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CURRENT OPINION

Assessing suspected angina: requiem for coronary computed tomography angiography or exercise electrocardiogram?

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Introduction

Assessment of symptoms in patients with suspected stable angina pectoris forms an important part of the daily clinical activity of most cardiologists. In the presence of very typical symptoms, history taking by an experienced cardiologist may be sufficient to make the diagnosis of stable angina pectoris; however, many patients present with atypical symptoms. Here, testing is necessary to confirm the diagnosis of angina pectoris, to exclude alternative diagnoses and most importantly to risk stratify patients.

During the last decades, the arsenal of diagnostic methods to examine patients with suspected stable angina has expanded enormously. Today, we are able to visualize non-invasively the coronary arteries, and different imaging methods are available for assessing the presence, extent, and severity of myocardial ischaemia. The increasing constraints on healthcare expenditures in the ageing populations in Europe may stimulate healthcare providers to look for the most cost-effective approach in the diagnosis and treatment of ischaemic heart diseases. In the future, cardiologists may become more accountable for prescribing the use of different diagnostic methods, or worse, healthcare providers may introduce managed care schemes that allow only predefined diagnostic algorithms. Healthcare providers in Europe advised by clinical healthcare excellence centres are already considering changing the reimbursement of some diagnostic techniques in cardiology in order to stimulate the practice of more cost-effective methods in the diagnosis of stable coronary artery disease (CAD). Recently, the results of two major clinical trials have been published that compared anatomic imaging by coronary computed tomography angiography (CCTA) with functional imaging by various methods[1] and with standard care[2] in the diagnosis of patients with suspected stable CAD. The imminent changes in healthcare reimbursement of diagnostic techniques and the new evidence on the use of CCTA in the diagnosis of stable CAD stimulated us to write a clinical opinion paper on the optimal diagnostic and cost-effective approach in patients with suspected stable angina.

Is exercise electrocardiogram still valid as a first-line diagnostic strategy?

Since the initial description of the electrocardiographic features of myocardial ischaemia both during and after standardized exercise testing,[3,4] exercise electrocardiogram (ECG) has become the most widely used investigation for diagnosing angina pectoris. The diagnostic accuracy of exercise ECG testing is, however, hindered by its low sensitivity, moderate specificity, and not infrequent equivocal results. Based additionally on considerations regarding cost-effectiveness, the National Institute for Health and Care Excellence (NICE), UK concluded that ECG testing should not be used for the diagnosis (or exclusion) of stable angina in patients without known CAD.[5] Further NICE recommendations were that direct anatomic assessment using invasive coronary arteriography is more cost-effective in high-risk patients, whereas for patients at intermediate risk, functional imaging for the detection of myocardial ischaemia is advised. At an international level, the latest European Society of Cardiology (ESC) guideline[6] on the management of stable CAD recommends the use of functional imaging over exercise ECG testing in patients at high-to-intermediate risk (66–90% estimated by the CAD consortium prediction rule[7]) and preferably also in patients with low-to-intermediate risk (15–65%), whereas the most recent AHA ACC guidelines[8] recommend the use of exercise ECG as a first-line investigation in all patients with low-to-intermediate pre-test probability (corresponding to

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values between 20 and 70% in the guidelines) who are able to exercise and have no relevant resting ST-T changes.

Although exercise ECG is hampered by a suboptimal sensitivity and specificity for the detection of myocardial ischaemia, in combination with its assessment of exercise capacity, heart rate, and blood pressure response, it provides important diagnostic and prognostic information that can be sufficient for risk stratification in patients at low-to-intermediate probability for having CAD (15–65% based on the CAD consortium prediction rule[7]). In this subset of patients, performing exercise ECG testing alone is more cost-effective than stress imaging with myocardial perfusion scintigraphy. This was demonstrated in the WOMEN trial[9]: in low-risk women who were able to exercise, a diagnostic strategy that used exercise ECG testing alone provided significant diagnostic cost savings (−48%). Moreover, this strategy resulted in similar 2-year post-test clinical outcomes as observed after exercise myocardial perfusion scintigraphy.

Functional imaging by stress echocardiography is a better first-line strategy in patients at intermediate risk

However, patients at high-to-intermediate probability of CAD (66–85%) present a different challenge, as ECG testing will more frequently result in false-negative test results due to its moderate sensitivity. In these patients, where more diagnostic certainty is needed, exercise/pharmacological stress echocardiography could be considered as the investigation of choice since it is performed without any ionizing radiation exposure. In addition to high diagnostic accuracy, stress echocardiography is very effective for stratifying patients according to their risk of subsequent cardiac events. In chest pain patients without a previous history of CAD, it provides independent and incremental prognostic value for the prediction of significant cardiac events, over and above that of clinical, ECG, and stress ECG data by its capacity to accurately assess the extent and severity of the ischaemic burden of the myocardium.[10] Notably, its negative predictive value is also excellent, as patients with a negative test have a very low event rate during follow-up. Use of exercise echocardiography instead of exercise ECG testing may enhance cost-effectiveness for the detection and management of patients with known or suspected stable CAD. In a large retrospective non-randomized observational study in patients with suspected or known CAD referred for the evaluation of chest pain symptoms, exercise echocardiography was more cost-effective than exercise ECG testing. Exercise echocardiography substratified levels of risk more effectively and this resulted in less downstream investigations and less unnecessary invasive coronary arteriographies than performed in the patients screened by stress ECG testing.[11] This was recently confirmed in another study in patients with no previous CAD presenting with suspected stable angina.[12] However, this study was a retrospective analysis of clinical practice that did not use either the Lauer or Duke treadmill score to interpret treadmill exercise tests, and used cost figures from the UK that show a cost ratio for stress echocardiography to treadmill testing that is likely not applicable to other countries.

Although stress echocardiography provides accurate diagnostic and important prognostic information in patients with suspected stable angina, it must also be emphasized that this technique, like other imaging techniques, only does so in the hands of well-trained non-invasive cardiologists with sufficient annual activity to maintain competence with this technique.[13]

Other functional imaging tests for the detection of obstructive coronary artery disease

Exercise myocardial perfusion scintigraphy and exercise echocardiography have similar high sensitivities for the detection of obstructive CAD, but exercise echocardiography has better specificity and, therefore, higher overall discriminatory capabilities.[14,15] Myocardial perfusion scintigraphy markedly improves diagnostic stratification in intermediate risk patients. However, in low-risk patients, it is less cost-effective than exercise ECG testing.[9,16] Also there is an increasing concern about the high radiation exposure during myocardial scintigraphy. In a recent US survey, the average radiation effective dose used during myocardial perfusion scintigraphy was 14.9 ± 5.8 mSv (range 1.4–42.4 mSv) and only 1.5% of participating imaging centres met current guidelines for an average laboratory radiation exposure ≤9 mSv.[17] However, new ultrafast cardiac single-photon emission computed tomography (SPECT) cameras with cadmium–zinc–telluride (CZT)-based detectors allow more frequently stress-only imaging with a marked reduction of radiation dose[18–20] and should therefore preferentially be used.

Stress myocardial perfusion imaging with MRI, computed tomography, or positron emission tomography are most promising innovative methods for the detection and functional assessment of CAD. Compared with invasive coronary arteriography with fractional flow reserve (FFR) measurement, these methods are more accurate in ruling out haemodynamically significant CAD than stress myocardial perfusion scintigraphy and exercise echocardiography.[21]

Diagnostic performance of coronary computed tomography angiography in stable coronary artery disease

The technique of CCTA has evolved significantly over the recent years, effectively allowing non-invasive coronary arteriography. Technological developments have led to a marked reduction in radiation dose; imaging with the first-generation 64-slice CT scanners was associated with radiation doses of 10–20 mSv,[22] whereas with the most recent dedicated CT scanners, low-dose (3–5 mSv)[23] and ultra-low-dose (<1 mSv)[24,25] acquisitions are possible. Coronary computed tomography angiography has superior three-dimensional visualization of the coronary lumen and plaque volume, and a greater sensitivity for coronary plaque composition (non-calcified vs. calcified) compared with invasive coronary arteriography. Further, the improved visualization provided by CCTA allows demonstration of the outward Glagov remodelling of the vessel wall, not appreciated by invasive coronary arteriography.

The diagnostic performance of CCTA is characterized by a very high sensitivity for the detection of coronary stenoses considered significant by invasive arteriography.[26–29] Some initial studies reported a very high negative predictive value approximating 100%[26,27] that led to the proposal that CCTA would be the most effective non-invasive imaging test to exclude obstructive CAD. This was, however, not confirmed by the CORE 64 trial that showed a negative predictive value of only 83%.[28] The divergent findings on the negative predictive value can be explained by differences in CAD prevalence. The negative predictive value is influenced by the pre-test probability of CAD: in study populations with a higher prevalence of CAD, the negative predictive value is much lower.[29] Other considerations exist; the blooming artefact occurring near densely calcified plaque can lead not only to overestimation of the angiographic severity of the coronary stenosis, but also to increasing number of non-assessable coronary artery segments thereby resulting in a decreased specificity and negative predictive value of CT angiography.[30] The negative predictive value of CCTA is highest in patients with a low pre-test probability (<30%) and no or a low-grade coronary calcification (*Table 1*).

Assessing the degree of coronary calcification by performing a calcium score may provide important diagnostic and prognostic information in the assessment of patients with suspected stable angina. In the CONFIRM registry, the majority of symptomatic patients (56%) had a zero calcium score; in those patients, obstructive CAD as detected by subsequent CCTA was present in only 1.36% of the patients, and associated with a very low annual event rate (0.3%).[31] A zero calcium score therefore almost completely excludes CAD in patients with suspected stable angina. This has been acknowledged by NICE in its recommendation to undertake CT calcium scoring instead of exercise testing as the first-line diagnostic investigation and additionally CCTA if the score is between 1 and 400 HU in patients with a low likelihood for stable CAD (10–29%).[5] This approach demands consideration as avoiding additional CCTA in patients with a zero calcium score obviates the need for contrast administration and further exposure to ionizing radiation. On the other hand, almost half of this very-low-risk group will have a calcium >0 HU[31] and will undergo CCTA with a proportion undergoing further investigations, thus rendering this strategy as questionable not the least because of the radiation exposure in this low-risk group.

Is coronary computed tomography angiography a better first-line diagnostic strategy in stable coronary artery disease?

On the basis of a recent meta-analysis, it has been suggested that in patients with a low-to-intermediate likelihood of CAD CCTA could

Table 1 Diagnostic performance of coronary computed tomography angiography for the detection of ≥50% stenosis on coronary angiography in a per patient analysis; effect of coronary calcification and pre-test probability of coronary artery disease

Study	*n*	Prevalence of CAD (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Budoff *et al.* ACCURACY[26]	230	25	95	83	64	99
Meijboom *et al.* Prospective multicentre study[27]	360	68	94	83	48	99
Miller *et al.* CORE 64[28]	291	56	85	90	91	83
Arbab-Zadeh *et al.* CORE 64[30]	371	63	85	90	92	78
Calcium score						
<600 HU	291	56	83	91	92	81
≥600 HU	80	89	96	56	94	63
Gueret *et al.* EVASCAN[29]	746	54	91	50	68	83
By pre-test probability						
CAD						
Low (1–30%)	102	21	86	49	31	93
Intermediate (31–70%)	201	44	87	55	61	84
High (71–100%)	402	69	92	45	79	73
By calcium score						
0	147	21	81	61	36	92
1–100	110	45	82	56	60	79
100–600	70	63	93	50	76	81
≥600	79	81	93	27	85	67

be a more accurate and efficient alternative non-invasive front-line diagnostic technique than conventional exercise ECG and SPECT testing.[32] In this study, a coronary CTA-based strategy was associated with an increased downstream utilization of other diagnostic tests (+38%) and a markedly increased use of coronary revascularization (+163%), but also with a 47% reduction of the risk for non-fatal myocardial infarction when compared with exercise ECG and SPECT-based strategies. Furthermore, in a recent large case-control study, upfront use of CCTA was associated with a 32% reduction in 2-year mortality compared with standard care.[33] Thus, these studies suggested that assessment by CCTA as a front-line investigation instead of functional testing could potentially lead not only to a more accurate and efficient diagnostic strategy, but also to improved clinical outcomes.

These potential benefits as suggested by the authors of the above-mentioned studies have, however, not been confirmed in the recently published randomized PROMISE and SCOT-HEART trials,[1,2] where both studies failed to demonstrate that a strategy of initial CCTA (compared with conventional functional testing) significantly improved clinical outcome, during a 1- to 3-year follow-up period. In the SCOT-HEART trial, the use of CCTA was associated with a 38% reduction in fatal and non-fatal myocardial infarction. Although this effect appears important, it was non-significant most probably due to the very low total number of the events. Indeed, most impressive in both trials was the very low event rate under medical therapy, with the majority of major adverse cardiac events being hospitalization for chest pain. Furthermore, the revascularization rate during follow-up was small in both studies (3–11%). The major implication of both these trials is therefore that patients with suspected stable angina are a low-risk population, and that once an acute coronary syndrome is excluded, the overwhelming majority can be managed with optimal medical therapy with an excellent outcome. The finding that the use of CCTA did not result in significantly improved clinical outcome in both trials was not totally unexpected. This was also observed in the FACTOR-64 trial, where preventive screening for the presence of CAD in asymptomatic higher risk diabetes patients did not reduce the composite rate of all-cause mortality, non-fatal myocardial infarction, or unstable angina requiring hospitalization at 4 years.[34]

Important differences between the PROMISE and SCOT-HEART trials merit further consideration. First, the patients in the PROMISE trial who were randomized into the initial functional testing strategy were subjected to an overall cumulative radiation dose (10.1 $\pm$ 9.0 mSv) that was almost as high as that used in the group of patients randomized to the CCTA first strategy (12.0 $\pm$ 8.5 mSv; $P < 0.001$ vs. functional testing). The relatively high radiation exposure in the functional testing group was mainly related to the use of nuclear stress testing in 67% of the patients. This practice was in sharp contrast to the SCOT-HEART trial where 85% of the patients in the standard care group underwent exercise ECG testing as a first-line investigation, and when further ischaemia testing was performed, only 10% underwent nuclear imaging, and in 33% stress echocardiography was performed. The low use of functional ischaemia imaging and heavy reliance on the suboptimal exercise ECG testing first strategy in the SCOT-HEART trial could explain the small, albeit non-significant, improvement in outcome that was observed in favour of the CCTA strategy. This is in contrast to the PROMISE trial where the coronary CT strategy conferred no outcome advantage over functional testing strategy arm in which state-of-the-art stress imaging was used in almost 90% of patients.

Furthermore, in the PROMISE trial, significantly more patients underwent cardiac catheterization and revascularization in the CCTA arm (12.2 and 6.2%) than in the functional test group (8.1 and 3.2%), with additionally more coronary artery bypass graft (CABG) procedures performed in the CCTA group (1.44 and 0.76%) (*Figure 1*). Thus, a diagnostic strategy using CCTA as a front-line test was associated with a 50% increase in invasive coronary arteriography and almost a doubling of subsequent revascularization, including CABG. These findings are completely in line with prior data from Medicare patients in the USA[35] and with those from a recent meta-analysis of studies on the use of CCTA in patients presenting with chest pain in the emergency department.[36] The increased revascularization rate observed in these studies exposes the Achilles heel of CCTA in stable CAD: non-invasive visualization of coronary plaque triggers further invasive testing ending in coronary revascularization. Furthermore, clinicians should also consider whether diagnostic strategies based on CCTA and/or on functional ischaemia imaging with nuclear stress testing as the first-line investigations in a low-risk population (as studied in PROMISE and SCOT-HEART) really respects the ALARA (As Low As Reasonably Achievable) principle with respect to radiation dosage: 23% patients who were assessed by stress echocardiography in the functional testing study group of the PROMISE trial had an exposure (1.3 $\pm$ 4.3 mSv) about 10 times lower than the patients with an CCTA first strategy (12.0 $\pm$ 8.5 mSv; $P < 0.001$) and the patients with a nuclear testing first strategy (14.1 $\pm$ 7.6 mSv; $P < 0.001$). Although the selection process in the PROMISE trial by which the patients were selected for the different diagnostic tests is uncertain, these data suggest that using a functional imaging first strategy by exercise echocardiography instead of CCTA or nuclear stress testing as initial test in the assessment of patients with suspected stable angina pectoris may potentially lead to a dramatic reduction in radiation exposure. This needs, however, confirmation by further clinical studies comparing the different first-line diagnostic tests.

Which diagnostic strategy is most cost-effective?

Given the increasing restrictions imposed on the growth of the healthcare budget in all developed countries, it becomes more and more important to consider the cost-effectiveness of diagnostic and therapeutic strategies. The diagnostic performance and comparative cost-effectiveness of the exercise ECG and non-invasive imaging tests in patients with suspected stable angina have been extensively studied. Most analyses suggest that CCTA is a cost-effective method to rule out CAD in patients with a low-to-intermediate (<50%) pre-test probability of disease and could be used as a gatekeeper for invasive coronary angiography.[37–42] Although anatomical imaging may be sufficient as the initial diagnostic test in low-to-intermediate risk patients (15–50%), it is clear that additional functional ischaemia testing provides incremental information that allows more accurately the determination of the haemodynamic significance of the visualized

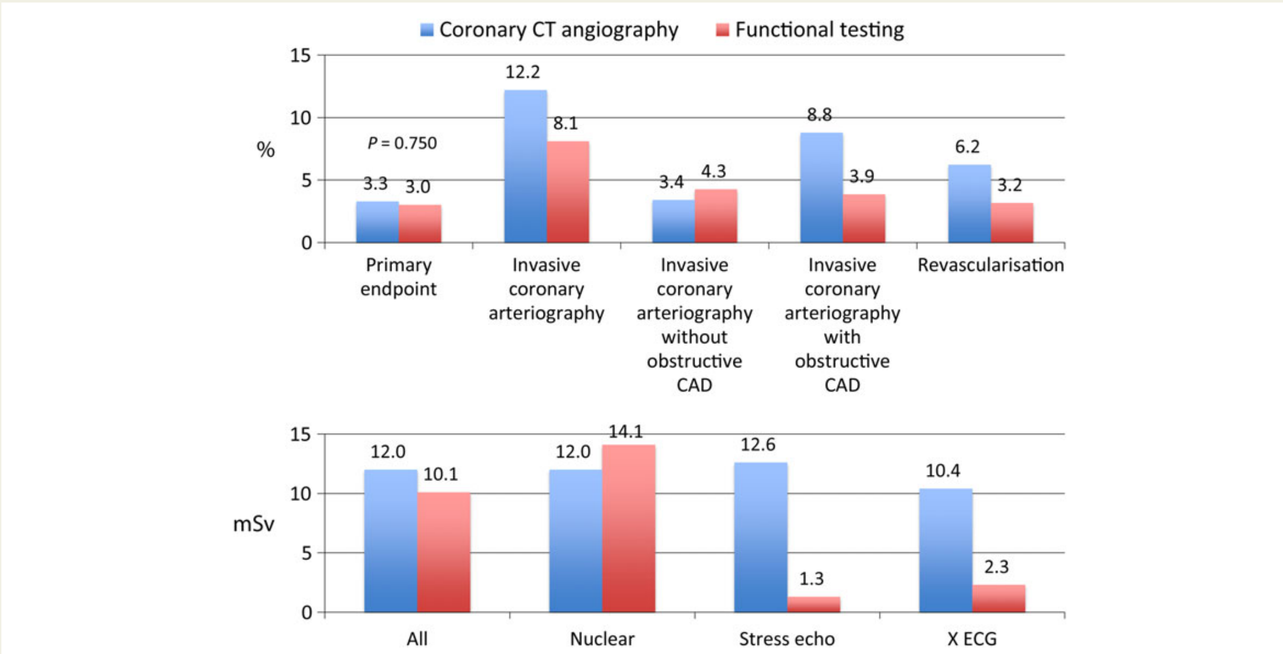

Figure 1 Clinical endpoints and mean exposures to ionizing radiation in patients included in the PROMISE trial. Top panel: a strategy of initial coronary computed tomography angiography, when compared with functional testing, did not result in an improved outcome over a median follow-up of 2 years for the composite primary endpoint (death, myocardial infarction, hospitalization for unstable angina, or major procedural complication). Although coronary computed tomography angiography resulted in lower number of invasive coronary arteriographies without obstructive coronary artery disease, the total number of heart catheterizations and coronary revascularizations were higher than in the functional testing study group. Bottom panel: the overall radiation exposure was higher with initial coronary computed tomography angiography and lowest in the functional-testing group patients in whom stress echocardiography was used. CAD, coronary artery disease; X ECG, ECG exercise stress test. Modified from Douglas *et al.*[1]

stenoses, improves prognosis, and optimizes the need for coronary revascularization.[43,44]

The cost-effectiveness of various diagnostic strategies in patients with suspected stable CAD was recently analysed using a Markov model with sensitivities and specificities based on previous meta-analyses of the literature that does not include the PROMISE trial or the SCOT-HEART trial.[45] This analysis was not corrected for referral bias and must therefore interpreted with great caution.[46] The strategy that maximized quality-adjusted life years (QALY) and was most cost-effective in 60-year-old patients with low-to-intermediate probability of CAD (10–50%) living in the USA or in the Netherlands began with coronary CT angiography, continued with stress echocardiography if angiography found an at least 50% stenosis in at least 1 coronary artery, and ended with catheter-based coronary angiography if stress imaging induced ischaemia of any severity. However, this strategy was expensive (50 000$/QALY and 80 000 Euro/QALY). If the willingness to pay was lower, then stress echocardiography was the most cost-effective strategy. Stress echocardiography was also consistently more effective and less expensive than the corresponding strategies with stress SPECT or cardiac stress MRI. Furthermore, in patients with a pre-test probability of CAD >50%, stress echocardiography was the preferred diagnostic strategy, which is consistent with the most recent ESC guidelines on stable CAD. Of note, strategies with initial exercise ECG followed by further imaging studies if results were positive were less expensive and at least as effective as initial imaging strategies in patients who showed no abnormalities on the rest ECG and were able to exercise.

Should revascularization strategies be based on knowledge of coronary anatomy?

Although attractive in many ways, most studies on the diagnostic performance of CCTA have been undertaken in patients referred for elective catheter-based coronary angiography, which may have induced a selection bias. Further, all studies have used angiographic estimation of the coronary stenosis severity, without the use of haemodynamic testing by FFR measurement. From the FAME trial, we know that there is a poor correlation between anatomic estimate of severity of an intermediate coronary stenosis and its functional significance.[47] With this lesson learned in mind, we should not fall into the same trap again and start to estimate the severity of a coronary artery stenosis anatomically from a non-invasive coronary CT angiogram without assessing its functional significance by stress ischaemia testing. Finally, the studies on the optimal diagnostic and most cost-effective strategy should be interpreted in the context of the recently published prospective PROMISE and SCOT-HEART trials: in the SCOT-HEART trial, a strategy using standard care and CCTA tended to improve the clinical outcome when compared with standard care but at the cost of an increasing number of (in part unnecessary) catheter-based coronary angiographies whereas the PROMISE trial underpinned the importance of a strategy based on functional stress ischaemia imaging as a first diagnostic step in patients with low-to-intermediate probability of CAD as no differences in clinical outcomes between anatomic testing and functional testing was observed.

How does myocardial ischaemia extent impact on the need for revascularization?

In a large single-centre observational registry study (>10 000 patients who underwent stress myocardial perfusion scintigraphy, 1991–97) in stable CAD patients with moderate to large amounts (>10% of the total myocardium) of inducible ischaemia, revascularization was associated with a significant reduction in the absolute and relative risk of cardiac death when compared with medical therapy.[48] Although the ischaemic threshold of 10% ischaemic myocardium is widely quoted, it is important to mention that the same investigators demonstrated in a later published update on a broader study population that the threshold above which early revascularization is associated with a survival benefit actually was higher: ≥15% ischaemic myocardium both in patients without prior known CAD and in patients with stable CAD and a scar ≤10% of the left ventricle.[49]

Yet, in the COURAGE[50] and BARI-2D[51] trials, revascularization by percutaneous coronary intervention (PCI) did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy. Accordingly, in a recent meta-analysis of randomized trials comparing PCI plus optimal medical therapy vs. optimal medical therapy alone in patients with ischaemia based on stress testing or FFR, no mortality benefit was found with PCI.[52] Ancillary imaging studies of the COURAGE[53,54] and BARI-2D[55] trials produced conflicting results on the impact of early revascularization and on the extend and severity of myocardial ischaemia as assessed by myocardial perfusion scintigraphy on clinical outcome. In a first most frequently cited imaging substudy of the COURAGE trial, adding PCI to optimal medical therapy resulted in greater reduction of stress-induced myocardial ischaemia than with optimal medical therapy alone.[53] Patients who showed ≥5% reduction of myocardial ischaemia treated by either PCI and/or optimal medical therapy showed an improved survival with less death or non-fatal myocardial infarctions during long-term follow-up. However, this effect was no longer significant after adjustment for differences in baseline variables and applied therapies. In a second substudy of the COURAGE trial, the relationship between the severity of myocardial ischaemia (SPECT) at baseline and clinical outcome was examined in a much larger series of patients.[54] Notably, the extent of myocardial ischaemia did not predict clinical outcome and the addition of PCI to optimal medical therapy had no beneficial effect either on mortality or on the incidence of non-fatal myocardial infarction. The imaging substudy of the BARI-2D trial demonstrated results similar to those of the second COURAGE substudy.[55] Indeed, patients randomized to revascularization exhibited less stress perfusion abnormalities at 1-year follow-up than patients treated with intensive medical treatment. More extensive and severe stress myocardial perfusion abnormalities at 1 year were associated with higher 5-year rates of death and a combined endpoint of cardiac death or myocardial infarction. However, the risk for cardiac death during long-term follow-up was more related to the presence and extent of scarred myocardium rather than myocardial ischaemia.

The intuitively logical and widely applied current strategy to revascularize all stable CAD patients with extensive myocardial ischaemia does not therefore stand on solid grounds.[56] The resulting on-going debate[57–59] as to whether the ischaemia burden effectively identifies patients who will have a lower risk of death or myocardial infarction using a strategy of routine revascularization will be hopefully solved by the ISCHEMIA trial (ClinicalTrials.gov NCT01471522). In this trial, stable CAD patients with moderate-to-severe myocardial ischaemia will be randomized to either optimal medical therapy or revascularization with optimal medical therapy. Follow-up will be for 4 years, with a composite endpoint of cardiovascular death or myocardial infarction. Different from previous randomized trials, randomization will be performed before the coronary anatomy is known, thus excluding a possible selection bias in favour of revascularization.

The importance of optimal medical therapy cannot be minimized even if revascularization is performed. A recent analysis of the SYNTAX trial showed that optimal medical therapy is often underused in patients with complex coronary disease requiring coronary intervention with PCI or coronary bypass surgery.[60] Suboptimal medical therapy after revascularization was associated with adverse clinical outcomes, including death, myocardial infarction, and stroke. After 5 years of follow-up, the treatment effect with optimal medical therapy was even greater than that obtained by the initial revascularization.

Conclusion

In summary, there is currently no evidence from prospective randomized trials that in patients with chest discomfort and with a low-to-intermediate risk for suspected stable CAD (15–65%), an initial anatomical assessment results in an improved outcome in the long term. Thus, there is no need to replace functional testing by exercise ECG and preferably in combination with stress echocardiography—with CCTA as the first-line standard investigation in this patient population. Assessment of coronary anatomy should remain the next step in the diagnostic strategy, and can be done either by CCTA if the calcium score is low (<400 HU), or by invasive coronary arteriography. Invasive coronary arteriography via the radial access could be preferred as it can be performed on an ambulatory basis, with high patient comfort and at low bleeding complication rates. Moreover, invasive coronary arteriography allows additional assessment of the functional impact of epicardial coronary atherosclerosis (either focal or diffuse) and of any microvascular dysfunction, with the use of intracoronary pressure or/and Doppler guidewires at baseline and after pharmacological stimulation. Furthermore, many patients with chest discomfort and suspected stable angina have normal epicardial coronary arteries or non-obstructive lesions.[61] Anginal symptoms in those patients can be explained by abnormal diffuse epicardial coronary vasoconstriction related to endothelial dysfunction[62] and/or vascular smooth muscle

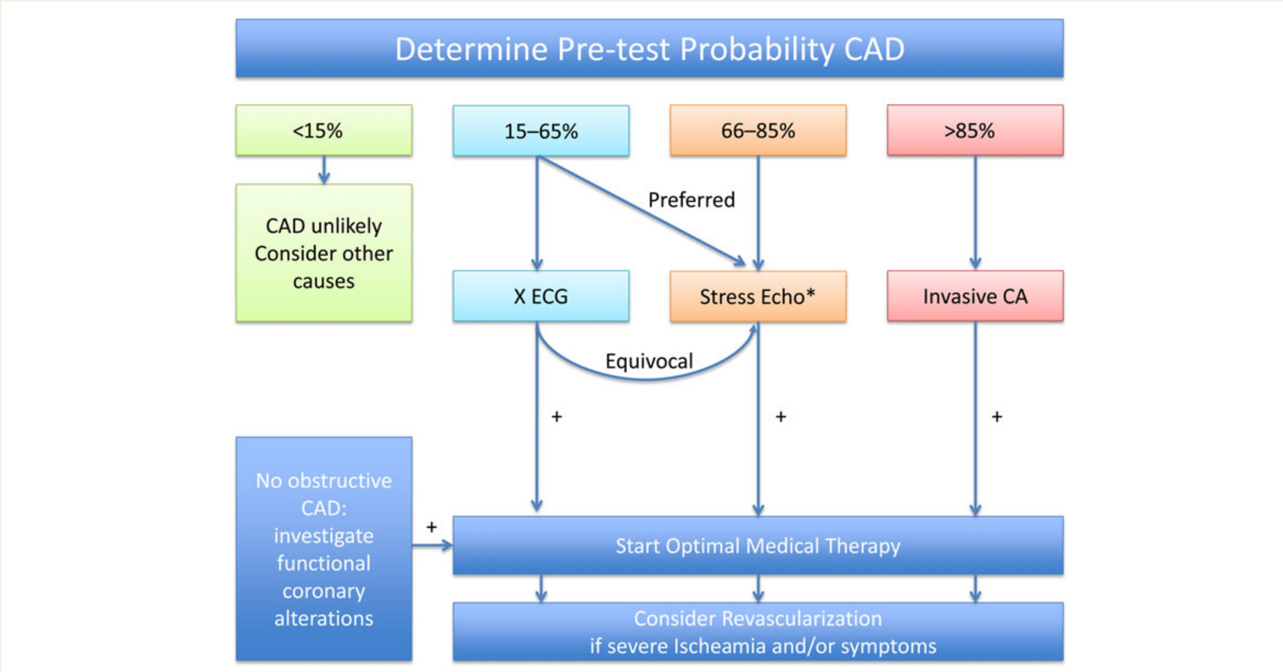

Figure 2 Initial diagnostic management of patients with suspected angina pectoris. The process begins with clinical assessment of the pre-test probability that stable coronary artery disease is present using the Coronary Artery Disease Consortium prediction rule.[7] In patients with a pre-test probability <15%, no further testing is necessary. Functional ischaemia testing by stress echocardiography is the preferred diagnostic method in patients at intermediate risk (pre-test probability 15–85%). Exercise electrocardiogram testing can be sufficient in patients with a low-to-intermediate risk (pre-test probability 15–65%) who are able to exercise. However, further evaluation by stress echocardiography should always be performed in patients with equivocal results after exercise electrocardiogram testing. In patients with a high-risk probability, the clinical diagnosis of angina can immediately be confirmed by invasive coronary arteriography. If no obstructive coronary artery disease is found, further investigation for functional coronary alterations should be considered. *Myocardial perfusion imaging by single-photon emission computed tomography is a valuable alternative if stress echocardiography cannot be performed. Taking into account the As Low As Reasonably Achievable principle, myocardial perfusion imaging is preferably performed using stress-only protocols on ultrafast modern single-photon emission computed tomography scanners.

hyper-reactivity, or much more frequently by microvascular dysfunction.[63] In these patients, invasive coronary arteriography can be completed by intracoronary acetylcholine provocation testing, which may trigger macrovascular or microvascular coronary spasm.[64,65] If normal coronary arteries are found on CCTA, this pathophysiological mechanism may pass unrecognized, or worse, untreated.

The presence of abnormal coronary vasomotion and/or microvascular dysfunction as possible causes of angina in patients with angiographically near-normal or normal coronary arteries can also be evaluated non-invasively by ergonovine stress echocardiography[66,67] or by Doppler coronary flow reserve measurement.[68]

The take-home message therefore remains: keep listening to the symptoms of your patients; assess your patient for the likelihood and risk of CAD based on symptom characteristics, age, and sex; and look first at the myocardium for myocardial ischaemia preferably by combining exercise ECG testing with stress echocardiography and only thereafter at the coronaries for the presence of obstructive CAD or of abnormal coronary vasomotion (*Figure 2*). If CAD is detected, commence with all measures of cardiovascular risk reduction and implement optimal medical therapy before considering coronary revascularization. Revascularization in patients with stable CAD who are at low-to-intermediate risk should be restricted to those who remain symptomatic in spite of optimal medical therapy. Until the results of the ISCHEMIA trial are known, revascularization in patients who are at higher risk based on the assessment of the extent of ischaemia will remain a matter of debate.

This discussion illustrates that the exercise ECG is not dead at all, but needs to be bolstered with stress echocardiography in selected cases, and CCTA is not yet fully alive.

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