

2019 ESC Guidelines on the diagnosis and management of chronic coronary syndromes: supplementary data

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

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This supplementary data file to the 2019 Guidelines for the diagnosis and management of chronic coronary syndromes (CCS) contains additional material that should be used for further clarification when reading the main document.

1 Patients with angina and/or dyspnoea, and suspected coronary artery disease

1.1 Diagnosis and assessment

The following sections describe some features of different diagnostic tests. It should be noted that the performance of a given test in different studies varies due to numerous reasons, such as population selection and referral bias. Another potentially important source of variation or bias is the inclusion of a patient in a study based on previous test results or known coronary artery disease (CAD), such as a stenosis on coronary computed tomography angiography (CTA).¹ Therefore, differences between techniques and summary estimates based on meta-analyses should be interpreted with caution, and considered as directional only.

1.1.1 Exercise electrocardiogram testing

Exercise electrocardiogram (ECG) testing aims to indirectly detect myocardial ischaemia through exercise-induced ST-T-segment changes. The main diagnostic ECG abnormality consists of horizontal or down-sloping ST-segment depression ≥ 0.1 mV, persisting for ≥ 0.06 – 0.08 s after the J-point, in one or more ECG leads. Exercise ECG is of no diagnostic value in the presence of left bundle branch block (LBBB), paced rhythm, and Wolff–Parkinson–White syndrome, in which cases the ST-T-segment changes are not interpretable. Additionally, false-positive results are more frequent in patients with abnormal resting ECG in the presence of left ventricular (LV) hypertrophy, electrolyte imbalance, intraventricular conduction abnormalities, atrial fibrillation,^{2,3} or who are being treated with digitalis. To obtain diagnostic information, the test should be symptom/sign-limited and performed without the influence of anti-ischaemic drugs.

There are numerous reviews and meta-analyses regarding the performance of exercise ECG for the diagnosis of CAD, which have shown variable diagnostic yields. In a recent meta-analysis, the sensitivity and specificity for the detection of CAD, defined as diameter stenosis $\geq 50\%$, was 58 and 62%, respectively.¹ Studies designed to avoid workup bias have reported lower sensitivities (45–50%) and higher specificities (85–90%).^{4,5} The addition of cardiopulmonary exercise testing may improve sensitivity, but this combination of tests is not widely used.⁶ The diagnostic performance of exercise ECG is inferior to imaging diagnostic tests and inconclusive results are not infrequent, for example, when 85% of maximum heart rate is not achieved in the absence of symptoms or signs of ischaemia, when exercise is limited by orthopaedic or other non-cardiac problems, or when ECG changes are equivocal. As a result, additional downstream testing is needed more frequently after exercise ECG than after diagnostic tests using imaging.^{7–9} However, depending on the availability of other tests, exercise ECG may be considered as an alternative diagnostic test to detect obstructive CAD.^{1,10}

Exercise testing on either a bicycle ergometer or a treadmill provides information other than ST-segment changes on event risk, as well as exercise tolerance, symptoms, heart rate response, arrhythmias, and blood pressure (BP) response (see section 3.1.3). Therefore, exercise ECG remains a useful test in many patients with

suspected CAD and is widely available. Exercise stress testing can also be useful to evaluate the efficacy of medical treatment or after revascularization, or to aid the prescription of exercise after control of symptoms. For these indications, exercise stress testing should be performed in patients receiving treatment to evaluate control of ischaemia or effort performance. The effect of routine periodic exercise testing on patient outcomes has not been formally evaluated.

1.1.2 Stress echocardiography

Stress echocardiography can be performed with exercise (treadmill or bicycle ergometer) or with pharmacological drugs.¹¹ An exercise test will provide important information on exercise time, workload changes in heart rate, BP, and ECG. Therefore, exercise has been advocated as the primary choice when feasible because of a more physiological situation compared with pharmacological tests. However, there are no differences in sensitivity and specificity between the two methods.¹² In a recent meta-analysis of diagnostic studies, the pooled sensitivity and specificity of stress echocardiography for the detection of obstructive CAD (defined as diameter stenosis $\geq 50\%$) was 85 and 82%, respectively.¹ However, an exercise test has fewer potential side effects compared with a pharmacological test.

A pharmacological test is useful when facilities for exercise testing are not available or if the patient is unable to do an adequate exercise test. The preferred pharmacological drug to produce supply-demand mismatch is dobutamine (inotropic stress). A contrast agent is necessary when ≥ 2 LV segments are not visualized at rest.¹³ The use of contrast also improves accuracy for CAD detection in patients with reasonable acoustic windows and might be used on a general basis in stress echocardiography.¹⁴ Strain imaging has been suggested for improved accuracy during stress echocardiography.¹⁵ However, a consensus statement from the American Society of Echocardiography/European Association of Cardiovascular Imaging does not encourage the clinical use of strain or tissue Doppler techniques in stress testing.¹⁶ The role of three-dimensional echocardiography is also somewhat unclear, and its prognostic value in terms of ischaemia has not yet been proved.^{17–20}

The main advantage of stress echocardiography compared with other functional tests is the good availability of the method. Stress echocardiography provides information on both LV systolic and diastolic function, in addition to valve function. The technique is free of radiation exposure, and provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging and cardiac magnetic resonance (CMR), but at a lower cost. It has also been shown that exercise stress echocardiography is more cost-effective than exercise ECG.²¹

The main challenge with stress echocardiography is its dependence on operator expertise and the visual assessment of wall motion abnormalities.

1.1.3 Single-photon emission computed tomography

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging produces images of regional myocardial tracer uptake, which reflect relative myocardial blood flow at rest, and during dynamic exercise or pharmacological stress.²² In addition to perfusion distribution, increased uptake of the perfusion agent in the

lung identifies stress-induced ventricular dysfunction in patients with severe and extensive CAD. Transient ischaemic dilatation and reduced post-stress ejection fraction are important non-perfusion predictors of severe CAD. The technique provides information on the presence or absence, as well as the location and extent, of myocardial ischaemia, myocardial infarction (MI) (and viability), and ventricular function. The SPECT studies can be performed either using an exercise test or using pharmacological stress testing, especially in patients who are unable to exercise adequately or present with LBBB. With the most commonly used technetium-99m radiopharmaceuticals, the estimated radiation exposure to the patient is ~10 mSv, but the radiation dose can be halved with the use of stress-only imaging and new high-efficiency cardiac SPECT cameras.²³

The diagnostic accuracy of exercise and pharmacological stress SPECT myocardial perfusion imaging in the detection of CAD has been studied extensively. A meta-analysis found pooled sensitivity of 87% and specificity of 70% when CAD was defined as angiographic coronary stenosis >50%.¹ The test also performs well in studies using a functional definition of CAD based on invasive fractional flow reserve (FFR) (sensitivity 73 - 74% and specificity 79 - 83%).^{1,24} Global reductions in myocardial perfusion, such as in the setting of multivessel disease, may cause underestimation of ischaemic burden in the relative perfusion images produced by SPECT. Compared with exercise ECG, SPECT myocardial perfusion imaging is more accurate for the detection of obstructive CAD, and provides additional information on the location of myocardial ischaemia and the extent of ischaemic burden.¹ The cost-effectiveness of SPECT myocardial perfusion imaging is highest in patients in the higher range of intermediate pre-test probability (PTP) of CAD.²⁵

1.1.4 Positron emission tomography

Positron emission tomography (PET) perfusion imaging uses ⁸²Rb, ¹³N-ammonia, or ¹⁵O-water as radioactive myocardial perfusion tracers to evaluate myocardial perfusion and function, at rest and during pharmacological stress.²⁶ Similar to SPECT, the technique provides information on the presence or absence of myocardial ischaemia, location and extent of ischaemia, MI, residual viability, and ventricular function. In addition, PET has the unique ability to quantify blood flow in mL/min/g, which allows the detection of microvascular disease and improved evaluation of ischaemic burden in multivessel CAD. The risks associated with pharmacological vasodilator stress with regard to SPECT similarly apply to PET. The radiation exposure to the patient is lower than that with SPECT (~1 - 4 mSv) due to the short radioactive half-life of PET perfusion tracers.

PET myocardial perfusion imaging has high diagnostic performance in the detection of CAD in terms of image quality, interpretative certainty, and diagnostic accuracy.²⁷⁻³⁰ A meta-analysis of diagnostic studies found pooled sensitivity and specificity of 90 and 85%, respectively, when CAD was defined as angiographic coronary stenosis of >50%, and sensitivity and specificity of 89 and 85%, respectively, when CAD was defined by FFR.¹ Image quality of PET is affected less than that of SPECT in obese patients.³⁰ Quantification of myocardial blood flow facilitates the detection of extensive, high-risk CAD (balanced ischaemia).³¹⁻³⁴ Compared with SPECT scanners and radiotracers, PET scanners and perfusion tracers are less widely available, and compared with the other stress imaging techniques, PET is less commonly used to diagnose CAD.

1.1.5 Stress cardiac magnetic resonance

Stress CMR can be performed with pharmacological drugs by assessing both myocardial perfusion and changes in LV wall motion in response to stress. Vasodilator and dobutamine are the main drugs.³⁵ In clinical practice, physical exercise is never used in stress CMR. Dobutamine will increase flow demand and induce wall motion abnormalities due to ischaemia in the presence of CAD, similar to dobutamine stress echocardiography, and the safety profiles are comparable.³⁶ Vasodilators will increase coronary flow and will cause differences in myocardial perfusion in patients with CAD. The perfusion technique with vasodilator stress perfusion is the most commonly used method. Analyses are either by visual assessment of low-signal areas with reduced perfusion or with different software tools. There have been several attempts to establish semiquantitative and quantitative CMR perfusion analysis, but the clinical use of these tools remains unclear.³⁷

The diagnostic accuracy of CMR perfusion imaging is high^{24,28,38,39} and has several advantages, with no attenuation artefacts, high spatial resolution, and no radiation exposure. In a meta-analysis, pooled sensitivity and specificity for the detection of CAD (defined as diameter stenosis ≥50%) was 90 and 80%, respectively.¹ CMR perfusion imaging is also well suited for women,⁴⁰ but the impact of microvascular disease remains unclear.⁴¹ The main disadvantages are CMR's low availability, the high-level of expertise that is required, non-quantitative analyses, and cost issues.

1.1.6 Computed tomography

Modern multidetector row computed tomography (CT) systems, with the ability to acquire at least 64 slices with submillimetre collimation simultaneously, and with the option of ECG-triggered image acquisition or ECG-gated image reconstruction, allow robust imaging of the coronary arteries in many patients.⁴² CT imaging can be performed without a contrast agent to detect and quantify coronary calcium. The coronary calcium score refines estimates of PTP of CAD compared with models based on age, sex, and the type of chest pain.⁴³ However, the extent of calcium shows no reliable correlation with the presence and severity of stenoses. After intravenous injection of a contrast agent, coronary CTA depicts the coronary lumen and calcified, as well as non-calcified, plaque.⁴² Acquisition protocols for coronary CTA should include special measures to keep radiation exposure as low as possible.⁴²

1.1.6.1 Coronary computed tomography angiography

According to expert consensus, only patients with adequate breath-hold capabilities, without being severely overweight, and in sinus rhythm, should undergo coronary CTA.⁴² Heart rate should be lowered, optimally to <60 b.p.m.⁴² Nitrates are given sublingually to achieve coronary dilatation. The presence of pronounced coronary calcium can hinder the interpretation of coronary CTA and negatively affect its specificity. 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 comparative studies to coronary angiography, coronary CTA displayed very high sensitivity for the detection of coronary artery stenoses in patients with suspected CAD (95.6% pooled sensitivity in a meta-analysis comprising 30 studies and 3722 individuals).⁴⁴ Pooled

specificity, at 81.5%, was lower. A very low negative likelihood ratio (0.022) results from the high sensitivity for identifying coronary stenoses. Several prospective registries have shown that the absence of stenoses in coronary CTA is associated with an extremely good prognosis,^{45,46} and the large, prospective randomized PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) 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 ischaemia testing as a first test.⁴⁷ In the prospective SCOT-HEART (Scottish Computed Tomography of the HEART) study, CAD-related event rates were lower in individuals with CAD in whom the initial workup was complemented by coronary CTA.⁴⁸ 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.⁴⁹ In patients with previous revascularization (e.g. bypass grafts or stents), the accuracy of coronary CTA is frequently impaired by blooming artefacts and incomplete evaluation of native vessels.

1.1.6.2 Computed tomography-based fractional flow reserve and computed tomography myocardial perfusion

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 (FFR_{CT})⁵⁰ or stress CT myocardial perfusion imaging^{24,51} to improve correlation with a combination of invasive angiography plus ischaemia testing. FFR_{CT} uses anatomical data sets acquired by CT at rest, based on which FFR results are simulated. Comparative studies have shown an accuracy of ~85% compared with invasive FFR measurements.⁵¹ Retrospective registry analyses and trial substudies, as well as small randomized trials in which management decisions were based on coronary CTA with FFR_{CT}, have demonstrated that non-ischaemic FFR_{CT} results are associated with a favourable prognosis.^{52–54} In patients with intermediate-range coronary stenosis, FFR_{CT} 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 invasive coronary angiography (ICA) and possibly intervention may be

Supplementary Table I Pressure-derived^a wire-based indexes to invasively measure haemodynamic stenosis severity

		Indexes	Validation	Diagnostic accuracy (%)	+LR	-LR	References
Diagnosis	Hyperaemic	FFR	Exercise ECG, thallium scintigraphy, DSE	93	88	0.12	61
			CMR	92	11.72	0.09	62
		FFR	H ₂ ¹⁵ O-PET	-	4.5	0.23	63
		FFR	¹³ N-PET	73.9	2.9	0.38	64
		cFFR	FFR	85.8	16.13	0.25	65
	Non-hyperaemic	iwFR	FFR	80.4–82.5	4.48–5.98	0.26–0.31	66,67
			¹³ N-PET	71.3	2.47	0.4	64
		Pd/Pa	FFR	81.5	6.41	0.27	66
			iwFR	93	16.32	0.09	68
			¹³ N-PET	74.8	3.03	0.37	64
		dPR	FFR	78	8.57	0.43	69
			iwFR	98	99	0.08	69
RFR	FFR	81.3	4.38	0.24	70		
	iwFR	97.4	94.5	0.06	70		
Prognosis		Comparator	Study design	Clinical benefit			
	Hyperaemic	FFR	Angiographic guidance, medical therapy	Superiority	MACE, spontaneous MI, urgent revascularization (5 years)		71–78
	Non-hyperaemic	iwFR	FFR guidance	Non-inferiority	MACE (1 year)		79,80
		Pd/Pa	-	-	-		-
		dPR	-	-	-		-
		RFR	-	-	-		-

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cFFR = contrast fractional flow reserve; CMR = cardiac magnetic resonance; dPR = diastolic pressure ratio; DSE = dobutamine stress echocardiography; ECG = electrocardiogram; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; +LR = positive likelihood ratio; -LR = negative likelihood ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; NHPI = non-hyperaemic pressure-derived indexes; Pd/Pa = coronary pressure to aortic pressure ratio; PET = positron emission tomography; RFR = resting full-cycle ratio.

^aOnly indexes derived from pressure measurements are included, and their diagnostic accuracy is compared with abnormal results by either non-invasive functional testing or FFR as the reference standard. FFR has the highest diagnostic accuracy. The NHPIs all have good diagnostic accuracy. Of note, Pd/Pa, dPR, and RFR have a high positive likelihood ratio (>10) and low negative likelihood ratio (<1) in predicting abnormal iwFR results, suggesting a class effect. This class effect of all NHPIs has been reflected in a recent change in the 'Appropriate use criteria for coronary revascularization in patients with stable ischaemic heart disease of the ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS' (American College of Cardiology/American Association for Thoracic Surgery/American Heart Association, American Society of Echocardiography/American Society of Nuclear Cardiology/Society for Cardiovascular Angiography and Interventions/Society of Cardiovascular Computed Tomography/Society of Thoracic Surgeons).⁸¹

needed.^{55,56} In a randomized study comparing coronary CTA with FFR_{CT} and ICA, CTA with FFR_{CT} was suitable for diagnosing and guiding revascularization in patients with advanced multivessel CAD.^{57,58} Prospective outcome trials comparing coronary CTA plus FFR_{CT} to alternative forms of non-invasive testing are currently not available.

Stress CT myocardial perfusion imaging can be performed with various protocols, and has a sensitivity of 88% and specificity of 80% in comparison with invasive FFR,²⁴ but has not been validated in prospective studies.

1.7 Hybrid imaging techniques

Hybrid SPECT/CT, PET/CT, and PET/CMR scanners have recently become available. Hybrid imaging enables the combination of coronary anatomy with non-invasive CTA with the detection of myocardial ischaemia by perfusion imaging. Since the previous version of the Guidelines, new diagnostic studies on hybrid imaging for evaluation of CAD have been published, and a meta-analysis of available evidence indicates a higher specificity without a significant decrease in sensitivity compared with single techniques.⁵⁹ However, there is still a need to clarify which patients can benefit from hybrid imaging and how to optimally combine different modalities.⁶⁰

1.8 Invasive coronary angiography

A number of new hyperaemic and resting indexes for physiological assessment have been introduced recently. Available evidence regarding

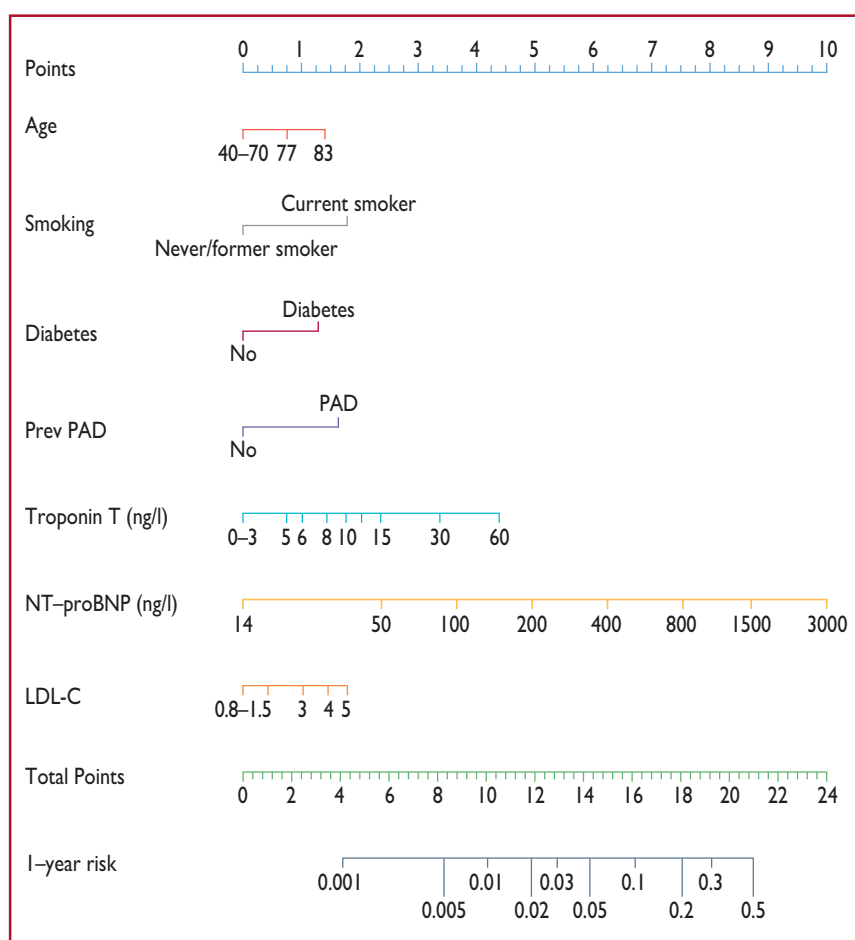
their diagnostic and prognostic power is listed in *Supplementary Table 1*. Most recently proposed indexes have been compared with FFR as the standard to test physiological equivalence. Prospective outcome trials are available for FFR and instantaneous wave-free ratio (iwFR).

1.2 Assessment of risk

1.2.1 Event risk stratification using clinical evaluation

Scores that apply clinical parameters have been shown to predict outcomes among patients with chronic CAD. Moreover, if the clinical parameters are complemented by biomarkers, such a risk score may be even more accurate. Recently, a biomarker-based risk model to predict cardiovascular mortality in patients with stable CAD was developed from a randomized trial cohort of 13 164 patients and externally validated in a cohort of 1547 patients.⁸² The three biomarkers found to be of greatest importance were N-terminal pro-B-type natriuretic peptide, high-sensitivity cardiac troponin T, and low-density lipoprotein cholesterol. The final prediction model included age (A), biomarkers (B), and clinical variables (C) (see *Supplementary Figure 1*). The ABC-CHD (coronary heart disease) model had high discriminatory ability for cardiovascular death (c-index of 0.81 in the derivation cohort and 0.78 in the validation cohort).

A 12 lead ECG should be a part of risk stratification in every patient to delineate heart rhythm and heart rate, to detect changes suggestive of silent ischaemia/infarction, and to discern abnormalities



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Supplementary Figure 1 The ABC-CHD score calculator. CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAD = peripheral artery disease; Prev = previous.

in the specific electrocardiographic segments (e.g. PR, QRS, and QT intervals).

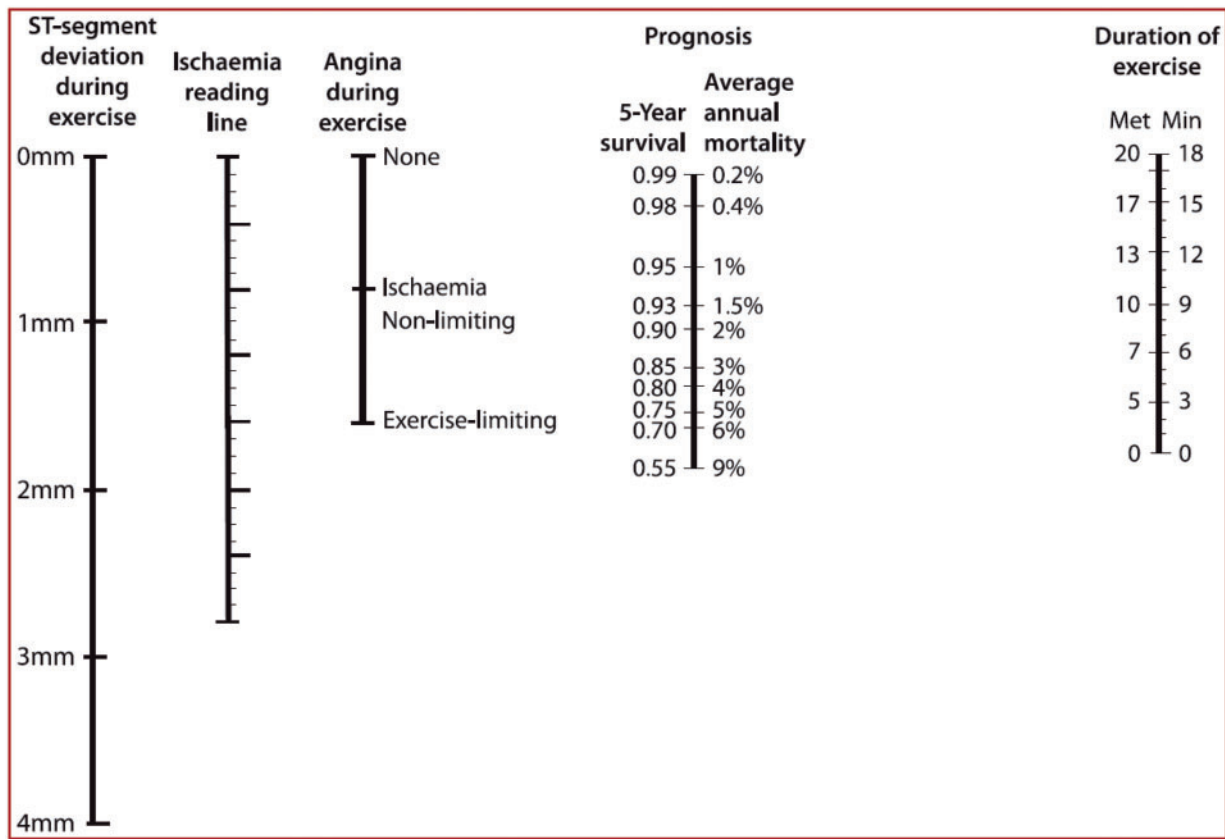
1.2.2 Event risk stratification using ventricular function

The strongest predictor of long-term survival is LV function. In patients with CCS, mortality increases as left ventricular ejection fraction (LVEF) declines. In the CASS (Coronary Artery Surgery Study) registry, the 12 year survival rates in patients with ejection fractions ≥ 50 , 35–49, and $< 35\%$ were 73, 54, and 21%, respectively ($P=0.0001$).⁸³ Hence, a patient with an LVEF $< 50\%$ is already at high risk for cardiovascular death (annual mortality $> 3\%$), even without accounting for additional event risk factors such as the extent of ischaemia. As a reduced LVEF $< 50\%$ confers such an important increase in event risk, it may be important not to miss obstructed vessels causing ischaemia in such patients.^{84,85}

Although the likelihood of preserved ventricular systolic function is high in patients with a normal ECG, a normal chest X-ray, and no

history of MI,⁸⁶ asymptomatic ventricular dysfunction is not uncommon.⁸⁷ Therefore, a resting echocardiogram is recommended in all patients with suspected CCS. An echocardiographic study is an excellent diagnostic tool for risk prediction in CCS. It will provide valuable information on valvular diseases and anatomy, in addition to ejection fraction and MI.

Newer diagnostic tools for the assessment of myocardial function have emerging importance. In patients with CAD, 50% of deaths occur suddenly and most of these patients have an ejection fraction $> 50\%$.⁸⁸ Therefore, ejection fraction has limited abilities as a risk marker in these patients. Systolic function can be reduced without a decrease in LVEF, and a global longitudinal strain (GLS) decreased by > 2 SD from the lower normal reference value has demonstrated incremental value in the risk assessment of patients with CCS, especially in those whose ejection fraction is $> 35\%$.^{89–91} The echocardiogram begins with visual assessment and measurement of LVEF, followed by the measurement of GLS if LVEF is normal. A finding of



Supplementary Figure 2 Duke Treadmill Score for risk stratification in chronic coronary syndromes. Nomogram of the prognostic relations embodied in the Duke Treadmill Score.⁹⁷ Determination of prognosis proceeds through five steps. First, the observed amount of exercise-induced ST-segment deviation (the largest elevation or depression after resting changes have been subtracted) is marked on the line for ST-segment deviation during exercise. Second, the observed degree of angina during exercise is marked in the line for angina. Third, the marks for ST-segment deviation and degree of angina are connected with a straight edge. The point where this line intersects the ischaemia-reading line is noted. Fourth, the total number of minutes of exercise in treadmill testing according to the Bruce protocol [or the equivalent in multiples of resting oxygen consumption (METs) from an alternative protocol] is marked on the exercise-duration line. In countries where a bicycle ergometer is used one may—as a rule of thumb—assume the following: 3 METs \approx 25 W, 5 METs \approx 75 W, 6–7 METs \approx 100 W, 9 METs \approx 150 W, and 13 METs \approx 200 W. Fifth, the mark for ischaemia is connected with that for exercise duration. The point at which this line intersects the line for prognosis indicates the 5 year survival rate and average annual mortality for patients with these characteristics.

decreased GLS is a risk marker of mortality and malignant arrhythmias.

1.2.3 Recommendations for risk assessment after diagnostic testing

1.2.3.1 Exercise electrocardiogram

Exercise ECG has been extensively validated for evaluation of event risk in CCS patients. The occurrence of ST-segment depression coupled with exertional angina at a low workload is associated with a high risk of cardiovascular mortality. Exercise capacity is also a strong prognostic indicator.^{92–94}

The prognosis of patients with a normal exercise ECG and a low clinical risk for severe CAD is excellent (annual rate of cardiac death or MI is <1%).⁹⁵ The Duke Treadmill Score (*Supplementary Figure 2*) is a validated tool for the identification of patients with a high event rate (>3% annual rate of cardiovascular death)⁹⁶ (<http://www.cardiol.org/tools/medcalc/duke/>).

1.2.3.2 Rest and stress echocardiography

An echocardiographic study is an excellent diagnostic tool for risk prediction for CCS patients. It provides valuable information on valvular diseases and anatomy, in addition to ejection fraction and myocardial function. Newer diagnostic tools for the assessment of myocardial function have emerging importance. Stress echocardiography is a very effective diagnostic tool for risk prediction and stratifying patients with CCS.⁹⁸ The risk of future events increases with the extent and severity of inducible wall motion abnormalities. Even in patients with apparently normal myocardial function at rest, findings of inducible wall motion abnormalities in ≥ 3 of the 16 segments of the standard LV model should be regarded as indicative of high event risk (corresponding to an annual mortality >3%).^{99,100} The prognostic value of inducible myocardial ischaemia together with other clinical risk markers is excellent.^{11,101} Exercise echocardiography has a high negative predictive value for primary and secondary cardiac events.¹⁰² A normal stress echocardiogram yields an annual risk of <1%, similar to that for a normal stress myocardial perfusion scan.¹⁰³ Stress echocardiography has the advantage of being able to identify the location of ischaemia and should therefore be preferred to an exercise ECG.

1.2.3.3 Single-photon emission computed tomography

Myocardial perfusion imaging using SPECT is a well-documented method of non-invasive risk stratification for CCS patients.¹⁰⁴ The prognostic value of inducible myocardial ischaemia together with other clinical risk markers is excellent. Large stress-induced perfusion defects, defects in multiple coronary artery territories, transient post-stress ischaemic LV dilatation, and increased lung uptake of perfusion tracer in post-stress images are adverse prognostic indicators.

A stress-induced reversible perfusion deficit $\geq 10\%$ of the total LV myocardium has been reported across a number of prognostic series to denote moderate-to-severe ischaemia associated with a high event rate in CCS patients (annual rate of cardiovascular death or MI >3%).¹⁰⁵ Based on observational studies, these patients may benefit from ICA and revascularization.^{84,106} The ongoing randomized ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial¹⁰⁷ will provide further

information on whether an initial invasive strategy in addition to optimal medical therapy in patients with CAD, and at least moderate inducible ischaemia, improves outcomes. A normal stress perfusion study is associated with a low ($\leq 1\%$ per year) subsequent rate of cardiac death and MI.⁹⁵

1.2.3.4 Positron emission tomography

The extent and severity of myocardial ischaemia on PET myocardial perfusion imaging has also been well validated for determining prognosis in patients with CCS, similar to SPECT.¹⁰⁸ Moreover, reduced coronary flow reserve based on quantification of myocardial perfusion predicts high coronary risk, independently of and incrementally to the presence and extent of relative perfusion defects in different patient populations.^{109–111} A normal PET perfusion study is associated with a low ($\leq 1\%$ per year) subsequent rate of cardiac events.^{95,108}

1.2.3.5 Stress cardiac magnetic resonance imaging

CMR is useful for risk prediction and for guidance of revascularization in patients with CCS.¹¹² A comprehensive study including cardiac anatomy, function, perfusion, and viability can be performed. Abnormal stress CMR has shown independent prognostic value in a 5 year follow-up study in patients with suspected CCS.¹¹³ Myocardial ischaemia detected by CMR stress perfusion or dobutamine can identify patients at high risk for subsequent cardiac death and non-fatal MI, with accuracy similar to other functional tests.^{114,115} The detection of myocardial scarring by late gadolinium enhancement CMR in patients without an inducible perfusion abnormality has also been associated with a greater risk of a bad prognosis.¹¹⁶ The prognostic value of a negative stress CMR is similar to that of other functional tests and is associated with a cardiovascular event rate of <1% per year.^{115,117} The number of LV segments with scarring is a predictor of mortality independently of LVEF.¹¹⁸ Novel T1 mapping techniques, showing diffuse scarring and infiltration, might also be promising future tools for risk prediction, but are not yet recommended for clinical use.¹¹⁹

1.2.3.6 Computed tomography

Several prospective registries have shown that an absence of stenoses in coronary CTA is associated with an extremely good prognosis.^{45,46} The large, prospective, randomized PROMISE trial showed that the event rate in patients in whom coronary CTA was used as the first diagnostic test did not differ from that in patients who underwent ischaemia testing as a first test.⁴⁷ In the prospective SCOT-HEART study, CAD event rates were lower in individuals with suspected CAD in whom the initial workup was complemented by coronary CTA.⁴⁸ The trials evaluating outcomes after coronary CTA included mostly patients with a low clinical likelihood.

In addition to visualizing the coronary artery lumen and stenoses, coronary CTA can display coronary atherosclerotic plaque if image quality is adequate. The specific clinical significance of non-obstructive plaque in coronary CTA has not been clarified. Trials and registries have demonstrated a slightly elevated event rate in individuals with non-obstructive coronary atherosclerotic plaque compared with individuals with completely normal coronary arteries on CT.^{120,121} One registry analysis has suggested that the prognostic

benefit of statin therapy is limited to individuals with coronary atherosclerotic plaque, while patients without detectable plaque derive no benefit from statin therapy.¹²² The use of coronary CTA as a risk-stratification tool in asymptomatic individuals is not supported by data as no prospective, randomized intervention studies have been performed to date.

1.2.3.7 Hybrid imaging techniques

Although the data on hybrid imaging are limited, this approach offers the possibility of improving prognostic value. Studies have shown that the coronary calcium score adds incremental prognostic value to perfusion imaging.¹⁰¹ In patients with intermediate coronary lesions, evidence of ischaemia at an anatomically appropriate location is associated with a high event risk after hybrid imaging.^{123,124}

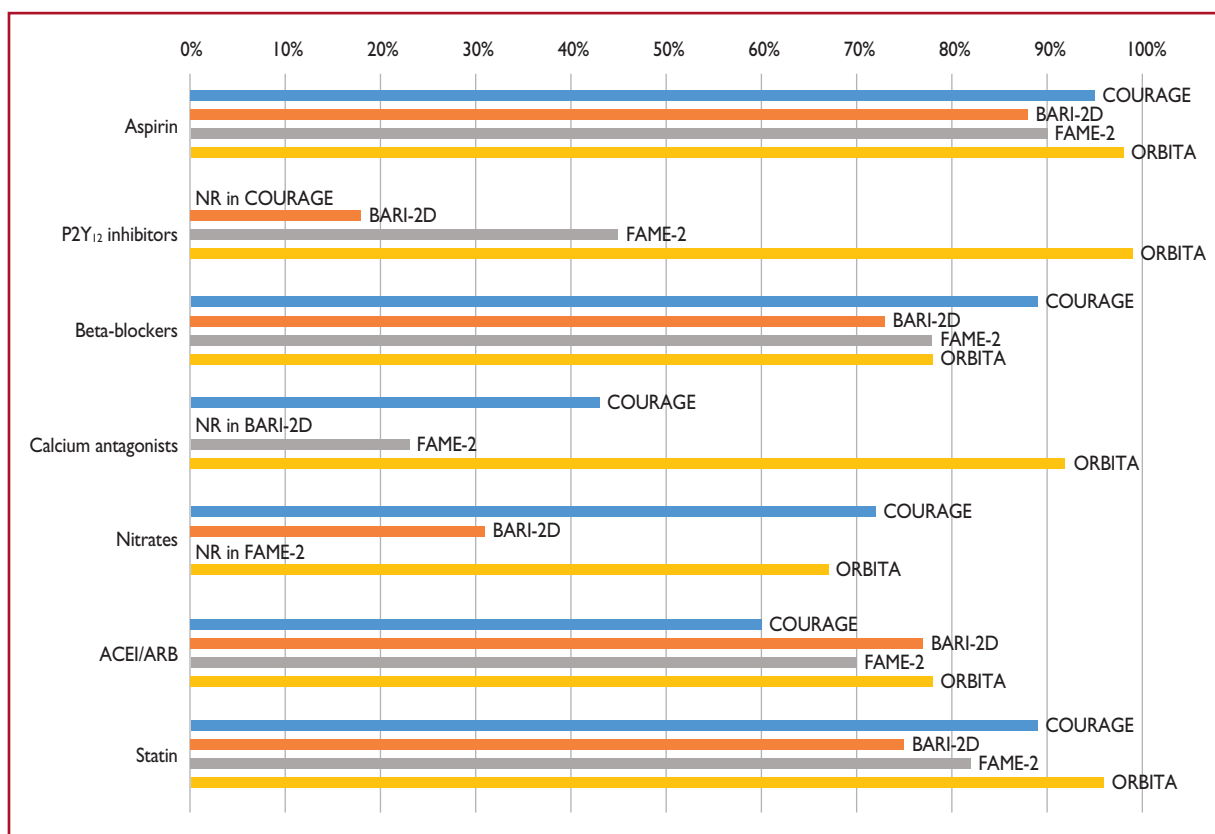
1.2.3.8 Invasive coronary angiography

Despite the recognized limitations of ICA in identifying ischaemia-inducing coronary stenoses and vulnerable plaques, the extent, severity of luminal obstruction, and location of coronary disease on coronary angiography are important prognostic indicators in patients with angina.^{125–127} Several prognostic indices have been used to relate the severity of disease to the risk of subsequent cardiac events; the simplest and most widely used is the classification of disease into one-, two-, or three-vessel, or left main (LM) stem CAD. In the CASS

registry of medically treated patients, the 12 year survival rate of patients with normal coronary arteries was 91%, compared with 74% for those with one-vessel disease, 59% for those with two-vessel disease, and 50% for those with three-vessel disease ($P < 0.01$).⁸³

With the exception of coronary stenoses >90%, which have unequivocally been associated with functional abnormalities, FFR should be performed during ICA in patients with coronary stenosis <90% and inconclusive non-invasive stress testing.¹²⁸ In addition, patient-level meta-analysis and prespecified subgroup analysis of randomized controlled trials have demonstrated an inverse relationship between FFR values, and the risk of clinical endpoints, at 1 and 2 years, respectively.^{129,130} Intravascular imaging techniques (e.g. intravascular ultrasound or optical coherence tomography) have demonstrated good diagnostic accuracy in predicting FFR, especially in stenoses located in the LM, and may be considered to assess LM stenosis severity, especially if further percutaneous coronary intervention optimization is being adopted.^{131,132} In addition, plaque burden, minimal luminal area, and thin-cap fibroatheroma, as defined by virtual histology intravascular ultrasound, were associated with future adverse lesion-specific cardiovascular events.¹³³

1.3 Pharmacological management



Supplementary Figure 3 Pharmacological management in randomized controlled trials comparing percutaneous coronary intervention and medical therapy in chronic coronary syndromes.^{73,134–136} ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BARI-2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME-2 = Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; NR = not reported; ORBITA = Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PCI = percutaneous coronary intervention.

Supplementary Table 2 Mechanisms of action of antianginal drugs

Drugs	Mechanisms of action
Beta-blockers	Beta-blockers reduce heart rate, contractility, and atrioventricular conduction, thus reducing myocardial oxygen demand and time-to-angina onset during exercise. By prolonging the diastolic period, beta-blockers may increase the perfusion of ischaemic areas. Beta-blockers differ with respect to several clinical features, including cardioselectivity (beta ₁ selectivity) and sympathomimetic activity, but their clinical efficacy seems to be equivalent. ¹³⁷ The most used beta-blockers in Europe are those with predominant beta ₁ blockade (e.g. metoprolol, bisoprolol, atenolol, and nebivolol). Carvedilol, a non-beta ₁ -selective beta-blocker, is also frequently used.
CCBs	CCBs act chiefly by vasodilation and reduction of the peripheral vascular resistance. CCBs are a heterogeneous group of drugs that can be classified chemically into the DHPs and the non-DHPs, their common pharmacological property being selective inhibition of the L-channel opening in vascular smooth muscle and in the myocardium. DHP drugs (amlodipine, nifedipine, and felodipine) have a greater vascular selectivity. The non-DHPs (diltiazem and verapamil) decrease heart rate and myocardial inotropism, both effects contributing to their antianginal properties and to their adverse effects.
Nitrates	By means of their active component nitric oxide, nitrates offer angina relief by dilatation of peripheral and coronary arteries, and, mostly, peripheral veins, with corresponding reductions in systemic vascular resistance, coronary blood flow redistribution, and preload. ^{138,139}
Ivabradine	Ivabradine is a heart rate-lowering drug that selectively inhibits the sinus node I _f pacemaker current, thereby decreasing myocardial oxygen demand without an effect on inotropism or BP. ¹⁴⁰
Nicorandil	Nicorandil promotes systemic venous and coronary vasodilation, and stimulates the ATP-sensitive potassium channels of the vascular smooth muscle, with no effect on contractility or conduction.
Ranolazine	Ranolazine is a selective inhibitor of the late inward sodium current, which, at doses of 500 - 2000 mg daily, exerts beneficial effects on angina frequency and exercise tolerance test through inhibition of calcium overload in the cardiomyocytes, without substantial changes in heart rate or BP. ^{141,142}
Trimetazidine	Although no single pharmacological mechanism has been universally accepted, trimetazidine is known to target deranged cellular energetics, particularly in ischaemic myocardial tissue. In persons with diabetes, trimetazidine improves HbA1c and glycaemia. ^{143,144}

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ATP = adenosine triphosphate; AV = atrioventricular; BP = blood pressure; CCB = calcium channel blocker; DHP = dihydropyridine; HbA1c = glycated haemoglobin.

Supplementary Table 3 Major side effects, contraindications, drug–drug interactions, and precautions of anti-ischaemic drugs

Drug class	Side effects ^a	Contraindications	DDIs	Precautions
Short- and long-acting nitrates ^{138,145,146}	<ul style="list-style-type: none"> ● Headache ● Flushing ● Hypotension ● Syncope and postural hypotension ● Reflex tachycardia ● Methaemoglobinaemia 	<ul style="list-style-type: none"> ● Hypertrophic obstructive cardiomyopathy ● Severe aortic stenosis ● PDE5 inhibitors 	<ul style="list-style-type: none"> ● PDE5 inhibitors (sildenafil or similar drugs) ● Alpha-adrenergic blockers ● CCBs 	<ul style="list-style-type: none"> ● Allow a nitrate-free or nitrate-low interval of about 10–14 h with long-acting nitrates
Beta-blockers ^{b 147,148}	<ul style="list-style-type: none"> ● Fatigue, depression ● Bradycardia ● Heart block ● Decreased inotropism ● Bronchospasm ● Peripheral vasoconstriction ● Postural hypotension ● Impotence ● Hypoglycaemia/mask hypoglycaemia signs 	<ul style="list-style-type: none"> ● Low heart rate or heart conduction disorder ● Cardiogenic shock ● Asthma ● COPD caution; may use beta₁-selective blockers if fully treated by inhaled steroids and long-acting beta-agonists ● Severe peripheral vascular disease ● Decompensated heart failure ● Vasospastic angina 	<ul style="list-style-type: none"> ● Heart rate-lowering CCBs ● Sinus node or atrioventricular conduction depressors 	<ul style="list-style-type: none"> ● Diabetes ● COPD

Continued

Supplementary Table 3 *Continued*

Drug class	Side effects ^a	Contraindications	DDIs	Precautions
CCBs ^{146,147} [heart rate-lowering (diltiazem and verapamil)]	<ul style="list-style-type: none"> ● Bradycardia ● Heart conduction defect ● Decreased inotropism ● Constipation ● Gingival hyperplasia 	<ul style="list-style-type: none"> ● Low heart rate or heart rhythm disorder ● Sick sinus syndrome ● Congestive heart failure 	<ul style="list-style-type: none"> ● Negative inotropes (beta-blockers, sodium channel blockers) ● Bradycardic drugs ● CYP3A4 substrates 	<ul style="list-style-type: none"> ● Low BP
CCBs ^{138,147} (dihydropyridines)	<ul style="list-style-type: none"> ● Headache ● Ankle swelling ● Fatigue ● Flushing ● Reflex tachycardia ● Gingival hyperplasia 	<ul style="list-style-type: none"> ● Cardiogenic shock ● Severe aortic stenosis ● Obstructive cardiomyopathy ● Low BP 	<ul style="list-style-type: none"> ● CYP3A4 substrates 	<ul style="list-style-type: none"> ● Hepatic impairment
Ivabradine ^{149,150}	<ul style="list-style-type: none"> ● Visual disturbances (phosphenes) ● Headache, dizziness ● Bradycardia ● Atrial fibrillation ● Heart block 	<ul style="list-style-type: none"> ● Heart rate <70 b.p.m. ● Acute myocardial infarction ● Severe hepatic disease 	<ul style="list-style-type: none"> ● QTc-prolonging drugs ● Combination with strong CYP450 or CYP3A4 inhibitors 	<ul style="list-style-type: none"> ● Age >75 years ● Severe renal failure ● Combination with verapamil or diltiazem ● Not to be used in patients with tachyarrhythmias
Nicorandil ^{146,151}	<ul style="list-style-type: none"> ● Headache ● Flushing ● Dizziness, weakness ● Nausea ● Hypotension ● Oral, anal, or gastrointestinal ulceration 	<ul style="list-style-type: none"> ● PDE5 inhibitors ● Cardiogenic shock ● Acute heart failure ● Low BP 	<ul style="list-style-type: none"> ● PDE5 inhibitors (sildenafil or similar drugs) 	<ul style="list-style-type: none"> ● Non-steroidal anti-inflammatory drugs are not advised in association with nicorandil
Trimetazidine ^{152,153}	<ul style="list-style-type: none"> ● Movement disorders ● Gastric discomfort ● Nausea ● Rash, pruritus, or urticaria ● Headache 	<ul style="list-style-type: none"> ● Allergy ● Parkinson's disease ● Tremors and movement disorders ● Severe renal impairment 	<ul style="list-style-type: none"> ● None reported 	<ul style="list-style-type: none"> ● Moderate renal impairment ● Elderly
Ranolazine ^{154,155}	<ul style="list-style-type: none"> ● Dizziness ● Constipation ● Nausea ● Asthenia ● QT prolongation 	<ul style="list-style-type: none"> ● Liver cirrhosis ● Severe renal impairment ● Moderate or severe hepatic impairment ● Potent CYP3A4 inhibitors ● Class Ia or III antiarrhythmics (other than amiodarone) 	<ul style="list-style-type: none"> ● CYP450 substrates (digoxin, simvastatin, and cyclosporine) and inhibitors (including CCBs) ● QTc-prolonging drugs 	<p>Careful dose titration in patients with:</p> <ul style="list-style-type: none"> ● Mild-to-moderate renal impairment ● Mild hepatic impairment ● Concomitant treatment with CYP3A4 and P-gp inhibitors
Allopurinol ^{156,157}	<ul style="list-style-type: none"> ● Rash ● Gastric discomfort 	<ul style="list-style-type: none"> ● Hypersensitivity 	<ul style="list-style-type: none"> ● Mercaptopurine/azathioprine 	<ul style="list-style-type: none"> ● Severe renal failure ● Consider genotyping for HLA-B*5801 allele in Asians ● Discontinue at the first appearance of skin rash or other signs of an allergic reaction

This list is not exhaustive; refer to the relevant summary of product characteristics for details.

BP = blood pressure; b.p.m. = beats per minute; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; CR = controlled release; CYP = cytochrome P; DDI = drug-drug interaction; HLA = human leukocyte antigen; PDE5 = phosphodiesterase type 5; P-gp = P-glycoprotein.

^aVery frequent or frequent; may vary according to specific drugs within the therapeutic class. Refer to the summary of product characteristics for more details.

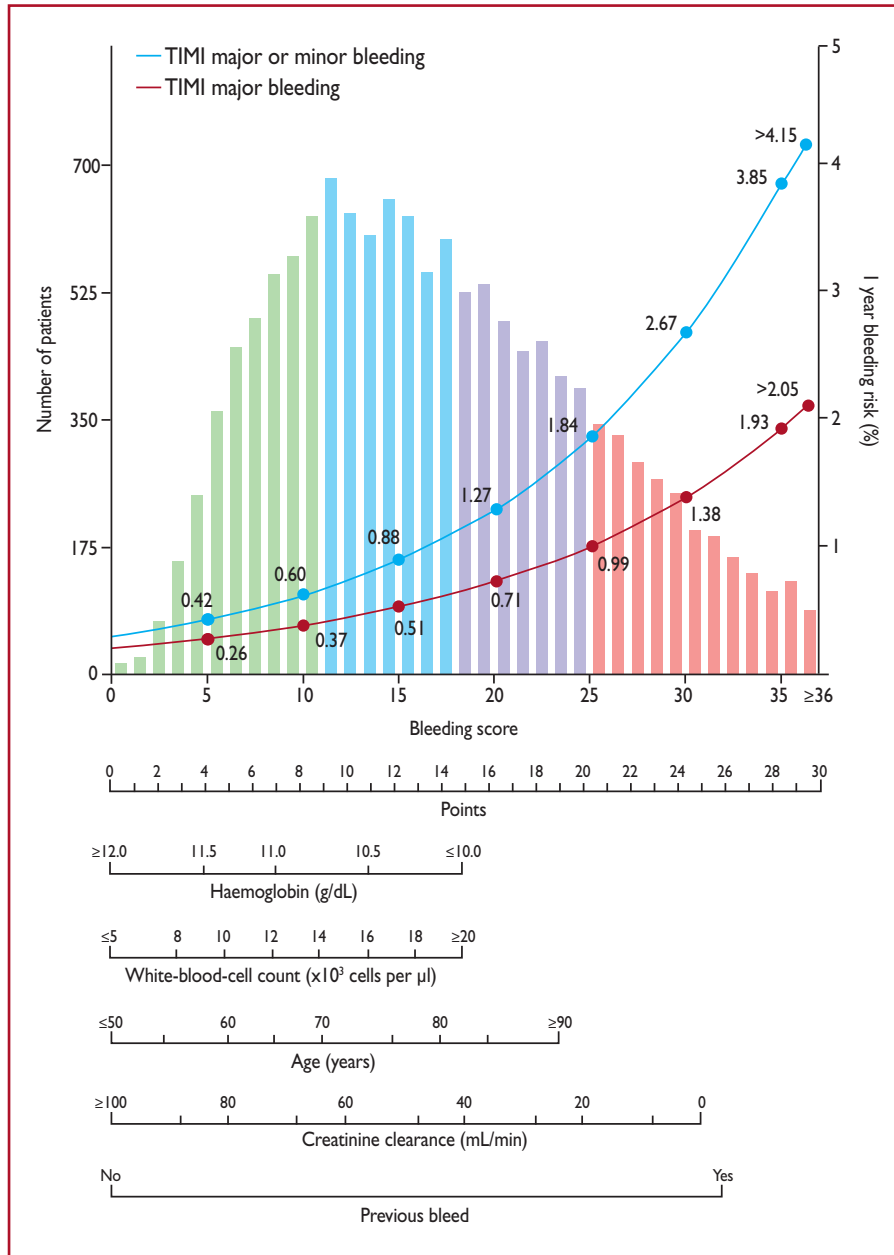
^bAtenolol, metoprolol CR, bisoprolol, and carvedilol.

1.3.1 Event prevention

Evaluation of bleeding risk is an important parameter that should be assessed in CCS patients with high ischaemic risk who might benefit from prolonged and/or intensified antithrombotic treatment. The PRECISE-DAPT (Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet

Therapy) score was validated as a clinical tool to support treatment decisions in patients after stent implantation.¹⁵⁷

Calculation of the PRECISE-DAPT score involves five items (Supplementary Figure 4), and the upper quartile score (≥ 25) is associated with high bleeding risk while on dual antiplatelet treatment.



Supplementary Figure 4 Nomogram for calculation of PRECISE-DAPT score. The upper quartile of the bleeding score (≥ 25) identifies high risk for out-of-hospital TIMI major (red curve), and major or minor (blue curve), bleeding at 1 year post-percutaneous coronary intervention while on dual antiplatelet therapy. TIMI = thrombolysis in myocardial infarction.

1.4 Revascularization

Supplementary Table 4 Characteristics and outcomes of randomized studies of percutaneous coronary intervention vs. medical therapy in patients with stable coronary artery disease

Study	Year	n	SCAD definition	Women ^a	DM ^a	MVD ^a	CCS class II–IV	Comparison	DES	Follow-up	Crossover from MT	Primary outcome (PCI vs. MT)	Secondary outcomes
COURAGE ¹³⁴	2007	2287	≥70% stenosis in ≥1 proximal epicardial coronary artery and objective evidence of myocardial ischemia, or ≥80% stenosis of ≥1 coronary artery and classic angina without provocative testing	15%	35%	70%	56%	PCI (with mostly POBA and BMS) and MT vs. MT	3%	4.6 years (median)	33%	Death or MI: 19.0 vs. 18.5%; P=0.62	<ul style="list-style-type: none"> No significant differences in: (i) death, MI, or stroke; (ii) rehospitalization for ACS; (iii) MI; (iv) death; (v) stroke; or (vi) death or non-procedural MI Less revascularization in the PCI+MT group and less angina throughout most of the follow-up period (but not at 5 years)
COURAGE Extended follow-up	2015									6.2 years (median)	NR	Death: 25 vs. 24%; P=0.77	
BARI 2D ¹³⁵	2009	2368	≥50% stenosis of a major epicardial coronary artery associated with a positive stress test, or ≥70% stenosis of a major epicardial coronary artery and classic angina	30%	100%	NR	NR	Revascularization by PCI (with mostly POBA and BMS) or CABG plus MT vs. MT	35% (PCI stratum)	5.3 years (mean)	42.1%	Survival: 88.3 vs. 87.8%; P=0.97	<ul style="list-style-type: none"> No significant differences in death, MI, or stroke overall and with PCI vs. MT Less death, MI, or stroke, and less MI, with CABG vs. MT
FAME 2 ⁷³	2012	888	At least one stenosis in a major epicardial coronary artery with an FFR ≤0.80	23%	27%	22%	67%	PCI with second-generation DES plus MT vs. MT	100%	7 months (mean)	NR	Death, MI, or urgent revascularization: 4.3 vs. 12.7%; P < 0.001	<ul style="list-style-type: none"> No significant differences in death and MI Less urgent, non-urgent, and any revascularization in the PCI group

Continued

Supplementary Table 4 Continued

Study	Year	n	SCAD definition	Women ^a	DM ^a	MVD ^a	CCS class II–IV	Comparison	DES	Follow-up	Crossover from MT	Primary outcome (PCI vs. MT)	Secondary outcomes
FAME 22 year ⁷⁴	2014									2 years	41%	Death, MI, or urgent revascularization: 8.1 vs. 19.5%; <i>P</i> < 0.001	<ul style="list-style-type: none"> Less angina in the PCI group No significant differences in death or MI Less death, MI, or urgent revascularization at 7 days in the MT group Less death or MI between 8 days and 2 years in the PCI group Less urgent revascularization at 2 years, and between 8 days and 2 years, in the PCI group (including urgent revascularization triggered by MI, ECG changes, or CCS class IV angina)
ORBITA 136	2017	200	At least one angiographically significant lesion (≥70%) in a single vessel that was clinically appropriate for PCI	24%	22%	0%	97%	PCI with second-generation DES plus MT vs. sham procedure plus MT	100%	6 weeks	4%	Exercise time increment between groups (PCI minus placebo 16.6 s, 95% CI: -8.9 to 42.0; <i>P</i> =0.20).	<ul style="list-style-type: none"> No differences in angina frequency, angina stability, physical limitation, and quality of life Significant but trivially higher peak stress wall motion index score with PCI

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ACS = acute coronary syndrome; BARI 2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; BMS = bare-metal stent; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CI = confidence interval; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DES = drug-eluting stent; DM = diabetes mellitus; ECG = electrocardiogram; FAME 2 = Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; FFR = fractional flow reserve; MI = myocardial infarction; MT = medical therapy; MVD = multivessel disease; NR = not reported; ORBITA = Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; SCAD = stable coronary artery disease.

^aProportions are reported for the control group.

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