Testing in Patients With Stable Coronary Artery Disease
– The Debate Continues –

Udo Sechtem, MD; Heiko Mahrholdt, MD; Peter Ong, MD; Anastasios Athanasiadis, MD; Tim Schäufele, MD

The major guidelines on stable coronary artery disease recommend revascularizing patients with large areas of myocardium at risk. The algorithms on how to prove that such high risk is present differ considerably. The opinions on the use of coronary CT (calcium scoring and angiography) vary widely. This review aims to summarize the recommendations of the major guidelines, commenting on differences between the guidelines and discussing whether extending the role of coronary CT angiography should be considered in the light of new CT data. (Circ J 2016; 80: 802–810)

Key Words: Coronary computed tomography angiography; Echocardiography; Guidelines; Stable coronary artery disease; SPECT

The Feasibility of a Procedure Is Not the Best Indication for Its Performance

(Adapted from Henry Cohen, 1st Baron Cohen of Birkenhead (1900–1977))

Cardiovascular diseases, and especially coronary artery disease (CAD), continue to be the most frequent causes of death, leading to high expenses for healthcare systems. Testing, including various forms of stress testing, is frequently performed in order to predict the presence of stenosing atherosclerotic disease of the coronary arteries and select patients who might benefit from subsequent coronary angiography. Ultimately, the aim is early intervention in the form of coronary revascularization in addition to medical therapy, with the expectation of relieving suffering and improving prognosis. This approach is supported by current European and US guidelines.1,2

The concept described above has been believed and followed over many years. Recently, however, 2 major challenges emerged. First, the ability of noninvasive ischemia testing to identify and appropriately select patients with significant coronary stenosis for coronary angiography has been questioned.3 Second, 2 randomized trials showed that percutaneous coronary intervention (PCI) in symptomatic patients who did not have high-risk CAD on invasive coronary angiography (ICA) did not lead to better results in terms of symptoms and infarct-free survival than medical therapy only.4,5 Even in patients who underwent PCI of vessels shown to cause ischemia, both survival and probability of subsequent myocardial infarction (MI) were not favorably influenced by revascularization.6,7

Over the past years, coronary computed tomography angiography (CTA) has made significant progress both technically and in terms of published experience with clinical application in patients with stable and low-risk unstable CAD. Thus, the currently quite restrictive recommendations for applying coronary CTA to such patients may need some reassessment in the light of new data.

This review will discuss current strategies of identifying patients with stable symptoms potentially caused by CAD. This will include a critical appraisal of the appropriate selection of imaging tests.

What Do the Guidelines Say About Appropriate Testing?

Recent guidelines from the USA and Europe make recommendations on the use of medical testing in patients suspected to have stable CAD.1,2,8 The common goal of the 3 guidelines is to noninvasively identify those patients who should undergo ICA and ultimately coronary revascularization because they are likely to profit in terms of prognosis, while treating medically those who would not necessarily benefit from revascularization. Although the algorithms differ somewhat among the guidelines, all have in common that diagnostic decisions should be made based on the patient’s pretest probability (PTP) of having coronary stenosis. This likelihood depends to a large degree on simple information such as the type of chest pain, age and sex. Patients with severe symptoms should undergo ICA without prior testing, but revascularization should nevertheless be based on the demonstration of regional ischemia using measurement of fractional flow reserve (FFR).

The central diagnostic algorithms of the ESC2 and ACC/
Figure 1. Effect of a focal calcified plaque on the interpretation of coronary computed tomography angiography examination. This 57-year-old woman had dyspnea when climbing 3 flights of stairs. She also had occasional mild resting chest pain. An exercise stress ECG was mildly abnormal (0.1 mV ST-segment depression). Her 64-line coronary computed tomography angiogram showed focal calcification in the left anterior descending (LAD) coronary artery (Panel A with magnification inset) and was read as diagnostic of a significant stenosis in the LAD. Invasive coronary angiography was advised. (Panel B. Left) The grey shadow of linear calcifications next to the LAD (yellow arrow) can be seen on the X-ray image without application of intracoronary contrast material. (Panel B. Right) It is evident that there is no LAD stenosis. Intracoronary acetylcholine testing (Panel C) demonstrated diffuse distal occlusive LAD spasm (Left) associated with her usual chest oppression, indicating an enhanced reaction to the substance, which is often associated with microvascular dysfunction. LAD after intracoronary nitroglycerine is shown on the Right.
AHA guidelines recommend the time-honored exercise ECG or stress imaging or cardiac CT in patients with an intermediate PTP of having a coronary stenosis as the cause of their symptoms. The goal is to identify provokable ischemia or high-grade stenoses and hence come to a diagnosis of obstructive CAD. The definition of intermediate PTP differs among the guidelines. The NICE guidelines on "Chest pain of recent onset" set the level from 10% to 90%, the ESC guidelines from 15% and 85%, and the US guidelines from 20% and 70%.

All 3 guidelines recommend omitting testing in patients with a low PTP. The reason for this is that the likelihood of a false-positive test (potentially leading to ICA) is higher than that of a true-positive test (see addenda to 2013 ESC guidelines under “Related Materials” http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Stable-Coronary-Artery-Disease-Management-of). Instead, these patients should be reassured and observed. There are also differences in the management of patients with high PTPs: whereas NICE and the ESC guidelines consider the diagnosis of obstructive CAD as based just on high PTP, further testing is recommended in the US guidelines.

Recommendations also differ with respect to the tests to be applied in patients with intermediate PTP. Whereas the ESC guidelines do not prohibit the use of the exercise ECG in patients whose PTP is in the lower intermediate range, this technique is strongly recommended in the US guidelines for the same group of patients but no longer considered in the NICE guidelines. Both the ESC and US guidelines recognize the usefulness of the exercise ECG to help with risk stratification when the DUKE treadmill score is used.

Stress imaging is the preferred test mode in the ESC guidelines and the only recommended ischemia test in patients in the higher intermediate range of PTP. No differential recommendations are made with respect to the use of specific imaging techniques. In contrast to the ESC guidelines, the US guidelines restrict the use of stress imaging to patients whose resting ECG is not interpretable and those with a high PTP of obstructive CAD. Pharmacologic stress imaging is recommended for patients who are unable to exercise.

Patients with an intermediate to high PTP can also be tested using CTA. In contrast, the ESC guidelines advise specifically against the use of coronary CTA in these patients! This is because the main problem of coronary CTA is that coronary calcifications appear artificially large (Figure 1), which prevents adequate determination of the degree of obstruction at the site. Thus in patients with a high calcium score (who are often older and male and hence have a high PTP) or focal calcifications, false-positive findings are very frequent and limit the clinical utility of coronary CTA. The only other patients in whom the US guidelines recommend coronary CTA are those who have contraindications to stress testing. In contrast to these rather restricted recommendations for using coronary CTA in the US guidelines, the ESC guidelines suggest coronary CTA as a second-line choice behind stress testing in patients with a PTP in the lower intermediate range (up to 50% pretest probability). This PTP margin was chosen as a surrogate for an upper limit of 400–600 Agatston units beyond which the specificity of coronary CTA drops to unacceptably low levels. The ESC guidelines also stipulate that coronary CT scans in patients suitable for coronary CTA according to PTP yet showing high global focal calcification should be read as “not interpretable”. The NICE guidelines chose to use cardiac CT calcium scoring as a first-line investigation in patients with a low PTP between 10% and 30%. In these patients, absence of calcium indicates that obstructive CAD was likely not the reason for the patient’s symptoms. Intermediate calcium scores between 1 and 400 are recommended to be followed by coronary CTA whereas patients with high calcium scores (>400) are recommended to undergo ICA. Thus, the largest disparities among the 3 guidelines with respect to testing for the presence of obstructive CAD are in the recommendations pertaining to cardiac CT.

In all 3 guidelines considered here, further management and therapeutic recommendations are based on separate risk-assessment algorithms that again are based on test results. The rationale for this is that only high-risk patients (those with large (>10–12.5% of LV) areas of ischemia or those with high-risk coronary anatomy (1–2-vessel disease with proximal left anterior descending (LAD) coronary artery involvement, 3-vessel disease with proximal stenoses and patients with left main stenoses) seem to profit from revascularization. Hence, only patients in whom such high risk is suspected on the basis of noninvasive testing (stress ECG, stress imaging or coronary CTA) or those in whom very severe angina at low workloads limits most activities in daily life or if angina...
persists despite antianginal medical therapy should proceed to ICA and revascularization.

**Problems With the Guideline Approach**

**How Should Pretest Probability Be Calculated?**

The NICE and the US guidelines use the time-honored Diamond-Forrester table for relating angina characteristics, sex and age of the patient to the probability of having obstructive CAD when undergoing ICA. It has, however, been shown that current probabilities are considerably lower because of the declining prevalence of obstructive CAD in the population. Hence, the European guidelines use a more recent database showing lower prevalences than the Diamond-Forrester table. Figure 2 compares the Diamond-Forrester and the ESC PTPs side-by-side. The ESC guideline probabilities are generally

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**Figure 2.** The ESC guideline probabilities are generally lower than the Diamond-Forrester table.

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**Figure 3.** Observed prevalence (blue bars) and expected prevalence (red bars) of angiographically confirmed ≥50% stenotic coronary artery disease (CAD50) in study men (A) and women (B) with no symptoms, nonanginal chest pain, atypical angina, and typical angina. Within each symptom group, each blue bar should be compared with the red bar to its immediate right (asymptomatic patients have no direct comparison). The value above each blue bar is the ratio of observed to expected CAD50 prevalence. (Adapted with permission from Cheng VY, et al.)

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*Figure 3.* Observed prevalence (blue bars) and expected prevalence (red bars) of angiographically confirmed ≥50% stenotic coronary artery disease (CAD50) in study men (A) and women (B) with no symptoms, nonanginal chest pain, atypical angina, and typical angina. Within each symptom group, each blue bar should be compared with the red bar to its immediate right (asymptomatic patients have no direct comparison). The value above each blue bar is the ratio of observed to expected CAD50 prevalence. (Adapted with permission from Cheng VY, et al.)
lower than the Diamond-Forrester values in patients with typical or atypical angina.

Taking the results of the CONFIRM registry as an example, observed prevalences were substantially lower than those predicted by guideline probabilities in the overall population (18% vs. 51% for ≥50% stenoses, P<0.001), driven by pronounced differences in patients with atypical angina (15% vs. 47% for ≥50% stenoses) and typical angina (29% vs. 86% for ≥50% stenoses). These data indicate that the currently used tables for determining PTPs need updating.

Is the Type of Chest Pain Reported by the Patient a Good Indicator of the Prevalence of Obstructive CAD?

Data from the CONFIRM registry also indicate that one of the cornerstones of guideline-directed management may not be as helpful as hoped for. One important assumption is that the kind of chest pain (ie, typical angina, atypical angina or nonanginal chest pain) is directly related to the probability of obstructive CAD being present. Theoretically, typical angina should indicate a high probability whereas nonanginal chest pain should indicate a very low probability of obstructive disease. Yet coronary CTA did not find this to be true. There was only a small difference in the prevalence of obstructive lesions between men and women with typical angina and those who were asymptomatic (Figure 3). This suggests that the recommendations given in the guidelines need reassessment. One caveat needs to be repeated: larger calcifications make it impossible to quantitate the degree of coronary stenosis on coronary CTA images, which may have influenced the results of the CONFIRM registry.

Is Dyspnea an Angina Equivalent Necessitating an Aggressive Search for Obstructive CAD?

Dyspnea is the most prevalent symptom among patients with cardiac and respiratory diseases. It is also an independent predictor of mortality in elderly patients. Is exercise-induced dyspnea a symptom that should raise suspicion that the patient may have CAD?

In a large registry of patients undergoing myocardial perfusion SPECT during stress and at rest the rate of death from cardiac causes and from any cause was significantly higher among patients with dyspnea than among patients with any form of chest pain (typical angina, atypical angina, nonanginal chest pain) or in those with no symptoms at presentation. The percentage of patients with dyspnea in this registry was rather

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*Compares trend in observed prevalence of CAD50 across all symptom categories. †Compares trend in observed prevalence across all decades of age. Patients with dyspnea as the leading cardiac symptom have a prevalence of coronary artery stenoses that is only a little higher than in asymptomatic persons and less than in patients with typical angina. The prevalence is usually lower than in asymptomatic patients who are 10 years older. CAD50, ≥50% diameter stenotic coronary artery disease; CTA, computed tomography angiography. (Adapted with permission from Cheng VY, et al.)
Is There Enough Evidence to Base Therapeutic Decision Making on Ischemia Imaging in Patients With CAD?

The guidelines implicitly assume that the adverse prognosis that is associated with the presence and extent of ischemia is also caused by the ischemia. Indirect evidence that stenoses may just be one determinant, with the extent of coronary plaque being the important other one, for determining the patient’s future course comes from various sources of coronary imaging. Intravascular ultrasound data reveal a strong relationship between baseline and the change in percent atheroma volume and total atheroma volume for major adverse cardiac vascular events. This has also recently been demonstrated by conventional coronary angiography in patients from the COURAGE study. Finally, coronary CTA data support the important prognostic role of diffuse coronary plaque formation. Among patients with nonobstructive CAD, those with extensive plaque experience similar rates of death as those who with obstructive multivessel disease (Figure 4). Thus, the extent of plaque detected by coronary CTA improves risk assessment and this may favor the more liberal use of this technique early in the evaluation of stable patients at risk of coronary events.

The sole focus on stenoses and ischemia has led to the belief that relief of ischemia would lead to an improved prognosis. This concept is mainly based on retrospective data demonstrating that revascularization is associated with better survival in patients with large (approximately >10–12.5% of the LV myocardium) regions of ischemia whereas those with smaller areas have a better outcome when treated conservatively. All 3 guidelines thus recommend conservative treatment of patients without significant ischemia on noninvasive testing. These treatment recommendations acknowledge the low risk for death and MI associated with such a low-risk test, irrespective of the extent of underlying anatomic disease. Patients with mild ischemia up to 10–12.5% should also be preferentially treated conservatively with the option of an...
invasive approach should thus be wished by the treating physician and/or patient after adequate information about advantages and disadvantages. Patients who do not respond adequately to optimal medical therapy should be offered ICA as a second choice. Only patients with large areas of ischemia should preferentially have invasive diagnosis and treatment.

The latter recommendation has spurred some dispute because of the lack of randomized data supporting such an aggressive and expensive therapeutic approach. A meta-analysis of randomized studies, which can be almost called historical now, showed a benefit of coronary artery bypass grafting over the limited options of medical treatment at that time. This evidence only refers to patients with severe anatomic disease (which can be assumed to go together with extensive ischemia) such as left main stenosis or proximal 3-vessel disease or 2-vessel disease involving the proximal LAD. In contrast, more recent studies that included a control group treated by optimal medication according to current standards failed to show a prognostic or quality-of-life benefit of revascularization. There are several meta-analyses of randomized trials all confirming that PCI relief of ischemia does not reduce mortality, cardiac death or MI during follow-up.

The latest randomized trial comparing current optimal medical therapy with ischemia (demonstrated by FFR)-driven PCI could not demonstrate a benefit of the interventional approach with respect to hard endpoints of MI and death. Although significantly fewer patients in the PCI group had urgent or nonurgent revascularizations (10% vs. 40%) during the 1-year follow-up period, that came at the price of having a 100% vs. 0% initial intervention rate in the control group. Ultimately for the same clinical outcome (in terms of hard events) almost 3-folds as many revascularizations had to be performed in the ischemia-driven PCI group as in the medically treated group of patients (110% vs. 40%).

Other recent nonrandomized studies also could not find an advantage of identifying ischemic regions (by cardiac imaging) for guiding revascularization in high-risk patients. Moreover, ischemia shown on stress imaging did not predict improvement of patients (110% vs. 40%).

Conclusions

We need a better understanding of how much testing is cost-effective and yet fulfills the demands of patients and physicians for speedy performance and optimal diagnostic yield and prognostic information. There are several theoretical advantages of using coronary CTA more widely in symptomatic low-risk patients: (1) ruling out any form of coronary disease (no stenoses, no plaques) makes a diagnosis of functional CAD probable and permits initiation of adequate therapy, especially in patients with recurrent symptoms; (2) ruling out significant stenoses >70%, yet demonstrating coronary plaques opens the possibility of intensive secondary prevention treatment; and (3) the few patients with anginal symptoms and significant stenoses can be risk-stratified and some can be sent to have ICA. However, overestimation of coronary obstruction is frequent in patients with calcifications, which may trigger useless additional testing. Such an approach also increases the radiation exposure of large numbers of patients as compared with the traditional European use of ECG exercise stress testing and stress echocardiography. Hence, using coronary artery calcium scoring as a first
step in a more CT-oriented approach, which alone may suffice in a considerable number of patients without coronary calcification,13 should also merit consideration.9 Whatever the final algorithm looks like, it will need prospective testing for practicality, efficacy and cost-effectiveness.

References


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