibrillation and atrial flutter. Atrial rates between 150 and 250 beats per minute may lead to rapid AV conduction, haemodynamic compromise, and sudden cardiac death (SCD). The recent recommendations of the NATO Cardiology working group provide useful guidance on the considerations for possible medical certification of the complex and diverse group of CHD patients.

Reference chapter #	Take away message
2.6	In patients with congenital heart diseases (CHD) who have an indication for anticoagulation (i.e. atrial fibrillation, atrial flutter) use of non-vitamin K antagonist oral anticoagulants (DOACs, NOACs) is considered safe and effective.
2.6	The recent recommendations of the NATO Cardiology working group provide useful guidance on the considerations for possible medical certification of the complex and diverse group of patients with congenital heart diseases.

Pericardial and endocardial disease (2.7)

In the field of endocarditis and pericarditis there are no recent developments that provide new opportunities for diagnosis and treatment. Complications of endocarditis range from persistent septicaemia, arrhythmias, distal embolism, and severe valvulopathies to heart failure. Pilots and ATCOs with suspected or known pericarditis should have an ECG performed and undergo transthoracic echocardiography (TTE) to quantify pericardial effusion. Cardiac MRI may confirm a diagnosis of pericarditis when ECG and TTE are inconclusive. Complications include persistent arrhythmias, pericardial tamponade and restricted ventricular filling. Use of aspirin or NSAIDs is recommended for the treatment of pericarditis until symptoms fully resolve, along with colchicine which is continued for 6 - 12 weeks. A period of 3 - 6 months of reduced physical activity is recommended following an episode of pericarditis. Recurrence occurs in approximately 15 - 30% of cases of acute pericarditis, although this percentage may be halved if colchicine is used.

Reference chapter #	Take away message
2.7	In safety-sensitive personnel ECG and transthoracic echocardiography (TTE) examination is indicated to quantify pericardial effusion in cases of suspected or known pericarditis. Cardiac MRI may confirm a diagnosis of pericarditis when ECG and TTE are inconclusive.
2.7	A period of 3 - 6 months of reduced physical activity is recommended following an episode of pericarditis

Myocardial disease (2.8)

The causal mechanisms and the symptomatology of myocarditis, hypertrophic cardiomyopathy (HCM), and restrictive cardiomyopathies (RCM) are discussed. The use of cardiac MRI to ascertain the diagnosis of myocarditis is strongly encouraged (check for oedema, or fibrosis). Approximately 75% of patients admitted with myocarditis have an uncomplicated course. Acute myocarditis that is complicated by acute heart failure or ventricular arrhythmias is associated with a 12% in-hospital mortality or need for heart transplant.
In hypertrophic cardiomyopathy (HCM) diastolic dysfunction, myocardial ischemia with angina, left ventricular outflow tract obstruction (LVTOT) with syncope, arrhythmias and heart failure are typical symptoms. HCM is associated with significant risk of Sudden Cardiac Death (SCD), particularly in those aged under 35 years. Treatment options include implantable defibrillators, surgical or interventional myectomy for permanent reversal of heart failure in patients with LVTOT, heart transplantation for patients with nonobstructive end-stage disease, and anticoagulant therapy. Most recently, the first cardiac myosin inhibitor mavacamten has been developed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy.
All forms of restrictive cardiomyopathy (RCM) are associated with impaired diastolic function, hypertrophy and restrictive filling patterns. In patients with suspected cardiac involvement of infiltrative or storage disease, cardiac MRI is strongly recommended in addition to ECG, echocardiography and Holter-ECG. Treatment options for infiltrative or storage cardiac disease depend on the specific underlying cause and the extent of cardiac involvement.

Reference chapter #	Take away message
2.8	The use of cardiac MRI to ascertain the diagnosis of myocarditis is recommended.
2.8	Pilots and ATCOs with a first-degree relative diagnosed with hypertrophic cardiomyopathy (HCM) should be screened with ECG and TTE (transthoracic echocardiogram) initially and for licence renewal.
2.8	Restrictive cardiomyopathies: in patients with suspected cardiac involvement of infiltrative or storage disease cardiac MRI is recommended in addition to ECG, echocardiography and Holter-ECG.

Heart failure (2.9)

Besides heart failure symptoms, ECG, echocardiography, and laboratory tests should be considered to establish the diagnosis of HF. Recent guidelines of the ESC concerning treatment recommend 4 classes of drugs, which should all be initiated at the time of first hospitalisation. This new treatment strategy has shown a significant reduction in mortality and rate of hospitalisation of patients with heart failure with reduced or mildly reduced ejection fraction (HFrEF, HFmrEF). In patients with HFrEF and LVEF ≤35% and QRS ≥130 ms device therapy with CRT-D (cardiac resynchronization therapy plus implantable cardioverter-defibrillator) is recommended to reduce mortality. In patients with HFpEF (HF with preserved ejection fraction), treatment should be aimed at reducing symptoms of congestion using diuretics. Recent trials suggest prognostic benefit from adding treatment with SGLT2-inhibitors and spironolactone. To avoid relapse in patients with HF, treatment should be continued without limit even if cardiac function has fully recovered under treatment.

Treatment options for patients suffering from advanced heart failure are limited. Heart transplantation remains the gold standard in these cases in the absence of contraindications. After successful heart transplantation the patient needs close follow up and therapeutic guidance in specialized centres. The post-transplantation phase poses highly complex challenges, such as acute complications in the perioperative setting, immune-modulatory therapy with the balance between organ rejection and infection, deterioration of target organ function (liver, kidneys), arrhythmia or transplant vasculopathy, and consequent risks to patient's quality of life and survival. In HF patients with severely impaired LV function, or refractory symptoms, and for whom no transplant is available the implantation of a Left ventricular assist device (LVAD) is a measure of last resort to unload the heart and stabilise circulation. Complications of LVADs include aortic insufficiency, thrombo-embolism, gastro-intestinal bleeding, and driveline infections. The 5-year survival rate with an LVAD lies around 50%. Many LVADs are implanted as "destination" (permanent) therapy instead as a bridge to transplantation.

Reference chapter #	Take away message
2.9	Recent guidelines of the ESC concerning Heart Failure recommend 4 classes of drugs, which should all be initiated at the time of first hospitalisation. This new treatment strategy has shown a significant reduction in mortality and rate of hospitalisation of patients with heart failure with reduced ejection fraction (HFrEF). To avoid relapse treatment should be continued without limit even if cardiac function has fully recovered

Syncope (2.10)

There is no new evidence regarding pathophysiology, diagnostic procedures or treatment of syncope. There is an important difference between syncope of cardiac origin and vasovagal reflex or orthostatic causes. Syncope of cardiac origin is considered as high risk and needs thorough investigation. Modern diagnostic tools for high risk syncope such as MRI, implantable loop recorders, stress-echocardiography, and electrophysiological studies should be considered to identify and manage high risk syncope of cardiac origin. Cardiac MRI can be used as a modern diagnostic standard in the assessment of structural, inflammatory and ischemic heart disease and an implantable loop recorder as modern diagnostic standard in the diagnosis of arrhythmias. Exercise treadmill test should be downgraded due to its low predictive value. It is recommended to make a risk stratification protocol for the aeromedical risk assessment of syncope.

Reference chapter #	Take away message
2.10	Exercise treadmill test should be downgraded due to its low predictive value.
2.10	It is recommended to make a risk stratification protocol for the aeromedical risk assessment of syncope.

Modern concepts of cardiovascular risk screening and use of these concepts for prevention and treatment of risk factors (2.11)

Recent developments in cardiovascular risk estimation have been described in the updated ESC guidelines on cardiovascular disease prevention in clinical practice. The guidelines provide evidence-based recommendations concerning cardiovascular prevention in apparently healthy persons and in medium and high-risk individuals. The ESC has adopted new standards of risk calculation: SCORE2 which estimates a 10-year risk of fatal and non-fatal CVD events in apparently healthy people aged 40-69 years with risk factors that are untreated or have been stable for several years; and SCORE2-OP which is applicable for people aged >70 years. Separate risk scores are recommended for diabetic patients: the ADVANCE score or SCORE2-Diabetes algorithm. In SCORE2 the following variables are used for risk estimation: age, sex, systolic blood pressure, smoking behaviour and non-HDL cholesterol levels. Non-HDL represents all atherosclerotic lipids such as VLDL, VLDL-remnants, IDL, LDL and Lp(a) and is considered a better predictor of cardiovascular risk than LDL-C. When determining the level of risk, non-traditional CV risk factors such as ApoA, ApoB, hsCRP, homocysteine, and interleukin 1 can also be taken into account. Country-specific baseline cardiovascular risk levels of a population should be determined before entering the clinical variables in the matching SCORE risk chart. Treatment of modifiable cardiovascular risk factors and expert cardiological evaluation is recommended in apparently healthy people without diabetes mellitus, chronic kidney disease, genetic/rarer lipid or blood pressure disorders who are at very high CVD risk (SCORE2 >7.5% for age <50; SCORE2 >10% for age 50-69; SCORE2-OP >15% for age >70).

Reference chapter #	Take away message
2.11	SCORE2 and SCORE2-OP are the new tools adopted by the ESC as the new standards of risk calculation: SCORE2 which estimates a 10-year risk of fatal and non-fatal CVD events in apparently healthy people aged 40-69 years with risk factors that are untreated or have been stable for several years; and SCORE2-OP which is applicable for people aged >70 years.
2.11	The 2021 ESC recommendations provide accurate and evidence-based cardiovascular risk estimations and preventive treatment guidelines and should, therefore, be considered for use in aeromedical risk assessments.

In-flight conditions which influence the status of a cardiovascular disease and implanted device (3)

No evidence is found showing an influence of hypoxia, lower humidity, or noise on medical devices. Modern CIEDs (Cardiac Implantable Electronic Devices) utilize shielding, filters, and bipolar leads to mitigate electromagnetic interference (EMI). Nano-magnetic insulation has recently been utilized in lead design to improve shielding from radiofrequency and time varying gradient magnetic fields. Activity-sensing rate-adaptive pacemakers and ICDs might be affected by vibrations particularly during take-off and landing. There is no evidence that hypobaric hypoxia has an effect the stimulation threshold of pacemakers. The overall risk of clinically significant adverse events during flight in recipients of CIEDs or ICDs is very low, although theoretically possible. Table 1 of chapter 5.8 shows different interference types on cardiac pacemakers and possible clinical consequences.

Reference chapter #	Take away message
3	The overall risk of clinically significant adverse events during flight in recipients of CIEDs or ICDs is very low. Most new PM are MR-compatible.

Chest pain, myocardial ischemia and indications for coronary artery revascularization (4.1)

The main causes of myocardial ischemia include (1) atherosclerotic flow-limiting stenoses (causing chronic stable angina); (2) coronary thrombus superimposed on an atherosclerotic plaque (causing acute coronary syndromes); (3) coronary artery spasm (causing vasospastic angina); and (4) coronary microvascular dysfunction. Myocardial ischemia and the severity of coronary lesions can be evaluated using coronary computed tomography angiography (CCTA) and/or invasive coronary angiography. Current methods for demonstration of myocardial ischemia are stress echocardiography, single-photon emission tomography (SPECT), positron emission tomography (PET), and cardiovascular magnetic resonance imaging (cardiac MR). Currently machine learning and artificial intelligence tools are (being) developed to play a diagnostic role. CCTA has presently a most prominent role and if complemented by the recently developed method of fractional flow reserve (FFR) measurements, it can also provide a functional judgement. Routine use of exercise ECG-testing for detection of ischemia is currently not recommended due to its low sensitivity. It may however be a useful tool in selected cases.

The primary goal of therapy in patients with chronic ischemic heart disease is to relieve symptoms, delay or prevent progression of coronary artery disease, and decrease the risk of major adverse cardiovascular events. This is primarily achieved with optimal medical therapy. Revascularization is justified if there is a large area of inducible ischemia or if there is persistent limiting angina despite optimal medical therapy. PCI as well as CABG are established methods for invasive coronary intervention. Independent of the chosen therapeutic option, it is important to pursue a healthy lifestyle to control the modifiable cardiovascular risk factors. A clear prognostic indication for revascularization is left main coronary artery (LM) disease with stenosis greater than 50%. Long-term risks after treatment of LM disease are high and should be considered in the medical certification of pilots and ATCOs. The following new (2023) ESC guidelines are discussed: management of myocardial infarction with non-obstructive coronary arteries (MINOCA), treatment of multivessel coronary artery disease (PCI of culprit lesion only or multi-vessel PCI), and a PCI technique guided by optical coherence tomography (OCT) which is able to characterise coronary plaques in detail.

Reference chapter #	Take away message
4.1	Routine use of exercise ECG-testing for detection of ischemia is not recommended due to its low sensitivity.
4.1	CCTA has currently the most prominent role in investigating coronary stenosis and, if complemented by fractional flow reserve (FFR) measurements, it can also provide a functional judgement.
4.1	PCI guided by optical coherence tomography (OCT) is able to characterise coronary plaques in detail, which is of great importance for prognosis and treatment.

Management of stenoses of the left main (LM) coronary artery (4.2)

The LM coronary artery supplies 75-100% of the circulation of the left ventricular (LV) myocardium and significant LM stenosis places the left ventricle at considerable risk. LM disease is the CAD subset with the strongest evidence that revascularization provides survival benefit over medical treatment alone in stable patients. Treatment options for significant LM disease are CABG, and PCI. The threshold for intervention in LM disease is set at 50% stenosis because of early observations that patients with 50% to 70% LM stenosis had a survival benefit after CABG. Nowadays, PCI is also used as treatment. Recent meta-analyses consistently have demonstrated a lack of significant mortality or stroke difference between CABG and PCI although the incidence of spontaneous MI and repeat-revascularisation were lower with CABG. CABG was associated with a significant longer-term survival benefit during a mean follow-up of 3.8 years. The long-term risks after invasive treatment of LM disease concerning mortality, non-procedural MI, stroke, and repeat revascularization are high and this should be taken into account in the risk assessment of pilots and ATCOs.

Reference chapter #	Take away message
4.2	Stenosis of the Left Main coronary artery is the CAD subset with the strongest evidence that revascularization provides survival benefit over medical treatment alone in stable patients.
4.2	Long-term risks after invasive treatment of LM disease concerning mortality, non-procedural MI, stroke, and repeat revascularization are high and this should be taken into account in the aeromedical risk assessment.

Indications for revascularization in coronary artery disease and follow-up data after revascularization (4.3)

In patients presenting with ST-elevation myocardial infarction (STEMI), direct or primary PCI of the culprit vessel is usually performed. Revascularization of remaining lesions improves prognosis and is currently standard practice. After a successful and complete revascularization, the risk of future cardiac events can be lowered with strict medical therapy, lowering non-HDL to target low levels, treating co-morbidities like hypertension and diabetes, and smoking cessation. After PCI, stent thrombosis may be a complication resulting in excess morbidity and mortality. Treatment with dual antiplatelet (DAPT) agents is therefore of great importance to prevent stent thrombosis. Survival curves show that stent thrombosis occurs only during the first month after stenting. The second issue of stenting is the development of in-stent restenosis (ISR). Restenosis rates are estimated at 10% after 6 months. ISR is related to stent properties and patient characteristics. Coronary stenting with 3rd generation drug eluting stents (DSE) is the current standard in percutaneous revascularization. With these DSE stents combined with adequate antithrombotic and LDL lowering therapy clinical in-stent restenosis and stent thrombosis has become a very infrequent event. With the current high quality of stenting, combined with adequate drug therapy the postprocedural risk may decrease significantly and the time span of elevated risk is considered shorter than before. Based on the estimated postprocedural level of risk, in selected cases pilots should be allowed to return to work earlier than the current requirements indicate, especially when chronic CAD is involved. After (multivessel) PCI follow-up invasive coronary angiography or coronary CT with FFR are considered the most accurate

diagnostic tools. After Coronary artery bypass graft surgery (CABG), SPECT, PET-CT or FFR-CCTA will have the highest sensitivity and specificity in detecting ischemia.

Reference chapter #	Take away message
4.3	After (multivessel) PCI follow-up invasive coronary angiography or coronary CT with FFR are considered the most accurate diagnostic tools. After CABG, SPECT, PET-CT or FFR-CCTA will have the highest sensitivity and specificity in detecting ischemia.
4.3	Coronary stenting with 3rd generation drug eluting stents (DSE) is the current standard in percutaneous revascularization. With the current high quality of stenting, combined with adequate drug therapy, the time span of elevated risk is considered shorter than before. Based on the estimated postprocedural level of risk, in selected cases pilots should be allowed to return to work earlier than the current requirements indicate.

Bleeding risks of antithrombotic medications, especially after PCI and after CABG (4.4)

Antithrombotic therapy is required in many cardiovascular diseases and all therapeutic agents involved are associated with an increased bleeding risk. Overall, the bleeding risk of the commonly used dose of aspirin (100 mg) ranges from 0.3% to 2.0%. The bleeding risk of monotherapy with clopidogrel, is similar to that of aspirin. Dual anti-platelet therapy (DAPT) with aspirin and clopidogrel or ticagrelor is currently the mainstay of antithrombotic therapy after myocardial infarction (MI) and/or PCI. Treatment with DAPT has a higher bleeding risk than the use of a single antiplatelet drug. Compared with oral anticoagulation (OAC) therapy alone, the addition of DAPT to OAC therapy results in at least a two- to three-fold increase in bleeding complications. This “triple” antithrombotic treatment medication should be avoided or used only for a short period on strict indication, such as after PCI or CABG in presence of atrial fibrillation (AF). In patients with AF or chronic coronary syndrome DOACs or NOACs have demonstrated superiority over aspirin monotherapy or DAPT for stroke prevention, and OACs (apixaban, dabigatran, edoxaban, rivaroxaban) are currently recommended for this indication and are preferred over a vitamin K antagonist. The bleeding risk of OACs is considered to be similar to the bleeding risk of vitamin K antagonists with some small individual differences.

Reference chapter #	Take away message
4.4	In AF patients OACs have demonstrated superiority over aspirin monotherapy or clopidogrel-based DAPT for stroke prevention. DOACs or NOACs are currently recommended for this indication and are preferred over a vitamin K antagonist.

Procedure in asymptomatic coronary artery disease (chronic coronary syndrome) (4.5)

Chronic coronary syndrome (CCS) is also known as stable angina and can lead to chest pain, myocardial infarction, heart failure, and arrhythmias. Appropriate management of the classic modifiable risk factors in combination with medication such as statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, and antiplatelet agents may significantly lower LDL-C and risk levels in patients with CCS. Presentations at the 2023 ESC-congress highlighted the role of inflammation as important contributor to

atherothrombotic disease. Chronic low-grade inflammation within the arterial wall as well as exposure to fine particles are considered to contribute to the formation and progression of atherosclerotic plaques. The currently recommended target levels of lipid-lowering therapy for low-to moderate risk patients are LDL-C <1.8 mmol/L and <1.3 mmol/L for CCS patients at high risk. Measuring the level of high-sensitivity CRP is considered to be a reliable indicator of inflammation as important risk factor of CAD. For future CCS prevention combined lipid-lowering and anti-inflammation treatment is likely to be recommended. In the 2023 ESC Guidelines, the relationship between diabetes, cardiovascular diseases and chronic kidney disease is highlighted. In patients aged ≥40 years with type 2 diabetes mellitus without atherosclerotic cardiovascular disease or severe target-organ damage, it is recommended to estimate 10-year CVD risk using the SCORE2-Diabetes algorithm. Patients with cardiovascular disease should be actively checked on diabetes and chronic kidney disease (and vice versa).
To determine the risk of coronary events, the degree, location, nature, and extent of stenoses in the coronary arteries have to be investigated using anatomical and functional methods. The recent ESC guidelines recommend non-invasive functional imaging or CCTA as the initial test for diagnosing Coronary Artery Disease (CAD).

Reference chapter #	Take away message
4.5	Non-invasive functional imaging or CCTA is currently recommended as the initial test for diagnosing coronary artery disease.
4.5	Appropriate management of the classic modifiable risk factors in combination with medication such as statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, and antiplatelet agents may significantly lower risk levels in patients with CCS. Currently recommended target levels for LDL-C are <1.8 mmol/L for low to moderate risk patients and <1.3 mmol/L for patients at high risk.
4.5	Measurement of hs-CRP level is considered to be a reliable indicator of inflammation as important risk factor of CAD.
4.5	In patients ≥40 years with type 2 diabetes mellitus without atherosclerotic cardiovascular disease or severe target-organ damage, it is recommended to estimate 10-year CVD risk using the SCORE2-Diabetes algorithm. Patients with cardiovascular disease should be actively checked on diabetes and chronic kidney disease (and v.v.).

Echocardiography (4.6)

Echocardiography can be used to detect signs of CAD, such as wall motion abnormalities, regional or global left ventricular dysfunction, and evidence of myocardial ischemia. Echocardiography can provide real-time guidance during interventional procedures, such as PCI, by helping to visualize the coronary arteries, guiding the placement of catheters and stents, and assessing the results of the intervention. Echocardiography provides information on cardiac function, including left and right ventricular ejection fraction (LVEF and RVEF), diastolic function and global longitudinal strain (GLS). Reduced LVEF and/or GLS may indicate impaired cardiac function due to CAD. Stress echocardiography, which combines echocardiography with a stress-inducing manoeuvre (exercise or pharmacological), can be used to assess inducible ischemia by changes in wall motion, LVEF, and other echocardiographic parameters during stress. There are many new developments in echocardiography, such as 3D and 4D

Echocardiography, Speckle Tracking Echocardiography, Strain Imaging, Contrast-enhanced Echocardiography, Pocket-sized and Handheld Echocardiography, combinations with CT and/or MRI techniques (Fusion Imaging), and use of AI and Machine Learning to improve analysis and diagnosis. These new techniques provide opportunities for more accurate and detailed anatomical and functional non-invasive diagnostic measurements.

Reference chapter #	Take away message
4.6	3D and 4D-Echocardiography, Speckle Tracking Echocardiography, Strain Imaging, Contrast-enhanced Echocardiography, and their combinations with CT and/or MRI techniques (Fusion Imaging), and use of AI and Machine Learning provide opportunities for more accurate and detailed anatomical and functional non-invasive diagnostic measurements.

The actual role of CT coronary artery calcium score (CACS) and Coronary computed tomographic angiography (CCTA) in the detection of Coronary artery disease (CAD) (4.7)

Higher amounts of calcium found by CACS are associated with a higher risk of future cardiovascular events. CACS is recommended to decide on the indication for statin therapy in low- to moderate-risk patients. Non-calcified soft plaques, which may cause a sudden cardiac emergency due to a plaque rupture, will remain undetected with CACS and can only be found with CCTA. CCTA can detect stenotic lesions as well as assess plaque morphology, plaque composition, and features of plaque instability. With CT-scanning it is possible to assess myocardial perfusion (CT perfusion or CTP) and Fractional Flow Reserve (CT-FFR). By combining anatomy and perfusion, CCTA has become the first line screening method in patients with a suspicion of coronary artery disease. Currently, coronary CCTA is recommended as the initial test for diagnosing CAD in symptomatic patients. A limitation of CCTA is that it is not accurate in detecting significant stenosis in the presence of extensive coronary calcifications. Due to its excellent sensitivity and high negative predictive value CCTA is considered the strongest test to rule-out flow limiting CAD, especially in patients with low to intermediate risk. Strong evidence supports the use of coronary CT-FFR for the diagnosis of CAD in patients presenting with stable chest pain syndromes. After coronary stenting, CCTA is able to detect the presence of restenosis. After CABG, CCTA can detect graft failure. CACS and CCTA are new techniques that have brought an upgrade in the diagnostic tools for further improvement in the risk-profiling of pilots and ATCO's. CT-scanning deserves an important place in the new EASA aeromedical requirements.

Reference chapter #	Take away message
4.7	Coronary artery calcium score (CACS) is recommended to decide on the indication for statin therapy in low- to moderate-risk patients. Non-calcified soft plaques will remain undetected with CACS and can only be found with Coronary computed tomographic angiography (CCTA).
4.7	With CT-scanning it is possible to assess myocardial perfusion (CT perfusion or CTP) and Fractional Flow Reserve (CT-FFR). By combining anatomy and perfusion, CT has become the first line screening method in patients with a suspicion of coronary artery disease.
4.7	Strong evidence supports the use of CT-FFR for the diagnosis of CAD in patients presenting with stable chest pain syndromes.

4.7	Currently, CCTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded.

Cardiac MRI in coronary artery disease (4.8)

Cardiac MRI can provide detailed images of the heart's structure, including the chambers, valves, and blood vessels and helps to evaluate the presence and extent of scar tissue caused by previous myocardial infarctions. Current ESC guidelines recommend Stress Perfusion MRI as the initial test for diagnosing CAD and as test if CCTA has shown CAD of uncertain functional significance. Quantitative perfusion MRI has an increasingly important role in the management of angina and non-obstructive CAD. MRI can be used to assess myocardial viability, which can guide treatment decisions, such as determining the potential benefit of revascularization procedures. Late Gadolinium enhancement (LGE) can detect fibrosis after myocardial infarction or myocarditis. It contributes to make a final diagnosis in up to 50% of patients with 'Myocardial infarction with non-obstructed coronary arteries' (MINOCA). LGE MRI is more sensitive than echocardiography for the detection of intracardiac thrombus. The combination of cardiac MRI with other imaging modalities, such as positron emission tomography (PET) can provide complementary information on myocardial perfusion, metabolism, and viability. The fusion of multiple imaging modalities could enhance the diagnostic accuracy and comprehensive assessment of cardiac disease.

Reference chapter #	Take away message
4.8	Current ESC guidelines recommend Stress Perfusion MRI as the initial test for diagnosing CAD and as test if CCTA has shown CAD of uncertain functional significance.

Nuclear medicine methods: SPECT and PET (4.9)

For detection of myocardial ischemia, the following functional techniques are used: Stress ECG, Stress echocardiography, Cardiovascular magnetic resonance imaging (CMR), Single-photon emission tomography (SPECT) and Positron emission tomography (PET). When using fractional flow reserve (FFR), CCTA is besides an anatomical also a functional method. Non-invasive functional tests are associated with high accuracy for the detection of flow-limiting coronary stenosis compared with invasive functional testing (FFR). It is concluded that Stress echocardiography, CMR, PET and CCTA (with FFR) have similar sensitivity and specificity for the detection of myocardial ischemia. PET is considered superior to SPECT. SPECT and PET can be combined with other imaging techniques, in particular with CMR or with CCTA. Such imaging fusions, labelled as hybrid imaging, allow the intrinsic combination of functional and anatomical image information.

Reference chapter #	Take away message
4.9	Stress echocardiography, CMR, PET and CCTA (with FFR) have similar significance for the detection of myocardial ischemia.

Role of artificial intelligence in CAD (4.10)

AI and machine learning procedures are increasingly used in cardiac imaging techniques such as CCTA (CT-perfusion, CT-FFR), echocardiography and MRI. AI and machine learning help to establish a more precise diagnosis which enables the assessment of cardiovascular risks.

Significance of genetic evaluation of coronary artery disease (4.11)

Genetic testing has become an established diagnostic procedure in several cardiac diseases, such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and hypertrophic cardiomyopathy. Genetic predisposition for CAD is not established yet and therefore currently not recommended, although testing of familial hypercholesterolemia can provide an indirect hint to atherosclerotic disease.

Reference chapter #	Take away message
4.11	Genetic testing has become an established diagnostic procedure in several cardiac diseases, such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and hypertrophic cardiomyopathy.

COVID-19 (4.12)

The frequency of myocarditis following messenger RNA-based COVID-19 vaccines is low although a slightly higher risk is found in adolescent and young adult men. Chest pain is the most common symptom, with typical onset within a few days of vaccine administration. Cardiac MRI plays an important role in the diagnosis of acute myocarditis following vaccination, with typical findings of subepicardial late gadolinium enhancement and co-localizing edema at the basal inferior lateral wall. The disease course of myocarditis following COVID-19 vaccination is transient and mild, with resolution of symptoms within 1 to 3 weeks in most patients. However, longer term follow-up is needed to determine whether abnormalities persist, to evaluate for adverse outcomes, and to estimate the risk associated with subsequent vaccination. It is concluded that despite rare cases of self-limited myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favourable balance for all age and sex groups. Myocarditis and/or pericarditis can be one the clinical or residual manifestations of Covid-19 infection. It can also occur in asymptomatic infected patients. Cardiac magnetic resonance (CMR) is a potent tool for the detection of myocarditis. Myocarditis and/or pericarditis are considered as important cardiological manifestations of long-COVID syndrome. In patients with long-COVID syndrome palpitations and arrhythmias were frequently associated with pericardial disease. Autonomic manifestations such as postural orthostatic tachycardia syndrome (POTS) also belong to the wide spectrum of clinical manifestations of long COVID syndrome.

Reference chapter #	Take away message

4.12	Myocarditis can be a complication of COVID vaccination as well as of COVID infection. Pericarditis and/or myocarditis are considered to be important cardiological manifestations of long-COVID syndrome. In long-COVID cases palpitations and arrhythmias were frequently associated with pericardial disease. Postural orthostatic tachycardia syndrome (POTS) can also be one of the clinical manifestations of long COVID syndrome or after COVID-vaccination.

Atrial fibrillation (5.1)

AF can be associated with valvular heart disease, CAD, cardiomyopathies, hypertension, hyperthyroidism, and respiratory diseases. Other causative or trigger factors include electrolyte disorders, sepsis, smoking, alcohol or caffeine excess, drug intake, excessive physical activity, fatigue, and exhaustion. For apparently healthy people with a low cardiovascular risk, opportunistic AF screening is recommended beyond the age of 65 and systematic AF screening above the age of 75. For asymptomatic individuals with increased cardiovascular risk, opportunistic AF screening of hypertensive people and in cases of obstructive sleep apnoea is recommended.

Due to the adverse effect profiles of medication used to restore or maintain sinus rhythm or to control ventricular rate, AF catheter ablation is increasingly recommended as a first line intervention in patients with paroxysmal AF (PAF), and in patients with persistent AF without major risk factors for AF recurrence. In PAF success rates >80% can be achieved. The long-term success rate in cases with persistent AF is 40–60% after a single ablation and many cases need a second or third intervention. When assessing pilots and ATCOs that have undergone AF ablation, the observation period to determine the success of the procedure should last at least 6 months; this includes an initial 'blanking period' of 3 months, during which the ablation itself may cause arrhythmias regardless of the ablation success and an additional observation time of at least 3 months. Thermal methods are associated with side effects due to coagulative tissue necrosis. The newly developed pulsed field ablation (PFA) technique for cardiac ablation of AF has higher myocardial tissue selectivity compared to conventional methods. PFA ablation is effective for paroxysmal and persistent AF and is associated with low AF recurrence at one-year follow-up.

Reference chapter #	Take away message
5.1	The newly developed pulsed field ablation (PFA) technique for cardiac ablation of AF has higher myocardial tissue selectivity compared to conventional methods. PFA ablation is effective for paroxysmal and persistent AF and is associated with low AF recurrence at one-year follow-up.

Indication of anticoagulation in atrial fibrillation (5.2)

In 2020 the ESC has published new recommendations for stroke prevention in AF. For patients who are eligible for oral anticoagulants (OACs) and have no mechanical heart valves or moderate-to-severe mitral stenosis, novel oral anticoagulants (NOACs) are recommended in preference to vitamin K antagonists (VKAs). Among patients with atrial high-rate episodes (AHREs) anticoagulation with edoxaban (OAC) did not significantly reduce the incidence of a composite of cardiovascular death, stroke, or systemic embolism as compared with placebo, but it led to a higher incidence of a composite of death or major bleeding. It is concluded that patients with AHREs shall not be anticoagulated, as

long as there is no ECG documentation of AF. Patients with AF remain at significant residual risk of developing complications including ischemic stroke despite anticoagulation therapy. The stroke risk should be identified using the risk-factor-based CHA2DS2VASc score. Based on the CHA2DS2VASc score, an indication for OAC can be considered. The HAS-BLED score should be considered for bleeding risk assessment. Stroke and bleeding risk reassessment is recommended at periodic intervals. In cases who are initially at low risk of stroke, first re-assessment of stroke risk should be made at 4 - 6 months after the index evaluation. Antiplatelet therapy alone is not recommended for stroke prevention. Left atrial appendage (LAA) occlusion may be considered for stroke prevention in patients with AF who have contraindications for long-term anticoagulant treatment and may also be considered for stroke prevention in patients with AF undergoing cardiac surgery.

Reference chapter #	Take away message
5.2	For patients who are eligible for oral anticoagulants (OACs) and have no mechanical heart valves or moderate-to-severe mitral stenosis, novel oral anticoagulants (NOACs) are recommended in preference to vitamin K antagonists (VKAs). Antiplatelet therapy alone is not recommended for stroke prevention. Patients with atrial high-rate episodes (AHREs) shall not be anticoagulated, as long as there is no ECG documentation of AF.

Ventricular and supraventricular ectopy (5.3)

According to recent ESC-Guidelines, a Premature Ventricular Complex (PVC) is defined as premature occurrence of an abnormal QRS complex (duration ≥120 ms, broad corresponding T-wave and in opposite direction of the major QRS deflection, no preceding P-wave) and a Ventricular tachycardia (VT) as ≥3 consecutive beats with a rate >100 bpm originating from the ventricles, independent from atrial and atrioventricular (AV) nodal conduction. Although PVCs are generally considered benign, they can lead to PVC induced cardiomyopathy (PIC) and, rarely, to syncope or sudden cardiac death. In most cases one or more PVCs are identified on a resting 12-lead ECG as an incidental finding in a routine physical examination. Although in most cases PVCs have an idiopathic origin, they are sometimes associated with underlying structural heart disease (SHD) and have a poorer prognosis which warrants specific treatment. Therefore, in individuals who have symptoms compatible with VT and/or a positive family history (SCD, cardiomyopathy) or a high PVC burden, imaging tests might be necessary (TTE, MRI) to screen for SHD and PIC. Suppression of ectopy with exercise is a sign of benignity, but occurrence of PVCs or VT during exercise is suspect for SHD and needs further specialistic evaluation. Beta -blockers and non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) remain first-line treatment for patients with frequent and symptomatic PVCs. If drugs are ineffective or poorly tolerated, catheter ablation is the next treatment option.
Although commonly considered benign, premature atrial contractions (PAC) have recently been associated with a higher risk of incident atrial fibrillation (AF), stroke, and all-cause mortality. There is evidence that PAC burden has a dose response effect on all-cause mortality and cardiovascular death and that beta-blockers and intensifying physical activity decrease long-term mortality in high- and low-burden patients. Sleep apnoea is associated both with PVCs and PACs, and should be included in the diagnostic process.

Reference chapter #	Take away message
5.3	For individuals with PVCs who have symptoms compatible with VT and/or a positive family history (SCD, cardiomyopathy) or a high PVC burden, imaging tests should be used (TTE, MRI) to screen for structural heart disease and cardiomyopathy (PIC).
5.3	Sleep apnoea is associated both with PVCs and PACs, and should be included in the diagnostic screening.
5.3	Premature atrial contractions (PAC) have recently been associated with a higher risk of incident atrial fibrillation (AF), stroke, and all-cause mortality.

Bundle branch and fascicular blocks (5.4)

Bundle branch or fascicular blocks (LBBB, (incomplete) RBBB, LAFB, LPFB) and non-specific intraventricular conduction delay are significantly associated with new-onset heart failure (HF), and increased risks of myocardial infarction, novel structural heart disease (SHD), and the need for pacemaker implantation. Therefore, the presence of bundle branch or fascicular blocks warrants careful cardiological evaluation even in absence of cardiovascular symptoms. Left bundle branch block (LBBB) has profound hemodynamic and clinical implications even among asymptomatic individuals, and its presence is associated with a multitude of cardiac diseases. A CMR scan is pivotal in risk stratifying patients with incident LBBB. Individuals with Right bundle branch block (RBBB) without cardiovascular disease were found to have an increased risk of all-cause mortality, and cardiovascular-related mortality, and lower exercise tolerance. In cases of newly acquired Left anterior fascicular bock (LAFB) over age 40, underlying CAD should be excluded using CTCA. Left posterior fascicular block (LPFB) is significantly associated with aborted cardiac arrest and sudden cardiac death and should be recognized as a pathological finding, prompting further investigation to detect underlying structural abnormalities.

Reference chapter #	Take away message
5.4	Bundle branch or fascicular blocks and non-specific intraventricular conduction delay are significantly associated with new-onset heart failure, and increased risks for myocardial infarction, structural heart disease, and the need for pacemaker implantation. Careful cardiological evaluation is required even in absence of cardiovascular symptoms.

Atrioventricular blocks (AVB) (5.5)

Diagnosis of the underlying cause of advanced AVB by routine use of cardiac magnetic resonance imaging (CMR) will enable cause-specific treatments and improve outcomes particularly in young and middle-aged patients. AVB of unknown etiology presenting before the age of 50 years and treated with pacemaker implantation is associated with a 3 to 4-fold higher rate of the composite endpoint of death or hospitalization for heart failure, ventricular tachyarrhythmia, or cardiac arrest with successful

resuscitation. Patients with severe bradycardia or advanced AVB during sleep should be screened for sleep apnoea syndrome (SAS).
The present report describes detailed recommendations for diagnostics and therapy of AVB as provided by the most recent (2021) ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.

Reference chapter #	Take away message
5.5	Diagnosis of the underlying cause of advanced AVB by routine use of Cardiac magnetic resonance imaging (CMR) will enable cause-specific treatments and improve outcomes.
5.5	Patients with severe bradycardia or advanced AVB during sleep should be screened for sleep apnoea syndrome (SAS).

Asymptomatic Ventricular Pre-excitation (5.6)

Ventricular pre--excitation (Wolff-Parkinson-White (WPW) syndrome) is in 60-70% of the asymptomatic cases characterised by a delta wave and a short PR interval on the ECG which indicates the presence of an accessory pathway (AP) between atria and ventricles bypassing the His-Purkinje system. Fast antegrade conduction over the AP may lead to ventricular fibrillation and sudden cardiac death in cases of atrial fibrillation, because APs lack the delaying properties of the AV node, while retrograde conduction over the AP may allow for AV re-entrant tachycardia. The most common arrhythmia in patients with WPW syndrome is atrioventricular nodal reentrant tachycardia (AVRT), followed by a 20-30% incidence of AF. The “2019 ESC-Guidelines for the management of patients with supraventricular tachycardia” provide detailed guidelines for the management of symptomatic and asymptomatic cases of WPW syndrome. Risk assessment by electrophysiological screening (EPS) with adrenergic stimulation using isoprenaline is strongly recommended for asymptomatic WPW patients with safety-sensitive occupations. When these patients show defined high-risk features, the accessory pathway(s) should be ablated. In the case of low-risk features catheter ablation may be considered. In all patients with symptomatic WPW syndrome catheter ablation of the accessory pathway is the treatment of choice.

Reference chapter #	Take away message
5.6	Risk assessment by electrophysiological screening (EPS) with isoprenaline is strongly recommended for asymptomatic WPW patients with safety-sensitive occupations.
5.6	In WPW patients with high-risk properties of the accessory pathway(s), the accessory pathway(s) should be ablated.

Channelopathies (5.7)

This chapter describes the causes, mechanisms, and risks of the following inheritable disorders caused by dysfunction of ion channels located in the membranes of cells: Long QT syndrome (LQTS), Brugada syndrome (BrS), Short QT syndrome (SQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), and Early Repolarization Syndrome (ERS). Identification of these disorders is of utmost importance in order to prevent their life-threatening symptoms, such as sudden death, cardiac arrest, ventricular tachyarrhythmia, or syncope, and to safeguard aviation safety. AMEs should therefore critically judge:

- Family history of sudden death <45 years of age.
- 12-lead ECG (typical changes in BrS type 1, prolonged QT time in LQTS, abnormal shortening of QT and/or tall peaked T-waves in SQTS, prominent J-waves in ERS).
- Evaluation of symptoms (syncope, palpitations, (aborted) cardiac arrest).

In case of any suspicion of one of the above disorders, risk stratification should be performed in cardiological centres using international guidelines such as the 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, which are summarised in the present sub-chapter. Crucial factors include medical and family history and genetic testing. Patients with LQTS should avoid QT-prolonging drugs (e.g. several antibiotics, antidepressants, antihistamines, opioids). In BrS patients it is recommended to avoid Class IC antiarrhythmics, cocaine, cannabis, excessive alcohol intake, and antipyretics. Treatment options are variable and may include treatment with beta-blockers. In high-risk patients, ICD implantation is often required to prevent sudden cardiac death. Invasive mapping and ablation strategies are currently discussed for BrS.

Reference chapter #	Take away message
5.7	Long QT syndrome, Brugada syndrome, Short QT syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia, and Early Repolarization Syndrome are inheritable ion channel disorders that may cause sudden death, cardiac arrest, ventricular tachyarrhythmia, or syncope.
5.7	Due to their life-threatening symptoms the AME should vigilantly consider family history, ECG patterns and QTc, and possible symptoms.

Cardiac Pacing (5.8)

Most common indications for cardiac pacing are bradycardia caused by sinus node dysfunction (SND) and/or Atrio-Ventricular Block. A new already widely applied development in cardiac pacing is conduction system pacing (CSP) with either His bundle pacing or left bundle branch area pacing. To avoid complications caused by transvenous leads and being able to treat patients with difficult or no transvenous access, Leadless Pacemakers have been developed consisting of a capsule-like device containing a generator and electrode system that is implanted into the right ventricle via a percutaneously inserted femoral venous catheter. Although Cardiac Resynchronization Therapy (CRT) is mainly used in patients with heart failure and left ventricular ejection fraction below 50%, there are CRT indications for patients with heart failure with preserved ejection fraction (HFpEF) in combination

with uncontrolled AF needing atrioventricular junction (AVJ) ablation. The most recent information of the ESC-congress (25.-20.08.2023) confirms the diagnostic methods and indications for pacemaker implantation as described in the present report.

Reference chapter #	Take away message
5.8	Bradycardia caused by sinus node dysfunction (SND) and/or Atrio-Ventricular Block (AVB) are important indications for cardiac pacing.
5.8	A new development in cardiac pacing is Conduction System Pacing (CSP) with His bundle pacing or left bundle branch area pacing.
5.8	To avoid complications caused by transvenous leads, Leadless Pacemakers may be considered as an alternative to standard single lead ventricular pacing.

Implantable Cardioverter Defibrillator (ICD) (5.9)

Implantable cardioverter-defibrillator (ICD) therapy is a well-established treatment option for ventricular tachyarrhythmia and improves primary and secondary prevention of sudden cardiac death (SCD). Device-related complications of ICD therapy include inappropriate shocks, lead fractures, and device-related infections. As an alternative to a transvenous lead implantation, a subcutaneous ICD (S-ICD) and an extravascular ICD (EV-ICD) have been developed for certain indications. S-ICD has no intravascular lead and therefore cannot deliver Anti-tachycardia Pacing (ATP). Several large studies have shown that the safety and efficacy of the S-ICD is non-inferior to transvenous devices. EV-ICD systems provide an alternative to transvenous ICDs in patients who do not need bradycardia pacing. The most recent recommendations concerning the indications for ICD therapy have been summarized in the 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD. The present chapter provides a summarised description of the multitude of indications for ICD therapy.

Reference chapter #	Take away message
5.9	Implantable cardioverter-defibrillator (ICD) is an established treatment option for ventricular tachyarrhythmia and improves prevention of sudden cardiac death (SCD).
5.9	Subcutaneous ICD (S-ICD) and extravascular ICD (EV-ICD) are efficacious alternatives to transvenous ICDs in patients who don't need Anti-tachycardia Pacing (S-ICD) or bradycardia pacing (EV-ICD).

Concepts of cardiological incapacitation risk estimation (6)

It is recommended to use a risk matrix approach, in which probability and severity are plotted, for the risk assessment of incapacitation caused by cardiological incapacitation events. Such matrices can provide a semiquantitative assessment of the flight safety and operational impact of a broad spectrum of medical conditions with variable probabilities of occurrence. The method offers structured and systematic decision making and may lead to more evidence-based reasoning. A 5X5 risk matrix is recommended and the ICAO standard risk matrix is preferred with the axes for risk severity horizontal,

and risk probability vertical. It is recommended to follow the risk probability categories of ICAO, preferably specified in percentages per year in order to enable using epidemiological data directly. Acceptability of the risk requires careful consideration taking into account the type of operation for which the risk is assessed (multi-crew ops, single pilot ops, different ATC ops).

Reference chapter #	Take away message
6	For risk assessment of incapacitation caused by cardiovascular events, it is recommended to use a risk matrix approach, in which probability is plotted against severity.

CONTENTS

ABBREVIATIONS

ACRONYM	DESCRIPTION
3D	Three-dimensional
4D	Four-dimensional
ABI	Ankle-brachial-index
ACC	American college of cardiology
ACA	Aborted cardiac arrest
ACS	Acute coronary syndrome
ADVANCE	Action in Diabetes and Vascular disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation
AE	Atrial ectopy
AF	Atrial fibrillation
AHA	American heart association
AHREs	Atrial high-rate episodes
AI	Artificial Intelligence
AME	Aeromedical Examiner
AP	Accessory path
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ARNI	Angiotensin receptor neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
ASD	Atrial septal defect
ATCO	Air traffic controller
ATE	Arterial Thrombo-Embolism
ATP	Antitachycardia pacing
AV	Atrioventricular
AVAi	indexed aortic valve area
AVB	Atrioventricular block
AVJ	Atrioventricular junction
AVRT	Atrioventricular reentrant tachycardia
AVS	Aortic valve sclerosis
BAV	Bicuspid aortic valve
BBB	Bundle branch block
BBR-VT	Bundle branch re-entrant ventricular tachycardia
BiV	Biventricular
BMI	Body mass index

BNP	B-type natriuretic peptide
BP	Blood pressure
BrS	Brugada syndrome
CA	Cardiac arrest
CABG	Coronary artery bypass graft surgery
CAC	Coronary artery calcium
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomographic angiography
CDC	Centers for Disease Control and Prevention
CFR	Coronary flow reserve
CHD	Coronary heart disease
CKD	Chronic kidney disease
CMD	Coronary microvascular dysfunction
CMP	Cardiomyopathy
CMR	Cardiovascular magnetic resonance
COPD	Chronic obstructive pulmonary disease
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CR	Cardiac rehabilitation
CRT	Cardiac resynchronization therapy
CRT-D	CRT-ICD
CRS	Cytokine release syndrome
CSANZ	Cardiac Society of Australia and New Zealand guidelines
CSM	Carotis sinus massage
CSP	Conduction system pacing
CT	Computed tomography
CTCA	Computed tomography coronary angiography
CTEPH	Chronic thrombo-embolic pulmonary hypertension
CTP	CT myocardial perfusion
CV	Cardiovascular
CVD	Cardiovascular disease
CVE	Cardiovascular event
DAPT	Dual antiplatelet therapy
DBP	Diastolic blood pressure
DCM	Dilated cardiomyopathy
DDD-PM	Dual chamber cardiac pacemaker

DES	Drug eluting stents
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
DPmax	Maximum pressure gradient
dPmean	Mean pressure gradient
DSA	Digital subtraction angiography
EACTS	European Association for Cardio-Thoracic Surgery
EAS	European Atherosclerotic Society
EAT	Ectopic atrial tachycardia
EBCR	Exercise-based cardiac rehabilitation
ECG	Electrocardiogram
ECV	Extracellular volume fraction
ED	Emergency department
ED	Erectile dysfunction
eGFR	Estimated glomerular filtration rate
EHRA	European Heart Rhythm Association
EHRs	Electronic health records
EMF	Electro-magnetic frequency
EMS	Emergency medical services
EP	Electrophysiology - or electrophysiological
EPA	Eicosa pentaenoic acid
EPS	Electrophysiology study
EROa	effective regurgitation orifice area
ERP	Early repolarization pattern - or: Effective refractory period
ERS	Early repolarization syndrome
ES	Eisenmenger’s syndrome
ESC	European Society of Cardiology
ESD	End systolic diameter
ETT	Exercise tolerance test
EV-ICD	Extravascular ICD
FDA	Food and Drug Administration
FFR	Fractional flow reserve
FH	Familial hypercholesterolemia
GDMT	Guideline-directed medical therapy
GI	Gastrointestinal
GLP-1RA	Glucagon like peptide-1 receptor antagonist
GLS	Global longitudinal strain

HbA1c	Hemoglobin A1c (glycated hemoglobin)
HBP	His bundle pacing
HCM	Hypertrophic cardiomyopathy
HDL	High-density lipoprotein
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human Immunodeficiency virus
HLH	Hemophagocytic lymph histiocytosis
HNDCM	Hypokinetic non-dilated cardiomyopathy
HOT-CRT	His-optimized CRT
HPR	High platelet reactivity
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
H-V interval	His bundle-ventricular interval
IART	Intraatrial reentrant tachycardia
IAS	Inappropriate shock
ICA	Invasive coronary angiography
ICD	Implantable cardioverter defibrillator
ICH	Intracranial hemorrhage
IDL	Intermediate-density lipoprotein
IE	Infective endocarditis
iFR	Instantaneous wave-free ratio
IHD	Ischemic heart disease
iLBBB	Incident LBBB
ILR	Implantable loop recorder
INR	International normalised ratio
ISR	In-stent restenosis
IVUS	Intravascular ultrasound
LA	Left atrium/atrial
LAA	Left atrial appendage
LAD	Left anterior descending
LAFB	Left anterior fascicular block
LAFP	Left anterior fascicle pacing
LBB	Left bundle branch

LBBAP	Left bundle branch area pacing
LBBB	Left bundle branch block
LBBP	Left bundle branch pacing
LCSD	Left cardiac sympathetic denervation
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LFP	Left fascicular pacing
LGE	Late gadolinium enhancement
LM	Left main
LMCA	Left main coronary artery
LMNA, PLN, FLNC and RBM20	Genetic and similar terms
LOE	Level of evidence
LOT-CRT	Left bundle branch optimized CRT
LP	Leadless pacemaker
Lp(a)	Lipoprotein A
LPFB	Left posterior fascicular block
LQTS	Long QT syndrome
LTAE	Life-threatening arrhythmic events
LV	Left ventricle/ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow tract obstruction
LVSI	Left ventricular systolic index
LVSP	Left ventricular septal pacing
MACE	Major adverse cardiac events
MAS	Macrophage activation syndrome
MBF	Myocardial blood flow
MBFR	Myocardial blood flow reserve
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
MS	Mid-septal
MT	Medical therapy
MVA	Mitral valve area

NEJM	New England Journal of Medicine
NIVCD	Non-specific intraventricular conduction delay
NNT	Number needed to treat
NOAC	Non-vitamin K antagonist oral anticoagulant
N-3 PUFAs	Omega-3 poly-unsaturated fatty acids
NSTEMI	Non ST-segment elevation MI
NSVT	Non-sustained ventricular tachycardia
NYHA	New York Heart Association
OAC	Oral anticoagulation
OCT	Optical coherence tomography
OMT	Optimal medical therapy
PA	Physical activity
PAC	Premature atrial contraction
PAD	Peripheral artery disease
PAF	Paroxysmal AF
PCCD	Progressive cardiac conduction disease
PCI	Percutaneous coronary intervention
PCS	Post-COVID syndrome
PCSK9	Proprotein convertase subtilisin-kexin type 9
PE	Pulmonary embolism
PES	Programmed electrical stimulation
PET	Positron emission tomography
PFA	Pulsed field ablation
PFO	Patent foramen ovale
PG	Pressure gradient
PHT	Pressure half time
PIC	Induced cardiomyopathy
pLAD	Proximal left anterior descending
PM	Pacemaker
PMP	Partial mitral valve prolaps
PM2.5	PM stands for particulate matter and 2.5 refers to size (less than 2.5 micrometers)
POTS	Postural orthostatic tachycardia syndrome
PPCM	Peripartum cardiomyopathy
PROs	Patient reported outcomes
PRS	Polygenic risk scores
PTP	Pre-test probability

PVC	Premature ventricular complex
PVE	Prosthetic valve endocarditis
PVT	Polymorphic ventricular tachycardia
RA	Right atrium/atrial
RV	Right ventricle/ventricular
QoL	Quality of life
RBBP	Right bundle branch pacing
RCM	Restrictive cardiomyopathy
RCTs	Randomized controlled trials
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
RVEF	Right ventricular ejection fraction
RVOT	Right ventricular outflow tract
RVP	Right ventricular pacing
SADS	Sudden arrhythmic death syndrome
SAS	Sleep apnea syndrome
SBP	Systolic blood pressure
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SCCT	Society of cardiovascular computed tomography
SCD	Sudden cardiac death
SCORE	Systematic coronary risk estimation
SCORE-OP	Systematic coronary risk estimation in older persons
SGLT2	Sodium-glucose cotransporter-2
SHD	Structural heart disease
S-ICD	Subcutaneous ICD
siRNA	Small interfering ribonucleic acid
SMVT	Sustained monomorphic ventricular tachycardia
SND	Sinus node dysfunction
SPAP	Systolic pulmonary artery pressure
SPECT	Single-photon emission computerized tomography
SPERRI	Shortest preexcited RR interval during AF
SQTS	Short QT syndrome
SR	Sinus rhythm
SSRI	Selective serotonin reuptake inhibitor
STEMI	ST-segment elevation myocardial infarction

T2DM	Type 2 diabetes mellitus
TEE	Transesophageal echocardiography
(T)EVAR	(thoracic) endovascular aneurysm repair
TGA	Transposition of the great arteries
TOD	Target organ damage
TOF	Tetralogy of Fallot
TPPM	Temporary permanent pacemaker
TRPM4	Transient receptor potential melastatin 4
TTR	Time in therapeutic range
TTE	Transthoracic echocardiography
TSH	Thyroidea stimulating hormone
TVF	Target-vessel failure
TV-ICD	Transvenous ICD
TVP	Transvenous pacemakers
UKPDS	United Kingdom Prospective Diabetes Study
USPSTF	US preventive services task force
VA	Ventricular arrhythmia
VC	Vena contracta
VE	Ventricular ectopy
VF	Ventricular fibrillation
VHD	Valvular heart disease
VKA	Vitamin K antagonist
VLDL	Very-low-density lipoprotein
Vmax	Maximum velocity
VT	Ventricular tachycardia
VTE	Venous thrombo-embolism
VTI	Velocity time integral
WES	Whole-exome sequencing
WGS	Whole-genome sequencing
WPW	Wolff-Parkinson-White

1. Introduction

One of the frequent problems encountered in aeromedical certification examinations concerns the assessment and determination of an applicant's cardiovascular fitness and consequent ability to safely exercise the privileges of the license applied for or held. Since the currently applicable EASA requirements concerning the assessment of cardiological fitness of pilots and ATCOs were developed, cardiological diagnostic methods, monitoring, and treatment possibilities have made progress with developments providing opportunities for more accurate identification and determination of cardiovascular risks and improved treatment results. In the context of flight safety standards, these recent developments could lead to more accurate determination of cardiovascular risk in pilots and ATCOs. New treatment and monitoring options might also provide opportunities for pilots and ATCOs with cardiovascular conditions to meet the aeromedical safety requirements.

The present document is to report the results of the first task that has been performed in the context of the CaVD PACE research project and will provide input to tasks 2 and 3. This first task was aimed at making an inventory of new diagnostic methods, new treatments, and monitoring options that may be considered potentially suitable to assess the cardiovascular risks and their consequences for safe task performance of pilots and ATCOs.

To achieve this aim, a dedicated search of the published peer-reviewed scientific literature and selected "grey" literature, published after 2017 and including older literature if needed, has been performed. As a primary basis for the scientific review the evaluation and assessment of the most recent guidelines of the European Society of Cardiology (ESC) and guidelines of the EAPC (European Association of Preventive Cardiology), ACA (American College of Cardiology), AHA (American Heart Association), and the ESH (European Society of Hypertension) were taken.

The cardiovascular conditions mentioned in EASA Part MED.B.010 (Cardiovascular system) were taken as a basis to define the cardiovascular issues relevant for all classes of pilots and ATCOs. The review considered the following issues which were also used as search terms for the designated literature search:

- Cardiological examination/ECG / ECG
- Blood pressure/ hypertension
- Peripheral arterial disease and aortic disease
- Valvular diseases (non-operated and operated status)
- Thromboembolic disorders
- Congenital heart disease
- Congenital heart disease
- Pericardial and endocardial diseases
- Myocardial diseases
- Heart failure (general causes, new medications, heart transplantation, heart-lung-transplantation, cardiac assist devices)
- Syncope
- Cardiovascular risk factors, risk scores, modern treatments, e.g. lipid treatment options

- Modern concepts of cardiovascular risk screening and use of these concepts for prevention
- Inflight conditions which influence the status of a cardiovascular disease and implanted devices
- Chest pain, myocardial ischemia and indications for coronary artery revascularization
- Management of stenoses of the left main coronary artery (LM)
- Follow-up after revascularization procedures in coronary artery disease (CAD)
- Bleeding risks of antithrombotic medications, especially after PCI and after CABG
- Procedure in asymptomatic CAD (chronic coronary syndrome)
- Echocardiography, especially in CAD
- Role of CT coronary artery calcium score (CACS) and Coronary computed tomographic angiography (CCTA) in CAD
- Cardiac MRI
- Nuclear medicine methods: SPECT/ PET
- Role of artificial intelligence in CAD
- Significance of genetic evaluation of CAD
- Cardiological considerations of Covid-19
- Atrial fibrillation (AF), status after ablation of AF
- Indication of anticoagulation in AF
- Ventricular and supraventricular ectopy
- Left and right bundle branch block, left anterior and left posterior fascicular block
- Atrioventricular blocks
- Pre-excitation syndrome (WPW-syndrome)
- Channelopathies, such as Long QT-syndrome, Brugada-syndrome etc.
- Pacemaker
- ICD
- New concepts of cardiological risk estimation

The project team reviewed the currently available scientific and “grey” literature concerning state-of-the-art tests, diagnostic and monitoring methods, and new treatment options related to the above-mentioned cardiovascular conditions, comorbidities, and cardiovascular risk factors. Attention was focused on the level of scientific evidence and their potential suitability for an aeromedical examination setting.

1.1 Structure of the document

This deliverable is structured as follows:

- Chapter 1: Introduction with background, aim, and methods of the research
- Chapters 2 - 6 and sub-chapters: Discussion and considerations concerning the state-of-the art diagnostic, monitoring, and treatment options for all cardiovascular conditions mentioned above. Each sub-chapter ends with a bibliography relevant for the issue discussed.
- Main conclusions and recommendations

2. General and miscellaneous CVD issues

2.1. Cardiological examination

This document contains main findings concerning the state-of-the-art of "Cardiologic examination" and summarizes diagnostic algorithms for major cardiac symptoms. This chapter focusses on diagnostic tools for examination and does not include any in-depth recommendations on therapy. However, guidance on initial clinical decision making is provided for severe clinical settings.

1. What is new? - Main findings

- The role of careful history-taking and physical examination remains unchanged in paving the way for further diagnostic workflow.
- Smart devices with potential of cardiovascular diagnostic tools become increasingly popular.
    - There is a need for more evidence of their reliability, but current data underline their potential.

2. Conclusion and recommendations

Epidemiology

Cardiovascular disease represents the most common cause of death in Europe and leads to loss of 60 million potential years of life (Townsend et al., 2022). Especially, men are more threatened by cardiovascular disease than women. As there are large regional disparities in treatment outcomes and mortality, there is a need for precise and accessible diagnostics for cardiovascular disease. In this context, the necessity of careful history taking, physical examination, and basic diagnostics like upper arm blood pressure measurements and 12 lead ECG is undisputed. Over recent years, wearables became increasingly popular and offer new insights into the individual supervision of health. The most popular functions include tracking physical activity, heart rate, heart rhythm, sleep, blood pressure, and peripheral oxygen saturation (Hughes, Shandhi, Master, Dunn, & Brittain, 2023). Recent studies revealed the impact of wearables in encouraging people to increase their daily physical activity (Ferguson et al., 2022) but also supported diagnosis of atrial fibrillation (Perez et al., 2019). However, there is a need for more studies to implement their value in clinical routines (Jensen et al., 2021). These results may pave the way for further cardiovascular diagnostic tools.

Classification and risk

Cardiovascular examination is divided into a general history taking and a physical examination. These general findings pave the way for further investigations that may include exercise testing by treadmill, spiro-ergometry, or imaging in a resting state as well as under physical strain (Malik & Goyal, 2023). It is important for the AME to identify individuals with a high risk for cardiovascular disease. These individuals need to be directed to a specialist or an emergency department for further assessment and care.

High-risk features

- New onset of chest pain,
  - in resting state
  - Inducible by physical activity grading according to CCS-classification
- Dyspnea,
  - in resting state
  - Inducible by physical activity grading according to NYHA-classification
- Syncope,
- Peripheral edema,
- Unilateral swelling of extremities,
- Symptomatic palpitations, tachycardia or bradycardia with or without hypotension,
- Symptomatic arterial hypertension,
- Heart murmurs, previously unknown or unclassified,
- Crepitations, wheezing or stridor in lung auscultation,
- Signs of anemia,
- Performance drop, unexplained

Every cardiovascular assessment should consist of a structured history taking and physical examination. In this context, the exploration of chest pain, shortness of breath, palpitation, presyncope/syncope, ankle swelling, or other signs of peripheral edema, are considered as elemental parts. The initial assessment is completed by a physical examination which implements inspection of the thorax, auscultation of heart and lungs, assessment of peripheral pulse status, including auscultation of the carotid arteries, inspection of the entire body including trunk, head, and extremities, as well as inspection of oral mucous membranes. Additional standard diagnostic tests include recording a 12-lead electrocardiogram (ECG) in a resting state and assessing upper arm blood pressure.

Hereby, we provide an overview of crucial steps on specific findings in cardiovascular assessment.

Acute chest pain and unstable angina

- Primary investigation and
- 12 lead ECG, consider V7-V9 and right precardiac leads
- High-sensitive Troponin testing
- Transfer to Chest Pain Unit or near cardiologic department by EMS

Chronic chest pain

- Careful history taking: when do the symptoms occur? Provoked by physical activity? Assessment of cardiovascular risk factors (smoking, obesity, family burden, dyslipidemia, diabetes, arterial hypertension)
- Physical examination: Auscultation of the heart: heart murmur, third heart sound; clinical signs of heart failure (peripheral or pulmonary edema, arrythmia); rule out signs of musculoskeletal disorders (does respiration, manual pressure, or changing body position affect the symptoms?), Dyspnea based on NYHA classification.

Further investigations:

- 12 lead ECG
- Blood testing: NTproBNP, high-sensitive Troponin
- Echocardiography: Regional wall motion abnormality? Valve defects? Systolic pulmonary artery pressure?
- Add non-invasive ischemia diagnostics: exercise testing (treadmill test, stress echocardiography) or cardiac computed tomography (CT) or scintigraphy or cardiac stress MRI.

In depth information is provided in the chapter “coronary artery disease”.

Acute Dyspnea

- Prioritize Primary Investigation
- History taking: Onset of symptoms? Accompanied by chest pain? Assessment of risk for venous thromboembolism (Wells score a.o.)
- Physical examination: Auscultation of the heart: severe valve defect? Tachycardia or bradycardia? Crepitations, wheezing, stridor, double sided breathing noise in lung auscultation?
- Further steps: Monitoring of pulse oximetry, heart rate and blood pressure

- *Further investigations:*
  - 12 lead ECG
  - Transthoracic echocardiography: Regional wall motion abnormality? Heart valve disease? Right-sided heart failure?
- Transfer to near hospital by EMS

Chronic Dyspnea

- *Careful history taking*: when do the symptoms occur? Provoked by physical activity: NYHA Class? Assessment of cardiovascular risk factors (smoking, obesity, family burden, dyslipidemia, diabetes, arterial hypertension, risk for venous thromboembolism)
- *Further investigation*: 12 lead ECG
- Blood testing: NTproBNP, high-sensitive Troponin
- Transthoracic echocardiography: Heart failure? Regional wall motion abnormality? Heart valve disease? Diastolic Dysfunction? Signs of right heart failure and elevated systolic pulmonary artery pressure?
- Assessment of lung function is recommended by bodyplethysmography, including blood-gas analysis.
- Consider further imaging including CT of the chest or bronchoscopy if indicated.
- In case of nicotine consumption: Strict recommendation to abstain from nicotine.

Syncope

- Primary investigation
- *History taking*: Clarify the frequency of syncope: first occurrence or recurrent?
- *Further steps:* Elaborate mitigating factors - potentially avoidable in aviation?
- In depth classification and recommendations are listed in the chapter “Syncope”

Peripheral edema

- *Careful history taking:* including period of edema and risk factors (immobilization, heart, kidney, liver disease, history of chronic venous insufficiency)
- *Physical examination:* Location of edema, unilateral or both sides? Local warming of the skin? Pitting oedema? Signs of chronic venous insufficiency? Auscultation of heart (rhythmic? Heart murmurs?) and lungs (signs of pulmonary edema?)
- *Further investigations:*
    - Blood resting: Aspartate-Aminotransferase (AST), Alanin-Aminotransferase (ALT), Creatinine and glomerular filtration rate (GFR), NTproBNP, in case venous thrombosis is suspected on physical examination and history: add D-Dimer in ambulant patients
    - 12-lead ECG, transthoracic echocardiography, abdomen sonography, venous ultrasound

Symptomatic palpitations, tachycardia or bradycardia with/or without hypotension

- *Careful history taking:* When do the symptoms occur? Provoked by physical activity? Medication history? History of arterial hypotension or hypertension under medical treatment?
- *Further investigations:* 12 lead ECG, upper arm blood pressure
- 24h-holter ECG including precise symptom records for correlation
- 24h-ambulatory blood pressure measurement including precise symptom records for correlation
- Recordings from smart devices may provide a clue to chronological correlates of symptoms. Based on this, the recorded findings should be further clarified using 12 lead ECG and 24h Holter ECG in combination with a precise protocol of occurred symptoms.
- In patients with medical treatment for arterial hypertension: consider the possibility of iatrogenic hypotension

Symptomatic arterial hypertension

- In case of hypertensive emergency: lower blood pressure by 25% in the first hour and afterwards to 160/100 over the next 2-6 hours and transfer to regional emergency medicine for further treatment
- *Careful history taking*: first diagnose is of arterial hypertension? Concomitant pain (e.g. thoracic, abdominal, headache); in case of known hypertension: Compliance in drug therapy?
- 24-hour ambulatory blood pressure recommended for further modification of treatment
- Additional information is listed in the chapter “Blood pressure”

Heart murmurs, previously unknown or unclassified

- *Careful history taking:* Known structural heart or valve disease? History of heart failure? Episodes of congestion, chest pain, dyspnea, palpitations, syncope, dizziness?
- *Physical examination*
- 12-lead ECG,
- transthoracic echocardiography for assessment of valve function
- In-depth information is provided in the section “Valvular heart disease”

Crepitations, wheezing or stridor in lung auscultation

- *Careful history taking:* history of pulmonary disease? Nicotine consumption? Coughing? Respiratory infection? Allergy? Dyspnea under physical exercise? Peripheral edema? Fever?
- *Further diagnostics on assumed structural lung disease*:
    - Pulmonary function testing is recommended by body plethysmography, including blood-gas analysis. Consider imaging of the chest, bronchoscopy, serological diagnostics if indicated.
- In case of nicotine consumption: Strict recommendation to abstain from nicotine.

Signs of anemia

- *Careful history taking* for elaborating the following issues*:* History of bleeding; iron-, B12, folic acid- deficiency, hematologic disease, cancer, history of platelet aggregation inhibitors or anticoagulants, neurological symptoms like dizziness, headache, fainting, impaired vision, fatigue, shortness of breath, performance drop; in women: anamnesis of menstruation
- *Physical examination* to asses following clinical signs*:* Pale skin, brittle nails, restless legs, atrophic glossitis or angular cheilitis, alopecia, cold intolerance, pica.
- *Further diagnostics:* Full blood count for classification of anemia, review of all myeloid cell lines, lactate dehydrogenase, reticulocytes including reticulocyte proliferation index, ferritin, folic acid, hemoccult for detection of gastrointestinal bleeding.
- In case of high clinical probability of GI-bleeding: gastroscopy, if no detection of bleeding sign add colonoscopy.
- Further steps:
    - neurological symptoms: immediate transfer to regional neurological department
    - hemoglobin levels below 7 mg/dl: transfusion of red cell concentrates
- history of bleeding under platelet inhibition or anticoagulant: reason for anticoagulation? Refer to local cardiologic department for reevaluation of therapy
- Signs for GI-bleeding:
    - acute bleeding: local emergency department
    - chronic: endoscopy for diagnosis and treatment
    - Anemia because of iron-, B12-, folic acid deficiency: initiate substitution

Performance drop, unexplained

A reduction in performance represents a complex symptom and implies manifold physical and mentalcauses. Therefore, precise history taking lays the foundation for a structured workup of this symptom. This document focusses on cardiovascular disease and therefore other reasons for a reduction in performance will not be discussed in-depth.

- *Careful history taking*: First occurrence of performance drop? Progressive, stable or variable? History of arterial hypertension, hypotension, or pulmonary hypertension? Heart failure or valvular disease? Palpitations or inappropriate heart rate? Stenosis of central arteries? Thyroid dysfunction? Rheumatic disease? Obstructive sleep apnea? Pulmonic disease? Anemia? Headache or other neurological symptoms? Abdominal pain? Gastrointestinal disease? Infection? Mental stress?
- *Physical examination*: detailed full body examination
- *Further diagnostics:* 12-lead ECG, upper arm blood pressure; consider ambulatory 24-hour ECG and blood pressure with symptom protocol for correlation, blood count, TSH, Creatinine, electrolytes, transaminases, ferritin, vitamin D, lactate dehydrogenase
- Spiro-ergometry represents an established method to assess cardiorespiratory fitness.
- Further diagnostic steps for clarification of performance drop should be taken by clinical probability in consultation with specialized departments.
- *Treatment*: Based on the underlying disease/syndrome. For the treatment of cardiovascular causes, please refer to the corresponding chapters of this document.

3. Relevance for risk assessment of pilots and ATCOs

Pilots and ATCOs should be declared unfit to fly upon any pathologic finding until a diagnosis is established and a cardiology specialist has certified safety. Further recommendations should be formulated as part of task 2.

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Additional comment:

Please refer to corresponding topics for in depth information on specific pathologies.

2.2. Blood pressure

This document contains main findings concerning the pathophysiological background, clinical manifestations, and diagnostics of blood pressure. In light of the high prevalence of arterial hypertension, this chapter includes evidence-based recommendations on therapy but also clarifies clinical settings that encourage in-detail diagnostics and therapy in expert centers. It does not include diagnostic and treatment algorithms for resistant or secondary hypertension because for these entities risk assessment is of primary importance for counseling pilots and ATCOs. Individuals should then be referred to specialist centres for further assessment.

1.What is new? - Main findings

Arterial hypertension

Diagnosis of arterial hypertension can be made based on repetitive ambulatory and office blood pressure measurements.

At blood pressure levels of 130-139/85-89 mmHg drug therapy may be considered in case of high risk for cardiovascular disease, especially coronary artery disease.

It is recommended to initiate drug therapy even in patients with low risk and without evidence of hypertension mediated organ damage if they remain hypertensive after lifestyle intervention.

Treatment target is set to <140/90 mmHg in all patients and 130/80 mmHg or lower if drug therapy is well tolerated.

A diastolic blood pressure of less than 80 mmHg should be considered.

Initiation of drug therapy should consist of a combination therapy, with exception of low risk patients with an initial systolic blood pressure lower than 150 mmHg.

It is recommended to add spironolactone and/or further diuretic therapy in resistant hypertension.

Use the SCORE2 system for cardiovascular risk assessment in patients without known cardiovascular disease.

Routine use of device-based-therapy is not recommended in everyday practice, but can be conducted in scientific studies.

Arterial hypotension

Arterial hypotension is defined as a blood pressure of 90/60 mmHg or less (Sharma, Hashmi, & Bhattacharya, 2023).

The diagnosis of orthostatic hypotension is made by a 20 mmHg systolic and/or 10 mmHg reduction of diastolic blood pressure while 3 minutes upright standing (Ringer & Lappin, 2023).

Treatment might include mineralocorticoids or droxidopa (Strassheim, Newton, Tan, & Frith, 2016).

Non-pharmacological treatments should be preferred.

Pulmonary hypertension

In the current guidelines published recently (Humbert et al., 2022) the threshold for the definition of pulmonary hypertension was lowered to a mean arterial pressure >20 mmHg in resting state.

Diagnosis, follow-up and guidance of therapy should be conducted in specialized pulmonary hypertension centres.

2. Conclusion and recommendations

Epidemiology

Arterial hypertension

Arterial hypertension represents the most common cardiovascular risk factor worldwide (Zhou, Perel, Mensah, & Ezzati, 2021). Respecting the increase in sedentary lifestyle and body mass index, the prevalence of arterial hypertension is estimated to rise to a worldwide prevalence close to 1.5 billion. By advancing age, the diagnosis of arterial hypertension rises as the prevalence is over 60% in people over the age of 60. The incidence of arterial hypertension is higher in low- and middle-income countries, which is explained by a reduced awareness in prevention and therapy of arterial hypertension. Current data suggest, that the prevalence of arterial hypertension does not differ between pilots and a reference population (Wilson, Driller, Johnston, & Gill, 2022).

Arterial hypotension

There are no definitive or generally accepted figures on prevalence. Constitutional hypotension is seen more often in younger patients while orthostatic hypotension (OH) is observed more frequently in elderly patients (Ricci, De Caterina, & Fedorowski, 2015).

Pulmonary hypertension

Pulmonary hypertension (PH) is a major global health issue. All age groups are affected. Present estimates suggest a PH prevalence of ∼1% of the global population. Due to the presence of cardiac

and pulmonary causes of PH, prevalence is higher in individuals aged >65 years (Hoeper et al., 2016). Globally, left heart disease (LHD) is the leading cause of PH. Lung disease, especially chronic obstructive pulmonary disease (COPD), is the second most common cause.

Classification and risk

Arterial hypertension

Arterial hypertension can be classified by etiology into different forms regarding its genesis. The most common form is primary hypertension, which is characterized by an increase in arterial blood pressure without an identifiable pathology. Secondary hypertension, which occurs as a consequence of an underlying disease, is distinguished from primary hypertension (Mills, Stefanescu, & He, 2020). The causes of secondary hypertension include renal artery stenosis, endocrinological diseases such as hyperthyroidism or hyperaldosteronism, but also hormonal changes during pregnancy can lead to secondary hypertension. Another relevant cause is obstructive sleep disorder, which is clinically manifested in particular by increased daytime fatigue (Dopp, Reichmuth, & Morgan, 2007)

Table 1: Classification of blood pressure levels

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and	80–84
High-normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[a]	≥140	and	<90
Isolated diastolic hypertension[a]	<140	and	≥90

Adapted from the 2023 ESH guidelines for the management of arterial hypertension

Arterial hypotension

Arterial hypotension is defined as blood pressure lower than 90/60 mmHg. This phenomenon can occur as consequence of heart failure, hypovolemia, sepsis, drug treatment or most commonly as a constitutional state (Owens, Lyons, & O'Brien, 2000). Arterial hypotension has to be distinguished from orthostatic hypotension, which is defined by a decrease in systolic blood pressure by 20 mmHg and/or diastolic blood pressure by 10 mmHg within three minutes of standing.

Risk is increased, especially in OH. The risk for syncope along with the danger of falling – with all its consequences – is the “immediate” risk in these patients, as fractures often occur in these conditions. Therefore, individuals with symptomatic hypotension should not operate machinery. Also, the impact on quality of life should not be underestimated. Furthermore, OH is associated with increased mortality, incident coronary heart disease, heart failure, as well as stroke, all of which increase the long-term risk of OH independent from the actual hypotensive event.

Pulmonary hypertension

The etiology of pulmonary hypertension is divided into 5 subgroups, which include various phenotypes and mechanisms of the corresponding disorder (Humbert et al., 2022)

Group 1: Pulmonary arterial hypertension (PAH):

This group is characterized by increased pulmonary vascular resistance >2 wood units. Typical causes of PAH include heritable disease, an association with drugs and toxins, connective tissue disease, HIV infection, congenital heart disease among others or may be idiopathic. Approximately 48–55 cases/million adults;

Group 2: Pulmonary hypertension associated with left heart disease. Most common in adults >65 years, increases with the severity of left heart disease, especially mitral valve disease, aortic valve stenosis and heart failure represent typical pathologies.

Group 3: Pulmonary hypertension associated with lung diseases and/or hypoxia
Common finding in lung diseases that affect the parenchyma and interstitium.

Group 4: Pulmonary hypertension associated with chronic pulmonary artery obstruction. Approximately 26–38 cases/million adults. Occurs as a consequence of pulmonary embolism, which increases pulmonary pressure.

Group 5: Pulmonary hypertension with unclear and/or multifactorial mechanisms
This is a heterogenic group with unclear prevalence. An association with various diseases that lead to an increase in pulmonary artery pressure has been established.
In patients with pulmonary hypertension hypoxia may further increase pulmonary pressure, which may lead to an intolerable rise in right ventricular afterload (Kylhammar & Radegran, 2017). Therefore, current ESC guidelines advise patients to avoid altitudes exceeding 1500 m without supplemental oxygen. As data on safety of patients with pulmonary hypertension in aviation are scarce, it remains unclear if specific types of pulmonary hypertension are more vulnerable to cabin atmosphere.

Diagnosis:

Primary/idiopathic arterial Hypertension

Medical history should include the assessment of personal or family cardiovascular disease, risk factors for hypertension (age, sex, smoking, sleep apnea, hypertension in pregnancy, nutrition). In addition, arterial hypertension can lead to structural or functional changes in blood vessels or organs that correlate with the outcome of arterial hypertension. Common clinical findings of hypertension-mediated organ damage (HMOD) are represented by left ventricular hypertrophy (LVH), kidney injury, hypertensive retinopathy, ischemic or hemorrhagic brain injury, and cognitive impairment. These pathologies can be present at the time of initial diagnosis of arterial hypertension but can also emerge in the course of long-standing arterial hypertension. Therefore, the diagnosis of arterial hypertension

demands a detailed analysis of HMOD in pilots and ATCOs, both, at the time of first diagnosis and repeatedly during follow-up.

Based on the current ESH guidelines (Mancia Chairperson et al., 2023) a comprehensive medical examination should include the following steps:

- Cardiovascular system:
  - Physical examination ◊ Signs of heart failure, valvular disease?
  - 12-lead ECG ◊ rhythm, heart rate and electric conductance, signs of ischemia, LVH?
  - Echocardiography ◊ LVH, atrial enlargement, systolic and diastolic function, pulmonary artery pressure, valvular disease, aortic root enlargement?
  - carotid artery ultrasound ◊ intima-media thickness, stenosis or regional plaques?
  - ankle brachial index ◊ signs of lower-extremity artery disease?
  - Pulse wave velocity ◊ arterial stiffness
  - Abdominal ultrasound ◊ Aortic aneurysm?
- Kidney:
  - Urine albumin creatinine ratio ◊ classification of chronic kidney disease
  - serum creatinine including estimated glomerular filtration rate◊ classification of chronic kidney disease
  - ultrasound including doppler sonography ◊ size and structure, renovascular disease, renal resistance index?
- Eye:
  - Fundoscopy ◊ microvascular changes?
- Brain:
  - Cognitive function testing ◊ early stages of dementia?
  - Imaging (MRI or CT) ◊ evidence of structural brain damage?

<u>Secondary hypertension</u>

Arterial hypertension can occur as a consequence of other medical conditions. Since the prevalence is by far lower than primary hypertension, a population-wide screening for secondary forms of hypertension is not cost-effective. Therefore, the following conditions indicative for secondary forms of hypertension have been defined:

- Grade 2 or 3 hypertension in patients under the age of 40
- Sudden onset of hypertension
- Aggravation of hypertensive blood pressure from previous regular values
- Resistent hypertension including missing reduction of blood pressure over night (“non-dippers”)

Treatment

Arterial hypertension

Treatment algorithms for arterial hypertension depend closely on its severity. Hereby, the modification of life style owns a central role and represents the first step in all patients. In patients with initial blood pressures below 150/95mmHg the effect of life style interventions should be waited for after 3 months. If blood pressures are not controlled thereafter, drug treatment should be initiated. In patients with initial blood pressures ≥150/95mmHg immediate drug treatment is recommended parallel to life style measures (Mancia Chairperson et al., 2023). The following flow-chart provides an overview on decision making regarding therapy of arterial hypertension.

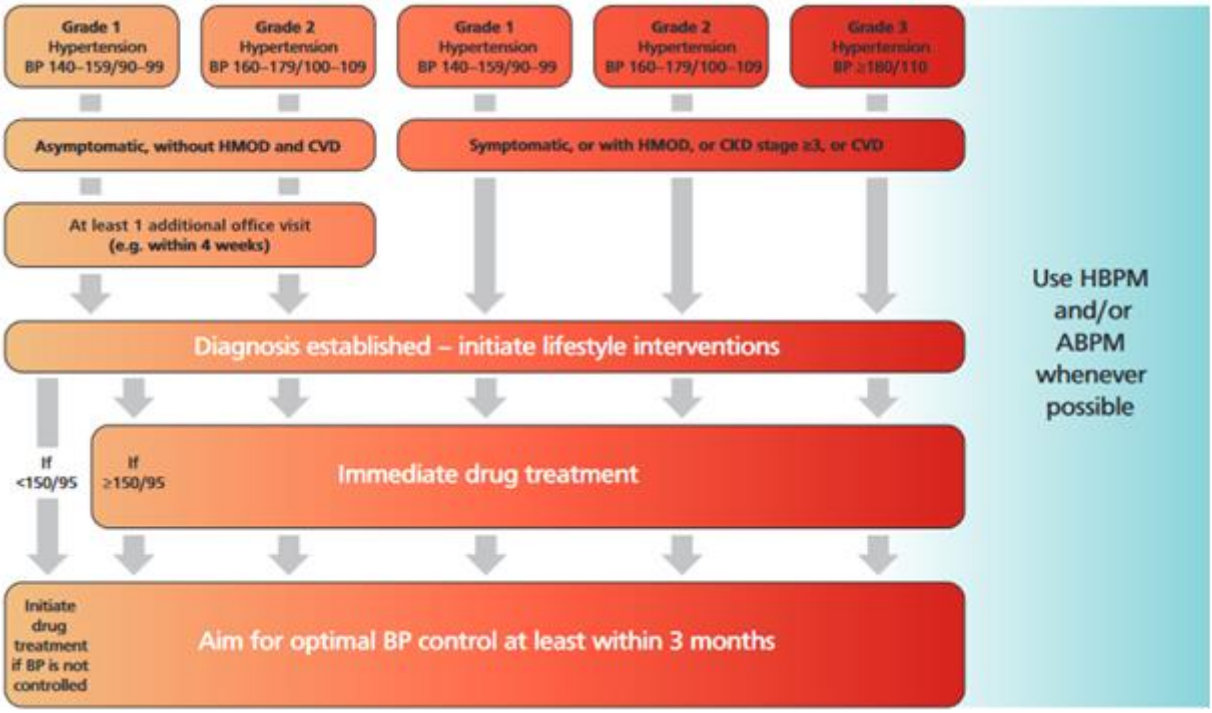

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Figure 1: Treatment algorithms for arterial hypertension depending on the levels of blood pressure, as well as the presence of symptoms and end organ damage, adapted from the 2023 ESH guidelines for the management of arterial hypertension. ABPM=ambulatory blood pressure monitoring, BP=blood pressure, CKD=chronic kidney disease, CVD=cardiovascular disease, HBPM=home blood pressure monitoring, HMOD=hypertension-mediated organ damage

The drug treatment of arterial hypertension offers a wide variety of possible medications. Therefore, the current ESH guidelines implemented an algorithm on appropriate combinations of drug therapy. The central objective of therapy is to lower blood pressure to <140/80mmHg, although a further reduction to <130/80mmHg has been shown to further reduce the risk of stroke (Mancia et al., 2016). Therefore, blood pressure in pilots and ATCOs ≤65 years of age should be targeted to 130/79mmHg. Individuals >65 years of age or with chronic kidney disease should aim at blood pressures <140/80mmHg. Pilots and ATCOs with uncontrolled blood pressure should be declared unfit to fly until an effective treatment has been established. The quality of blood pressure control should be documented by ambulatory blood pressure monitoring (ABPM). AME should decide on unfitness period when starting a new medication until assessing its impact and performance of the pilots and ATCOs.

The following flow charts provide an overview on decision making in drug therapy. Further steps including device-based therapy should be made in dialogue with regional expert centres for arterial hypertension.

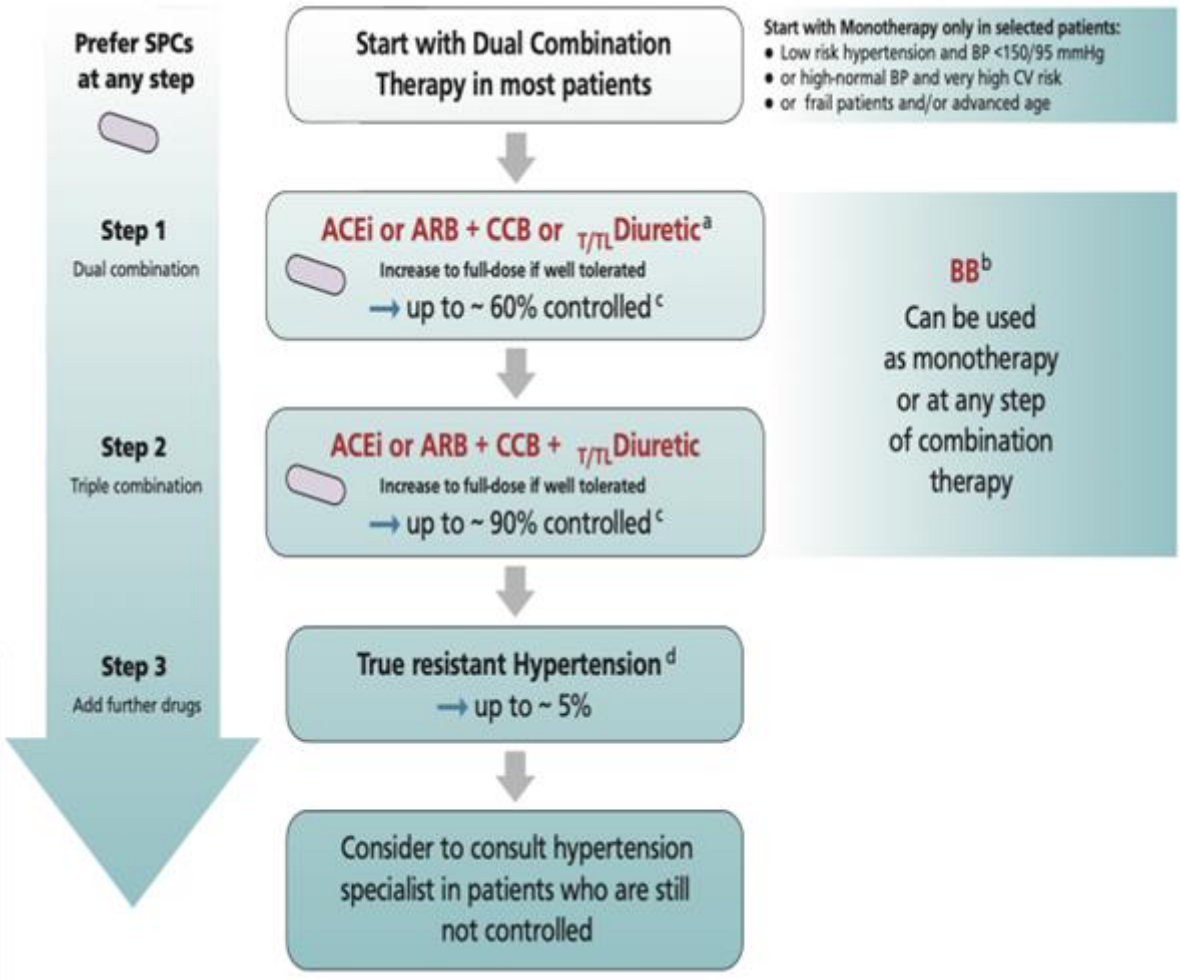

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Figure 2: General BP lowering strategy in patients with Hypertension, adapted from the 2023 ESH guidelines for the management of arterial hypertension; ACEi= angiotensin-converting-enzyme inhibitor, ARB= angiotensin receptor blocker, BB=beta blocker BP=blood pressure, CCB=calcium channel blocker, CV=cardiovascular, SPCs=single pill combinations, T/TL diuretics=thiazide, thiazide-like diuretics,

a) Diuretics:

- A transition to loop diuretics should be considered in case eGFR is between 30 to 45 ml/min/1.73 m²
- Loop diuretics should be used in patients with eGFR lower than 30 ml/min/1.73m²

b) Beta blocker:

- The therapy should always be implemented in the context of guideline-directed medical therapy in ischemic heart disease, tachycardic arrhythmias, atrial fibrillation, pregnancy

c) Controlled refers to a blood pressure below 140/90 mmHg

d) When SBP is ≥ 140mmHg or DBP ≥ 90 mmHg following aspects need to be considered:

- The maximum recommended and patient-tolerated dose of a three-drug combination of RAS blocker, CCB, and thiazide/thiazide-like diuretic were used
- Appropriate measurements of ABPM or HBPM for BP control
- Compliance based on adherence to medication is elaborated and secondary hypertension is excluded

Table 2: Blood pressure targets under antihypertensive treatment depending on age and comorbidities

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

Adapted from the 2018 ESC/ESH guidelines for the management of arterial hypertension (Williams et al., 2018); CKD=chronic kidney disease, DBP=diastolic blood pressure; SBP=systolic blood pressure, TIA= transient ischemic attack

Arterial hypotension

Arterial hypertension is the most common cardiovascular risk factor, often underestimated and not treated to the state of the art. This emphasizes the need for a strict supervision.

In case of drug-induced arterial hypotension, the treatment strategy needs to be critically revised.

If the diagnosis of arterial hypotension is made, non-pharmacological strategies provide a risk reduction for fainting and correcting the 24h- blood pressure profile. These approaches include a head-up tilted bed for sleep, wearing compression of legs and/or the abdomen, drinking cold water prior to orthostatic reactions, or an increase in salt intake (Clement, 2019). Pharmacological therapy may contain fludrocortisone or midodrine, which is also discussed in the ESC guidelines on

syncope (Brignole et al., 2018). However, pharmacologic therapy of orthostatic hypotension should be decided in regional expert centres and requires an in-depth patient education.

Pulmonary hypertension
Given the complexity of the different entities of pulmonary hypertension the specific treatments should be decided in regional expert centres for pulmonary hypertension. This is clearly supported by the current guidelines on diagnosis and treatment of pulmonary hypertension of the ESC (Humbert et al., 2022).

- Pilots/ATCOs with uncontrolled and/or symptomatic arterial hypertension should be grounded until blood pressure control is established. Return to flight duties can be considered thereafter, provided that good blood pressure control is documented by ABPM.
- Pilots and ATCOs with arterial hypertension ≥grade 2 should be examined by an ophthalmologist yearly as long as hypertension persists to exclude end organ damage to the eye that may impair vision.
- After changes in antihypertensive medication has been undertaken, pilots and ATCOs should be grounded for 4 weeks. Return to flight duties can be considered thereafter, provided that good blood pressure control is documented by ABPM.
- Pilots and ATCOs with arterial hypotension should be declared unfit to fly. Exceptions can be considered in individuals with asymptomatic constitutional hypotension, provided that organic causes of hypotension have been excluded.

3. Relevance for risk assessment of pilots and ATCOs

- Pilots and ATCOs with uncontrolled and/or symptomatic arterial hypertension should be grounded until blood pressure control is established. Return to flight duties can be considered thereafter, provided that good blood pressure control is documented by ABPM.
- Pilots and ATCOs with arterial hypertension ≥grade 2 should be examined by an ophthalmologist yearly as long as hypertension persists to exclude end organ damage to the eye that may impair vision.
- After changes in antihypertensive medication has been undertaken, AME should decide on unfitness period of pilot/ATCO. Return to flight duties can be considered thereafter, provided that good blood pressure control is documented by ABPM.
- Pilots and ATCOs with arterial hypotension should be declared unfit to fly. Exceptions can be considered in individuals with asymptomatic constitutional hypotension, provided that organic causes of hypotension have been excluded.

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2.3. Peripheral arterial disease and aortic disease

1. What is new? – Main findings

- Emphasis on screening in special populations
- Importance on individual and interdisciplinary approach by specialized teams in regard to patient's will
- Encouraging primary prophylaxis

Epidemiology

Peripheral artery disease

Peripheral artery disease comprises atherosclerotic lesions in almost any location in the human body, the most common being lower limb-, renal, mesenteric, upper limb and carotid artery disease. The incidence of peripheral artery disease independent from the region of perfusion is increasing over the last decades, especially in the western world (Fowkes et al., 2013). Peripheral artery disease of the lower extremities is a common pathology in European population with up to 40 million affected individuals (Fowkes et al., 2013). The prevalence is estimated to be as high as 18% in patients beyond 65 years. However only 10% being symptomatic (Diehm et al., 2004). The prevalence of chronic limb ischaemia as one of the most severe consequences is 0.4% with an incidence of 50 to 100 per 100.000 cases (Norgren et al., 2007). Similar numbers could be demonstrated for the prevalence of carotid artery disease in patients older than 70 with 12,5 % (Razzouk et al., 2015). In populations older than 65 years mesenteric artery disease reaches a prevalence of up to 15%, whereas renal disease is less common (Hansen et al., 2002; Hansen et al., 2004).

Regardless of the location of artery disease these pathologies share common risk factors. The most important being Smoking, Hypertension, Dyslipidemia, Diabetes mellitus and chronic inflammation or autoimmune disorders (Allison et al., 2006; Bossone & Eagle, 2021; Bots et al., 1992; Chuang et al., 2016; Criqui & Aboyans, 2015; Joosten et al., 2012; Meijer, Grobbee, Hunink, Hofman, & Hoes, 2000; Newman et al., 1993).

Aortic disease

Aortic diseases comprise acute aortic syndromes (e.g. dissection) and thoracic as well as abdominal aneurysms. Risk factors for these pathologies includes arterial hypertension, smoking, obesity, dyslipidemia, atherosclerosis, connective tissue disorders (Marfan's syndrome, Ehlers-Danlos' syndrome), congenital disorders like bicuspid aortic valve, inflammatory vasculitis and acquired risk factors such as cocaine abuse and trauma (Bossone & Eagle, 2021; Bossone et al., 2016; Erbel et al., 2014; Hiratzka et al., 2010; Kent et al., 2010; Lederle et al., 1997; Lee et al., 2018). 21% of all cases show a genetic background with overt disease in younger patients (Albornoz et al., 2006; Coady et al., 1999).

Due to the worldwide aging population the incidence of both the aortic aneurysms and acute dissection are increasing to 10 or 4.6 cases per 100.000 in the 2020s (Bickerstaff et al., 1982; Clouse et al., 1998; McClure et al., 2018). Alongside the pathologies, mortality caused by aortic diseases increased as well to 2.78 per 100.000 (Sampson et al., 2014).

Classification and risk

Peripheral artery disease

The severity of peripheral artery disease is assessed by the Fontaine classification system. The classification system is based on the severity of symptoms and is divided into four stages: stage I (asymptomatic), stage II (claudication during exercise), stage III (rest pain), and stage IV (tissue loss) (Fontaine, Kim, & Kieny, 1954). An alternative classification is the Rutherford classification system is used, assessing the severity of symptoms and the extent of disease, and is divided into seven categories: category 0 (asymptomatic), category 1 (mild claudication), category 2 (moderate claudication), category 3 (severe claudication), category 4 (rest pain), category 5 (minor tissue loss), and category 6 (major tissue loss) (Rutherford et al., 1997). The European Society of Cardiology (ESC) guidelines recommend the Fontaine and Rutherford classification systems for peripheral artery disease (PAD) assessment and management. These two systems are considered complementary and are commonly used in clinical practice (Aboyans et al., 2018). The Fontaine classification is particularly useful for describing the severity of PAD symptoms, while the Rutherford classification is helpful in determining the extent of disease and the likelihood of limb loss.

Peripheral artery diseases regardless of the location poses risks for the whole circulatory system and especially the tissue and organs downstream of the arterial lesion. The general risk is increased because atherosclerotic lesions are an independent risk factors for atherosclerotic lesions in any location (Belcaro et al., 2001; Criqui & Aboyans, 2015; Giannopoulos et al., 2015). Sequelae and risks include: acute thromboembolic events, such as limb ischemia, stroke, mesenteric infarction, myocardial infarction. Furthermore, symptoms of peripheral artery disease are an enormous spectrum consisting of claudication, loss of function, immobility, nausea, pain, malabsorption, infection or ulcers among others.

Therefore, symptomatic peripheral artery disease and its sequelae affect morbidity, mortality and quality of life in the individual patient.

Aortic disease

The Crawford's classification categorizes thoracic and abdominal aortic aneurysms in regard to morphology, location and stratifies patients on the basis of risk of major postoperative complications including mortality, spinal cord injury, and renal failure (Green, Palumbo, & Lau, 2018).

For the classification of aortic dissection two major systems are broadly used, the Stanford and the De-Bakey classification. The first categorizing dissections into involving the ascending aorta (A) and not involving the ascending aorta (B); with type A showing a multifold increased mortality (Debakey et al., 1965). The De-Bakey classification system is based on the extent of aortic involvement and is divided into three types: type I (involving the ascending aorta, arch, and descending aorta), type II (involving only the ascending aorta), and type III (involving only the descending aorta) (DeBakey et al., 1982).

Aortic aneurysms regardless of their origin pose a risk for acute aortic syndromes, such as acute aortic dissection with or without involvement of the aortic valve or aortic aneurysm rupture and a broad consecutive amount of acute sequelae. Additionally, they pose a risk for peripheral artery disease, thromboembolic events or acute limb ischemia.

The risk increases with the size of the aneurysm. This poses an even greater challenge as most aneurysms remain symptomatically silent while growing (Bossone & Eagle, 2021; Davies et al., 2002).

2. Conclusions and recommendations

Peripheral artery disease

Diagnostic work up in PAD aims at early detection of patients at risk, early stages of diseases with correct classification for optimal treatment and preventing progression as well as sequelae. Assessment of medical history and symptoms should include among others cardiovascular risk factors, co-morbidities, medication, skin tone, oedema, claudicatio or other pain as well as pain free walking distance and neurological deficiencies, reduced muscle function, freezing. Clinical examination consists of general pulse status, auscultation (cervical, abdominal), neurological and strength testing, skin temperature, hairiness and blood pressure measurement on both arms as well as Doppler ultrasound sonography of occlusion pressure in the dorsal pedal and posterior tibial arteries (Frank et al., 2019) for calculating the ankle-brachial index (pathological with ABI <0.9) (Layden, Michaels, Bermingham, Higgins, & Guideline Development, 2012; Writing Group, Writing Committee, & Accf/Aha Task Force, 2011; Xu et al., 2013). Exercise testing grant insights into pain-free walking distance and combined with an ABI before and after exercise increases the sensitivity of the diagnostic workup (Rose, 2000).

In cases with clinically suspected PAD Duplex sonography is the next step to confirm the findings and assess severity as well as potentially planning treatment strategies regardless of the affected location. (Collins et al., 2007; Schlager et al., 2007). CT and MRI imaging may be additionally considered in patients with complex anatomy, poor ultrasound imaging quality or for guiding interventional decision (Met, Bipat, Legemate, Reekers, & Koelemay, 2009; Ouwendijk et al., 2006). Digital subtraction

angiography (DSA) remains to be the gold standard in diagnosis of PAD (Frank et al., 2019). With emerging high diagnostic validity of the lesser invasive approaches DSA is favoured in combination with interventional treatment.

Screening method of choice should be the detailed medical history and physical examination. Ultrasonographic examination should be applied in patients with high risk or suspected PAD.

Aortic disease

Early diagnose of aortic aneurysm is crucial to prevent progression into acute aortic syndromes or other diseases. However, because of the long asymptomatic natural cause of aortic aneurysms, most often the diagnosis especially of thoracic aneurysms occurs accidently on imaging for other indications such as echocardiography, chest x-ray, CT- or MRI-scans (Erbel et al., 2014; Hiratzka et al., 2010).

Although ultrasound of the abdominal aorta is a good screening tool for aneurysms and is recommended in patients beyond 65 or patients with high individual risk (Erbel et al., 2014), it suffers from severe limitations in identifying aneurysms of the thoracic aorta. Due to anatomical restrictions for the ultrasound technique such as post-costal shadowing, impenetrable lug tissue and individual patient's factors a screening in the general population is not recommended. Only in individuals with a high pre-test-probability or special populations such as Pilots and ATCOs screening should be performed by transthoracic echocardiography. A comprehensive assessment of these patients naturally consists of a physical examination including auscultation (aortic murmur) and pulse status as well as a detailed medical history with symptomatic evaluation symptoms (hoarseness, stridor, shortness of breath, dysphagia, plethora, oedema, pain) (Bossone & Eagle, 2021).

Serial testing and time of treatment

Peripheral artery disease

Up to now current guidelines and literature does not provide standard of care follow up examinations of patients with PAD or screening intervals. According to other cardiovascular pathologies patients at high risk or confirmed PAD an annual follow up should be considered.

Therapy of PAD follows general strategies with the aim of mitigating symptoms, enhancing outcome in respect to mortality and morbidity and reducing complications. Especially in active pilots the risk of complications with the potential of incapacitation needs to be rigorously controlled.

Regardless of the location and symptomatic status of the disease first step of treatment is risk factor management, especially for smoking, dyslipidemia, diabetes, hypertension (Emdin et al., 2015; Engelhardt et al., 2012; Hirsch, Treat-Jacobson, Lando, & Hatsukami, 1997; Tunstall-Pedoe, Peters, Woodward, Struthers, & Belch, 2017). Regular physical exercise is a cornerstone of reducing individual cardiovascular risk and is a potent therapy for pad, predominantly of the lower extremities (Halliday et al., 2010).

In general, according to current guidelines interventional or surgical therapy of asymptomatic PAD regardless of disease location is not recommended with exception of extreme disease severity, or

interventions due to other indications with opportunistic treatment options (Aboyans et al., 2018; Cooper et al., 2014; Halliday et al., 2010). Invasive treatment options include balloon angioplasty, atherectomy, and new treatments such as shockwave lithoplasty and lumivascular optical coherence tomography–guided atherectomy. Indications for invasive treatment are given in detail by current guidelines and recommendations (Aboyans et al., 2018; Criqui et al., 2021; Frank et al., 2019).

Aortic disease

Once detected, aortic aneurysms need to be followed up closely to determine the optimal time of treatment and to prevent progression to acute aortic syndromes. Surveillance in thoracic aneurysms should be undertaken annually using echocardiography and MRI if diameter is 50% lager compared to age- and sex matched healthy individuals in this location but still smaller than 45 mm. If the diameter is between 45 and 55 mm risk of acute aortic syndromes increases (Erbel et al., 2014; Hiratzka et al., 2010), therefore a follow-up every 6 months is recommended (Bossone & Eagle, 2021). For abdominal aneurysms it is recommended to perform abdominal ultrasound every 3 years if the diameter is 30 – 39 mm, annually in 40-49 mm and every 3-6 months above 50 mm (Bossone & Eagle, 2021).

The treatment options for aneurysms comprise to approaches, open surgery and (thoracic) endovascular aneurysm repair ([T]EVAR). Optimal timing and approach of treatment is depending on individual risk factors, potentially underlying connective tissue disease and should be decided in an expert team considering patient's wish (epidemiology aorta). Depending on location, size, growth rate, symptomatic status and patient's surgical risk favoured approaches vary (table 3) (Bossone & Eagle, 2021).

Table 3: Indication and favored approach of intervention in aortic aneurysms in respect to location, patient's sex and size.

Location	Sex	Size	Favoured approach*
Ascending thoracic aorta		>55 mm	open surgery
Descending thoracic aorta	male female	>60 mm >50-55 mm	[T]EVAR
Abdominal Aorta	male female	> 55 mm > 50 mm	open surgery

*Favoured approach refers to otherwise healthy patients with long life expectancy and low surgical risk. Factors leading to lower thresholds: connective tissue disease, growth rate >10 mm/year, symptomatic status, complications and aortic valve impairment in aneurysms of the ascending aorta (NICE guidelines, NG156, 2020; Riambau et al., 2017; Swerdlow, Wu, & Schermerhorn, 2019).

3. Relevance for risk assessment of pilots and ATCOs

Pilots and ATCOs with peripheral artery disease or aortic disease threatening to impair their performance demand an interdisciplinary, high standard and individual medical approach. Screening testing has a higher value in this special population with low tolerance to overlooked medical

conditions. Stricter thresholds guiding interventional or surgical approaches may be considered to ensure safety from progression to acute syndromes with the risk of incapacitation.

Only treatment options considering fit and otherwise healthy patients should be favoured in active pilots, as relevant co-morbidities, high surgical risk or general frailty pose a contraindication to licence-renewal. Cases with peripheral artery disease needing surgical therapy are considered as cardio- and cerebrovascular high-risk cases, who -in consultation with the cardiologist and vascular surgeon - should be thoroughly evaluated after surgical intervention before a renewal of the aeromedical license might be considered.

To fly as a pilot after aortic surgery is possible, however the choice of procedure is crucial for license renewal. Licensing restrictions are likely to apply and the postoperative follow-up requires a tight scheduling. The cardiac surgeon should always liaise and communicate with the pilot's AME prior to and following cardiac surgery (Syburra et al., 2018).

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2.4. Valvular heart disease

1. What is new? – Main findings

- Emphasis on echocardiography as central diagnostic tool
- Strengthening an individual therapeutic approach in patients, especially in Pilots and ATCOs due to special group characteristics
- Emphasis on the clinical judgment of the AME in conjunction with new objective thresholds to ensure safety from incapacitation due to valvular heart disease inflight

Epidemiology

In the general population of the western hemisphere the prevalence of valvular heart disease is estimated to be around 2% in 55-year olds with a rapid increase beyond 60 years reaching up to 20% in individuals older than 75 years. The prevalence is threefold higher in men compared to women (Iung & Vahanian, 2014; Nkomo et al., 2006; Yadgir et al., 2020). Most common are the calcific aortic valve and degenerative mitral valve diseases. However, in populations younger than 55 years congenital heart diseases such as bicuspid aortic valve (BAV) or partial mitral valve prolapse (PMP) play a crucial role (D'Arcy et al., 2019). The prevalence of both BAV and PMP reaches up to 2% in these individuals (Fernandez et al., 2009; Marijon et al., 2007; Sievers & Schmidtke, 2007). These pathologies therefore have a relevant impact on pilots and ATCOs.

Rheumatic valvular disease is another possible cause of relevant valvular pathologies. Its prevalence and incidence are strongly dependent on the global region and infrastructure, especially access to early medical treatment. It is rarely seen in the western hemisphere but the prevalence reaches up to 5.5% in the Chinese (Sriharibabu, Himabindu, & Kabir, 2013) and 9.2% in the Indian population (Iung et al., 2018).

As to the impact of severe valvular heart disease on pilots or emergencies on airplanes we lack sufficient data to comprehensively evaluate its risk potential.

Classification and risk

Valvular heart disease is subdivided with respect to the affected valve and its pathology; in detail regurgitation or stenosis. The mechanism of the pathology is important for the treatment and longevity of potential interventions or surgery. Of prognostic value is the individual symptomatic status and the severity of the valvular heart disease.

Treatment options for symptomatic valvular heart disease include guideline-directed medical treatment and lifestyle interventions, treatment of underlying comorbidities and finally surgery or interventional approaches.

Relevant common forms of VHD

- Aortic Stenosis
- Aortic Regurgitation
- Mitral Regurgitation
- Tricuspid Regurgitation

Less common forms of VHD

- Mitral Stenosis (in rheumatic heart disease)
- Tricuspid stenosis
- Pulmonary valve disease

Valvular heart disease poses a risk for the affected individual, and especially pilots and ATCOs due to hemodynamic restriction. This includes the cardiac incompetence to adequately adapt or stabilize cardiac output under exercise, orthostatic stimulus or flight manoeuvres. Furthermore, valvular heart

diseases might predispose to various cardiac arrhythmia ranging from asymptomatic to life threatening. For pilots and ATCOs a relevant risk of disturbance of workflow by symptoms or even incapacitation is possible (D'Arcy et al., 2019).

Even for patients under treatment relevant risks can be observed. These may be due to persistent hemodynamic restrictions even after surgical or interventional therapeutic strategies (Syburra et al., 2018). But even prior to invasive strategies the use of guideline recommended medical therapy may impair the performance of the individual, with a potentially higher impact on pilots. This risk might be inherent for medication such as diuretics, betablockers, antiarrhythmics, anticoagulative medication or heart failure medication leading to electrolyte imbalances, volume status changes, impaired kidney function, bleeding, central nervous symptoms, arrhythmias and syncope among others.

2. Conclusion and recommendations

Screening

In individuals undergoing routine cardiovascular clinical evaluation or in patients with known valvular heart disease a thorough examination and testing is necessary to correctly diagnose, quantify and assess different valvular pathologies and determine their potential consequences and treatment options.

A comprehensive assessment consists of a thorough clinical examination, detailed medical history, especially focussing on auscultation (Popescu et al., 2009), patient's symptoms and clinical signs of heart failure. A central role plays state-of-the-art echocardiography in trained hands (Chambers et al., 2017; Hahn et al., 2019) as emphasized in the ESC and AHA-Guidelines (Otto et al., 2021; Vahanian et al., 2022). Non-invasive imaging should take advantage of available special techniques – such as cardiac strain, speckle tracking and 4-dimensional imaging - to assess the aetiology of suspected valvular heart disease and the feasibility of potential surgical or interventional approaches (Magne et al., 2019; Prihadi et al., 2019).

For further assessment of the severity of valvular heart disease and the optimal point of time for invasive treatment it is recommended to use biomarkers (e. g. natriuretic peptides, (Clavel et al., 2016)).

If the above-mentioned screening process confirms valvular heart disease further evaluation using multimodal-imaging and functional testing is crucial. This includes stress testing if assessment at rest is inconclusive or patient is asymptomatic, especially in mitral regurgitation and aortic stenosis (Henri et al., 2014; Monin et al., 2003; Picano, Pibarot, Lancellotti, Monin, & Bonow, 2009).

Tomographic imaging such as MRI and CT may provide additional information in guidance of treatment in some cases. Yet, they are not suitable tools for screening.

Serial testing

After identifying the presence of non-severe valvular heart disease in the individual patient in the

screening process and confirming the asymptomatic status (even after stress testing), follow up examinations are recommended. Serial testing is crucial to determine the dynamics of the disease and to identify the earliest point of time with a relevant risk of impairment of the performance, especially in pilots and ATCOs. Therefore, echocardiographic imaging in these individuals should occur yearly or even in shorter intervals in case of new onset symptoms such as shortness of breath, reduced physical fitness, peripheral oedema, arrhythmias or dysregulation of volume homeostasis (Otto et al., 2021; Vahanian et al., 2022).

Time of invasive treatment:

The optimal timing of surgery or interventional treatment of valvular heart disease is dependent on several aspects such as mechanism of the valvular pathology, evident cardiac dysfunction, symptomatic status, comorbidities and life expectancy among others. The integration of all information can be challenging. The recent guidelines of AHA and ESC focus especially on this topic to guide evidence-based decision making in the individual patient. Detailed indications and thresholds for intervention are provided integrating all available therapeutic strategies (Otto et al., 2021; Vahanian et al., 2022).

According to these guidelines, an interdisciplinary heart team should be the centre of the decision-making process integrating all available clinical data with respect to the patient's will regarding therapeutic strategies. With this approach standardization of care is promoted and better outcome for patients is achieved (Agricola et al., 2021; Hahn et al., 2019) (Lancellotti et al., 2018). However, in everyday clinical practice of the individual AME with assessment of the health status of applicants this resource may not be regularly available or necessary. Therefore, the echocardiographic thresholds outlined in table 4 in conjunction with clinical judgement should be emphasized to identify applicants who need to be referred to a specialized centre for individual therapy as well as to ensure a minimized risk of incapacitation due to valvular heart disease in flight.

Table 4: Summary of vascular heart disease categorization and derived recommendations (D'Arcy et al., 2019).

VHD	Echocardiography	Hemodynamic Consequences	Symptoms	Recommendation
Aortic stenosis	Vmax < 2.9 m/s	none	none	fit for flight
Mild	dPmean < 20 mmHg			
	Vmax 2.9 - 4 m/s	LV diastolic dysfunction	none	no solo flight
Intermediate	dPmean 20-40 mmHg	LV hypertrophy		no high perfomance
	AVAi > 0.6 cm²/m²	systolic LV dysfunction under exercise		further assessment
Severe	Vmax > 4 m/s	severe LV diastolic dysfunction	at rest	unfit for flight
	dPmean > 40 mmHg	systolic LV dysfunction at rest	under exercise	
	AVAi < 0,6 cm²/m²			
Aortic regurgitation (chronic)	jet width < 25% of LVOT			
Mild	VC < 3 mm	none	none	fit for flight
	regurgitation volume < 30 ml			
Intermediate	jet width 25-65% of LVOT			no solo flight
	VC 3-6 mm	systolic LV dysfunction	none	no high perfomance
	regurgitation volume 30-60 ml	under exercise		further assessment
	regurgitation fraction < 50%			
Severe	jet width > 65% of LVOT	LV dilation	at rest	unfit for flight
	VC > 6 mm	systolic LV dysfunction at rest	under exercise	
	regurgitation volume > 60 ml	holodiastolic flow reversal in aorta descendes		
Mitral stenosis	MVA > 1.5 cm²	mild LA dilation	none	fit for flight
Mild	diastolicPHT < 150 ms			
Intermediate	MVA > 1.5 cm2	moderate LA dilation	none	no solo flight
	diastolic PHT < 150 ms	SPAP 30-50 mmHg		no high perfomance
				further assessment
Severe	commissural fusion of leaflets	severe LA dilation	at rest	
	MVA <1.5 cm²	SPAP > 50 mmHg	under exercise	unfit for flight
	diastolic PHT > 150 ms			
Mitral regurgitation (chronic)	central jet			
Mild	VC < 5 mm			
	EROa < 0.29 cm²	mild LA dilation	none	fit for flight
	regurgitation volume < 44 ml			
	regurgitation fraction < 39%			
Intermediate	VC 5-7 mm	moderate LA dilation	none	no solo flight
	EROa 0.29-0.4 cm²	diastolic LV dysfunction		no high perfomance
	regurgitation volume 44-60 ml	SPAP 30-50 mmHg		further assessment
	regurgitation fraction 39-50%			
Severe	VC > 7 mm	severe LA dilation		
	EROa > 0.4 cm²	LV dilation	at rest	unfit for flight
	regurgitation volume > 60 ml	systolic LV dysfunction	under exercise	
	regurgitation fraction >50%	SPAP > 50 mmHg		
	flail of leaflet	pulmonary vein systolic flow reversal		
Tricuspid regurgitation	VC < 5 mm			
Mild	EROa < 0.3 cm²	none	none	fit for flight
	regurgitation volume < 40 ml			
Intermediate	VC 5-7 mm			no solo flight
	EROa 0.3-0.4 cm²	mild RA dilation	none	no high perfomance
	regurgitation volume 40-50 ml			further assessment
Severe	VC > 7 mm	severe RA dilation		
	EROa > 0.4 cm²	RV dilation	at rest	unfit for flight
	regurgitation volume >50 ml	RV dysfunction	under exercise	
		hepatic vein systolic flow reversal		
Pulmonic regurgitation				
Mild	trace jet, soft density		none	fit for flight
	long jet with narrow origin	RV dysfunction under exercise		no solo flight
Intermediate	regurgitation fraction 20-40%	mild RA dilation	none	no high perfomance
				further assessment
	broad and dense jet	RV hypertrophy	at rest	unfit for flight
Severe	regurgitation fraction >40%	RV dilation	under exercise	
		RV dysfunction		
Pulmonic stenosis	thickened leaflets			no solo flight
Mild	dPmax 25-36 mmHg		none	no high perfomance
	Vmax 2-3 m/s			further assessment
Intermediate & severe	thickened leaflets	RA or RV dilation	at rest	unfit for flight
	dPmax >36 mmHg	RV dysfunction	under exercise	
	Vmax > 3m/s	RV hypertrophy		

Mild pathologies are defined below the given thresholds. Severe pathologies are to be diagnosed when one criterion is met. In inconclusive cases recommendations are the same as for intermediate pathologies. AVAi –

indexed aortic valve area, dPmax – maximum pressure gradient, dPmean – mean pressure gradient, EROa – effective regurgitation orifice area, LA – left atrial, LV – left ventricular, LVOT – left ventricular outflow tract, MVA – mitral valve area, PHT – pressure half time, RA – right atrial, RV – right ventricular, SPAP – systolic pulmonary artery pressure, Vmax – maximum velocity, VC – vena contracta

3. Relevance for risk assessment of pilots and ATCOs

Pilots and ATCOs with severe or symptomatic valvular heart disease preventing them to continue their occupation without impairment of performance demand an interdisciplinary, high standard and individual medical approach.

Returning to fly or to ATC as a pilot or ATCO after cardiac surgery is possible, however, it is critical to pay special attention to perioperative planning. To determine their suitability to resume their aviation career or recreation, the cardiac surgeon should collaborate with the pilot's or ATCO's AME before the operation, to discuss the implications of different courses of action and the need for certain clinical investigations (Syburra et al., 2018).

Additional comments

Although risk stratification and recommendation for the optimal time of invasive treatment of valvular heart disease are provided in current guidelines they are only partially attributable to pilots and ATCOs. The tolerance of performance impairment in pilots and ATCOs is heavily restricted. Therefore, pathologies that might not yet be eligible for treatment in the general population need to be considered for surgery in pilots and ATCOs (D'Arcy et al., 2019; Syburra et al., 2018). This poses a therapeutic dilemma in balancing perioperative risk, longevity of prosthetics, progress of disease, patients' performance and patients' will. Furthermore, it does affect the choice of the surgical approach, for example favouring reconstructive surgery over valve replacement or biological over mechanical prosthesis potentially conflicting current guidelines.

Current EASA guidelines give no clear recommendation concerning the risk of anticoagulation in pilots and ATCOs. However, this poses a central concern in the individual having to undergo valvular surgery. Especially for younger patients' guidelines recommend using mechanical prosthetics needing oral anticoagulation after implantation. If this medication prevents patients from holding their pilot or ATCO license, therapeutic choices might be made that do not provide optimal medical care because of professional necessities.

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2.5. Thromboembolic disorders

This document describes the clinical aspects of thromboembolic diseases with emphasis on pulmonary embolism (PE) being an important and in some cases life threatening event. The cardiac consequences of PE can vary considerably and, in many occasions, cardiologic consultation is warranted. As a consequence of PE some patients develop pulmonary hypertension leading to right ventricular hypertrophy and ultimately, right ventricular failure. This document also describes the clinical aspects of arterial thromboembolism. In arterial thromboembolism, it is argued that cardiological evaluation is always warranted.
The necessity of routine cardiological evaluation in patients with thromboembolic diseases, and especially PE is discussed. From a recent position paper presenting the state-of-the art in the cardiological follow-up after pulmonary embolism, advice is given for the update of the Aeromedical Requirements.

Background

In cardiovascular medicine, thromboembolic diseases can roughly be divided in venous thromboembolism (VTE) an arterial thromboembolism (ATE).

In venous thromboembolism, pulmonary embolism (PE) is the most important clinical manifestation. In some cases, pulmonary embolism is caused by emboli from the heart itself (septic embolism with endocarditis of the tricuspid valve or cardiac tumor). The majority of cases of pulmonary embolism result from venous thrombosis related to immobilization, trauma, inflammation, malignancy or postoperative.

Cardiac involvement in pulmonary embolism is related to acute or chronic pressure overload of the right ventricle. A sudden and significant pressure overload can be seen when more than 40% of the pulmonary vascular bed is obstructed. In this setting patients can present with dyspnea, hypotension and supraventricular arrhythmias. Classical ECG changes are right axis deviation, right bundle branch block and atrial fibrillation. Echocardiography will show acute pressure and volume overload of the right ventricle with a leftwards septal shift.

The sequelae of pulmonary embolism can vary from total resolution of the clinical picture with full restoration of pulmonary flow and normalization of echocardiographic abnormalities. Arrhythmias will then disappear. At the other side of the spectrum persistent pulmonary vascular occlusions will lead to pulmonary hypertension (CTEPH).

In arterial thromboembolism cerebrovascular stroke and peripheral arterial embolization are the main clinical manifestations. Arterial thromboembolism can result from both cardiac and noncardiac sources. Cardiac sources of arterial thromboembolism are predominantly related to atrial fibrillation. In a minority of cases, atrial septal defect and left-sided endocarditis. Also, after acute anterior myocardial infarction the formation of left ventricular thrombus can result in arterial thromboembolism. In rare cases, tumor invasion of pulmonary veins can lead to arterial thromboembolism.

Non-cardiac causes of arterial thromboembolism are predominantly related to atherosclerotic disease with plaque formation in the arterial system. Examples are carotid, aortic and femoral artery plaques. Aortic aneurysm with thrombus formation can also lead to arterial embolization.

1. What is new? – Main findings

From the current understanding of cardiovascular consequences of thromboembolic disorders, it can be concluded that in many but not all cases there is a role for cardiological evaluation. In the acute setting of pulmonary embolism, cardiac ultrasound has only limited value as it will not result in better understanding of the clinical picture, better diagnosis and will not change choice of treatment. In the late phase of recovery, however, echocardiographic evaluation can play a role, especially when symptoms of dyspnea persist, and the presence of pulmonary hypertension is suspected (Barco et al., 2019). In this specific situation, it is worthwhile to perform a cardiological assessment at 3 to 6 months after the acute phase of pulmonary embolism. When this evaluation does not show any abnormalities (no persistent arrhythmias and no signs of pulmonary hypertension) there will be no indication for further follow up. There is no indication for routine Holter monitoring. Also, ischemia testing will not be necessary. Some reviews observed an increase in cardiovascular events in patients who suffered from venous thromboembolism (VTE). It is thought that the pro-inflammatory state existing in these patients predisposes them for cardiovascular events (Becattini, Vedovati, Ageno, Dentali, & Agnelli, 2010; Ng et al., 2011; Noumegni et al., 2021; Riva, Donadini, & Ageno, 2015). It has also been shown that patients with VTE in general have a higher cardiovascular risk profile as it was found that patients with VTE were older, had higher BMI's and more often were smoking (Gregson et al., 2019). In clinical practice, however, the chance of detecting significant coronary artery disease in patients who suffered from recent pulmonary embolism is very low. Therefore, after pulmonary embolism there is no clear indication to search routinely for coronary artery disease. Also, ischemia testing as a routine is not necessary. It is, however, indicated to look for and, when possible, treat cardiovascular risk factors given the increased risk of future cardiovascular events. This approach is also described in an ESC position paper (Klok et al., 2022) where the authors state that "since no biomarkers and surrogate measures to refine cardiovascular risk assessment in patients with PE have been established, we propose to perform systematic cardiovascular risk assessment in all PE patients, using validated scores and risk calculators, and according to current guidelines".

In arterial thromboembolism there will always be an indication for echocardiography (transthoracic and sometimes also trans esophageal). In some cases, CT scan or MRI will be necessary to detect subtle forms of intracardiac thrombosis or tumor and aortic abnormalities. MRI can detect cardiac tumors and left ventricular thrombus with higher sensitivity than echocardiography. In arterial embolism Holter monitoring is indicated to search for the presence of atrial fibrillation.

In the follow up after arterial thromboembolism, the indication for cardiac follow-up will depend on the initial diagnosis. When no cardiac thromboembolic sources have been found, and a clear non-cardiac source is present, echocardiographic follow up is not indicated.

Depending on the diagnosis, however, an estimation has to be made as to the likelihood of coexisting coronary artery disease. In most cases, arterial thromboembolism will occur in patients who are older and have comorbidities like peripheral arterial atherosclerotic disease, hypertension or diabetes.

Therefore, in these patients, ischemia testing or direct imaging of the coronary arteries should be considered depending on the clinical context and the implications of the findings for choice of treatment. In pilots and air traffic controllers, however, even without cardiac complaints, a coronary calcium score and coronary CT angiography should be advised, given the low threshold used for the risk of incapacitation.

2. Conclusions and recommendations

In a subgroup of patients with thromboembolic disorders there is a place for cardiological evaluation during the acute phase and during follow-up.

The type of cardiological evaluation depends on the initial clinical picture and in many cases of pulmonary embolism, after the acute phase there is no indication for a routine cardiological follow-up. Only in patients with persistent complaints or with cardiovascular risk factors consultation of a cardiologist is warranted. Although there is a suggestion of a relationship between VTE and atherosclerotic coronary artery disease, the investigation of coronary arteries in most cases is not indicated. Decisions about coronary CT-scanning should be based on the cardiovascular risk-profile (see also the issue on risk factors/prevention and on CT-scanning in CAD).

In patients with arterial thromboembolism cardiologic evaluation is always indicated. Dependent on the clinical picture, investigation of coronary arteries will sometimes be necessary. In patients with peripheral arterial atherosclerotic disease a coronary artery calcium score and subsequently coronary CT-angiography can be used as first-line diagnostic tool.

3. Relevance for the risk assessment of pilots and ATCOs

Venous thromboembolism

Pilots and ATCO's suffering from VTE should be thoroughly screened for the presence of cardiovascular risk factors. A cardiovascular risk-assessment should then be performed with the use of applicable risk-calculators. Consequently, risk-reducing measures should be taken. Investigation of the coronary arteries is not routinely advised and should be based on the cardiovascular risk-profile using pertinent risk-evaluation tools.

In pilots and ATCO's suffering from pulmonary embolism consultation of a cardiologists is indicated in the following events:

1. When after three to six months there are complaints of dyspnea and/or a subnormal exercise tolerance.
2. When after the acute event a supraventricular arrhythmia persists or reoccurs.
3. When, after three to six months the ECG shows signs of right ventricular overload.

Arterial thromboembolism

In pilots and ATCOs suffering from arterial thromboembolism consultation of a cardiologist is mandatory. Depending on the initial diagnosis, cardiac evaluation should consist of echocardiography and Holter monitoring. Also, the presence of coronary atherosclerosis should be investigated with a coronary calcium score and subsequently, CT-coronary angiography.

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2.6 Congenital heart disease

This document contains main findings concerning the state-of-the-art of “congenital heart disease (CHD)”, like pathophysiological background, clinical manifestations, etc.. But it does not contain comments concerning treatment options, because in this field risk assessment is of utmost importance for counseling pilots and ATCOs. Surgery or interventional techniques are the only treatment options for CHD, which are to be performed in specialized centers.

1. What is new? – Main findings

- Cyanotic and other complex CHD are almost always incompatible with pilot and ATCO licensing due to significant physiological impairment and reduced life expectancy.
- There is no clear evidence to support anticoagulation in patients with CHD and no additional thrombo-embolic risk.
- In patients with a general indication for anticoagulation (i.e. atrial fibrillation, atrial flutter, a.o.) NOACs appear to be safe also in CHD.

Epidemiology

Individuals with CHD are more prone to cardiac symptoms like arrhythmia, chest pain and have more hospitalizations as well as emergency department visits than the general population. The hypoxic and hypobaric environment at high altitude may expose pilots to additional stressors that may further increase risk. Therefore, appropriate risk assessment is paramount to ensure flight safety.

Classification and risk

The classification system for congenital heart diseases (CHD) can be complicated, but for the purpose of aeromedical assessment, they can be broadly dichotomized into either acyanotic or cyanotic. Cyanotic pathologies arise due to right-to-left shunt and result in diversion of deoxygenated blood from the venous to the arterial circulation. Besides the significant physiological impairment in complex CHD, acute risk in adult patients with CHD arises primarily from thrombosis, arrhythmia and hypoxia. Therefore, the following conditions are to be considered in private and commercial aviation:

1. Cyanotic CHD
2. Eisenmenger syndrome (ES)
3. Conditions with increased thromb-embolic risk
4. Arrhythmias and sudden cardiac death (SCD)

Cyanotic CHD

The term cyanotic CHD comprises the types of CHD that are characterized by a right-to-left cardiac shunt, which leads to deoxygenated blood entering the systemic circulation. The resulting hypoxemia manifests clinically as cyanosis, which may occur as acute, life-threatening episodes. The group of cyanotic CHD comprises the following pathologies:

- Tetralogy of Fallot
- Transposition of the Great Arteries
- Persistent Truncus Arteriosus
- Tricuspid Atresia
- Total Anomalous Pulmonary Venous Return

Eisenmenger syndrome (ES)

ES develops gradually over time as a consequence of unrepaired, non-restrictive cardiac shunt lesions at the atrial, ventricular or arterial level. On a pathophysiological level, ES results from the reversal of a left-to-right shunt following the progressive increase in pulmonary vascular resistance typically due to the increased blood flow in the pulmonary circulation.

Conditions with increased thrombo-embolic risk

The altered circulation in patients with CHD as well as special conditions like the Fontan operation increase thrombo-embolic risk. In addition, atrial arrhythmias, namely atrial fibrillation, atrial flutter, and intra-atrial reentrant tachycardia have a high prevalence in adult patients with CHD. These events further enhance the risk for thrombo-embolic events (Egbe et al., 2016), and are associated with increased morbidity and mortality (Khairy & Landzberg, 2008).

There is substantial evidence from adult patients with different types of CHD and indication for thromboprophylaxis, indicating that NOACs (non-vitamin K antagonist oral anticoagulants) are safe and effective in these populations (Georgekutty et al., 2018; Pujol et al., 2016; Stalikas et al., 2020).

Arrhythmias and sudden cardiac death (SCD)

The entire spectrum of arrhythmias can be documented in adult CHD patients. However, some arrhythmia substrates are related to the congenital malformation itself. The increasing life expectancy in this population further increases the prevalence of arrhythmias related to structural remodelling, which often occur earlier in life compared to the general population, e.g. atrial fibrillation.

Other arrhythmias are related to the type and timing of the CHD repair. Right atrial surgery, together with haemodynamic overload resulting in cardiac remodelling, contribute to the high prevalence of atrial tachycardias in many types of CHD. Of special consideration is late intraatrial reentrant tachycardia (IART), in particular cavotricuspid isthmus-dependent atrial flutter, which has the highest prevalence in CHD. Atrial rates between 150 and 250 beats per minute impose the risk of rapid AV conduction, haemodynamic compromise, and SCD.

Table 5: Risk estimates for arrhythmic events and bradycardias in CHD (taken from the ESC guidelines for the management of adult congenital heart (Baumgartner et al., 2021)).

	Supraventricular arrhythmias			Ventricular arrythmias and SCD		Bradycardia			
Type of CHD	AVRT	IART/ EAT	AF	Sustained VT	SCD	SND		AV block	
						Congenital	Acquired	Congenital	Acquired
Secundum ASD		++	++			(+)	+		(+)
Superior sinus venosus defect		++	+				+		
AVSD/primum ASD		++	++	(+)		(+)		(+)	++
VSD		+	(+)	+	(+)[a]				+
Ebstein anomaly	+++	++	+	(+)	++[b]		++		
TOF		++	++	++	++		+		+
TGA									
Atrial switch		+++	+	++[c]	+++[b]		+++		+
Arterial switch		+		+[c]	(+)		(+)		
ccTGA	++	+	+	(+)	++[b]			+	++
Fontan operation									
Atriopulmonary connection		+++	++		+[b]		++		
Intracardiac lateral tunnel		++	+		+[b]		++		
Extracardiac conduit		+	+		+[b]		+		
Eisenmenger physiology Incompletely palliated CHD		++	++		++[d]				

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Empty cells indicate that although not specifically indicated, arrhythmic events may occur (no symbol).

(+) = minimal risk + = mild risk ++ = moderate risk +++ = high risk

AF = atrial fibrillation; ASD = atrial septal defect; AV = atrioventricular; AVRT = atrioventricular reentrant tachycardia; AVSD = atrioventricular septal defect; ccTGA = congenitally corrected transposition of the great arteries; CHD = congenital heart disease; EAT = ectopic atrial tachycardia; IART = intraatrial reentrant tachycardia; SCD = sudden cardiac death; SND = sinus node dysfunction; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; VT = ventricular tachycardia.

a) Considering the high prevalence of VSD, the overall risk in unselected patients with VSD is considered to be minimal.

b) SCD may be due to supraventricular arrhythmias with rapid AV conduction.

c) VT higher estimated risk in complex dextro-TGA.

d) Non-arrhythmic.

2. Conclusion and recommendations

Cyanotic CHD and Eisenmenger syndrome

- Acute exposure to high altitude (>2500 m) should be avoided in individuals with CHD and Eisenmenger syndrome. The oxygen partial pressure during commercial flights is typically maintained at a level equivalent to that found at an altitude of 1.800 - 2.400 meters (6.000 - 8.000 feet).
- Cyanotic and other complex CHD are almost always incompatible with pilots/ATCOs licensing and often associated with significant physiological impairment and reduced life expectancy. The only exception to this may be tetralogy of Fallot after surgical correction (Nicol et al., 2019). ATCOs might be assessed as fit following cardiological assessment after successful surgical correction or with minor abnormalities that are functionally unimportant.

Conditions with increased thromboembolic risk

- Risk reduction strategies include avoidance of travel- and non-travel related stress, dehydration, alcoholic drinks, and measures to prevent deep vein thrombosis.
- There is no clear evidence to support anticoagulation in patients with CHD and no additional thromboembolic risk.
- In patients with a general indication for anticoagulation (i.e. atrial fibrillation, atrial flutter, a.o.) NOACs appear to be safe also in CHD.

Arrhythmias

- Conditions that impose an increased risk of hemodynamically relevant arrhythmias should be incompatible with pilot/ATCO licensing. Exceptions are bradycardic arrhythmias under pacemaker protection.

3. Relevance for risk assessment of pilots and ATCOs

Simple CHD, especially if repaired in childhood, may be acceptable, and allow either full or restricted pilot/ATCO duties to be undertaken (Nicol et al., 2019). These simple CHD may include coronary artery anomalies, bicuspid aortic valve disease and coarctation, patent foramen ovale (PFO), atrial septal defects (ASD) and small ventricular septal defects. Conditions that require routine and regular cardiovascular follow-up, have residual physiological consequence, or increase risk of aeromedically important sequelae (such as palpitations and chest pain) are unlikely to be compatible with unrestricted professional pilot/ATCO duties (Nicol et al., 2019). Further recommendations should be formulated as part of task 2.

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2.7 Pericardial and endocardial disease

This document contains main findings concerning the state-of-the-art of pericarditis and endocarditis like pathophysiological background, clinical manifestations, diagnostic techniques etc., and it contains also few comments concerning treatment options of this disease.

1. What is new? – Main findings

- Nothing is really new in the field of endocarditis and pericarditis
- Pilots/ATCOs with acute disease are unfit.
- Pilots or ATCOs may return to flying or ATC duties, provided that symptoms have fully resolved, medication is terminated and the first-line investigations by a board-certified cardiologist show satisfactory results. These investigations should focus especially on the most common complications.

Epidemiology

The spectrum of endocarditis, pericarditis, and myocarditis constitute the 3 commonest entities of cardiac inflammatory reactions arising from infective or immune-mediated insults, or less commonly

metabolic/radiation/toxins induced injury, with a multitude of structural and functional consequences. Other non-inflammatory diseases of the pericardium and the endocardium are extremely rare and beyond the scope of this tender.

Classification and risk

Endocarditis

For the diagnosis of a probable or definite endocarditis clinical criteria, laboratory findings, including microbiology, and imaging techniques are to be used according to current guidelines (Habib et al., 2015). The diagnosis is based on the modified Duke criteria (see table 6 below). Complications can range from persistent septicemia, arrhythmias, distal embolism, severe valvulopathies, to heart failure.

Table 6: Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis

Major criteria
1. Blood cultues positive for IE a. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus;* or • Community-acquired enterococci, in the absence of a primary focus; or b. Microorganisms consistent with IE from persistently positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart; or • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
2. Imaging positive for IE a. Echocardiogram positive for IE: • Vegetation; •Abscess, pseudoaneurysm, intracardiac fistula; • Valvular perforation or aneurysm; • New partial dehiscence of prosthetic valve. b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT. c. Definite paravalvular lesions by cardiac CT.
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use. 2. Fever defined as temperature >38°C. 3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions. 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor. 5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

Definite IE
Pathological criteria • Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or • Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis **Clinical criteria** • 2 major criteria; or • 1 major criterion and 3 minor criteria; or • 5 minor criteria
Possible IE
• 1 major criterion and 1 minor criterion; or • 3 minor criteria
Rejected IE
• Firm alternate diagnosis; or • Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or • No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or • Does not meet criteria for possible IE, as above

CT = computed tomography; FDG = fluorodeoxyglucose; HACEK = Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans; IE = infective endocarditis; Ig = immunoglobulin; PET = positron emission tomography; SPECT = single photon emission computerized tomography. Adapted from Habib et al 2015.

Pericarditis

Pilots/ATCOs with suspected or known pericarditis should have an ECG performed and undergo transthoracic echocardiography (TTE) to quantify pericardial effusion. Cardiac MRI may confirm a diagnosis of pericarditis when ECG and TTE are inconclusive. The most common complications include persistent arrhythmias, pericardial tamponade and restricted ventricular filling.

2. Conclusion and recommendations

Endocarditis

- patients with endocarditis should be hospitalized and receive intravenous antibiotic treatment for 2 - 6 weeks (or even longer in prosthetic valve endocarditis (PVE)).
- during and after treatment patients are to be thoroughly examined to document complications, especially neurologic complications, renal failure, arrhythmias and valvulopathies.
- The treatment of complications is to be decided in accordance with current recommendations for the specific disease (i.e. heart failure, valvular insufficiencies, arrhythmias, renal failure a.o.).

Pericarditis

- The use of aspirin or non-steroidal anti-inflammatory drugs is recommended for the treatment of pericarditis until symptoms fully resolve, along with colchicine which is continued for 6 - 12 weeks (Adler et al., 2015).
- A period of 3 - 6 months of reduced physical activity is recommended following an episode of pericarditis (Pelliccia et al., 2006; Seidenberg & Haynes, 2006).
- Recurrence occurs in approximately 15 - 30% of cases of acute pericarditis. The recurrence rate may be halved if colchicine is used (Imazio et al., 2005).
- The treatment of complications following pericarditis is to be decided in accordance with current recommendations for the specific disease (i.e. arrhythmias, restrictive cardiomyopathy, a.o.).

3. Relevance for risk assessment of pilots and ATCOs

Pilots and ATCOs with confirmed diagnosis of endocarditis or pericarditis should be grounded or taken off the roster for a minimum of 3 months. It appears reasonable that pilots may return to flying or ATC work after this period, provided that symptoms have fully resolved, medication is terminated and the first-line investigations by a professional cardiologist show satisfactory results. These investigations should focus especially on the most common complications, including persistent arrhythmias, severe valvulopathies, heart failure, pericardial tamponade and restricted ventricular filling.

Due to the chronic nature of pericarditis and its high recurrence rate, return to unrestricted flying or ATC duties after an episode of pericarditis should not be considered before a 6 months time interval without relapse. For ATCOs this time interval is limited to 3 months.

If complications occur, these may require restrictions to flying or ATC duties themselves. Type and duration of these restrictions is to be decided in accordance with the specific recommendations for the disease (i.e. heart failure, valvular insufficiencies, arrhythmias, restrictive cardiomyopathy, renal failure a.o.).

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2.8 Myocardial disease

This document contains main findings concerning myocardial disease, including pathophysiological background, clinical manifestations, diagnostic techniques etc., and it contains also the current treatment options of the respective diseases.

1. What is new? – Main findings

- the aetiology of any myocardial disease should be elucidated, as it impacts risk assessment, treatment and prognosis.
- symptomatic individuals with myocardial disease should be grounded.
- new treatment options have improved morbidity and mortality in hypertrophic cardiomyopathy and some forms of restrictive cardiomyopathy.
- myocardial diseases usually are complex entities which should be diagnosed and guided long-term by cardiology specialists.

Epidemiology

Myocarditis

In Europe, cardiotropic viruses are the most common cause for myocarditis. In addition, myocarditis can be triggered by systemic autoimmune disorders (systemic lupus erythematosus, sarcoidosis a.o.), drugs (high incidence by immune checkpoint inhibitors) and vaccines (currently smallpox and mRNA COVID-19 vaccines, a.o.). Typical symptoms include the acute onset of chest pain symptoms (82% to 95% of adult patients), arrhythmias (72% - 80%), dyspnea (19% to 49%), and / or syncope (5% to 7%). But even more severe symptoms of heart failure may lead to the first diagnosis in some cases.

Hypertrophic cardiomyopathy (HCM)

HCM is a genetic disease, commonly inherited in an autosomal dominant pattern, but disease penetrance is incomplete and related to age. The presence of multiple mutations may in some cases result in a more extreme phenotype. For some specific HCM disease patterns the specific mutations have been elucidated in recent years. HCM is not uncommon with a population prevalence ratio of approximately 1:500 in an echocardiographic study, but even a higher prevalence (1 case per 200) when both clinical and genetic diagnoses, including those in family members, are taken into account (Semsarian, Ingles, Maron, & Maron, 2015).

Restrictive cardiomyopathies (RCM)

RCM are usually classified into primary and secondary forms. Primary RCM forms are extremely rare and include Löffler's endocarditis and endomyocardial fibrosis. Primary RCM is associated with poor outcomes. Secondary RCM forms result from infiltrative diseases (e.g. sarcoidosis or amyloidosis), storage diseases (e.g. haemocromatosis or Fabry's disease) or radiation injury. The inherited forms of RCM are most commonly associated with an autosomal dominant disorder and, less commonly, autosomal recessive or sporadic. Genes causing RCM encode structural and regulatory proteins of the sarcomeres as well as cytoskeletal intermediate filaments.

Restrictive cardiomyopathy is associated with the worst prognosis of all the cardiomyopathy phenotypes. Survival data are limited to small windows of observation. The prognosis of RCM largely depends on the restrictive physiology, regardless of the underlying cause (Arbelo et al., 2023).

Classification and risk

Myocarditis

The diagnosis of myocarditis can be suggested by presenting symptoms, elevated biomarkers such as troponins, electrocardiographic changes of ST segments, and wall motion abnormalities in echocardiography. In these patients, coronary artery disease should be excluded as alternative diagnosis by coronary angiography or coronary CT scan. Myocarditis is frequently missed in patients with subtle symptoms or can be detected as incidental finding on MRI following an asymptomatic episode. Cardiac MRI or endomyocardial biopsy are required for definitive diagnosis.

In 20% of patients with myocarditis the disease progresses to dilated cardiomyopathy (DCM). Furthermore, sudden cardiac death (SCD) is often feared as complication of acute myocarditis, most commonly in younger patients and in association with strenuous physical activity, with the highest risk being in the 6 months following diagnosis. Therefore, heart rate is usually monitored in patients with a definite diagnosis of myocarditis over several days to estimate the risk for malignant arrhythmias. Acute myocarditis that is complicated by acute heart failure or ventricular arrhythmias is associated with a 12% rate of either in-hospital mortality or need for heart transplant (Ammirati & Moslehi, 2023).

Cardiac MRI is currently the gold standard in the diagnosis of myocarditis and is therefore strongly encouraged in pilots and ATCOs with suspected disease. In affected patients, T2-weighted sequences may identify oedema, or signs of fibrosis may be visualized by late gadolinium enhancement (LGE). It has been suggested that the presence of LGE in myocarditis is associated with a worse prognosis (Grani et al., 2017), which further supports its use in the examination of pilots and ATCOs.

Although 80% of affected patients recovery fully from myocarditis, there are no clinical measures to predict outcomes reliably. Following an episode of myocarditis, reduced exercise capacity and other features of postviral syndromes may persist for months. This should also be borne in mind when considering returning pilots to flying duties.

Hypertrophic cardiomyopathy

Typical symptoms of HCM include diastolic dysfunction, myocardial ischemia with angina, left ventricular outflow tract obstruction (LVTOT) with the risk for syncopal events, arrhythmias and heart failure. HCM is associated with increased mortality, accordingly, and shows a significant risk of SCD, especially in individuals under the age of 35 (Maron, 2010). Up to 8% of patients with HCM also develop systolic LV-dysfunction, i.e. an ejection fraction <50%. The severity of such condition is underlined by a median time from the recognition of systolic dysfunction to a composite outcome of all-cause death (23%), cardiac transplantation (9%), or LVAD implantation (2%) of only 8 years (Marstrand et al., 2020) Mortality rates in HCM are doubled compared to the general population, are higher in women and most frequently due to SCD and heart failure (Lorenzini et al., 2020). Spirito and coworkers described an association of severe left ventricular hypertrophy, family history of SCD, syncope and certain genetic phenotypes with the risk of death due to SCD (Spirito et al., 2000). Ischemia and fibrosis as well as LVTOT have further been identified as potential triggers for arrhythmia in HCM. Overall, non-sustained VTs have been found in up to 31% of patients with HCM (Adabag, Casey, Kuskowski, Zenovich, & Maron, 2005; Monserrat et al., 2003).

With the use of modern treatment strategies, a reduction of mortality rates from up to 6% in former times to currently as low as 0,5% per year have been achieved, independent of age. According to current guidelines (Arbelo et al., 2023) therapy in symptomatic patients without LVOTO focuses on management of arrhythmia, reduction of LV filling pressures, and treatment of angina. Hence, symptomatic patients with HCM and diastolic heart failure should be treated with either beta-blockers, verapamil or diltiazem in combination with a low dose diuretic. Symptomatic patients with HCM and an ejection fraction <50% on the other hand should be treated for systolic heart failure with

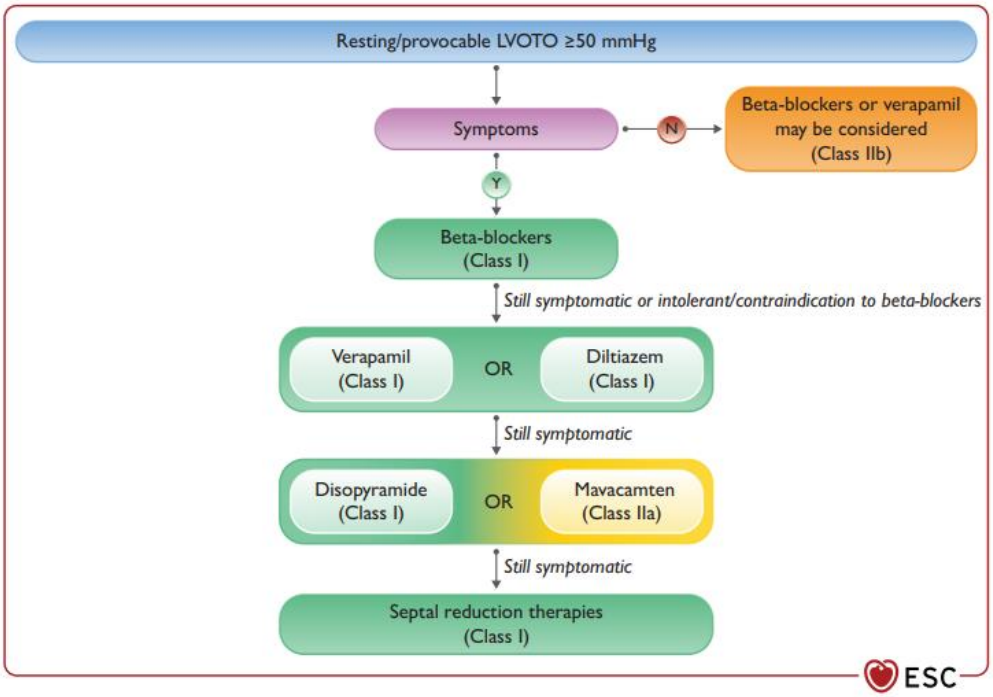
a combination of beta-blockers, angiotensin-receptor-neprilysin inhibitors (ARNI), mineralocorticoid-receptor antagonists, SGLT-2 inhibitors and diuretics.

By convention, LVOTO is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mmHg, but the threshold for invasive treatment is usually considered to be ≥50 mmHg (Arbelo et al., 2023). In these patients, general recommendations include weight loss and the prevention of dehydration as well as excess alcohol consumption to avoid or alleviate symptoms.

The aim of drug treatment in symptomatic patients with HCM and LVTOT is to reduce basal LV outflow pressure gradients, to lower the risk of arrhythmias and to improve exercise tolerance. It is therefore recommended to initiate treatment with non-vasodilating beta-blockers titrated to the maximum tolerated dose. In case of intolerance or contraindications against beta-blockers an alternative therapy with verapamil or diltiazem should be considered. If beta-blockers alone are ineffective, the class IA antiarrhythmic drug disopyramide may be added and titrated up to a maximum tolerated dose (Arbelo et al., 2023).

Most recently, the first cardiac myosin inhibitor mavacamten has been developed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy. In the pivotal phase 3 trial EXPLORER HCM, treatment with mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status but had no effect on mortality in patients with obstructive HCM (Olivotto et al., 2020).

In patients with persistent symptoms, basal LV outflow pressure gradients ≥50mmHg and/or an increased risk of death further invasive or surgical interventions should be evaluated. These strategies include implantable defibrillators to reduce the risk of sudden death, surgical or interventional (alcohol septal ablation) myectomy for permanent reversal of heart failure in patients with LVTOT, and heart transplantation for patients with nonobstructive end-stage disease.



©2023 ESC Guidelines for the management of cardiomyopathies, Arbelo et al, 2023

Figure 3: Flow chart on the management of left ventricular outflow tract obstruction published by the European Society of Cardiology (ESC), (Arbelo et al., 2023). LVOTO, left ventricular outflow tract obstruction.

Figure 3 provides an overview on the treatment algorithm currently recommended by the European Society of Cardiology (ESC) for patients with HCM and resting or provocable LVOTO ≥50mmHg.

Restrictive cardiomyopathies

All forms of RCM are associated with impaired diastolic function, myocardial hypertrophy and restrictive filling patterns, regardless of the underlying disease. From an aeromedical perspective the major concern arises from the potential for conduction defects and significant physical impairment. Cardiac manifestations of storage and infiltrative diseases are variable and depend on individual differences in relative cardiac involvement, severity and duration of the disease as well as modern treatment options.

Therefore, precise diagnosis is essential for genetic phenocopies with available target treatments. This may include genetic testing in individuals, in whom a sprecific genetic disorder is suspected. Furthermore, endomyocardial biopsy should be considered in patients with RCM to exclude specific diagnoses (including iron overload, storage disorders, mitochondrial cytopathies, amyloidosis, and granulomatous myocardial diseases) and to diagnose restrictive myofibrillar disease caused by desmin variants, according to current guidelines (Arbelo et al., 2023).

The treatment options for infiltrative or storage cardiac disease depend on the specific underlying cause and the extend of cardiac involvement. Among others, these specific treatment options include tafamidis and diflunisal for ATTR amyloidosis, immunosuppressive agents like corticosteroids, immunomodulators or monoclonal antibodies for sarcoidosis or AA amyloidosis, chemotherapy or bone marrow transplantation for AL amyloidosis, phlebotomy and iron chelation therapy (deferoxamine) for hemochromatosis and enzyme replacement therapy for Anderson-Fabry disease or glycogenosis such as Pompe disease.

2. Conclusion and recommendations

Myocarditis

- the management of myocarditis typically involves a combination of supportive care, treating underlying causes, and addressing complications.
- rest is recommended and activities that may increase the workload of the heart should be avoided during the acute phase of myocarditis. This is strongly recommended as long as symptoms prevail and is commonly extended for 3 to 6 months.
- medications may be prescribed to manage heart failure, reduce inflammation, or control arrhythmias.
- it is recommended to monitor heart function and potential ventricular arrhythmias.

Hypertrophic cardiomyopathy

- Due to the variable disease progression, serial evaluation of individuals with a first-degree relative diagnosed with HCM may be required over long periods of follow-up. It is recommended that screening continue at 5 yearly intervals in the general population up to the age of 50 years (Maron et al., 2003).
- genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives (Elliott et al., 2020).
- The lack of robust data on specific genotype–phenotype associations means that the impact of genetic testing on clinical management is limited mostly to some of the rare genetic causes of HCM (Elliott et al., 2020).
- Economic decision models have compared the cost effectiveness of molecular screening to clinical screening alone and have shown that the combination of genetic testing and clinical screening identifies more individuals at risk of developing HCM and allows a greater number to be discharged from follow-up (Ingles, McGaughran, Scuffham, Atherton, & Semsarian, 2012; Wordsworth et al., 2010).

Restrictive cardiomyopathies

- in patients with suspected cardiac involvement of infiltrative or storage disease cardiac MRI is strongly recommended in addition to ECG, echocardiography and Holter-ECG.
- the etiology of any restrictive cardiomyopathy should be elucidated, as it impacts risk assessment, treatment and prognosis.
- genetic testing is required for many infiltrative or storage diseases like Fabry's disease or hemochromatosis to establish the diagnosis and for genetic counselling.
- endomyocardial biopsy should be considered in patients with RCM to exclude specific diagnoses and to diagnose restrictive myofibrillar disease caused by desmin variants.

3. Relevance for risk assessment of pilots and ATCOs

Myocarditis

- Pilots or ATCOs with confirmed diagnosis of myocarditis should be declared unfit for at least 6 months. For ATCOs this time interval can be reduced to 3 months.
- Cardiac MRI is strongly recommended for the diagnosis of myocarditis and for follow up.
- Prior to return to flight a comprehensive examination by a cardiology specialist, including ECG at rest, 24hr-Holter ECG, echocardiography and exercise stress testing is strongly recommended.
- Ongoing restrictions are required if LV dysfunction or significant arrhythmia is detected.

Hypertrophic cardiomyopathy

- Pilots/ATCOs with a first-degree relative diagnosed with HCM should be screened with ECG and TTE initially and for relicensing.

- Due to the variable disease progression, biannual screening should strongly be considered for pilots/ATCOs with a first-degree relative diagnosed with HCM.
- Screening should include genetic testing, if a causal genetic mutation for HCM has been identified in a first-degree relative.

Restrictive cardiomyopathies

- Pilots/ATCOs with cardiac involvement in any type of infiltrative or storage disease should be considered unfit to fly due to physical restraint and the risk of significant arrhythmia.

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2.9 Heart failure

This document contains main findings concerning heart failure, including pathophysiological background, clinical manifestations, diagnostic techniques etc., and it contains also the current treatment options for heart failure (see part 1 and 2).

1. What is new? – Main findings

- The etiology of any myocardial disease should be elucidated, as it impacts risk assessment, treatment and prognosis.
- New treatment options have improved morbidity and mortality in heart failure.
- In heart failure patients, treatment should be continued without limit even if cardiac function has fully recovered under treatment to avoid relapse.
- Due to technical advances left ventricular assist devices (LVADs) have become a viable option with 5-year survival rates of 50%.
- Myocardial diseases usually are complex entities which should be diagnosed and guided long-term by cardiology specialists.

Epidemiology

The age-adjusted incidence of heart failure (HF) may be falling in developed countries, presumably reflecting better management of CV disease. However, due to the demographic changes in the western world with increasing life expectancies, the overall incidence is rising (Conrad et al., 2018; Roth et al., 2015; Savarese & Lund, 2017). The estimated prevalence of heart failure lies around 1-2% in adults (2018; Conrad et al., 2018). The prevalence correlates with age: while only 1% are affected in the age group <55 years, numbers rise to over 10% in those aged 70 years or over (Ceia et al., 2002; van Riet et al., 2016). According to the individual ejection fraction (EF) of the heart, heart failure is divided into forms with reduced EF (EF ≤40%, HFrEF); with mildly reduced EF (41 - 49%, HFmrEF) and heart failure with preserved EF (EF ≥50%, HFpEF). Prevalence between HFrEF and HFmrEF or HFpEF is equally distributed with each group accounting for approximately 50%. The etiology of HF varies according to geography. In Western-type and developed countries, coronary artery disease (CAD) and hypertension are predominant factors (2018).

Classification and risk

Diagnosis

For the diagnosis of HF symptoms and/or signs of HF as well as objective evidence of cardiac dysfunction are required. Typical symptoms include signs of congestion (pulmonary oedema, ancle swelling a.o.), breathlessness and fatigue. Symptoms and signs lack sufficient accuracy to be used alone to make the diagnosis of HF. Therefore, ECG, echocardiography and laboratory tests should also be considered to make the diagnosis (McDonagh et al., 2021).

Treatment

The primary goals of treatment for patients with HFrEF include:

1. reduction in mortality,
2. prevention of recurrent hospitalizations, and
3. improvement in clinical status, functional capacity, and quality of life (QOL).

The current guidelines of the ESC recommend 4 drug classes, which all convey prognostic benefit in patients with HFrEF:

- ACE-Inhibitors/Angiotensin Receptor Neprilysin Inhibitors (ARNI)
- Beta-blockers
- Mineralocorticoid-Receptor Antagonists (MRA)
- SGLT-2 Inhibitors (Dapagliflozin/Empagliflozin)

These four drug classes have each shown a reduction in mortality and rate of hospitalisation in addition to guideline-recommended therapy at time of investigation. Therefore, all four drug classes should all be initiated at the time of first hospitalisation. In addition, loop diuretics should be administered to relieve congestion (McDonagh et al., 2021). These drugs have to be adapted constantly according to the clinical situation and the doses should be uptitrated to the maximal

tolerated dose. Therefore, even stable HF patients should consult a cardiologist at least in 6 - 12 months intervals.

In patients with HFrEF and LVEF ≤35% and QRS ≥130 ms device therapy with CRT-D (cardiac resynchronization therapy plus implantable cardioverter-defibrillator) is strongly recommended to further reduce mortality.

Under specific treatment, some individuals with heart failure may recover completely [e.g. those due to alcohol-induced cardiomyopathy (CMP), viral myocarditis, Takotsubo syndrome, peripartum cardiomyopathy (PPCM), or tachycardiomyopathy]. Other patients with LV systolic dysfunction may show a substantial or even complete recovery of LV systolic function after receiving drug and device therapy (McDonagh et al., 2022). In HF patients, treatment should be continued without limit even if cardiac function has fully recovered under treatment to avoid relapse.

Heart transplantation

Advanced heart failure, defined by “persistent symptoms despite maximal therapy” (McDonagh et al., 2022) resembles the end stage of chronic heart failure regardless of its aetiology. Due to rising numbers of patients with chronic heart failure and the ageing population worldwide the prevalence is increasing, however, still showing a poor prognosis with a 1-year mortality of 25 to 75% (Ammar et al., 2007; Rose et al., 2001; Xanthakis et al., 2016). Treatment options for patients suffering from advanced heart failure are scarce. Heart transplantation remains the gold standard in these cases in the absence of contraindications (McDonagh et al., 2022). The contraindications to heart transplantation include among others:

- active infection
- irreversible pulmonary hypertension
- malignancy with poor prognosis
- irreversible liver or kidney dysfunction
- severe obesity with a BMI > 35 kg/m²
- alcohol or drug abuse
- Impaired psychological stability or decreased compliance.

After transplantation the 1-year survival is up to 90% with a median survival of 12.5 years (Khush et al., 2019; Lund et al., 2013).

According to current guidelines and due to low donor numbers especially in Europe patient selection for heart transplantation is of paramount importance to ensure the best possible outcome (McDonagh et al., 2021) and the most ethical usage of a donor’s organ. Patients who might be eligible for heart transplantation need to be referred to specialized centers with nationally and internationally certified transplantation programs undergoing thorough, standardized and transparent diagnostic workup for assessing patient status, prognosis and comorbidities (McDonagh et al., 2021). Selection should always include an interdisciplinary approach with individual and shared decision making process.

After successful heart transplantation the individual patient needs close follow up and therapeutic guidance in specialized centers. The post-transplantation phase poses highly complex challenges with a risk to patient's quality of life and survival. These include among others acute complications in the perioperative setting, immune-modulatory therapy with the balance between organ rejection and infection, deterioration of target organ function such as liver and kidneys, arrhythmia or transplant vasculopathy (Potena, Zuckermann, Barberini, & Aliabadi-Zuckermann, 2018).

Left ventricular assist devices (LVADs)

In heart failure patients with severely impaired LV function, refractory symptoms and no transplant available the implantation of an LVAD is often a measure of last resort to unload the heart and stabilize circulation. In general, 3 different goals may be pursued with the implantation of an LVAD:

- bridge to transplantation
- bridge to recovery
- bridge to destination

The 1-year survival rate with an LVAD to date lies around 80%, after 5 years 50% of patients are still alive. Therefore, 70% of LVADs are implanted as destination therapy. The most frequent complications of LVADs include aortic insufficiency, thromb-embolism, gastro-intestinal bleeding due to inactivation of von Willebrand-factor and driveline infections. Infections have an incidence of approx. 10% per year. LVADs only allow for minor hemodynamic adaptations. Therefore, and for the high risk for complications pilots with LVAD should be declared unfit to fly without exception.

Heart failure with preserved ejection fraction (HFpEF)

In patients with HFpEF, risk factors like arterial hypertension, diabetes and obesity should be controlled since these factors may influence the course of the disease. In addition, treatment should be aimed at reducing symptoms of congestion with diuretics. Recent trials showed a significant reduction in the rate of hospitalization for worsening heart failure or cardiovascular death under treatment with the SGLT2-inhibitors Dapagliflozin as well as Empagliflozin (Anker et al., 2021; Solomon et al., 2022). Furthermore, the subgroup of individuals in the TOPCAT study recruited in the Americas had a significant reduction in the primary endpoint of CV death and HF hospitalization under treatment with Spironolactone (Pfeffer et al., 2015). Based on these results from randomized controlled trials the SGLT-2 inhibitors dapagliflozin or empagliflozin are recommended in patients with HFpEF and HFmrEF to reduce the risk for hospitalizations due to heart failure or cardiovascular death (McDonagh et al., 2023). In addition, spironolactone may be considered for the treatment of HFmrEF and HFpEF.

Prognosis

A cohort in Olmsted County observed over the years 2000 to 2010 showed 1-year and 5-year mortality rates after diagnosis of 20% and 53%, respectively, for all types of HF patients (Gerber et

al., 2015). This study was performed before the implementation of modern heart failure therapies with ARNI and SGLT-2 inhibitors. Hence, further improvement of survival in patients with HFrEF and HFmrEF can be expected under current guideline recommended therapy.

The principal causes of death in heart failure are circulatory decompensation due to pump failure, congestion with respiratory and/or renal failure as well as malignant arrhythmias. Therefore, patients with heart failure require frequent medical consultation for adaption of medical treatment and for monitoring the risk of malignant arrhythmias.

HFpEF is often considered to confer a better survival than HFrEF, but most observational studies show that this difference is negligible (Gerber et al., 2015; Tsao et al., 2018).

2. Conclusion and recommendations

- Diagnostic tests for the diagnosis of heart failure should include (McDonagh et al., 2021):
    - BNP/NT-proBNP,
    - 12-lead ECG,
    - Transthoracic echocardiography,
    - Chest radiography (X-ray),
    - Routine blood tests for comorbidities
- The four drug classes with proven prognostic benefit for HFrEF should all be initiated at the time of first hospitalisation and uptitrated thereafter:
    - ACE-Inhibitors/Angiotensin Receptor Neprilysin Inhibitors (ARNI)
    - Beta-blockers
    - Mineralocorticoid-Receptor Antagonists (MRA)
    - SGLT-2 Inhibitors (Dapagliflozin/Empagliflozin)
- In patients with HF treatment should be continued without limit even if cardiac function has fully recovered under treatment to avoid relapse.
- Modern treatment strategies significantly reduce morbidity and mortality, including arrhythmic events in HFrEF.
- In patients with HFpEF, treatment should be aimed at reducing symptoms of congestion with diuretics.
- Furthermore, the SGLT-2 inhibitors dapagliflozin or empagliflozin are recommended in patients with HFpEF and HFmrEF to reduce the risk for hospitalizations due to heart failure or cardiovascular death (Anker et al., 2021; Solomon et al., 2022).

3. Relevance for risk assessment of pilots and ATCOs

- Pilots or ATCOs with symptomatic heart failure (NYHA II-IV) should be declared unfit to fly or perform ATC work.
- Pilots/ATCOs with HFrEF (EF ≤40%) should be declared unfit to fly.
- Pilots/ATCOs with left ventricular assist devices (LVAD) should be declared unfit to fly.
- Any pilot/ATCO with confirmed heart failure should be made unfit to fly; return to flying duties may be possible but only in those with mild, asymptomatic disease (D'Arcy et al., 2019).

Further recommendations will be part of task 2

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2.10 Syncope

This document contains main findings concerning the state-of-the-art of “Syncope”, like pathophysiological background, clinical manifestations, diagnostic techniques etc.. But it does not contain comments concerning treatment options, because in this field risk assessment is of utmost importance for counseling Pilots and ATCOs.

1. What is new? - Main findings

- Clear cut differentiation between syncope of cardiac origin (high risk) and benign reflex or orthostatic causes.
- Cardiac MRI as modern diagnostic standard in the assessment of structural, inflammatory and ischemic heart disease.
- Implantable loop recorder as modern diagnostic standard in the diagnosis of arrhythmias.
- Downgrading of exercise treadmill test for its low predictive value (Knuuti et al., 2020; Zacharias et al., 2017).

Epidemiology

The incidence of first episodes of syncope in the general population is estimated to be 0.6% per year (Soteriades et al., 2002), accounting for approximately 6% of all hospital admissions in the United States (Costantino et al., 2016; Hayes, 1998). Notably, syncope has a high recurrence rate, with 21% of affected individuals reporting multiple events, and just under 1% reporting even three or more recurrences (Costantino et al., 2016). The age groups in which syncope most often occurs typically show two peaks - one at ages around 20 years, and one at 65 years and over. Syncope accounts for 25 - 37.4% of all medical emergencies in commercial airline flights (Peterson et al., 2013).

Classification and risk

The aetiologies of syncope are usually divided into reflex (neurally-mediated), cardiac, and orthostatic (hypotension), with the remainder being classified as „unknown“. The most common cause of syncope is reflex syncope, which includes vasovagal and situational syncope, the latter occurring upon micturition, anxiety, cough among others.

Orthostatic syncope is seen predominantly in older populations, often in combination with polypharmacy and is, therefore, not expected to be a common finding in the pilot population. The prevalence ranges from <5% in age groups below 50 years to 20% in those above the age of 70 (Rutan et al., 1992). Causal comorbidities in orthostatic hypotension include neurodegenerative disorders, heart failure, diabetes, and renal failure among others (Fedorowski et al., 2022). There is increasing evidence indicating that orthostatic hypotension is associated with higher mortality, risk of incident coronary heart disease, heart failure, as well as stroke and is an independent risk factor beyond associated concomitant and causal conditions (Fedorowski, Ricci, & Sutton, 2019; Ricci et al., 2015).

Cardiac syncope is per definition considered a high-risk syncope since it has an underlying cardiac cause. The underlying disorders include structural heart abnormalities, including different types of cardiomyopathies or heart valve diseases or conduction abnormalities resulting in brady- and tachyarrhythmias. For cardiac syncope an up to four-fold increased risk of death has been described (Ruwald et al., 2014).

High Risk Features

- New onset of chest discomfort, breathlessness, abdominal pain, or headache (Quinn, McDermott, Stiell, Kohn, & Wells, 2006),

- syncope during or shortly after exertion (Del Rosso et al., 2008),
- syncope when supine or sitting (Del Rosso et al., 2008),
- sudden onset palpitation directly followed by syncope (Del Rosso et al., 2008),
- no prior warning symptoms or short (<10s) prodrome (Quinn et al., 2006),
- history of structural or coronary artery disease (Quinn et al., 2006),
- family history of SCD at young age (Colman et al., 2009),
- Red flags in ECG: signs of ischemia, conduction abnormalities, abnormal repolarisation (long or short QTc), or indications for channelopathies (Brugada et al., 2020).

2. Conclusion and recommendations

Risk categories

Category 1

- Single episode, typical for a reflex or orthostatic mechanism precipitated by non-aviation situation.

Category 2

- Initial syncopal event without mitigating factors (provocation, prodrome, posture) **or**
- recurrent syncope with indication for mitigating factors **and**
- no high-risk feature present **and**
- potentially avoidable (non-aviation)

Category 3

- Loss of consciousness without prior warning **or**
- signs indicating cardiac cause (e.g. palpitations, chest pain, dyspnoea) **or**
- any high-risk feature present

Investigations according to risk category

Category 1

- Careful history taking, including eyewitness accounts **and**
- Physical examination **and**
- lying & standing BP (Schellong Test) **and**
- Carotid sinus massage (CSM) at age >40yrs. **and**
- resting and 24hr Holter ECG **and**
- blood gas analysis and standard blood test, including haematology, electrolytes, renal function, TSH, BNP

Category 2

- add echocardiography at rest **and**
- additional 24hr Holter ECGs may be required on clinical indication
- head-up tilt table test may be considered to confirm clinically suspected orthostatic

hypotension (Kulkarni, Mody, & Levine, 2020)
- if features of epilepsy or neurological cause are present, refer to neurology specialist

Category 3

- add stress echocardiography (no exercise ECG due to low predictive value) **and**
- implantable loop recorder
- cardiac MRI may be required on clinical indication
- electrophysiological studies may be required on clinical indication

3. Relevance for risk assessment of pilots and ATCOs

There is no new evidence regarding pathophysiology or treatment of syncope. However, the current version of EASA Medical Requirements lack a clear risk stratification. This has to be the main focus of our tender. Furthermore, modern diagnostic tools for high risk syncope such as MRI, implantable loop recorders, stress echocardiography, and electrophysiological studies are not mentioned in the current version of EASA Medical Requirements.

The UK Civil Aviation Authority has recently published a new regulators guidance for syncope in commercial pilots (Anderton, Mitchell, & SS, 2021) suggesting the period of grounding and OML under different circumstances.

Further description will be provided in Task 2.

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2.11 Modern concepts of cardiovascular risk screening and use of these concepts for prevention and treatment of risk factors

This document describes the newest guidelines for the assessment and management of cardiovascular risk. New class 1 and class 2 recommendations adopted from the most recent ESC guidelines are listed.

The impact of these guidelines on current clinical practice is being addressed. New ESC risk calculators are described and they are used in the updated advice for the Aeromedical Requirements. These risk assessment tools have shown to improve the accuracy in predicting future cardiovascular events in adults with cardiovascular risk factors.

Probably even better performing than the ESC risk calculators is the coronary artery calcium score (CACS). This new diagnostic tool uses CT-scanning to assess the amount of coronary calcium. With the CACS, cardiovascular risk can be determined, as it is shown that with increased calcification cardiovascular risk increases. New biomarkers like Lp(a) are currently being used to assess risk as high levels of Lp(a) are associated with an increased cardiovascular risk independent from other risk factors. Attention is given to non-traditional cardiovascular risk factors that should be taken into account. Management of risk factors and recommendations about prevention goals are described.

1. What is new? - Main findings

Although important advances have been made in the diagnosis and treatment of patients with cardiovascular disease, concern exists about unfavourable changes in cardiovascular risk profiles in the general population. Therefore, preventive medicine has gained much attention, because only with better prevention it will be possible to lower the burden of cardiovascular disease and eventually lower global costs of healthcare.

In 2021 a working group of the ESC has updated the European guidelines on cardiovascular disease prevention in clinical practice (Visseren et al., 2021). In these guidelines important evidence-based recommendations can be found about how cardiovascular prevention should be applied in apparently healthy persons but also in medium and high-risk individuals.

In whom should we assess cardiovascular risk?

Risk assessment and screening for cardiovascular disease (CVD) can be done opportunistically or systematically. Opportunistic screening, which means screening without a predefined strategy, is done when a person presents for some other reason. Systematic screening can be done in the general population as part of a formal screening program, with call and recall of patients, or in targeted subpopulations such as subjects with type 2 DM, or a family history of premature CVD. Systematic screening results in improvements in risk factors, but has no effect on CVD outcomes. Opportunistic screening for ASCVD risk factors, such as blood pressure or lipids, is effective at increasing detection rates and is recommended, although a beneficial effect on clinical outcome is uncertain. Systematic CVD risk assessment in the general population (adult men >40 and women >50 years of age) with no known CV risk factors appears not cost-effective in reducing subsequent vascular events and premature death, at least in short-term follow-up, but does increase detection of CV risk factors. Risk assessment is not a one-time event; it should be repeated, for example, every 5 years, although there are no empirical data to guide intervals.

Traditional and non-traditional risk factors for the development of ASCVD

It is important to realize that apart from the common risk factors, several other non-traditional risk factors may exist that have to be taken into account when evaluating cardiovascular risk.

The following list summarizes traditional and non-traditional risk factors for the development of atherosclerotic cardiovascular disease (ASCVD).

1. Main causal and modifiable risk factors for ASCVD

- Apolipoprotein-B-containing lipoproteins (mainly consisting of LDL-cholesterol) (Boren et al., 2020)
- High blood pressure
- Cigarette smoking
- Diabetes mellitus
- Adiposity (increases CVD risk via both major conventional risk factors and other mechanisms).

2. Other risk factors and risk modifiers

- Psychosocial factors
- Ethnicity
- Family history
- Genetics
- Socioeconomic determinants
- Environmental exposure
- Body composition (BMI and waist circumference)

3. **Clinical conditions associated with increased risk**
   - Chronic kidney disease (CKD)
   - Atrial fibrillation (AF is associated with increased risk of death, CVD and kidney disease)
   - Heart failure
   - Cancer
   - COPD
   - Inflammatory conditions (rheumatoid arthritis, psoriasis, etc.)
   - Infections (HIV, influenza, periodontitis)
   - Migraine
   - Sleep disorders and obstructive sleep apnea
   - Mental disorders
   - Non-alcoholic fatty liver disease
   - Sex-specific conditions (pre-eclampsia, pregnancy-related hypertension, gestational DM, polycystic ovary syndrome, premature menopause, erectile dysfunction)

Use of new cardiovascular risk-score tools (SCORE2, SCORE2-OP)

In the updated ESC guidelines on cardiovascular disease prevention in clinical practice new risk score tools have been adopted as the new standards of risk calculation (SCORE2 and SCORE2-OP) (SCOR2-OP working group & E. S. C. C. r. collaboration, 2021; SCORE2 working group & E. S. C. C. r. collaboration, 2021). For diabetic patients separate risk scores are available (ADVANCE an UKPDS) (Kengne et al., 2011; Stevens, Kothari, Adler, & Stratton, 2001). These scores date from before 2011 and, therefore, the use of these scores has been cautioned by the guideline committee.

In the 2016 ESC prevention guidelines the Systemic Coronary Risk Estimation (SCORE) algorithm was used to estimate 10-year risk of CVD death. However, CVD morbidity (non-fatal myocardial infarction, non-fatal stroke) combined with CVD mortality better reflects the total burden of ASCVD.

The updated SCORE algorithm (SCORE2) used in these guidelines estimates an individual's 10-year risk of fatal and non-fatal CVD events (myocardial infarction, stroke) in apparently healthy people aged 40-69 years with risk factors that are untreated or have been stable for several years.

In the 50-69-year age range, a 10-year CVD mortality risk threshold of 5% estimated with the previously used SCORE algorithm corresponds, on average, to a 10-year fatal and non-fatal CVD risk

threshold of 10% estimated with SCORE2, as approximately the same number of people are above the risk threshold and would qualify for treatment.

Several specific considerations apply to CVD risk estimation in older people. First, the gradient of the relationship between classical risk factors, such as lipids and BP, with CVD risk attenuates with age. Second, CVD-free survival dissociates from overall survival progressively with increasing age, because risk for non-CVD mortality increases ('competing risk'). For these reasons, traditional risk models that do not take into account the competing risk of non-CVD mortality, tend to overestimate the actual 10-year risk of CVD, and hence overestimate the potential benefit of treatment. Therefore, the SCORE2-OP algorithm estimates 5-year and 10-year fatal and nonfatal CVD events (myocardial infarction, stroke) adjusted for competing risks in apparently healthy people aged >70 years.

In SCORE2 and SCORE2-OP the following variables are used for risk estimation: age, sex, systolic blood pressure, smoking behaviour and non-HDL cholesterol levels. In previous risk calculators, total cholesterol was used. Non-HDL is now being used because it is a better predictor of cardiovascular risk than LDL-cholesterol. Non-HDL represents all atherosclerotic lipids like VLDL, VLDL-remnants, IDL, LDL and Lp(a). Age is the major driver of CVD risk. Women below 50 years and men below 40 years of age are almost invariably at low 10-year CVD risk, but may have unfavourable modifiable risk factors that sharply increase their longer-term CVD risk. Conversely, men over 65 years and women over 75 years of age are almost always at high 10-year CVD risk. Only between the ages of 55 and 75 years in women and 40 and 65 years in men does the 10-year CVD risk vary around commonly used thresholds for intervention. The age categories <50, 50-69, and >70 years should, therefore, be used with common sense and flexibility.

When using the new risk assessment tools, first the baseline risk has to be determined. This baseline cardiovascular risk varies considerably between European countries. Therefore, European countries have been divided into four categories: low-risk, moderate-risk, high-risk and very-high risk. When

using the risk calculators, first the country-specific risk level must be determined before entering the clinical variables in the corresponding risk chart.

Importantly, risk categories do not 'automatically' translate into recommendations for starting drug treatment. In all age groups, consideration of risk modifiers, lifetime CVD risk, treatment benefit, comorbidities, frailty, and patient preferences may further guide treatment decisions. Also, many patients can move themselves towards a lower risk category without taking drugs just by stopping smoking. Finally, persons >70 years old may be at very high risk whilst being at target SBP, whereas primary prevention with lipid-lowering drugs in older persons is a Class IIb recommendation ("might be considered").

New cardiovascular risk factors

1. Coronary artery calcium score.

Coronary artery calcium (CAC) scoring can reclassify CVD risk upwards and downwards in addition to conventional risk factors, and may thus be considered in men and women with calculated risks around decision thresholds. Availability and cost effectiveness of large-scale CAC scanning must, however, be considered in a locoregional context. If CAC is detected, its extent should be compared with what would be expected for a patient of the same sex and age. Higher-than-expected CAC increases the person's calculated risk, whereas absent or lower-than-expected CAC is associated with lower than calculated risk. CAC scoring does not provide direct information on total plaque burden or stenosis severity, and can be low or even zero in middle-aged patients with soft non-calcified plaque. Very recently, it was demonstrated that the CAC score outperformed a polygenetic risk score in the prediction of future cardiovascular events. The coronary artery calcium score but not the polygenic risk score significantly improved risk discrimination and risk reclassification for CHD when added to traditional risk factors (Khan et al., 2023).

2. Lipoprotein (a)

Lipoprotein (a), or Lp(a), is an important lipoprotein contributing to atherosclerotic cardiovascular disease (ASCVD). Epidemiologic and genetic studies involving hundreds of thousands of individuals strongly support a causal and continuous association between Lp(a) concentration and cardiovascular outcomes in different ethnicities. High Lp(a) is associated with both microcalcification and macrocalcification of the aortic valve. Current findings do not support Lp(a) as a risk factor for venous thrombotic events and impaired fibrinolysis. Very low Lp(a) levels may associate with increased risk of diabetes mellitus meriting further study. Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to the oxidized phospholipids carried by Lp(a).

The association between Lp(a) and major cardiovascular disease (CVD) outcomes is continuous. The risk for major adverse cardiovascular (CV) events increases with increasingly higher Lp(a). Elevated Lp(a) is a risk factor even at very low low-density lipoprotein (LDL-C) concentration.

The presence of other known CV risk factors, (e.g., high age, male sex, hypertension, diabetes, elevated LDL-C) does not significantly influence the risk of coronary heart disease associated with high Lp(a).

An individual's Lp(a) level is strongly influenced by several factors. Lp(a) level is 80% to 90% genetically determined by variation in the LP(a) gene. Furthermore, ethnicity and nongenetic factors including chronic kidney disease and hepatic impairment influence LP(a) levels.

The European Atherosclerosis Society (EAS) published a 2022 consensus statement on Lp(a) and ASCVD and aortic stenosis (Kronenberg et al., 2022) with the following recommendations regarding Lp(a) testing:

- Lp(a) should be measured at least once in all adults to identify those with high CV risk.
- Screening is recommended in youth with a history of stroke, family history of high Lp(a), or premature ASCVD without other identifiable risk factors.
- Family cascade screening for high Lp(a) is recommended in the settings of familial hypercholesterolemia, family history of (very) high Lp(a), and family history of ASCVD.

The Consensus panel recommendations for managing high Lp(a) concentration include the following:

- Early and aggressive management of modifiable CV risk factors
- Lipoprotein apheresis can be considered in patients with very high Lp(a) and progressive CVD, despite optimally managed CV risk factors
- Aspirin and niacin are not recommended for lowering Lp(a)

Currently, there are no Lp(a)-specific lowering drug therapies that are commercially available. Whether Lp(a) lowering reverses accelerated atherogenesis and AVS progression and reduces cardiovascular events has to be tested. The extent of Lp(a) lowering required for clinical benefit is also not known. Several trials are currently being conducted to assess the clinical effects of Lp(a) lowering drugs. Pelacarsen: antisense oligonucleotide therapy with monthly dosing. Outcome results from phase 3 study are expected in 2025. Olpasiran: small-interfering RNA (siRNA) technology. Longer acting. Phase 2 dose-finding study recently completed. SLN360: siRNA technology. Longer acting. Phase 1 finished.

How to use the ESC risk calculators.

With table 7 the outcome of the risk assessment calculators can be used to determine the individual, age-related risk level and the treatment advice accordingly. In table 8 the actual treatment goals are summarized.

Table 7: Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently

CVD risk	<50 years	50-69 years	≥ 70 years	recommendation
Low-to-moderate	<2,5%	<5%	<7,5%	Risk factor treatment generally not recommended
High	2,5 to <7,5%	5 to <10%	7,5 to <15%	Risk factor treatment should be considered
Very high	≥7,5%	≥10%	≥15%	Risk factor treatment generally recommended

Table 8: Treatment goals for different patient categories (Visseren et al., 2021).

Patient category	Prevention goals (STEP 1)	Intensified/additional prevention goals (depending on 10-year (residual) risk and/or estimated lifetime benefit, comorbidities and patient preference (STEP 2)
Apparently healthy persons	For BP and lipids: initiation of drug treatment based on CVD risk assessment or SBP >160 mmHg	
<50 years	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated LDL-C <2.6 mmol/L (100 mg/dL)	SBP <130 mmHg if tolerated LDL-C <1.8 mmol/L (70 mg/dL) and ≥50% reduction in high-risk patients: LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% in very-high-risk patients
50 - 69 years	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated LDL-C <2.6 mmol/L (100 mg/dL)	SBP <130 mmHg if tolerated LDL-C <1.8 mmol/L (70 mg/dL) and ≥50% reduction in high-risk patients LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% in very-high-risk patients
≥70 years	Stop smoking and lifestyle optimization SBP <140 mmHg if tolerated LDL-C <2.6 mmol/L (100 mg/dL)	
Patients with CKD	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated LDL-C <2.6 mmol/L (100 mg/dL) and ≥50% LDL-C reduction Otherwise according to ASCVD and DM history	 LDL-C <1.8 mmol/L (70 mg/dL) in high-risk patients and <1.4 mmol/L (55 mg/dL) in very-high risk patients
Patients with FH	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated LDL-C <2.6 mmol/L (100 mg/dL) and ≥50% LDL-C reduction Otherwise according to ASCVD and DM history	 LDL-C <1.8 mmol/L (70 mg/dL) in high-risk patients and <1.4 mmol/L (55 mg/dL) in very-high risk patients
People with type 2 DM		
Well-controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Stop smoking and lifestyle optimization	
Without established ASCVD or severe TOD	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated LDL-C <2.6 mmol/L (100 mg/dL) HbA1c <53 mmol/mol (7.0%)	SBP <130 mmHg if tolerated LDL-C <1.8 mmol/L (70 mg/dL) and ≥50% reduction SGLT2 inhibitor or GLP-1RA
With established ASCVD and/or severe TOD	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated LDL-C <1.8 mmol/L (70 mg/dL) HbA1c <64 mmol/mol (8.0%) SGLT2 inhibitor or GLP1-RA CVD: antiplatelet therapy	SBP <130 mmHg if tolerated LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% reduction SGLT2 inhibitor or GLP-1RA if not already on May additionally consider novel upcoming treatments: DAPT, dual pathway inhibition, colchicine, icosapent ethyl (EPA)
Patients with established ASCVD	Stop smoking and lifestyle optimization SBP <140 down to 130 mmHg if tolerated Intensive oral lipid-lowering therapy aiming at ≥50% LDL-C reduction and LDL-C <1.8 mmol/L (70 mg/dL) Antiplatelet therapy	SBP <130 mmHg if tolerated LDL-C <1.4 mmol/L (55 mg/dL) May additionally consider novel upcoming treatments: DAPT, dual pathway inhibition, colchicine, icosapent ethyl (EPA)

2. Conclusion and recommendations

The new, updated recommendations can be found in the newest paper on the ESC guidelines on cardiovascular prevention (Visseren et al., 2021). The following summarize the newest recommendations for global management of risk factors and for the management of risk factors on the individual level. It can be concluded that the use of the newest risk-assessment calculators improves our accuracy in assessing cardiovascular risk and enables us to make better predictions about the occurrence of future cardiovascular events at an individual level. At the same time, new cardiovascular risk factors like LP(a) and non-traditional risk factors like inflammatory diseases have to be taken into account. And finally, the coronary calcium score can help in further refining risk estimates and guide individuals in decisions about medical therapy like statins.

Recommendations for global CVD risk assessment.

1. Systematic global CVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, FH, CVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing CVD risk) (Class Ic).
2. Systematic or opportunistic CV risk assessment in the general population in men >40 years of age and in women >50 years of age or postmenopausal with no known ASCVD risk factors may be considered (Class IIb, LOE C).
3. In those individuals who have undergone CVD risk assessment in the context of opportunistic screening, a repetition of screening after 5 years (or sooner if risk was close to treatment thresholds) may be considered (Class IIb, LOE C).
4. Opportunistic screening of blood pressure (BP) in adults at risk for the development of hypertension, such as those who are overweight or with a known family history of hypertension, should be considered (Class IIa, LOE B).
5. Systematic CVD risk assessment in men <40 years of age and women <50 years of age with no known CV risk factors is not recommended (Class III, LOE C)

Risk factors and clinical conditions

A. New Class I recommendations

1. In apparently healthy people <70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders, estimation of 10-year fatal and non-fatal CVD risk with SCORE2 is recommended.
2. In apparently healthy people >70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorder, estimation of 10-year fatal and non-fatal CVD risk with SCORE2-OP is recommended.
3. Patients with established ASCVD and/or DM and/or moderate-to-severe renal disease and/or genetic/rarer lipid or BP disorders are to be considered at high or very high CVD risk.
4. A stepwise treatment-intensification approach aiming at intensive risk factor treatment is recommended for apparently healthy people at high or very high ASCVD risk, as well as patients

with established ASCVD and/or DM, with consideration of CVD risk, treatment benefit of risk factors, risk modifiers, comorbidities, and patient preferences.
5. Treatment of ASCVD risk factors is recommended in apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at very high CVD risk (SCORE2 >7.5% for age under 50; SCORE2 >10% for age 50-69; SCORE2-OP >15% for age >70).
6. An informed discussion about CVD risk and treatment benefits tailored to the needs of a patient is recommended.
7. It is recommended that mental disorders with either significant functional impairment or decreased use of healthcare systems be considered as influencing.

B. New Class IIa recommendations

1. Treatment of ASCVD risk factors should be considered in apparently healthy people without DM, CKD, genetic/rarer lipid, or BP disorders who are at high CVD risk (SCORE2 2.5 to <7.5% for age under 50; SCORE2 5 to <10% for age 5069; SCORE2-OP 7.5 to <15% for age >70 years), taking ASCVD risk modifiers, lifetime risk and treatment benefit, and patient preferences into account.
2. In apparently healthy people, after estimation of 10-year fatal and non-fatal CVD risk, lifetime risk and treatment benefit, risk modifiers, frailty, polypharmacy, and patient preferences should be considered.
3. Presence of migraine with aura should be considered in CVD risk assessment.
4. Assessment of CVD risk should be considered in men with erectile dysfunction (ED).

C. New Class IIb recommendations

1. In women with a history of premature or stillbirth, periodic screening for hypertension and DM may be considered.
2. Assessment of total CVD risk may be considered in adults with chronic inflammatory conditions.
3. Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura.

Risk factors and interventions at the individual level

A. New Class I recommendations

1. It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.
2. It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.
3. It is recommended to restrict alcohol consumption to a maximum of 100 g per week.
4. It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.
5. Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.
6. Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.

7. In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a >50% reduction of LDL-C vs. baseline is recommended.
8. For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.
9. In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD), intensive lipid-lowering therapy, ultimately aiming at >50% LDL-C reduction and an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.
10. In patients with type 2 DM >40 years of age at high risk, lipid-lowering treatment with an ultimate LDL-C goal of >50% LDL-C reduction and an LDL-C of <1.8 mmol/L (70 mg/dL) is recommended.
11. It is recommended that the first objective of treatment is to lower BP to <140/90 mmHg in all patients, and that subsequent BP targets are tailored to age and specific comorbidities.
12. In treated patients aged 18-69 years, it is recommended that SBP should ultimately be lowered to a target range of 120-130 mmHg in most patients.
13. In treated patients aged >70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.
14. In all treated patients, DBP is recommended to be lowered to <80 mmHg.
15. In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes.
16. In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve CVD and/or cardiorenal outcomes.
17. In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.
18. Participation in a medically supervised, structured, comprehensive, multidisciplinary EBCR and prevention program for patients after ASCVD events and/or revascularization, and for patients with HF (mainly HFrEF), is recommended to improve patient outcomes.

B. New Class IIa recommendations

1. Lifestyle interventions, such as group or individual education, behavior-change techniques, telephone counselling, and use of consumer-based wearable activity trackers, should be considered to increase PA participation.
2. New Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.
3. ASCVD patients with stress should be considered for referral to psychotherapeutic stress management to improve CVD outcomes and reduce stress symptoms.
4. Patients with CHD and moderate-to-severe major depression should be considered for antidepressive treatment with an SSRI.
5. New An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and LDL-C reduction of >50% from baseline should be considered in apparently healthy persons <70 years at very high risk.
6. An ultimate LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of >50% from baseline should be considered in apparently healthy persons <70 years at high risk.
7. For those motivated to try, considerable weight loss with use of low-calorie diets followed by food reintroduction and weight maintenance phases early after diagnosis can lead to DM remission and should be considered.

C. New Class IIa recommendations

1. In patients with type 2 DM and TOD, the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits may be considered to reduce future CVD and total mortality.
2. For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.
3. In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) may be considered in combination with a statin.
4. Initiation of statin treatment for primary prevention in older people aged >70 may be considered, if at high risk or above.
5. Statin therapy may be considered in persons aged <_40 years with type 1 or type 2 DM with evidence of TOD and/or an LDL-C level >2.6 mmol/L (100 mg/dL), as long as pregnancy is not being planned.
6. In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.
7. Home-based CR, telehealth, and mHealth interventions may be considered to increase patient participation and long-term adherence to healthy behaviors.

3. Relevance for the risk assessment in pilots and ATCO's

1. Apparently healthy pilots with no cardiovascular (CV) risk factors

Systematic CVD risk assessment in male pilots/ATCO's <40 years of age and female pilots/ATCO's <50 years of age with no known CV risk factors is not recommended (Class III, LOE C).

Systematic (or opportunistic) CV risk assessment in male pilots/ATCO's >40 years of age and female pilots/ATCO's >50 years of age may be considered (Class IIb).

2. Apparently healthy pilots/ATCO's with one or more CV risk factors

In pilots and ATCO's >40 and <70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders, estimation of 10-year fatal and non-fatal CVD risk with SCORE2 is recommended. For pilots >70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorder, estimation of 10-year fatal and non-fatal CVD risk with SCORE2-OP is recommended. Therefore, in these groups systolic blood pressure, smoking habits and non-HDL cholesterol has to be taken into account.

Treatment of ASCVD risk factors is recommended in apparently healthy pilots and ATCO's without DM, CKD, genetic/rarer lipid or BP disorders who are at very high CVD risk (SCORE2 >7.5% for age under 50; SCORE2 >10% for age 50-69; SCORE2-OP >15% for age >70).

Coronary Artery Calcium (CAC) Score might be used to improve risk assessment of pilots and ATCO's with increased cardiovascular risk. The use of the CAC score should depend on clinical judgement and local availability. An abnormal CAC scan should lead to intensification of treatment of modifiable risk factors. Dependent on the results of the CAC score, it could be decided to perform non-invasive testing like CT coronary angiography.

Measurement of Lp(a) may be considered as increased values should prompt early and aggressive management of modifying risk factors.

It is recommended to measure Lp(a) in young individuals with a history of stroke, a family history of high Lp(a), or premature ASCVD without other identifiable risk factors.

When determining the level of risk, non-traditional CV risk factors should also be taken in to account.

3. Pilots/ATCO's with known cardiovascular disease

Pilots and ATCO's with established ASCVD and/or DM and/or moderate-to-severe renal disease and/or genetic/rarer lipid or BP disorders are to be considered at high or very high CVD risk.

A stepwise treatment-intensification approach aiming at intensive risk factor treatment is recommended in pilots and ATCO's with established ASCVD and/or DM, with consideration of CVD risk, treatment benefit of risk factors, risk modifiers, comorbidities, and patient preferences.

Further recommendations should be formulated as part of task 2.

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3 In-flight conditions which influence the status of a cardiovascular disease and implanted devices

This document describes effects of in-flight conditions on cardiovascular implanted devices (e.g., peacemaker or ICD) and their influence on the crew as well as the relevance of different environmental factors. For identification of relevant literature and evidence, a systematic PubMed (https://pubmed.ncbi.nlm.nih.gov/) query was generated and results analyzed concerning the relevance of the retrieved data. Overall, there is scarce evidence from the recent five years on this topic which are useful for this task.

What factors can influence cardiovascular implanted devices?

Multiple factors can affect cardiovascular health during air travel, including decreased atmospheric pressure, decreased humidity, gas expansion, prolonged immobility, and increased physical and emotional stress [6]. The aircraft cabin significantly differs from the atmosphere at the ground. It is well known, that the pressure decreases equilibrating to a height of approx. 1,800-2,400m or 5,000 to 8,000 ft, respectively (Martin-Gill, Doyle, & Yealy, 2018). Also, relative humidity decreases to as low as 10% but temperature is usually stable around 20-30 degrees Celsius (Martin-Gill et al., 2018). Vibration and electromagnetic fields of aircraft equipment may also have an influence, especially on electronic devices. Vice versa, medical devices may have an influence on aviation electronics.

Evidence

To identify relevant evidence of the last 5 years, a systematic and standardized PubMed query (https://pubmed.ncbi.nlm.nih.gov/) was generated. The used search strings were as follows:

(pilot OR aircrew OR passenger OR patient) AND (humidity OR "dry air" OR climatization OR temperature OR vibration OR pressure OR radiation OR "oxygen saturation" OR altitude) AND (cardiovascular OR pacemaker OR myocardial OR defibrillator OR ICD) AND (aircraft OR airplane) AND (Date=2018 to 2023)

This specific search identifies the relevant papers/evidence in the PubMed data base and also limits the results for the last 5 years. By the query, a total of 32 papers were directly identified in PubMed (table 1). Additionally, the references of the papers identified were also screened to relevant literature. Also, specific searches for the topics of interest were performed. All additional papers were screened to relevant evidence in the field and integrated in this document.

For analysis, the following medical devices and their relevance were analysed in the literature:

- Pacemakers
- ICDs

1. What is new? - Main findings

Hypoxia

Certain physical and physiological changes occur in the atmospheric levels where flight and space activities take place. Air pressure decreases with increasing altitude and the partial pressure of O_2 decreases in parallel with the atmospheric pressure drop and creates hypoxia in the flight crew and in the passengers. Normal oxygen saturation in the blood is 90-94% during flight.

In case of acute hypobaric hypoxia, blood is redistributed to the brain and the heart, whereas blood supply to internal organs, such as kidney and skin is reduced. Peripheral cyanosis can be observed on the fingertips and the lips during hypoxia-induced blood redistribution. Tachycardia develops, but the stroke volume does not change. The coronary blood flow increases in parallel with the rise of cardiac output; however, the presence of severe hypoxia leads to myocardial depression (Ercan, 2021).

However, no evidence was found showing an influence of hypoxia on medical devices.

Noise

Epidemiological studies have provided evidence that traffic noise exposure is linked to cardiovascular diseases such as arterial hypertension, myocardial infarction, and stroke. Noise is a non-specific stressor that activates the autonomous nervous system and endocrine signalling. According to the noise reaction model introduced by Babisch and colleagues, chronic low levels of noise can cause so-called nonauditory effects, such as disturbances of activity, sleep, and communication, which can trigger a number of emotional responses, including annoyance and subsequent stress. Chronic stress in turn is associated with cardiovascular risk factors, comprising increased blood pressure and dyslipidemia, increased blood viscosity and blood glucose, and activation of blood clotting factors, in animal models and humans (Münzel et al., 2018).

Whereas acute and chronic noise can have a significant influence on the human body, no evidence was found showing an influence on medical implanted devices.

Electromagnetic fields

Electromagnetic field is the term used to describe combined electric and magnetic fields. Electric fields exist whenever electric charges are present, i.e., whenever electricity or electrical equipment is in use. A magnetic field is produced when electrical current flows in a conductor with magnetic field lines perpendicular to the current flow. Electromagnetic interference can occur as a result of conducted or radiated electromagnetic energy [9]. Modern CIEDs (Cardiac Implantable Electronic Devices) utilize shielding, filters, and bipolar leads to mitigate electromagnetic interference (EMI) (Beinart & Nazarian, 2013).

CIEDs generators are typically shielded by hermetically sealed titanium or stainless-steel cases. Nano-magnetic insulation has recently been utilized in lead design to improve shielding from radiofrequency and time varying gradient magnetic fields. Additionally, body tissues add to the shielding of leads because leads placed in a conductive medium are poor antennas. The extent of CIEDs shielding vary depending upon the manufacturer and can impact product weight, handling, and dimensions (Beinart & Nazarian, 2013).

In addition to the EMI characteristics, programming of CIEDs is a significant determinant of device response to EMI. During inhibited pacing modes (AAI, VVI, or DDI), EMI results in pacing inhibition and bradycardia or asystole. Whereas in tracking mode (DDD), preferential sensing of EMI in the atrial channel (which often occurs due to higher programmed sensitivity) could result in a) increased rate ventricular pacing, or b) atrial arrhythmia detection and CIEDs “mode-switch” to inhibited pacing (AAI, VVI, or DDI) (Beinart & Nazarian, 2013).

Although not relevant for the in-flight phase, there is some data on problems with medical implanted devices at airports. So far, several studies have reported no significant interference between ICD/pacemakers and security devices, including handheld metal detectors and airplane devices [6].

Evidence from helicopters

There is scarce or no relevant evidence from the recent years on this topic. Data is usually old and well known. As an example, electromagnetic fields in helicopters may cause dysfunction which was published already several decades ago (French & Tillman, 1989).

Evidence from cars

However, recent relevant literature concerning aircraft and devices is not available – except some data from cars. Electric cars are increasingly used for public and private transportation and represent possible sources of electromagnetic interference (EMI). Potential implications for patients with cardiac implantable electronic devices (CIED) range from unnecessary driving restrictions to life-threatening device malfunction [5]. In this study, no change in device function or programming was seen in this cohort which is representative of contemporary CIED devices. The largest electromagnetic field detected was along the charging cable during high current charging (116.5 µT). The field strength in the cabin was lower (2.1-3.6 µT). At least, electric cars produce electromagnetic fields; however, they did not affect CIED function or programming in our cohort. Driving and charging of electric cars is likely safe for patients with CIEDs (Lennerz et al., 2020).

Pressure

Most commercial aircraft fly at an elevation somewhere between 22,000 and 44,000 feet above sea level (cruising altitude), with a corresponding decline in partial pressure of inspired oxygen of approximately 4 mm Hg per 1,000 feet above sea level (Hammadah et al., 2017).

It has been suggested that hypoxia induced by high altitude could influence the stimulation threshold of pacemakers; however, a study consisting of 30 patients with implantable pacemakers exposed to an altitude of 4,000 meters above sea level simulated by exposure to a hypobaric chamber demonstrated no change of the stimulation threshold (Hammadah et al., 2017; Weilenmann et al., 2000).

Vibration

There is scarce or no relevant evidence from the recent years on this topic. Data is usually old and well known. As an example, vibration in helicopters may cause dysfunction which was published already several decades ago (French & Tillman, 1989).

Activity-sensing rate-adaptive pacemakers and ICDs could be also affected by the vibrations associated with air travel, particularly during take-off and landing. Device reprogramming to attenuate or disable the rate-response function prior to flying or applying a magnet to disable the rate-adaptive function of a pacemaker could address this concern if needed (Hammadah et al., 2017; Smith et al., 2010).

2. Conclusion and recommendations

There may be some differences between different models of PMs or ICDs of different manufacturers. Also, there may be differences in the certification by the manufacturer for specific devices. The decision should, therefore, being based on the individual case. The overall risk of clinically significant adverse events during flight in recipients of CIEDs or ICDs is very low, although theoretically possible.

3. Relevance for risk assessment of pilots and ATCOs

In contrast to pilots, ATCOs are not exposed to changes in pressure, temperature, humidity or vibrations. However, electromagnetic influences have the greatest effect in ATCOs.

There are no specific studies for ATCOs and medical devices. However, it may be accepted that the risk of exposure for pilots and ATCOs in terms of electromagnetic fields is approximately the same.

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4. Coronary artery disease (CAD)

4.1. Chest pain, myocardial ischaemia and indications for coronary artery revascularization

This document contains an analysis of actual diagnostic measures and decision strategies which are applied in the evaluation of chest pain, of suspicion of myocardial ischemia, of the severity of coronary lesions etc. In relation to the outcomes of the investigations, the question raises which therapeutic options should be undertaken. The therapeutic options are also mentioned in this document, without going into details. For example, a detailed list of medications used for angina or a detailed list about cardiovascular risk factors etc. are not listed here.

1. What is new? – Main findings

What is the state-of-the-art analysis for the assessment of chest pain, of suspected myocardial ischemia, of the severity of coronary lesions etc., and what are the therapeutic consequences of the outcoming results?

Chest pain is a common reason for presentation in an emergency department, in the practice of a general practitioner or in presence of a cardiologist. Chest pain can be of cardiac origin (mainly myocardial ischemia), or it can correspond to a symptom not related to any cardiovascular disease. Patients presenting with chest pain belong either to the situation where no cardiological disease/findings are known, or to the situation with already known/ proven coronary artery disease (chronic coronary syndrome). There are various, specific approaches to the many different situations of patients with chest pain. If chest pain can be referred to myocardial ischemia, then the question arises which treatment must be chosen: Medical treatment, invasive treatment either by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)?

The targets of this report are, a) to distinguish chest pain related to myocardial ischemia from other causes of chest pain, b) to have an overview about the procedures which shall be undertaken when there is a suspicion of myocardial ischemia and c) to summarize which therapeutic procedures shall be undertaken, when it is known that the patient/pilot/ATCO has proven coronary artery disease (CAD) and the chest pain is caused by myocardial ischemia.

In the first part of this document several citations are derived from the following textbook: "The ESC Textbook of Cardiovascular Medicine (third edition)" (from Camm AJ, Lüscher TF, Maurer G and Serruys PW), published in July 2018 (a few chapters have been updated in 2020) (*ESC CardioMed*, 2018):

Crea F, Lanza GA (Version April 2020). Title: Myocardial ischaemia: definition and causes.

"Myocardial ischaemia is caused by a mismatch between myocardial oxygen demand and myocardial blood flow supply, which results in reversible myocardial suffering and, when prolonged, in irreversible injury. The main causes of myocardial ischaemia include (1) atherosclerotic flow-limiting stenoses which are responsible for chronic stable angina; (2) coronary thrombus superimposed on an atherosclerotic plaque which is responsible for acute coronary syndromes; (3) coronary artery spasm which is responsible for vasospastic angina; and (4) coronary microvascular dysfunction which is responsible for microvascular angina and can also contribute to myocardial ischaemia in various clinical settings. Functional alterations (thrombus, spasm, and microvascular dysfunction) may act on angiographically normal coronary arteries or arteries presenting stenoses of variable severity. Less frequent coronary causes of myocardial ischaemia include spontaneous coronary artery dissection, myocardial bridge, coronary thromboembolism, an abnormal origin of the right or left coronary artery, and ascending aorta dissection involving coronary ostia. Finally, myocardial ischaemia can occur in the presence of severe left ventricular hypertrophy as observed in aortic stenosis and hypertrophic cardiomyopathy."

Bax JJ (Version July 2018). Title: Coronary artery disease: from atherosclerosis to obstructive disease, inducible ischaemia, and the ischaemic cascade.

"The early phase of atherosclerotic coronary artery disease is often asymptomatic (and anatomical imaging can be used to detect/exclude coronary atherosclerosis), whereas with progression of

atherosclerotic disease, symptoms occur related to myocardial ischaemia. Non-invasive imaging can facilitate in the detection of both early (asymptomatic) and more advanced (symptomatic, ischaemic) coronary artery disease. The pathophysiological cascade of cardiac abnormalities that occur once ischaemia is induced is referred to as the ischaemic cascade. The ischaemic cascade consists of chronological development of perfusion abnormalities, followed by diastolic dysfunction, then systolic dysfunction, and finally electrocardiographic abnormalities." … "At present, the three main functional imaging techniques that are important in assessing the functional consequences of a coronary stenosis are stress echocardiography (with contrast), (gated) nuclear imaging using single-photon emission computed tomography (SPECT) or positron emission tomography (PET), and stress CMR." … "The ischaemic cascade is a continuum of abnormalities that occur with increasing stress and can be visualized with functional imaging. First myocardial perfusion becomes compromised, then diastolic left ventricular dysfunction occurs, and finally systolic dysfunction develops. At the last stage of the ischaemic cascade, ECG abnormalities occur, followed by chest pain. Modern imaging techniques help the clinician to diagnose coronary artery disease, as well as to stage the disease, which can then guide therapeutic decision-making."

Fischer-Rasokat U, Hamm C (Version July 2018). Title: Clinical symptoms of stable ischaemic heart disease.

"Ischaemic heart disease (IHD) becomes symptomatic when myocardial demand exceeds blood supply. Myocardial ischaemia leads to a wide range of symptoms, including chest pain as well as diffuse, worrisome sensations, all of which can be summarized under the term 'chest discomfort'. Cardiac chest discomfort may be characterized according to four attributes: character, location, duration, and association with provoking or relieving factors. Typical angina pectoris, with a very high probability of significant epicardial coronary stenosis, can be diagnosed if three pre-specified criteria are met, whereas atypical angina pectoris, with only a moderate probability of IHD, and non-anginal chest pain fulfil fewer of these criteria. Angina pectoris can be quantified according to the Canadian Cardiovascular Society classification, which is based on threshold activities of angina-limited physical exertion. Some patients with IHD do not complain of chest discomfort but report symptoms such as sweating, nausea, or dyspnoea that have been demonstrated to be early indicators of IHD, denoted here as 'angina equivalents'. Patients who do not experience any symptoms at all although myocardial ischaemia is detected are said to have 'silent' ischaemia. Patients with chest pain or discomfort use certain uniform hand gestures to describe the localization and character of the pain; thus, body language may be complementary to diagnostic criteria for IHD. Women are more likely to present with atypical forms of chest discomfort, and IHD is diagnosed roughly 10 years later in women than in men. Careful interpretation of patients' descriptions of their symptoms is crucial to correctly diagnosing IHD."

Knuuti J, Saraste A (Version July 2018). Title: Non-invasive functional evaluation.

"Imaging is useful to confirm the diagnosis of coronary artery disease and to guide therapy in patients with an intermediate pretest likelihood of disease. This chapter gives an overview of the indications, special features, and diagnostic performance of different functional imaging modalities in the detection of myocardial ischaemia. Computed tomography and invasive coronary angiography can visualize coronary stenosis at high resolution and reliably rule out the presence of significant coronary artery disease. However, evaluation of the haemodynamic significance of coronary artery disease is

difficult based on anatomy alone. Therefore, demonstration of myocardial ischaemia with the use of stress echocardiography, single-photon emission tomography, positron emission tomography, and cardiovascular magnetic resonance imaging is important to identify patients who can benefit from revascularization."

Achenbach S (Version July 2018). Title: Invasive and non-invasive (computed tomography) angiography.

"Invasive coronary angiography is not a first-line test in patients with suspected coronary artery disease. Invasive coronary angiography should be performed when non-invasive testing indicates the presence of relevant ischaemia, when symptoms are compelling and cannot be controlled by medication, or when symptoms are accompanied by reduced left ventricular ejection fraction. In order to determine the presence or absence of ischaemia, invasive coronary angiography can be complemented by fractional flow reserve measurements. Coronary computed tomography angiography is a non-invasive alternative method to visualize the coronary lumen, but requires careful patient selection, data acquisition, and processing. It is not as stable and robust as invasive coronary angiography. However, the use of coronary computed tomography angiography can be considered in patients with a low-to-intermediate risk for coronary artery disease in order to rule out coronary artery stenoses when patient characteristics indicate a high likelihood of fully diagnostic image quality."

Oldroyd KG, Berry C (Version July 2018). Title: Invasive functional evaluation.

"Based on an understanding of how a stenosis impacts the ability of a coronary artery to deliver adequate myocardial blood flow, coupled with the results of the DEFER, FAME, and FAME 2 studies, fractional flow reserve (FFR) has become the most widely used and the only guideline-recommended method for the invasive functional evaluation of patients with stable ischaemic heart disease."

Ryan N, Gonzalo N, Escaned J (Version July 2018). Title: Intracoronary imaging.

"Intracoronary imaging allows detailed *in vivo* assessment of atheromatous plaques in patients who present with stable coronary artery disease. Although atheromatous plaques have been classified as stable and unstable or vulnerable, based on their histological and imaging features, plaque type and clinical presentation are not mutually exclusive. Longitudinal studies using intracoronary imaging have allowed assessment of the prognostic relevance of atheromatous plaques and their modification by various therapeutic strategies."

Farooq V, Serruys PW (Version July 2018). Title: Risk stratification and risk scores.

"Risk stratification is an essential part of appropriately informing patients electing to undergo percutaneous coronary intervention or coronary artery bypass graft surgery. In addition, there is a greater need than ever to tailor revascularization appropriately, taking into consideration a patient's co-morbidities, coronary anatomy, personal preferences, and individual perception of risk. This chapter examines the important established and evolving contemporary clinical tools used to aid the Heart Team in this risk-stratification process. Risk scores based on clinical and anatomical variables alone and in combination are all explored. Other areas of discussion include risk scores based upon completeness of revascularization and decision-making between surgical and percutaneous-based

revascularization in complex coronary artery disease." … "Conclusion: Advances in percutaneous and surgical-based technology have led to a blurring of the classical divisions between which patients and coronary lesions are suitable exclusively for CABG or PCI. These welcome changes have increased the importance of assessing patients as individuals, taking into consideration their co-morbidities, angiographic findings, and ultimately where appropriate, their personal preferences and individual perceptions of risk prior to establishing a treatment strategy. The importance of these clinical tools in contemporary practice is in part now emphasized by their inclusion in society guidelines on myocardial revascularization."

Danchin N, Puymirat E, Aissaoui N (Version July 2018). Title: Medical management: lifestyle and behavioural changes.

"Numerous epidemiological studies have reported diverse associations between lifestyle and coronary artery disease. Clinical trials assessing the long-term impact of lifestyle modification, however, are scarce, and most of current recommendations are therefore based upon weak scientific evidence. Smoking cessation is a major component of lifestyle adaptation in smokers, and its benefits are not disputed. Regular physical activity is also beneficial, although the optimal amount of physical exercise is uncertain. Regarding nutrition, a balanced diet with increased vegetable and fruit intake, as well as olive oil and nuts are likely to be beneficial; the conventional regimen limiting the amount of saturated fat is not supported by the most recent meta-analyses on the topic. Finally, other lifestyle aspects are important, in particular stress management and addressing specific risk factors such as obesity and diabetes."

Shaul AA, Hasdai D (Version July 2018). Title: Medical management: pharmacological therapy.

"The current armamentarium for the treatment of chronic ischaemic heart disease includes agents that are used to relieve angina or attenuate ischaemia, as well as agents that are administered regardless of symptom status to ameliorate prognosis. Beta blockers and calcium channel blockers are the mainstay treatments for angina and ischaemia relief. Adjunct therapy includes nitrates, ivabradine, ranolazine, nicorandil, and trimetazidine. Aspirin (alternatively, clopidogrel), statins (possibly with ezetimibe), and angiotensin-converting enzyme inhibitors (alternatively, angiotensin receptor blockers), are the mainstay agents to improve outcomes."

Tardif J-C, L'Allier PL, Picard F (Version July 2018). Title: Myocardial revascularization: symptomatic and prognostic indications.

"The primary goal of therapy in patients with chronic ischaemic heart disease is to relieve symptoms, delay or prevent progression of coronary artery disease, and decrease the risk of major adverse cardiovascular events. This is primarily achieved with optimal medical therapy. When coronary revascularization is considered, symptomatic and prognostic indications must be differentiated. For symptomatic indications, revascularization is justified if there is a large area of inducible ischaemia or if there is persistent limiting angina despite optimal medical therapy. The key prognostic indications for revascularization are left main disease with stenosis greater than 50%, any proximal left anterior descending artery stenosis greater than 50%, two-vessel or three-vessel disease with stenosis greater than 50% with impaired left ventricular function (left ventricular ejection fraction <40%), a large area

of ischaemia (>10% of the left ventricle), or a single remaining patent coronary artery with stenosis greater than 50%."

Osnabrugge RLJ, Kappetein AP (Version July 2018). Title: Cost-effectiveness.

"Approximately 2% of the total healthcare expenditure in the European Union is spent on coronary artery disease and these expenditures are expected to increase. In order to make rational decisions on resource allocation, clinical and economic outcomes of treatment strategies need to be analysed together. Cost-effectiveness studies provide a framework for making such decisions. The early

economic studies comparing balloon angioplasty with coronary artery bypass grafting (CABG) show that the early cost benefit of angioplasty is lost at long-term follow-up. CABG provides a clinically and economically attractive treatment option in patients with severe coronary artery disease. Later studies with bare-metal or drug eluting stents showed that the higher invasiveness of CABG leads to a longer hospital stay and higher upfront costs. However, at longer follow-up the cost difference is small and clinical outcomes with CABG are better than with percutaneous coronary intervention (PCI). This makes CABG superior to PCI at long-term follow-up, both clinically and economically in patients with extensive coronary disease. Nevertheless, in patients with less complex coronary artery disease, PCI with drug-eluting stents may be preferred on both clinical and economic grounds. Although reduction in stent price does not have a big impact, several other developments may impact future economic comparisons between PCI and CABG. Newer-generation stents will enhance the clinical and economic profile of PCI. Moreover, better clinical decision-making tools and fractional flow reserve will impact the cost-effectiveness equation."

Giacoppo D, Byrne RA (Version July 2018). Title: Percutaneous coronary intervention versus coronary artery bypass grafting.

"Although coronary artery bypass grafting (CABG) has been considered the standard of care for patients with advanced obstructive coronary artery disease (CAD), percutaneous coronary intervention (PCI) with drug-eluting stents has emerged as an alternative strategy, especially in patients with high surgical risk and multiple co-morbidities. Current clinical practice guidelines recommend both CABG and PCI for left main coronary artery (LMCA) or proximal left anterior descending artery stenosis with overall mild-to-intermediate complexity. CABG remains preferred in patients presenting with three-vessel disease with intermediate-to-severe complexity or patients with LMCA stenosis with overall high-complexity CAD. This chapter summarizes the results of major randomized and observational studies comparing PCI and CABG. Specifically, the critical role of CAD anatomical pattern-with or without LMCA involvement-and CAD complexity and extent-mainly defined by SYNTAX score-are presented along with implications of patient characteristics such as diabetes mellitus. Finally, discussion is provided on the results of the recent, large-scale, multicentre EXCEL and NOBLE trials enrolling patients with CAD and LMCA involvement, and comparing PCI with second-generation drug-eluting stent implantation versus contemporary surgical revascularization."

Ong P, Sechtem U (Version July 2018). Title: Vasospastic angina.

"The hallmark of vasospastic angina is angina at rest that promptly responds to short-acting nitrates. Classically, there is a preserved exercise capacity and the underlying mechanism is a focal occlusive spasm of the epicardial arteries with transient ST-segment elevation on the electrocardiogram (i.e.

Prinzmetal's, or variant angina). However, the clinical presentation of epicardial spasm may also comprise exercise-related symptoms. Intracoronary provocation testing with acetylcholine is the method of choice to establish the diagnosis and this can be performed with a good safety profile. Coronary spasm may occur in patients with normal or unobstructed coronary arteries but also in patients with epicardial stenoses and those with previous coronary revascularization. Distribution of epicardial spasm can be focal or diffuse and involve multiple locations. In European patients, diffuse spasm of the distal left anterior descending coronary artery is a frequent finding. Coronary spasm may also exist at the level of the coronary microcirculation which represents a form of coronary microvascular dysfunction. Despite good efficacy of calcium channel blockers and short-acting nitrates, a substantial number of patients have refractory symptoms. Apart from optimal risk factor control, emerging drugs for these patients include, for example, rho kinase inhibitors."

Azzano A, Verheye S (Version July 2020). Title: Refractory angina.

"A growing number of patients who are no longer candidates for surgical or percutaneous coronary revascularization, continue to experience persistent and invalidating angina despite optimal medical therapy. Despite the advances in medical and invasive therapies for the treatment of ischaemic heart disease, the management of patients with refractory angina remains a clinical challenge. Since mortality in this patient population has decreased, the treatment of refractory angina should therefore be focused on improving quality of life. Myocardial ischaemia is traditionally treated with risk factor modification and antianginal medications, as well as percutaneous or surgical revascularization, increasing coronary blood flow, blood oxygen-carrying capacity, and decreasing oxygen consumption. Based on new therapeutic principles, such as metabolic modulation, oxygen sparing, and coronary flow redistribution, emerging treatment options have emerged. They include novel medical agents (ivabradine, nicorandil, ranolazine, or trimetazidine) and novel interventional techniques (percutaneous coronary intervention for chronic total occlusions, and the narrowing of the coronary sinus), therapeutic angiogenesis through gene or cell therapy, shockwave therapy, and neuromodulation. The contemporary management of refractory angina might be individualized, patient-centred, and arise from an interdisciplinary approach (including psychological and self-management approaches)."

Camici PG, Rimoldi O (Version July 2020). Title: Microvascular angina.

"Atherosclerotic disease of the epicardial coronary arteries has been accepted as the cause of angina pectoris for more than two hundred years while sudden, thrombotic occlusion of an epicardial coronary artery has been well established as the cause of myocardial infarction for more than one hundred years. However, the epicardial arteries, also known as conductance vessels, are only one segment of the arterial coronary circulation. These vessels give rise to smaller arteries and arterioles which in turn feed the capillaries and constitute the coronary microcirculation, the main site of regulation of myocardial blood flow. In the past two decades, a number of studies have demonstrated that abnormalities in the function and structure of the coronary microcirculation occur in many clinical conditions. In some instances these abnormalities represent epiphenomena, whereas in others they represent important markers of risk or may even contribute to the pathogenesis of myocardial ischaemia, thus becoming therapeutic targets."

End of citations from the textbook "The ESC Textbook of Cardiovascular Medicine (third edition)".

The two American cardiological societies American heart association (AHA) and American college of cardiology (ACC) and some other American societies have published guidelines for the evaluation and diagnosis of chest pain, it is a Circulation paper published in 2021 (Gulati et al., 2021). “A comprehensive literature search was conducted from November 11.2017, to May 1.2020, encompassing randomized and nonrandomized trials, observational studies, registries, reviews, etc.”. “This guideline presents an evidence-based approach to risk stratification and the diagnostic workup for the evaluation of chest pain. Cost-value considerations in diagnostic testing have been incorporated, and shared decision-making with patients is recommended”. There is a differentiation of patients with chest pain in low-risk, intermediate-risks (here three groups) and high-risk patients. There are recommendations concerning the use or nonuse of specific techniques for the different categories of patients with chest pain like Coronary computed tomographic angiography (CCTA), Coronary artery calcium score (CACS), Exercise ECG, Stress echocardiography, Nuclear stress methods and Stress cardiovascular magnetic resonance (CMR). There is a summary with ten top take-home messages for the evaluation and diagnosis of chest pain, among others “Testing not needed routinely for low-risk patients” or “Identify patients most likely to benefit from further testing” or “Noncardiac is in. Atypical is out (“Noncardiac” should be used if heart disease is not suspected. “Atypical” is a misleading descriptor of chest pain, and its use is discouraged)”.

Similar information as mentioned above (guidelines for the evaluation and diagnosis of chest pain) (Gulati et al., 2021) can be found in another ACC/AHA-publication (“2022 ACC/AHA Key data elements and definitions for chest pain and acute myocardial infarction”) (Anderson et al., 2022). Here, there is also a list of ten top take-home messages which resembles the one of the publication cited above (Gulati et al., 2021). The tenth take-home message is: “This clinical lexicon and data standard should be broadly applicable in various settings, including patient care, electronic health records (EHRs), quality and performance improvement initiatives, registries, and public reporting programs.”

According to the ESC-guidelines, published a few years earlier, namely in 2019 (Knuuti et al., 2020), the diagnostic management approach of patients with angina and suspected obstructive CAD includes six steps, from assessing symptoms until specific testing procedures. “Once a diagnosis of obstructive CAD has been confirmed, the patient’s event risk will be determined (step 6) as it has a major impact on the subsequent therapeutic decisions”. First-line testing in patients with suspected CAD includes standard laboratory biochemical testing, a resting ECG, echocardiography and, in selected patients, a chest X-ray. It is recommended to use either non-invasive functional imaging of ischemia or anatomical imaging using CCTA as the initial test for diagnosing CAD. For the detection of myocardial ischemia the following techniques are used: Stress echocardiography, Stress CMR, Single-photon emission CT (SPECT), Positron emission tomography (PET). Most of these methods have been used since many years, but the accuracy of them has much improved in the last years. - The Exercise ECG-testing for detection of ischemia has no longer its value like in earlier days (sensitivity in the average below 60%), but it can still be used in selected cases. In asymptomatic persons with few or no risk factors, the likelihood of a false positive outcome is high and will result in psychological stress and/or expensive and possibly invasive test.

The consequences of the presence of myocardial ischemia have changed and have led to a different therapeutic approach within the last years. “Management of stable coronary artery disease has been based on the assumption that flow-limiting atherosclerotic obstructions of epicardial coronary

arteries are the proximate cause of angina and myocardial ischemia in most patients and represent an important target for revascularization" (Boden et al., 2023). This attitude has recently been changed. The indications when a revascularization procedure should be performed have become much more selective. "While, indeed, revascularization may reduce incident cardiac events in high-risk subsets with stable CAD (e.g., left main disease, 3-vessel CAD with diabetes, and decreased ejection fraction), evidence from multiple randomized controlled trials (RCTs) has shown that revascularization of epicardial coronary obstructions, particularly with the use of PCI, does not reduce mortality or morbidity compared with guideline-directed medical therapy (GDMT) in the great majority of stable CAD patients" (Boden et al., 2023). Nonobstructive causes of angina should also be considered when checking patients with chest pain. "These causes include epicardial or microvascular coronary vasospasm, coronary microvascular dysfunction (CMD), and derangements of myocardial energy or metabolism".

The newer therapeutic strategy for patients with chest pain and/or with proven coronary artery stenoses leads to a reduction of the number of indications for invasive therapies (Percutaneous coronary intervention = PCI or coronary artery bypass graft = CABG) in favour of more conservative therapy (medical treatments). A milestone in this context plays the ISCHEMIA-trial (Maron et al., 2020). In this study, more than 5000 patients with moderate or severe ischemia were randomized to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed. In most cases, ischemia was assessed by stress imaging, and the presence of coronary obstruction was performed by CCTA. The results of this trial led to the following conclusions: "Among patients with stable coronary disease and moderate or severe ischemia, we did not find evidence that an initial invasive strategy, as compared with an initial conservative strategy, reduced the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years" (Maron et al., 2020).

In the editorial report to the ISCHEMIA-trial (Antman & Braunwald, 2020), we find among others the following text: "The preferred contemporary approach to the management of stable ischemic heart disease, also referred to as chronic coronary syndrome, is not well defined. Two strategies are commonly used. The conservative strategy uses guideline-based medical therapy, including antianginal drugs as well as disease-modifying agents, such as hypolipidemic, antithrombotic, and renin-angiotensin blocking therapies. The invasive strategy adds coronary angiography, followed by either percutaneous coronary intervention or coronary-artery bypass grafting, to guideline-based medical therapy. Important advances have occurred in both strategies, leading to equipoise as to which approach is preferable for patients with stable ischemic heart disease" (Antman & Braunwald, 2020). And the final conclusion of this editorial is: "Although there is some uncertainty regarding the interpretation of the ISCHEMIA results - given that the difference in outcomes between the two strategies is driven by results for myocardial infarction, and those results depend on the definition used in the analysis - the invasive strategy does not appear to be associated with clinically meaningful differences in outcomes during 4 years of follow-up. This finding underscores the benefits of disease-modifying contemporary pharmacotherapy for coronary artery disease. Thus, provided there is strict adherence to guideline-based medical therapy, patients with stable ischemic heart disease who fit the profile of those in ISCHEMIA and do not have unacceptable levels of angina can be treated with an initial conservative strategy. However, an invasive strategy, which more effectively relieves symptoms

of angina (especially in patients with frequent episodes), is a reasonable approach at any point in time for symptom relief".

Since the appearance of the ISCHEMIA-study many publications were made related to the ISCHEMIA trial. Chaitman et al. showed that the choice of myocardial infarction (MI) definition influences MI event rates, which were the most frequent component of the primary end point in the ISCHEMIA trial (Chaitman et al., 2021). Spontaneous type 1 MIs were more strongly associated with an increased risk of death and were significantly reduced in patients randomly assigned to the invasive strategy. - And the result of a meta-analysis, performed by Navarese et al. also differed from the outcome of the ISCHEMIA-trial (Navarese et al., 2021), but this meta-analysis was criticized in the corresponding editorial (Brown & Boden, 2021). - And a long-term analysis of the ISCHEMIA-patients with a median follow-up of 5.7 years revealed the following conclusions: "There was no difference in all-cause mortality with an initial invasive strategy compared with an initial conservative strategy, but there was lower risk of cardiovascular mortality and higher risk of non-cardiovascular mortality with an initial invasive strategy during a median follow-up of 5.7 years" (Hochman et al., 2023).

The ISCHEMIA trial led to a reconsideration concerning the strategy of management of patients with ischemia in presence of relevant coronary stenoses. Even if this trial emphasizes the importance of medical treatment instead of invasive coronary intervention in many cases, the treatment strategy which was summarized in the textbook from 2018 "The ESC Textbook of Cardiovascular Medicine (third edition)" has not generally changed; see the many citations out of this book in the initial part of this document. - Then we recommend to check also the text "Management of stenoses of the left main (LM) coronary artery"; this issue is reviewed in a separate document of task 1. In that document, there is clear information concerning the indications for invasive coronary interventions in LM disease.

As mentioned above, CCTA plays an important role in the evaluation of patients with chest pain with the question if relevant coronary artery disease is present or not. The indication for the application of CCTA is especially given for patients with stable chest pain and intermediate pretest probability for obstructive CAD. The DISCHARGE-trial gives important information about CCTA (Maurovich-Horvat et al., 2022). In this multicentre, randomized trial, including 3561 patients, "CCTA was compared with invasive coronary angiography (ICA) as initial diagnostic imaging strategies for guiding the treatment of patients with stable chest pain who had an intermediate pretest probability of obstructive CAD". This trial showed that the risk of major adverse cardiovascular events was similar in the CT group and the ICA group, and that the frequency of major procedure-related complications was lower with an initial CT strategy.

In the editorial to the DISCHARGE-trial (Loscalzo, 2022), we find among others the following text sequences: "Correctly interpreting the cause of chest pain is a crucial diagnostic skill that is essential for effective medical practice. Before the development of coronary angioplasty and stenting, the great majority of patients with stable angina (typical or atypical) were treated medically. Currently, patients with stable angina often undergo early invasive coronary angiography with an eye toward intervention for sufficiently stenotic lesions. The goal of this approach has been to eliminate angina rather than to reduce the risk of cardiovascular events. This more aggressive approach has improved the lives of many patients with stable angina, to be sure. Yet, this strategy has not been without risks and challenges. First, a substantial percentage of patients (approximately 60%) who are referred for angiography have no hemodynamically significant coronary artery stenoses. Thus, many patients

without coronary artery disease (CAD) are subjected to the low but real risk of complications from angiography. Second, defining the anatomy does not necessarily provide useful information about the hemodynamic importance of a lesion unless such definition is accompanied by some demonstration of impaired perfusion. For these reasons, a variety of non-invasive stress studies have been developed to aid in the identification of a flow-limiting lesion, each with reasonable sensitivity and specificity". … "Over the past 20 years, CCTA has emerged as another non-invasive method for diagnosing obstructive CAD. Among patients with intermediate or high pretest probability of obstructive CAD, CCTA has been found to have a sensitivity, specificity, positive predictive value, and negative predictive value for identifying obstructive CAD of 0.92, 0.75, 0.84, and 0.87, respectively". … "CCTA has become the preferred imaging approach for the assessment of patients with stable chest pain, especially in those with an intermediate pretest probability of obstructive CAD". The result of the DISCHARGE-trial "is probably a consequence of the lack of effect of revascularization on cardiovascular events among most patients with stable angina and the limited number of those with high-risk anatomy who would benefit from revascularization in the trial". In this editorial, several questions are raised, for example if a CT-based estimates of fractional flow reserve (FFR) would further improve the predictive accuracy of CCTA. And we find also the comment: "The most recent guidelines of the American College of Cardiology - American Heart Association for the evaluation and diagnosis of chest pain recommend no testing and intensification of goal-directed medical therapy in low-risk patients".

There is more and more evidence, that the assessment of the new method CT-FFR improves the indication for invasive coronary angiography. Bucciarelli et al. showed in their study that the application of on-site CT-FFR reduced the proportion of patients with stable coronary artery disease undergoing invasive coronary angiography without obstructive disease or requiring intervention within 90 days (Bucciarelli-Ducci & Ajmone-Marsan, 2023). And this trial used the new machine learning technique.

It is interesting to see that the application of CACS has a IIa/B-classification, whereas CCTA is not recommended as routine risk estimation method in the ESC-Guidelines 2021 (2021 ESC Guidelines on cardiovascular disease prevention in clinical practice) (Visseren et al., 2021). This deviates from the above-mentioned ESC-guidelines 2019 (Knuuti et al., 2020), where CCTA had a IB-classification: "Noninvasive functional imaging for myocardial ischaemia or coronary CTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone" (Boden et al., 2023). - All the same, it must be repeated that CCTA is actually widely used in general cardiological settings, it has been established as an important non-invasive method for diagnosing obstructive CAD (Maurovich-Horvat et al., 2022), (Loscalzo, 2022), (Bucciarelli-Ducci & Ajmone-Marsan, 2023).

Interesting aspects in the evaluation of chest pain in relationship with myocardial ischemia and diagnosis of relevant coronary artery disease, are gender differences. There a several new publications concerning this issue, three of them are mentioned here: In the study of Vergallo and Volpe (Vergallo & Volpe, 2023), the following differences between women and men are found: As compared with men, women were more likely to have typical angina (23% vs. 3%). Mean pre-test probability of obstructive CAD was lower (33% vs. 44%). Irrespective of the diagnostic imaging strategy, signs of CAD were less frequent in women than in men (47% vs. 32%) and were less likely to show obstructive CAD (19% vs. 34%) or high-risk coronary anatomy (9% vs. 17%)." (Comment: There must be an error, it

probably should be correctly written “32% vs. 47%”). - In “a state-wide population-based cohort study”, published by Dawson et al. (Dawson et al., 2023), it was the aim “to assess sex differences in epidemiology and care pathways from emergency medical services (EMS) contact through to clinical outcomes following discharge.” The conclusions were: ”Substantial differences in care are present across the spectrum of acute chest pain management form first contact through to hospital discharge. Women have higher mortality for STEMI, but better outcomes for other etiologies of chest pain compared with men.” - In the editorial of the publication of Dawson et al. (Dawson et al., 2023), written by Brush (Brush, 2023), the importance of the study of Dawson et al. is emphasized. Here a citation of the last section of this editorial: “The present study is a large and comprehensive investigation and a valuable addition to the literature. This important contribution extends our knowledge of patients with undifferentiated acute chest pain and how care patterns differ between women and men. New strategies (e.g., timely ECGs and new methods to distinguish patients with undifferentiated chest pain into those with and without cardiac aetiologies) are urgently needed to eradicate sex disparities in AMI. Observational studies like this one are important because they identify gaps in care and disparities in outcomes, and highlight opportunities to further improve care and reduce disparities.”

In the following, some recent information of the ESC-congress (2023) is presented

1) *2023 ESC Guidelines for the management of acute coronary syndromes (Byrne et al., 2023):*

These guidelines contain a total number of 193 recommendations, but in respect to pilots and ATCOs, only a few of these recommendations must be mentioned. There are several categories of acute coronary syndromes (ACS). The situation of acute myocardial infarctions (MI) like ST-segment elevation or non-ST-segment elevation MI (STEMI or NSTEMI respectively) is not relevant for pilots and ATCOs, because in those acute situations, they are clearly unfit to fulfil their duties. But the long-term follow-up is of importance. Most of these patients with an ACS undergo an immediate invasive strategy, and secondary prevention after ACS with or without invasive treatment is essential to decrease the risk for a relevant second cardiovascular event. Secondary prevention includes issues like cardiac rehabilitation, lifestyle management, pharmacological treatment, considerations of comorbid conditions (mainly chronic kidney disease and diabetes) etc. - A special situation is given with MINOCA. It is described in the guidelines as: “The term MINOCA refers to the situation where patients present with symptoms suggestive of ACS and demonstrate troponin elevation and non-obstructive coronary arteries at the time of coronary angiography, i.e. coronary artery stenosis < 50% in any major epicardial vessel. MINOCA is best considered as a working diagnosis that encompasses a heterogenous group of underlying causes (both cardiac and extra-cardiac) and is found in 1-14% of patients with ACS. In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying cause. CMR imaging is a key diagnostic tool in patients with a working diagnosis of MINOCA.“ In pilots and ATCOs presenting MINOCA, it is important to find the underlying cause; only then, a judgement about the fitness to fulfil their duties can be made, which in selected cases must not be negative.

2) *Study “MULTISTAR AMI”:*

This study was presented at the ESC-congress 2023 and published in the NEJM at the same time (Stähli et al., 2023). It is an international, open-label, randomized, noninferiority trial including 37 sites in Europe, which studied the question, if in patients with ST-segment elevation myocardial infarction (STEMI) with multivessel coronary artery disease, immediate multivessel revascularization of the nonculprit lesions should be performed. A total of 840 patients were involved. The conclusion was: "Among patients in hemodynamically stable condition with STEMI and multivessel coronary artery disease, immediate multivessel PCI was noninferior to staged multi-vessel PCI with respect to the risk of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year". - In regards to the risk situation of pilots and ATCOs, the number of end-points is of special interest: The primary end-point event (composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year after randomization) occurred in 8.5% of patients, who had undergone immediate multivessel PCI (= immediate group), and in 16.3% in patients, who had got PCI of the culprit lesion followed by staged multivessel PCI of the nonculprit lesions within 19 to 45 days after the index procedure (= staged group). Nonfatal myocardial infarction and unplanned ischemia-driven revascularization occurred in 2.0% and 4.1%, respectively, in the immediate group, and in 5.3% and 9.3%, respectively, in the staged group. These figures show that patients with acute STEMI, presenting with multivessel coronary artery disease and treated with PCI have a cardiovascular risk in the long-term follow-up which is not negligible; this applies as well for patients with the immediate multivessel PCI- as for patients with the staged multivessel PCI-situation. This long-term risk must be considered when checking pilots and ATCOs for the fitness to fulfil their duties.

3) Studies "OCTOBER" and "ILUMIEN IV: OPTIMAL PCI":

These studies, which were also presented at the ESC-congress 2023, were published in the NEJM at the same time (Holm et al., 2023), (Ali et al., 2023). These two trials emphasize the importance of the imaging-guided PCI technique "Optical coherence tomography" (OCT). The background question of the study in OCTOBER was, whether routine OCT guidance in PCI of lesions involving coronary-artery branch points (bifurcations) improves clinical outcomes as compared with angiographic guidance or not. And the answer was yes: "Among patients with complex coronary-artery bifurcation lesions, OCT-guided PCI was associated with a lower incidence of major adverse cardiac events (MACE) at 2 years than angiography-guided PCI." - The ILUMIEN IV: OPTIMAL PCI-study was a prospective, randomized, single-blind trial, in which OCT-guided PCI was compared with angiography-guided PCI in patients with medication-treated diabetes or complex coronary-artery lesions. OCT-guided PCI led to a larger minimal stent area, enhanced the safety of the PCI procedure and resulted in a nearly 2/3 reduction in stent thrombosis during 2-year follow-up. However, OCT guidance did not reduce the two-year rate of target-vessel failure (TVF) compared with angiography-guided PCI. - Another method for in vivo imaging of the vessel wall of the coronary arteries is "Intravascular ultrasound" (IVUS), which is already widely used. It is a catheter-based diagnostic ultrasound procedure used to view the inside of a coronary artery, providing a real-time view. On the other hand, OCT uses near-infrared light to create images of the inside of the coronary arteries. Both techniques deliver very high-resolution images. - At the ESC-congress, there was further a presentation of a real-time updated network meta-analysis, integrating data from the ILUMIEN IV: OPTIMAL PCI and OCTOBER trials with prior studies (a total of

20 randomized controlled trials), to examine the effects of intravascular imaging guidance vs angiography guidance. This meta-analysis showed that compared with angiography-guided PCI, intravascular imaging-guided PCI with OCT or with IVUS reduced significantly all the outcomes (target lesion failure, cardiac death, target lesion revascularization, stent thrombosis, any MI and all cause death). The outcomes were similar for OCT guided PCI and IVUS-guided PCI, but OCT was a bit less "persuasive". - Intravascular coronary imaging is mainly indicated to guide left main revascularization, to optimize stent implantation and to detect reasons for restenosis. Short: Intravascular coronary imaging either with IVUS or with OCT should become standard in cases with "complex" coronary lesions.

2. Conclusion and recommendations

- Chest pain can be of cardiac origin (mainly myocardial ischemia), or it can correspond to a symptom not related to any cardiovascular disease.
- There are specific lists for the investigation of chest pain.
- The main causes of myocardial ischemia include
  (1) atherosclerotic flow-limiting stenoses which are responsible for chronic stable angina;
  (2) coronary thrombus superimposed on an atherosclerotic plaque which is responsible for acute coronary syndromes;
  (3) coronary artery spasm which is responsible for vasospastic angina; and
  (4) coronary microvascular dysfunction which is responsible for microvascular angina and can also contribute to myocardial ischemia in various clinical settings.
- As first step, non-invasive specific methods shall be used for the evaluation of myocardial ischemia and of the severity of coronary lesions. Coronary computed tomography angiography (CCTA) and invasive coronary angiography can visualize coronary stenosis at high resolution and reliably rule out the presence of significant coronary artery disease. And for the demonstration of myocardial ischemia the following methods can be used: stress echocardiography, single-photon emission tomography (SPECT), positron emission tomography (PET), and cardiovascular magnetic resonance imaging (cardiac MR). Also, machine learning techniques and techniques based on artificial intelligence respectively play a role in some investigation methods nowadays.
- The exercise ECG-testing for detection of ischemia has no longer its value like in earlier days (sensitivity in the average below 60%), but it can still be used in selected cases.
- The important role of CCTA in these diagnostic procedures must be highlighted. If it is complemented by fractional flow reserve (FFR) measurements, then it provides also a functional statement (significant ischemia yes or no?).
- Invasive coronary angiography should be performed when non-invasive testing indicates the presence of relevant ischemia, when symptoms are compelling and cannot be controlled by medication, or when symptoms are accompanied by reduced left ventricular ejection fraction. In order to determine the presence or absence of ischemia, invasive coronary angiography can be complemented by FFR measurements.
- The characterization of the coronary plaque is of great importance, in order to estimate the risk of plaque rupture. Intravascular coronary imaging techniques ("Intravascular ultrasound"

= IVUS and “Optical coherence tomography” = OCT) allow detailed in vivo assessment of atheromatous plaques. These techniques are established methods, now. They should become standard in cases with “complex” coronary lesions.

- The indication for an invasive therapeutic intervention is not any more alone dependent on the severity of a coronary stenosis. Even the presence of myocardial ischemia must not automatically lead to an invasive therapeutic intervention. Concerning the different therapeutic options (medical treatment, invasive revascularization intervention - PCI or CABG -), a very differentiated approach is mandatory, and this approach is very much demanding. The ISCHEMIA-study mentioned above played an important role for the new attitude in which medical options have gained more weight when treating coronary stenoses and ischemia.
- The primary goal of therapy in patients with chronic ischemic heart disease is to relieve symptoms, delay or prevent progression of CAD, and decrease the risk of major adverse cardiovascular events. This is primarily achieved with optimal medical therapy. When coronary revascularization is considered, symptomatic and prognostic indications must be differentiated. For symptomatic indications, revascularization is justified if there is a large area of inducible ischemia or if there is persistent limiting angina despite optimal medical therapy. A clear prognostic indication for revascularization is left main disease with stenosis greater than 50%. - For task 1, there is a separate document about “Management of stenoses of the left main (LM) coronary artery”, which is recommended to read together with this document here.
- If there is an indication for invasive coronary intervention, as well PCI as CABG are established methods. For the decision which of these two options should be chosen, the individual aspects of the given patient must be considered. It is recommended to make such a decision within a multidisciplinary heart team.
- There are several categories of ACS. The situation of acute MI like ST-segment elevation or non-ST-segment elevation MI (STEMI or NSTEMI respectively) is not relevant for pilots and ATCOs, because in those acute situations, they are clearly unfit to fulfil their duties. But secondary prevention after ACS with or without invasive treatment is essential to decrease the risk for a relevant second cardiovascular event.
- A special situation of ACS is given with MINOCA. In pilots and ATCOs presenting MINOCA, it is important to find the underlying cause; only then, a judgement about the fitness to fulfil their duties can be made, which in selected cases must not be negative.
- Patients with acute STEMI, presenting with multivessel CAD and treated with PCI have a cardiovascular risk in the long-term follow-up which is not negligible. This long-term risk must be considered when checking pilots and ATCOs for the fitness to fulfil their duties.
- Independent of the chosen therapeutic decision in patients with significant CAD, besides medication, lifestyle actions including controlling the classic cardiovascular risk factors play an important role.
- In the evaluation of chest pain in relationship with myocardial ischemia and diagnosis of relevant CAD, gender differences should be considered.
- Cost-benefit ratios have to be taken into consideration for all investigations and treatment options mentioned above.

Treatment options have been included into these conclusions, but in a general way (for example non-invasive against invasive procedures). But a detailed list of medications used for angina or a detailed list about cardiovascular risk factors etc. are not listed in the present report.

There are some other documents within task 1, which have a direct relationship to this document "Chest pain, myocardial ischemia and indications for coronary artery revascularization". It is recommended also to check these documents, which are:

- "Management of stenoses of the left main (LM) coronary artery"
- "Follow-up after revascularization procedures in coronary artery disease"
- "The actual role of CT coronary artery calcium score (CACS) and Coronary computed tomographic angiography (CCTA) in coronary artery disease"
- "Cardiac MRI"
- "Echocardiography"
- "Nuclear medicine methods like SPECT and PET"

Concerning pilots and ATCOs, when they are checked for the fitness to fulfill their duties, the following questions must be raised:

- Which investigations have to be met in pilots/ATCOs with chest pain?
- Which investigations have to be met in pilots/ATCOs with suspicion of CAD, especially when there is suspicion of myocardial ischemia?
- Which investigations have to be met in pilots/ATCOs with proven myocardial ischemia?
- Which investigations have to be met in pilots/ATCOs with proven CAD (for example with previous MI) with new onset of chest pain or proven new onset of myocardial ischemia?
- Which are the treatment options for relevant CAD?
- Are secondary prevention measures undertaken in the situation of proven CAD with or without history of invasive treatment?

As mentioned above, concerning the different therapeutic options (medical treatment, invasive revascularization intervention - PCI or CABG -), a very differentiated approach is mandatory, and this approach is very much demanding. To translate this difficult issue into recommendations for the EASA medical requirements for pilots and ATCOs (task 2) will even be more demanding.

3. Relevance for risk assessment of pilots and ATCOs

Application of the methods and/or treatments for risk assessment will be described in detail in task 2.

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4.2. Management of stenoses of the left main (LM) coronary artery

This document contains a summary of important publications describing how stenoses of the left main (LM) coronary artery should be managed. As this issue contains primarily treatment options, there is no separation of clinical and diagnostic settings etc. on one side and of treatment options on the other side in this document.

1. What is new? - Main findings

Which is the state-of-the-art concerning the management of LM coronary artery disease? And which are the risks in the long-term outcome after intervention of this disease?

The treatment of left main (LM) coronary artery is a complex and challenging issue. We can find a description of most aspects of LM disease including useful recommendations in the comprehensive state-of-the-art review from Davidson et al. (Davidson et al., 2022). This document is the outcome of an agreement between the American College of Cardiology Cardiac Surgery Team Council and the American College of Cardiology Interventional Council. These organizations aimed “to develop a practical approach to the treatment of LM CAD, taking into account randomized clinical trial, meta-analyses, and clinical practice guidelines”. Because of the importance of this state-of-the-art review, this article is the main reference for our document “Management of stenoses of the left main (LM) coronary artery”. Several citations of this article will be made, and most of them are self-explanatory and do not need additional comments.

Here the citation of the first introductory part of this article, which is related to what has been the defined treatment practice many years ago: “The natural history of medically treated left main (LM) disease has been associated with 73% mortality at 15 years, and historically, coronary artery bypass grafting (CABG) has been recommended in all patients with stable ischemic heart disease and significant LM disease to prevent fatal acute myocardial infarction (MI). Randomized clinical trials on the survival benefit of CABG over medical therapy in that era showed a substantial treatment effect of CABG in the subset of LM stenosis, precluding any further studies involving medical treatment alone for patients with LM disease. Unlike the other epicardial arteries in which significant stenosis is defined as diameter reduction >70%, the threshold for intervention in LM disease is set at 50% because of early observations that patients with 50% to 70% LM stenosis derive a survival benefit after CABG.” It was and is clear, that “LM disease is the CAD subset with the strongest evidence that revascularization provides survival benefit over medical treatment alone in stable patients.” Since several years, percutaneous coronary intervention (PCI) has evolved as an alternative invasive treatment option to CABG.

Other citations (Davidson et al., 2022): “The LM coronary artery supplies circulation to a large portion (75% to 100%) of the left ventricular (LV) myocardium; as a result, significant LM stenosis places the left ventricle at considerable risk. MI after LM plaque rupture involves the entire left ventricle and the inferior wall of the right ventricle in patients with left dominant anatomy. LM stenosis can occur in the ostial (23%), mid-shaft (15%), and distal (61%) segments, and depending on the location and severity of the disease, treatment strategies may differ.”

For the optimal therapeutic evaluation of LM coronary artery disease, the following considerations are mentioned in detail: “clinical factors”, “procedural considerations”, “operator and institution issues” as well as “clinical practice guidelines” (Davidson et al., 2022). Different factors may favor CABG, PCI or Medical Therapy.

“Several randomized clinical trials have studied the comparative effectiveness of CABG and PCI for LM CAD”. … “Published outcomes of LM disease have generated controversy. However, several meta-analyses have been conducted analysing the 4 major LM PCI vs CABG trials; the most recent of which is a collaborative, individual patient-level analysis that seeks to critically evaluate the available data. These meta-analyses consistently have demonstrated a lack of significant mortality difference between CABG and PCI.” (Ahmad et al., 2020), (Gallo et al., 2022), (Kuno et al., 2020), (Sabatine et al., 2021). … “Although differences in the rates of procedural MI depended upon the ascertainment of biomarkers (and definition of MI) used within the specific trials, the incidence of spontaneous MI was lower with CABG compared with PCI. With respect to other outcomes, stroke was found to be similar between PCI and CABG and repeat revascularization was consistently less after CABG.”

The article of Davidson et al. denotes the following highlights: (Davidson et al., 2022): “LM CAD can be categorized as ostial/shaft and distal lesions, and may be complicated by multivessel disease. / Clinical, procedural, and institutional factors should be considered along with clinical practice guidelines in selecting the mode of revascularization for patients with LM CAD. / Engagement of a multidisciplinary heart team and shared decision making are key components of management for patients with LM CAD.”

The article of Davidson et al. (Davidson et al., 2022) is based on many trials, one of them is the publication "2018 ESC/EACTS Guidelines on myocardial revascularization", which were set up by a task force formed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) (Neumann et al., 2019). Concerning the treatment of LM disease, we find the following text: "The available evidence from RCTs and meta-analyses comparing CABG with PCI using DES among patients with LM disease suggests equivalent results for the safety composite of death, MI, and stroke up to 5 years of follow-up. A significant interaction with time is notable, providing early benefit for PCI in terms of MI and periinterventional stroke which is subsequently offset by a higher risk of spontaneous MI during long-term follow-up. The need for repeat revascularization is higher with PCI than with CABG." These Guidelines from Neumann et al. (Neumann et al., 2019) were published three years before the publication of Davidson et al. which has been cited above several times (Davidson et al., 2022). But the conclusions of 2019 have been already quite similar to those from 2022.

How are the long-term results after invasive intervention of LM coronary artery stenoses? How big are the risks? This is an important question concerning pilots and ATCOs, when they are checked concerning the fitness to fulfil their duties. In the document of Neumann et al., several trials are mentioned with data about the outcome after invasive intervention of LM disease (Neumann et al., 2019). Here three citations in this respect out of the article of Neumann et al.; they are especially chosen to get an idea about the long-term risks:

- "3 years of follow-up the primary endpoint of death, stroke, or MI occurred with similar frequency in the CABG and PCI group (14.7 vs. 15.4%; HR 1.00, 95% CI 0.79-1.26, P = 0.98)."
- "At a median follow-up of 3.1 years, the primary endpoint of death, non-procedural MI, stroke, and repeat revascularization occurred more frequently in the PCI than the CABG group (29 vs. 19%; HR 1.48, 95% CI 1.11-1.96, P = 0.007)."
- "A pooled analysis of randomized trials: The primary outcome was all-cause mortality. CABG was associated with a significant survival benefit during a mean follow-up of 3.8 $\pm$ 1.4 years (5 year all-cause mortality 11.2% after PCI vs. 9.2% after CABG; HR 1.20, 95% CI 1.06-1.37, P = 0.0038)."

These citations also show that there are differences in the outcomes after PCI or after CABG depending on the study. But as mentioned above, as well in the publication of Neumann et al. (Neumann et al., 2019) as in the one of Davidson et al. (Davidson et al., 2022), there are differences between these two procedures, but one disadvantage might be offset by another aspect being an advantage. And it seems to be no difference in all-cause mortality between these two invasive interventions. It is highlighted that the decision, which therapeutic approach should be chosen, must be done on an individual basis and should be made within a multidisciplinary heart team.

An interesting study has been performed by Gaba et al. (Gaba et al., 2023). A meta-analysis showed no mortality differences between PCI and surgery to treat left main stenosis between patients with acute and patients with chronic coronary syndrome. In four trials (SYNTAX, PRECOMBAT, NOBLE and EXCEL), 4394 patients with left main stenosis were randomized to either PCI with drug eluting stents of surgery. In the pool analysis, five-year event rates were higher for patients presenting an acute coronary syndrome than for those with chronic coronary disease. Regardless of the clinical presentation PCI was associated with higher rates of spontaneous myocardial infarction and repeat

revascularization compared to surgery. However, the primary outcome of five year all-cause mortality was similar for PCI and surgery, both in chronic and acute coronary syndromes.

2. Conclusion and recommendations

- LM disease is the CAD subset with the strongest evidence that revascularization provides survival benefit over medical treatment alone in stable patients.
- Treatment options for significant LM disease are CABG, PCI and medical treatment. But medical treatment is only an option, if there are contraindications for CABG or PCI.
- Several meta-analyses have been conducted analysing LM PCI vs LM CABG trials. Even if there are some differences between PCI and CABG, for example the amount of procedural MI or of repeat revascularization, those trials have consistently demonstrated a lack of significant mortality difference between CABG and PCI.
- There is also no mortality difference between PCI and surgery to treat left main stenosis between patients with acute and patients with chronic coronary syndrome.
- The treatment options of PCI and CABG in LM disease can be considered more or less as equal.
- For the decision if PCI or CABG (or even only a medical treatment) should be chosen, the individual aspects of the given patient must be considered. It is recommended to make those decisions within a multidisciplinary heart team.
- The long-term risks after invasive treatment of LM disease are quite high, they cannot be neglected. This is also caused by the facts, that patients with LM coronary artery disease very often have multivessel coronary artery disease, and that they have a very high cardiovascular risk level (related to several cardiovascular risk factors).
- These long-term risks must be taken into account concerning pilots and ATCOs, when they are checked for the fitness to fulfill their duties.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in task 2.

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4.3. Indications for revascularization in coronary artery disease and follow-up data after revascularization

This document describes the current state-of-the-art with respect to the indications for revascularization in patient with coronary artery disease (CAD). It also describes the inherent risks related to revascularization procedures like percutaneous coronary interventions (PCI) and coronary artery bypass surgery (CABG). Furthermore, it describes the level of risk and the time course of the rate of adverse events following PCI and CABG. The different therapeutic options related to this issue are also part of this document.

1. What is new? - Main findings

Revascularization procedures play an important role in the management of patients with acute coronary syndrome and with stable angina pectoris. In most patients, percutaneous coronary intervention (PCI) is the preferable treatment option either to improve prognosis or to treat symptoms.

In patients presenting with ST-elevation myocardial infarction (STEMI), direct or primary PCI of the culprit (occluded) vessel is usually performed (Ibanez et al., 2018). Revascularization of remaining lesions improves prognosis and is now standard practice (Mehta et al., 2019). Remaining non-culprit lesions can be treated in the subacute phase using a fractional flow reserve (FFR)-guided approach.

In patients presenting with Non-ST-elevation myocardial infarction (NSTEMI), culprit vessel identification is more difficult than in STEMI and often, multivessel coronary artery disease (CAD) is found (Collet et al., 2021). The decision about the mode of revascularization in this case depends on patient characteristics and angiographic criteria. CABG will be the preferred treatment option in

patients with multivessel disease and diabetes. Also, with a high (angiographic) SYNTAX score, in general, CABG will be the first choice of treatment (Neumann et al., 2019).

In acute coronary syndromes revascularization improves prognosis, and it is unquestioned that a revascularization procedure should be timely performed. In these patients, it is important to realize that instable vulnerable plaques are not only present in the culprit coronary vessel. Some of these plaques are non-significant lesions and will not be stented. These non-significant vulnerable plaques will only slowly stabilize during the six months following an acute coronary event (Okada et al., 2011; Takano et al., 2005).

In patients with chronic CAD however, the impact of revascularization on prognosis is less well established. The outcome of the ISCHEMIA trial suggests that in patients with moderate to severe ischemia, revascularization with PCI or CABG does not improve event-free survival when compared to optimal medical therapy (OMT) (Maron et al., 2020). However, in this trial during the first year of follow-up the PCI-group showed a higher rate of non-fatal myocardial infarction (MI) related to periprocedural MI and stent thrombosis. After two years of follow-up, an increase in non-fatal MI was seen in the OMT-group, and the primary endpoint was higher in the OMT group than in de PCI-group (9,5% vs 9,0%). In the following years this difference slowly but steadily increased. Although the differences remained non-significant, the authors argue that a periprocedural MI carries a lower risk than spontaneous MI's occurring at a later stage outside the hospital (Lansky & Stone, 2010; Prasad et al., 2009). Until now, the results of the ISCHEMIA trial have not changed the ESC guidelines on revascularization (Neumann et al., 2019). In these guidelines five class I indications for revascularization (related to the extent of CAD) are mentioned to improve prognosis and one class I indication for revascularization to improve symptoms.

After a successful and complete revascularization, the risk of future cardiac events can be lowered with strict medical therapy, lowering non-HDL-cholesterol to target low levels and treating co-morbidities like hypertension and diabetes. Also, smoking cessation is of great importance (Cassese et al., 2014; Ullrich, Olschewski, Munzel, & Gori, 2021). We should realize that after PCI, stent-related events can and will occur. First of all, stent thrombosis is a feared complication resulting in excess morbidity and mortality. Patients with stent thrombosis often present with acute MI or death. Treatment with dual antiplatelet agents is therefore of great importance to prevent stent thrombosis. Survival curves show that stent thrombosis occur mainly during the first month after stenting and varies between 0,5% and 1,5% (figure 4) (Tada et al., 2013). After 30 days the risk of stent thrombosis is very low and will only occur in patients with significant comorbidity or when treatment with dual antiplatelet therapy (DAPT) has been interrupted (Jarrah, Alrabadi, & Alzoubi, 2018; Kufner et al., 2020; Kuramitsu et al., 2021; Polimeni et al., 2020).

In the days that clopidogrel was used for DAPT after stenting, a subgroup of patients with MI and a persistent high platelet reactivity on clopidogrel showed a 2% stent thrombosis rate in the first two months (figure 5) (Stone et al., 2013). With the currently used antiplatelet drug ticagrelor, this issue of platelet resistance has been eliminated, and a 35% reduction in the rate of stent thrombosis in the first month was seen in patients, who were stented in the setting of an acute coronary syndrome (Steg et al., 2013).

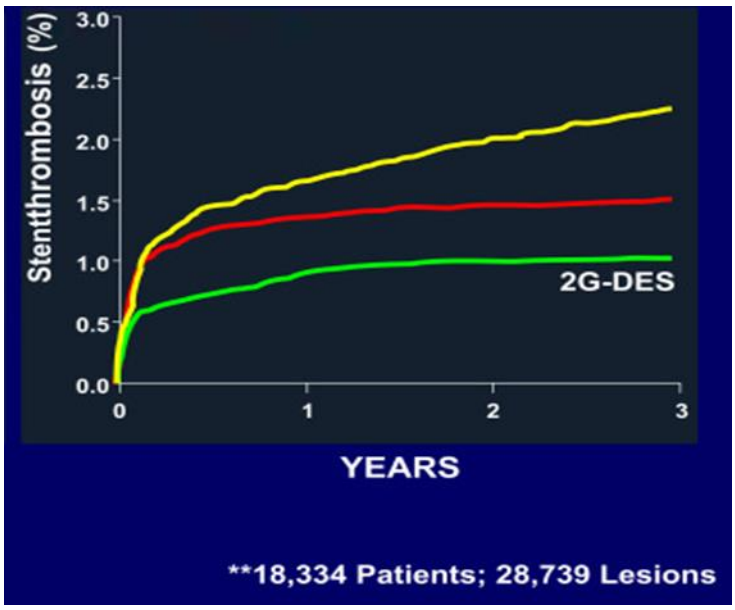

Figure 4: Definite stent thrombosis related to type of stent (Munich Registry). Yellow line: first generation drug eluting stent (DES), Red line: Bare Metal Stent, Green line: second generation DES.
Figure adapted from the publication of Tada, T. et al. "Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients". JACC Cardiovasc Interv, 2013;6(12), 1267-1274.

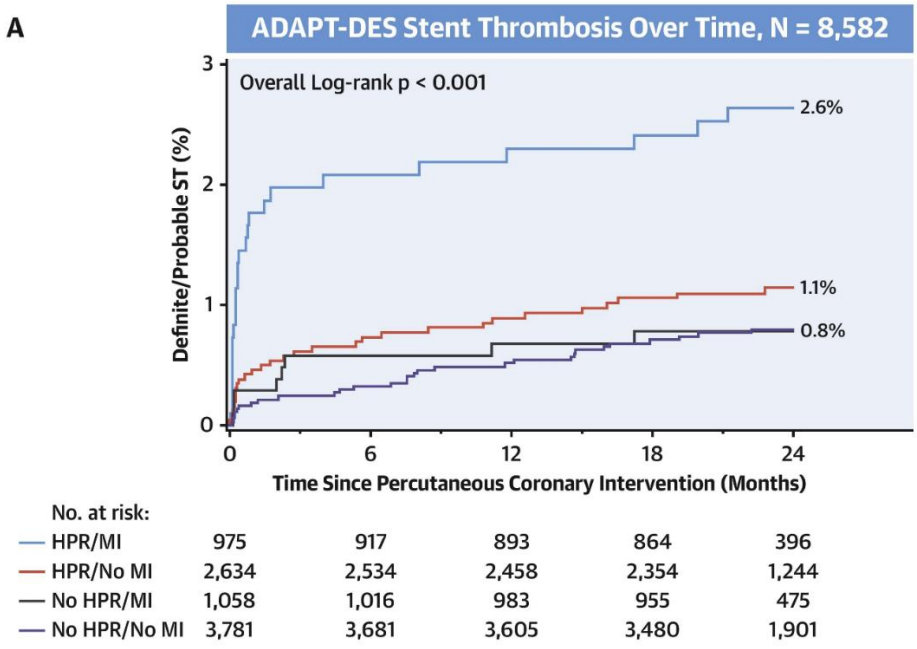

Figure 5: ADAPT-DES study showing rate of stent thrombosis dependent on platelet reactivity in the era that clopidogrel was used as a second antiplatelet drug. (HPR = high platelet reactivity. MI = myocardial infarction*). Figure adapted from the publication of Stone, G. W. et al. "Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study". Lancet 2013, 382(9892), 614-623.*

The second issue of stenting is the development of in-stent restenosis (ISR). Angiographic restenosis rates are estimated to be about 10% after 6 months. Studies have shown that ISR is related to stent properties and patient characteristics (Cassese et al., 2014; Ullrich et al., 2021). Coronary stenting with 3rd generation drug eluting stents (DES) is the current standard in percutaneous revascularization. When PCI is being combined with adequate antithrombotic and LDL-cholesterol lowering therapy, with these stents, clinical in-stent re-stenoses have become very infrequent events. In a retrospective clinical study, stent thrombosis in the first year after stent-implantation was only 1,1%. Death or non-fatal MI occurred in only 1-2% (Jarrah et al., 2018).

After CABG, recurrent ischemic events are related to graft failure. A recently published meta-analysis of 7 randomized trials showed that graft failure occurs in 33% of patients during the first year after surgery (Gaudino et al., 2023). It was also shown that age, female sex and smoking were associated with graft failure whereas lipid lowering therapy protected against graft failure. Graft failure was associated with an increased risk of MI or repeat revascularization (7.8%). All-cause death was also higher in the graft failure group (11% vs 2.1%). An abnormal single-photon emission computed tomography (SPECT)-scan at one year after CABG is associated with higher mortality and an increased incidence of heart failure (Al Aloul et al., 2012; Ortiz et al., 2020).

Another commonly encountered problem after CABG is the occurrence of atrial fibrillation or atrial flutter. The management of these patients depends in part on the CHADS-VASC score. Many patients develop complete right bundle branch block after CABG, which has no prognostic implication.

After a complete revascularization, the best strategy to assess recurrent ischemia during follow-up depends on the mode of revascularization. After (multivessel) PCI, follow-up invasive coronary angiography or coronary CT with FFR most likely are the most accurate diagnostic tools. After CABG, SPECT, positron emission tomography (PET) or FFR- coronary computed tomography angiography (CCTA) will have the highest sensitivity and specificity in detecting ischemia, also correlating the area of ischemia to a specific coronary artery or failing bypass graft (Seraphim et al., 2021). Ischemia detection should be performed using the most sensitive and specific diagnostic methods. The added clinical value of this approach can, however, be debated in patients with stable CAD since it has been shown in the ISCHEMIA trial (Maron et al., 2020) that complete revascularization with PCI or CABG in stable CAD to treat ischemia does not change prognosis. A meta-analysis of Chacko (Chacko et al., 2020), which included the data from the ISCHEMIA trial, also showed no benefit from revascularization in patients with chronic coronary artery disease. However, a meta-analysis of twelve randomized controlled trials (including the ISCHEMIA trial) performed by Laukkanen (Laukkanen & Kunutsor, 2021), including a total of 15,774 patients, showed that when compared to medical therapy alone (MT), revascularization combined with MT significantly reduced the risk of the composite outcome of all-cause mortality, MI, revascularizations, rehospitalizations, or stroke (0.69, 95% CI: 0.55–0.87), unplanned revascularization (0.53, 95% CI: 0.40–0.71) and fatal MI (0.65, 95% CI: 0.49–0.84). And revascularization plus MT reduced also the risk of stroke at 1 year (0.44, 95% CI: 0.30–0.65). There was no significant difference in all-cause mortality risk (0.95, 95% CI: 0.86–1.06).

2. Conclusion and recommendations

With the current high quality of stenting, combined with adequate drug therapy it has become clear that postprocedural risk has decreased significantly. The time span of elevated risk is also shorter than before. Based on the estimated postprocedural level of risk, in selected cases pilots should, therefore, be allowed to return to work earlier than the current requirements indicate, especially when chronic coronary artery disease is involved.

The current use of 3th generation DES, combined with improved techniques of PCI and adequate drug treatment for secondary prevention has led to lower levels of stent related risks like stent thrombosis and ISR. Dependent on the initial diagnosis, a postprocedural level of risk level can be defined. Especially, patients with chronic CAD who have been optimally stented have a low risk of postprocedural cardiac events beyond two months after PCI.

Residual risk after PCI with stenting varies and depends on individual risk-profiles. Therefore, after revascularization it is recommended to define three levels of risk:

Low-risk

PCI performed for stable angina.

Procedural data show that stenting was optimally performed.

All significant lesions have been stented.

There are no significant co-morbidities.

Intermediate risk:

PCI performed for stable angina.

Procedural data show that stenting was optimally performed.

All significant lesions have been stented.

Presence of co-morbidities (prior bypass surgery, hypertension, diabetes, renal insufficiency, continued smoking or drug intolerance).

High risk:

CABG performed (with complete or incomplete revascularization).

PCI performed for an acute coronary syndrome.

Procedural data show that stenting was suboptimal or was performed in relatively small vessels.

Some lesions were treated without the use of a stent (plain old balloon angioplasty).

Presence of co-morbidities (prior bypass surgery, hypertension, diabetes, renal insufficiency, continued smoking or drug intolerance).

3. Relevance for risk assessment of pilots and ATCOs

General recommendations:

Pilots and ATCOs might inevitably develop CAD and might present with an acute coronary syndrome or with stable angina. When diagnosed as such, they will be withheld from working duties. Treatment of these pilots and ATCO's will follow most recent guidelines. Thus, many of them will have been revascularized in the setting of an acute coronary syndrome or in order to relieve symptoms related to chronic coronary artery disease. After revascularization, the question should be answered when they can return to work. Current aeromedical requirements allow pilots and ATCO's to return to work after 6 months, when aeromedical assessment is satisfactory, showing a good left ventricular function (LVEF>50%) and no signs of ischemia. Appropriate operational limitations in the medical certificate will then apply.

With the current high quality of stenting, combined with adequate drug therapy it has become clear that postprocedural risk has decreased significantly. The time span of elevated risk is also shorter than before. Based on the estimated postprocedural level of risk, in selected cases, pilots should, therefore, be allowed to return to work earlier than the current requirements indicate, especially when chronic CAD is involved.

Therefore, in updating the aeromedical requirements, the question should be answered whether the presence of ischemia should always preclude pilots and ATCOs with chronic CAD from returning to work. Knowing that revascularization does not always improve prognosis would eventually result in a permanent unfit to fly status for all pilots with chronic CAD, even when a revascularization procedure has been performed. Therefore, in chronic CAD, risk stratification would be a better approach, and only pilots with increased risk should undergo revascularization, according to the most recent ESC guidelines (Knuuti et al., 2020; Neumann et al., 2019). Thus, a subset of pilots should be able to return to work without being revascularized, also when there is a small to moderate amount of ischemia. This means that ischemia testing in chronic CAD will remain part of the aeromedical requirements, but consequently, revascularization will not always be necessary and should be driven by anginal complaints and/or high-risk features.

When decisions about returning to work depend on the basic risk profile of individual pilots, consultation of an aviation cardiologist is necessary in an early stage after revascularization. During this consultation, the risk profile should be determined. In case of incomplete revascularization, it should be evaluated whether an additional revascularization procedure is needed in order to regain the fit-to-fly status. This holds true also for Class 2 pilots.

In all pilots and ATCOs who are known with CAD, treatment of modifiable risk factors is of great importance, including smoking cessation.

A. Recommendation for pilots and ATCO's after coronary stenting:

Low risk

Pilots/ATCOs with a low risk profile might return to work 3 months after PCI when they remained asymptomatic and an ischemic test rules our relevant ischemia.

Intermediate risk

In pilots/ATCOs with an intermediate risk profile, all modifiable risk factors should be addressed and adequately treated. When after 3 months all modifiable risk factors are on target level, pilots/ATCOs can return to work when they are asymptomatic and an ischemic test rules our relevant ischemia.

High risk

Pilots/ATCOs with a high-risk profile are more likely to develop in-stent restenosis. Therefore, in these pilots/ATCOs, it seems reasonable to wait six months before returning to work. In this time period all modifiable risk factors should have been adequately addressed and treated. Depending on the clinical status it could then be decided to perform a non-invasive myocardial perfusion test or invasive coronary angiography with FFR to rule out in-stent restenosis.

B. Recommendation for pilots and ATCOs after CABG:

Pilots and ATCO's who underwent CABG with complete or incomplete revascularization should be evaluated after 6 months for clinical and angiographic signs of graft failure and assess the amount of ischemia. Graft failure can be detected with CCTA or FFR-CT or PET-CT. As an alternative, it can be decided to perform myocardial perfusion imaging with SPECT, also being a good diagnostic tool to detect graft disease.

Application of the method and/or treatment for risk assessment will be described more in detail in task 2.

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4.4. Bleeding risks of antithrombotic medications, especially after PCI and after CABG

This document contains a summary of data describing the bleeding risks of the different antithrombotic medications, especially after percutaneous coronary intervention (PCI) and after coronary artery bypass graft surgery (CABG). Several of these studies have contributed to a change of specific medical treatment options, now being the basis of up-to-date antithrombotic therapy. This actual treatment options will also be commented in this document.

1. What is new? - Main findings

What is the state-of-the-art of the great number of antithrombotic medications used in coronary artery disease (CAD) in respect to their bleeding risks? And which are the consequences in regard to treatment options?

Antithrombotic therapy is required in many cardiovascular diseases, the list of these drugs is wide, distending from aspirin on one side of the spectrum until anticoagulation on the other side of the spectrum. All these medications are related with an increased bleeding risk. This bleeding risk must be considered when evaluating pilots and ATCOs for the fitness to fulfil their duties. The purpose of this document is to summarize the bleeding risks of the different antithrombotic drugs per se and the bleeding risks when antithrombotic drugs are combined. In addition to the estimation of these bleeding risks, also the risks given by the different underlying cardiovascular situations must be considered in each single case.

Aspirin

The bleeding risk of aspirin is reported in numerous publications. For example, Baigent et al. analysed the effect of aspirin in primary and secondary prevention of vascular disease in 2009 (Baigent et al., 2009). In this meta-analysis, serious cardiovascular events and major bleedings in several primary and secondary prevention trials were analysed by comparing long-term aspirin versus control. Apart from any effect on intracerebral haemorrhage, aspirin increased major gastrointestinal and other extracranial bleeds by about half in the primary prevention trials (0.10% vs 0.07% per year). And perhaps by chance - as the authors state - there were fewer fatal bleeds in participants allocated aspirin than in controls. And major bleedings were recorded in only five of the 16 secondary prevention trials. There was, however, an increased number of major extracranial bleeding among those allocated aspirin (RR 2.69).

Abdelaziz et al. examined the clinical outcomes with aspirin for primary prevention of CAD in several randomized controlled trials (Abdelaziz et al., 2019). “Safety outcomes included major bleeding, intracranial bleeding, fatal bleeding, and major gastrointestinal (GI) bleeding.” … “Aspirin use for primary prevention was associated with a significant increase in the risk of major bleeding (1.47% vs. 1.02%; RR: 1.50; 95% CI: 1.33 to 1.69; $p < 0.001$; $I^2 = 25\%$), intracranial bleeding including hemorrhagic stroke (0.42% vs. 0.32%; RR: 1.32; 95% CI: 1.12 to 1.55; $p = 0.001$; $I^2 = 0\%$), and major GI bleeding (0.80% vs. 0.54%; RR: 1.52; 95% CI: 1.34 to 1.73; $p < 0.001$; $I^2 = 0\%$) compared with the control group.”

The COMPASS study, which will be described in more detail below, compared three treatment groups: Rivaroxaban plus aspirin, rivaroxaban alone and aspirin (100 mg once daily) alone (Eikelboom et al., 2017). The study evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention. In the aspirin-alone group, major bleeding events occurred in 1.9%, fatal bleeding in 0.3%, and minor bleeding in 5.5%. Intracranial major bleeding events occurred in 0.3%.

The ARRIVE- and ASCENT-studies published in 2018 confirmed the upcoming strategy, that aspirin should not be generally prescribed in primary cardiovascular preventive settings (Gaziano et al., 2018), (Bowman et al., 2018), (Ridker, 2018). - Concerning bleeding risk, the ARRIVE-trial mainly reported data on gastrointestinal bleedings are reported. In the safety analysis, gastrointestinal bleeding events

occurred in 61 (0·97%) of 6270 patients in the aspirin group and 29 (0·46%) of 6276 patients in the placebo group (hazard ratio, 2.1; 95% CI, 1.36 to 3.28; P < 0.001). There was no significant difference between the trial groups in the rate of fatal bleeding events, and all-cause mortality did not differ between groups (Gaziano et al., 2018). - In the ASCEND-study, the aspirin group showed significant adverse outcomes compared with the placebo group with respect to the incidence of all major bleedings (314 participants [4.1%] vs. 245 [3.2%]; rate ratio, 1.29; 95% CI, 1.09 to 1.52; P = 0.003). Intracranial bleeding was found in 0.7% for the aspirin group and 0.6% for the control group (Bowman et al., 2018).

Other antiplatelets medications

$P2Y_{12}$ receptor blockers are another group of antiplatelet drugs. This group of drugs includes: clopidogrel, ticlopidine, ticagrelor, prasugrel, and cangrelor. Clopidogrel, the first $P2Y_{12}$ inhibitor, is widely used in clinical settings instead of aspirin since long time, which is documented for example in the CAPRIE-study 1996 (Committee., 1996). In this trial, it was shown, that «long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death. The overall safety profile of clopidogrel is at least as good as that of medium-dose aspirin". Clopidogrel also belonged to the standard dual antiplatelet therapy (DAPT) until newer options became available.

It is not easy to find trials in which a direct comparison between clopidogrel and aspirin or between another $P2Y_{12}$ receptor blockers and aspirin is performed. But out of many trials where dual antiplatelet therapy (DAPT) with a single antiplatelet drug is checked, one can draw the conclusion that the outcome of the CAPRIE-trial (see above) is still valid now. The meta-analysis of Wa et al. might be considered as such trial (Wa, Zhu, & Long, 2019). - *For DAPT-trials see below. Dual antiplatelet therapy (DAPT)*

Dual antiplatelet therapy (DAPT) is the standard medication after PCI in most cases. This approach - amongst others - is confirmed in the "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes" (Knuuti et al., 2020): "Dual anti-platelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ inhibitor is the mainstay of antithrombotic therapy after MI and/or PCI." (MI = myocardial infarction).

An outline concerning DAPT is given in an overview publication (corresponding to Guidelines) from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) (Valgimigli et al., 2018).

Already in 1996, there has been the first randomized clinical trial which established the superiority of DAPT over anticoagulant therapy among patients undergoing PCI (Schömig et al., 1996): "As compared with conventional anticoagulant therapy, combined antiplatelet therapy after the placement of coronary-artery stents reduces the incidence of both cardiac events and hemorrhagic and vascular complications." In the meantime, many other studies have supported this knowledge, which will not be mentioned here more in detail.

That DAPT results in an increased bleeding risk is proven by many studies, one of them is the study of Mauri et al., called the DAPT-Study (Mauri et al., 2014). See also the editorial to this DAPT-study

(Colombo & Chieffo, 2014); here the final words of this editorial: “The safest and most effective duration of dual anti-platelet therapy therefore remains uncertain and must be individualized for each patient; presumably in making this judgment, physicians should balance risk factors favoring atherothrombosis against the risk of bleeding.”

The overview of Valgimigli et al. gives differentiated treatment recommendations concerning DAPT, weighing the reduction of major adverse cardiovascular events (MACE) after PCI on one side and the bleeding risk on the other side (Valgimigli et al., 2018). Here an important citation: “Nonetheless, because continued antiplatelet therapy is also associated with increased bleeding risk, it is necessary to weigh this risk against the potential benefit. Current evidence suggests that the risk of bleeding in patients on DAPT is proportionally related to its duration both within and beyond 1 year of treatment duration. Since the benefits of prolonged DAPT, especially for mortality endpoints, appear highly dependent on prior cardiovascular history [such as prior acute coronary syndrome (ACS)/MI vs. stable CAD], and prediction models to estimate on-DAPT bleeding risk have been developed, an individualized approach based no ischaemic vs. bleeding risk assessment is warranted.” At the end of these guidelines of Valgimigli et al., there is a list of eleven important key messages. Concerning DAPT and coronary artery bypass grafting (CABG), it is written: “Stable CAD patients treated with CABG: There is insufficient data to recommend DAPT in this patient populations.”

Concerning DAPT combined with anticoagulation: see below.

Other antithrombotic therapy, including oral anticoagulation (OAC)

As mentioned above, at the end of the important guidelines of Valgimigli et al. (Valgimigli et al., 2018), there is a list of eleven important key messages. Concerning the use of anticoagulation, we find the following text: “Patients with indication for oral anticoagulation: Compared with OAC therapy alone, the addition of DAPT to OAC therapy results in at least a two- to three-fold increase in bleeding complications. Therefore, these patients should be considered at high risk of bleeding and the indication for OAC should be reassessed and treatment continued only if a compelling indication exists. The duration of triple therapy should be limited up to a maximum of 6 months or omitted after hospital discharge, taking into account the ischaemic (e.g. complexity of treated CAD, amount of disease left untreated, technical considerations regarding stent implantation techniques, and results) as well as the bleeding risk. The use of ticagrelor or prasugrel in this setting is not recommended.” Thus, a triple antithrombotic therapy results in a very high bleeding risk. - For example, an (additional) anticoagulation is recommended after PCI or CABG in presence of atrial fibrillation (AF).

There are different antithrombotic options for patients being at a very high cardiovascular risk level. One newer such option follows the recommendation described in the editorial of the COMPASS-trial (Eikelboom et al., 2017), the editorial being written by Braunwald (Braunwald, 2017). The recommendation is: Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily. Braunwald writes among others: “The rates of major bleeding events were significantly higher in the rivaroxaban groups than in the aspirin-alone group, but the rates of fatal or intracranial bleeding were not significantly higher. The COMPASS trial was stopped for overwhelming efficacy when only one half of the primary end-point events had occurred.” Braunwald also underlines the importance of individual approaches to different clinical situations. “It is possible that different subgroups of patients with stable ischemic

heart disease, such as those with a history of an acute coronary syndrome or those with heart failure, will have different responses to these various drug combinations, and this could lead to a more personalized approach to patients with stable ischemic heart disease." And this specific antithrombotic therapy related to the COMPASS study is also mentioned in the "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes" (Knuuti et al., 2020).

Anticoagulation is the preferred antithrombotic treatment in atrial fibrillation (AF), also in presence of chronic coronary syndrome (CCS). We find in the "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes" (Knuuti et al., 2020) the following text: "Anticoagulant therapy is recommended in patients with AF and CCS for reduction of ischaemic stroke and other ischaemic events. Anticoagulants in AF patients have demonstrated superiority over aspirin monotherapy or clopidogrel-based DAPT for stroke prevention, and are therefore recommended for this indication. When oral anticoagulation is initiated in a patient with AF who is eligible for a non-vitamin K antagonist oral anticoagulant (NOAC; apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist (VKA)."

What is the bleeding risk of anticoagulants? - Warkentin et al. studied the difference of the bleeding risk between warfarin and aspirin therapy in a systematic review und meta-analysis trial (Warkentin, Donadini, Spencer, Lim, & Crowther, 2012): "This meta-analysis failed to find a statistically significant difference in major bleeding between warfarin, target INR 2.0–3.5, and ASA, 50–650 mg daily. The trend towards increased bleeding with warfarin appears to be explained by an excess of intracranial bleeding in warfarin patients."

Levi makes the following statement in his review paper "Epidemiology and management of bleeding in patients using vitamin K antagonists" (Levi, 2009): "According to well documented studies of patients using vitamin K antagonists, the incidence of major bleeding is 0.5% per year and the incidence of intracranial bleeding is 0.2% per year, however, in real life practice this incidence may be even higher. Risk factors for bleeding are the intensity of anticoagulation, the management strategy to keep the INR in the desired range, and patient characteristics."

Concerning anticoagulation with NOAC, we know that the bleeding risk in most cases is not superior or is inferior compared to the bleeding risk of vitamin K antagonists, and this is the case with all commonly used four NOAC-drugs with some small individual differences. A list of references for this well-known fact is not presented here.

2. Conclusion and recommendations

Conclusions concerning bleeding risk of antithrombotic medication:

- The use of aspirin is connected with an increased bleeding risk. And the figures of this risk vary in different studies. But overall, the occurrence of cranial bleeding, which is the worst bleedingcondition, lies below 1.0% in almost all short- and long-term follow-up studies; in the average it is around 0.3%, what can be considered as low. The data concerning other forms of bleedings are higher, often below 2.0%, sometimes higher. It depends which kind of bleeding is analyzed. Many of the bleedings with the label "major, noncranial bleeding" have a significance of course, but this does not automatically mean, that the person having such a

bleeding is not able to perform her/his usual daily activities. This remark is especially important for the classification of those bleeding forms in respect to the fitness of fulfilling their duties in pilots and ATCOs. In the actual EASA-cardiovascular requirements there is no limitation for pilots and ATCOs using aspirin per se. If there are limitations, they are related at the underlying diseases.

- Concerning the bleeding risk when using the antiplatelet drugs $P2Y_{12}$ receptor blockers as monotherapy, the statement is the same as for the use of aspirin as monotherapy (see above).
- The application of DAPT has a higher bleeding risk than the use of a single antiplatelet drug. Patients who need DAPT have also an underlying disease which is not negligible. There are also many combinations of DAPT or even combinations of an antiplatelet drug with another kind of antithrombotic medication. As stated in many publications (see above), the risk of patients in those situations must be analysed on an individual basis.
- Triple antithrombotic medication (anticoagulation included) has a very high risk and should be even avoided or maintained only for a short period, whenever possible.
- The bleeding risk of anticoagulation with vitamin K antagonists without any other antithrombotic medication is in general equal or only increased to a small degree compared with the bleeding risk of aspirin.
- Anticoagulation applied by NOAC has either not a higher bleeding risk or has an inferior bleeding risk compared with vitamin K antagonists. And this is the case with all commonly used four NOAC-drugs with some small individual differences.

Conclusions concerning specific medical treatment options, now being the basis of up-to-date antithrombotic therapy

- Aspirin for primary prevention use is not recommended. The basis of this new strategy are the ARRIVE- and ASCENT-studies published in 2018. In patients who have atherosclerotic manifestations - but being still in the primary prevention group -, the use of statin instead of the application of aspirin is recommended.
- DAPT has become standard after PCI. But there are many different possibilities with which drugs and how long such a therapy should be performed. As mentioned above, the safest and most effective duration of dual anti-platelet therapy therefore remains uncertain and must be individualized for each patient; presumably in making this judgment, physicians should balance risk factors favouring atherothrombosis against the risk of bleeding.
- Here a confirmed concept of treatment is mentioned which is not new (known since 1996), but which is important: It is established that there is a superiority of DAPT over anticoagulant therapy among patients undergoing PCI.
- There are different new therapeutic options for patients with a high risk or very high cardiovascular risk. A new and already quite established method is based on the COMPASS study, it consists of the medication: Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily.
- As mentioned above, a triple antithrombotic therapy results in a very high bleeding risk. This can be performed only with very high caution and with a duration which is as short as possible. If for example, atrial fibrillation (AF) is one reason for a triple antithrombotic therapy after PCI or CABG, one of the three substances should be an anticoagulant medication.

- Anticoagulation is the preferred antithrombotic treatment in AF.
- If there is a need for anticoagulation, NOAC is the first choice, non-vitamin K antagonists like warfarin is the second choice.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in task 2.

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4.5. Procedure in asymptomatic coronary artery disease (chronic coronary syndrome)

This document describes the state-of-the-art of asymptomatic coronary artery disease (CAD), also called “chronic coronary syndrome” (CCS), its clinical presentations, the actual diagnostic measures, and the decision strategies, also considering the various risks. The different therapeutic options are also mentioned in this document.

1. What is new? - Main findings

Some general comments

In autopsied U.S. civil aviation pilots involved in fatal accidents, incidental cardiac findings were reported in 85% (Ricaurte, 2018). Thus, early detection and treatment of potentially life-threatening cardiac conditions could improve flight safety.

Chronic coronary syndrome (CCS), also known as stable angina, is a common cardiovascular condition worldwide. Its prevalence increases with age, and it is more prevalent in men than in women. As the population ages and risk factors such as obesity and diabetes become more prevalent, the burden of CCS is expected to rise.

The incidence of CCS varies depending on the population and region. The progression of CCS can be influenced by various factors, including lifestyle modifications, medication adherence, and comorbidities. With appropriate management, the progression of CCS can be slowed or even halted in some cases.

CCS can lead to significant morbidity and mortality. Complications may include angina (chest pain), myocardial infarction (heart attack), heart failure, and arrhythmias. It is crucial to diagnose and manage CCS promptly to improve outcomes and reduce the risk of complications.

Several **risk factors** contribute to the development and progression of CCS. These include:

1. Age: Advanced age is a significant risk factor for CCS.

2. Gender: Men are more likely to develop CCS compared to premenopausal women. After menopause, the risk for women catches up with the one of men.
3. Smoking: Cigarette smoking is a major modifiable risk factor for CCS.
4. Hypertension: High blood pressure increases the risk of developing CCS.
5. Dyslipidemia: Abnormal lipid levels, such as elevated LDL cholesterol, elevated Lp(a) (Kronenberg, Mora, & Stroes, 2022) and reduced HDL cholesterol, are associated with an increased risk.
6. Diabetes: Individuals with diabetes are at higher risk of developing CCS.
7. Obesity: Excess body weight, particularly abdominal obesity, is a risk factor.
8. Family history: Having a close family member with premature coronary artery disease (CAD) increases the risk.

Prevention and management strategies for CCS typically involve lifestyle modifications; e.g., regular exercise (Dibben et al., 2021), healthy diet (Dinu, Pagliai, Casini, & Sofi, 2018), smoking cessation (Ding et al., 2019), psychological interventions (Richards et al., 2018), medications e.g., statins, antiplatelet agents (Indraratna et al., 2022), weight control (Jastreboff et al., 2022) and, in some cases, invasive procedures e.g., percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).

The **assessment of cardiovascular risk** is an important component in the management of CCS. The aim of risk estimation is to identify patients who are at a higher risk of developing cardiovascular events. Here are some methods used for risk estimation in CCS:

1. Clinical history and physical examination.
2. Risk prediction models: Various risk prediction models have been developed to estimate the risk of cardiovascular events in patients with CCS. Examples of these models include the Framingham Risk Score, the European Systematic Coronary Risk Evaluation (SCORE), and the American College of Cardiology/American Heart Association (ACC/AHA) risk estimator. These models use multiple risk factors to calculate an individual's 10-year risk of experiencing a cardiovascular event.
3. Imaging studies such as coronary angiography, cardiac CT scan, and stress testing can provide additional information about the extent and severity of CAD and help in risk estimation.
4. Biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and cardiac troponins can provide information about inflammation and myocardial injury, respectively, they can be used to estimate the patient's risk of cardiovascular events.

Inflammation is thought to play an important role in the development and progression of CCS. Chronic low-grade inflammation within the arterial wall is believed to be a key contributor for the formation and progression of atherosclerotic plaques that can narrow the coronary arteries and cause CCS. Inflammation can lead to the activation of immune cells and the release of inflammatory mediators which can promote the recruitment of more immune cells and the formation of fatty streaks and plaques. In addition, inflammation can make these plaques more unstable and more likely to rupture, which can trigger the formation of blood clots which can cause heart attacks and other serious cardiovascular events. Inflammatory biomarkers such as CRP and interleukin-6 (IL-6) have been shown to be associated with an increased risk of cardiovascular disease, including CCS. Measuring these

biomarkers may help to identify patients who are at increased risk of developing CCS or experiencing cardiovascular events. Treatment of inflammation may be an important component of the management of CCS. Lifestyle modifications such as regular exercise, healthy diet, and weight management can help to reduce inflammation. In addition, medications such as statins, which have anti-inflammatory effects, are commonly used to treat CCS. Other medications that have anti-inflammatory effects, such as aspirin and colchicine, may also be used in the management of CCS (Opstal et al., 2021).

PM2.5 refers to fine particles which are smaller than 2.5 micrometres in diameter; they can be inhaled deeply into the lungs and can have negative health effects. There is growing evidence that exposure to PM2.5 can increase the risk of cardiovascular disease, including CCS as well as worsening symptoms and outcomes in patients with pre-existing CCS (Lee et al., 2022). This may be due to several mechanisms, including inflammation, oxidative stress, and autonomic dysfunction. Exposure to PM2.5 can lead to activation of inflammatory pathways in the body, what can contribute to the development and progression of CCS. PM2.5 exposure has also been shown to increase oxidative stress, which can lead to damage to the endothelium (the inner lining of blood vessels) and to increase the risk of atherosclerosis. Additionally, exposure to PM2.5 can lead to autonomic dysfunction, which can contribute to the development of arrhythmias and worsening of CCS symptoms. Reducing exposure to PM2.5 is an important component of the prevention and management of CCS. This can be achieved through several measures, including reducing outdoor air pollution, using air filters indoors, and avoiding exposure to other sources of indoor air pollution such as cigarette smoke. Patients with pre-existing CCS should also be advised to avoid exposure to PM2.5 during periods of high pollution, such as wildfires or urban smog (Montone et al., 2023).

Functional imaging techniques play a crucial role in the evaluation and management of CAD. These imaging modalities provide valuable information about the blood flow and metabolism of the heart, helping to assess the presence, extent, and severity of CAD, and as such giving information about the presence of myocardial ischemia or not. The information gained by these imaging methods results in guidance for treatment decisions. Here are some commonly used functional imaging techniques in CAD:

Scintigraphy, usually performed as single-photon emission computed tomography (SPECT), assesses the blood flow to the myocardium. It helps to identify areas of reduced blood flow due to narrowed or blocked coronary arteries. Radiotracers such as technetium-99m are commonly used in SPECT, whereas thallium-201 has been abandoned.

Stress echocardiography combines echocardiography with physical or pharmacological stress to evaluate myocardial blood flow. It assesses regional wall motion abnormalities induced by stress, indicating areas of reduced blood flow due to CAD. Stress can be induced by exercise or pharmacological agents like dobutamine.

Cardiac Magnetic Resonance Imaging (MRI) provides detailed images of the heart. Techniques like stress perfusion MRI, using contrast agents, can assess myocardial blood flow and identify areas with

compromised perfusion due to CAD. MRI also allows the evaluation of myocardial viability and scar tissue following a heart attack.

Coronary computed tomography angiography (CCTA) is a non-invasive imaging technique that uses X-rays and computer processing to create detailed images of the coronary arteries. It helps to identify the presence and severity of coronary artery stenosis or blockages, providing anatomical information about CAD. With recent advancements, CCTA also allows functional assessment of blood flow using computational fluid dynamics.

Positron Emission Tomography (PET) imaging with specific radiotracers, such as oxygen-15 water or rubidium-82, can directly measure myocardial blood flow. PET can provide absolute quantification of blood flow and metabolism, aiding in the assessment of ischemia and viability of the myocardium.

Lipid-lowering therapy, particularly with statins, is an important component of the management of CCS. Lowering low-density lipoprotein cholesterol (LDL-C) with statins has been shown to significantly reduce the risk of cardiovascular events, including heart attack and stroke, in patients with CCS. The primary goal of lipid-lowering therapy in CCS is to reduce the level of LDL-C to a target level, which is typically determined based on the patient's individual cardiovascular risk factors. In general, the target level for LDL-C is < 1.8 mmol/l for patients at high risk, and < 1.3 mmol/l for patients at very high risk. Statins are the most commonly used medications for lipid-lowering therapy in CCS. Statins not only lower LDL-C levels, but have also other beneficial effects, such as reducing inflammation and stabilizing atherosclerotic plaques. Other medications, such as ezetimibe, PCSK9 inhibitors and bempedoic acid, may also be used in combination with statins to further lower LDL-C levels in patients with CCS, who are at very high risk of cardiovascular events (Nissen et al., 2023), (O'Donoghue et al., 2022).

The **2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes** (Knuuti et al., 2020) focus on CCS rather than on stable CAD. Six clinical scenarios are identified:

Suspected CAD in patients with chest pain and/or dyspnoea

1. New onset of heart failure and suspected CAD
2. < 1 year after an Acute coronary syndrome (ACS) or revascularization
3. > 1 year after initial diagnosis or revascularization
4. Symptoms and suspected vasospastic or microvascular disease
5. Asymptomatic CAD detected at screening

In the 2019 ESC Guidelines mentioned above (Knuuti et al., 2020), there are also recommendations concerning tests and measures which shall be undertaken in the evaluation and management of CAD:

- Non-invasive functional imaging or CCTA as the initial test for diagnosing CAD
- Non-invasive functional imaging if CCTA has shown CAD of uncertain functional significance
- Lipid lowering drugs: Statins, ezetimibe, bempedoic acid, PCSK9 inhibitor
- Diabetes and CAD: SGLT2-inhibitors and/or GLP-1 agonists
- ACE inhibitors should be considered
- Lifestyle recommendations

- Vaccinations (COVID-19, Influenza, Pneumococci) (Block et al., 2022), (Yedlapati et al., 2021), (Vlachopoulos, Terentes-Printzios, Aznaouridis, Pietri, & Stefanadis, 2015)

Recent studies showed that routine screening for CCS, follow-up after PCI or an early invasive strategy does not reduce total death, CV death or MI (Lindholt et al., 2022), (Park et al., 2022).

Future perspectives:

Precision Medicine
Advances in genetics and personalized medicine may lead to the development of tailored treatments for CCS. In the future, genetic testing could help to identify individuals at a higher risk of developing CCS, allowing for early interventions and personalized treatment plans based on a person's genetic profile. But actually, genetic testing cannot not yet be recommended in patients for CAD risk stratification; this strategy might change in the future.

Novel Therapies
Researchers are continuously exploring innovative therapies for CCS. One area of interest is the development of targeted drug therapies that can reduce plaque buildup, stabilize existing plaques, or promote plaque regression. New classes of medications may emerge to improve outcomes and reduce the need for invasive procedures like PCI or CABG.
Improved Diagnostic Tools
Advancements in diagnostic tools, such as non-invasive imaging techniques, may provide more accurate assessments of CAD. Imaging technologies like CCTA and PET may become more refined, enabling earlier and more precise detection of CCS.

Regenerative Medicine
Research into regenerative medicine approaches, such as stem cell therapy, holds promise for treating damaged heart tissue caused by CCS. Stem cells may be used to regenerate new blood vessels or repair existing ones, potentially restoring normal blood flow to the heart.

Targeted Risk Factor Management
Future interventions may focus on more targeted and individualized management of risk factors for CCS. This could involve advanced monitoring devices that continuously track blood pressure, glucose levels, and lipid profiles, allowing for early detection and prompt management of abnormalities.

Artificial Intelligence (AI) and Machine Learning
The integration of AI and machine learning algorithms into healthcare systems may enhance risk prediction models, improve diagnostic accuracy, and optimize treatment strategies. AI could help to analyze vast amounts of patient data, to identify patterns, to detect high-risk individuals, and to suggest personalized treatment plans.

Patient education and empowerment
With increasing emphasis on patient-centred care, future developments in CCS may focus on educating and empowering patients to actively participate in their treatment and lifestyle

modifications. Advanced mobile apps, wearables, and telemedicine tools could help patients to monitor their symptoms, track progress, and receive timely guidance from healthcare professionals.

In the following section, two selected recent informations of the ESC-congress (2023) are presented

1. The significance of inflammation in CAD

The aspect of inflammation as contributor to atherothrombotic disease was highlighted. As already described in detail above under "inflammation", this correlation is not new. It has already been discussed several years ago, for example in a publication from 2014 (Kaptoge et al., 2014) or in the CANTOS-trial from 2017 (Ridker et al., 2017), (Harrington, 2017). The actual presentations at the ESC congress were based on a newer publication from Ridker (Ridker et al., 2023): hsCRP seems to be an ideal candidate for measuring inflammation for CAD, and among 31,245 contemporary statin-treated patients, hsCRP was even a more powerful determinant of CV death than LDL-cholesterol. But lipid lowering and inflammation inhibition are not in conflict, they are synergistic. Even if anti-cytokine and other inflammation inhibition therapies are under discussion, in clinical practice they are not yet established treatment options. But the presenters at the ESC-congress think, that in the future, the combined use of aggressive LDL-cholesterol-lowering and inflammation inhibiting therapies may well become standard of care for almost all atherosclerosis patients.

2. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (Marx et al., 2023)

It is well known that diabetes is a strong CV risk factor (see also comments in the upper part of this document). In the new Guidelines, the relationship between diabetes, CV diseases (CVD) and chronic kidney disease (CKD) is highlighted. "The combination of diabetes with these cardio-renal comorbidities enhances the risk not only for CV events but also for CV and all-cause mortality. The current European Society of Cardiology (ESC) Guidelines on the management of CVD in patients with diabetes are designed to guide prevention and management of the manifestations of CVD in patients with diabetes based on data published until end of January 2023." The diagnostic and therapeutic correlations of CVD and CKD in patients with diabetes are summarized in the figure below.

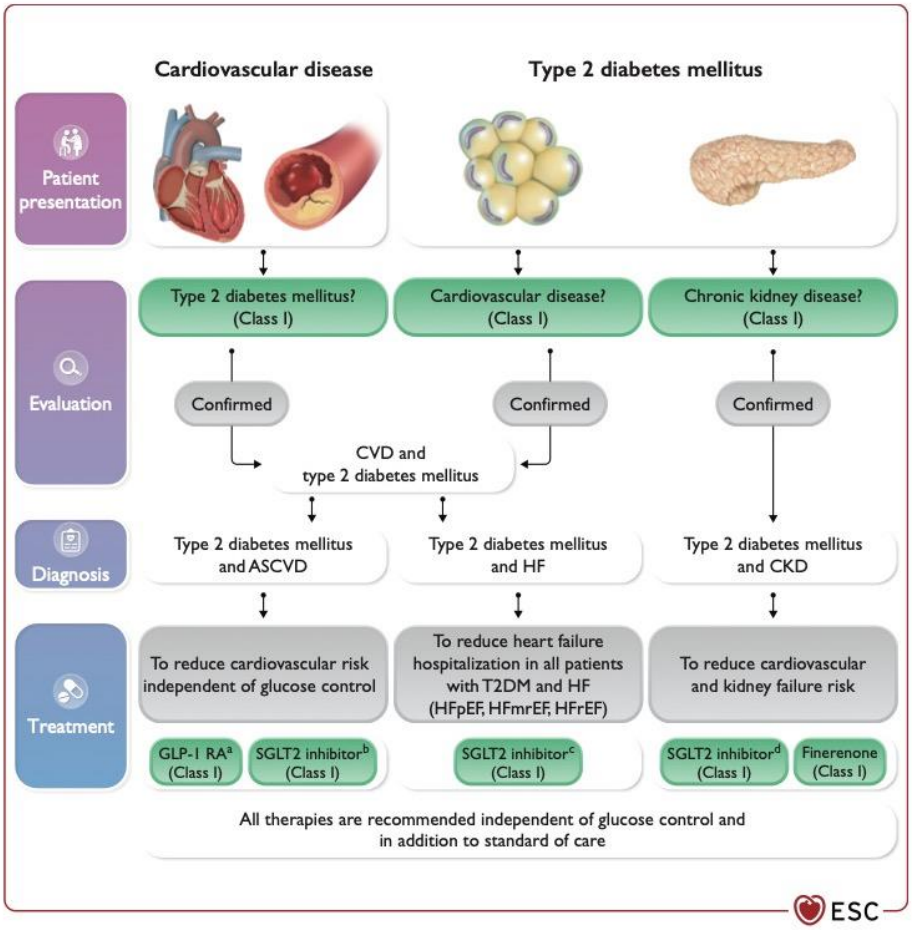

Figure 1 Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; s.c. subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus. [a]GLP-1 RAs with proven cardiovascular benefit: lir-aglutide, semaglutide s.c., dulaglutide, efpeglenatide. [b]SGLT2 inhibitors with proven cardiovascular benefit: empagliflozin, canagliflozin, dapagliflozin, sotagli-flozin. [c]Empagliflozin, dapagliflozin, sotagliflozin in HFrEF; empagliflozin, dapagliflozin in HFpEF and HFmrEF. [d]Canagliflozin, empagliflozin, dapagliflozin.

@2023 Guidelines for the management of cardiovascular disease in patients with diabetes (Marx et al, 2023).

Detailed recommendations are given concerning the choice of antidiabetic drugs. The significance of SGLT2-inhibitors and GLP-1 receptor agonists is specifically described. And a SCORE2-Diabetes algorithm is mentioned: “In patients aged ≥40 years with type 2 diabetes mellitus (T2DM) without atherosclerotic cardiovascular disease (ASCVD) or severe target-organ damage (TOD), it is recommended to estimate 10-year CVD risk using the SCORE2-Diabetes algorithm”. Conclusions related to these guidelines: Patients with CV disease must actively be checked if diabetes or CKD are present and vice versa, and if yes, adequate treatment measures (lifestyle and specific medication) must be undertaken; detailed information about all these measures can be found in the guidelines.

2. Conclusion and recommendations

- CCS, also known as stable angina, is a common cardiovascular condition worldwide.

- The incidence of CCS varies depending on the population and region.
- The progression of CCS can be influenced by various factors, including lifestyle modifications, medication adherence, and comorbidities. With appropriate management, the progression of CCS can be slowed or even halted in some cases.
- Complications of CAD is not rare. Manifestations may be angina (chest pain), myocardial infarction, heart failure, and arrhythmias.
- There exist established concepts in which way a clear diagnose of CAD can be achieved (including also the choice of the different functional imaging techniques), and how therapeutic options shall be chosen in order to reduce the risk of complications and to improve outcomes (see above).
- An important preventive role in this respect plays the management of the classical cardiovascular risk factors, also including the specific choice of medication.
- A special role plays the presence of diabetes. Patients with CV disease must actively be checked if diabetes or CKD are present and vice versa, and if yes, adequate treatment measures (lifestyle and specific medication) must be undertaken. As cited above, detailed information about all these measures can be found in the "2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes".
- The indication if an invasive coronary artery intervention (PCI or CABG) or "only" a medical treatment are necessary, depends on the established diagnosis of the CAD situation.
- Newer studies suppose that inflammation plays also an important role in the development and progression of CCS. Inflammatory biomarkers such as CRP and interleukin-6 (IL-6) have been shown to be associated with an increased risk of cardiovascular disease, including CCS. There are some suggestions in which way inflammation can be countered, also - among others - with medical treatments. In the future, the combined use of aggressive LDL-cholesterol-lowering and inflammation inhibiting therapies may well become standard of care for almost all atherosclerosis patients.
- Exposure to pollution is a newly recognized cardiovascular risk factor. Especially, fine dust which has a diameter below 2.5 um (called PM2.5) provide a health risk because of its small size. There are recommendations how the exposure to PM2.5 can be reduced or avoided.
- Diagnostic and therapeutic guidelines are well summarized in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes (Knuuti et al., 2020) (see above).
- Actually, there is an enormous technical progress of the so far used functional and anatomic imaging techniques. And in combination with new methods like for example AI and Machine Learning techniques it can be expected that this will lead to an improvement of the diagnostic accuracy, and to an optimization of treatment strategies.
- In the future genetic testing might help to identify individuals at a higher cardiovascular risk, and might be a promising issue. Currently, genetic testing cannot not yet be recommended in patients for CAD risk stratification.
- Future developments in CCS may also focus on educating and empowering patients to actively participate in their treatment and lifestyle modifications.

3. Relevance for risk assessment of pilots and ATCOs

In low-risk non-diabetic asymptomatic pilots/ATCOs, CCTA or functional imaging is not indicated.

In asymptomatic diabetic adults (>40 years) functional imaging or CCTA may be considered for advanced CV risk assessment.

Pilots/ATCOs with unexplained chest pain/shortness of breath, the following methods are recommended:

- Exclude ACS (troponin, resting ECG)
- Additional blood tests: full blood count, eGFR, lipid profile, hs-CRP, screening for diabetes, thyroid function
- Chest X-ray
- Resting echocardiography and/or functional imaging should be part of the initial investigation
- CCTA in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone

Pilots/ATCOs with known chronic CAD, there are the following recommendations

- Functional imaging should be part of follow-up investigations
- Lifestyle recommendations (smoking cessation, healthy diet, physical activity, healthy weight, adherence to medications, avoid air pollution)
- Antithrombotic therapy: Low-dose ASS or better Clopidogrel 75mg/day (Koo et al., 2021)
- Lipid lowering drugs: LDL-target < 1.8 mmol/l, < 1.3 mmol/l in very high-risk patients
- Hypertension treatment: Blood pressure targets are < 130/80 mmHg
- Diabetes treatment: HbA1c target < 7%

Features for high event risk

- Exercise ECG: Dukes treadmill score < -10
- SPECT or PET perfusion imaging: area of ischaemia $\geq$ 10% of the left ventricular myocardium
- Stress echocardiography: $\geq$ 3 of 16 segments with stress-induced hypokinesia or akinesia
- Cardiac MRI: $\geq$ 2 of 16 segments with stress perfusion defects or $\geq$ 3 dobutamine-induced dysfunctional segments
- CCTA or invasive coronary angiography: 3-vessel disease with proximal stenoses, left main disease, proximal anterior descending disease
- Invasive functional testing: Fractional flow reserve (FFR) $\leq$ 0.8, instantaneous wave-free ratio (iFR) $\leq$ 0.89
- Impaired left ventricular function
- Chronic kidney disease
- Diabetes
- Older age

Application of the method and/or treatment for risk assessment will be described more in detail in task 2.

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4.6. Echocardiography

This document contains main findings concerning the state-of-the-art of the wide diagnostic spectrum which the imaging technique echocardiography provides. Echocardiography is not a therapeutic

technique per se, but the results of the echocardiographic examinations are important for the definition of the therapeutic options. This means, that this document contains no direct comments concerning treatment options.

1. What is new? – Main findings

Echocardiography, which is a non-invasive imaging technique, plays a critical role in the diagnosis, assessment, and management of coronary artery disease (CAD). Here are some key roles of echocardiography, especially in CAD:

Diagnosis of CAD

Echocardiography can be used to detect signs of CAD, such as wall motion abnormalities, regional or global left ventricular dysfunction, and evidence of myocardial ischemia. It can also help to identify other cardiac conditions that may mimic CAD, such as valvular heart disease or cardiomyopathies, and differentiate them from CAD.

Assessment of Cardiac Function

Echocardiography provides information on cardiac function, including left and right ventricular ejection fraction (LVEF and RVEF respectively), diastolic function and global longitudinal strain (GLS). Reduced LVEF and/or GLS may indicate impaired cardiac function due to CAD, and serial echocardiographic assessments can help to monitor changes in LVEF over time, which can be useful in evaluating the effectiveness of medical or interventional therapies. A recent study suggests that relatively subtle impairments of systolic function (detected based on LVEF or strain) are independently associated with incident heart failure (HF) and HF with reduced LVEF in late life (Reimer Jensen et al., 2021).

Evaluation of Wall Motion Abnormalities

Echocardiography allows the assessment of regional wall motion abnormalities, which can indicate areas of the heart that are not receiving adequate blood supply due to CAD. This can help to identify the location and extent of ischemic regions and guide treatment decisions, such as revascularization strategies, e.g., percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Stress Echocardiography

Stress echocardiography, which combines echocardiography with a stress-inducing manoeuvre (such as exercise or pharmacological stress), can be used to assess inducible ischemia, which is a hallmark of CAD. By evaluating changes in wall motion, LVEF, and other echocardiographic parameters during stress, stress echocardiography can help to identify patients with CAD who may benefit from further evaluation or intervention (Anand et al., 2021)

Monitoring of Cardiac Remodelling

Echocardiography can be used to monitor changes in cardiac structure and function over time, including left ventricular hypertrophy, dilatation, and remodelling, which may occur as a result of CAD. Serial echocardiographic assessments can help to track disease progression and guide management decisions.

Guidance for Interventional Procedures

Echocardiography can provide real-time guidance during interventional procedures, such as PCI, by helping to visualize the coronary arteries, guiding the placement of catheters and stents, and assessing the results of the intervention.

Follow-up after Revascularization

Echocardiography is commonly used for follow-up evaluations after revascularization procedures, such as PCI or CABG, to assess the effectiveness of the intervention, to monitor for complications, and to guide ongoing management.

In summary, echocardiography plays a crucial role in the diagnosis, assessment, and management of CAD by providing valuable information on cardiac function, wall motion abnormalities, stress testing, cardiac remodelling, and guiding interventional procedures. It is a non-invasive, widely available, and relatively low-cost imaging modality that is an important tool in the evaluation and management of patients with suspected or confirmed CAD. However, it should be used in conjunction with other clinical and diagnostic tools, and the interpretation of echocardiographic findings should be done by qualified healthcare professionals experienced in cardiac imaging.

Echocardiography, as a widely used imaging modality for evaluating the heart, has seen several advancements and innovations in recent years. Here are some of the new developments in echocardiography:

3D Echocardiography

Three-dimensional (3D) echocardiography allows a real-time acquisition and display of 3D images of the heart, providing a more detailed and comprehensive assessment of cardiac structures and function. It enables improved visualization of complex cardiac anatomy, such as the mitral valve, and allows a better assessment of cardiac function, volumes, and ejection fraction.

Speckle Tracking Echocardiography

Speckle tracking echocardiography is a technique that allows the assessment of myocardial deformation or strain, which provides information about the contractility and function of the heart. It can help to detect subtle changes in myocardial function before changes occur in traditional parameters such as ejection fraction, making it a sensitive tool for early detection of cardiac dysfunction in conditions such as heart failure and cardiomyopathies.

Strain Imaging (Smiseth, Aalen, & Skulstad, 2021)

Strain imaging is a technique that measures the deformation or strain of the myocardium during the cardiac cycle, providing information about regional myocardial function. It can be used to assess myocardial viability, detect early changes in myocardial function, and evaluate response to therapy in conditions such as heart failure, myocardial ischemia, and cardiomyopathies. Strain is more sensitive to left ventricular dysfunction than ejection fraction and provides additional prognostic information (Potter & Marwick, 2018). Left ventricular global longitudinal strain (GLS) is associated with all-cause mortality and may be useful for risk stratification in patients with aortic valve disease (Saijo et al., 2021). Furthermore, the use of GLS in surveillance for cancer therapy-related cardiac dysfunction is strongly recommended (Thavendiranathan et al., 2021).

Contrast-enhanced Echocardiography

Contrast-enhanced echocardiography involves the use of ultrasound contrast agents, which are microbubbles that enhance the visibility of blood flow and cardiac structures. It can help to improve the detection of myocardial perfusion abnormalities, assess myocardial viability, and evaluate intracardiac shunts, making it a valuable tool in assessing patients with suspected or known CAD.

Artificial Intelligence (AI) and Machine Learning (Asch et al., 2021), (Asch et al., 2019), (Bellfield, Ortega-Martorell, Lip, Oxborough, & Olier, 2022), (Cikes et al., 2019):

AI and machine learning techniques are being increasingly applied to echocardiography in order to improve image analysis, automate measurements, and aid in diagnosis. AI algorithms can assist in automated image segmentation, quantification of cardiac parameters, and detection of abnormal findings, potentially enhancing the accuracy and efficiency of echocardiographic assessments.

Pocket-sized and Handheld Echocardiography

There has been a development of compact, pocket-sized, and handheld echocardiography devices that are portable, affordable, and easy to use, making echocardiography more accessible in various clinical settings, including point-of-care applications, emergency medicine, and resource-limited settings.

Fusion Imaging

Fusion imaging involves the combination of echocardiography with other imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), to provide a more comprehensive and integrated assessment of cardiac anatomy and function. This can help to improve the accuracy and reliability of echocardiographic findings, particularly in complex cases or when assessing cardiac structures that may be difficult to visualize with echocardiography alone.

2. Conclusion and recommendations

Echocardiography is an established imaging technique which is widely used, also in the context of CAD. Many updated versions of its application have come up within the last years. The wide spectrum of information which can be obtained when using echocardiography has been listed above.

According to the “2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes” (Knuuti et al., 2020) the following recommendations for the applicatiom of echocardiography are important:

Indication of resting echocardiography in the initial diagnostic management of patients with suspected coronary artery disease (Class I, Level B) for:

(1) Exclusion of alternative causes of angina

(2) Identification of regional wall motion abnormalities suggestive of CAD

(3) Measurement of LVEF for risk stratification

(4) Evaluation of diastolic function

There are also recommendations for functional imaging (i.e. stress-echocardiography). - And non-invasive functional imaging for myocardial ischaemia (i.e. stress-echocardiography) or coronary CTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone (Class I, Level B). - It is further recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests (Class I, Level C). - Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic (Class I, Level B).

It is important, that reports of echocardiographic examinations are written according to published standards. This is especially important in follow-up investigations. Galderisi et al. and Badano et al. give clear informations about reporting echocardiographic findings (Galderisi et al., 2017), (Badano et al., 2018). As example, here the tables 9 and 10 (table 9 and 10 out of the publication of Galderisi et al.).

Table 9: Standard echocardiographic measurements (Table 1 below)

Table 10: Advanced echocardiographic Doppler parameters (Table 2 below)

(Sourse of both tables: Galderisi et al., 2019)

Table 1 Standard echocardiographic and Doppler measurements

Chamber	Parameter	Normal values
Left ventricle	LV end-diastolic dimension (mm)	≤58.4 (M), ≤52.2 (F)
	LV end-systolic dimension (mm)	≤39.8 (M), ≤34.8 (F)
	LV EDV index (mm/m^2)	<75 (M), <62(F)
	LV ESV index (mm/m^2)	<32 (M), <25(F)
	Relative wall thickness	≤0.42
	LVM index (g/m^2)	≤102 (M), ≤88(F)
	LVEF, biplane (%)	≥52 (M), ≥54(F)
	Transmitral *E* velocity (cm/s)	<50
	Transmitral *E* velocity DT (ms)	>160 to < 220
	Transmitral *E/A* ratio	>0.8 to < 2.0
	Septal annular e′ velocity (cm/s)	>7
	Lateral annular e′ velocity (cm/s)	>10
	LV *E/e′* (average) ratio	<14
Left atrium	Maximal LAVi (mL/m^2)	≤34
Thoracic aorta	Annulus (cm/m^2)	≤1.4 (M and F)
	Sinus of Valsalva (cm/m^2)	≤1.9 (M), ≤2.0 (F)
	Sinotubular junction (cm/m^2)	≤1.7 (M and F)
	Proximal ascending aorta (cm/m^2)	≤1.7 (M), ≤1.9 (F)
Right ventricle	RV basal diameter (mm)	<42
	RV mid diameter (mm)	<36
	RVOT proximal diameter (mm)	<36
	RVOT distal diameter (mm)	<28
	TAPSE (mm)	>17
	Tricuspid annular s′ velocity (cm/s)	>9.5
	Fractional area change (%)	>35
Right atrium	RAVi (mL/m^2)	<30 (M), <28 (F)

DT, deceleration time; *E*, transmitral early diastolic velocity; e′, mitral annular early diastolic velocity; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAVi, left atrial volume index; LV, left ventricular; LVM, left ventricular mass; RAVi, right atrial volume index; RV, right ventricular; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Advanced echocardiographic parameters

Chamber	Parameter	Normal values
Left ventricle	LV GLS (%)	>20%[a]
	3D EDV index (mL/m^2)	<80 (M), <72 (F)
	3D ESV index (mL/m^2)	<33 (M), <29 (F)
	3D LVEF (%)	>54 (M), >57 (F)
Right ventricle	Free wall GLS	>23%[a]

[a]Expressed in absolute value despite of negative sign.
EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; LV, left ventricular; RV, right ventricular.

Possibilities for potential advancements in the future may include

Improved Image Resolution: Advances in ultrasound technology may lead to higher resolution images, allowing more detailed and precise visualization of the heart. This could enable better detection and characterization of heart conditions, such as subtle changes in cardiac anatomy and function.

Artificial Intelligence (AI)-assisted Analysis: AI algorithms could be integrated into echocardiography systems to assist image analysis. These algorithms could automatically identify and measure key parameters, such as ejection fraction, wall thickness, and blood flow velocities, and they could provide real-time feedback to clinicians and potentially improve accuracy and efficiency of diagnoses.

3D/4D Echocardiography: Three-dimensional (3D) and four-dimensional (4D) echocardiography could become more common , allowing a more comprehensive and intuitive assessment of cardiac anatomy and function.

Portable and Wearable Echocardiography: Advances in miniaturization and wireless technology could lead to the development of portable and wearable echocardiography devices. These devices could enable real-time monitoring of the heart in various settings, such as at home or during physical activity, allowing for earlier detection of abnormal heart conditions and more personalized care.

Telemedicine and Remote Echocardiography: Telemedicine could play a larger role in echocardiography, allowing for remote interpretation of echocardiographic images by experts in different locations.

Recommendations for the risk assessment of pilots and ATCOs:

Routine use of echocardiography in asymptomatic pilots/ATCOs without clinical findings of cardiac anomalies (murmurs, etc.) is not recommended.

Pilots/ATCOs with unexplained chest pain/shortness of breath: Resting echocardiography and/or functional imaging should be part of the initial investigation.

Pilots/ATCOs with known chronic coronary artery disease: Functional imaging (for example stress-echocardiography) should be part of follow-up investigations.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method for risk assessment will be described in task 2.

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4.7 The actual role of CT coronary artery calcium score (CACS) and Coronary computed tomographic angiography (CCTA) in the detection of Coronary artery disease (CAD)

This document describes the state-of-the-art of the use of coronary CT-scanning as a diagnostic tool in cardiovascular medicine. The content of this document reflects the most recent ESC and ACC/AHA guidelines. It also follows the statements of the latest expert consensus document of the Society of Cardiovascular Computed Tomography. It is concluded that in contemporary cardiovascular medicine CT-scanning has become a very important and often first-line diagnostic tool in the detection and the

management of coronary artery disease. The different therapeutic options which are derived from the results of the CT-scanning are also described in this document.

1. What is new? - Main findings

Coronary artery calcium score (CACS)

When CT-scans became clinically available, the first cardiac application was measuring of the coronary calcium score (CACS). It soon became clear that the presence of coronary calcium is a marker of coronary atherosclerosis. Furthermore, the higher the amount of calcium the higher the risk of future cardiovascular events (Rijlaarsdam-Hermsen et al., 2020). It was found that the CACS provides relevant prognostic information in addition to the usual clinical risk markers in patients with suspected coronary artery disease (CAD). The latest AHA/ACC cholesterol guidelines on primary prevention of CAD (Arnett et al., 2019) recommend the use of the CACS to help in decision making for the use of statins: If the CACS is 0, it is reasonable to withhold statin therapy (as long as higher conditions are absent). If the CACS is 1 - 99, it is reasonable to initiate statin therapy for patients ≥55 years of age. If the CACS is ≥100, it is reasonable to initiate statin therapy. In the ESC 2021 guidelines on cardiovascular disease prevention, the use of CACS is considered less useful (Visseren et al., 2021). In these guidelines, it was stated that CAC scoring may be considered to improve risk classification around treatment decision thresholds, and that plaque detection by carotid ultrasound could be used as an alternative when CAC scoring is unavailable or not feasible (level of evidence IIa, B). The evidence for this classification, however, dates from two review studies published in 2012 and 2018. - Inherent to its principle of the visualization of calcium, non-calcified plaques will remain undetected with CACS. These plaques can only be found with Coronary computed tomographic angiography (CCTA). Despite this limitation, we should realize that CACS is a simple technique that brings a refinement and improvement of risk profiling as it will show the presence of coronary atherosclerosis that previously remained undetected by any other screening method (except CCTA). CACS can be used in decision making when treatment with statins is considered. Therefore, many countries around the world use CACS nowadays, albeit in different ways. A recent state-of-the-art paper has described these variations (Golub et al., 2023). Most clinical practice guidelines agree that CACS is vital to up- or down-classify intermediate-risk individuals. None of the countries, however, has a simple protocol. Key agreements among country guidelines for common indications for CACS is to begin at age >40 years, and for intermediate-risk and asymptomatic patients with threshold CACS >100, initiate/consider statin; and for CACS = 0, downgrade risk and withhold statin with repeat in 5-10 years. US-guidelines recommend statins with a CACS = 1-99 at any age, especially after age 55 years. Additionally, for a CACS ≥100 or ≥75th percentile for age/sex statin therapy should be initiated at any age. Interestingly, the US Preventive Services Task Force (USPSTF) finds insufficient evidence for the use of the CACS in addition to traditional cardiovascular risk assessment in asymptomatic adults for atherosclerotic cardiovascular disease (ASCVD) prevention. They conclude that one of the most valuable uses of CACS is to help the patient to make the statin decision. - The International Atherosclerosis Society guidelines recommend CACS to decide on statin therapy in low- to moderate-risk patients, and patients with a CACS ≥100 should be considered for statins. - The Society of Cardiovascular Computed Tomography (SCCT) recommends CACS for all but those with 10-year ASCVD risk >20%. Those with a CACS = 0 should not be treated with statins and those with a CACS >100 should have high-intensity statin

combined with aspirin. The SCCT encourages the CACS to facilitate the decision for statins and need for intensifying dosing. The low-risk cohort, defined as <5%, has too few CACS >0 to benefit from CACS, but the CACS can help decide on statin therapy in those with risk enhancing factors, which vary, but are used by nearly all countries. - The Cardiac Society of Australia and New Zealand guidelines (CSANZ) have tighter thresholds for treatment with statins: CACS = 0 withhold statins, CACS = 1-100 favors lifestyle improvement, CACS 101-400 indicates statin if score is >75th percentile, and >400 requires statin therapy. The use of CACS is recommended for lower-risk patients (10-year cardiovascular risk 6%-10%) with a family history of premature CVD and diabetic patients 40-60 years of age.

Advises on the use of the CACS for updating the EASA Aeromedical Requirements will be based on the European Society of Cardiology and European Atherosclerosis Society guidelines. These guidelines recommend the use of CACS to decide on statin therapy. In low- to moderate-risk patients with CACS ≥100 treatment with statins should be considered. The CACS can facilitate decisions about preventive treatment. The CACS can be used to upgrade risk (e.g., in young patients and in women) or to downgrade risk (if CACS = 0). With CACS = 0, treatment with statins is not justified except in diabetes, a family history of premature CHD, or in cigarette smokers. A CACS of 1-99 favors statin therapy, especially after the age of 55 years. If CACS is ≥100 and ≥75th percentile for age/sex, statin treatment is advised at any age.

Coronary computed tomographic angiography (CCTA)

Cardiac CT-scanning has evolved in such a way that it is now possible to acquire accurate images of the coronary arteries with the use of an intravenous contrast agent. With this technique called Coronary computed tomographic angiography (CCTA) not only stenotic lesions can be detected, but also plaque morphology and plaque composition can be assessed. It is even possible to detect features of plaque instability (Versteylen et al., 2013). Recent studies have shown that patients with non-obstructive coronary lesions on CCTA also significantly benefit from treatment with statins (Indraratna et al., 2022). - In addition to acquire anatomical and histological images, nowadays, with CT-scanning, it is possible to assess myocardial perfusion (CT perfusion or CTP) and Fractional flow reserve (FFR) (Branch et al., 2017; Nieman & Balla, 2020; Seitun et al., 2020). By combining anatomy and perfusion, CCTA has become a very promising first line screening method in patients with a suspicion of CAD. In 2021, an Expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT) on the appropriate use of CT-scanning was published (Narula et al., 2021). The clear and evidence-based statements in this document are of great value as they describe the methodology, the sensitivity and specificity of CT-scanning and the value and applicability of CCTA in current clinical practice. Also, recommendations have been made with respect to FFR-CT. Some of these recommendations have been adopted by the guideline committees of the AHA/ACC and ESC (Arnett et al., 2019; Knuuti et al., 2020). In the ESC guidelines 2019 for the diagnosis and management of chronic coronary syndromes CCTA has gained a class I indication as it is stated that non-invasive functional imaging for myocardial ischemia or CCTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. In these guidelines, several limitations of CCTA are described, one of which is the lack of accuracy of CCTA to detect significant stenosis in the case of extensive coronary calcifications. In this situations CCTA has a class III recommendation.

Summary of the 2019 SCCT consensus document on CCTA (Narula et al., 2021):

CAD is the most important etiology of chest pain in clinical practice, it has significant prognostic implications and it is eminently treatable. Moreover, CAD is highly prevalent and may exist in various forms, extending from the presence of non-obstructive plaque to flow limiting disease and to complete obstruction of a vessel. Not only the presence, but the location and extent of stenosis, the composition of the plaque underlying the stenosis, its physiologic effect and the health of the distal bed, all determine hard outcomes (death or MI) (Chang et al., 2018). Thus, identifying the presence of CAD is a critical part of cardiac practice requiring significant investment in time and resources. A plethora of non-invasive testing options are available for evaluating patients presenting with chest pain that could be related to ischemic heart disease but there is significant controversy about what is the most optimal testing strategy. Consistent with past paradigms for CAD, these have all focused mainly on identifying flow limiting disease that could cause ischemia. Broadly, these can be divided into those assessing anatomy, those assessing physiology and those that can combine some characteristics of both anatomy and physiology. While there is a significant body of evidence for each strategy and current randomized controlled trials (albeit, with all their limitations as pragmatic studies) have not found a consistent difference in major outcomes with one strategy or the other, they are not equivalent. There is already evidence that some strategies influence hard outcomes through advantages other than revascularization (e.g., better titration of preventive medical therapy after seeing an atherosclerotic plaque with CCTA vs. physiologic testing), and future studies may show intrinsic advantages of one strategy over the others.

In general, CCTA has the advantage of reducing cardiovascular mortality and myocardial infarction (Williams and SCOT-Heart study by Newby) (Investigators et al., 2018; Williams et al., 2016). It visualizes the stenosis and the atheromatous plaque as opposed to making an educated guess about its presence, as with physiologic testing. CCTA has excellent sensitivity for identifying flow limiting disease and has very high negative predictive value, making it the strongest test to rule out flow limiting CAD, especially in patients with low to intermediate risk. It has the best evidence so far for decreasing the number of procedures in patients in whom a decision to define coronary anatomy with invasive coronary angiography (ICA) was already taken based on other non-invasive criteria. Moreover, deferring ICA in this manner has been shown to be safe. Using CCTA as the first test for stable chest pain syndromes also reduces non-productive ICA (patients where ICA does not show CAD that needed a class I indicated intervention) with a slightly increased rate of diagnostic catheterization (Chang et al., 2019). This has led to the NICE guidelines recommending of CCTA as the first line test in patients without known CAD who present with typical or atypical chest pain. - CCTA has lower specificity and positive predictive value, which places it in the same diagnostic performance band as most tests using stress imaging. However, the newer value-added modalities of CCTA (CT-FFR and CTP) may significantly minimize this disadvantage. A reasonably strong body of evidence supports the use of CT-FFR for the diagnosis of CAD in patients presenting with stable chest pain syndromes and this results in diagnostic rates comparable to invasive FFR (Ko et al., 2019). Early data from studies using CTP seem to suggest a similar gain in diagnostic accuracy. It is likely that a suite of CT based testing (CACS, CCTA, FFR-CT, CTP in some combination), often needing only a small increment in time, effort, contrast agent or radiation, is likely to elevate its positive predictive value to the best of breed range. Tiered testing as in CRESCENT I and II has shown distinct advantages in early discharge and safe outcomes in small randomized control trial settings (Lubbers et al., 2018; Lubbers et al., 2016).

However, robust evidence-based recommendations await well conducted prospective studies in this arena. Hybrid strategies involving both CCTA and positron emission tomography (PET) are also in development to improve the predictive value of a positive CCTA. - CTA also has a unique advantage possessed by no other testing, based as they are on identifying a flow limiting stenosis indirectly through an ischemic response. It provides a look at the plaque extent and nature even if there is no flow limiting lesion; multiple studies show that it is better at parsing out future risk than physiologic testing. Through its ability to visualize calcified and non-calcified plaque, it identifies the majority of patients with future events in prospectively tested cohorts, far better than by identifying flow limiting stenosis by any test (Chang et al., 2018; Hell et al., 2017; Williams et al., 2020). It also promotes better initiation and maintenance of preventive therapy (use of guideline directed medication like statins and anti-platelet therapy) and may thus reduce future hard events without a difference in revascularization rates. It has a small cost in terms of dye load and radiation, but many centers are already using protocols to decrease both, and newer strategies are likely to significantly minimize this risk further. - Thus, CCTA is a robust test that, in addition to reducing myocardial infarction and cardiovascular mortality, serves as a gatekeeper for invasive testing, is cost effective and better allocates the use of high cost downstream testing as well. The data support the widespread use of CCTA as the first line test in the assessment of patients without known CAD who present with stable chest pain. - A number of limitations to the application of CCTA include the limitations imposed by the spatial resolution of current CT scanners, challenges from variations between reconstruction algorithms, and the additional time to perform these assessments. Future advances that improve CT resolution, standardize acquisition techniques and reconstruction algorithms and automate image analysis will further improve the clinical utility of these techniques (Choi et al., 2021; Dey et al., 2019; Hong et al., 2019; Kang et al., 2015; Nakanishi, Motoyama, Leipsic, & Budoff, 2019; Williams, Earls, & Hecht, 2022; Zreik et al., 2019).

2. Conclusion and recommendations

In current practice of cardiovascular medicine CT-scanning has become an indispensable and often first-line diagnostic tool in the management of asymptomatic adults with increased cardiovascular (CV) risk. In this group simple non-contrasted CT-scanning can reveal the presence (or absence) of coronary calcifications. With CACS the amount and severity of calcification can be determined. The CACS has shown to be a reliable indicator for the presence of coronary atherosclerosis and the amount of calcification is related to future risk of cardiac events.

Furthermore, in adults presenting with chest pain suspected to be of cardiac origin, having a low to intermediate likelihood of CAD, contrasted CT-scanning can reveal the presence of CAD and will also show the presence of coronary artery stenoses. In the majority of patients, with CCTA, the severity of coronary stenoses can be assessed. However, at the site of severe coronary calcification the grading of coronary stenosis with CT is unreliable, and in this case, additional diagnostic tests should be used. Nowadays, with modern CT-scanning technique, it has become possible to measure FFR-CT. When these techniques are not available, other diagnostic tools will have to be applied like PET-CT, exercise-single-photon emission tomography (SPECT), dobutamine stress echocardiography or, eventually, ICA.

Finally, in the management of patients with known CAD and recurrent symptoms, CCTA can play an important role in assessing coronary stenosis. Subsequently, myocardial perfusion in the area subtending the coronary stenosis can be measured with FFR-CT.

After coronary stenting, CCTA will be able to detect the presence of restenosis. After coronary artery bypass surgery (CABG), CCTA can detect graft failure.

For the newest aeromedical requirements, it will be indisputable that CT-scanning will play an important and probably pivotal role as diagnostic tool in the risk-assessment of asymptomatic pilots and ATCOs with elevated cardiovascular risk and in pilots and ATCOs who present with symptoms suspected to be related to CAD.

Recommendations for the use of CACS

Adopted from the ESC-guidelines and from the SCCT expert consensus document.

1. For risk stratification, CAC scoring is vital to up- or down-classify intermediate-risk individuals.
2. A common indication for CACS is to begin at age >40 years, and for intermediate-risk and asymptomatic patients with threshold CACS >100, initiate/consider statin; and for CACS = 0, downgrade risk and withhold statin with repeat in 5-10 years. CACS of 101-400 is high-risk and could benefit from statins.
3. CACS helps in deciding statin use in diabetics by type 1 versus 2 and age without other risk factors.
4. CACS should not be used in adults with 10-year ASCVD risk >20%. Those with a CACS = 0 should not be treated with statins and those with a CACS >100 should have high-intensity statin + aspirin.

Recommendations for the use of CCTA (1)

Adopted from the SCCT expert consensus document.

A. Evaluation of stable CAD: CCTA in native vessels

1. It is appropriate to perform CCTA as the first line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g., dyspnea on exertion, jaw pain).
2. It is appropriate to perform CCTA as a first line test for evaluating patients with known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g., dyspnea on exertion, jaw pain).
3. It is appropriate to perform CCTA following a non-conclusive functional test, in order to obtain more precision regarding diagnosis and prognosis, if such information will influence subsequent patient management.
4. It is recommended to perform CCTA as the first line test when considering evaluation for revascularization strategies using the ISCHEMIA Trial.
5. It may be appropriate to perform CCTA in selected asymptomatic high risk individuals, especially in those who have a higher likelihood of having a large amount of non-calcified plaque.
6. It is rarely appropriate to perform coronary CCTA in very low risk symptomatic patients, e.g., <40 years of age with non-cardiac symptoms (chest wall pain, pleuritic chest pain).
7. It is rarely appropriate to perform CCTA in low- and intermediate risk asymptomatic patients.

B. Evaluation of stable CAD: CCTA post revascularization:

1. It is appropriate to perform CCTA in symptomatic patients with intracoronary stent diameter ≥3.0 mm. Measures to improve accuracy of stent imaging should be utilized, to include strict heart rate control (goal <60 bpm), iterative reconstruction, sharp kernel reconstruction, and mono-energetic reconstructions (when available). Protocols to optimize stent imaging should be developed and followed.
2. It may be appropriate to perform CCTA in symptomatic patients with stents <3.0 mm, especially those known to have thin stent struts (<100 mm) in proximal, non-bifurcation locations.
3. It is appropriate to perform CCTA for evaluation of patients with prior CABG, particularly if graft patency is the primary objective.
4. It is appropriate to perform CCTA to visualize grafts and other structures prior to re-do cardiac surgery.

C. Evaluation of stable CAD: CCTA with FFR or CTP:

1. It may be appropriate to perform CT derived FFR and CTP imaging to evaluate the functional significance of intermediate stenoses on CCTA (30-90% diameter stenosis) particularly in the setting of multivessel disease to help guide ICA referral and revascularization treatment planning. LM stenosis ≥50% and severe triple vessel disease should undergo ICA.
2. Adding FFR-CT and stress-CTP to CCTA increases specificity, positive predictive value, and diagnostic accuracy over regular CCTA.
3. FFR-CT and stress-CTP may be largely comparable in diagnostic utility. CTP is a potentially valuable alternative particularly when CT-FFR is technically difficult (e.g., suboptimal CCTA quality, prior revascularization).

D. Evaluation of stable CAD: CCTA in other conditions:

1. It is appropriate to perform CCTA for coronary artery evaluation prior to noncoronary cardiac surgery as an equivalent alternative to ICA in selected patients, e.g., low-intermediate probability of CAD, younger patients with primarily non-degenerative valvular conditions.
2. CCTA may be considered an appropriate alternative to other noninvasive tests for evaluation of selected patients prior to noncardiac surgery.
3. It is appropriate to perform CCTA to exclude CAD in patients with suspected non-ischemic cardiomyopathy.
4. It may be appropriate to perform late enhancement CT imaging to detect infiltrative heart disease or scar in selected patients who have non-ischemic or ischemic cardiomyopathy and who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for ablation therapy).
5. It may be appropriate to perform CCTA as an alternative to invasive coronary angiography for the screening of patients for coronary allograft vasculopathy in selected clinical practice settings.
6. It is appropriate to perform CCTA for the evaluation of coronary anomalies.

7. It is appropriate to ECG gate aortic dissection and aneurysm CT-testing, as well as pulmonary embolus studies in men >45 years and women >55 years, and analyze and report the coronary arteries.
8. CT-testing with a limited delayed image (60-90 sec) is an appropriate alternative to TEE when the primary aim is to exclude LA/LAA thrombus and in patients where the risks associated with TEE outweigh the benefits. In all situations CT-testing and TEE should be discussed with the patient in the setting of shared decision making.
9. It may be appropriate to perform late enhancement CT imaging for the evaluation of myocardial viability in selected patients who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for revascularization).

Recommendations for the use of CCTA (2)

Adopted from the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

A. Class I recommendations:

1. Non-invasive functional imaging for myocardial ischemia or CCTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.
2. It is recommended that selection of the initial non-invasive diagnostic test be based on the clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests.
3. Functional imaging for myocardial ischemia is recommended if CCTA has shown CAD of uncertain functional significance or is not diagnostic.
4. ICA is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood and severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).

B. Class IIa recommendations:

1. ICA with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing.
2. CCTA should be considered as an alternative to ICA if another non-invasive test is equivocal or non-diagnostic.

C. Class III recommendations:

1. Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make good image quality unlikely.

In summary, CACS and CCTA are new techniques that have brought an upgrade in our diagnostic armamentarium for further improvement in the risk-profiling of pilots and ATCOs. In this respect, CT-scanning deserves a firm place in the new EASA aeromedical requirements. With CT-scanning we will be able to further downsize the clinical risk inherent to the presence of coronary atherosclerosis as we will be able to intervene earlier in the pathological process of coronary atherosclerosis.

3. Relevance for the risk assessment of pilots and ATCOs

In healthy pilots and ATCOs without CV risk factors, there is no indication for CACS or CCTA.

In asymptomatic, apparently healthy pilots with an increased cardiovascular risk a SCORE-2 or ADVANCE risk score predicting ≥10% mortality and non-fatal cardiovascular events in the following 10 years, a CACS should be performed and, when indicated, CCTA should follow. This advice follows the assumption that the acceptable 1% annual risk level for acute incapacitation for pilots is applied.

In subjects with very high CACS, an alternative imaging modality than CCTA should be used as with high CACS, CCTA has limited accuracy to detect significant coronary stenosis with too many false positive readings. This shortcoming can be overcome by adding FFR-CT to assess myocardial perfusion.

In pilots and ATCOs with a CACS >100 (>75th percentile) statin therapy should be considered.

CCTA can be used as the first line diagnostic test in the assessment of pilots and ATCOs without known CV disease who present with stable chest pain and a low to intermediate CV risk.

In symptomatic pilots and ATCOs who are known with CV disease, CCTA with FFR is recommended as a first line imaging modality to determine if flow-limiting stenoses are present.

When clinically available, after PCI or CABG, CT-FFR could replace the currently advised perfusion tests like SPECT or stress-MRI. Dobutamine stress echocardiography will have a lower performance with a lower sensitivity than CT-FFR to rule out myocardial perfusion abnormalities.

Application of the method and/or treatment for risk assessment will be described more in detail in task 2.

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4.8 Cardiac MRI in coronary artery disease (CAD)

This document describes the state-of-the-art and future perspectives of Cardiac magnetic resonance imaging (MRI), especially in patients with known or suspected coronary artery disease. Cardiac MRI is a diagnostic and not primarily a therapeutic method, even if the results when applying this technique influence the therapeutic options. Therefore, there are just a few comments concerning treatment options in this document.

1. What is new? - Main findings

While cardiac MRI is not the primary imaging modality used to diagnose CAD, it can provide valuable information about the structure and function of the heart.

Cardiac MRI focuses on imaging the heart. It can provide detailed images of the heart's structure, including the chambers, valves, and blood vessels. Cardiac MRI can help to assess the size and function of the heart, to detect any abnormalities, and to evaluate the presence and extent of scar tissue caused by previous heart attacks.

Stress perfusion MRI: This technique involves performing an MRI while the heart is stressed, usually by medication like adenosine, in order to assess blood flow to the heart muscle. Comparing images taken before and after stress can help to identify areas of the heart that may not be receiving adequate blood supply due to coronary artery narrowing or blockages. In a meta-analysis, the comparison with invasive measured fractional flow reserve (FFR) showed a high sensitivity and specificity (Kiaos, Tziatzios, Hadjimiltiades, Karvounis, & Karamitsos, 2018). The event rate within 4 years in normal stress perfusion MRIs was below 1% (Kwong et al., 2019). - Quantitative perfusion MRI has an increasingly important role in the management of patients frequently encountered with angina and non-obstructive CAD (Rahman et al., 2021).

Myocardial viability assessment: In patients with known coronary heart disease (CHD), MRI can be used to assess myocardial viability, which refers to the amount of viable, functioning heart tissue in areas affected by reduced blood flow. This information can help to guide treatment decisions, such as to determine the potential benefit of revascularization procedures like angioplasty or bypass surgery.

Late Gadolinium enhancement (LGE) and T1/T2-weighted imaging: LGE can detect fibrosis after myocardial infarction or myocarditis. It helps to make a final diagnosis in up to 50% of patients with ‘Myocardial infarction with non-obstructed coronary arteries’ (MINOCA) (Lintingre et al., 2020). LGE MRI is more sensitive than echocardiography for the detection of intracardiac thrombus (Velangi et al., 2019). The probability for major adverse cardiovascular events in patients with myocarditis is twice higher within 4,7 years when fibrosis is detected. (Dastidar et al., 2019). However, the sensitivity of LGE is only 60%. - Myocardial native T1 and extracellular volume fraction (ECV) mapping have emerged as cardiac magnetic resonance biomarkers providing unique insight into cardiac pathophysiology (Robinson, Chow, & Salerno, 2019; Treibel et al., 2020). When native T1 mapping is added, the

diagnostic accuracy is much better with an AUC 0.95 (Kotanidis et al., 2018). With T2 mapping early identification of chemotherapy induced myocardial damage is possible (Galan-Arriola et al., 2019).

In patients with chronic coronary syndrome, current clinical practice does often not adopt guideline-recommendations (Knuuti et al., 2020) on the use of diagnostic tests in a significant proportion of patients. When the diagnostic approach would adopt guideline-recommendations, invasive procedures would less frequently be used and the diagnostic yield and therapeutic utility would be superior (Neglia et al., 2023).
Cardiac MRI is feasible in patients with intermediate pretest probability of obstructive CAD in the setting of centres with a small volume of using this technique. However, as opposed to infarct detection with LGE, the interpretation of stress perfusion imaging is more challenging. Therefore, collaboration with reference centres is useful (Gleditsch et al., 2023).
The development of faster imaging techniques can significantly reduce scan times while maintaining image quality. This would enhance patient comfort and allow for broader utilization of cardiac MRI. Artificial intelligence and machine learning algorithms have the potential to automate and optimize various aspects of cardiac MRI, including image acquisition, reconstruction, and analysis. (van Assen, Razavi, Whelton, & De Cecco, 2023). These technologies can improve efficiency, accuracy, and reproducibility in interpretation and diagnosis. Further advancements in cardiac MRI techniques for tissue characterization, such as improved T1 and T2 mapping, extracellular volume quantification, and diffusion-weighted imaging, can provide more detailed and specific information about myocardial tissue properties. This could aid in the early detection, characterization, and monitoring of cardiac diseases. The combination of cardiac MRI with other imaging modalities, such as positron emission tomography (PET) can provide complementary information on myocardial perfusion, metabolism, and viability. The fusion of multiple imaging modalities could enhance the diagnostic accuracy and comprehensive assessment of cardiac disease (Daubert et al., 2021). Efforts to make cardiac MRI more accessible and cost-effective are ongoing. This includes the development of smaller and more affordable MRI systems, as well as streamlined protocols that optimize imaging efficiency and reduce resource utilization.

Safety: Some publications about safety showed no alterations of DNA and of cell integrity (Critchley et al., 2018). A cardiac MRI can be performed also in pregnancy without risk and can guide clinical decision making (Herrey, Francis, Hughes, & Ntusi, 2019).

When to use cardiac MRI? The indication for using the one or the other anatomical or functional non-invasive imaging technique (or a combination of those techniques) is mainly dependent on the likelihood of the presence of coronary lesions. Of course, this important information is also valid for cardiac MRI. This is well described in the “2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes” (Knuuti et al. 2020).

2. Conclusion and recommendations

- Cardiac MRI is one of the important non-invasive imaging techniques for the assessment of the structure and function of the heart, including the coronary artery situation.
- It is a safe method.
- Cardiac MRI can be performed as a stress test: Stress perfusion MRI. In this application cardiac MRI operates as a functional test. This technique allows to determine the blood flow to the

heart muscle. It is a test mainly used to asses if myocardial ischemia is present or not. This stress test has a high sensitivity and specificity.

- Cardiac MRI allows the assessment of the myocardial viability. And it is also used to detect fibrosis after myocardial infarction or myocarditis by involving the imaging methods Late Gadolinium enhancement (LGE) and T1/T2-weighted imaging.
- The extent of application of cardiac MRI is dependent on the size of the hospital, where cardiac MRI is performed, on the MRI devices, and on the expertise of the specialists executing this method.
- The indication if cardiac MRI shall be used is dependent on several parameters, the most important one is the likelihood of the presence of coronary lesions.
- Cardiac MRI experiences an enormous development. Artificial intelligence and machine learning techniques will result in faster and more precise imaging techniques. This will improve efficiency, accuracy, and reproducibility in interpretation and diagnosis, and will improve the indications for treatment options (for example if an invasive coronary artery intervention is necessary or not).

3. Relevance for risk assessment of pilots and ATCOs

In low-risk non-diabetic asymptomatic pilots/ATCOs, cardiac MRI is not indicated.

In asymptomatic diabetic adults (>40 years), stress perfusion MRI may be considered for advanced CV risk assessment.

Pilots/ATCOS with unexplained chest pain/shortness of breath, Stress perfusion MRI could be part of the initial investigation.

In pilots/ATCOS with known chronic coronary artery disease, Stress perfusion MRI could be part of the follow-up investigations.

A cardiac MRI, which has $\geq$ 2 of 16 segments with stress perfusion defects, is considered as feature for high event risk.

More detailed application of the method and/or treatment for risk assessment of pilots and ATCOs will be described in task 2.

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4.9 Nuclear medicine methods: SPECT and PET

This document contains an analysis of the state-of-the-art concerning the nuclear medicine methods SPECT and PET, when applied in the evaluation of myocardial ischemia. These techniques are diagnostic methods. They are not direct therapeutic options, they have only indirect therapeutic effects, as they form a basis for the decision concerning therapeutic procedures. Therefore, there are no specific comments about therapeutic options in this document in relationship of SPECT and PET.

1. What is new? - Main findings

What is the state-of-the-art analysis concerning the nuclear medicine methods SPECT and PET? In which way do they differ from other functional imaging techniques in the evaluation of myocardial ischemia?

For the analysis of coronary artery alterations, a wide range of methods exist. These tests can be divided into those which give information about the anatomical situation of the coronary artery lesions and into those which give insight into their functional consequences. Coronary computed tomographic angiography (CCTA) and invasive coronary angiography belong to the first group; they visualize coronary stenosis at high resolution and reliably rule out the presence of significant coronary artery disease. Functional imaging techniques are used for the assessment of the functional consequences of a coronary stenosis, with the main question “Is there evidence of myocardial ischemia or not?”. For the detection of myocardial ischemia, the following techniques are used: Stress ECG, Stress echocardiography, Cardiovascular magnetic resonance imaging (MRI), Single-photon emission tomography (SPECT) and Positron emission tomography (PET). When using fractional flow reserve (FFR), then CCTA is besides an anatomical also a functional method. Machine learning techniques and procedures based on artificial intelligence respectively are used more and more in these methods; they enhance the accuracy of the results. - In this document, we focus on the nuclear medicine methods SPECT and PET in relationship to cardiac ischemia. Stress echocardiography and CMR are discussed in separate documents within task 1. And concerning the application of Stress ECG, appropriate comments are found in the document “Chest pain, myocardial ischemia and indications for coronary artery revascularization”.

The important role of SPECT and PET is verified in numerous publications, for example in the one of Gulati et al. (Gulati et al., 2021) or the one of the “2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes” (Knuuti et al., 2020).

Here a citation of the publication of Gulati et al. (Gulati et al., 2021): “After ACS (comment: ACS = acute coronary syndrome) has been ruled out, rest/stress positron emission tomography (PET) or single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) allows for detection of perfusion abnormalities, measures of left ventricular function, and high-risk findings, such as transient ischemic dilation. For PET, calculation of myocardial blood flow reserve (MBFR, the ratio of peak hyperaemia to resting myocardial blood flow) adds diagnostic and prognostic information over MPI data.” The different tests used for the analysis of the coronary artery situation are summarized in the following figure (Gulati et al., 2021):

Pretest likelihood of CAD					
	Low	→ No testing necessary	→ Option for CAC for ASCVD risk stratification		
	Intermediate-high	→ Younger patient (<65 y of age)	OR	Less obstructive CAD suspected	→ CCTA favored
	Intermediate-high	→ Older patient (≥65 y of age)	OR	More obstructive CAD suspected	→ Stress testing favored

	Favors use of CCTA	Favors use of stress imaging
Goal	• Rule out obstructive CAD • Detect nonobstructive CAD	• Ischemia-guided management
Availability and expertise	• High-quality imaging and expert interpretation routinely available	• High-quality imaging and expert interpretation routinely available
Likelihood of obstructive CAD	• Age <65 y	• Age ≥65 y
Prior test results	• Prior functional study inconclusive	• Prior CCTA inconclusive
Other compelling indications	• Anomalous coronary arteries • Require evaluation of aorta or pulmonary arteries	• Suspect scar (especially if PET or stress CMR available) • Suspect coronary microvascular dysfunction (when PET or CMR available)

Stress testing information					
	ETT	Stress echocardiography	SPECT MPI	PET MPI	Stress CMR MPI
Patient capable of exercise	✓	✓	✓		
Pharmacologic stress indicated		✓	✓	✓	✓
Quantitative flow				✓	✓
LV dysfunction/scar		✓	✓	✓	✓

Figure 7: Choosing the Right Diagnostic Test. ASCVD indicates atherosclerotic cardiovascular disease; CAD,

coronary artery disease; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance; ETT, exercise tolerance test; LV, left ventricular; MPI, myocardial perfusion imaging; PET, positron emission tomography and SPECT, single-photon emission computed tomography.

@ 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines (Gulati et al., 2021).

Other citations of Gulati et al. (Gulati et al., 2021): "Testing choice will be influenced by site expertise and availability, but knowledge regarding which test may be preferable is useful when selecting between different modalities. Cost should also be considered, when known by the ordering clinician and there is equipoise between available modalities. The exercise ECG is the lowest cost procedure used in the diagnostic evaluation when compared with stress imaging or anatomic procedures, with the exception of coronary artery calcium (CAC) scoring. For all imaging procedures, costs vary by payer and site of services." … "Although PET and SPECT are grouped together, PET has improved diagnostic and prognostic performance, especially when quantitative assessment of MBF can be performed. A recent clinical trial (n=475) reported a higher diagnostic accuracy with stress PET MPI compared with other stress test modalities." (MBF = myocardial blood flow).

Here a citation of the "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes" (Knuuti et al., 2020). "Functional non-invasive tests: Functional non-invasive tests for the diagnosis of obstructive CAD are designed to detect myocardial ischaemia through ECG changes, wall motion abnormalities by stress CMR or stress echocardiography, or perfusion changes by single-photon emission CT (SPECT), positron emission tomography (PET), myocardial contrast echocardiography, or contrast CMR. Ischaemia can be provoked by exercise or pharmacological stressors, either by increased myocardial work and oxygen demand, or by heterogeneity in myocardial perfusion by vasodilatation. Non-invasive functional tests are associated with high accuracy for the detection of flow-limiting coronary stenosis compared with invasive functional testing [fractional flow reserve (FFR)]. However, lower-grade coronary atherosclerosis not linked with ischaemia remains undetected by functional testing and, in the presence of a negative functional test, patients should receive risk-factor modification based on commonly applied risk charts and recommendations."

Knuuti and Ballo et al. (Knuuti et al., 2018) made a meta-analysis concerning the post-test disease probabilities of the above mentioned anatomical and functional methods used for the analysis of the significance of coronary artery stenoses. They defined as aim: "To determine the ranges of pre-test probability (PTP) of coronary artery disease (CAD) in which stress electrocardiogram (ECG), stress echocardiography, coronary computed tomography angiography (CCTA), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance (CMR) can reclassify patients into a post-test probability that defines (>85%) or excludes (<15%) anatomically (defined by visual evaluation of invasive coronary angiography [ICA]) and functionally (defined by a fractional flow reserve [FFR] <_0.8) significant CAD." … "Table 11 summarizes the performance estimates for every diagnostic technique according to each reference standard. Some techniques had various subcategories typically according to the type of stressor utilized. Some of these

subcategories are less commonly used or did not yield adequate information for a summary estimate (e.g. stress echo with dobutamine stress n = 30, dobutamine stress SPECT n = 2, and dobutamine stress CMR n = 2) and were not included in these estimates."

Table 11 (Knuuti et al., 2018)**:**

Table 1 The performance of different tests for anatomically and functionally significant coronary artery disease

Anatomically significant CAD					Functionally significant CAD				
Test	**Sensitivity (%), (95% CI)**	**Specificity (%), (95% CI)**	**+LR (95% CI)**	**−LR (95% CI)**	**Test**	**Sensitivity (%), (95% CI)**	**Specificity (%), (95% CI)**	**+LR (95% CI)**	**−LR (95 CI)**
					ICA	68 (60–75)	73 (55–86)	2.49 (1.47–4.21)	0.44 (0.36–0.
Stress ECG	58 (46–69)	62 (54–69)	1.53 (1.21–1.94)	0.68 (0.49–0.93)					
Stress echo	85 (80–89)	82 (72–89)	4.67 (2.95–7.41)	0.18 (0.13–0.25)					
CCTA	97 (93–99)	78 (67–86)	4.44 (2.64–7.45)	0.04 (0.01–0.09)	CCTA	93 (89–96)	53 (37–68)	1.97 (1.28–3.03)	0.13 (0.06–0.
SPECT	87 (83–90)	70 (63–76)	2.88 (2.33–3.56)	0.19 (0.15–0.24)	SPECT	73 (62–82)	83 (71–90)	4.21 (2.62–6.76)	0.33 (0.24–0.
PET	90 (78–96)	85 (78–90)	5.87 (3.40–10.15)	0.12 (0.05–0.29)	PET	89 (82–93)	85 (81–88)	6.04 (4.29–8.51)	0.13 (0.08–0.
Stress CMR	90 (83–94)	80 (69–88)	4.54 (2.37–8.72)	0.13 (0.07–0.24)	Stress CMR	89 (85–92)	87 (83–91)	7.10 (5.07–9.95)	0.13 (0.09–0.

Note: ICA itself was used as a reference standard for the anatomically significant CAD estimates but was included as a technique when FFR was used as the reference. Not every test had enough data using FFR as reference.

CCTA, coronary computed tomography angiography; CI, confidence interval; CMR, stress cardiac magnetic resonance; ECG, electrocardiogram; ICA, invasive coronary angiography; LR, likelihood ratio; PET, positron emission tomography; SPECT, single-photon emission computed tomography (exercise stress SPECT with or without dipyridamole or adenosine); Stress echo, exercise stress echocardiography.

Another citation of this paper of Knuuti and Ballo et al.: "Certain techniques are broadly available because of their relative low technical and personnel demands [such as stress electrocardiogram (ECG)] or good availability [stress echocardiography, coronary computed tomography angiography (CCTA), and single-photon emission computed tomography (SPECT)], while others, like positron emission tomography (PET) and stress cardiac magnetic resonance (CMR), although powerful, are much less available and their applicability is still limited by infrastructural and capacity requirements." The conclusions of this meta-analysis are: "The various diagnostic modalities have different optimal performance ranges for the detection of anatomically and functionally significant CAD. Stress ECG appears to have very limited diagnostic power. The selection of a diagnostic technique for any given

patient to rule-in or rule-out CAD should be based on the optimal PTP range for each test and on the assumed reference standard." (PTP = pre-test probability).

There are two review articles in the Journal of Nuclear Cardiology which each summarize a selection of articles on single-photon emission computed tomography (SPECT) and of articles on positron emission tomography (PET) respectively, which have been published in the same journal during 2022 (AlJaroudi & Hage, 2023), (Murphy, AlJaroudi, & Hage, 2023). In these two publications, we concentrate on the chapters which are related to the analysis of coronary lesions according to ischemia.

Articles on single-photon emission computed tomography (SPECT) (AlJaroudi & Hage, 2023):

In the introductory words we find among others: "This review will place emphasis on myocardial perfusion imaging using single-photon emission computed tomography summarizing advances in the field including in prognosis, non-perfusion variables, attenuation compensation, machine learning and camera design."

Many of the following citations are self-explaining: "In a separate manuscript, Rozanski et al. assessed 27,615 patients referred for stress-rest SPECT MPI between January 1, 2004 and December 31, 2017, and ascertained that known coronary artery disease (CAD), resting LVEF, and typical angina were the most potent predictors of ischemia. (MPI = stress myocardial perfusion imaging).

Stress myocardial perfusion imaging techniques like SPECT can be combined with anatomic methods, for example with invasive coronary angiography, also called 3D fusion. Citation: "Compared with the side-by-side analysis, the 3D fusion of SPECT MPI and invasive angiography provided incremental diagnostic and prognostic value. Prospective validation studies with larger sample size, quantitative assessment of reconstructed vessel diameter, and reproducibility assessment are still warranted."

"There is also potential role for artificial intelligence to facilitate the timely merging process of anatomic and functional information in the chronic coronary syndrome setting which might help to carry out the most appropriate revascularization procedures."

"Patients with microvascular disease or severe three-vessel CAD (balanced ischemia) may have falsely normal stress SPECT MPI. In such cohort, coronary flow reserves (CFR) adds value to perfusion defect size and improves diagnostic accuracy of the test. Although traditionally done with PET, there are growing data that dynamic SPECT imaging can provide CFR information." … But: "Large prospective studies in collaborative centers are still needed to evaluate the potential role of quantitative SPECT flow measurement as the gatekeeper for invasive FFR or even guiding clinical decision for revascularization for patients with CAD." (CFR= coronary flow reserve).

"Although exercise is the preferred stress modality since it is physiologic and provides hemodynamic and functional data, the proportion of patient unable to complete exercise stress testing and requiring pharmacological stress testing has increased, mainly due to growing comorbidities. Among patients who are unable to reach adequate heart rate or complete exercise stress MPI, hybrid testing is often performed as a rescue."

"The future holds promise for the development of newer software and hardware that will provide us with more accurate tools for better diagnostic accuracy and prognostication, and better patient centered approach and management."

Articles on positron emission tomography (PET) (Murphy et al., 2023):

In the introductory words we find among others: "In this second part, we focus on positron emission tomography, cardiac computed tomography, and cardiac magnetic resonance. We specifically review advances in imaging of non-ischemic cardiomyopathy, cardio-oncology, infectious disease cardiac manifestations, atrial fibrillation, detection and prognostication of atherosclerosis, and technical improvements in the field." We concentrate here on the issue PET and this in relationship to the analysis of coronary lesions according to ischemia, as it has been done with SPECT (see above).

Here some citations out of this review article:

"Recent studies have found that ^{18}F-NaF PET can detect high-risk coronary atherosclerosis plaques that are vulnerable to rupture."

"^{18}F-NaF PET-CT has been used as a marker for macrocalcifications, and can show increased uptake even in patients with low coronary artery calcium scores."

"(11)C-acetate PET/CT has recently shown promise in imaging of fatty acid synthesis in the atherosclerotic vessel wall, but clinical implications are unclear."

"Non-ACS chest pain remains a common and challenging diagnosis in the emergency department. Shaukat Ali et al evaluated the use of Rubidium-82 PET MPI and the proportion that underwent coronary angiography without CAD, length of stay, and downstream testing. When PET is available, the proportion of invasive coronary angiography without significant CAD was similar (18.5% vs 21.4%, P = .24), and median length of stay in the emergency department was shorter (16.6 vs 18.1 hours, P = .03). When compared to PET MPI, SPECT MPI had significantly more downstream testing (8.9% vs 6.4%, P = .003) and a trend towards a higher rate of coronary angiography without significant CAD (21.2% vs 14.2%, P = .09). Thus, availability of PET MPI in the ED was associated with shorter length of stay and required less downstream testing compared to SPECT MPI. (ED = emergency department).

And PET can be applied as part of "hybrid-techniques", for example together with CMR: "After a myocardial infarction, evolution of myocardial injury and inflammation are drivers for adverse events. In companion articles, a group studied the use of Gd-DTPA and ^{18}F-FDG hybrid PET/MRI to further understand post-infarction myocardial evolution using extracellular volume (ECV)."

Here a very well-known statement:

In presence of relevant 3-vessel coronary disease, SPECT should not be used. In such a situation PET is clearly superior to SPECT, because PET gives - as stated above - absolute (quantitative) findings

concerning the severity of coronary lesions, whereas the findings of SPECT are relative, this means, in SPECT, the findings of different coronary lesions are put into relationship from one to each other; they are not quantitative.

Actual disadvantages of PET are

1) Higher costs.

2) The availability is limited to larger cardiac centers like university hospitals etc. This is caused by the short half-lives of most radioactive tracer substances which are used in general. The consequence is that the tracer substances must be produced within the centre, where the PET-examination takes place, and where a cyclotron is available, which is necessary for the production of these radiotracers. In order to overcome this shortcoming, the selection of radionuclides with longer half-lives for PET imaging is an actual topic of research and development in nuclear medicine. The primary reason for considering longer half-lives is to improve the availability and logistics of radiotracers, especially in regions with limited access to on-site cyclotrons or radiopharmaceutical production facilities. It is expected, that - in the near future - the performance of PET-examinations is not bound any more exclusively to large medical centres, but that PET-scans can be more widely used also in middle-sized hospitals, what probably will also have an impact on costs (lower costs of PET-examination).

2. Conclusion and recommendations

- For the detection of myocardial ischemia, the following techniques are used: Stress ECG, Stress echocardiography, Cardiovascular magnetic resonance imaging (CMR), Single-photon emission tomography (SPECT) and Positron emission tomography (PET). When using fractional flow reserve (FFR), then Coronary computed tomographic angiography (CCTA) is besides an anatomical also a functional imaging method.
- Stress echocardiography, CMR, PET and CCTA (with FFR) have similar significance for the detection of myocardial ischemia (similar sensitivity and specificity). Also SPECT belongs to the first line methods, but PET is superior to SPECT.
- Compared to SPECT, PET has improved diagnostic and prognostic performance, especially when quantitative assessment of MBF can be performed (MBF = myocardial blood flow). Thus, in presence of relevant 3-vessel coronary disease, SPECT should not be used. In such a situation PET is clearly superior to SPECT; PET gives quantitative findings, SPECT not.
- Non-invasive functional tests are associated with high accuracy for the detection of flow-limiting coronary stenosis and are comparable with invasive functional testing using the FFR-method.
- Stress-ECG (exercise ECG-testing) should be used for detection of ischemia only as an exception (sensitivity and specificity are low: around or lower than 60%), even if this method has the lowest costs of all methods used for identification of myocardial ischemia.
- The choice, which method should be used for the detection of myocardial ischemia, is influenced by site expertise and availability of the methods. Some centres have more experience with CMR than with nuclear medicine methods, and in other centres it is vice versa.

- SPECT and PET can be combined with other imaging techniques, especially with CMR or with CCTA. Such imaging fusions, labelled as hybrid imaging, allow the intrinsic combination of functional and anatomical image information.
- All methods mentioned above are continuously improving their technical basis. The development of newer software and hardware will provide more accurate tools for better diagnostic accuracy and prognosis, leading to a better patient centred approach and management. An important step in this direction is also the involvement of the new methods machine learning techniques and procedures based on artificial intelligence respectively, which are used more and more in these methods; they enhance the accuracy of the results.
- Modern PET techniques also allow an evaluation of the atherosclerotic vessel wall, for example an analysis of coronary atherosclerotic plaques.
- Disadvantages of PET are higher costs and the limitation to larger cardiac centers, caused by the short half-lives of most radioactive tracer substances. The selection of radionuclides with longer half-lives for PET imaging is an actual topic of research and development in nuclear medicine. If this is established, we can expect, that - in the near future - the performance of PET-examinations is not bound any more exclusively to big medical centres.

3. Relevance for risk assessment of pilots and ATCOs

Application of the methods and/or treatments for risk assessment will be described in task 2.

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4.10 Role of artificial intelligence in CAD

This document contains main findings concerning the state-of-the-art of the "Role of artificial intelligence (AI) in coronary artery disease (CAD)", especially its diagnostic value. Specific comments concerning treatment options will not be discussed, because data derived from AI analyses do only indirectly result in treatment procedures.

1. What is new? - Main findings

Which are new achievements in artificial intelligence in the context of CAD? Is there a need to include new knowledges of this field into clinical practice, and if yes, which of them?

Artificial intelligence (AI) has the potential to improve different aspects in medicine like diagnosis, treatment, and management. AI algorithms can analyze large amounts of data and identify patterns that may be difficult for cardiologists or other specialists involved in medicine to detect. "The use of AI and machine learning has already become accepted medical practice in the interpretation of some types of medical images, such as ECGs, plain radiographs, computed tomographic (CT) and magnetic resonance imaging (MRI) scans, skin images, and retinal photographs" (Haug & Drazen, 2023). But Haug et al. raise also critical questions in their paper, which concern problems with the use of AI and machine learning in medicine: "How does bias in the way AI and machine learning algorithms were "taught" influence how they function when applied in the real world? How do we interject human values into AI and machine learning algorithms so that the results obtained reflect the real problems faced by health professionals? What issues must regulators address to ensure that AI and machine learning applications perform as advertised in multiple-use settings? How should classic approaches in statistical inference be modified, if at all, for interventions that rely on AI and machine learning?" These critical questions do not cast doubt in general the great potential of AI and machine learning. The last sentence of this publication is: "AI and machine learning will not put health professionals out of business; rather, they will make it possible for health professionals to do their jobs better and leave time for the human-human interactions that make medicine the rewarding profession we all value" (Haug & Drazen, 2023).

The importance of AI in medicine nowadays is underlined by the fact that a new journal is announced for 2024, called NEJM AI (ai.nejm.org), "which aims to provide a forum for high-quality evidence and resource sharing for medical AI along with informed discussions of its potential and limitations" (Beam et al., 2023).

How the application of new digital methods improves performing clinical trials is well described in a recently published viewpoint document (Kotecha, DeVore, & Asselbergs, 2023). Here is a citation of this document: "Changes are required to rapidly accelerate advancements in cardiovascular diseases (and reverse withdrawal of industry investment), based on more efficient cardiovascular outcome trials which remain the bedrock of our discipline. In this viewpoint, we highlight the need for a paradigm change to reinitialize large-scale pragmatic cardiovascular trials. A modern clinical trials pipeline can use digital methods to improve screening and recruitment of participants, the processes within trials, and the ascertainment of outcomes. … Digital innovation is already helping to fill major

evidence gaps and empower stakeholders to deliver new, clinically relevant trials within the healthcare setting".

Cardiovascular AI applications achieve more and more an established place in cardiac imaging. When making a publication research with the term search "Artificial intelligence and coronary artery disease", such a research shows that the majority of the corresponding references covers the field of cardiac imaging techniques. According to van Assen et al., AI applied in cardiac imaging is changing the medical sector, it improves the results of cardiac imaging and patient outcome (van Assen, Razavi, Whelton, & De Cecco, 2023). Here two citations of the publication of van Assen et al.: "Echocardiography, coronary computed tomography angiography (CCTA), and cardiac magnetic resonance imaging (CMR) can significantly benefit from AI-based solutions, making these techniques easier to deploy in clinical setting by improving reproducibility in obtaining quantitative morphological and functional information, all of which can improve patient care and outcomes." And: "In the future, these AI algorithms for CCTA will likely incorporate identification of vulnerable plaque features and quantification of plaque burden that will further improve cardiovascular disease risk assessment, as both have shown value in identifying patients at risk for adverse outcomes. These AI algorithms may also be used to evaluate disease progression and effectiveness of lipid-lowering therapies for plaque progression".

There are numerous publications which show that using AI in CCTA-examinations improves the assessment of the severity and of the qualitive appearance of coronary plaques. It is not possible to cite all these publications. A similar comment can be made for other cardiac imaging techniques.

In the context of CAD, AI has also a place for improvement of the accuracy in stress echocardiography and as such of the estimation of the severity of cardiac ischemia (Upton et al., 2022).

Risk stratification of CAD can be performed in many ways, and AI supports the different specific approaches. Imaging techniques, as mentioned above, play an important role in this context. The analysis of cardiovascular risk factors (for example using cardiovascular risk scores) forms a classical way for the CAD risk evaluation. There are also combinations of the analysis of classical risk factors and imaging techniques, one example is given in the publication of Johri et al. (Johri et al., 2022).

Therefore, AI has also an important place for CAD risk stratification and outcome prediction, respectively.

AI and machine learning models respectively can be applied in many other specific cardiovascular diseases. One example is the non-invasive diagnosis of the atherosclerotic coronary artery aneurysm, where specific models are able to increase the clinical decision accuracy for low-risk selection of treatment options (Rostam-Alilou, Safari, Jarrah, Zolfagharian, & Bodaghi, 2022). Another example is the application of AI for the data analysis of wearable devices for ambulatory cardiac monitoring. Smart phones are used for the examination of arrhythmias, and AI is helpful for the evaluation of such data (Giansanti & Monoscalco, 2021). The spectrum of arrhythmias is wide, one part of it is related to CAD.

2. Conclusion and recommendations

- AI and machine learning models have the potential to revolutionize the field of cardiology by improving the accuracy and efficiency of diagnosis as well as indirectly of treatment, and ultimately by improving patient outcome.
- Actually, AI and machine learning have a special significance in situations where results of classical methods do not lead to a clearly defined outcome. Such a doubtful situation might be the question about the magnitude of myocardial ischemia or the question, if the treatment for given coronary stenoses should be fulfilled invasively or only medically; just to give two examples.
- AI and machine learning procedures are especially used in cardiac imaging techniques like CCTA, echocardiography and MRI.
- AI and machine learning models influence treatment option only indirectly. Having a more precise diagnosis, the choice of treatment is based on this diagnosis. Or, treatment options might change as a result of specific trials, in which AI and machine learning models have been involved.
- AI and machine learning help to establish a better cardiovascular risk stratification.
- These conclusions are valid as well for patients in general as well for pilots and ATCOs.

It is important that AMEs and the medical assessors are aware that a broad modern spectrum of diagnoses and treatments in the different cardiovascular fields exists. In order to make a clear decision about fitness to fly for pilots and about the fitness to fulfil their duties for ATCOs respectively, the AMEs must have clear information/data as basis for this decision, if a cardiovascular disease or suspicious symptoms are present. In single specific cases he might suggest to perform an additional, more modern technique to enhance the information about the severity of the given disease or the given symptoms. This might lead to an improved decision for pilots and ATCOs about fitness to fulfil their duties.

3. Relevance for risk assessment of pilots and ATCOs

Application of the methods AI and machine learning models for risk assessment will be described more in detail in task 2. AI and machine learning help to establish a more precise diagnosis, and the amount of the cardiovascular risk is related to that diagnosis.

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4.11 Significance of genetic evaluation of coronary artery disease

This document contains main findings concerning the state-of-the-art of "Genetic evaluation of coronary artery disease (CAD)". It does not contain comments about treatment options, because the actual status of genetic testing does not result into recommendations concerning treatment options for CAD.

1. What is new? - Main findings

Which are new achievements in genetic research in the context of CAD. Which is the state-of-the-art concerning transforming such new knowledge into clinical practice?

Genetic testing gains more and more an established place in medicine, as such also in cardiology. Here a citation of the first introductory words of a consensus paper of different international rhythm societies, published in Europace in 2022 (Wilde et al., 2022): "Genetic testing has advanced significantly since the publication of the 2011 HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies. In addition to single-gene testing, there is now the ability to perform whole-exome sequencing (WES) and whole-genome sequencing (WGS). There is growing appreciation of oligogenic disorders, the role of modifier genes, and the use of genetic testing for risk stratification, even in common cardiac diseases such as coronary artery disease or atrial fibrillation (AF), including a proposal for a score awaiting validation" (Wilde et al., 2022). This consensus document is a comprehensive review of the actual significance of genetic evaluation in cardiac diseases. It reveals that genetic testing has become an established diagnostic procedure in several cardiac diseases like long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, hypertrophic cardiomyopathy etc. But there are other cardiac diseases, in which it has not yet reached such an established position, and coronary artery disease belongs to these situations.

Even if there has been significant progress in genetic testing in various cardiovascular diseases, direct genetic testing in order to define a genetic predisposition for CAD is not yet established (Wilde et al., 2022), (Kessler & Schunkert, 2021). Genetic testing for atherosclerotic cardiovascular disease is

neither recommended according to the "2021 ESC Guidelines on cardiovascular disease prevention in clinical practice" (Visseren et al., 2021). "The routine collection of other potential modifiers, such as genetic risk scores, … is not recommended." This is classified as IIIB, this means, it should not be performed. This does not exclude that some inherited conditions, which can be identified directly by genetic testing, give information about the risk of CAD, the best example is familial hypercholesterolemia. But these are indirect hints for CAD. The term of "Polygenic risk scores" (PRS) is used in this context (Lambert, Abraham, & Inouye, 2019), (Elliott et al., 2020), (Mosley et al., 2020). "PRS aggregate the effects of many genetic variants across the human genome into a single score" (Lambert et al., 2019) and "Advances on polygenic risk scores for risk stratification could increase the use of genetics in prevention" (Visseren et al., 2021). But actually, such scores are not yet routinely used in clinical practice for the risk assessment of atherosclerotic cardiovascular disease (Wilde et al., 2022) (Kessler & Schunkert, 2021), (Visseren et al., 2021), (Elliott et al., 2020), (Mosley et al., 2020).

2. Conclusion and recommendations

Even if genetic testing is a promising issue, currently, it cannot be recommended in patients for CAD risk stratification. Therefore, genetic testing is neither a tool to be applied when checking pilots of all classes and ATCOs for their cardiovascular risk situation. This is an important message, because we can observe, that more and more medical doctors and medical institutes apply genetic testing for CAD risk stratification in the false belief that this procedure gives additional information to the CAD risk stratification as compared to the "classical" way. In future, genetic testing might also be an issue for CAD-risk evaluation, but not yet now.

As mentioned initially, this document does not contain comments about treatment options, because the actual status of genetic testing does not result into recommendations concerning treatment options for CAD.

3. Relevance for risk assessment of pilots and ATCOs

There will be no extensive comments in task 2, because genetic testing for CAD risk evaluation of pilots and ATCOs is not yet an issue for the time being, as stated above

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4.12 COVID-19

This document contains main findings concerning the state-of-the-art of COVID-19 disease like pathophysiological background, clinical manifestations, diagnostic techniques etc., and it includes also some comments concerning treatment options of this disease.

1. What is new? - Main findings

Which are actual relevant aspects of COVID-19 disease? And which are the consequences, especially for pilots and ATCOs in respect to the fitness to fulfill their duties?

COVID-19 disease is less relevant now compared with the years 2020 until 2022. Therefore, many publications about COVID-19 disease and about COVID-19 vaccination dating from the years 2020 until 2022 have actually a lower significance. On the other hand, COVID-19 cannot be ignored entirely, because first, COVID-19 has not disappeared completely, and second, long COVID syndrome has become an issue which has an actual relevance.

As soon as COVID-19 became a global epidemic, numerous studies were published where possible pathophysiological mechanisms, clinical manifestations, diagnostics and therapeutic options etc. are mentioned. One example is a publication from Rai et al. (Rai, Kumar, Deekshit, Karunasagar, & Karunasagar, 2021). From 2021 on, additional publications were made concerning COVID-19 vaccination (which vaccination product, side effects, vaccination success, immune status, etc.). And many publications describe how the cardiovascular system has been affected by COVID-19.

The wide clinical spectrum and the pathophysiological mechanisme of cardiovascular involvement are well described in an article from Aleksova et al. (Aleksova et al., 2022) and in a publication of Xie et al. (Xie, Xu, Bowe, & Al-Aly, 2022). Here two citations out of the publication from Xie et al.: “We provide evidence that, beyond the first 30 d of infection, people with COVID-19 exhibited increased risks and 12-month burdens of incident cardiovascular diseases, including cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease and other cardiac disorders. The risks were evident regardless of age, race, sex and other cardiovascular risk factors, including obesity, hypertension, diabetes, chronic kidney disease and hyperlipidemia; they were also evident in people without any cardiovascular disease before exposure to COVID-19, providing evidence that these risks might manifest even in people at low risk of cardiovascular disease.” … “Our results provide evidence that the risk and 1-year burden of

cardiovascular disease in survivors of acute COVID-19 are substantial. Care pathways of those surviving the acute episode of COVID-19 should include attention to cardiovascular health and disease."

There is no need to enter in detail into the clinical manifestation etc. of patients, pilots and ATCOs who suffer from COVID-19 disease. The decision for pilots and ATCOs concerning fitness to fulfil their duties is clear in such a situation (they are not fit). Requirements and recommendations in respect to vaccination (which vaccination product? May vaccination booster immunity?) or to corona-certificates are neither an issue in the present project. It is an administrative subject, which is handled by the aviation authorities. On the other hand, there are two situations, which shall be studied thoroughly in this document: 1) Suspicion of myo- and/or pericarditis after vaccination or when the involved person has had COVID-19 infection. 2) Long COVID syndrome.

Suspicion of myo- and/or pericarditis after vaccination or when the involved person has had COVID-19 infection

A representative review article concerning myo- and/or pericarditis after vaccination is the one of Marschner et al. (Marschner et al., 2022): "The purpose of the review is to evaluate the current literature related to myocarditis following COVID-19 vaccination, including the incidence, risk factors, clinical presentation, imaging findings, proposed pathophysiologic mechanisms, treatment, and prognosis." The results of the analysis of several data sets reporting myocarditis and pericarditis out of millions of persons who have had COVID-19 vaccination are described in this article. The following key points are:

- "Myocarditis following messenger RNA-based COVID-19 vaccines is rare; however, adolescent and young adult men are at highest risk.
- Chest pain is the most common symptom, with typical onset within a few days of vaccine administration.
- Cardiac MRI plays an important role in the diagnosis of acute myocarditis following vaccination, with typical findings of sub-epicardial late gadolinium enhancement and co-localizing edema at the basal inferior lateral wall.
- The disease course of myocarditis following COVID-19 vaccination is typically transient and mild, with resolution of symptoms within 1 to 3 weeks in most patients.
- However, longer term follow-up is needed to determine whether imaging abnormalities persist, to evaluate for adverse outcomes, and to understand the risk associated with subsequent vaccination."

The low incidence of myo- and pericarditis after COVID-19 vaccination is confirmed in numerous publications. One such example is the report of Bozkurt et al., published in Circulation in 2021 (Bozkurt, Kamat, & Hotez, 2021). Here the citation of the summary: "In summary, >177 million people have received at least 1 dose of COVID-19 vaccine (>300 million doses) in the United States, and CDC and other international organizations continue to monitor the safety of COVID-19 vaccines for any health problems including rare cases of myocarditis after vaccination. Despite rare cases of self-limited myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favourable balance for all age and sex groups; therefore, COVID-19 vaccination is currently recommended for everyone 12 years of age and older." (CDC = Centers for Disease Control and Prevention). This article describes also

clinical symptoms and diagnostic strategies in patients with myocarditis after vaccination. One out of several recommendation is: “Management should include a cardiologist for initial assessment, evaluation, treatment, and follow-up, and an infection disease specialist for guidance on subsequent immunization strategies” (Bozkurt et al., 2021).

Myo- and/or pericarditis can be one out of several clinical manifestations of COVID-19 disease, it can be just a residual finding after the main manifestations of the illness have already disappeared, or it can occur in asymptomatic infected patients. In the publication of Daniels et al., 1597 US competitive athletes who have had COVID-19 infection were analysed in respect to the presence of myocarditis (Daniels et al., 2021). The authors formed three groups according to the clinical situation. “Myocarditis diagnoses were divided into 3 categories: (1) clinical myocarditis (cardiac symptoms present before or at the time of cardiac testing), (2) subclinical probable myocarditis (no cardiac symptoms) with abnormal ECG, echocardiogram, or troponin findings consistent with myocarditis, and (3) subclinical possible myocarditis (no cardiac symptoms) without abnormal ECG, echocardiogram, or troponin findings and only abnormal CMR imaging findings.” Like the study of Marschner et al. (Marschner et al., 2022), the study from Daniels et al. showed among others also the importance of cardiac magnetic resonance (CMR) imaging for the diagnosis of myocarditis: 37 athletes (2.3%) were diagnosed with clinical and subclinical myocarditis; and cardiac CMR yielded a 7.4-fold increase in detection of myocarditis (clinical and subclinical). “These unique CMR imaging data provide a more complete understanding of the prevalence of clinical and subclinical myocarditis in college athletes after COVID-19 infection.”

As mentioned above, Aleksova et al. describe in their article the wide clinical spectrum and the pathophysiological mechanism of cardiovascular involvement (Aleksova et al., 2022). In that publication, we find statements concerning the myocardial injury due to SARS-CoV-2 infection. And also, the value of CMR as a potent tool for the detection of myocarditis is emphasized. “CMR allows the differentiation between ischemic and non-ischemic injury”. And this publication also teaches us, that acute and chronic cardiovascular effects of COVID-19 occur even among those who were not hospitalized.

Acute pericarditis or myocarditis can represent an important manifestation of long COVID-19 syndrome (Dini et al., 2023), see below.

Long COVID syndrome

“Many patients report persistent symptoms after resolution of acute COVID-19, regardless of SARS-CoV-2 variant and even if the initial illness is mild. A multitude of symptoms have been described under the umbrella term “long COVID”, otherwise known as “post-COVID syndrome” or “post-acute sequelae of SARS-CoV-2 (PASC)”. These are the introducing words of Liew et al. in their publication “Long Covid: clues about causes” from 2023 (Liew, Efstathiou, & Openshaw, 2023). Here some other selected citations from this article which are self-explanatory: “Long COVID can be debilitating, with 45.2% of patients requiring a reduced work schedule. The World Health Organization estimates that 17 million people in Europe experienced long COVID during the first 2 years of the pandemic. SARS-CoV-2 variants continue to circulate and the risk of post-acute complications remains; a recent study of 56 003 UK patients found that even after Omicron infection, 4.5% suffered persistent symptoms. It is therefore likely that long COVID will provide a substantial medical and economic burden for the

foreseeable future. There is an urgent need to understand the mechanisms of the disease and develop effective treatments based on this understanding." … "This work provides an important contribution to the growing body of evidence that long COVID is a multi-various disease with diverse causes. Given the growing evidence that different patterns of symptoms might be driven by distinct pathophysiological pathways, it is essential that rigorous and evidence-based classifications of disease are used to design trials of specific interventions based on this knowledge. Many clinical trials are underway to identify potential treatments, but there is a risk that these trials will show no benefits if patients with different pathogenic pathways are not differentiated."

Concerning the etiology of long COVID syndrome, immunologic mechanisms seem to play an importing role. This relationship is well described in the review article from Stoian et al. (Stoian, Procopiescu, Șeitan, & Scarlat, 2023). Here a citation of this publication: "These manifestations include immunological disturbances, which, according to certain clinical findings, may persist post-infection, in the form of a presumed systemic inflammatory entity, defined by several clinical concepts with a common pathological significance: post-COVID-19 multisystem (or systemic) inflammatory syndrome, post-COVID syndrome or long-COVID. Although the pathophysiological mechanisms of the post-COVID-19 syndrome are elusive at the present moment, there are currently several studies that describe a systemic inflammatory or autoimmune phenomenon following the remission of the COVID-19 infection in some patients, which suggests the existence of molecular and cellular immune abnormalities, most probably due to the host's initial violent immune response to the viral infection, in the form of three overlapping entities: secondary hemophagocytic lymph histiocytosis (HLH), macrophage activation syndrome (MAS) and cytokine release syndrome (CRS). Thus, this is reminiscent of different classic autoimmune diseases, in which various infections are risk factors in developing the autoimmune process." The variety of clinical presentation of long COVID syndrome is also mentioned in this publication from Stoian et al.: "PCS is currently considered a clinically and biologically polymorphic entity, and its pathophysiology, although governed mainly by immunopathological or hyperinflammatory phenomena, requires refinement through future investigations to have clear diagnostic tools and a proper therapeutic or pharmacological strategy. Given that the clinical and biological presentation of PCS is polymorphic and may raise numerous differential diagnostic issues, internists should possess the main role in the management of PCS. Nevertheless, internists should collaborate with other medical specialists." (PCS = post-COVID syndrome).

As mentioned above, myo- and/or pericarditis might be one manifestation of long COVID syndrome. Dini et al. analyzed retrospectively 180 patients in whom COVID-19 had been previously diagnosed and who exhibited persistence of new-onset symptoms $\geq$ 12 weeks from a negative naso-pharyngeal SARS CoV2 swamp test (Dini et al., 2023). The aim of this study was to identify the prevalence and clinical characteristics of patients with long COVID syndrome, presenting with acute pericarditis. The diagnosis of acute pericarditis was made in 39 patients (22%). And the following symptoms were found in the whole cohort (patients with and without acute pericarditis): "Brain fog" and lack of concentrations (18%), chest pain and discomfort (34%), cough (11%), headache (7%), heart palpitations and arrhythmias (37%), shortness of breath and fatigue (52%). The conclusion was: "Our findings suggest a high prevalence of acute pericarditis in patients with long COVID-19 syndrome. Autoimmune and allergic disorders, and palpitations/arrhythmias were frequently associated with pericardial disease."

Several publications describe, that autonomic manifestations such as postural orthostatic tachycardia syndrome (POTS) also belong to the wide spectrum of clinical manifestations of long COVID syndrome (Raman, Bluemke, Lüscher, & Neubauer, 2022), (Fedorowski & Sutton, 2023), (Raj et al., 2021). POTS is characterized by an excessive heart rate increase of at least 30 bpm from supine to standing position. It is primarily related to changes in blood flow and autonomic nervous system dysfunction. The whole clinical picture is often complicated by other debilitating symptoms, including unexplained chest pain, migraine, muscle weakness, sleep disturbances etc. This syndrome can occur a few months after COVID-19-infection (then called "Long-COVID POTS") as well as after COVID-19-vaccination. There are many open questions in relation to Long-COVID-POTS or to POTS after COVID-19-vaccination including the one concerning the best treatment of this syndrome.

A comprehensive review article from Astin et al. gives detailed information about different aspects of long COVID syndrome (Astin et al., 2023). The authors describe the "New Findings" of their review analysis as: "What is the topic of this review? The emerging condition of long COVID, its epidemiology, pathophysiological impacts on patients of different backgrounds, physiological mechanisms emerging as explanations of the condition, and treatment strategies studied. The review leads from a Physiological Society online conference on this topic. - What advances does it highlight? Progress in understanding the pathophysiology and cellular mechanisms underlying Long COVID and potential therapeutic and management strategies." Further citations out of that article: "With an ever-expanding patient population, long COVID is now a common condition with societal as well as personal impacts that necessitate a better understanding of the symptom trajectory, underlying mechanisms and treatments in order to improve population health across the globe. Much progress has been made in terms of testing paradigms that reveal the pattern of pathophysiological changes to the respiratory, autonomic and cardiovascular systems, which aid diagnosis as well as revealing the underlying functional changes in long COVID." … "Rehabilitation can be effective, but presents a resource challenge in providing sufficient monitoring to match activity to physiological capabilities to avoid exacerbating damage. Pharmacological treatments are likely to only be effective in subpopulations of patients with specific symptoms and underlying pathology. Multi-disciplinary approaches spanning epidemiology, immunology, multi-system physiology and clinical research are therefore required to understand the different, interacting processes at play and to understand how to best combat them to restore health." … "Overall, this review show cases how physiological research reveals the changes that occur in long COVID and how different therapeutic strategies are being developed and tested to combat this condition." Indirectly we find a definition of long COVID syndrome: Obviously, many authors define long COVID syndrome if there are persistent post COVID symptoms 12 weeks or more after COVID-19-infection.

It is also worth to read the broad research article from Taquet et al. (Taquet et al., 2021). It represents data concerning the variety of symptoms of persons after coronavirus disease infection (long COVID clinical features). Here, the citation of the authors summary:

"Why was this study done?

- Long-COVID has been described in recent studies. But we do not know the risk of developing features of this condition and how it is affected by factors such as age, sex, or severity of infection.

- We do not know if the risk of having features of long-COVID is more likely after Coronavirus Disease 2019 (COVID-19) than after influenza.
- We do not know about the extent to which different features of long-COVID co-occur.

What did the researchers do and find?

- This research used data from electronic health records of 273,618 patients diagnosed with COVID-19 and estimated the risk of having long-COVID features in the 6 months after a diagnosis of COVID-19. It compared the risk of long-COVID features in different groups within the population and also compared the risk to that after influenza.
- The research found that over 1 in 3 patients had one or more features of long-COVID recorded between 3 and 6 months after a diagnosis of COVID-19. This was significantly higher than after influenza.
- For 2 in 5 of the patients who had long-COVID features in the 3- to 6-month period, they had no record of any such feature in the previous 3 months.
- The risk of long-COVID features was higher in patients who had more severe COVID-19 illness, and slightly higher among females and young adults. White and non-white patients were equally affected."

And a last citation of this study: "The data presented here shed light on the incidences and relative risks of long-COVID features, but say nothing about the causation or mechanisms involved, nor about the predictors beyond the limited demographic and severity markers we measured" (Taquet et al., 2021).

2. Conclusion and recommendations

- The conclusions concerning this issue of COVID-19 are related to the situation, when pilots and ATCOs are checked concerning fitness to fulfil their duties (checked in the sense of risk stratification).
- Because the manifestations of the COVID-19 infection are broad, and because reactions to COVID-19 vaccination also vary a lot, the assessment of a pilot or ATCO must be performed on an individual basis.
- It is obvious that those presenting with relevant symptoms must be declared as unfit for the time they are in this situation.
- Good news is that side effects of COVID-19 vaccination are rare and are of significance only in few cases.
- Special attention must be given to symptoms which are suspicious for long COVID syndrome. This can be very challenging. Also, in this situation, the assessment of a pilot or an ATCO must be performed on an individual basis.
- If a person, who has had COVID-19 infection, presents thereafter with some symptoms like fatigue, chest pain, breathlessness etc., it is important to analyse carefully such symptoms, as many of these symptoms might be caused by a clinical situation, which is not related to an undergone COVID-19 infection, and which therefore are not a manifestation of long COVID syndrome.

- As acute peri- and/or myocarditis is often an important manifestation of long COVID syndrome, and because acute peri- and/or myocarditis is related with an increased risk for arrhythmias and with an increased overall risk, this condition must be specifically searched if there is any suspicion for it.
- In uncertain cases CMR shall be applied which is the best imaging technique for identification of myocarditis.
- Postural orthostatic tachycardia syndrome (POTS) can be one of the debilitating clinical manifestations of long COVID syndrome or after COVID-vaccination. It is related to autonomic nervous system dysfunction.
- Treatment option of manifested COVID-19 disease, of side effects of vaccination or of long COVID syndrome is dependent on the clinical manifestation. In most situations, the treatment corresponds to a symptomatic treatment. For example, acute pericarditis is treated in the same way as pericarditis of other than COVID-19 origin.
  There are some established treatment options for patients with severe COVID-19 disease (mainly hospitalized patients), including classical medication like dexamethasone or anticoagulation etc. And there exist also several specific new drugs for severe cases. In this document, there is no need to describe all these options, because pilots and ATCOs presenting with relevant clinical symptoms are not fit anyway to fulfil their duties - as mentioned above.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described more in detail in task 2.

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5 Arrhythmias

5.1 Atrial fibrillation

This document describes the state-of-the-art of atrial fibrillation (AF), its clinical presentations, the actual diagnostic measures, and the decision strategies, also considering the various risks. The different therapeutic options are also mentioned in this document.

1. What is new? – Main findings

What is new and relevant for pilots and ATCOs in the "2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)" (Hindricks et al., 2021)?

Diagnosis of Atrial Fibrillation (AF)

ECG documentation by a physician is required to establish the diagnosis of AF. A standard 12-lead ECG recording, or a single-lead ECG tracing of ≥ 30 s are both accepted. Such a single-lead ECG tracing can be recorded by a wearable device and must be documented. But a diagnosis by an automated

algorithm without documented ECG and review by a physician (e. g. by a wearable device) is not accepted.

Structured Characterization of AF

A structured characterization of AF including a clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate should be considered to streamline the assessment and optimal management of AF patients. It should replace AF classification purely regarding the duration of AF episodes in paroxysmal, persistent, and permanent AF.

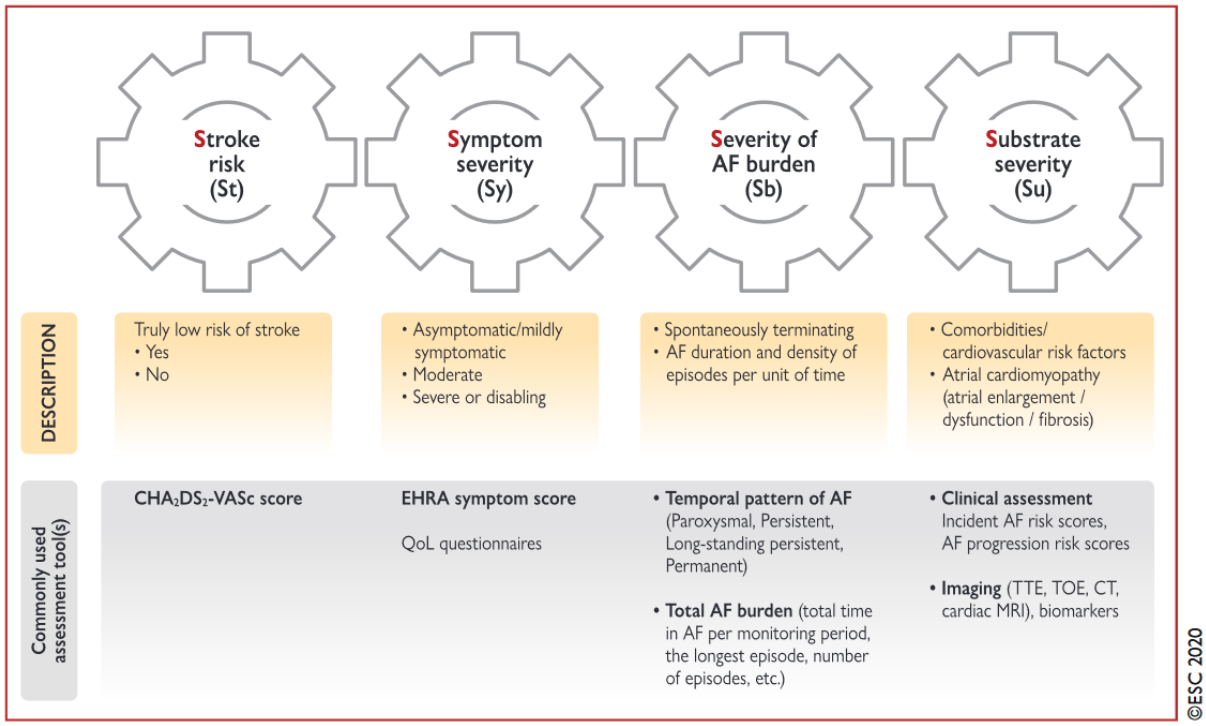

Figure 8: AF Screening

@2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) (Hindricks et al, 2021).

Opportunistic screening is recommended in patients ≥ 65 years of age, systematic screening in patients ≥ 75 years of age, or those at high risk of stroke. Opportunistic screening is also recommended in hypertensive patients and should be considered in patients with obstructive sleep apnea.

Integrated AF Management

It is recommended to routinely collect PROs (Patient Reported Outcomes) to measure treatment success and improve patient care.

Risk of thrombo-embolic events and bleeding

Risk of thrombo-embolic events and bleeding are dynamic and should be reassessed at periodic intervals. For the assessment of bleeding risk, the HAS-BLED score should be considered (high risk of bleeding if HAS-BLED ≥ 3). For the assessment of thrombo-embolic risk the CHA_2DS_2VASc score should still be used (with some changes regarding the inclusion of specific diseases in the risk factors).

Cardioversion

Pharmacological cardioversion of AF is indicated only in a hemodynamically stable patient, after consideration of the thrombo-embolic risk. Cardioversion can be performed "early" (< 48 h) or "delayed" (after several days).

Catheter Ablation

For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risk and the major risk factors for AF recurrence following the procedure and discuss them with the patient.

Catheter ablation after antiarrhythmic drug therapy failure should be considered after one failed beta-blocker treatment.

To improve the outcome of catheter ablation, strict control of risk factors (e. g. obesity) and avoidance of triggers (e. g. alcohol consumption) are recommended.

Long-Term Antiarrhythmic Drug Treatment

Sotalol should be used with caution. In AF patients treated with sotalol, close monitoring of QT interval, serum potassium level, and other proarrhythmic risk factors is recommended.

Risk factors and comorbidities

Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.

Recommendations for quality measures in AF

The introduction of tools to measure quality of care and identify opportunities for improved treatment quality and AF patient outcome should be considered.

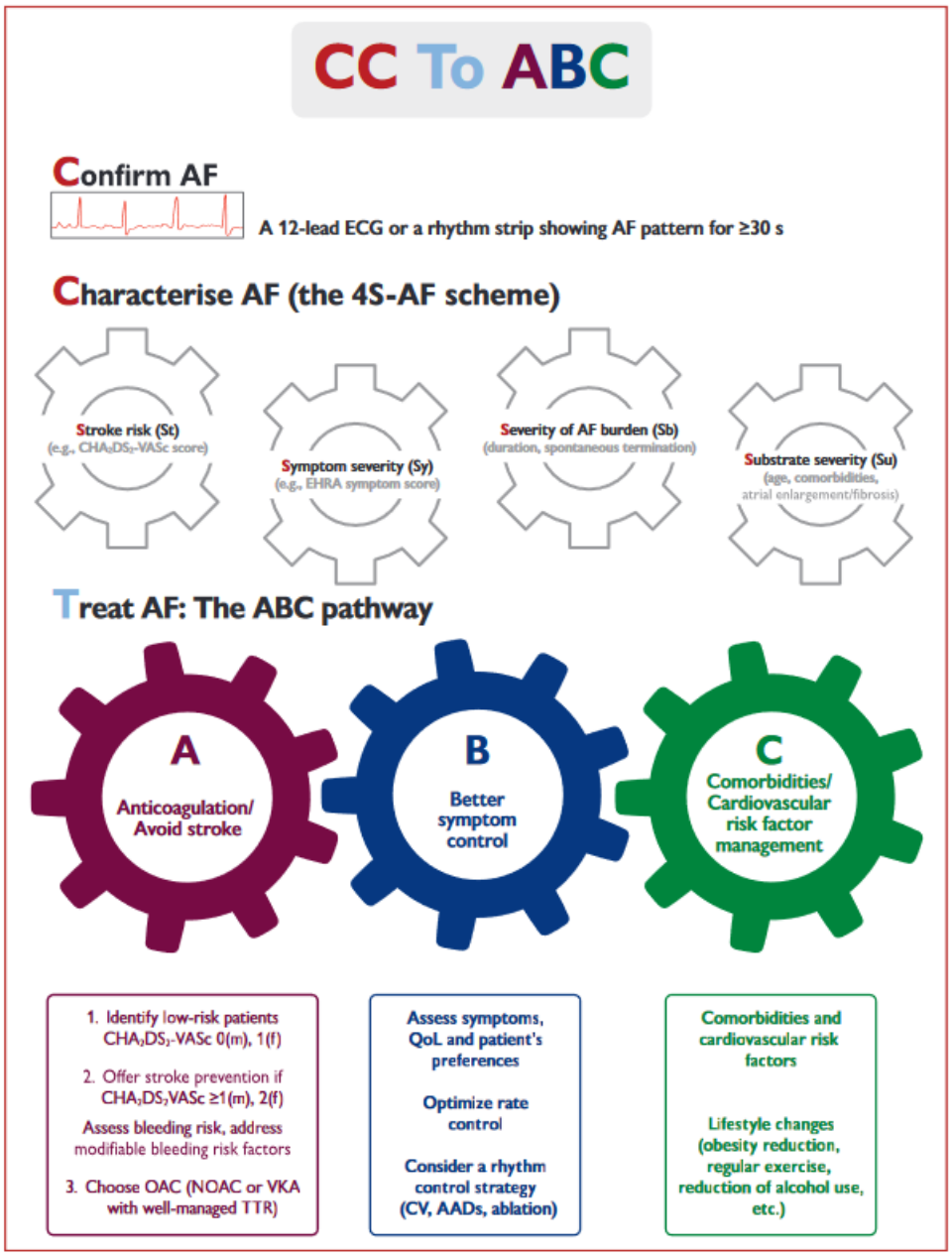

Figure 9: Management of AF (Central Illustration)

@2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) (Hindricks et al, 2021).

The following text is taken from the consensus recommendations in Heart published 2019 by the NATO HFM-251 Occupational Cardiology in Military Aircrew Working Group with very few updates (Guettler et al., 2019):

Pilots and ATCOs diagnosed with AF are initially to be made unfit for pilot and ATCO duties. Investigations are required to confirm or exclude underlying causes (echocardiography, laboratory

tests, chest X-ray, and a risk-factor dependent examination to exclude CAD). The investigation and management of AF in pilots and ATCOs requires a comprehensive and integrated approach as it may have a cardiac or non-cardiac aetiology (Fabritz et al., 2021). AF can be associated with valvular heart disease, CAD, cardiomyopathies, hypertension, hyperthyroidism, and respiratory diseases. Other potential causative or trigger factors include electrolyte disorders, sepsis, smoking, alcohol or caffeine excess, drug intake (including metabolic supplements), excessive physical activity, fatigue, and exhaustion.

In cases where there is a clear causative aetiology for AF, the underlying disease guides treatment. AF should be managed in accordance with international guidelines (Hindricks et al., 2021), (January et al., 2014), (January et al., 2019). Possible side effects of medication used to restore or maintain sinus rhythm or to control ventricular rate make AF a difficult condition to manage in pilots and ATCOs. Flecainide and propafenone (Vaughan-Williams class IC) as well as amiodarone, dronedarone, and sotalol (Vaughan-Williams class III) are all incompatible with unrestricted flying due to their side effect profile. β-blockers are often used for rate control; however, given the negative chronotropic effects and blunted blood pressure response to these agents they are not recommended for pilots and ATCOs flying high performance aircraft.

In a 2012 focused update of the ESC guidelines for the management of AF, catheter ablation was first recommended as a possible first-line treatment for selected patients, especially those with paroxysmal AF (PAF) depending on patient choice. Currently, catheter ablation for first-line treatment is a class IIa indication in patients with PAF, and a class IIb indication in patients with persistent AF without major risk factors for AF recurrence. Given the adverse side effect profile of these agents, AF catheter ablation is increasingly recommended as a first line intervention in pilots and ATCOs, as with the general population (Calkins et al., 2018). Isolation of the pulmonary vein ostia within the left atrium may be achieved by radiofrequency, cryotherapy or laser-based procedures. In PAF success rates >80% can be achieved, with cryo-balloon ablation non-inferior compared with radiofrequency ablation (Ouyang et al., 2010), (Kuck et al., 2016). Unlike PAF, the long-term success rate in patients with persistent AF is only 40–60% after a single ablation (Cappato et al., 2010), (Charitakis et al., 2022), and in many cases a second or third intervention is necessary. When assessing pilots and ATCOs that have undergone AF ablation, the observation period to determine the success of the procedure should last at least 6 months; this includes an unfit period of 3 months, during which the ablation itself may cause arrhythmias regardless of the ablation success, and an additional observation time of at least 3 further months.

Beyond pulmonary vein isolation, several techniques of AF focal ablation and substrate modification have been studied. Energy sources include radiofrequency, cryotherapy, laser, and ultrasound. Many ablation methods are associated with indiscriminate tissue damage leading to esophageal, phrenic nerve, and aortic injuries. The thermal methods work by inducing coagulative necrosis and subsequently reparative fibrosis, which may result in pulmonary vein stenosis and impaired left atrial reservoir function. In contrast, pulsed field ablation (PFA) is a new approach to cardiac ablation of AF. It employs a non-thermal ablative mechanism in which cell death is obtained by applying ultra-short electrical pulses to induce pores in cell membranes. It has higher myocardial tissue selectivity compared to conventional methods. PFA ablation is effective for paroxysmal and persistent AF and is associated with low AF recurrence at one-year follow-up (Shaheen, Shaheen, Ramadan, & Nashwan, 2023), (Shtembari et al., 2023) (Verma et al., 2023).

As in the general population, anticoagulation should be determined by the CHA_2DS_2VASc score. Most pilots and ATCOs have a CHA_2DS_2VASc score of 0 and do not need anticoagulation. If anticoagulation is needed, it can be done with vitamin K antagonists or direct oral anticoagulants (DOACS), which should be preferred (excluding pilots and ATCOs with mechanical heart valves). For military pilots and ATCOs, permanent anticoagulation is often, but not universally, disqualifying; however, civil regulations are usually less restrictive (Keithler, Wilson, Yuan, Sosa, & Bush, 2022b).

Return to pilot or ATCO duties requires a detailed cardiovascular assessment and consideration of the pilot or ATCO role. Return to unrestricted flying is usually only possible after a single episode of AF without underlying disease, but with an identified trigger factor. In all other cases, restricted flying in low-performance aircraft may be possible after a minimum observation period of 3–6 months depending on flying duties, with extensive investigation to confirm stable sinus rhythm or rate control at rest and during effort (long-duration Holter monitoring, exercise ECG). In both PAF and persistent AF, recurrences may occur years after ablation therapy, and as a result, most licensing authorities do not allow a return to single seat flying operations or high-performance flying. In severe situations that require surgical ablation, mostly performed as a concomitant procedure to coronary bypass or valve surgery (Calkins et al., 2018) or a left atrial appendage exclusion with internal devices because of contraindication to anticoagulation, pilots and ATCOs are likely to be unfit to perform their duties.

According to the most recent information of the ESC-congress (2023), *it is especially worth to mention the PFA-method and the NOAH-AFNET 6-trial:*

PFA was declared as a very promising method for catheter ablation of AF, which has many advantages compared to “traditional” catheter methods. Because PFA has already been described in detail in this document (see text above), there is no need to go again into details of this method.

In the NOAH-AFNET 6-trial, which was presented in a Hot-Line session at the congress, the efficacy and safety of oral anticoagulation in patients with atrial high-rate episodes (AHREs), but without ECG-documented AF was investigated (Kirchhof et al., 2023). The background question was, if patients with AHREs shall be anticoagulated or not. Across 18 European countries, a total number of 2536 patients were eligible for inclusion if they were aged ≥ 65 years with AHREs episodes ≥ 6 minutes detected by implantable devices, and with at least one additional stroke risk factor (heart failure, hypertension, diabetes, prior stroke or transient ischaemic attack, vascular disease or age ≥ 75 years). Participants were randomised to anticoagulation (with the NOAC-drug edoxaban) or no anticoagulation. The trial was stopped early due to safety signals and a trend towards futility for efficacy after enrolment of all planned patients. There was no significant difference between groups for the primary efficacy outcome (a composite of stroke, systemic embolism or CV death). The primary safety outcome (a composite of major bleeding and all-cause death) occurred in 149 patients in the anticoagulation group (5.9%/year) and in 114 patients in the no anticoagulation group (4.5%/year) (HR 1.3; 95% CI 1.0 to 1.7; p=0.03). The difference in safety outcomes was driven by an increase in major bleeding in patients receiving anticoagulation (HR 2.10; 95% CI 1.30 to 3.38; p=0.002). In summary, “Among patients with AHREs detected by implantable devices, anticoagulation with edoxaban did not significantly reduce the incidence of a composite of cardiovascular death, stroke, or systemic embolism as compared with placebo, but it led to a higher incidence of a composite of death or major bleeding. The incidence of stroke was low in both groups.” Thus, the results of NOAH-AFNET 6 clearly

suggest that patients with AHREs shall not be anticoagulated, as long as there is no ECG documentation of AF.

2. Conclusion and recommendations

"General recommendations" (Guettler et al., 2019)

Group 1: Healthy pilots with a "normal" cardiovascular risk:

Opportunistic AF screening for pilots and ATCOs ≥ 65 years of age, systematic AF screening for pilots and ATCO's ≥ 75 years of age. Single-lead ECG of ≥ 30 s and diagnosis by a physician required.

Group 2: Apparently healthy pilots with increased cardiovascular risk:

Opportunistic AF screening of hypertensive pilots and ATCOs and opportunistic AF screening of pilots and ATCOs with obstructive sleep apnea.

Group 3: Pilots with manifestations of cardiovascular disease:

Pilots and ATCOs diagnosed with AF are initially to be made unfit for pilot or ATCO duties. The investigation and management of AF in pilots and ATCOs requires a comprehensive and integrated approach with regard to aeromedical requirements and clinical guidelines. Return to unrestricted flying is usually only possible after a single episode of AF without underlying disease, but with an identified trigger factor. In all other cases, restricted flying in low-performance aircraft may be possible after a minimum observation period of 3–6 months depending on flying duties, with extensive investigation to confirm stable sinus rhythm or rate control at rest and during effort (long-duration Holter monitoring, exercise ECG). In both PAF and persistent AF, recurrences may occur years after ablation therapy, and as a result, the actual EASA-medical requirements do not allow a return to single seat flying operations or high-performance flying (Katkat, 2021), (Keithler, Wilson, Yuan, Sosa, & Bush, 2022a).

3. Relevance for risk assessment of pilots and ATCOs

Detailed risk assessments of the different categories of pilots and of ATCOs will be described in task 2.

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5.2 Indication of anticoagulation in atrial fibrillation

This document describes stroke and bleeding risk assessment in atrial fibrillation (AF), indications and contraindications for oral anticoagulation, different stroke prevention therapies, and the process of decision making to avoid stroke. Therefore, treatment options are part of this document.

1. What is new? - Main findings

<u>New recommendations and class of recommendations according to the 2020 ESC Guidelines (Hindricks et al., 2021):</u>

For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients with high risk of bleeding (HAS-BLED ≥3) for early and more frequent clinical review and follow-up (IIa).

Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (i. e. initiation of oral anticoagulants (OAC) in patients no longer at low risk for stroke) and address potentially modifiable bleeding risk factors (I).

In patients with AF initially at low risk of stroke, first assessment of stroke risk should be made 4 – 6 months after the index evaluation (IIa).

Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention (III).

Clinical pattern of AF (i. e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication for thromboprophylaxis (III).

Stroke risk assessment

Overall, AF increases the risk of stroke five-fold, but this risk is not homogeneous, depending on the presence of specific stroke risk factors/modifiers. In addition, non-paroxysmal AF is associated with an increase in thrombo-embolism (multivariable adjusted hazard ratio (HR) 1.38; 95% confidence interval (CI) 1.19 – 1.61; p < 0.001) compared to paroxysmal AF (Ganesan et al., 2016). Notably, many of the risk factors for AF-related complications are also risk factors for incident AF (Allan et al., 2017). Common stroke risk factors are summarized in the clinical risk-factor-based CHA_2DS_2VASc [Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female)] score (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010) (Table 12).

Table 12: CHA_2DS_2VASc score

CHA_2DS_2-VASc score Risk factors and definitions		Points awarded	Comment
C	**Congestive heart failure** Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1	Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging[335]; HCM confers a high stroke risk[336] and OAC is beneficial for stroke reduction.[337]
H	**Hypertension** or on antihypertensive therapy	1	History of hypertension may result in vascular changes that predispose to stroke, and a well-controlled BP today may not be well-controlled over time.[324] Uncontrolled BP - the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120 - 129/<80 mmHg.[338]
A	**Age 75 years or older**	2	Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards.[339] Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥75 years.
D	**Diabetes mellitus** Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1	Diabetes mellitus is a well-established risk factor for stroke, and more recently stroke risk has been related to duration of diabetes mellitus (the longer the duration of diabetes mellitus, the higher the risk of thromboembolism[340]) and presence of diabetic target organ damage, e.g. retinopathy.[341] Both type 1 and type 2 diabetes mellitus confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged <65 years with type 2 diabetes mellitus compared to patients with type 1 diabetes mellitus.[342]
S	**Stroke**Previous stroke, TIA, or thromboembolism	2	Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischaemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including haemorrhagic stroke) are at very high risk of subsequent ischaemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation.[343–345]
V	**Vascular disease** Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1	Vascular disease (PAD or myocardial infarction) confers a 17 - 22% excess risk, particularly in Asian patients.[346–348] Angiographically significant CAD is also an independent risk factor for ischaemic stroke among AF patients (adjusted incidence rate ratio 1.29, 95% CI 1.08 - 1.53).[349] Complex aortic plaque on the descending aorta, as an indicator of significant vascular disease, is also a strong predictor of ischaemic stroke.[350]
A	**Age 65 – 74 years**	1	See above. Recent data from Asia suggest that the risk of stroke may rise from age 50 - 55 years upwards and that a modified CHA_2DS_2-VASc score may be used in Asian patients.[351,352]
Sc	**Sex category (female)**	1	A stroke risk modifier rather than a risk factor.[353]
Maximum score		**9**	

AF = atrial fibrillation; BP = blood pressure; CAD = coronary artery disease; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); CI = confidence interval; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICH = intracranial haemorrhage; LV = left ventricular; LVEF = left ventricular ejection fraction; OAC = oral anticoagulant; PAD = peripheral artery disease; RCT = randomized controlled trial; TIA = transient ischaemic attack.

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Female sex is an age-dependent stroke risk modifier rather than a risk factor per se (Tomasdottir, Friberg, Hijazi, Lindbäck, & Oldgren, 2019; Wu et al., 2020). Observational studies showed that women

with no other risk factor (CHA_2DS_2VASc score of 1) have a low stroke risk, similar to men with a CHA_2DS_2VASc score of 0 (Friberg, Benson, Rosenqvist, & Lip, 2012).

For many risk factors (e. g. age), stroke risk is a continuum rather than an artificial low-, moderate-, or high-risk category. Risk factors are dynamic and, given the elderly AF population with multiple (often changing) comorbidities, stroke risk needs to be re-evaluated at each clinical review.

Bleeding risk assessment

When initiating antithrombotic therapy, potential risk for bleeding also needs to be assessed. The HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs/alcohol concomitantly] score (Pisters et al., 2010) had the best evidence for predicting bleeding risk (moderate strength of evidence), consistent with other systematic reviews and meta-analyses comparing bleeding risk prediction approaches (Caldeira, Costa, Fernandes, Pinto, & Ferreira, 2014; Chang et al., 2020; Zhu, He, Guo, Wang, & Hong, 2015) (Table 13).

Table 13: HAS-BLED score

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR[b]** TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SBP = systolic blood pressure; INR = international normalized ratio; NSAID = Non-steroidal anti-inflammatory drug; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Haemorrhagic stroke would also score 1 point under the 'B' criterion.
[b]Only relevant if patient receiving a VKA.
[c]Alcohol excess or abuse refers to a high intake (e.g. >14 units per week), where the clinician assesses there would be an impact on health or bleeding risk.

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A high bleeding risk score should not lead to withholding OAC, as the net clinical benefit of OAC is even greater amongst such patients. However, the formal assessment of bleeding risk informs management of patients taking OAC, focusing attention on modifiable bleeding risk factors that should be managed and (re)assessed at every patient contact, and identifying high-risk patients with non-modifiable bleeding risk factors who should be reviewed earlier (for instance in 4 weeks rather than 4 - 6 months) and more frequently (Chao et al., 2018; Lip & Lane, 2016). Bleeding risk is dynamic,

and attention to the change in bleeding risk profile is a stronger predictor of major bleeding events compared with simply relying on baseline bleeding risk.

Absolute contraindications to oral anticoagulants

The few absolute contraindications to OAC include active serious bleeding (where the source should be identified and treated), associated comorbidities (e. g. severe thrombocytopenia <50 platelets/µl, severe anemia under investigation, etc.), or a recent high-risk bleeding event such as intracranial hemorrhage (ICH).

Stroke prevention therapies

Vitamin K antagonists

Compared with control or placebo, vitamin K antagonist (VKA) therapy (mostly warfarin) reduces stroke risk by 64% and mortality by 26% (Hart, Pearce, & Aguilar, 2007) and is still used in many AF patients worldwide. VKAs are currently the only treatment with established safety in AF patients with rheumatic mitral valve disease and/or an artificial heart valve.

The use of VKAs is limited by the narrow therapeutic interval, necessitating frequent international normalized ratio (INR) monitoring and dose adjustments (De Caterina et al., 2013). At adequate time in therapeutic range [(TTR) >70%], VKAs are effective and relatively safe drugs. Quality of VKA management (quantified using the TTR based on the Rosendaal method, or the percentage of INRs in range) correlates with hemorrhagic and thromboembolic rates.

Non-vitamin K antagonist oral anticoagulants (NOACs)

In four pivotal RCTs, apixaban, dabigatran, edoxaban, and rivaroxaban have shown non-inferiority to warfarin in the prevention of stroke/systemic embolism (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011). In a meta-analysis of these RCTs, NOACs were associated with a 19% significant stroke/systemic embolism risk reduction, a 51% reduction in hemorrhagic stroke (Ruff et al., 2014), and similar ischemic stroke risk reduction compared with VKAs, but NOACs were associated with a significant 10% reduction in all-cause mortality. There was a non-significant 14% reduction in major bleeding risk, significant 52% reduction in ICH, and 25% increase in gastrointestinal bleeding with NOACs vs. warfarin. A recent meta-analysis included 71,683 patients and showed more favorable efficacy and safety profiles among patients with AF treated with NOACs compared with warfarin (Carnicelli et al., 2022). Persistence to NOAC therapy is generally higher than to VKAs, being facilitated by a better pharmacokinetic profile of NOACs (Ingrasciotta et al., 2018).

Combination therapy with oral anticoagulant and antiplatelet

The use of antiplatelet therapy remains common in clinical practice, often in patients without an indication beyond AF. There is limited evidence to support the combination therapy solely for stroke

prevention in AF, with no effect on reductions in stroke, myocardial infarction, or death, but with a substantial increase in the risk of major bleeding and ICH (Lip, 2011; Mant et al., 2007).

Left atrial appendage (LAA) occlusion

Only the Watchman device has been compared with VKA therapy in RCTs [the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy)] (D. R. Holmes, Jr. et al., 2014; D. R. Holmes et al., 2009; Reddy, Doshi, et al., 2013), where LAA occlusion was non-inferior to VKA stroke prevention treatment in AF patients with moderate stroke risk, with a possibility of lower bleeding rates on longer follow-up (D. R. Holmes, Jr. et al., 2015). The LAA occlusion may also reduce stroke risk in patients with contraindications to OAC (Boersma et al., 2016; Reddy, Möbius-Winkler, et al., 2013). A large European registry reported a high implantation success rate (98%), with an acceptable procedure-related complication rate of 4% at 30 days (Boersma et al., 2017).

Surgical left atrial appendage occlusion or exclusion

Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available (Healey et al., 2005; Tsai et al., 2015; Whitlock et al., 2013). Residual LAA flow or incomplete LAA occlusion may be associated with an increased risk of stroke (Aryana et al., 2015). In most studies, LAA occlusion/exclusion was performed during other open-heart surgery, and in more recent years in combination with surgical ablation of AF (Gillinov et al., 2015; Tsai et al., 2015) or as an isolated thoracoscopic procedure. The most common justification for LAA occlusion/exclusion in clinical practice is a perceived high bleeding risk or, less often, contraindications for OAC (Boersma et al., 2017).

Residual adverse events despite anticoagulation in patients with AF

Patients with AF remain at significant residual risk of developing complications including ischemic stroke despite anticoagulation therapy. Using data from phase II/III of the prospective GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) registry, Ding et al. studied anticoagulated patients with newly diagnosed AF and an increased risk of stroke (CHA_2DS_2-VASc ≥1). The primary outcome of interest was ischemic stroke. Secondary outcomes were all-cause death, cardiovascular death and myocardial infarction. A total of 22,410 patients were included; median age 65 (interquartile range 71–78) and 10,044 (44.8%) were female. During a median follow-up period of 3.0 (interquartile range 2.2–3.1) years, the incidence of ischemic stroke was 0.60 (95% CI, 0.54–0.67) per 100-PYs, all-cause death 3.22 (95% CI, 3.08–3.37) per 100-PYs, cardiovascular death 1.08 (95% CI, 1.00–1.16) per 100-PYs and myocardial infarction 0.59 (95% CI, 0.53–0.66) per 100-PYs. Using multivariable Cox proportional hazards analysis, independent predictors of residual ischemic stroke were age (HR 1.05 [95% CI, 1.03–1.07]), diabetes (HR 1.42 [95% CI, 1.08–1.87]), prior thromboembolism (HR 2.27 [95% CI, 1.73–2.98]) and use of antiarrhythmic drugs (HR 0.66 [95% CI, 0.47–0.92]). The incidence of ischemic stroke was comparable among patients

treated with non-vitamin K antagonist oral anticoagulants versus vitamin K antagonist; however, there were differences in the independent predictors between both groups (Ding, Lane, Gupta, Huisman, & Lip, 2022).

Decision making to avoid stroke

The first step in decision making ('A' Anticoagulation/Avoid stroke) is to identify low-risk patients who do not need antithrombotic therapy. Step 2 is to offer stroke prevention (i. e. OAC) to those with > 1 non-sex stroke risk factors (the strength of evidence differs, with multiple clinical trials for patients with ≥ 2 stroke risk factors, and subgroups from trials/observational data on patients with 1 non-sex stroke risk factor). Step 3 is the choice of OAC, a NOAC (given their relative effectiveness, safety and convenience, these drugs are generally first choice as OAC for stroke prevention in AF) or VKA (with good TTR at >70%). This 'AF 3-step' patient pathway (Freedman, Potpara, & Lip, 2016; Lip & Lane, 2015) for stroke risk stratification and treatment decision making is shown in Figure 10.

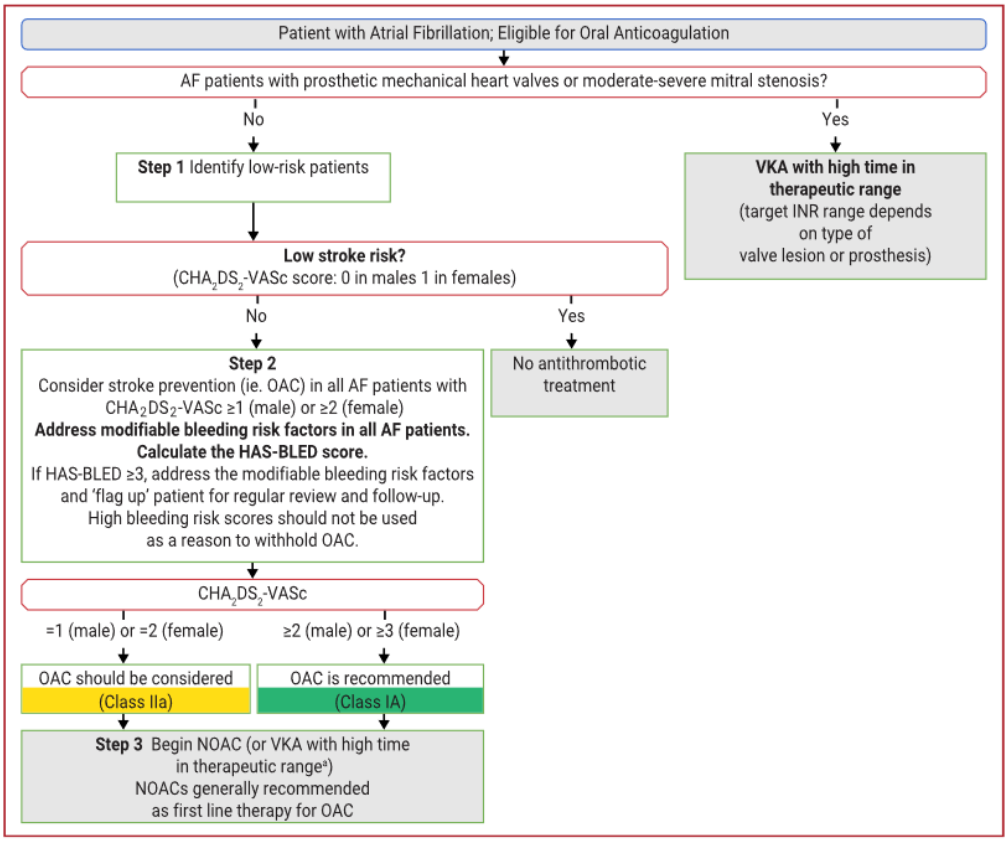

Figure 10: Anticoagulation to avoid stroke: The "AF 3-step pathway".

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2. Conclusion and recommendations

- For stroke prevention in AF, patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) (IA).
- Using the risk-factor-based CHA_2DS_2VASc score initially, patients at "low stroke risk" should be identified (CHA_2DS_2VASc score 0 in men, 1 in women) who should not be offered antithrombotic therapy (IA).
- OAC is recommended for stroke prevention in AF patients with CHA_2DS_2VASc score ≥2 in men or ≥3 in women (IA).
- OAC should be considered for stroke prevention in AF patients with a CHA_2DS_2VASc score of 1 in men or 2 in women. Treatment should be individualized (IIaB).
- A score-based bleeding risk assessment is recommended to identify non-modifiable and address modifiable risk factors in AF patients. Patients at high risk of bleeding should be scheduled for early and more frequent clinical review and follow-up (IB).
- The HAS-BLED score should be considered for bleeding risk assessment. Patients with a HAS-BLED score > 3 are considered at high risk of bleeding (IIaB).
- Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (IB).
- In patients initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation (IIaB).
- If a VKA is used, a target international normalized ratio (INR) of 2.0 – 3.0 is recommended, with individual TTR ≥70% (IB).
- Antiplatelet therapy alone is not recommended for stroke prevention in AF (IIIA).
- Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention (IIIA).
- Clinical pattern of AF (i. e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis (IIIB).
- LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (IIbB).
- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery (IIbC).

3. Relevance for risk assessment of pilots and ATCOs

Decisions on fitness to fly or perform ATCO duties and possible limitations / restrictions should depend on:

- Flying class
- Stroke risk (CHA_2DS_2VASc score)
- Bleeding risk (HAS-BLED score)
- Antithrombotic therapy (NOAC or VKA)
- Stability of anticoagulation if VKAs are used

Application of the method and/or treatment for risk assessment will be described more in detail in task 2.

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5.3 Ventricular and supraventricular ectopy

This document describes the state-of-the-art of ventricular and supraventricular ectopy, its clinical presentations, the actual diagnostic measures, and the decision strategies, also considering the various risks. The different therapeutic options are also mentioned in this document.

1. What is new? - Main findings

Ventricular ectopy (VE)

According to recent ESC-Guidelines, ventricular ectopy and non-sustained ventricular tachycardia are defined as follows (Zeppenfeld et al., 2022):

- Premature ventricular complex (PVC): Premature occurrence of an abnormal QRS complex (duration typically ≥120 ms, corresponding T-wave typically broad and in the opposite direction of the major QRS deflection, no preceding P-wave).
- Unifocal or monomorphic PVCs: PVCs with a single QRS morphology.
- Multifocal, multiform, or polymorphic PVCs: PVCs with different QRS morphologies.
- Short-coupled PVC: A PVC that interrupts the T-wave of the preceding conducted beat.
- Ventricular tachycardia (VT): ≥3 consecutive beats with a rate >100 bpm originating from the ventricles, independent from atrial and atrioventricular (AV) nodal conduction.
- Non-sustained ventricular tachycardia (NSVT): Run of consecutive ventricular beats persisting for 3 beats to 30 s.

PVCs are one of the most common arrhythmias seen in daily practice (Koester, Ibrahim, Cancel, & Labedi, 2020). Their management are described in various articles. Although PVCs are generally considered benign, they can lead to the development of cardiomyopathy and, rarely, can be associated with syncope or even sudden cardiac death (Babayiğit, Ulus, & Görenek, 2020), (Prisco, Castro, Roukoz, & Tholakanahalli, 2023), (von Alvensleben, Etheridge, Viskin, & Collins, 2020).

PVCs, also known as premature ventricular contractions, ventricular premature beats or ventricular extrasystoles, can be defined as any cardiac single depolarization originated below the atrioventricular node, either in His-Purkinje tissue or in ventricular myocytes. They represent the most common ventricular arrhythmia and are frequently observed even in healthy individuals. Some risk factors for

the appearance of PVCs are male gender, African-American ethnicity, hypertension and advanced age, showing an exponential increase in prevalence after the third or fourth decade of life (Marcus, 2020).

Most frequently, PVCs have an idiopathic origin, not associated with any underlying cardiac disease, and arise mainly from some specific ventricular areas, being particularly common in the right ventricular outflow tract (RVOT), it remains unclear the reason for this preferential location. Other prevalent foci are the left ventricular outflow tract (LVOT), the aortic sinus of Valsalva, the AV valve annulus, the Purkinje fibres or the papillary muscles. Idiopathic PVCs can appear spontaneously or be favoured by increased sympathetic tone in situations such as anxiety, sleep deprivation, physical exercise, electrolyte disturbances and intake of drugs like cocaine, caffeine, alcohol or tobacco. In some occasions PVCs may be related to an underlying cardiac condition, either affecting the electrical properties of the heart such as Brugada or long QT syndromes or being linked to structural heart disease (SHD) like hypertrophic or dilated cardiomyopathy, ischaemic heart disease, mitral valve prolapse implying a poorer prognosis (Marcus, 2020).

The pathophysiology of this phenomenon remains not totally clarified. Three possible mechanisms have been proposed: 1. Abnormal automaticity consists in the spontaneous progressive depolarisation of the resting membrane potential (phase 4 of the action potential) until it finally reaches the electrical threshold and initiates a new action potential. 2. In triggered activity, impulse formation results as a consequence of oscillations in the membrane potential related to the previous action potential (after-depolarisations) which, if they are of sufficient amplitude, can trigger a new action potential. Based on their temporal relationship, after-depolarisations are classified as early (if they happen in phase 2 or 3 of the action potential) or delayed (phase 4) (Marcus, 2020), (Hoogendijk, Géczy, Yap, & Szili-Torok, 2020). 3. In re-entry, the electrical impulse propagates around a circuit enclosed by functional or physical barriers (usually scars) of unexcitable tissue. Reentry is the main mechanism for ventricular arrhythmias in patients with structural heart disease, most typically involved in sustained VT but also possible for single PVCs (Marcus, 2020), (Hoogendijk et al., 2020).

There can be a wide variety of symptoms related to the presence of PVCs ranging from patients completely asymptomatic to others with more severe or even disabling symptoms. The most common clinical presentation consists in palpitations attributed to the abnormal heart contraction produced by the PVC itself. Other possible symptoms could be chest discomfort, dyspnoea, exertional limitation or even overt heart failure particularly in those patients with very frequent PVCs who can develop ventricular systolic dysfunction (Huizar et al., 2021). This condition called PVC induced cardiomyopathy (PIC) is generally reversible following the reduction of the PVC burden after adequate treatment (Latchamsetty & Bogun, 2019). Systolic function and left ventricular (LV) end-systolic dimension were inversely associated with PVC burden. Decreased LVOT flow velocity and pressure gradient (PG) were related to increased PVC burden. LVOT velocity time integral (VTI) and left ventricular systolic index (LVSI) were smaller when the PVC burden exceeded 20%. These negative hemodynamic manifestations of idiopathic PVC were considerable even in structural normal hearts, hence the early elimination of PVC is strongly advised (T. E. Chen et al., 2023). If the PVCs are associated with another heart condition, there can be specific symptoms related to the latter, for instance chest pain in patients with ischaemic heart disease. Malignant arrhythmias or sudden cardiac death (SCD) have also been reported even in the absence of any other apparent heart disease

(although exceptional in these cases), happening mainly when PVCs present with short coupling intervals (Ip & Lerman, 2018).

Initial diagnostic evaluation usually starts with a resting 12-lead electrocardiogram (ECG) showing one or more PVCs, sometimes as an incidental finding in a routine physical examination. On other occasions, PVCs are discovered on a Holter monitoring during the investigation of the symptoms of the patient. If possible, the site of origin of the PVC should be identified. Globally, the most frequent location of PVCs is the RVOT, generally not related to any underlying cardiac disease. Analysis of the morphology of these PVCs deserves special attention. The typical pattern consists of tall R waves in the inferior leads with a left bundle branch block (LBBB) pattern in V1 with precordial transition happening after V3. If precordial transition occurs before V3, the origin is more likely to be in the LVOT or within the aortic root on the right or left coronary cusps. When precordial transition occurs at V3, the site of origin is more unpredictable and may be either right or left sided.

The moderator band in the right ventricle is being increasingly recognised as a source for arrhythmias in the absence of identifiable structural heart disease (Barber, Chinitz, & John, 2020). Because it carries part of the conduction system from the right ventricle septum to the free wall, it is a source of Purkinje-mediated ventricular arrhythmias that manifest as PVCs or repetitive ventricular tachycardia. More importantly, short coupled PVCs triggering polymorphic VT and ventricular fibrillation (VF) have been localised to the moderator band, and ablation of these Purkinje mediated PVCs can effectively prevent recurrent VF. The exact mechanism of arrhythmogenesis is still debated, but stretch, fibrosis and ion channel alterations might be responsible. Arrhythmias originating in this region of the right ventricle may thus be another cause for idiopathic VF that is potentially treatable with catheter-based ablation techniques.

Although most of the times, PVCs have an idiopathic origin, they may sometimes be associated with underlying SHD with a poorer prognosis and would warrant a specific treatment. Consequently, investigation with cardiac imaging techniques is usually required. These imaging tests however might be unnecessary if there is no evidence of high PVC burden, patient is otherwise healthy and physically active, no history of syncope or symptoms compatible with VT, no family history of early or sudden death or cardiomyopathy, and neither the resting ECG nor physical examination suggest the presence of other abnormalities (Marcus, 2020). Transthoracic echocardiography (TTE) is the preferable initial imaging modality for both screening for SHD and evaluation of possible PIC in patients with high PVC burden (Marcus, 2020). When conventional TTE is non-diagnostic but suspicion of possible SHD remains, additional techniques like myocardial strain, transoesophageal echocardiography and particularly cardiac magnetic resonance imaging (MRI) may be necessary. Thanks to its high resolution and sensitivity for identification of early stages of SHD and the possibility of scar analysis, cardiac MRI plays a key role in uncovering undiagnosed cardiac structural abnormalities even in those patients with previously presumed idiopathic PVCs. Several studies have indeed demonstrated that routine diagnostic tests could be suboptimal, enhancing the role of cardiac MRI. Specific findings, which suggest arrhythmogenic substrates are: late gadolinium enhancement, myocardial oedema, fatty infiltration or altered T1 mapping and increased extracellular volume (Muser, Santangeli, Selvanayagam, & Nucifora, 2019), (Muser et al., 2020). Cardiac MRI should therefore be considered in situations which have proven a positive connection with underlying SHD like the presence of multifocal PVCs, induction of PVCs or more complex ventricular arrhythmias during exercise, PVCs

with a non-LBBB inferior axis morphology or clinical factors like male gender, advanced age or family history of SCD or cardiomyopathy (Muser et al., 2020). In a recent study, one in 7 patients with frequent PVCs with no known SHD had myocardial abnormality detected on MRI, and these abnormalities were associated with adverse clinical outcomes. These findings highlight the important role of MRI in the evaluation of patients with frequent PVCs (Hosseini et al., 2022).

Exercise testing should be taken into consideration in those patients with PVCs which occur or worsen during exertion. It can also be used as a tool to add diagnostic and prognostic values. The appearance of PVCs or even VT during exercise is more frequent in individuals with SHD, fact that implies a worse prognosis and a need for deeper evaluation. Suppression of ectopy with exercise is mostly reassuring (Guettler et al., 2019).

Electrophysiology study (EPS) may serve to determine the mechanism and origin of the PVCs which can later be used to plan proper treatment, sometimes even catheter ablation during the same procedure.

Specific treatment to reduce PVC burden will be necessary in symptomatic patients or in those who develop PIC, as this condition is generally reversible after adequate control of PVCs. In addition, some patients diagnosed of idiopathic dilated cardiomyopathy with impaired systolic function and a high PVC burden may have a certain component of PIC. It has been reported that some of these patients experience a significant improvement in ventricular contraction and volumes after successful reduction of their PVC burden, particularly in the ones with a ventricular dysfunction that is out of proportion in relation to the degree of myocardial fibrosis detected in cardiac MRI (Latchamsetty & Bogun, 2019). Another situation, in which treatment of PVCs should be pursued is in cases where PVCs are followed by initiation of malignant ventricular arrhythmias. Successful ablation of these PVCs can lead to a decrease of the risk of ICD shocks.

Beta blockers and non-dihydropyridine calcium channel blockers remain first-line pharmacological therapy for patients with frequent and symptomatic PVCs. A favourable safety profile and the added benefit of beta blockers in patients with ischaemic heart disease or with heart failure with reduced ejection fraction make them the best initial medical therapy. Nevertheless, several studies have showed only a slight reduction (between 12 and 24%) of PVC burden in patients with symptomatic outflow tract PVCs treated with these agents (Marcus, 2020). If these drugs were ineffective or poorly tolerated, catheter ablation should be the next therapeutical option (Sorgente et al., 2022). Asymptomatic patients without structural heart disease with high PVC burdens have a low risk of progression to cardiomyopathy, and a significant amount will resolve spontaneously. If concern for cardiomyopathy arises, then catheter ablation has been proven effective at elimination of PVCs and reversing the cardiomyopathy in the majority of patients. Given these factors, a conservative approach without offering upfront catheter ablation is preferred with clinical surveillance in these asymptomatic patients (Hoffmayer, 2021).

Atrial ectopy (AE)

Premature atrial contractions (PAC) are a common cardiac phenomenon. Although previously considered a benign electrocardiographic finding, they have now been associated with a higher risk

of incident atrial fibrillation (AF) and other adverse outcomes such as stroke and all-cause mortality (Sajeev et al., 2019). Since premature atrial contractions can be associated with these adverse clinical outcomes independently of AF occurrence, different explanations have been proposed. The concept of atrial cardiomyopathy, where AF would be an epiphenomenon outside the causal pathway between premature atrial contractions and stroke, has received traction recently. This concept suggests that structural, functional, and biochemical changes in the atria lead to arrhythmia occurrence and thromboembolic events (Farinha, Gupta, & Lip, 2023), (Guichard, Guasch, Roche, Da Costa, & Mont, 2022).

The distribution of PAC burden and its dose–response effects on all-cause mortality and cardiovascular death were analysed in a recent study. The authors analysed 15,893 patients in a medical referral centre from July 1st, 2011, to December 31st, 2018. Multivariate regression driven by ln PAC (beats per 24 h plus 1) or quartiles of PAC burden were examined. Older group had higher PAC burden than younger group (p for trend < 0.001), and both genders shared similar PACs distribution. In Cox model, ln PAC remained an independent risk factor for all-cause mortality (hazard ratio (HR) = 1.09 per ln PAC increase, 95% CI = 1.06–1.12, p < 0.001). PACs were a significant risk factor in cause-specific model (HR = 1.13, 95% CI = 1.05–1.22, p = 0.001) or sub-distribution model (HR = 1.12, 95% CI = 1.04–1.21, p = 0.004). In ordinal PAC model, 4th quartile group had significantly higher risk of all-cause mortality than those in 1st quartile group (HR = 1.47, 95% CI = 1.13–1.94, p = 0.005), but no difference in cardiovascular death were found in competing risk analysis. In subgroup analysis, the risk of high PAC burden was consistently higher than in low-burden group across pre-specified subgroups. In conclusion, PAC burden has a dose response effect on all-cause mortality and cardiovascular death (Huang, Lee, Huang, Su, & Liu, 2021).

Beta blockers consistently decreased long-term mortality in high-burden and low-burden patients. Interestingly, in a recent study, this effect was not achieved through reduction of new-onset stroke or AF (Huang et al., 2022).

Predictors of baseline PAC frequency were examined using a Holter Study among 1392 participate in the Cardiovascular Health Study, a community-based cohort of individuals aged ≥65 years. Participants were then followed for their first diagnosis of AF. Independent predictors of PACs were identified, and the extent to which PACs might mediate the relationship between those predictors and AF was determined. The median hourly frequency of PACs was 2.7 (interquartile range 0.8–12.1). After multivariable adjustment, increasing age, increasing height, decreasing body mass index, and a history of myocardial infarction were each associated with more PACs. Regarding modifiable predictors, participants using beta blockers had 21% less [95% confidence interval (95% CI) 9–30%, P= 0.001] and those performing at least moderate intensity exercise vs. lower intensity exercisers had 10% less (95% CI 1–18%, P= 0.03) PACs. Higher PAC frequency explained 34% (95% CI 22–57%, P< 0.0001) of the relationship between increasing age and AF risk and 27% (95% CI 10–75%, P= 0.004) of the relationship between taller height and AF risk (Kerola 2019). Enhancing physical activity and use of beta blockers may represent fruitful strategies to mitigate PAC frequency (Kerola et al., 2019). A substantial proportion of the excess risk of AF due to increasing age and taller height may be explained by an increase in PAC frequency (Kerola et al., 2019).

The Apple Heart Study has shown that in participants with an irregular pulse notification on the Apple Watch and no AF observed on ECG patch, atrial and ventricular arrhythmias, mostly PACs and PVCs,

were detected in 40% of participants. Defining optimal care for patients with detection of incidental arrhythmias other than AF is important as AF detection is further investigated, implemented, and refined (Perino et al., 2021).

Sleep apnea is associated with both, PVC and PAC, and should be included in the diagnostic process (Gellert et al., 2020).

For patients with symptomatic, drug-refractory PACs, or frequent residual PACs after atrial tachyarrhythmia ablation, a novel ablation strategy called dual-reference approach shortens the procedural time and improves both instant and long-term success of PAC ablation, serving as a promising approach in mapping PACs with non-pulmonary vein and non-superior vena cava origins (M. Chen et al., 2023). In this method, a constant time difference between two reference catheters helps to discriminate the target arrhythmia from other mechanical or non-targeted ectopies.

2. Conclusion and recommendations

Although PVCs are generally considered benign, they can lead to the development of cardiomyopathy and, rarely, can be associated with syncope or even sudden cardiac death. Triggering of polymorphic VT has also been reported in literature.

Most frequently, PVCs have an idiopathic origin, not associated with any underlying cardiac disease, and arise mainly from some specific ventricular areas, being particularly common in the RVOT; the reason for this preferential location remains unclear.

Pathophysiologically, three mechanisms are possible, abnormal automaticity, triggered activity, and re-entry.

There can be a wide variety of symptoms related to the presence of PVCs ranging from patients completely asymptomatic to others with more severe or even disabling symptoms. Other possible symptoms could be chest discomfort, dyspnoea, exertional limitation or even overt heart failure particularly in those patients with very frequent PVCs who can develop ventricular systolic dysfunction. This condition called PIC is generally reversible following the reduction of the PVC burden after adequate treatment. Besides ECG, Holter, and exercise ECG; cardiac MRI is gaining importance for the evaluation for SHD.

Beta blockers and non-dihydropyridine calcium channel blockers remain first-line pharmacological therapy for patients with frequent and symptomatic PVCs. If these drugs were ineffective or poorly tolerated, catheter ablation should be the next therapeutical option. Asymptomatic patients without structural heart disease with high PVC burdens generally have a low risk of progression to cardiomyopathy, and a significant amount will resolve spontaneously.

PAC are a common cardiac phenomenon. Although previously considered a benign electrocardiographic finding, they have now been associated with a higher risk of incident AF and other adverse outcomes such as stroke and all-cause mortality. Beta blockers consistently decreased long-term mortality in high-burden and low-burden patients.

Sleep apnea is associated with both, PVC and PAC, and should be included in the diagnostic process.

If catheter ablation is needed for drug-refractory patients, new mapping strategies like the dual-reference approach are being evaluated.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in detail in task 2.

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5.4 Bundle branch and fascicular blocks

This document describes the state-of-the-art of bundle branch and fascicular blocks, its clinical presentations, the actual diagnostic measures, the various risks and the decision strategies, also including the different therapeutic options.

1. What is new? - Main findings

In a population study of individuals aged 30 or older with long-term follow-up, left bundle branch block (LBBB) and non-specific intraventricular conduction delay (NIVCD), independently of several baseline variables, were associated with a more than threefold risk of new-onset heart failure (HF). Furthermore, LBBB was associated with novel structural heart disease (SHD). The presence of these electrocardiography (ECG) abnormalities should alert physicians for careful cardiac evaluation even in absence of cardiovascular symptoms (Rankinen et al., 2020).

Bundle branch block (BBB) is partial or complete interruption of impulse conduction in a bundle branch; fascicular block is similar interruption in a hemifascicle of the left bundle.

There are incomplete and complete left and right bundle branch blocks (RBBB) as well as left anterior fascicular blocks (LAFB) and left posterior fascicular blocks (LPFB). A combination of RBBB and LAFB is called bifascicular block (BFB). A QRS width of 120 ms is usually used as cut-off between incomplete and complete BBBs. This document usually explains complete BBB.

Electrocardiographic BBB is common but the prognostic implications in primary care are unclear. A recent study investigated the relationship between electrocardiographic BBB subtypes and the risk of cardiovascular (CV) outcomes in a primary care population free of major CV disease (CVD) (Rasmussen et al., 2019). The authors included 202 268 individuals with a median follow-up period of 7.8 years (Inter-quartile range [IQR] 4.9–10.6). LBBB was associated with HF in both men (hazard ratio (HR) 3.96, 95% confidence interval (CI) 3.30 to 4.76) and women (HR 2.51, 95% CI 2.15 to 2.94) and with CV death in men (HR 1.80, 95% CI 1.38 to 2.35). RBBB was associated with pacemaker implantation in both men (HR 3.26, 95% CI 2.74 to 3.89) and women (HR 3.69, 95% CI 2.91 to 4.67), HF in both sexes and weakly

associated with CV death in men. Regarding LBBB, an increasing hazard of HF with increasing QRS-interval duration (HR 1.25, 95% CI 1.11 to 1.42 per 10 ms increase in men and HR 1.23, 95% CI 1.08 to 1.40 per 10 ms increase in women) was found. Absolute 10-year risk predictions across age-specific and sex-specific subgroups revealed clinically relevant differences between having various BBB subtypes. The authors found significant associations between RBBB, LBBB, nonspecific intraventricular *conduction* delay (NIVCD) and the hazard of incident HF, myocardial infarction (MI) as well as pacemaker implantation. Absolute risk predictions of HF and pacemaker implantation revealed clinically relevant differences between having various BBB subtypes versus no BBB.

Compared to men, women with unexplained syncope and BBB have a lower risk of atrioventricular block (AVB) and of requiring cardiac pacing. A stepwise diagnostic approach has a similar diagnostic yield in both sexes, and it seems appropriate to guide the treatment and avoid unnecessary pacemaker implantation, especially in women (Francisco-Pascual et al., 2022).

Left bundle branch block (LBBB)

The impact of LBBB on cardiac mechanical function ranges from minimal effect in some patients to marked reduction in left ventricular (LV) systolic function in others. This variability in part reflects differences in anatomical location of the bundle block. In most patients with LBBB and congestive heart failure, however, there is associated cardiac disease such as cardiomyopathies or coronary artery disease (CAD) which contributes to LV dysfunction. The mechanism of harmful effect of LBBB on cardiac function is in-coordinated ventricular contractions which result in LV contractile inefficiency. Septal contribution to LV systolic function is lost or attenuated, and an excessive workload is placed on the LV free wall which responds with remodelling and in some cases it decompensates. The magnitude of the contractile inefficiency depends on the extent of electrical conduction delay and degree of associated heart disease. Another mechanism, which in many patients contributes to cardiac dysfunction in LBBB, is mitral regurgitation due to in-coordinated contractions of the papillary muscles and altered mitral valve function due to LV remodelling. Potentially, reduced LV filling time due to pro-longed LV systole may contribute to cardiac dysfunction, but there is limited knowledge about the clinical importance of this mechanism. In LBBB there is typically reduced septal perfusion, probably not as a sign of ischemia, but reflecting physiologic autoregulation of coronary flow in response to reduced septal work that reduces metabolic demand (Smiseth & Aalen, 2019).

LBBB has profound hemodynamic and clinical implications even among asymptomatic individuals, and its presence is associated with a multitude of cardiac diseases. Prompt identification of LBBB, particularly in certain clinical scenarios, is, therefore, critical in determining optimal management strategies for patients (Tan, Witt, Oh, & Cha, 2020). The prognosis of LBBB in asymptomatic individuals remains controversial. Although a study among US Airforce personnel did not reveal an association between LBBB and CVD, data from the Framingham study showed a significantly elevated risk of CV deaths (50% within 10 years of onset) among individuals with LBBB. More recent studies have highlighted LBBB as an independent predictor for adverse events, including sudden cardiac death (10-fold incidence increase) as well as mortality from HF (3.08× increased risk) and MI (2.90× increased risk), particularly among individuals aged 50 years and above. Furthermore, in a Swedish prospective study of middle-aged men spanning 28 years, LBBB at baseline was associated with a markedly increased risk of high-grade AVB compared with men without BBB (adjusted risk ratio, 12.9). Hence,

although the prognosis of LBBB in younger patients may be relatively benign, its presence in older subjects may serve as an important marker for CVD or death.

In summary, LBBB has profound hemodynamic and clinical implications even among asymptomatic individuals, and its presence is associated with a multitude of cardiac diseases. Prompt identification of LBBB, particularly in certain clinical scenarios, is, therefore, critical in determining optimal management strategies for patients (Kusumoto et al., 2019), (Tan et al., 2020).

Another study determined the utility of CV magnetic resonance (CMR) in the risk stratification of patients with incident LBBB (iLBBB) (Zegard et al., 2020). Clinical events were collected in patients with iLBBB who had CMR. Controls had no cardiac symptoms or cardiac disease, a normal CMR scan and electrocardiogram. Amongst patients with iLBBB [n = 193, aged 62.7 ± 12.6 years (mean ± SD)], 110/193 (56.9%) had an abnormal phenotype ($iLBBB_{CMR+}$) and 83/110 (43.0%) had a normal phenotype ($iLBBB_{CMR-}$). Over 3.75 years (median; inter-quartile range: 2.7–5.5), $iLBBB_{CMR+}$ had a higher total mortality [adjusted hazard ratio (aHR) 6.49, 95% confidence interval (CI) 1.91–22.0] and total mortality or major adverse cardiac events (MACEs; aHR 9.15, 95% CI 2.56–32.6) than controls (n = 107). In contrast, $iLBBB_{CMR-}$ had a similar risk of total mortality compared with controls, but total mortality or MACEs was higher (aHR 4.24, 95% CI 1.17– 15.4; P = 0.028). Amongst iLBBB patients, both myocardial fibrosis (aHR 5.15, 95% CI 1.53–17.4) and left ventricular ejection fraction (LVEF) ≤50% (aHR 3.88, 95% CI 1.67–9.06) predicted total mortality. Myocardial fibrosis plus LVEF ≤50% was associated with the highest risk of total mortality (aHR: 9.87, 95% CI 2.99–32.6) and total mortality or MACEs (aHR 3.98, 95% CI 1.73–9.11). The authors concluded that outcomes in $iLBBB_{CMR+}$ were poor whereas survival in $iLBBB_{CMR-}$ was comparable with controls. Myocardial fibrosis and LVEF <50% had an additive effect on the risk of clinical outcomes. A CMR scan is pivotal in risk stratifying patients with iLBBB (Zegard et al., 2020).

The risk of developing LV systolic dysfunction among LBBB patients with preserved left ventricular ejection fraction (LVEF) is high enough to warrant serial imaging.

A recent study screened records of 1000 consecutive patients with LBBB from their ECG database and identified subjects with an initially preserved LVEF (≥45%) without clinically relevant CAD or other cause for cardiomyopathy. Baseline imaging, clinical data, and follow-up imaging were recorded to determine the risk of subsequent LV systolic dysfunction (LVEF ≤40%). 784 subjects were excluded, the majority for CAD or depressed LVEF upon initial imaging. Of the remaining 216, 37 (17%) (Data are mean + SD) developed a decline in LVEF (≤40%) over a mean follow-up of 55 ± 31 months; 94% of these patients had a baseline LVEF ≤60% and LV end systolic diameter (ESD) ≥ 2.9 cm indicating that these measures may be useful to define which patients warrant longitudinal follow-up. The negative predictive value of a LVEF >60% and LVESD <2.9 cm was 98%. In conclusion, seventeen percent of patients with LBBB and initial preserved LVEF developed dyssynchrony cardiomyopathy. The risk of developing dyssynchrony cardiomyopathy is high enough to warrant serial assessment of LV systolic function in this high-risk population (Sharma et al., 2020).

According to several studies, isolated LBBB is not benign. In a recent study (Sze et al., 2017) comparing 2 groups of patients with normal LVEF (LBBB versus normal QRS), LV dysfunction was observed in 36% in the LBBB group compared with 10% in the control group. In this study, about one-quarter of patients with LBBB and normal LVEF later develop significant LVEF drop. Around 5% appear LBBB-

induced with LVEF decline occurring on average after 4 to 5 years. These patients tended to be younger and were at high risk of developing heart failure/death. Similar to pacing-induced cardiomyopathy patients, the cardiac resynchronization therapy response appears to be excellent; however, is underutilized. Randomized study is needed to justify early interventions for prevention of cardiomyopathy (Barake, Witt, Vaidya, & Cha, 2019).

Right bundle branch block (RBBB)

In a study of Alventosa-Zaidin et al., a general population cohort with no CVD was analysed. Eight percent had RBBB, with a higher prevalence among men and elderly patients. Although all-cause mortality and cardiovascular events (CVE) tended to increase in the presence of complete RBBB, only bifascicular block showed a statistically significant association with complete RBBB. Patients with incomplete RBBB who progressed to complete RBBB had a higher incidence of CVE. No effect of incomplete RBBB on morbidity and mortality was observed (Alventosa-Zaidin et al., 2019).

A recent study reviewed the Mayo Clinic Integrated Stress Center database for ±exercise stress tests performed from 1993 to 2010. Patients with no known CVD -defined as absence of coronary disease, structural heart disease, heart failure, or CVD - were selected. Only Minnesota residents were included, all of whom had full mortality and outcomes data. There were 22 806 patients without CVD identified; 220 of whom (0.96%) had RBBB, followed for 6 to 23 years (mean 12.4±5.1). There were 8256 women (36.2%), mean age was 52±11 years; and 1837 deaths (8.05%), including 645 cardiovascular-related deaths (2.83%), occurred over follow-up. RBBB was predictive of all-cause (hazard ratio [HR], 1.5; 95% CI, 1.1–2.0; *P*=0.0058) and CV-related mortality (HR,1.7; 95% CI, 1.1–2.8; *P*=0.0178) after adjusting for age, sex, diabetes mellitus, hypertension, obesity, current and past history of smoking, and use of a heart rate-lowering drug. Patients with RBBB exhibited more hypertension (34.1% versus 23.7%, *P*<0.0003), decreased functional aerobic capacity (82±25% versus 90±24%; *P*<0.0001), slower heart rate recovery (13.5±11.5 versus 17.1±9.4 bpm; *P*<0.0001), and more dyspnea (28.2% versus 22.4%; *P*<0.0399) on exercise testing. In conclusion, patients with RBBB without CVD have increased risk of all-cause mortality, CV-related mortality, and lower exercise tolerance. These data suggest, that RBBB may be a marker of early CVD and merit further prospective evaluation (Gaba et al., 2020).

After acute coronary syndrome, Patients with BBB have worst outcome, particularly with RBBB. For that reason, special attention should be payed and these patients should be treated as aggressively as patients with normal QRS duration or LBBB (Timóteo et al., 2019).

Fascicular blocks

The impact of fascicular blocks on the clinical outcome was evaluated in several studies.

The LAFB is nourished by the septal perforators from the left anterior descending (LAD) coronary artery mainly and therefore, is more sensitive to ischemia. Since the septal perforators of the LAD coronary artery are the main source of blood supply for the left anterior fascicle, the presence of LAFB can predict obstructive stenoses of the left main (LM) and/or proximal left anterior descending (pLAD) coronary arteries in patients with stable angina pectoris. LAFB carries no appreciable risk of

progression to higher degrees of block. However, it may be associated with myocardial ischaemia and, if newly acquired over age 40, underlying CAD should be excluded with computerized tomography coronary angiography (CTCA) (Guettler et al., 2019).

Left posterior fascicular block (LPFB) is an extremely rare ECG finding (0.06% to 0.1% in the general population). Because scar patterns in nonischaemic cardiomyopathy (NICM) commonly involve the inferoposterior left ventricle, it was hypothesized that LPFB may be an ECG biomarker of LV scarring and associated with increased risk of sudden cardiac death (SCD) in young people. In a case-control study, the authors compared the frequency of LPFB in a consecutive series of young individuals who experienced SCD or aborted cardiac arrest (ACA) and a control population of apparently healthy young people (Calò et al., 2021). The study explored the associations among LPFB and CMR and histopathological findings. A total of 10 of the 109 (9.2%) individuals in the study group had LPFB (9 men; median age 27.5 years [interquartile range: 22.8 to 36.5 years]): 6 had ACA/SCD during or immediately after sport activity. In total, 8 of the 8,892 (0.09%) control subjects (5 men; median age 28.6 years [interquartile range: 22.0 to 38.7 years]) had LPFB. LPFB was significantly associated with ACA/SCD (unadjusted odds ratio (OR): 112.2; 95% CI: 43.3 to 290.2; $p < 0.0001$). The findings suggest that isolated LPFB could be a valuable tool for arrhythmic risk stratification in young people, should be recognized as a pathological finding, and should prompt further investigation to detect underlying structural abnormalities (Calò et al., 2021).

Bifascicular block (BFB)

Syncope followed by presyncope should be taken seriously in patients with BFB. Invasive electrophysiology is safe in these patients and often identifies high risk group who needs pacemaker therapy. Asymptomatic patients of BFB without PR prolongation should not be subjected to electrophysiology study (EPS) study but should be made aware about above mentioned symptoms and should seek immediate cardiac advice if someone gets such symptoms. In asymptomatic group, the rate of progression or of the development of complete heart block is low. However asymptomatic BFB with PR prolongation may be subjected to elective EPS in order to risk stratify them.

Most patients with syncope and BFB develop advanced AV block and/or syncope during follow-up. The results of another study show that treatment according to EPS does not improve the results of another treatment strategy with empirical pacemaker.

2. Conclusion and recommendations

Electrocardiographic BBB is common, but the prognostic implications in primary care are unclear. LBBB has the potential to impair LVEF due to in-coordinated ventricular contractions which result in LV contractile inefficiency, and mitral regurgitation. LBBB has profound hemodynamic and clinical implications even among asymptomatic individuals, and its presence is associated with a multitude of cardiac diseases. Prompt identification of LBBB, particularly in certain clinical scenarios, is, therefore, critical in determining optimal management strategies for patients. The prognosis of LBBB in asymptomatic individuals remains controversial. Although a study among US Airforce personnel did not reveal an association between LBBB and CV disease, data from the Framingham study showed a

significantly elevated risk of CV deaths among individuals with LBBB as well as mortality from HF and MI, particularly among individuals aged 50 years and above. Hence, although the prognosis of LBBB in younger patients may be relatively benign, its presence in older subjects may serve as an important marker for CV disease or death. CMR is important for risk stratification in patients with iLBBB. According to several studies, isolated LBBB is not benign, the risk of HF and death is often increased.

Patients with incomplete RBBB who progressed to complete RBBB had a higher incidence of CV events. An effect of incomplete RBBB on morbidity and mortality was not detected. In other studies, patients with RBBB without CVD have increased risk of all-cause mortality, CV-related mortality, and lower exercise tolerance.

In patients with suspected stable angina, LAFB is associated with known CV risk factors. It acts as a marker rather than a determinant of obstructive LM and/or pLAD coronary artery lesions.

Isolated LPFB could be a valuable tool for arrhythmic risk stratification in young people, it should be recognized as a pathological finding, and should prompt further investigation to detect underlying structural abnormalities. It is an extremely rare ECG finding (0.06% to 0.1% in the general population). Because scar patterns in NICM commonly involve the inferoposterior left ventricle, LPFB may be an ECG biomarker of left ventricular (LV) scarring and associated with increased risk of SCD in young people.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in detail in task 2.

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5.5 Atrioventricular block

This document describes the state-of-the-art of atrioventricular block (AVB), its definitions, clinical presentations, the actual diagnostic measures, and the decision strategies, also considering the various risks. The different therapeutic options are also described in this document.

First-degree AVB is a prolongation of the PR interval. In asymptomatic patients it can be regarded as a normal variant up to a PR interval of 300 ms. It is a common finding in young athletes (Sharma et al.,

2018). If the PR interval exceeds 300 ms as a new finding, further investigation and follow-ups are recommended. During exercise ECG (and after atropine), a significant shortening of the PR interval should be observed.

The most common type of second-degree AVB is Mobitz type I (Wenckebach). In most cases this is an incidental finding in asymptomatic individuals, and further examination is usually not required. As with first degree heart block, further investigation is only required in those with symptoms, diurnal occurrence of Mobitz type I or in those aged over 40 years at first presentation.

In contrast to Mobitz type I, second-degree AVB Mobitz type II is more commonly related to infra-Hisian block, located below the AV node, and carries a risk of progression to third degree (complete) AVB. Patients with Mobitz type II and complete AVB must be investigated for underlying structural heart disease. In most cases pacemaker therapy is indicated.

Notably, a 2:1 AVB can indicate both second-degree AVB Mobitz I and Mobitz II. Features suggestive for Mobitz I would be episodes with Wenckebach periodicity in the same recording, occurrence at night and during rest, adequate increase of heart rate during daytime and exercise, appearance in young, sporty, asymptomatic individuals with high vagal tone, narrow, unchanged QRS complexes, and prolonged PR intervals (N. Guettler, Rajappan, JL, & Nicol, 2019).

1. What is new? - Main findings

<u>New recommendations for diagnostics and therapy of AVB according to 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy (Glikson et al., 2021) with class of recommendation and level of evidence in blue:</u>

In patients with intra-ventricular conduction disease or AVB of unknown level, exercise testing may be considered to expose infranodal block (IIbC).

Screening for sleep apnea syndrome (SAS) and in the presence of severe bradycardia or advanced AVB during sleep (IC).

Pacing is indicated in patients with atrial arrhythmia (mainly AF) and permanent of paroxysmal third- or high-degree AVB irrespective of symptoms (IC).

Dual chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged > 40 years with severe, unpredictable, recurrent syncope who have spontaneous documented symptomatic asystolic pause(s) > 3 s of asymptomatic pause(s) > 6 s due to sinus arrest or AVB (IA).

In patients treated with His bundle pacing (HBP) device programming tailored to specific requirements is recommended (IC).

In patients treated with HBP, implantation of a right ventricular lead used as “backup” for pacing should be considered in specific situations (e. g. pacemaker-dependency, high-grade AVB, infranodal bock, high pacing threshold, planned AV junction ablation), or for sensing in case of issues with detection (e. g. risk of ventricular undersensing or oversensing of atrial/His potentials) (IIaC).

Other recently discussed aspects concerning AVB

Reflex AVB is well-recorded although it is considered rare. Recent data suggest that it is less rare than has been supposed. It has been shown to occur in both vasovagal and carotid sinus reflexes. It has to be distinguished from paroxysmal AVB due to ventricular conduction tissue disease. The relevance of reflex AVB to clinical decision-making is as a possible indication for pacing the heart with consideration given to the vasodepressor component of the reflex (Sutton, 2020).

Functional AVB due to autonomic influences can be identified in a minority of patients presenting with high-grade AVB. Cardioneuroablation (catheter ablation of ganglionated plexus) for these patients results in encouraging medium-term outcomes (Aksu, Guler, Bozyel, & Yalin, 2019), (Aksu, Gopinathannair, Bozyel, Yalin, & Gupta, 2021).

High-degree AVB has been reported as a possible complication of COVID-19 probably as part of a myocarditis. Given its transient nature, conservative treatment should be preferred if possible (Abe et al., 2021), (Ashok & Loke, 2020), (Dagher et al., 2021), (Gubitosa, Xu, Ahmed, & Pergament, 2020), (Sardana, Scheinman, & Moss, 2021).

AVB can be part of the inherited progressive cardiac conduction disease (PCCD) with autosomal mutations in most of the cases. A new mutation of the transient receptor potential melastatin 4 (TRPM4) gene causing AVB has recently been described (Dong et al., 2021).

AVB of unknown aetiology presenting before the age of 50 years and treated with pacemaker implantation was associated with a three- to four-fold higher rate of the composite endpoint of death or hospitalization for heart failure, ventricular tachyarrhythmia, or cardiac arrest with successful resuscitation. And patients with persistent AVB were at higher risk (Dideriksen et al., 2021).

In a nationwide cohort in Denmark, the aetiology of AVB was identified in only half the patients younger than 50 years referred for first-time pacemaker implantation. The number of patients with unknown aetiology increased during the study period. These findings indicate need for better insight into aetiologies of AVB and improved diagnostic work-up guidelines (Rudbeck-Resdal et al., 2019).

Age, male sex, elevated blood pressure and fasting glucose were identified as risk factors for AVB (Kerola et al., 2019), (Shan et al., 2021).

Left bundle branch pacing and HBP have been observed to be superior to right ventricular pacing in patients with AVB requiring a high burden of ventricular pacing regarding preservation of left ventricular ejection fraction (LVEF) (Li et al., 2021), (Vijayaraman et al., 2022), (Chung et al., 2023), (Ye et al., 2021), (S. Zhang et al., 2021), (Y. Zhang, Jia, Liu, & Du, 2022).

Electrical remodelling seems to be a key mechanism underlying AVB in athletes (Mesirca et al., 2021).

Marked first-degree AVB (PR > 300 ms) may lead to complete AVB development (Zupan Meznar, Mrak, Stublar, & Zizek, 2023).

In the CODE study (Clinical Outcomes in Digital Electrocardiology) AVB was an independent risk factor for overall mortality, with the exception of Mobitz type I (Paixão et al., 2022).

Timely and accurate diagnosis of the underlying cause of advanced AVB by the routine use of Cardiac magnetic resonance imaging (CMR), particularly in young and middle-aged patients, will enable cause-

specific treatments, and improve outcomes. Using temporary permanent pacemaker (TPPM) in patients who need continuous pacing will make this clinical practice easier (von Wald & Shenoy, 2022).

AVB in pilots and ATCOs

The management in pilots and ATCOs has been summarized by the NATO Occupational Cardiology in Military Aircrew working group (N. Guettler, Bron, et al., 2019):

First-degree AVB in asymptomatic pilots and ATCO can be regarded as a normal variant up to 300 ms (N. Guettler & Sammito, 2021) with no further examinations needed. If the PR interval exceeds 300 ms, further evaluation is necessary. In case of normal results most pilots and ATCOs can remain flying.

In asymptomatic pilots and ATCOs with second-degree heart block Mobitz type I (Wenckebach) as an incidental finding further examination is usually not required. As with first degree AVB, further investigation is only required in pilots and ATCOs with symptoms, diurnal occurrence or in those aged over 40 years at first presentation. Most pilots and ATCOs with Mobitz type I may be returned to unrestricted duties.

In contrast to Mobitz type I, Mobitz type II is rarely seen in pilots and ATCOs. Pilots and ATCOs with Mobitz type II and complete AVB must be investigated for underlying structural heart disease and, although often asymptomatic, they are unfit because of the risk of sudden cardiac death (SCD), syncope, bradycardia-related hemodynamic symptoms, and heart failure. In most cases pacemaker therapy is indicated. A review by an electrophysiologist is recommended.

Pilots and ATCOs with implanted pacemakers are initially unfit. According to current EASA medical requirements, a return to pilot or ATCO duties may be possible if individuals are not pacemaker-dependent, have bipolar lead systems, and have regular pacemaker follow-up. The possibility of pacemaker failure and the risk of electromagnetic interference, even if considered low in modern pacemaker systems (De Rotte & Van Der Kemp, 2002), (N. J. Guettler, Cox, Holdsworth, Rajappan, & Nicol, 2022) are also important factors, and pilots and ATCOs are usually restricted to low performance aircraft that do not routinely employ equipment that use high electro-magnetic frequencies (EMF). EMF sources are common in many military aircraft and other radar systems and should always be considered by occupational physicians before return to military pilot or ATCO duties.

In some instances, discrimination between second degree AVB Mobitz type I and II can be challenging on the ECG, and in pilots and ATCOs, invasive electrophysiological (EP) testing with measurement of the H-V interval may be helpful.

2. Conclusion and recommendations

- First degree AVB block is common in young sporty people and can be regarded as a normal variant up to a PR interval of 300 ms. If the PR interval exceeds 300 ms, further evaluation and regular follow-ups are necessary.
- Second-degree AVB Mobitz type I (Wenckebach) is usually an incidental finding in asymptomatic individual. As with first degree heart block, further investigation is only required in those with symptoms, diurnal occurrence of Mobitz type I or in those aged over 40 years at

first presentation. Most pilots and ATCOs with Mobitz type I may be returned to unrestricted duties

- Second-degree AVB Mobitz type II is more commonly related to infra-Hisian block, located below the AV node, and carries a risk of progression to third degree (complete) AVB. Pilots and ATCOs with Mobitz type II and complete AVB must be investigated for underlying structural heart disease and, although often asymptomatic, pilots and ATCOs are unfit for flying because of the risk of sudden cardiac death (SCD), syncope, bradycardia-related hemodynamic symptoms, and heart failure. Pacemaker therapy is indicated.
- Pilots and ATCOs with third-degree (total) AVB are unfit for flying and need further investigation. Pacing will usually be required in paroxysmal or permanent third-degree AVB.
- Screening for SAS is recommended in patients with symptoms of SAS and in the presence of severe bradycardia or advanced AVB during sleep (IC).
- Pacing is indicated in patients in SR with permanent or paroxysmal high-degree AVB (third or second-degree type 2) or infranodal 2:1 block, irrespective of symptoms (IC).
- Pacing is indicated in patients with atrial arrhythmia (mainly AF) and permanent or paroxysmal high-degree AVB or infranodal 2:1 block, irrespective of symptoms (IC).
- Pacing is not recommended in patients with AVB due to transient causes that can be corrected and prevented (IIIC).
- Dual-chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged >40 years, with severe, unpredictable, recurrent syncope who have spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest or AVB (IA).

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in more detail in task 2.

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5.6 Asymptomatic ventricular pre-excitation

This document describes the state-of-the-art of asymptomatic ventricular pre-excitation, its actual diagnostic measures, its risk assessment, and the decision strategies including also_therapeutic options.

1. What is new? - Main findings

There has been consensus that Wolff-Parkinson-White (WPW)-Syndrome caused by an accessory pathway (AP) and with a clinical manifestation of typical atrioventricular (AV) nodal re-entrant tachycardias (AVRT) should be treated by catheter ablation.

Ventricular pre-excitation without AVRT is an electrocardiographic finding characterised by a delta wave and a short PR interval. It is estimated that 1 in 1000 people will exhibit this pattern on the electrocardiogram (ECG); however, the true prevalence is likely under-represented because at least half of known patients with pre-excitation do not develop symptoms. This ECG pattern indicates the presence of an AP, an alternate electrical connection between atria and ventricles bypassing the normal His-Purkinje system. APs can conduct in antegrade direction, retrograde direction or both. Approximately 60%–75% of these pathways are considered 'manifest', meaning they are capable of antegrade conduction, and can inscribe the classic pre-excitation pattern on the ECG, and the rest are 'concealed', meaning they are only capable of retrograde conduction, cannot produce pre-excitation, but can still participate in AVRT (Antiperovitch, Skanes, Klein, & Tang, 2023).

Fast antegrade conduction over the accessory pathway may lead to ventricular fibrillation (VF) and sudden cardiac death (SCD) in cases of atrial fibrillation (AF), as accessory pathways lack the decremental properties of the AV node, while retrograde conduction over the accessory pathway may allow for AV re-entrant tachycardia (Guettler et al., 2019), (Nunes, Lebreiro, Campelo, Adão, & Maciel, 2022), (Moskal et al., 2020).

The most common arrhythmia in patients with WPW syndrome is AVRT (80%), followed by a 20-30% incidence of AF. SCD secondary to pre-excited AF that conducts rapidly to the ventricle over the AP, resulting in VF, is the most feared manifestation of WPW syndrome. The risk of cardiac arrest/VF has been estimated at 2.4 per 1000 personyears (95% confidence interval 1.3 - 3.9**)** (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020).

Clinical and electrophysiological features associated with an increased risk of SCD include younger age, inducibility of AV-reciprocating tachycardia during electrophysiologic study (EPS), multiple APs, and demonstration of a capability of the AP to allow rapid conduction to the ventricles. These variables include the shortest preexcited RR interval during AF (SPERRI) of ≤250 ms at baseline or a short antegrade effective refractory period (ERP) of the AP (≤250 ms) (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020), (Guettler et al., 2019). With non-invasive testing, identification of an abrupt and complete normalization of the PR interval with loss of delta wave during exercise testing, or following procainamide, propafenone, or dispopyramide administration, has been considered a marker of low risk (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020). Catecholamine sensitivity is a major limiting factor of all tests, both invasive and non-invasive, including exercise testing. Intermittent loss of pre-excitation on a resting ECG or ambulatory monitoring has also been associated with APs with longer ERPs, and has been accepted as a credible risk-stratification tool. However, a number of recent studies, which have included both symptomatic and asymptomatic patients, have indicated that more than one fifth of patients with intermittent pre-excitation have AP ERPs <250 ms. Thus, intermittent pre-excitation is now recognized as an imperfect marker of a low-risk AP (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020), (Facin & Samesima, 2023), (Lim et al., 2022).

Pappone et al. published a prospective randomized controlled trial of catheter ablation (37 patients) vs. clinical follow-up without treatment (35 patients) of patients with asymptomatic pre-excitation (Pappone et al., 2003), (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomström-Lundqvist, et al., 2020). Catheter ablation reduced the frequency of arrhythmic events (7 vs. 77%, $P < 0.001$) over 5 years. One patient in the control group had an episode of cardioverted VF.

Invasive screening with an EPS should be performed in patients with asymptomatic pre-excitation who either have high-risk occupations or are competitive athletes (Figure 11) (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomström-Lundqvist, et al., 2020), (Książczyk, Pietrzak, & Werner, 2020).

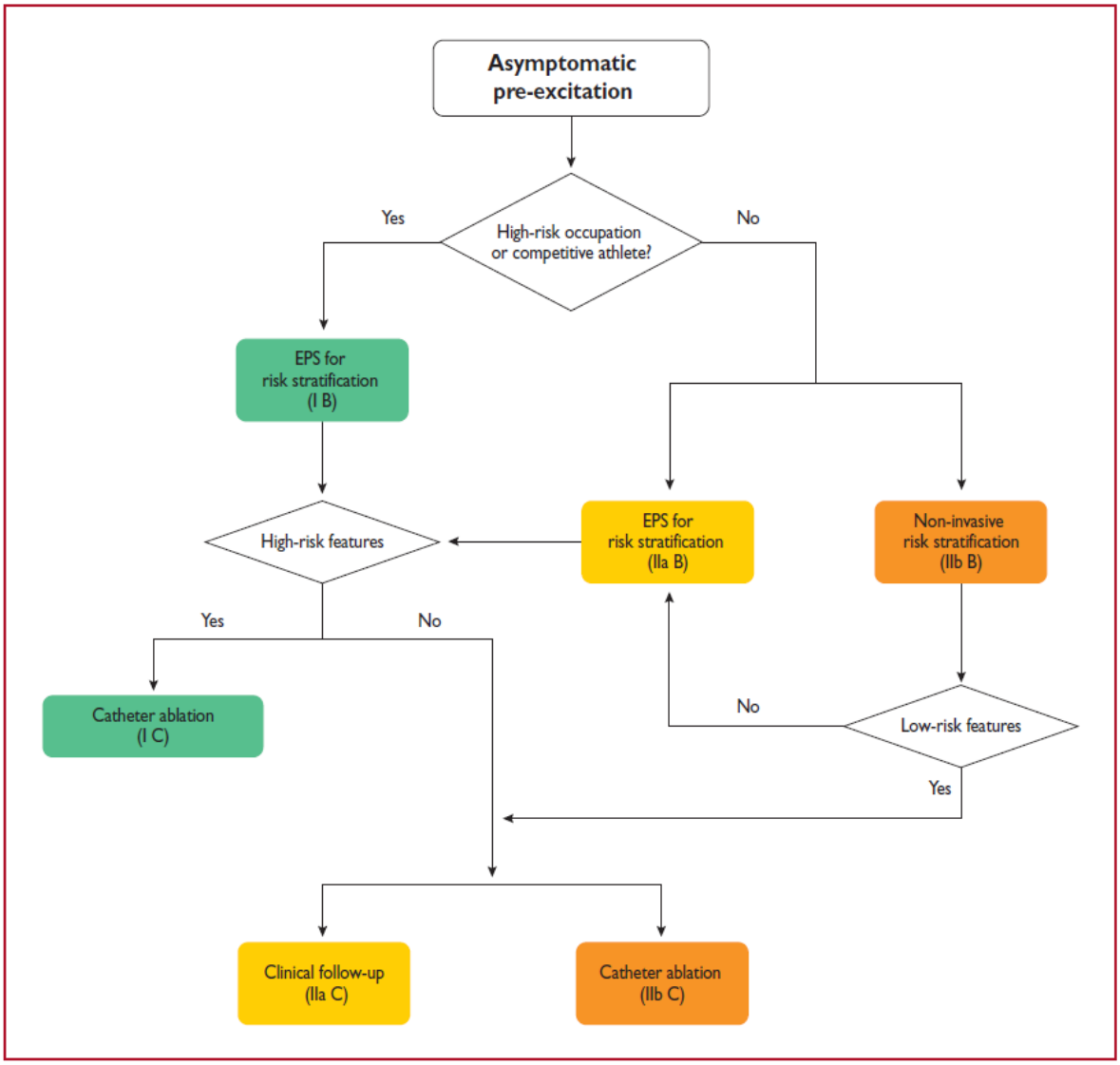

Figure 11: Risk stratification and therapy of patients with asymptomatic pre-excitation. High-risk features at electrophysiology study are shortest preexcited RR interval during atrial fibrillation ≤250 ms, accessory pathway effective refractory period ≤250 ms, multiple accessory pathways, and inducible atrioventricular re-entrant tachycardia. Low-risk features at non-invasive risk stratification are induced or intermittent loss of pre-excitation on exercise or drug testing, resting ECG, and ambulatory ECG monitoring. - EPS = electrophysiology study.

@2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomström-Lundqvist, et al., 2020).

Variables on the EPS that identify patients with a high-risk AP include a noninvasive shortest preexcited R-R interval (SPERRI) ≤250 ms, AP effective refractory period (ERP) ≤250 ms, multiple APs, and an inducible AP-mediated tachycardia in the baseline state or during isoproterenol infusion, which should always be tried. The options for screening patients who do not fall into these groups include the use of EPS as a risk-stratifying tool or the use of non-invasive screening with exercise testing, drug testing, and ambulatory monitoring as risk-stratification tools.

If a patient undergoes screening with an EPS and is found to have an AP with 'high-risk' characteristics, catheter ablation should be performed. Catheter ablation of an AP, when performed by an experienced operator, is associated with a high cure rate (>95%) and low risk (<0.5%) of major complications. However, it should be noted that even invasive studies do not confer absolute certainty about risk assessment.

There has also been evidence supporting the notion of left ventricular (LV) dysfunction related to electrical asynchrony in patients, especially children, with asymptomatic pre-excitation. It seems reasonable to recommend EPS and consider ablation if a link between pre-excitation and LV dysfunction can be made (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020).

Catheter ablation of an asymptomatic 'low-risk' AP also appears reasonable in appropriately experienced centres according to informed patient choice. However, when a decision is made to perform catheter ablation, it is important to recognise that ablation of APs in the anteroseptal or mid-septal (MS) region is associated with a small risk of AV block. The risk of heart block associated with ablation of anteroseptal or MS APs may preclude ablation of an anteroseptal or MS AP in an asymptomatic patient (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020), (Mohan & Balaji, 2019).

Intravenous adenosine is a simple test that can uncover latent preexcitation via an AP and is useful in the diagnostic workup of sudden cardiac arrest survivors without an identifiable cause. Latent preexcitation is usually associated with left free wall pathways but may also occur in right-sided APs with slow antegrade conduction (Foo, Stiles, & Heaven, 2020).

ESC-Guidelines for the management of patients with supraventricular tachycardia (Brugada, Katritsis, Arbelo, Arribas, Bax, Blomstrom-Lundqvist, et al., 2020) (Class of recommendation and level of evidence are given in blue)

Performance of an EPS with the use of isoprenaline, is recommended to risk stratify individuals with asymptomatic pre-excitation who have high-risk occupations/hobbies, and those who participate in competitive athletics (IB).

Catheter ablation is recommended in asymptomatic patients in whom electrophysiology testing with the use of isoprenaline identifies high-risk properties, such as SPERRI ≤250 ms, AP ERP ≤250 ms, multiple APs, and an inducible AP-mediated tachycardia (IB).

Catheter ablation is recommended in high-risk patients with asymptomatic pre-excitation after discussing the risks, especially of heart block associated with ablation of anteroseptal or MS APs, and benefits of the procedure (IC).

Performance of an EPS to risk stratify individuals with asymptomatic pre-excitation should be considered (IIaB).

Non-invasive evaluation of the conducting properties of the AP in individuals with asymptomatic pre-excitation may be considered (IIbB).

Invasive risk stratification with an EPS is recommended in patients without 'low-risk' characteristics at non-invasive risk stratification (IC).

Clinical follow-up should be considered in a patient with asymptomatic pre-excitation and a low-risk AP at invasive risk stratification (IIaC).

Catheter ablation may be considered in a patient with asymptomatic pre-excitation, and a low-risk AP at invasive or non-invasive risk stratification (IIbC).

Catheter ablation should be considered in patients with asymptomatic pre-excitation and LV dysfunction due to electrical dyssynchrony (IIaC).

Catheter ablation may be considered in patients with low-risk asymptomatic pre-excitation in appropriately experienced centres according to patient preferences (IIbC).

2. Conclusion and recommendations

- Detailed and clear guidelines are found the "2019 ESC-Guidelines for the management of patients with supraventricular tachycardia" from Brugada et al. (see above).
- In 60-70% of cases, AP represents as a "classical" pre-excitation pattern in the ECG. The APs which cannot be recognized in the ECG are called "concealed" forms of AP. APs can conduct in antegrade and retrograde direction or both.
- SCD secondary to pre-excited AF that conducts rapidly to the ventricle over the AP, resulting in VF, is the most feared manifestation of WPW syndrome.
- Intravenous adenosine is a simple test that can uncover latent preexcitation via an AP and is useful in the diagnostic workup of sudden cardiac arrest survivors without an identifiable cause.
- While there is broad consensus that in patients with symptomatic WPW syndrome catheter ablation of the AP is the treatment of choice, for asymptomatic patients with ventricular pre-excitation non-invasive and/or invasive risk assessment should be considered.
- Invasive risk assessment by EPS is a class I recommendation for patients with high-risk occupations and competitive athletes. High-risk features are SPERRI ≤250 ms, AP ERP ≤250 ms, multiple APs, and an inducible AP-mediated tachycardia.
- In patients with high-risk occupations or competitive athletes and high-risk features, the APs should be ablated (class I indication), in case of low-risk features catheter ablation may be considered as well as clinical follow-up. For other patients, invasive as well as non-invasive risk assessment may be considered.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in detail in task 2.

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5.7 Channelopathies

This document describes the state-of-the-art of channelopathies, their clinical presentations, the actual diagnostic measures, and the decision strategies, also considering the various risks. The different therapeutic options are also mentioned in this document.

1. What is new? - Main findings

Channelopathies are a heterogeneous group of disorders resulting from the dysfunction of ion channels located in the membranes of all cells and many cellular organelles. These include diseases of the cardiovascular system, which arise from mutation in the genes which encode for ion channels, the glycoproteins embedded in the membrane of cardiac myocytes, which allow the flux of ions in and out of the cell. Depolarising currents are mediated mainly by channels that allow the entry of sodium and calcium ions into the cell; repolarising currents are mediated by channels that allow the exit of potassium ions, with the order of activation giving rise to electrical currents that are responsible for myocyte excitability. When these channels do not work properly there is a tremendous potential to cause lethal arrhythmias. The cardiac channelopathies Long QT syndrome (LQTS), Brugada syndrome (BrS), Short QT syndrome (SQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), and Early Repolarization Syndrome (ERS) (the latter is not constantly included in this group of diseases in the literature) will be the focus of this document.

Channelopathies are rare, but LQTS and BrS cases predominate in the aviation medicine literature (Guettler et al., 2019). Risk stratification should be performed in specialist centres using international guidelines and can be very challenging. Crucial factors include medical and family history and genetic testing. High risk patients usually need implantable cardioverter-defibrillator (ICD) implantation to prevent sudden cardiac death (SCD).

Brugada syndrome (BrS):

BrS is an “inherited” condition characterized by predisposition to syncope and cardiac arrest, predominantly during sleep. The prevalence is ~ 1:2,000, and is more commonly diagnosed in young to middle-aged males, although patient sex does not appear to impact prognosis. Despite the perception of BrS being an inherited arrhythmia syndrome, most cases are not associated with a single causative gene variant. Electrocardiogram (ECG) findings support variable extent of depolarization and repolarization changes. Three different electrocardiogram (ECG) patterns are distinguished, type 1-, type 2- and type 3-Brugada ECG (see below). The ECG changes are often intermittent and may be provoked by fever or sodium channel blocker challenge. Growing evidence from cardiac imaging, epicardial ablation, and pathology studies suggests the presence of an epicardial arrhythmic substrate within the right ventricular outflow tract (Krahn, Behr, Hamilton, Probst, Laksman, & Han, 2022). The yield of genetic testing in BrS patients is approximately 20%, with the SCN5A gene being the only gene with evidence of association for clinical testing purposes (Zeppenfeld et al., 2022).

Recommendations for risk stratification in BrS were already published in 2010 (Probst et al., 2010).

A recent multicentre study identified 4 risk factors for ventricular arrhythmia (VA) / SCD in a primary prevention BrS population (Honarbakhsh et al., 2021). A total of 1,110 patients with BrS from 16 centers in 8 countries were included (mean age 51.8 - 13.6 years; 71.8% male). Median follow-up was 5.33 years; 114 patients had VA/SCD (10.3%) with an annual event rate of 1.5%. Of the 16 proposed risk factors, probable arrhythmia–related syncope (hazard ratio [HR]: 3.71; $p < 0.001$), spontaneous type 1 Brugada ECG (HR: 3.80; $p < 0.001$), early repolarization (HR: 3.42; $p < 0.001$), and a type 1 Brugada ECG pattern in peripheral leads (HR: 2.33; $p < 0.001$) were associated with a higher risk of VA/SCD. A risk score model incorporating these factors revealed a sensitivity of 71.2% (95% confidence interval: 61.5% to 84.6%) and a specificity of 80.2% (95% confidence interval: 75.7% to 82.3%) in predicting VA/SCD at 5 years. Calibration plots showed a mean prediction error of 1.2%. The model was effectively validated by using out-of-sample cross-validation according to country. A risk score model was generated to quantify risk of VA/SCD in BrS and inform ICD prescription (Figure 12).

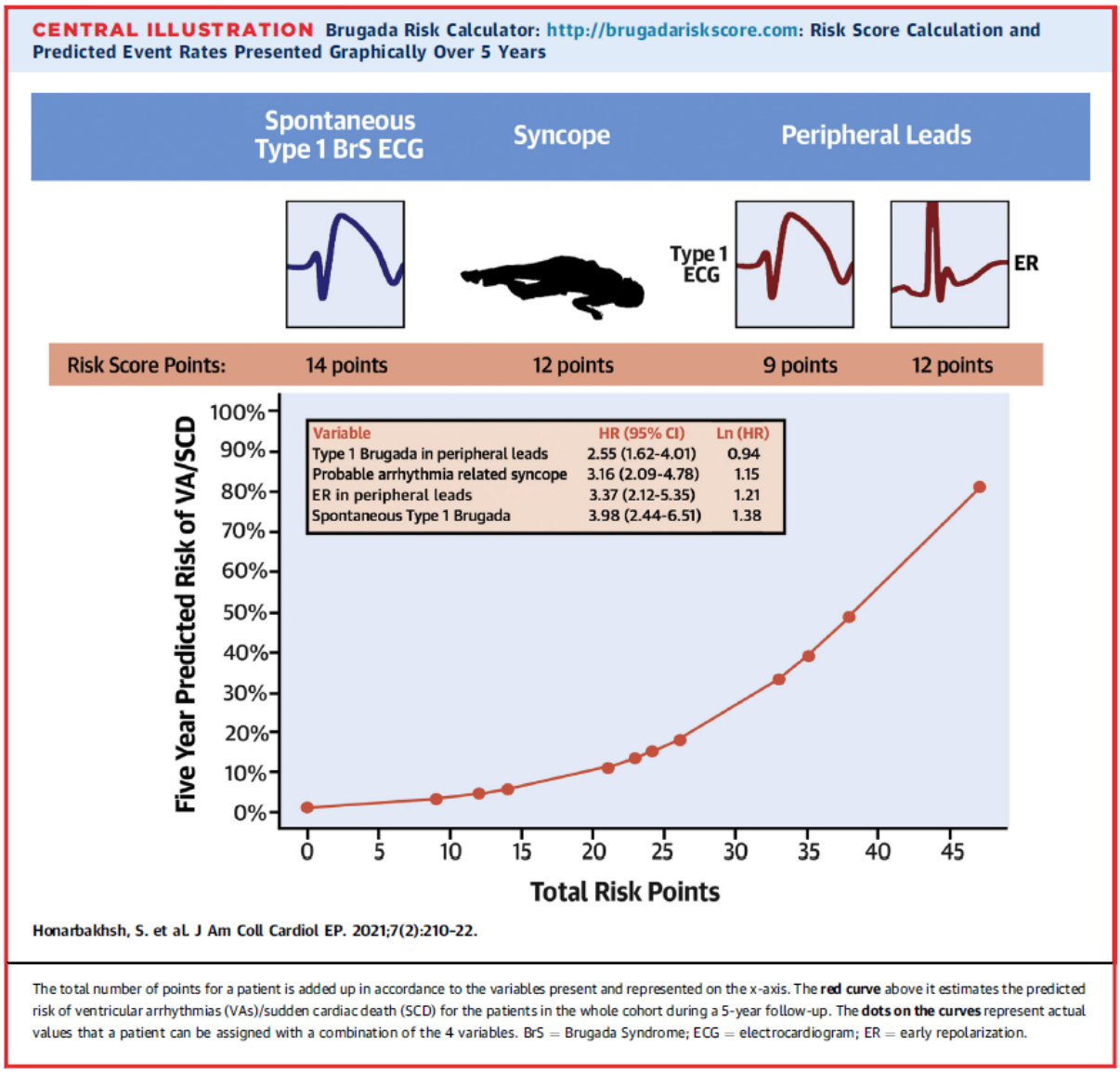

Figure 12: Brugada risk calculator.

@A Primary Prevention Clinical Risk Score Model for Patients With Brugada Syndrome (BRUGADA-RISK) (Honarbakhsh et al, 2021).

BrS is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2mm in ≥1 lead in the right precordial leads V1, V2, positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of class I antiarrhythmic drugs (= sodium channel blockers) (Sieira & Brugada, 2017). Two important aspects must be highlighted. First, only the type 1 ECG pattern is diagnostic, either spontaneously or after a drug challenge. A type 2 ECG pattern may raise the suspicion of BrS, but the diagnosis can only be made when the type 1 pattern appears or is induced by sodium channel blockers. This fact has also prognostic significance as those patients, who do not display the type 1 spontaneously, have a better outcome, but arrhythmic events and SCD can still occur. Interestingly, nowadays the type 3 ECG pattern is no longer considered in BrS (Bayés de Luna et al., 2012). The three different electrocardiogram (ECG) pattern originally described in the first consensus article are shown in figure 13.

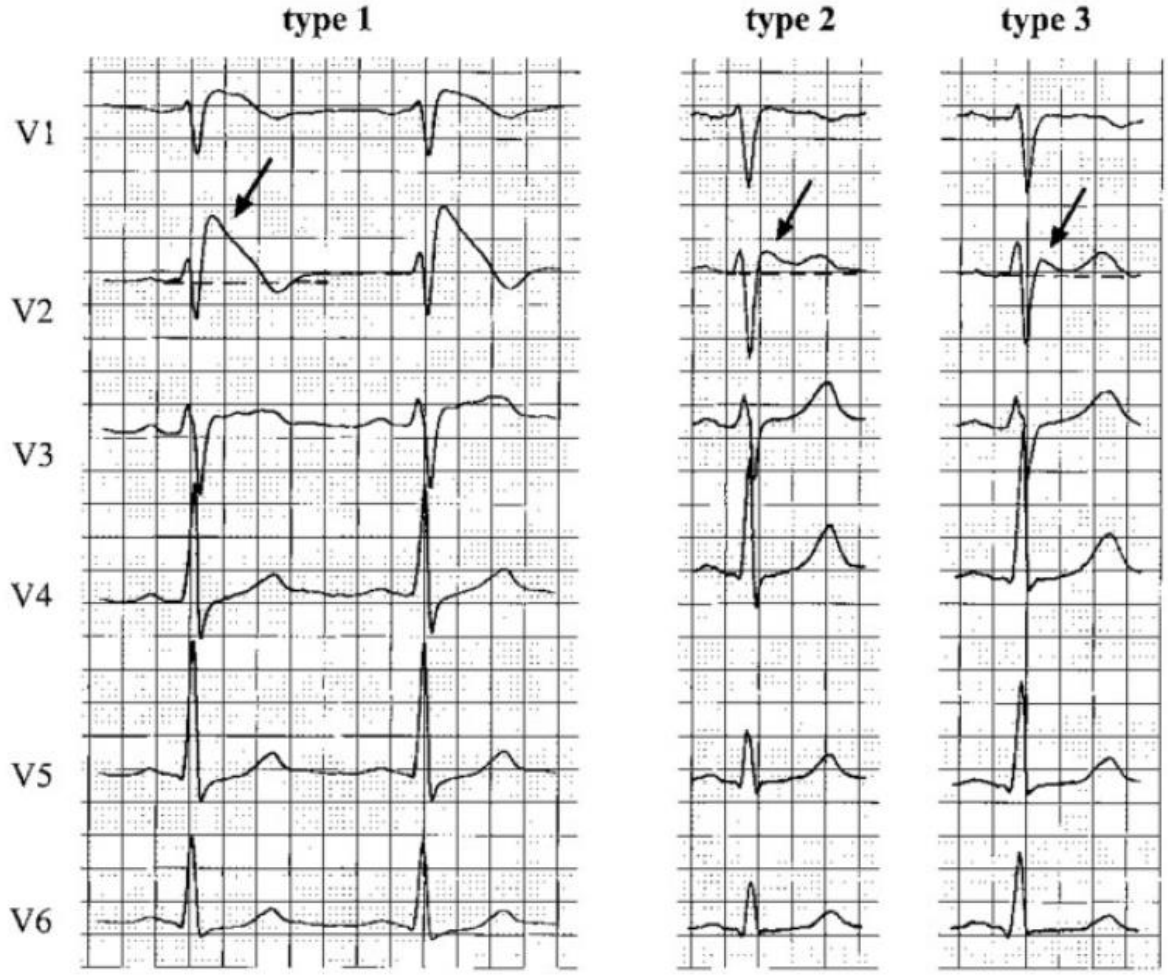

Figure 13: The three different ECG patterns shown in the first consensus article.

@Proposed diagnostic criteria for the Brugada syndrome: consensus report (A. A. Wilde et al, 2002).

Current ESC Guideline recommendations are as follows (class and evidence of recommendations in blue) (Zeppenfeld et al., 2022)

It is recommended that BrS is diagnosed in patients with no other heart disease and a spontaneous type 1 Brugada ECG pattern (IC).

It is recommended that BrS is diagnosed in patients with no other heart disease who have survived a cardiac arrest (CA) due to ventricular fibrillation (VF) or polymorphic ventricular tachycardia (PVT) and exhibit a type 1 Brugada ECG induced by sodium channel blocker challenge or during fever (IC).

Genetic testing for SCN5A gene is recommended for probands with BrS (IC).

BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of:

a) Arrhythmic syncope or nocturnal agonal respiration.
b) A family history of BrS.
c) A family history of sudden death (SD) (<45 years old) with a negative autopsy and circumstance suspicious for BrS (IIaC).

BrS may be considered as a diagnosis in patients with no other heart disease who exhibit an induced type 1 Brugada ECG (IIbC).

Sodium channel blocker test is not recommended in patients with a prior type I Brugada pattern (IIIC).

The following is recommended in all patients with BrS

a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org).
b) Avoidance of cocaine, cannabis, and excessive alcohol intake.
c) Treatment of fever with antipyretic drugs (IC).

ICD implantation is recommended in patients with BrS who

a) Are survivors of an aborted CA and/or
b) have documented spontaneous sustained ventricular tachycardia (VT) (IC).

ICD implantation should be considered in patients with type 1 Brugada pattern and an arrhythmic syncope (IIaC).

Implantation of a loop recorder should be considered in BrS patients with an unexplained syncope (IIaC).

Quinidine should be considered in patients with BrS who qualify for an ICD but have a contraindication, decline, or have recurrent ICD shocks (IIaC).

Isoproterenol infusion should be considered in BrS patients suffering electrical storm (IIaC).

Catheter ablation of triggering premature ventricular complexes (PVCs) and/or right ventricular outflow tract (RVOT) epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy (IIaC).

Programmed electrical stimulation (PES) may be considered in asymptomatic patients with a spontaneous type I Brugada ECG (IIbB).

ICD implantation may be considered in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extra stimuli (IIbC).

Catheter ablation in asymptomatic BrS patients is not recommended (IIIC).

Long QT Syndrome (LQTS):

Congenital long QT syndrome (LQTS) is characterised by heart rate corrected QT interval prolongation and life-threatening arrhythmias, leading to syncope and SD. Variations in genes encoding for cardiac ion channels, accessory ion channel subunits or proteins modulating the function of the ion channel have been identified as disease-causing mutations in up to 75% of all LQTS cases. Based on the underlying genetic defect, LQTS has been subdivided into different subtypes. Growing insights into the genetic background and pathophysiology of LQTS has led to the identification of genotype–phenotype relationships for the most common genetic subtypes, the recognition of genetic and non-genetic modifiers of phenotype, optimisation of risk stratification algorithms and the discovery of gene-specific therapies in LQTS. Nevertheless, despite these great advancements in the LQTS field, large gaps in knowledge still exist (A. A. M. Wilde, Amin, & Postema, 2022).

LQTS is characterized by a prolonged QT interval and VAs mainly triggered by adrenergic activation. The mean age at presentation is 14 years. The annual rate of SCD in asymptomatic patients with untreated LQTS has been estimated to be less than 0.5%, while it increases to around 5% in those with history of syncope. Rare variants in 17 genes have been associated with LQTS. However, the causality for several of the identified genes has been questioned. The undisputed genes are those causing LQT1, LQT2 and LQTS3: KCNQ1, KCNH2 and SCN5A, respectively, with gene-specific triggers being exercise (LQTS1), emotional stress (LQTS2) and sleep (LQTS3). Genetic screening identifies a mutation in 75% of LQTS cases, and three main genes account for 90% of positively genotyped cases. The subtypes of LQTS may be grouped as follows (Zeppenfeld et al., 2022):

(1) Autosomal-dominant LQTS (prevalence: 1 in 2500) without extra-cardiac manifestation.
(2) Autosomal-dominant LQTS with extra-cardiac manifestation, comprising:

    a. Andersen–Tawil Syndrome (LQT7), increasingly considered its own entity.933,934,
    b. Timothy Syndrome (LQT8), characterized by prolonged QT, syndactyly, cardiac malformations, autism spectrum disorder and dysmorphism.

(3) Autosomal-recessive LQTS (Jervell and Lange–Nielsen Syndrome), combining extreme QT prolongation with congenital deafness.

Risk stratification of patients with LQTS represents a difficult task. The prognostic model (1-2-3-LQTS-Risk model) (Mazzanti, Trancuccio, et al., 2022) was derived using data from a prospective, single-centre longitudinal cohort study published in 2018 (discovery cohort) and was validated using an independent cohort of 1689 patients enrolled in the International LQTS Registry (Rochester NY, USA). The validation study revealed a C-index of 0.69 [95% confidence interval (CI): 0.61–0.77] in the validation cohort, when compared with C-index of 0.79 (95% CI: 0.70–0.88) in the discovery cohort. Adopting a 5-year risk ≥5%, as suggested by the receiver operating characteristic (ROC) curve analysis as the most balanced threshold for ICD implantation, would result in a number needed to treat (NNT) of nine (NNT = 9; 95% CI: 6.3–13.6). This model being the first validated 5-year risk score model for patients with LQTS, can be used to aid clinicians to identify patients at the highest risk of life-threatening arrhythmic events who could benefit most from an ICD implant and avoid unnecessary implants (Mazzanti, Trancuccio, et al., 2022)

ESC-Guideline recommendations are as follows (Zeppenfeld et al., 2022)

It is recommended that LQTS is diagnosed with either QTc ≥480 ms in repeated 12-lead ECGs with or without symptoms or LQTS diagnostic score >3 (IC).

In patients with clinically diagnosed LQTS, genetic testing and genetic counselling are recommended (IC).

It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration (IC).

The LQTS diagnosis should be considered in the presence of a QTc ≥460 ms and <480 ms in repeated 12-lead ECGs in patients with an arrhythmic syncope in the absence of secondary causes for QT prolongation (IIaC).

Routine diagnostic testing with epinephrine challenge is not recommended in LQTS (IIIC).

The following is recommended in LQTS

• Avoid QT-prolonging drugs.

• Avoid and correct electrolyte abnormalities.

• Avoid genotype-specific triggers for arrhythmias (IC).

Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol), are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events (IB).

Mexiletine is indicated in LQT3 patients with a prolonged QT interval (IC).

Beta-blockers should be considered in patients with a pathogenic mutation and a normal QTc interval (IIaB).

ICD implantation in addition to beta-blockers is recommended in LQTS patients with CA (IB).

ICD implantation is recommended in patients with LQTS who are symptomatic while receiving beta-blockers and genotype-specific therapies (IC).

Left cardiac sympathetic denervation (LCSD) is indicated in patients with symptomatic LQTS when: (a) ICD therapy is contraindicated or declined; (b) patient is on beta-blockers and genotype-specific drugs with an ICD and experiences multiple shocks or syncope due to VA (IC).

Either ICD implantation or LCSD should be considered in patients with symptomatic LQTS, when beta-blockers and genotype-specific therapies are not tolerated or contraindicated at the therapeutic dose (IIaC).

In LQTS, it should be considered to calculate the arrhythmic risk before initiation of therapy based on the genotype and the duration of QTc interval (IIaC).

ICD implantation may be considered in asymptomatic LQTS patients with high-risk profile (according to the 1-2-3 LQTS Risk calculator) in addition to genotype-specific medical therapies (mexiletine in LQT3 patients) (IIbB).

Invasive electrophysiologic study is not recommended in LQTS (IIIC).

Short QT Syndrome (SQTS)

Short QT syndrome (SQTS) is an inherited cardiac channelopathy principally caused by defective functioning of both potassium– and calcium-ion channels that lead to abnormal shortening of QT interval and an increased risk of ventricular and atrial arrhythmias. Tall T waves in all lead ECG, peaked T waves and narrow-based T waves that are reminiscent of the typical “desert tent” T waves of hyperkalemia are frequently associated with SQTS. Diagnosis is based on patient’s family history, evaluation of symptoms (palpitations and CA), and 12-lead ECG. It can be time challenging because of the wide range of QT interval in healthy subjects. ICD is the first-line therapy in SQTS. Quinidine has the potential to be an effective pharmacological therapy for SQTS patients (Dewi & Dharmadjati, 2020). Based on ESC, the diagnosis of SQTS is based on the QT interval ≤340 ms, but the diagnosis is still needed to be studied further, and screening is still needed at this time (Dewi & Dharmadjati, 2020). A recent study showed that genotype positive SQTS patients have no higher long-term risk of arrhythmic events and/or SCD than genotype negative patients (Raschwitz et al., 2019).

SQTS has been associated with gain of function mutations in KCNH2, KCNQ1 and loss of function in SLC4A. This panel proposed two QTc cut-off threshold for diagnosis: A QTc ≤320 ms alone, or B a QTc ≤360 ms combined with a family history of SQTS, aborted CA in the absence of heart disease or pathogenic mutation. The disease has high lethality in all age groups, including the first months of life. The probability of a first CA by the age of 40 years is 40%. While an ICD is used for secondary

prevention, primary prevention remains contentious and is based upon prior symptoms and QTc interval.

ESC-Guideline recommendations are as follows (Zeppenfeld et al., 2022)

It is recommended that SQTS is diagnosed in the presence of a QTc ≤360 ms and one or more of the following: (a) a pathogenic mutation, (b) a family history of SQTS, (c) survival from a VT/VF episode in the absence of heart disease (IC).

Genetic testing is indicated in patients diagnosed with SQTS (IC).

SQTS should be considered in the presence of a QTc ≤320 ms (IIaC).

SQTS should be considered in the presence of a QTc ≥320 ms and ≤360 ms and arrhythmic syncope (IIaC).

SQTS may be considered in the presence of a QTc ≥320 ms and ≤360 ms and a family history of SD at age ,40 years (IIbC).

ICD implantation is recommended in patients with a diagnosis of SQTS who: (a) are survivors of an aborted CA and/or (b) have documented spontaneous sustained VT (IC).

Implantable loop recorder (ILR) should be considered in young SQTS patients (IIaC).

ICD implantation should be considered in SQTS patients with arrhythmic syncope (IIaC).

Quinidine may be considered in (a) SQTS patients who qualify for an ICD but present a contraindication to the ICD or refuse it, and (b) asymptomatic SQTS patients and a family history of SCD (IIbC).

Isoproterenol may be considered in SQTS patients with an electrical storm (IIbC).

PES is not recommended for SCD risk stratification in SQTS patients (IIIC).

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT is an inherited arrhythmia syndrome characterized by adenergically mediated bidirectional and/or polymorphic VT. CPVT is a significant cause of autopsy-negative sudden death in children and adolescents, although it can also affect adults.

There are two main genetic types: a dominant disorder due to mutations in the gene encoding for the cardiac ryanodine receptor (RYR2) and a recessive disorder caused by mutations in the cardiac calsequestrin gene (CASQ2). Mutations in TRDN and CALM1-3 have been identified in patients with atypical forms of catecholaminergic Vas. At the present time, however, it is unclear whether they are distinct arrhythmic entities. Patients with KCNJ2 mutations causing Andersen–Tawil syndrome type 1 may sometimes exhibit bidirectional and PVT, but are distinguished by their symptom associations (Zeppenfeld et al., 2022).

Early identification and risk stratification is of major importance. Beta-blockers are the cornerstone of therapy. Sodium channel blockers, specifically flecainide, have an additive role. Left cardiac sympathetic denervation is playing an increasing role in suppression of arrhythmia and symptoms. Concerns have been raised, however, about the efficacy of ICD therapy and the risk of catecholamine driven proarrhythmic storms (Abbas, Miles, & Behr, 2022).

In a recent cohort study, selective beta-blockers were associated with a higher risk of life-threatening arrhythmic events (LTAE) as compared with nadolol which is a nonselective beta-blocker. Independently from treatment, LTAE and syncope before diagnosis and C-terminal domain variants

identified patients at higher risk of beta-blocker failure, and the ICD was associated with reduced mortality in high-risk patients with CPVT (Mazzanti, Kukavica, et al., 2022).

The international multicentre study *CASQ2*-CPVT redefined its heritability and confirms that pathogenic heterozygous *CASQ2* variants may manifest with a CPVT phenotype, indicating a need to clinically screen these individuals. A dominant mode of inheritance appears intrinsic to certain missense variants because of their location and function within the CASQ2 filament structure.

Recommendations according to current ESC-Guidelines (Zeppenfeld et al., 2022)

It is recommended that CPVT is diagnosed in the presence of a structurally normal heart, normal ECG, and exercise- or emotion-induced bidirectional, or PVT (IC).

It is recommended that CPVT is diagnosed in patients who are carriers of a mutation in disease-causing genes (IC).

Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT (IC).

Epinephrine or isoproterenol challenge may be considered for the diagnosis of CPVT when an exercise test is not possible (IIbC).

Avoidance of competitive sports, strenuous exercise, and exposure to stressful environments is recommended in all patients with CPVT (IC).

Beta-blockers, ideally non-selective (nadolol or propranolol) are recommended in all patients with a clinical diagnosis of CPVT (IC).

ICD implantation combined with beta-blockers and flecainide is recommended in CPVT patients after aborted CA (IC).

Therapy with beta-blockers should be considered for genetically positive CPVT patients without phenotype (IIaC).

LCSD should be considered in patients with diagnosis of CPVT when the combination of beta-blockers and flecainide at therapeutic dosage are either not effective, not tolerated, or contraindicated (IIaC).

ICD implantation should be considered in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on highest tolerated beta-blocker dose and on flecainide (IIaC).

Flecainide should be considered in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose (IIaC).

PES is not recommended for stratification of SCD risk (IIIC).

Early repolarization syndrome (ERS)

ERS is diagnosed in a patient resuscitated from PVT or VF without any heart disease and the early repolarization pattern (ERP): J-point elevation ≥1 mm in ≥2 adjacent inferior and/or lateral ECG leads. However, ERP is most often a benign finding, and the prevalence of ERP has been reported as 5.8% in adults and is more common in young males and athletes. Nonetheless, ERP is over-represented in relatives of sudden arrhythmic death syndrome (SADS) cases, and of CA survivors. The diagnostic yield and utility of genetic testing is low. High-risk ECG features have been proposed to increase likelihood of ERS: prominent J-waves ≥2 mm, dynamic changes in J-point elevation (>0.1 mV) and J-waves associated with a horizontal or descending ST-segment. ERP with a horizontal ST-segment was associated with arrhythmic risk in an elderly and idiopathic VF population. Nonetheless, ERS survivors and relatives of SADS cases also exhibit a higher prevalence of the ascending/upsloping ST segment than controls. At least 40% of ERS patients with VF have subsequent episodes, with 27% suffering multiple episodes (Zeppenfeld et al., 2022).

Recommendations according to current ESC-Guidelines (Zeppenfeld et al., 2022)

It is recommended that the ERP is diagnosed as J-point elevation of ≥1 mm in two adjacent inferior and/or lateral ECG leads (IC).

It is recommended that the ERS is diagnosed in a patient resuscitated from unexplained VF/PVT in the presence of ERP (IC).

In an SCD victim with a negative autopsy and medical chart review, and an ante-mortem ECG demonstrating the ERP, the diagnosis of ERS should be considered (IIaC).

First-degree relatives of ERS patients should be considered for clinical evaluation for ERP with additional high-risk features (IIaB).

Genetic testing in ERS patients may be considered (IIbC).

Clinical evaluation is not recommended routinely in asymptomatic subjects with ERP (IIIC).

ICD implantation is recommended in patients with a diagnosis of ERS who have survived a CA (IB).

Isoproterenol infusion should be considered for ERS patients with electrical storm (IIaB).

Quinidine in addition to an ICD should be considered for recurrent VF in ERS patients (IIaB).

ILR should be considered in individuals with ERP and at least one risk feature or arrhythmic syncope (IIaC).

PVC ablation should be considered in ERS patients with recurrent VF episodes triggered by a similar PVC non-responsive to medical treatment (IIaC).

ICD implantation or quinidine may be considered in individuals with ERP and arrhythmic syncope and additional risk features (IIbC).

ICD implantation or quinidine may be considered in asymptomatic individuals who demonstrate a high-risk ERP in the presence of a family history of unexplained juvenile SD (IIbC).

ICD implantation is not recommended in asymptomatic patients with an isolated ERP (IIIC).

2. Conclusion and recommendations

- Channelopathies are a heterogenous group of ion channel disorders with the potential to cause ventricular tachyarrhythmia and even sudden cardiac death, often in younger age groups.
- These ion channel disorders can be inherited or acquired by other disorders, drugs, or toxins.
- There are many diseases within the group of channelopathies. The most frequent ones are presented in detail in this document, these are Long QT syndrome (LQTS), Brugada syndrome (BrS), Short QT syndrome (SQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), and Early Repolarization Syndrome (ERS) (the latter is not constantly included in this group of diseases in the literature).
- Risk assessment is often challenging and depends on the specific disease, medical history, family history, and findings in cardiological examinations and often also in genetic testing.
- Treatment options are variable and may include drug treatment, for example with beta-blockers. In high-risk patients, ICD implantation is often required. Invasive mapping and ablation strategies are currently discussed for BrS.
- For diagnosis, risk assessment, and treatment, current ESC-Guidelines should be followed (details of these guidelines have been described above).

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in task 2.

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5.8 Cardiac Pacing

This document describes the state-of-the-art of cardiac pacing including new recommendations concerning the evaluation of patients with suspicion of documented bradycardia or conduction system disease, and new developments in alternate site pacing and leadless pacing. As treatment options per se are part of this issue and therefore, discussion of clinical and diagnostic settings and treatment options are integrated in the present document.

1. What is new? - Main findings

New guideline recommendations for the evaluation of the patient with suspected or documented bradycardia or conduction system disease (Glikson et al., 2021):

Monitoring

In patients with infrequent (less than once a month) unexplained syncope or other symptoms suspected to be caused by bradycardia, in whom a comprehensive evaluation did not demonstrate a cause, long-term ambulatory monitoring with an implantable loop recorder (ILR) is recommended (IA).

Ambulatory electrocardiographic monitoring is recommended in the evaluation of patients with suspected bradycardia to correlate rhythm disturbances with symptoms (IC).

Carotid massage

Once carotid stenosis is ruled out, carotid sinus massage is recommended in patients with syncope of unknown origin compatible with a reflex mechanism or with symptoms related to pressure/manipulation of the carotid sinus area (IB).

Tilt test

Tilt testing should be considered in patients with suspected recurrent reflex syncope (IIaB).

Exercise test

Exercise testing is recommended in patients who experience symptoms suspicious of bradycardia during or immediately after exertion (IC).

In patients with suspected chronotropic incompetence, exercise testing should be considered to confirm the diagnosis (IIaB).

In patients with intra-ventricular conduction disease or AV block (AVB) of unknown level, exercise testing may be considered to expose infranodal block (IIbC).

Imaging

Cardiac imaging is recommended in patients with suspected or documented symptomatic bradycardia to evaluate the presence of structural heart disease, to determine left ventricular systolic function, and to diagnose potential causes of conduction disturbances (IC).

Multimodality imaging (cardiac magnetic resonance (CMR), computed tomography (CT), positron emission tomography (PET)) should be considered for myocardial tissue characterization in the diagnosis of specific pathologies associated with conduction abnormalities needing pacemaker (PM) implantation, particularly in patients younger than 60 years (IIaC).

Laboratory tests

In addition to preimplant laboratory tests, specific laboratory tests are recommended in patients with clinical suspicion for potential causes of bradycardia (e. g. thyroid function tests, Lyme titre, digitalis level, potassium, calcium, and pH) to diagnose and treat these conditions (IC).

Sleep evaluation

Screening for sleep apnea syndrome (SAS) is recommended in patients with symptoms of SAS and in the presence of severe bradycardia or advanced AVB during sleep (IC).

Electrophysiological study

In patients with syncope and bifascicular block, electrophysiology study (EPS) should be considered when syncope remains unexplained after non-invasive evaluation or when an immediate decision about pacing is needed due to severity, unless empirical PM implantation is preferred (especially in elderly and frail patients) (IIaB).

In patients with syncope and sinus bradycardia, EPS may be considered when non-invasive tests have failed to show a correlation between syncope and bradycardia (IIbB).

Genetics

Genetic testing should be considered in patients with early onset (age <50 years) of progressive cardiac conduction disease (IIaC).

Genetic testing should be considered in family members following the identification of a pathogenic genetic variant that explains the clinical phenotype of cardiac conduction disease in an index case (IIaC).

Cardiac pacing for bradycardia and conduction system disease (Glikson et al., 2021)

Pacing is indicated in symptomatic patients with the bradycardia-tachycardia form of sinus node dysfunction (SND) to correct bradyarrhythmias and enable pharmacological treatment unless ablation of the tachyarrhythmia is preferred (IB).

Pacing is indicated in patients with atrial arrhythmia (mainly atrial fibrillation (AF)) and permanent or paroxysmal third- or high-degree AVB irrespective of symptoms (IC).

In patients with SND and Dual chamber cardiac (DDD)-PM, minimization of unnecessary ventricular pacing through programming is recommended (IA).

DDD-pacing is indicated to reduce recurrent syncope in patients aged >40 years with severe, unpredictable, recurrent syncope who have:

- spontaneous documented symptomatic asystolic pause >3 s or asymptomatic pause >6 s due to sinus arrest or AVB; or
- cardioinhibitory carotid sinus syndrome; or
- asystolic syncope during tilt testing (IA).

In patients with recurrent unexplained falls, the same assessment as for unexplained syncope should be considered (IIaC).

AF ablation should be considered as a strategy to avoid PM implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pauses, after AF conversion, considering the clinical situation (IIaC).

In patients with the bradycardia-tachycardia variant of SND, programming of atrial antitachycardia pacing (ATP) may be considered (IIbB).

DDD-PM may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope (IIbB).

Long-term complications (1 – 36 months) after PM implantation have been reported in a study from the US (Cantillon et al., 2017) and from Germany (Ludwig et al., 2019). Total complication rates were 6.42% in single-chamber- and 5.88% in DDD-PM. This included generator complications in 0.00% and 0.06%, respectively, and lead complications requiring revision in 2.85% and 2.84%, respectively.

Electromagnetic interference on PM by aircraft systems is very rare, although theoretically possible (Napp et al., 2015), (Guettler, Cox, Holdsworth, Rajappan, & Nicol, 2022). Table 14 shows different interference types on PM and clinical consequences.

Table14: Interference types on PM and clinical consequences.

Device	Interference type	Clinical consequence
Pacemaker	Atrial oversensing	• Inappropriate mode switch (DDI/VVI) with AV dyssynchrony • Increased ventricular pacing in the event of atrial oversensing (especially if mode switch (DDI/VVI) is disabled, see *Figure 5*)
	Ventricular oversensing	Pacing inhibition
	Switch to noise mode (strong EMFs)	Completely asynchronous pacing with risk of pacing in the vulnerable phase and subsequent induction of arrhythmia
	Reed switch activation	Asynchronous pacing (mode sometimes programmable)

@Are patients with cardiac implants protected against electromagnetic interference in daily life and occupational environment? (Napp et al, 2015).

Alternate site pacing (Conduction system pacing (CSP)):

Recommendations according to ESC guidelines (Glikson et al., 2021)

CSP means placing the ventricular lead either at the His bundle or in the area of the left bundle branch (LBB) for mainly two purposes:

- in lieu of right ventricular pacing (to prevent a pacing-induced cardiomyopathy)
- in lieu of biventricular pacing in cardiac resynchronization therapy (CRT)

His bundle pacing (HBP)

In patients treated with HBP, device programming tailored to specific requirements of HBP is recommended (IC).

In CRT candidates in whom coronary sinus lead implantation is unsuccessful, HBP should be considered as a treatment option along with other techniques such as surgical epicardial lead (IIaB).

In patients treated with HBP, implantation of a right ventricular lead used as “backup” for pacing should be considered in specific situations (e. g. PM-dependency, high-grade AVB, infranodal block, high pacing threshold, planned atrioventricular junction (AVJ) ablation), or for sensing in case of issues with detection (e. g. risk of ventricular undersensing or oversensing of atrial/His potentials) (IIaC).

HBP with a ventricular backup lead may be considered in patients in whom a “pace-and-ablate” strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when intrinsic QRS is narrow (IIbC).

HBP may be considered as an alternative to right ventricular pacing in patients with AVB and left ventricular ejection fraction (LVEF) >40%, who are anticipated to have >20% ventricular pacing (IIbC).

Left bundle branch area pacing (LBBAP)

Left bundle branch pacing (LBBP) is defined as capture of the pre-divisional LBB with simultaneous activation of all of its fascicles. This part of the conduction axis is demarcated proximally by the branching of the His bundle and distally by the first division of the main LBB.

LBBP is characterized by lead position deep in the interventricular septum, ~1–2 cm from the distal His bundle potential (or the tricuspid valve summit), LBB potential to QRS interval in the range of 34–25 ms, normal QRS axis, and fulfilled criteria for conduction system capture (discussed later). In the MELOS registry reporting 2533 patients with LBBAP from 14 European centres, LBBP was encountered in only 9% of the patient cohort (Jastrzębski et al., 2022), (Burri et al., 2023). Figure 14 shows different categories of CSP.

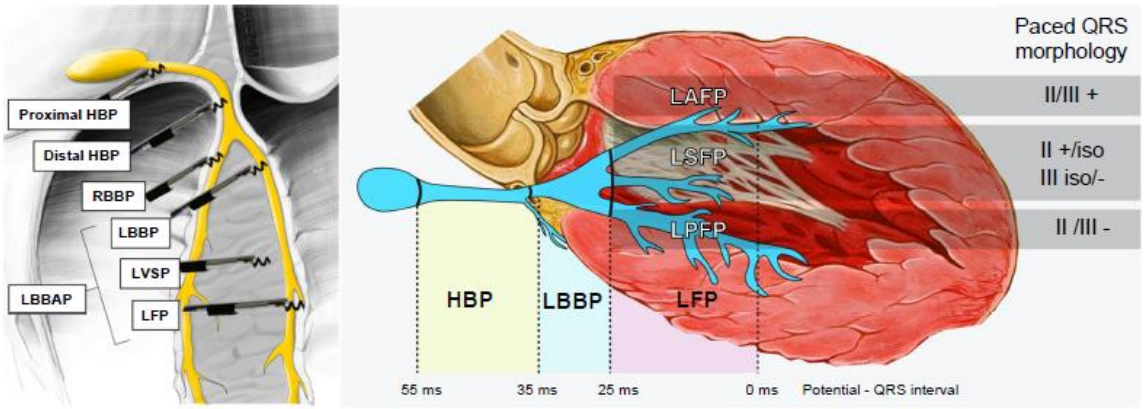

Figure 14: Categories of conduction system pacing (CSP). Anatomical position of the pacing lead, potential to QRS interval (if visualized), and paced QRS morphology in leads II and III are used to determine the level of CSP. RBBP and LVSP are not shown on the right panel. HBP = His bundle pacing; iso = isoelectric; LAFP = left anterior fascicle pacing; LBBAP = left bundle branch area pacing; LBBP = left bundle branch pacing; LFP = left fascicular pacing; LPFP = left posterior fascicle pacing; LSFP = left septal fascicle pacing; LVSP = left ventricular septal pacing; RBBP = right bundle branch pacing.

@EHRA clinical consensus statement on conduction system pacing implantation: endorsed by the Asia Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS), and Latin American Heart Rhythm Society (LAHRS) (Burri et al, 2023).

The advantage of LBBAP as compared to HBP is a broader target area and the higher likelihood of an effective lead positioning.

CSP has emerged as being one of the most exciting developments in pacing therapy over the last years and is progressively gaining mainstream clinical practice worldwide. Although limited, the currently available data heralds a promising future for this therapy, which should nevertheless be implemented in a safe and effective manner (Burri et al., 2023), (Chung et al., 2023). For CSP, the commercially available pacing leads and lead delivery systems, as well as the indications for CSP are likely to broaden

in the future. Nevertheless, many aspects of CSP lead implantation need to be improved. The pacing leads and delivery systems were not originally designed for CSP, and the implant tools are not suitable for challenging anatomies. Prototypes are in the pipeline, which will no doubt facilitate procedures. Leadless pacemakers (see below) designed for CSP are being developed (Burri et al., 2023).

The distribution of pacing types for different indications in a recent European Heart Rhythm Association (EHRA) survey is shown in figure 15 For anti-bradycardia pacing, CSP was preferred only if ventricular pacing was frequent (>20% of the time), in 42.9% of the respondents, whereas CSP and right ventricular pacing (RVP) were preferred by default in 30.6 and 26.5% of the respondents respectively. On average, 44.4± 34.8% of all anti-bradycardia pacing was performed using CSP, but responses were very heterogenous, ranging from 1 to 100% of the cases. The majority of the respondents opted for biventricular (BiV) pacing in patients with a CRT indication and left bundle branch block (LBBB) but in only half of the patients in case of non-LBBB. On average, CSP was implanted in 33.0±30.8% of the patients with a CRT indication (ranging from 0 to 90% of patients). In the case of failed coronary sinus lead implantation, 94.7% of respondents replied that they would switch to CSP.

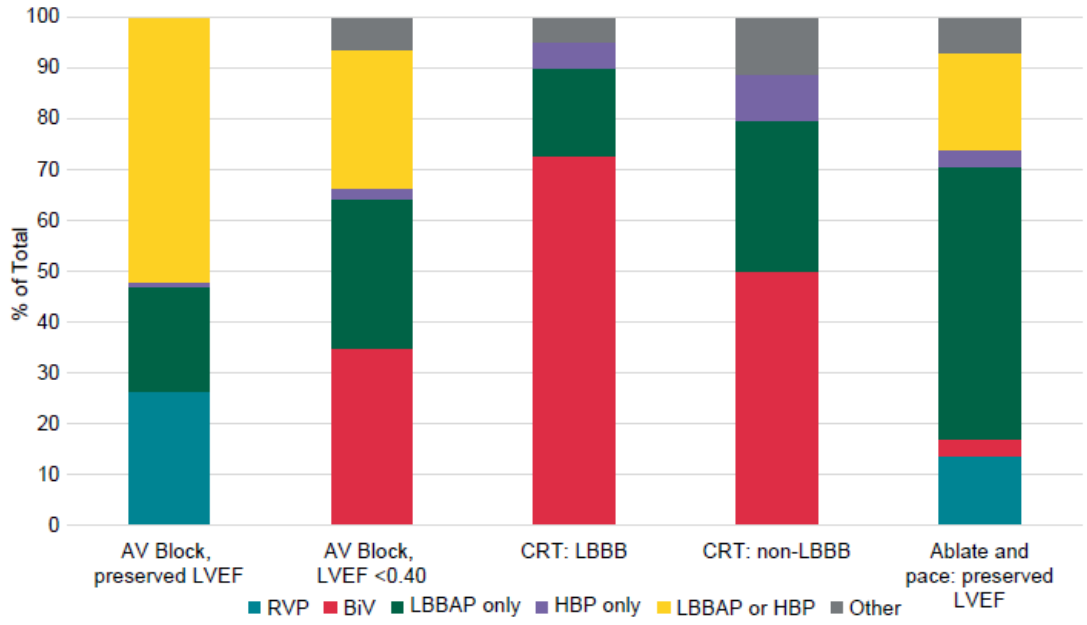

Figure 15: Preferred pacing modality according to indication amongst physicians who implant conduction system pacing. 'Other' includes His-optimized and left bundle pacing optimized CRT (HOT-CRT and LOT-CRT, respectively). AV, atrioventricular; BiV, biventricular; CRT, cardiac resynchronization therapy; HBP, His bundle pacing; LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RVP, right ventricular pacing.

@Conduction system pacing in everyday clinical practice: EHRA physician survey (Kircanski et al, 2023).

Leadless pacing

Transvenous pacemakers (TVP), consisting of a subcutaneously implanted pulse generator and one or more transvenous electrodes extending to the heart chamber(s), are a well-established treatment for bradyarrhythmias. Nevertheless, implantation of these devices is not devoid of substantial complications (Cantillon et al., 2017), (Ludwig et al., 2019). Studies have shown that TVP are consistently associated with a 7.76% to 12.4% risk of serious complications at 90 days, with nearly half of these attributable to lead-and generator-related complications. In the longer term, TVP have a 1% to 2% risk of complications per year, mainly attributable to lead failure and infection. The leadless pacemaker (LP) is a novel alternative consisting of a capsule-like device containing a generator and electrode system that is implanted into the right ventricle via a percutaneously inserted femoral venous catheter. By omitting the need for a generator pocket and transvenous leads, a LP may avoid many of the lead-and generator pocket–related complications typically associated with a TVP. Although the LP was first solely indicated for right ventricular pacing, the emergence of LPs capable of atrioventricular synchronous pacing promises expanding indications for these novel devices (Ngo et al., 2021), (Neugebauer et al., 2022).

Current ESC guidelines (Glikson et al., 2021) mention the following indications for LP: LP should be considered as an alternative to TVP when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as previous infection and patients on haemodialysis (IIaB).

LP may be considered as an alternative to standard single lead ventricular pacing, taking into consideration life expectancy and using shared decision-making (IIbC).

Cardiac resynchronization therapy (CRT):

Although CRT is mainly used in patients with heart failure and left ventricular ejection fraction below 50%, there are CRT indications for patients with heart failure with preserved ejection fraction (HFpEF) in combination with uncontrolled AF needing atrioventricular junction (AVJ) ablation. New CRT recommendations according to current ESC guidelines are therefore summarized as follows (Glikson et al., 2021):

In patients who are candidates for an implantable cardioverter defibrillator (ICD) and who have CRT indication, implantation of a CRT-ICD (CRT-D) is recommended (IA).

In patients who are candidates for CRT, implantation of a CRT-D should be considered after individual risk assessment and using shared decision-making (IIaB).

In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT rather than standard RVP should be considered in patients with heart failure with mildly reduced ejection fraction (HFmrEF) (IIaC).

In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), RVP should be considered in patients with HFpEF (IIaB).

In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT may be considered in patients with HFpEF (IIbB).

According to the most recent information of the ESC-congress (2023), most of the established diagnostic methods and indications for PM implantation are the same according to previous guidelines. But the newer alternate site pacing methods, which have been also cited above, are especially highlighted. Even if pacing leads and lead delivery systems and the indications as well for CSP as for LP undergo an intensive development, all the same, these newer pacing techniques can be considered as almost established methods nowadays. Concerning conduction system pacing (CSP), left bundle branch area pacing (LBBAP) is regarded as the preferred method compared to His bundle pacing (HBP).

2. Conclusion and recommendations

- Patients with bradycardia or conduction system disease should be evaluated properly according to the ESC guidelines. The various clear diagnostic recommendations have been described in detail above. Most important indications for cardiac pacing are bradycardia because of SND and/or AVB.
- One of the new developments in cardiac pacing is CSP with either HBP or LBBAP in lieu of RVP to prevent pacing-induced cardiomyopathy, or in lieu of BiV pacing in CRT. LBBAP is regarded as the preferred method compared to HBP in most cases.
- To avoid complications caused by transvenous leads and being able to treat patients with difficult or without transvenous access, LP has been developed with devices implanted by percutaneously inserted femoral venous catheters.
- Complications of cardiac pacing mainly affect transvenous leads but can rarely also be caused by generator dysfunction or by electromagnetic interference.

3. Relevance for risk assessment of pilots and ATCOs

- Most of the actual EASA-requirements concerning pilots and ATCOs with PM will probably not change.
- According to the so far published studies, the newer alternate site pacing methods have not higher complication rates than the classical pacing techniques; in contrary, some of them have lower complications rates. Thus, it seems that restrictions for pilots and ATCOs with newer PM-methods will not be higher, they will be equal or lower.
- Application of the method and/or treatment for risk assessment will be described in detail in task 2.

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5.9 Implantable Cardioverter Defibrillator (ICD)

This document describes the state-of-the-art of prevention of sudden cardiac death by Implantable Cardioverter Defibrillator (ICD). It includes descriptions and new recommendations for the use of transvenous ICD, subcutaneous ICD (S-ICD) and extravascular ICD (EV-ICD). As the implantation of ICD is a therapeutic procedure, the therapeutic options of this issue are per se part of this document.

1. What is new? - Main findings

Several landmark studies have established since long time, that implantable cardioverter-defibrillator (ICD) therapy improves survival for primary and secondary prevention of sudden cardiac death (SCD). ICD have, therefore, been considered routine treatment since inclusion in international guidelines (Zabel et al., 2020).

New recommendations for ICD therapy have been summarized in the 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD (Zeppenfeld et al., 2022), (classes of recommendations are given in blue):

- Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good-quality survival of 1 year (I).
- In sudden cardiac arrest (SCA) survivors with coronary artery spasm, implantation of an ICD should be considered (IIa).
- ICD therapy should be considered in patients with coronary artery disease (CAD), New York Heart Association (NYHA) class I, and left ventricular ejection fraction (LVEF) ≤30% despite ≥3 months of optimal medical treatment (OMT) (IIa).
- ICD implantation should be considered in patients with CAD, LVEF ≤40% despite ≥3 months of optimal medical treatment and non-sustained ventricular tachycardia (NSVT), if they are inducible for sustained monomorphic ventricular tachycardia (SMVT) by programmed electrical stimulation (PES) (IIa).
- In patients with CAD and haemodynamically well-tolerated SMVT and LVEF ≥40%, catheter ablation in experienced centres should be considered as an alternative to ICD therapy, provided that established endpoints have been reached (IIa).
- ICD implantation should be considered in DCM/HNDCM patients with an LVEF<50% and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20 genes) (IIa). (ICMR = Cardiovascular magnetic resonance/ PES = programmed electrical stimulation (*PES*)/ LMNA, PLN, FLNC and RBM20 = genetic and similar terms. For the other abbreviations see text above and below).
- ICD implantation should be considered in patients with dilated cardiomyopathy (DCM), hypokinetic non-dilated cardiomyopathy (HNDCM) and haemodynamically tolerated SMVT (IIa).
- ICD implantation should be considered in symptomatic patients with definite arrhythmogenic right ventricular cardiomyopathy (ARVC), moderate right or left ventricular dysfunction, and either NSVT or inducibility of SMVT at PES (IIa).
- In ARVC patients with indication for ICDs, a device with the capability of anti-tachycardia pacing (ATP) programming for SMVT up to high rates should be considered (IIa).
- ICD implantation should be considered in HCM patients aged 16 years or more with an intermediate 5-year risk of SCD (≥4 to <6%), and with (a) significant LGE at CMR (usually ≥15% of LV mass); or (b) LVEF <50%; or (c) abnormal blood pressure response during exercise test; or (d) LV apical aneurysm; or (e) presence of sarcomeric pathogenic mutation (IIa).
- In children, 16 years of age with hypertrophic cardiomyopathy (HCM) and an estimated 5-year risk of sudden death ≥6% (based on HCM Risk-Kids score), ICD implantation should be considered (IIa).
- In patients with HCM presenting with haemodynamically tolerated SMVT, ICD implantation should be considered (IIa).

- ICD implantation may be considered in HCM patients aged 16 years or more with a low estimated 5-year risk of SCD (<4%), and with (a) significant late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR) (usually ≥15% of LV mass); or (b) LVEF <50%; or (c) left ventricular (LV) apical aneurysm (IIb).
- In patients with a LVNC cardiomyopathy phenotype based on CMR or echocardiography, implantation of an ICD for primary prevention of SCD should be considered to follow DCM/HNDCM recommendations (IIa) (LVNC = left ventricular non-compaction).
- An ICD should be considered in patients with light-chain amyloidosis or transthyretin-associated cardiac amyloidosis and haemodynamically not-tolerated ventricular tachycardia (VT) (IIa).
- ICD implantation is recommended in patients with myotonic dystrophy and SMVT or aborted cardiac arrest (CA) not caused by bundle branch re-entrant ventricular tachycardia (BBR-VT) (I).
- In myotonic dystrophy patients without atrioventricular (AV) conduction delay and a syncope highly suspicious for ventricular arrhythmia (VA), ICD implantation should be considered (IIa).
- In myotonic dystrophy patients with palpitations highly suspicious for VA and induction of a non-BBR-VT, ICD implantation should be considered (IIa).
- In patients with limb-girdle type 1B or Emery–Dreifuss muscular dystrophies and indication for pacing, ICD implantation should be considered (IIa).
- Implantation of an ICD may be considered in patients with Duchenne/Becker muscular dystrophy and significant LGE at CMR (IIb).
- Implantation of an ICD over a permanent pacemaker may be considered in myotonic dystrophy patients with additional risk factors for VA and SCD (IIb).
- In patients with haemodynamically not-tolerated sustained VT or ventricular fibrillation (VF) during the acute phase of myocarditis, ICD implantation before hospital discharge should be considered (IIa).
- In patients with haemodynamically tolerated SMVT occurring in the chronic phase of myocarditis, ICD implantation should be considered (IIa).
- In patients with cardiac sarcoidosis who have an LVEF >35% but significant LGE at CMR after resolution of acute inflammation, ICD implantation should be considered (IIa).
- In patients with cardiac sarcoidosis, LVEF 35–50%, and inducible SMVT at PES, ICD implantation should be considered (IIa).
- ICD implantation may be considered in asymptomatic long QT syndrome (LQTS) patients with high-risk profile (according to the 1-2-3 LQTS Risk calculator) in addition to genotype-specific medical therapies (mexiletine in long QT (LQT)3 patients) (IIb).
- ICD implantation is recommended in patients with Andersen–Tawil syndrome after aborted CA or not-tolerated sustained VT (I).
- ICD implantation may be considered in patients with Andersen–Tawil syndrome who have a history of unexplained syncope or suffer from tolerated sustained VT (IIb).
- ICD implantation is recommended in patients with a diagnosis of early repolarization syndrome (ERS) who have survived a CA (I).
- ICD implantation or quinidine may be considered in individuals with early repolarization pattern (ERP) and arrhythmic syncope and additional risk features (IIb).

- ICD implantation or quinidine may be considered in asymptomatic individuals who demonstrate a high-risk ERP in the presence of a family history of unexplained juvenile SD (IIb).
- ICD implantation is not recommended in asymptomatic patients with an isolated ERP (III).
- ICD implantation should be considered in short QT syndrome (SQTS) patients with arrhythmic syncope (IIa).

To estimate the benefit of an implanted ICD, a Multicentre Automatic Defibrillator Implantation Trial (MADIT)-ICD benefit score was developed based on integrated assessment of the VT/VF and non-arrhythmic mortality scores with a range of 0–100, wherein a score of 100 denotes the highest potential ICD benefit and 0 the lowest potential benefit. Thus, within the highest benefit group, the personalized ICD benefit score is in the range of 76–100. In the intermediate benefit group, the corresponding range is 26–75; and in the lowest benefit group, it is ≤25. The personalized ICD benefit score can be derived from the online calculator (https://is.gd/madit), (Younis et al., 2021).

The European Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter-Defibrillators (EU-CERT-ICD), a prospective investigator-initiated, controlled cohort study, was conducted in 44 centres and 15 European countries. It aimed to assess current clinical effectiveness of primary prevention ICD therapy (Zabel et al., 2020). In contemporary ICM/DCM patients (LVEF ≤35%, narrow QRS), primary prophylactic ICD treatment was associated with a 27% lower mortality after adjustment. There appear to be patients with less survival advantage, such as older patients or diabetics.

As an alternative to a transvenous lead implantation, a subcutaneous ICD (S-ICD) and recently also an extravascular ICD (EV-ICD) have been developed for certain indications.

In a survey analyzing the impact of the ICD on quality of life (QoL) metrics from the patient's perspective, device-related complications were reported by 22.4%, including one or more inappropriate shocks (11.6%) (Januszkiewicz et al., 2022). Almost half the respondents reported improved QoL, with a more favourable impact for those receiving cardiac resynchronization therapy-defibrillator (CRT-D), and only a 10th experienced a significant decrease in QoL. The occurrence of complications remained a major predictor of deteriorated QoL (odds ratio 2.1, 95% confidence interval 1.4–3.0, P < 0.001). Most patients had a globally positive view and acceptance of ICD therapy, reporting preserved to improved QoL after device implantation. Complications, namely inappropriate shocks, affect the expectation of living a normal life post-implant and are associated with a significant decrease in QoL.

S-ICD

S-ICD use for sudden cardiac death prevention is rapidly growing, with >100,000 devices implanted worldwide (Gold et al., 2023). This device has demonstrated safety and efficacy for treating ventricular tachyarrhythmias. Early S-ICD studies included younger cohorts with less LV dysfunction and fewer comorbidities compared with traditional transvenous implantable cardioverter-defibrillator (TV-ICD) recipients. More recently, 3 large prospective trials with broad inclusion criteria have been undertaken: PRAETORIAN (A Prospective, rAndomizEd Comparison of subcuTaneOous and

tRansvenous ImplANtable Cardioverter Defibrillator Therapy), UNTOUCHED (UNdersTanding OUtComes WitH the EMBLEM S-ICD in Primary Prevention Patients With Low Ejection Fraction), and S-ICD PAS (Subcutaneous Implantable Cardioverter-Defibrillator [S-ICD] System Post Approval Study; NCT01736618). The PRAETORIAN study demonstrated that safety and efficacy of the S-ICD was noninferior to transvenous devices (Knops et al., 2020). 849 patients with an ICD but no pacing indication were randomized to an S-ICD or a transvenous ICD. Over a mean follow-up of 49 months, non-inferiority was shown for the primary endpoint of device-related complications and inappropriate shocks. The rate of inappropriate shocks was 9.7% in the S-ICD group and 7.3% in the ICD group (HR 1.43; 95% CI 0.89–2.30) and the rate of device related complications was 5.9% in the S-ICD and 9.8% in the ICD group (HR 0.69; 95% CI 0.44–1.09). The UNTOUCHED study showed a very low inappropriate shock (IAS) rate and excellent safety and efficacy over 18-month follow-up despite a requirement that all patients had moderate to severe left ventricular dysfunction. S-ICD PAS was a U.S. Food and Drug Administration (FDA)–mandated study of S-ICD in clinical practice (Boersma et al., 2019), (Gold et al., 2021). The S-ICD PAS is the largest S-ICD trial to date and was intended to be a real-world registry with a large number of diverse U.S. centers and patient groups included during a prolonged follow-up (Gold et al., 2023). A total of 1,643 patients were prospectively enrolled, with a median follow-up of 4.2 years. All prespecified safety and efficacy endpoint goals were met. Shock efficacy rates for discrete episodes of VT or VF were 98.4%, and they did not differ significantly across follow-up years (P = 0.68). S-ICD–related and electrode-related complication-free rates were 93.4% and 99.3%, respectively. Only 1.6% of patients had their devices replaced by a TV-ICD for a pacing need. Cumulative all-cause mortality was 21.7%. These results demonstrate the 5-year S-ICD safety and efficacy for a large, diverse cohort of S-ICD recipients (Gold et al., 2023). S-ICD has no intravascular lead and therefore cannot deliver ATP.

EV-ICD

Extravascular ICD (EV-ICD) systems provide an alternative to the transvenous ICDs in patients without the need for bradycardia pacing (Burke et al., 2023). Commercially available S-ICDs have been shown to have low complication rates and similar efficacy to the TV-ICD but have no pacing capability and require an unique ICD pulse generator (PG) capable of delivering higher energy shocks (80 J) and is, therefore, larger than modern TV-ICDs (Baalman, Quast, Brouwer, & Knops, 2018), (Knops et al., 2020). Placement of extravascular electrodes in closer proximity to the heart requires less shock energy for defibrillation, and therefore smaller PGs, compared with S-ICDs (Crozier et al., 2020), (Crozier et al., 2021). To that end, substernal EV-ICD leads (Medtronic, Inc) have been developed. Friedman et al. reported successful substernal implantation in 299 of 316 subjects (95%) with no procedural complications observed (Friedman et al., 2022). Shock termination of induced ventricular arrhythmias was successful in 298 of 302 subjects (98.7%) when connected to a custom extravascular-ICD PG placed into a left posterior-lateral pocket. A recent study documented the safe and reliable placement of a novel EV ICD lead with effective sensing and defibrillation of induced VF using commercially available PGs (Burke et al., 2023).

2. Conclusion and recommendations

- ICD is a well-established treatment option for ventricular tachyarrhythmia and the primary and secondary prevention of SCD.

- There are clear recommendations concerning the different indications for implantation of ICD (see above).
- Complications of ICD therapy include inappropriate therapies, lead fractures, and device-related infections.
- Specially to mention are inappropriate ICD shocks, a very undesirable complication. Inappropriate ICD shocks differ in frequency and in cardiovascular impact depending on the ICD-system used and on several other factors.
- Subcutaneous implantable cardioverter defibrillator (S-ICD) has been introduced to address problems related to transvenous leads. S-ICD has no intravascular lead and therefore cannot deliver ATP.
- Extravascular ICD (EV-ICD) systems provide an alternative to the transvenous ICDs in patients without the need for bradycardia pacing. Placement of EV electrodes in closer proximity to the heart requires less shock energy for defibrillation, and therefore smaller PGs, compared with the S-ICD. Delivery of ATP is possible.

3. Relevance for risk assessment of pilots and ATCOs

Application of the method and/or treatment for risk assessment will be described in task 2.

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6 Concepts of cardiological incapacitation risk estimation

This chapter contains the discussion and considerations concerning new concepts of cardiological incapacitation risk assessment in order to develop a method that enables structured and evidence-based decision making in aeromedical certification procedures involving cardiovascular conditions.

1. What is new? - Introduction to a new approach

Current aeromedical incapacitation risk assessment methods

Prevailing methods to estimate the incapacitation risk of Pilots and ATCOs caused by medical events are generally based on expert opinion and/or on the principles of the 1% rule, as developed by Tunstall-Pedoe (Tunstall-Pedoe, 1984) and later formally described in a manual of the International Civil Aviation Organization (ICAO) (*Manual of Civil Aviation Medicine*, 2012). Considering the acceptable risk of incapacitation of flight crew caused by medical events, this document states that "a pilot flying a two-pilot aircraft can have an incapacitation risk of no more than one in 10^6 hours, and the operation will achieve the target medical cause fatal accident rate of no more than one in 10^9 hours, because the presence of a second pilot reduces the risk by a factor of 1000" (*Manual of Civil Aviation Medicine*, 2012). Assuming that there are 8760 hours in a year (~10^4), the acceptable annual medical event rate to meet this target is 1% per year ($10^4 \times 10^2 = 10^6$). This forms the basis of the '1% rule'. It should, however, be considered that this rule has significant limitations. It is based on a series of assumptions only relevant to short (1 hour) flights with critical flight times limited to take-off and landing (6 min). Moreover, medical events are assumed to result in complete incapacitation of one pilot and it is assumed that a co-pilot could safely deal with incapacitation of the other pilot, occurring during a critical period of landing and take-off, in 99 times out of 100. It assumes that an incapacitation occurring outside the 6 minutes of safety critical phases of flight poses no safety risk because it is expected that the other pilot, who has followed a mandatory inflight incapacitation training, takes over and lands the aircraft safely in all cases. The 1% rule cannot be applied to single pilot operations, because it is derived from two pilot operations and the availability of a second pilot to take over in the event of incapacitation of the other pilot.

It should be considered that the 1% rule is based on debatable assumptions that only allow a prediction of the risk of complete incapacitation during the take-off and landing phase of flight. The debatable assumptions allow for different interpretations of the rule and it has been argued that a 2% risk per year (or up to 5% per year in certain circumstances) may be acceptable (Mitchell & Evans, 2004). It is considered that the 1% rule does insufficiently take operational aspects and requirements into account and that this rule is less suitable for risk prediction of incapacitation levels ranging from subtle to complete with variable probabilities of occurrence. For these reasons it is recommended to

explore alternatives based on modern risk management principles to estimate incapacitation risks related to cardiovascular health.

New: Risk Assessment using Risk Matrices

Risk management in many safety-critical fields, such as aerospace engineering, is based on the principle that the assessment of risk involves the probability of an occurrence and the potential operational consequences (severity) of any event. This led to the development of risk matrices, which plot the potential operational impact of an event (risk severity) against the probability of occurrence of the event.

In their Safety Management Manual Doc 9859, ICAO (2018) advocates and explains these principles. (*Safety Management Manual*, 2018) An example is a 5×5 risk matrix as described in Doc 9859 shown in figure 16.

Risk Probability		Risk Severity				
		Catastrophic A	Hazardous B	Major C	Minor D	Negligible E
Frequent	5	5A	5B	5C	5D	5E
Occasional	4	4A	4B	4C	4D	4E
Remote	3	3A	3B	3C	3D	3E
Improbable	2	2A	2B	2C	2D	2E
Extremely Improbable	1	1A	1B	1C	1D	1E

Figure 16. 5x5 Risk Matrix showing the risk probability and the risk severity (ICAO, 2018).

Severity Levels

To measure the safety impact of cardiovascular incapacitation events, severity and probability levels have to be defined.

The five severity levels in fig. 1 are defined as:

- Catastrophic: multiple fatalities – equipment destroyed;
- Hazardous: crew cannot perform their tasks, serious injury, major damage;
- Major: significant reduction in safety margins, serious incident, injury to persons;
- Minor: Nuisance, operating limitations, use of emergency procedures, minor incident;
- Negligible: no significant consequences.

Colours indicate the levels of tolerability (acceptability) of the risk. According to the ICAO Manual (*Safety Management Manual*, 2018) recommended consequences (actions) related to each colour and level of tolerability are:

- Red = Intolerable: Take immediate action to mitigate the risk to tolerable or stop the activity.
- Yellow = Tolerable: Can be tolerated based on safety risk mitigation. Management decision to accept the risk.
- Green = Acceptable: Acceptable as is. No further safety risk mitigation is required.

The example of ICAO (2018) shown in figure 1 is a generic matrix derived from risk management of mechanical failures which is suited to be used and adapted for assessment and management of medical incapacitation risks in aviation. The generic example version uses five severity levels. When determining the severity of a medical event some military organisations considered to use a classification in 4 severity levels as in the classification of the Royal Canadian Air Force and Gray et al. (G. W. Gray, Sargsyan, & Davis, 2010; *Medical standards for Canadian forces aircrew*, 2020). For each class of medical event, the outcome of this military severity classification is based on evaluation of three variables: (a) the impact on the flight operation (flight safety) and/or mission, (b) the effect on the operational performance of the individual crew member, and (c) the requirement for medical attention (G. W. Gray et al., 2010; *Medical standards for Canadian forces aircrew*, 2020). It should, however, be considered this classification is made for risk assessments related to military and space missions. In these settings, the urgent need for medical care might be a reason to abort the mission (while flight safety may not be compromised). These military risk matrices are also aimed to estimate the risks of mission failures, whereas risk assessment in civil aviation is to estimate the safety risk of flight operations. It is therefore considered that for reasons of uniformity and practical civil aeromedical use the generic ICAO 5x5 matrix is recommended giving a wider range of relevant severity levels (and giving a wider range of relevant probabilities). It should be considered that the potential consequences of a medical event may differ for single pilot, multi-crew, or the different ATC operations. It is recommended to define different severity levels which are tailored to single pilot, multi-crew, and ATC operations.

Probability levels

The probability of a technical failure to occur in an aircraft is generally expressed as the risk per flight hour (e.g. “occurrence of major failure conditions must be between 10^{-5} and 10^{-7} per flight hour”), but the risk and consequences of technical failures is not univocally comparable to that of incapacitation of human beings where the range of incapacitation levels is likely to be broader than that of technical failure levels. An important consideration is that expression of risk per flight hour is less practical and less insightful for the medical risk assessor. For many medical disorders epidemiological data are available about prognosis and risks of complications or deterioration of the condition. These epidemiological data are generally expressed as the percentage of risk per year, per 5 years, or per 10 years. These data are perfectly suited to be used for an assessment of the probability of a medical event occurring related to the medical condition under review. The probability of a medical event is in that case derived from a careful evidence-based review of available medical literature, along with best estimates from clinical experts. In the concept of US Air Force Aeromedical Consultation Service Medical Risk Assessment and Airworthiness Matrix (Mayes et al., 2023) the term likelihood is preferred instead of probability as it is more technically accurate because likelihood connects both known and uncertain data (Mayes et al., 2023). This terminology is also consistent with Gray et al. (G. Gray et al., 2019). For the likelihood (~ probability) the AMRAAM matrix provides the possibility to use likelihood percentages per person year, per 5 years, and per 10 years. This has the advantage of facilitating the translation between medical epidemiological literature and the risk matrix.

If there are multiple potential medical events related to the condition, a best estimate for the probability of each separate event can be included in the matrix, but in that case, it might be practical and prudent to take the risk of the condition with the highest probability of a medical event as leading to estimate the overall incapacitation risk.

The classification of probability levels can be based on cardiovascular risk matrices, such as recommended by Gray et al. (G. Gray et al., 2019) which classifies likely as >2%/year; possible as 1%–2%/year; unlikely as 0.5%–1%/year; and highly unlikely as <0.5%/year. The AMRAAM risk matrix (Mayes et al., 2023) which uses 5 levels of probability in a 5x4 matrix defined as frequent (>99%/year); probable (60-90%/year); occasional (10-60%/year); remote (1-10%/year); and improbable (<1%/year). It should be considered that these probability levels were defined for military missions in which not only flight safety is a factor but also mission effectiveness. In analogy with the AMRAAM risk matrix (Mayes et al., 2023) we propose 5 levels of probabilities:

- Frequent
- Occasional
- Remote
- Improbable
- Extremely Improbable

To quantify the probabilities, estimations should be based on expert clinical judgement combined with available epidemiological data. Probability levels of cardiovascular incapacitation events should measure their potential occurrence by number or percentage per year (or per 5 or 10 years as in the AMRAAM matrix). The actual numbers to be used for the probability classification may be derived from the AMRAAM matrix mentioned above, or related matrices, such Gray et al. (G. Gray et al., 2019). A careful consideration regarding the recommended probability levels will be made in future tasks of the CaVD PACE project.

The probability that a cardiovascular incapacitation event would happen depends on:

- presence of a cardiovascular disorder and/or comorbidities
- risk of recurrence/complications
- recent occurrences of symptoms
- adverse effects of treatment
- effectiveness of treatment and protective factors

Both probability and severity levels can be lowered by mitigation measures. These will be addressed in future tasks of the CaVD PACE project.

A single risk matrix cannot reflect the operational impact of a medical event for all Pilot and ATCO roles. To reflect the operational impact of a medical event incorporating different operational roles, a series of risk matrices that reflect the varying operational risk pertinent to specific Pilot and ATCO roles should be developed.

This applies in the PACE project to the following classes and roles:

- Class 1: Single pilot, Multi-Pilot (Captain /First officer)
- Class 2
- Class 3: ATCO Area/Terminal control, Tower/ Remote and Virtual tower
- LAPL

In the context of cardiovascular incapacitation risk, single pilots have a higher attributable risk than those working in a multicrew setting. ATCOs are considered to have an attributable risk equivalent to professional pilots in a multicrew setting, except single ATCOs working on a remote location.

The difference in redundancy of multicrew or single pilot, and the different ATCO roles may be portrayed in different risk matrices or scored in one single matrix where severity related to the different operational roles is taken in to account. The single matrix would use the crew roles as risk reducing or risk mitigation factor where this would be appropriate.

The PACE cardiological risk assessment concept

This section is to implement the aforementioned approach into a methodology for cardiovascular incapacitation risk assessment. This methodology includes the following steps:

1. Identify the diagnosis or diagnoses
2. Identify the symptoms potentially causing the cardiovascular incapacitation events (CVIEs)
3. Decide which certification Class to consider
4. Define the severity of the potential CVIE
5. Define the probability of the CVIE to occur
6. Complete the risk matrix for each CVIE per each class and professional role
7. Identify the risk level: acceptable, tolerable (+ mitigation measures), unacceptable

2. Conclusion and Recommendations

To assess the flight safety risks of cardiovascular conditions, it is recommended to use a risk matrix approach, in which probability and severity are plotted, for the risk assessment of incapacitation caused by cardiological incapacitation events. Based on the principle that the assessment of risk involves the probability of an occurrence and the potential consequences (severity) of any event, risk matrices allow for a more detailed and evidenced risk assessment than the one-dimensional 1% rule. These matrices can provide a semiquantitative assessment of the flight safety and operational impact of a broad spectrum of medical conditions with variable probabilities of occurrence.

A 5X5 risk matrix is recommended and the ICAO standard risk matrix is preferred with the axes for risk severity horizontal, and risk probability vertical. The risk probability categories from ICAO are followed, but specified in percentages per year in order to enable using epidemiological data directly.

Using the risk matrix requires knowledge of operational consequences of cardiovascular incapacitation events. Such a risk matrix should be used by an AME assisted by an (aviation) cardiologist and in consultation with operational competence if necessary.

The determination of the acceptability of the risk, and thus the colour associated with each cell of the matrix, requires careful consideration taking in to account the type of operation for which the risk is assessed (multi-crew ops, single pilot ops, different ATC ops).

3. Relevance for risk assessments of pilots and ATCOs

The opportunities that the risk matrix method offers are very relevant to enhance structured decision making in the context of medical certification of all classes of pilots and ATCOs.

- The matrix method offers structured and systematic decision making and may lead to more evidence-based reasoning.
- A risk matrix visualises several levels of probability, thus providing the possibility of assessing events that do not cause full incapacitation, where higher probabilities may be accepted depending on severity.
- A risk matrix visualizes several levels of severity, thus providing the possibility of assessing different flight safety outcomes of a given event and probability, and is therefore usable for different crew roles and air traffic control operations.
- A risk matrix offers better and clearer communication with pilots and ATCOs regarding risk than the 1% rule because the matrix concept is focused on cardiovascular incapacitation events and their consequences rather than on cardiological diagnoses.

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