ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2019) **20**, 1187–1197
doi:10.1093/ehjci/jez219

REVIEW

Imaging in ESC clinical guidelines: chronic coronary syndromes

Antti Saraste [1,2], Emanuele Barbato[3], Davide Capodanno[4], Thor Edvardsen[5], Eva Prescott[6], Stephan Achenbach[7], Jeroen J. Bax[8], William Wijns[9], and Juhani Knuuti[1]*

[1]Turku PET Centre, Turku University Hospital, University of Turku, Kiinamllynkatu 4-8, 20520 Turku, Finland; [2]Heart Center, Turku University Hospital, Hämeentie 11, 20520, Turku, Finland; [3]Division of Cardiology, Department of Advanced Biomedical Sciences, University Federico II, Via S. Pansini, 5, 80131, Naples, Italy; [4]CardioThoracic-Vascular and Transplant Department, A.O.U. 'Policlinico-Vittorio Emanuele', University of Catania, Via Citelli 6, 95100, Catania, Italy; [5]Department of Cardiology, Oslo University Hospital, University of Oslo, Oslo, Norway; [6]Department of Cardiology, Bispebjerg University Hospital, Bispebjerg Bakke 23, 2400, Copenhagen, Denmark; [7]Department of Cardiology, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany; [8]Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333ZA, Leiden, The Netherlands; and [9]The Lambe Institute for Translational Medicine and Curam, National University of Ireland, Galway, University Road, Galway, H91 TK33, Ireland

Received 5 August 2019; editorial decision 7 August 2019; accepted 18 August 2019

The European Society of Cardiology (ESC) has recently published new guidelines on the diagnosis and management of chronic coronary syndromes (CCS). The 2019 guideline identified six common clinical scenarios of CCS defined by the different evolutionary phases of coronary artery disease (CAD), excluding the situations in which an acute coronary event, often with coronary thrombus formation, dominates the clinical presentation. This review aims at providing a summary of novel or revised concepts in the guidelines together with the recent data underlying the major changes on the use of cardiac imaging in patients with suspected or known CCS.

Based on data from contemporary cohorts of patients referred for diagnostic testing, the pre-test probabilities of CAD based on age, sex and symptoms have been adjusted substantially downward as compared with 2013 ESC guidelines. Further, the impact of various risk factors and modifiers on the pre-test probability was highlighted and a new concept of 'Clinical likelihood of CAD' was introduced. Recommendations regarding diagnostic tests to establish or rule-out obstructive CAD have been updated with recent data on their diagnostic performance in different patient groups and impact on patient outcome. As the initial strategy to diagnose CAD in symptomatic patients, non-invasive functional imaging for myocardial ischaemia, coronary computed tomography angiography or invasive coronary angiography combined with functional evaluation may be used, unless obstructive CAD can be excluded by clinical assessment alone. When available, imaging tests instead of the exercise electrocardiogram are recommended when following the non-invasive diagnostic strategy.

Keywords coronary artery disease • coronary computed tomography angiography • echocardiography • single-photon emission computed tomography • cardiac magnetic resonance • positron emission computed tomography

Introduction

Assessment of symptomatic patients with suspected obstructive coronary artery disease (CAD) is a common clinical task and a major component of healthcare cost. Due to variable and often atypical symptoms, objective tests are most often necessary to confirm the diagnosis, exclude alternative diagnoses, and assess the severity of underlying disease. The European Society of Cardiology (ESC) recently published the 2019 ESC guidelines on the diagnosis and management of chronic coronary syndromes (CCS).[1] In this article, we will highlight the major new or revised concepts in these guidelines, as they relate to the use of imaging tests for the assessment of patients with suspected or known CCS.

Patient population

The 2019 guidelines focus on the spectrum of CCS rather than solely on stable CAD.[1] This change emphasizes the fact that the clinical presentations of CAD can be categorized as either acute coronary syndromes (ACS) or CCS. CAD is a dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation that can be modified by lifestyle, pharmacological therapies, and revascularization which result in disease stabilization or regression patterns.[1] In the new guidelines, we identified six clinical scenarios most frequently encountered in practice: (i) patients with suspected CAD and 'stable' angina symptoms and/or dyspnoea; (ii) patients with new onset of heart failure or left ventricular (LV) dysfunction

* Corresponding author. Tel: +35823130000; Fax: +35823138191. E-mail: juhani.knuuti@tyks.fi

and suspected CAD; (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with recent revascularization; (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; as well as (vi) asymptomatic subjects in whom CAD is detected at screening.

Diagnostic approach

The diagnostic approach in a patient with suspected obstructive CAD can be divided into a series of subsequent steps.[1] Step 1 is to assess the symptoms and signs to identify patients with possible unstable angina or other forms of ACS. If an ACS is suspected, the further course should proceed according to the respective guidelines.[2] In patients without unstable angina or other ACS, step 2 is to evaluate the patient's general condition and quality of life. Comorbidities that could potentially influence therapeutic decisions are to be assessed and other potential causes of the symptoms are considered. Step 3 includes basic testing and assessment of LV function. A resting transthoracic echocardiogram is recommended in all patients for exclusion of alternative causes of angina, identification of regional wall motion abnormalities suggestive of CAD, determination of left ventricular ejection fraction (LVEF) for risk-stratification purposes as well as evaluation of diastolic function (*Table 1*). Cardiac magnetic resonance (CMR) imaging may be considered in patients with an inconclusive echocardiographic examination (*Table 1*).

In step 4, the pre-test probability (PTP) and clinical likelihood of obstructive CAD are estimated and, on this basis, diagnostic testing strategies, either non-invasive or invasive, are offered to selected patients to establish the diagnosis of CAD (step 5). Once the diagnosis of obstructive CAD has been confirmed, the patient's event risk will be determined (step 6). Risk stratification has major impact on therapeutic decisions, in particular, identification of patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms. Event risk stratification is recommended based on clinical assessment and the result of the diagnostic test initially employed for making a diagnosis of CAD (*Table 1*). Risk assessment includes evaluation of LVEF by echocardiography in all patients. Systolic function can be reduced without a decrease in LVEF, and a decreased global longitudinal strain (GLS) by >2 standard deviations from the lower normal reference value has demonstrated incremental value in risk assessment of patients with CCS, especially in those with LVEF >35%.[3–5]

PTP and clinical likelihood of CAD

Estimation of the PTP and clinical likelihood of obstructive CAD serves to identify patients who require further investigation or treatment, and to distinguish them from those who do not need further investigation. As in the previous version of the guidelines, determination of the PTP of obstructive CAD by the practical clinical prediction model incorporating age, sex, and nature of symptoms remains the main component of this process in the new guidelines (*Table 2*).[1]

In the previous version of these guidelines, the recommended PTP model was based on data gathered by Genders *et al.*,[6] which were an update of previous data from Diamond and Forrester.[7] However, several studies have indicated that the prevalence of obstructive disease among contemporary patients with suspected CAD is even lower than in the last update.[8–11]

A pooled analysis[12] of three contemporary study cohorts including patients evaluated for suspected CAD[8,9,11] used in the new guidelines[1] indicates that the PTP based on age, sex, and symptoms in contemporary patients is approximately one-third of that predicted by the model used in the previous version of the guidelines.[6,13] The updated PTPs are presented in *Table 2*. Changes in the PTP have two important implications. First, an overestimation of PTP is an important contributory factor to a low diagnostic yield of non-invasive and invasive testing. Second, the new set of PTP presented in *Table 2* may substantially reduce the need for non-invasive and invasive tests in patients with suspected stable CAD. It should, however, be noted that the PTP presented in *Table 2* (as well as the PTP table in the previous version of the guideline) is based mainly on patients from countries with low cardiovascular disease risk and PTP may vary between different regions and countries. In addition to chest pain, the table now also includes patients presenting with dyspnoea as their main symptom.

Application of the new PTP (*Table 2*) has important consequences for the referral of patients to diagnostic testing.[1] If diagnostic testing was deferred in patients with new PTP <15%, this would result in a large increase in the proportion in whom diagnostic testing is not recommended. In data derived from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, 50% of patients previously classified as having an intermediate likelihood of obstructive CAD were reclassified to a PTP <15% according to the new PTP.[9] In data derived from the pooled analysis,[12] 57% of all patients were classified to a PTP <15%.

Studies have shown that outcome in patients with the new PTP up to 15% is good (annual risk of cardiovascular death or myocardial infarction (MI) <1%).[9,11] Hence, it is safe to defer routine testing in patients with PTP <15%, thus reducing unnecessary procedures and costs. However, currently there are no randomized controlled trials that include evaluation of outcomes with 'no-test' strategy.

Recent studies have demonstrated that when tested, the true observed prevalence of obstructive CAD has been <5% in patients who had PTP <15% according to the 2013 version of these guidelines.[10,11] Therefore, performing diagnostic testing also in patients with a new PTP of 5–15% more closely reflects current clinical practice and may be considered appropriate, in particular, if symptoms are limiting and require clarification.[1] Patient preference, local resources and availability of tests, clinical judgement, and appropriate patient information remain important for the decision to proceed with non-invasive diagnostic testing in an individual patient when the PTP is 5–15%, and the higher likelihood of a false-positive test must be considered. A practical and reasonable approach would be to assume that patients with a PTP ≤5% can be assumed to have such a low probability of disease that diagnostic testing should be performed only for compelling reasons (such as additional signs and symptoms not reflected in the guidelines).

A new phrase 'Clinical likelihood of CAD' that incorporates modifiers of PTP other than age, sex, and nature of symptoms was introduced in the new guidelines.[1] Clinical models that incorporate information on risk factors for cardiovascular disease, resting

Table 1 Summary of recommendations on imaging in the 2019 ESC Guidelines on the management of CCS

Recommendations	Class[a]	Level[b]
Resting echocardiography and CMR in initial diagnostic management of patients with suspected CAD		
A resting transthoracic echocardiogram is recommended in all patients for: (a) Exclusion of alternative causes of angina; (b) Identification of regional wall motion abnormalities suggestive of CAD; (c) Measurement of LVEF for risk-stratification purpose; (d) Evaluation of diastolic function.	I	B
Ultrasound of the carotid arteries should be considered to be performed by adequately trained clinicians to detect plaque in patients with suspected CCS without known atherosclerotic disease.	IIa	C
CMR may be considered in patients with an inconclusive echocardiographic test.	IIb	C
Chest X-ray in initial diagnostic management of patients with suspected CAD		
Chest X-ray is recommended for patients with an atypical presentation, signs and symptoms of HF, or suspicion of pulmonary disease.	I	C
Use of diagnostic imaging tests in initial diagnostic management of symptomatic patients with suspected CAD		
Non-invasive 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.	I	B
It is recommended that selection of the initial non-invasive diagnostic test is done based on clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests.	I	C
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.	I	B
ICA is recommended as an alternative test to diagnose CAD in patients with high clinical likelihood and severe symptoms refractory to medical therapy or typical angina at 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).	I	B
ICA with the availability of invasive functional evaluation should be considered for confirmation of diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing.	IIa	B
Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	IIa	C
Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to co-operate with breath-hold commands, or any other conditions makes good image quality unlikely.	III	C
Coronary calcium detection by CT is not recommended to identify individuals with obstructive CAD.	III	C
Performing exercise ECG in the initial diagnostic management of patients with suspected CAD		
Exercise ECG is recommended for assessment of exercise tolerance, symptoms, arrhythmias, blood pressure response, and event risk in selected patients.	I	C
Exercise ECG may be considered as an alternative test to rule-in or rule-out CAD when non-invasive imaging is not available.	IIb	B
Exercise ECG may be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIb	C
Exercise ECG in patients with ≥0.1 mV ST-segment depression on resting ECG or taking digitalis is not recommended for diagnostic purposes.	III	C
Recommendations on risk assessment		
Risk stratification is recommended based on clinical assessment and the result of the diagnostic test initially employed for making a diagnosis of CAD.	I	B
Resting echocardiography is recommended to quantify LV function in all patients with suspected CAD.	I	C
Risk stratification using preferably stress imaging or coronary CTA (if local expertise and availability permit) or alternatively exercise stress ECG (if significant exercise can be performed and the ECG is amenable to the identification of ischaemic changes) is recommended in patients with suspected or newly diagnosed CAD.	I	B
In symptomatic patients with a high-risk clinical profile, ICA complemented by invasive physiological guidance (FFR) is recommended for cardiovascular risk stratification, particularly, if the symptoms are inadequately responding to medical treatment and revascularization is considered for improvement of prognosis.	I	A

Continued

Table 1 Continued

Recommendations	Class[a]	Level[b]
In patients with mild or no symptoms, ICA complemented by invasive physiological guidance (FFR/iwFR) is recommended for patients on medical treatment in whom non-invasive risk stratification indicates a high event risk and revascularization is considered for improvement of prognosis.	I	A
ICA complemented by invasive physiological guidance (FFR) should be considered for risk stratification purposes in patients with inconclusive or conflicting results from non-invasive testing.	IIa	B
If coronary CTA is available for event risk stratification, additional stress imaging should be performed before the referral of a patient with few/no symptoms to ICA.	IIa	B
Echocardiographic assessment of GLS provides incremental information to LVEF and may be considered when LVEF is >35%.	IIb	B
Intravascular ultrasound may be considered for the risk stratification of patients with intermediate LM stenosis.	IIb	B
ICA is not recommended solely for risk stratification.	III	C
Recommendations for patients with long-standing diagnosis of CCS		
Asymptomatic patients		
In patients with mild or no symptoms receiving medical treatment in whom non-invasive risk stratification indicates a high risk, and for whom revascularization is considered for improvement of prognosis, ICA (with FFR when necessary) is recommended.	I	C
Coronary CTA is not recommended as a routine follow-up test for patients with established CAD.	III	C
ICA is not recommended solely for risk stratification.	III	C
Symptomatic patients		
Risk stratification is recommended in patients with new or worsening symptom levels, preferably using stress imaging or, alternatively, exercise stress ECG	I	B
ICA (with FFR/iwFR when necessary) is recommended for risk stratification in patients with severe CAD, particularly if the symptoms are refractory to medical treatment, or with a high-risk clinical profile.	I	C
Investigations in patients with suspected coronary microvascular angina		
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.	IIb	B
Recommendations for investigations in patients with suspected vasospastic angina		
ICA or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes that resolve with nitrates and/or calcium antagonists to determine the extent of underlying coronary disease.	I	C
Screening for CAD in asymptomatic subjects		
Assessment of coronary artery calcium score with computed tomography may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects.	IIb	B
Atherosclerotic plaque detection by carotid artery ultrasound may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects.	IIb	B
In high-risk asymptomatic adults (with diabetes, strong family history of CAD, or when previous risk-assessment tests suggest high risk of CAD), functional imaging or coronary CTA may be considered for cardiovascular risk assessment.	IIb	C
Carotid ultrasound IMT for cardiovascular risk assessment is not recommended	III	A
In low-risk non-diabetic asymptomatic adults, coronary CTA or functional imaging for ischaemia are not indicated for further diagnostic assessment.	III	C

[a]Class of recommendation.
[b]Level of evidence.
CAD, coronary artery disease; CCS, chronic coronary syndromes; CFR, coronary flow reserve; CMR, cardiac magnetic resonance imaging; CTA, computed tomography angiography; ECG, electrocardiogram; FFR, fractional flow reserve; HF, heart failure; IMT, intima-media thickness; iwFR, instantaneous wave-free ratio; LAD, let anterior descending coronary artery; LM, left main coronary artery; LVEF, left ventricle ejection fraction; PET, positron emission tomography.

electrocardiogram (ECG) changes, or coronary calcification provide improved identification of patients with obstructive CAD compared with age, sex, and symptoms alone.[11,14–20] Therefore, the presence of risk factors for cardiovascular disease (such as family history of cardiovascular disease, dyslipidaemia, diabetes, hypertension, smoking, and other lifestyle factors) that increase the probability of obstructive CAD can be used as modifiers of the PTP estimate.[1] If available, Q-wave or ST-segment or T-wave changes on the ECG, LV dysfunction suggestive of ischaemia, and findings on exercise ECG as well as information on coronary calcium by computed tomography can also be used to improve estimations of PTP of obstructive CAD.[1] In particular, the absence of coronary calcium (Agatston score = 0) is

Table 2 PTPs of obstructive CAD in 15 815 symptomatic patients according to age, sex, and the nature of symptoms in pooled analysis of contemporary data

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	Men (%)	Women (%)	Men (%)	Women (%)	Men (%)	Women (%)	Men (%)	Women (%)
30–39	3	5	4	3	1	1	0	3
40–49	22	10	10	6	3	2	12	3
50–59	32	13	17	6	11	3	20	9
60–69	44	16	26	11	22	6	27	14
70+	52	27	34	19	24	10	32	12

[a]In addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as the primary symptom are included. The dark green-shaded regions denote the groups in which non-invasive testing is most beneficial (PTP >15%). The light green-shaded regions denote the groups with PTP of CAD between 5% and 15% in which the testing for diagnosis may be considered after assessing the overall clinical likelihood based on modifiers of PTP presented in Figure 1. Reproduced with permission from Ref.[12]
PTP, pre-test probability.

associated with a low prevalence of obstructive CAD (<5%) and risk of death or non-fatal MI (<1% annual risk).[20,21] However, it is notable that the absence of coronary calcium does not exclude coronary stenosis caused by a non-calcified atherosclerotic lesion,[21] and the presence of coronary calcium as such is a weak predictor of obstructive CAD.[20] Although the optimal use of these factors in improving PTP assessment has not yet been established, the guidelines indicate that they should be considered in addition to the PTP based on sex, age, and nature of symptoms to determine overall clinical likelihood of obstructive CAD, as summarized in *Figure 1*.[1] This is particularly important in refining the likelihood of CAD patients with PTP of 5–15% based on age, sex, and nature of symptoms alone.

Diagnostic tests

During recent years, numerous large studies have evaluated the performance of diagnostic tests and several randomized clinical trials have compared the effects of diagnostic strategies on clinical outcomes. A summary of the performance of diagnostic tests for the detection of obstructive CAD based on recent meta-analyses is shown in *Table 3*.[22,23] Of note, the performance of a given test in different studies varies for numerous reasons, including selection- and referral-bias. Another potentially important source of bias in the underlying meta-analysis is inclusion of patients with known CAD or with previous test results, such as an 'intermediate' stenosis on coronary computed tomography angiography (CTA). Therefore, the differences between individual diagnostic tests as well as summary estimates based on these meta-analyses should be interpreted cautiously.

Functional imaging tests

Functional imaging includes myocardial perfusion imaging with single-photon emission computed tomography (SPECT) or positron emission computed tomography (PET), stress echocardiography, or stress CMR imaging assessing myocardial perfusion and/or wall motion. Ischaemia is provoked by exercise or pharmacological stressors either by increased myocardial work and oxygen demand or by heterogeneity in myocardial perfusion by vasodilatation. Any perfusion defect or wall motion abnormality provoked by stress is diagnostic for inducible myocardial ischaemia.

Non-invasive functional imaging tests have superior diagnostic performance to exercise ECG for the detection of obstructive CAD (*Table 3*).[22] In particular, functional tests have shown high accuracy for the detection of flow-limiting coronary stenosis in studies that have used invasive fractional flow reserve (FFR) as the reference standard (*Table 3*).[22] Imaging tests have the further advantage of indicating the location of ischaemia and are, therefore, preferable to an exercise ECG.

Functional imaging tests are effective diagnostic tools for risk-stratifying patients with CCS.[24] Stress-induced wall motion abnormalities or reversible perfusion defects corresponding to ≥10% of the total LV myocardium has been reported across a number of prognostic series to denote moderate–severe ischaemia associated with a high event rate in CCS (annual rate of cardiovascular death or MI >3%).[20] Based on observational studies, these patients may benefit from invasive coronary angiography (ICA) and revascularization.[25,26] The ongoing randomized clinical trial ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches)[27] is expected to provide further information on whether an invasive strategy in addition to optimal medical therapy improves outcomes in patients with CAD and at least moderate inducible ischaemia.

A normal functional test is associated with a low (≤1% per year) subsequent rate of cardiac death and MI.[28] However, it should be noted that lower grade coronary atherosclerosis not linked with ischaemia remains undetected by functional testing.[29] In the presence of a negative functional test, patients should receive risk-factor modification based on commonly applied risk charts and recommendations.[30]

In comparative trials and a network meta-analysis, functional imaging tests have been associated with fewer referrals for downstream ICA compared with a strategy relying on anatomical imaging or exercise ECG.[31–35] The CE-MARC 2 (Clinical Evaluation of Magnetic Resonance imaging in Coronary heart disease)—trial randomized 1202 patients with suspected angina and PTP of 10–90% to three parallel groups and showed that investigation with CMR or myocardial perfusion scintigraphy resulted in a lower probability of unnecessary

Table 3 The performance of different diagnostic tests for the detection of anatomically significant (>50% stenosis) or functionally significant (FFR ≤0.80) CAD

Test	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	+LR	−LR
Anatomically significant CAD				
Exercise 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)
Coronary CTA[a]	96 (93–98)	82 (75–87)	8.9 (6.1–13.5)	0.022 (0.01–0.04)
SPECT	87 (83–90)	70 (63–76)	2.88 (2.33–3.56)	0.19 (0.15–0.24)
PET	90 (78–96)	85 (78–90)	5.87 (3.40–10.15)	0.12 (0.05–0.29)
Stress CMR	90 (83–94)	80 (69–88)	4.54 (2.37–8.72)	0.13 (0.07–0.24)
Functionally significant CAD				
Coronary CTA	93 (89–96)	53 (37–68)	1.97 (1.28–3.03)	0.13 (0.06–0.25)
SPECT	73 (62–82)	83 (71–90)	4.21 (2.62–6.76)	0.33 (0.24–0.46)
PET	89 (82–93)	85 (81–88)	6.04 (4.29–8.51)	0.13 (0.08–0.22)
Stress CMR	89 (85–92)	87 (83–91)	7.10 (5.07–9.95)	0.13 (0.09–0.18)

Modified from Ref.[22]
[a]Data from Ref.[23]
CAD, coronary artery disease; CI, confidence interval; CTA, computed tomography angiography; ECG, electrocardiogram; PET, positron emission tomography; SPECT, single-photon emission computed tomography (exercise SPECT with or without dipyridamole or adenosine); stress CMR, stress cardiac magnetic resonance; stress echo, exercise stress echocardiography; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

angiography within 12 months as compared with 2010 NICE guidelines directed care (recommending coronary CTA or ICA instead of functional testing if PTP <30% or >60%, respectively), with no statistically significant difference in major adverse cardiovascular outcomes between groups.[32] The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial randomized 10 003 symptomatic patients referred to non-invasive testing due to suspected CAD to either coronary CTA or functional testing.[33] There was an increase in the use of ICA in the coronary CTA group compared with the functional testing group (12% vs. 8%). Although the coronary CTA strategy was associated with a lower incidence of ICA showing no obstructive CAD and more patients underwent revascularization, there was no difference in the primary outcome of all-cause mortality, MI, hospitalization for unstable angina, or major complications of cardiovascular procedures or diagnostic testing between groups after 25 months of follow-up (3.3% in the coronary CTA group vs. 3.0%).[33]

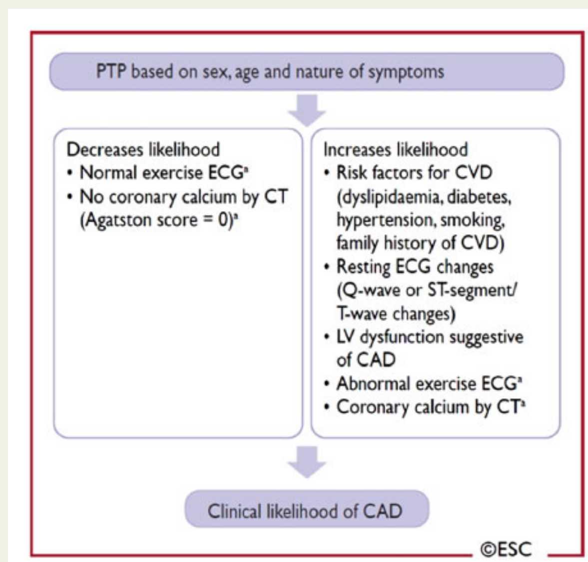

Figure 1 Determinants of clinical likelihood of obstructive CAD. CAD, coronary artery disease; CT, computed tomography; CVD, cardiovascular disease; ECG, electrocardiogram; LV, left ventricular; PTP, pre-test probability. Reproduced with permission from Ref. 1.
[a]When available.

Anatomical imaging

Non-invasive anatomical imaging, by visualizing the coronary artery lumen and wall using an intravenous contrast agent, can be performed with coronary CTA, which provides very high sensitivity for the detection of coronary artery stenoses defined by ICA (*Table 3*).[22,23] However, it has lower specificity, particularly in studies using invasive FFR rather than ICA as the reference standard (*Table 2*). Stenoses estimated to be 50–90% by visual inspection are not necessarily functionally significant, i.e. they do not always induce myocardial ischaemia. Therefore, either non-invasive or invasive functional testing is recommended for further evaluation of angiographic stenosis detected by coronary CTA or invasive angiography, unless a very high grade (>90% diameter stenosis) stenosis is detected by invasive angiography.[1]

It is important to note that poor image quality, severe calcifications and non-expert interpretation may lead to overestimation of stenosis severity in coronary CTA.[36] Therefore, coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to co-operate with breath-hold commands, or any other condition make good image quality unlikely.[1,37] The decision to proceed with coronary CTA in patients with severe calcification must be made on an individual basis, taking overall image quality and the distribution of calcium into account. In patients with previous revascularization (bypass grafts, stents), the accuracy of coronary CTA is frequently impaired by blooming artefacts and incomplete evaluation of native vessels.[38] Acquisition protocols for coronary CTA should include special measures to keep radiation exposure as low as possible.[37]

The presence or absence of non-obstructive coronary atherosclerosis on coronary CTA provides prognostic information and can be used to guide preventive therapy. Several prospective registries have shown that the absence of stenosis in coronary CTA is associated with an extremely good prognosis.[39,40] The large, prospective randomized PROMISE trial showed that the event rate in patients in whom coronary CTA was used as the first diagnostic test was not different from the event rate in patients who underwent functional testing as a first test.[33] The SCOT-HEART (Scottish Computed Tomography of the Heart) trial demonstrated a significantly lower rate of the combined endpoint of cardiovascular death or non-fatal MI (2.3% vs. 3.9% during 5-year follow-up) in patients in whom coronary CTA was performed in addition to routine testing, which consisted predominantly of exercise ECG.[41,42] Furthermore, the SCOT-HEART trial[41–43] and other prospective randomized outcome trials comparing coronary CTA and predominantly exercise ECG[44,45] have shown that patients in the coronary CTA group were more likely to be diagnosed with significant CAD, required less downstream testing, and medications were altered in a significant proportion of patients, compared with the control group. Some, although not all, registry studies have also shown similar benefits with the use of coronary CTA in patients treated in everyday clinical practice.[46,47]

Coronary CTA is a morphological imaging tool that does not provide information on the haemodynamic relevance of a coronary artery stenosis. It can be complemented by 'virtual' CT-based FFR (FFRCT) or stress CT myocardial perfusion imaging to improve correlation with a combination of invasive angiography and FFR.[48] Stress CT myocardial perfusion imaging can be performed with various protocols, whereas FFRCT uses anatomic datasets acquired by CT at rest, based on which FFR results are simulated off-line.[48] A recent meta-analysis of comparative studies showed sensitivities of 83% and 89%, and specificities of 79% and 76% for CT myocardial perfusion imaging and FFRCT, respectively, for the detection of obstructive CAD defined by invasive FFR.[48] Retrospective registry analyses and trial substudies as well as small randomized trials in which management decisions were based on coronary CTA complemented with FFRCT have demonstrated that non-ischaemic FFRCT results are associated with a favourable prognosis.[49–51] In patients with intermediate-range coronary stenosis, FFRCT has been shown to be effective in differentiating patients who do not require further diagnostic testing or intervention from higher-risk patients in whom further testing with ICA and possibly intervention may be needed.[52,53] In a randomized study comparing coronary CTA with FFRCT and ICA, CTA with FFRCT was suitable for diagnosing and guiding revascularization in advanced multivessel CAD.[54,55] Prospective outcome trials comparing these modalities to alternative forms of non-invasive testing are currently not available. These evolving technologies were discussed in the guideline, but no specific recommendations were given.

Selection of appropriate testing

A summary of the three main diagnostic pathways in symptomatic patients with suspected obstructive CAD is displayed in *Figure 2*.[1] Depending on clinical conditions and the healthcare environment, patient workup can start with either of three options: non-invasive functional testing, coronary CTA, or ICA. Through each pathway, both functional and anatomical information are gathered to inform an appropriate diagnostic and therapeutic strategy. Risk-factor modification should be considered in all patients.

Either functional imaging for myocardial ischaemia or coronary CTA is recommended as the initial non-invasive tests for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.[1] It is recommended that choice of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance (see below) as well as on local expertise and availability of tests.

The likelihood ratios of diagnostic tests constitute useful parameters of their ability to correctly classify patients, and can be used to facilitate the selection of the most useful test in any given patient.[22,56] Each non-invasive diagnostic test has a particular range of clinical likelihood of obstructive CAD where the usefulness of its application is maximal. Given a clinical likelihood of obstructive CAD and the likelihood ratios of a particular test, one can assess the post-test probability of obstructive CAD after performing such a test. Using this approach, one can estimate the optimal ranges of clinical likelihood for each test where they can reclassify patients from intermediate to either low or high post-test probability of CAD (*Figure 3*).[22]

Coronary CTA is the preferred test in patients within the lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. It detects subclinical coronary atherosclerosis, but can also accurately rule-out both anatomically and functionally significant CAD (*Figure 3*). It has the highest accuracy values when low clinical likelihood populations are subjected to the examination.[57] The trials evaluating outcomes after coronary CTA also included mostly patients with a low clinical likelihood.[33,41] Coronary CTA should also be considered as an alternative to ICA if another non-invasive test is equivocal or non-diagnostic. Coronary calcium detection by computed tomography is not recommended to identify individuals with obstructive CAD.

The non-invasive functional tests for ischaemia typically have better rule-in power. For revascularization decisions, functional evaluation of ischaemia (either non-invasive or invasive) is required in most patients. Therefore, functional non-invasive testing may be preferred in patients at the higher range of clinical likelihood, if revascularization is likely or the patient has previously been diagnosed with CAD. Functional imaging for myocardial ischaemia is also recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.

Direct ICA is recommended as an alternative to non-invasive testing in order 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

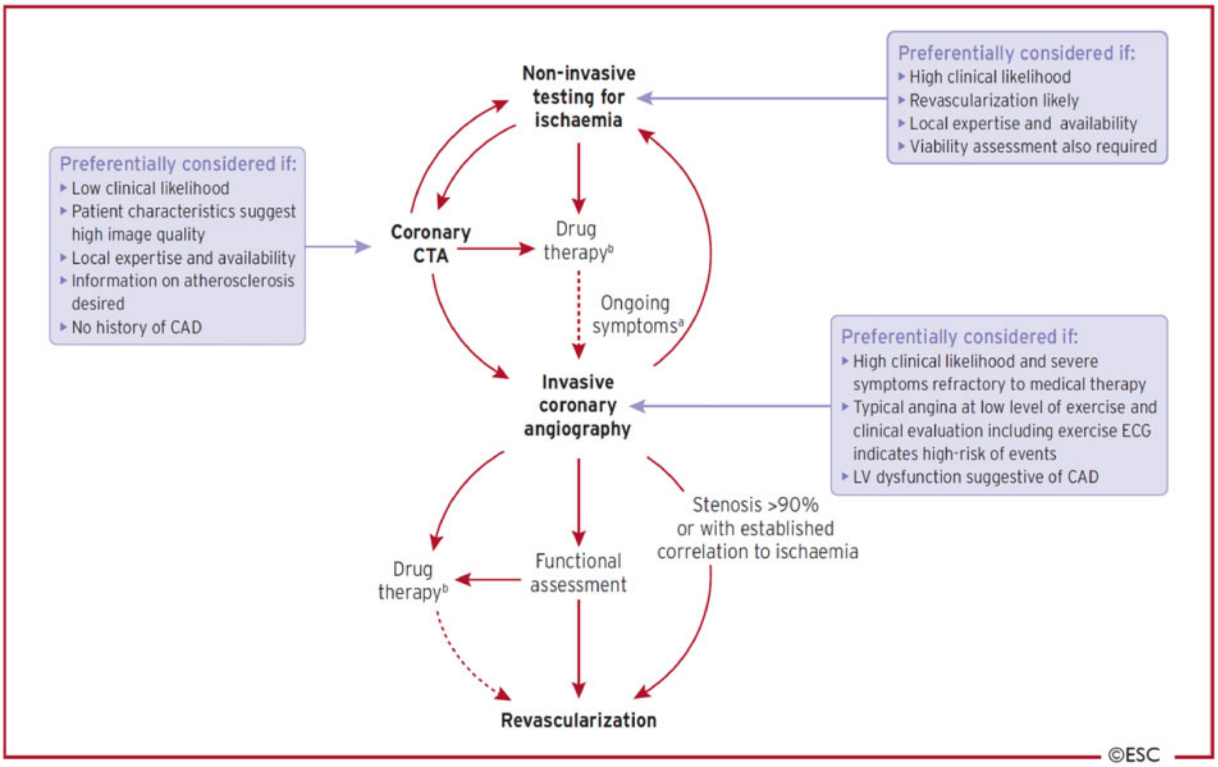

Figure 2 Main diagnostic pathways in symptomatic patients with suspected obstructive coronary artery disease. CAD, coronary artery disease; CTA, computed tomography angiography; ECG, electrocardiogram. [a]Consider microvascular angina. [b]Antianginal medications and risk factor modification. Reproduced with permission from Ref.[1]

event risk.[1] Patients at high event risk should undergo invasive investigation for consideration of revascularization, even if they have mild or no symptoms.[1] Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).

Risks related to different diagnostic tests need to be weighed against the benefits to the individual.[58] For example, exposure to ionizing radiation associated with coronary CTA and nuclear perfusion imaging needs to be taken into account, especially in young individuals. Similarly, contraindications to pharmacological stressors and contrast agents (iodine-based contrast agents and gadolinium-based chelates) need to be considered. When testing is used appropriately, the clinical benefit from accurate diagnosis and therapy exceeds the projected risks of testing itself.[58]

Role of the exercise ECG

Exercise ECG has an inferior diagnostic performance compared with diagnostic imaging tests and has limited power to rule-in or rule-out obstructive CAD (*Table 3*).[22] As discussed above, randomized clinical trials have shown that the addition of coronary CTA or functional imaging clarifies the diagnosis, enables targeting of preventive therapies and interventions, and potentially reduces the risk of MI compared with a diagnostic workup relying on the exercise ECG. Therefore, the new guidelines recommend the use of an imaging diagnostic test instead of exercise ECG as the initial test for diagnosing obstructive CAD.[1] However, an exercise ECG alone may be considered as an alternative to diagnose obstructive CAD if imaging tests are not available, keeping in mind the risk for false-negative and false-positive test results.[22,59]

An exercise ECG provides complementary clinically useful information beyond ECG changes and valuable prognostic information. Therefore, exercise ECG may also be used to complement other clinical evaluation for assessment of symptoms, ST-segment changes, exercise tolerance, arrhythmias, blood pressure response, and event risk,[1] and thereby to inform an appropriate diagnostic and therapeutic strategy. The occurrence of ST-segment depression at a low workload combined with exertional symptoms (angina or dyspnoea), low exercise capacity, complex ventricular ectopy, or arrhythmias and abnormal blood pressure response are markers of a high event risk.[60]

Angina without obstructive disease in the epicardial coronary arteries

The possibility of a microcirculatory origin of angina should be considered in patients with clear-cut angina and coronary vessels that are

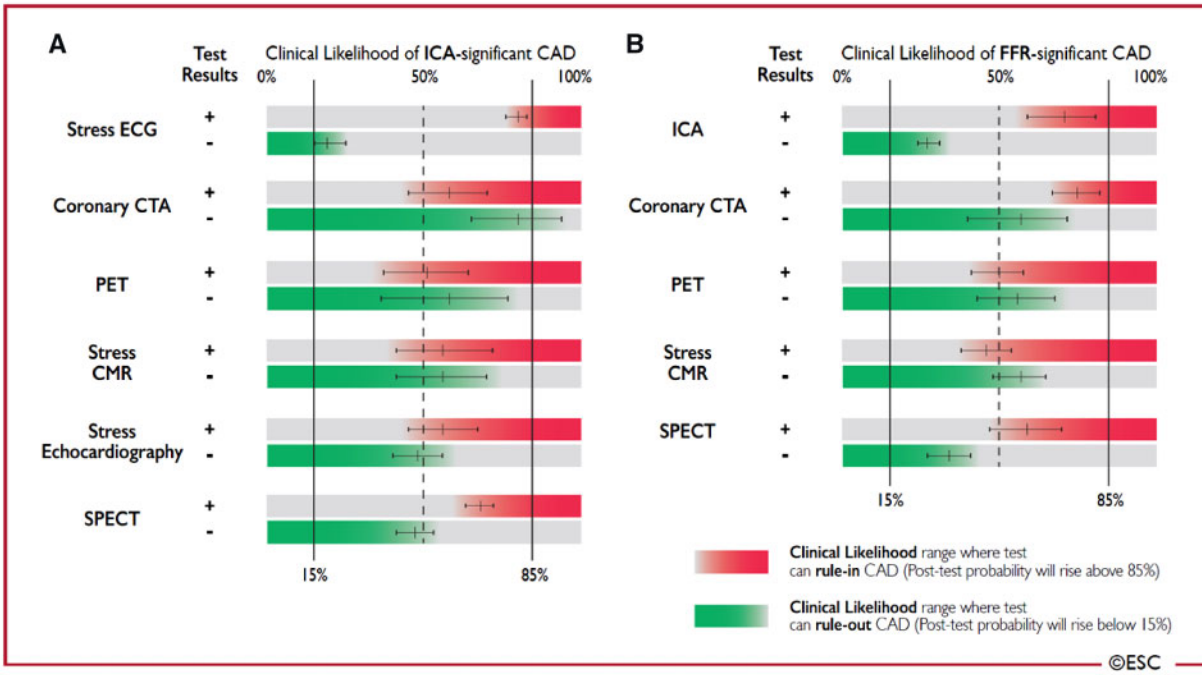

Figure 3 Ranges of clinical likelihood of CAD in which a given test can rule-in (red) or rule-out (green) obstructive CAD. The graph displays in red colour the range of clinical likelihood of CAD when a given test can rule-in CAD when positive. The green colour shows the range of clinical likelihood of CAD when a given test can rule-out CAD when negative. The ideal range of clinical likelihood for a given test is when red and green colours overlap and the test can simultaneously rule-in and rule-out CAD depending the test result. (*A*) Reference standard is anatomical assessment using ICA. (*B*) = Reference standard is functional assessment using FFR. Note, in (*B*), that the data with stress echocardiography and SPECT are more limited than with the other techniques. The crosshairs mark the mean value and their 95% confidence intervals. CAD, coronary artery disease; CMR, cardiac magnetic resonance; CTA, computed tomography angiography; ECG, electrocardiogram; FFR, fractional flow reserve; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single-photon emission computed tomography. Reproduced with permission from Ref.[1]

either normal or have mild stenosis deemed functionally non-significant on ICA or CTA. Impaired microcirculatory conductance can be diagnosed by measuring coronary flow reserve (CFR) non-invasively with transthoracic Doppler echocardiography [by imaging left anterior descending (LAD) flow][61] magnetic resonance imaging (myocardial perfusion index),[62,63] or PET.[64] However, non-invasive methods provide limited assessment of microvascular function, because assessment of endothelial function (arteriolar dysregulation) in the coronary microcirculation requires selective acetylcholine infusion into the epicardial vessels. In patients with suspected vasospastic angina and documented ECG changes, coronary CTA or ICA is indicated to rule out the presence of fixed coronary stenosis.

Summary and perspectives

The PTP estimations of CAD based on age, sex, and nature of symptoms have undergone major update with significantly lower probabilities than in previous estimates. In addition, a new phrase 'Clinical likelihood of CAD' that incorporates other modifiers of PTP beyond age, gender, and nature of symptoms has been introduced. More information on the effects of various risk factors, biomarkers, and comorbidities on the clinical likelihood of obstructive CAD is needed. Recommendations for the application of various diagnostic tests in different patient groups to rule-in or rule-out CAD have been updated. Non-invasive functional imaging for myocardial ischaemia, coronary CTA or ICA combined with functional evaluation may be used as the initial test to rule out or establish diagnosis of CCS. Selection of the initial non-invasive diagnostic test is based on the clinical likelihood of CAD, the test's performance in ruling-in or ruling-out obstructive CAD, patient characteristics, local expertise, and the availability of the test. For revascularization decisions, both anatomy and functional evaluation are to be considered. Assessment of risk serves to identify CCS patients at high event risk who are projected to derive prognostic benefit from revascularization. Risk stratification includes the assessment of LV function. Adequately powered RCTs are needed to compare the effectiveness of different diagnostic strategies, and to evaluate how to best integrate diagnostic tests in patient care in terms of clinical outcomes and the use of healthcare resources.

Conflict of interest: E.B.: Speaker fee from BSCI, Abbott Vascular and GE. J.J.B.: The department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Biotronik, Boston Scientific, Medtronic, Edwards Lifesciences and GE Healthcare. Speaker fee from Abbott Vascular. W.W.: Research grants from MicroPort, HealthWatch and MiCell. Speaker fee from MicroPort and Biotronik. All remaining authors have declared no conflicts of interest.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C *et al.* 2019 ESC Guidelines on the diagnosis and management of chronic coronary syndromes: the Task Force for diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 2019:**1**–71. doi: 10.1093/eurheartj/ehz425.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F *et al.* 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
3. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging* 2009;**2**:356–64.
4. Haugaa KH, Grenne BL, Eek CH, Ersboll M, Valeur N, Svendsen JH *et al.* Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. *JACC Cardiovasc Imaging* 2013;**6**:841–50.
5. Ersboll M, Valeur N, Mogensen UM, Andersen MJ, Moller JE, Velazquez EJ *et al.* Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2013;**61**:2365–73.
6. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K *et al.* A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–30.
7. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–8.
8. Cheng VY, Berman DS, Rozanski A, Dunning AM, Achenbach S, Al-Mallah M *et al.* Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). *Circulation* 2011;**124**:2423–32, 1–8.
9. Foldyna B, Udelson JE, Karady J, Banerji D, Lu MT, Mayrhofer T *et al.* Pretest probability for patients with suspected obstructive coronary artery disease: re-evaluating Diamond-Forrester for the contemporary era and clinical implications: insights from the PROMISE trial. *Eur Heart J Cardiovasc Imaging* 2019;**20**:574–81.
10. Adamson PD, Newby DE, Hill CL, Coles A, Douglas PS, Fordyce CB. Comparison of international guidelines for assessment of suspected stable angina: insights from the PROMISE and SCOT-HEART. *JACC Cardiovasc Imaging* 2018;**11**: 1301–10.
11. Reeh J, Therming CB, Heitmann M, Hojberg S, Sorum C, Bech J *et al.* Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. *Eur Heart J* 2019;**40**:1426–35.
12. Juarez-Orozco LE, Capodanno D, Prescott E, Saraste S, Bax JJ, Wijns W, Contemporary pre-test probability of coronary artery disease: a pooled analysis of 3 cohorts with 15815 symptomatic patients. *Eur Hear J Cardiovasc Imaging* 2019;**20**:1198–1207.
13. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
14. Genders TS, Steyerberg EW, Hunink MG, Nieman K, Galema TW, Mollet NR *et al.* Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ* 2012;**344**:e3485.
15. Versteylen MO, Joosen IA, Shaw LJ, Narula J, Hofstra L. Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events. *J Nucl Cardiol* 2011;**18**:904–11.
16. Wasfy MM, Brady TJ, Abbara S, Nasir K, Ghoshhajra BB, Truong QA *et al.* Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography. *Am J Cardiol* 2012;**109**:998–1004.
17. Jensen JM, Voss M, Hansen VB, Andersen LK, Johansen PB, Munkholm H *et al.* Risk stratification of patients suspected of coronary artery disease: comparison of five different models. *Atherosclerosis* 2012;**220**:557–62.
18. Sharma A, Sekaran NK, Coles A, Pagidipati NJ, Hoffmann U, Mark DB *et al.* Impact of diabetes mellitus on the evaluation of stable chest pain patients: insights from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial. *J Am Heart Assoc* 2017;**6**:e007019.
19. Winther S, Nissen L, Westra J, Schmidt SE, Bouteldja N, Knudsen LL *et al.* Pretest probability prediction in patients with a low to intermediate probability of coronary artery disease: a prospective study with a fractional flow reserve endpoint. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1208–18.
20. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT *et al.* Prognostic value of coronary artery calcium in the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation* 2017;**136**: 1993–2005.
21. Villines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S *et al.* Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry. *J Am Coll Cardiol* 2011;**58**:2533–40.
22. Knuuti J, Ballo H, Juarez-Orozco LE, Saraste A, Kolh P, Rutjes AWS *et al.* The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J* 2018;**39**:3322–30.
23. Menke J, Kowalski J. Diagnostic accuracy and utility of coronary CT angiography with consideration of unevaluable results: a systematic review and multivariate Bayesian random-effects meta-analysis with intention to diagnose. *Eur Radiol* 2016;**26**:451–8.
24. Shaw LJ, Berman DS, Picard MH, Friedrich MG, Kwong RY, Stone GW *et al.* Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. *JACC Cardiovasc Imaging* 2014;**7**: 593–604.
25. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–7.
26. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD *et al.* Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011;**32**:1012–24.
27. ISCHEMIA Trial Research Group. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J* 2018;**201**:124–35.
28. Smulders MW, Jaarsma C, Nelemans PJ, Bekkers S, Bucerius J, Leiner T *et al.* Comparison of the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease-a meta-analysis. *Eur Heart J Cardiovasc Imaging* 2017;**18**:980–7.
29. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR *et al.* Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation* 2017;**135**:2320–32.
30. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–81.
31. Siontis GC, Mavridis D, Greenwood JP, Coles B, Nikolakopoulou A, Juni P *et al.* Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. *BMJ* 2018;**360**:k504.
32. Greenwood JP, Ripley DP, Berry C, McCann GP, Plein S, Bucciarelli-Ducci C *et al.* Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA* 2016;**316**:1051–60.
33. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B *et al.* Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;**372**:1291–300.
34. Zacharias K, Ahmed A, Shah BN, Gurunathan S, Young G, Acosta D *et al.* Relative clinical and economic impact of exercise echocardiography vs. exercise electrocardiography, as first line investigation in patients without known coronary artery disease and new stable angina: a randomized prospective study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:195–202.
35. Karthikeyan G, Guzic Salobir B, Jug B, Devasenapathy N, Alexanderson E, Vitola J *et al.* Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: an international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study). *J Nucl Cardiol* 2017;**24**: 507–17.
36. Lu MT, Meyersohn NM, Mayrhofer T, Bittner DO, Emami H, Puchner SB *et al.* Central core laboratory versus site interpretation of coronary CT angiography: agreement and association with cardiovascular events in the PROMISE trial. *Radiology* 2018;**287**:87–95.
37. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK *et al.* SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society

for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* 2016;**10**: 435–49.
38. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ *et al*. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014;**8**:342–58.
39. Hadamitzky M, Freißmuth B, Meyer T, Hein F, Kastrati A, Martinoff S *et al*. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. *JACC Cardiovasc Imaging* 2009;**2**:404–11.
40. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ *et al*. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–60.
41. SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–91.
42. . SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–33.
43. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J *et al*. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol* 2016;**67**:1759–68.
44. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T *et al*. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J* 2016;**37**:1232–43.
45. McKavanagh P, Lusk L, Ball PA, Verghis RM, Agus AM, Trinick TR *et al*. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. *Eur Heart J Cardiovasc Imaging* 2015;**16**:441–8.
46. Jorgensen ME, Andersson C, Norgaard BL, Abdulla J, Shreibati JB, Torp-Pedersen C *et al*. Functional testing or coronary computed tomography angiography in patients with stable coronary artery disease. *J Am Coll Cardiol* 2017;**69**:1761–70.
47. Roifman I, Wijeysundera HC, Austin PC, Rezai MR, Wright GA, Tu JV. Comparison of anatomic and clinical outcomes in patients undergoing alternative initial noninvasive testing strategies for the diagnosis of stable coronary artery disease. *J Am Heart Assoc* 2017;**6**:e005462.
48. Celeng C, Leiner T, Maurovich-Horvat P, Merkely B, de Jong P, Dankbaar JW *et al*. Anatomical and functional computed tomography for diagnosing hemodynamically significant coronary artery disease: a meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:1316–25.
49. Nørgaard BL, Hjort J, Gaur S, Hansson N, Bøtker HE, Leipsic J *et al*. Clinical use of coronary CTA–derived FFR for decision-making in stable CAD. *JACC Cardiovasc Imaging* 2017;**10**:541–50.
50. Douglas PS, Bruyne B, De Pontone G, Patel MR, Norgaard BL, Byrne RA *et al*. 1-year outcomes of FFR CT—guided care in patients with suspected coronary disease. *J Am Coll Cardiol* 2016;**68**:435–45.
51. Lu MT, Ferencik M, Roberts RS, Lee KL, Ivanov A, Adami E *et al*. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE trial. *JACC Cardiovasc Imaging* 2017;**10**:1350–8.
52. Nørgaard BL, Terkelsen CJ, Mathiassen ON, Grove EL, Bøtker HE, Parner E *et al*. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2018;**72**: 2123–34.
53. Sand NPR, Veien KT, Nielsen SS, Nørgaard BL, Larsen P, Johansen A *et al*. Prospective comparison of FFR derived from coronary CT angiography with SPECT perfusion imaging in stable coronary artery disease: the ReASSESS study. *JACC Cardiovasc Imaging* 2018;**11**:1640–50.
54. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S *et al*. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J* 2018;**39**:3689–98.
55. Collet C, Miyazaki Y, Ryan N, Asano T, Tenekecioglu E, Sonck J *et al*. Fractional flow reserve derived from computed tomographic angiography in patients with multivessel CAD. *J Am Coll Cardiol* 2018;**71**:2756–69.
56. Steurer J, Fischer JE, Bachmann LM, Koller M, ter Riet G. Communicating accuracy of tests to general practitioners: a controlled study. *BMJ* 2002;**324**:824–6.
57. Gueret P, Deux JF, Bonello L, Sarran A, Tron C, Christiaens L *et al*. Diagnostic performance of computed tomography coronary angiography (from the Prospective National Multicenter Multivendor EVASCAN Study). *Am J Cardiol* 2013;**111**:471–8.
58. Knuuti J, Bengel F, Bax JJ, Kaufmann PA, Le Guludec D, Perrone Filardi P *et al*. Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease. *Eur Heart J* 2014;**35**:633–8.
59. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E *et al*. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation* 2011; **124**:1239–49.
60. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR *et al*. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;**325**:849–53.
61. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. *Am J Cardiol* 2009;**103**:626–31.
62. Liu A, Wijesurendra RS, Liu JM, Forfar JC, Channon KM, Jerosch-Herold M *et al*. Diagnosis of microvascular angina using cardiac magnetic resonance. *J Am Coll Cardiol* 2018;**71**:969–79.
63. Shufelt CL, Thomson LE, Goykhman P, Agarwal M, Mehta PK, Sedlak T *et al*. Cardiac magnetic resonance imaging myocardial perfusion reserve index assessment in women with microvascular coronary dysfunction and reference controls. *Cardiovasc Diagn Ther* 2013;**3**:153–60.
64. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J *et al*. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015;**131**:19–27.