Review Article

CT as gatekeeper of invasive coronary angiography in patients with suspected CAD

Carlos A. G. Van Mieghem

Cardiovascular Center Aalst, Moorselbaan 164, 9300 Aalst, Belgium

Correspondence to: Carlos A. G. Van Mieghem, MD, PhD, FESC. Cardiovascular Center Aalst, Moorselbaan 164, 9300 Aalst, Belgium. Email: Carlos.Van.Mieghem@olvz-aalst.be.

Abstract: Cardiac CT has been accepted as a valuable diagnostic tool in today's patient care. However, several other noninvasive, in particular, functional diagnostic tests are available on the menu for the ordering clinician and target more or less the same patient population. These tests come with a cost and financial constraints in the present economic environment will no longer allow its indiscriminate use. The gatekeeper function of a diagnostic testing strategy implies that a test is selected judiciously with the aim of preventing access to invasive yet expensive coronary angiography. On the basis of current knowledge, cardiac CT stands a good chance to claim the position of effective gatekeeper to the cathlab.

Keywords: Coronary artery disease (CAD); computed tomography coronary angiography (CTCA); diagnostic test; gatekeeper; invasive coronary angiography (ICA)

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Introduction

Coronary artery disease (CAD) continues to be a major cause of mortality and disability in the 21 century (1). The disease often manifests itself with chest pain but could be fatal even in its first manifestation and occur without warning signals in asymptomatic subjects. The clinician's desire to avoid missing clinically-relevant CAD explains the recent surge in usage of advanced medical imaging. However, this "defensive" approach did not translate into a reduction in cardiac events (2). A cross-sectional, population-based sample of Medicare patients from 1993 to 2001 found that overall hospitalizations for acute myocardial infarction remained flat at 8.7 per 1,000 patients despite significant increases in imaging and revascularization rates (3). The clinician nowadays is equipped with an increasing number of tests for the assessment of individuals who have symptoms suggestive of CAD or for risk-stratifying the asymptomatic individual. However, these tests come with a cost and financial constraints in the present economic environment will no longer allow its indiscriminate use. The gatekeeper function of a diagnostic testing strategy implies that a test is selected judiciously with the aim of preventing access to invasive yet expensive coronary angiography. An effective gatekeeper function is defined when, after the test is performed, patient management is promptly targeted by the noninvasive test findings without the need for additional diagnostic procedures (4,5).

In accordance with current practice guidelines, the diagnostic work-up of suspected CAD is still mainly advocated by the results of noninvasive stress tests (6,7). With the emergence of computed tomography coronary angiography (CTCA) noninvasive access to coronary anatomy has become available and offers a viable alternative to the traditional workup using functional tests. Noninvasive imaging now unravels coronary anatomy in many cases, including asymptomatic subjects, who would normally not undergo invasive coronary angiography (ICA) and changes the gatekeeper function to the cathlab that until very recently was exclusively reserved to noninvasive functional imaging.

CTCA as a robust diagnostic and prognostic test

The diagnostic performance of CTCA in comparison with ICA has been demonstrated in numerous single-center studies and three prospective multicenter trials (8-11). CTCA has a demonstrated 94% to 99% sensitivity and 64% to 83% specificity across a range of disease prevalence and inclusive of patients with both acute and stable chest pain. The 97% to 99% negative predictive value means that CTCA can effectively rule out anatomically significant CAD, which is defined as the presence of at least one 50% or greater coronary artery stenosis.

The prognostic value of CTCA has also been extensively studied (12,13). What becomes clear from these data is that subjects with signs of CAD, also in its early stages, are at higher risk than those who have no coronary plaque. Individuals without evidence of CAD by CTCA have a benign outcome, with annualized cardiac event rates of 0.01% to 0.24%, and this for a long-term period of at least 5 years (14). On the other hand, whenever CAD is present, data from several large clinical registries consistently demonstrate a risk continuum of adverse events with the extent of atherosclerotic disease, without a threshold effect for lumen obstruction or hemodynamically significant CAD (12).

Nonobstructive coronary atherosclerosis: redefining the criteria for CAD and implications for management

Recent clinical practice guidelines support the use of CTCA as a primary or secondary diagnostic option in symptomatic patients with an intermediate likelihood of CAD (6,7). Accordingly, when using CTCA as an up-front diagnostic test, atherosclerosis is often detected during its early stages in "healthy" carriers of the disease or subjects with mild or atypical symptoms. This new terminology of obstructive and nonobstructive plaque challenges existing clinical practice. Indeed, patients who have evidence of CAD, but without inducible ischemia or significant stenosis, are considered low risk for cardiovascular death, and the appropriate use of preventive measures is currently not endorsed by practice guidelines (15). As a result, secondary prevention is less frequently implemented in these patients. However, the demonstration of nonobstructive CAD by means of CTCA may prove to be a valuable tool for the appropriate allocation of preventive therapies such as statin and aspirin. In a recent study, statin therapy was associated with a significantly lower mortality for individuals with atherosclerotic plaque on CTCA, but not for individuals with normal coronary arteries (16). Symptomatic patients assigned to a CTCA strategy in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and Scottish Computed Tomography of the Heart (SCOT-HEART) trials were found to have a trend towards lower rates of myocardial infarction at follow-up than those randomized to functional testing, which is attributed to greater utilization of secondary preventive measures in response to visualizing (mostly nonobstructive) CAD (17,18).

These new insights make it necessary to redefine the criteria to establish the diagnosis of CAD, which date back 50 years when coronary atherosclerosis could only be detected by ICA (19). The old paradigm defined disease based on the simple categorization of presence or absence of obstructive CAD, using the criterium of 50% or greater diameter stenosis by ICA. In the new paradigm, risk from CAD does not abruptly increase with the presence of a stenosis, but reflects the burden of disease on a wide spectrum (20). The risk of myocardial infarction or cardiovascular death is exceedingly low unless disease is detectable by CTCA (21). Patients with limited nonobstructive disease have worse prognosis than patients with normal coronary arteries, but do better than subjects with extensive nonobstructive disease. In patients with extensive nonobstructive disease, risk equals those with single-vessel obstructive CAD. In this newly proposed CAD classification scheme suitable for both conventional and CT angiography assessment, the extent of CAD was classified in stages as follows: stage 0, no coronary atherosclerotic disease by coronary angiography; stage 1, mild coronary atherosclerotic disease: <30% lumen stenosis affecting 1 or 2 vessels; stage 2, moderate coronary atherosclerotic disease: 30–49% lumen stenosis affecting 1 or 2 vessels or mild disease in 3 vessels; stage 3, severe coronary atherosclerotic disease: ≥50% lumen stenosis affecting 1 or 2 vessels or moderate disease in 3 vessels; and stage 4, very severe coronary atherosclerotic disease: ≥50% lumen stenosis affecting 3 vessels, or 2 vessels including proximal LAD, or left main disease. Such CAD stages were directly related to an increasing annual risk of myocardial infarction or cardiovascular death (stage 0: <0.1%; stage 1: 0.1–0.9%; stage 2: 1–1.9%; stage 3: 2–4%, and stage 4: >4%) (20).

Which diagnostic test to use in clinical practice?

Cardiac CT has been accepted as a valuable diagnostic tool in today's patient care. However, several other noninvasive, in particular, functional diagnostic tests are available on the menu for the ordering clinician and target more or less the same patient population. In the present economic environment with limited budgets, the cost-effectiveness of a diagnostic strategy comes into play and it therefore becomes essential to select the appropriate diagnostic test. Several randomized clinical trials have been conducted to evaluate the health outcomes of patients in need of a diagnostic work-up comparing a CT-based anatomic approach with traditional functional tests (17,18,22,23). It turns out that the choice of the diagnostic test does not result in a difference in clinical outcome, leading to the conclusion that a CT-based anatomical and functional strategy is comparable. Pooling of data from these 14,817 patients in a meta-analysis demonstrated two salient features (24). First, selecting cardiac CT as a default strategy was associated with lower rates of myocardial infarction at follow-up than those randomized to functional testing, which is attributed to greater utilization of secondary prevention measures in response to visualizing (mostly nonobstructive) CAD. Second, choosing CTCA as the initial test increased the rate of revascularizations as well as a trend toward more ICAs. Data from another multicentre randomized study, the CRESCENT trial, demonstrated that the use of cardiac CT in clinical practice was at least as effective as the traditional approach using functional testing, but with less downstream diagnostic testing and thus lower cumulative diagnostic costs when following these patients for more than 1 year (25).

The potential for overuse of ICA and revascularizations when using CTCA instead of functional testing is of concern both from a patient (risk of harm in low-risk individuals) and society (higher costs) perspective and has been reported in several studies (24,26). Unfamiliarity with the technique, both its possibilities and limitations, is one possible explanation. More importantly, the practice to directly refer patients with CAD on CTCA for invasive confirmation, finds it origin in the tendency of CTCA to overestimate stenosis severity, or in other words its low positive predictive value (10). In addition, catheter-based confirmation of a significant stenosis on CTCA is often not enough for adequate patient management (27). Once CAD has been identified on CTCA (or ICA), documentation of the ischemic potential of a stenosis becomes important to guide patient therapy (28). Patients with anatomically proven CAD but no evidence of ischemia do well with drug therapy (such as statins and antiplatelet drugs) only. Patients with anatomical disease and evidence of ischemia are in general better off with revascularisation on top of drug therapy (29). Hence, in clinical practice both anatomic and functional data often will be necessary (*Figure 1*). This awareness has been the trigger to assess the functional significance of anatomical disease as detected by CTCA, using different modalities, including the exercise treadmill, single-photon emission computed-tomography, positron emission tomography and CT myocardial perfusion imaging (30-34). One particular and relatively new approach, is the calculation of fractional flow reserve (FFR) from standard CTCA acquisitions using computational fluid dynamics (FFR_{CT}) (35-37). This method allows to calculate FFR at any point in the coronary vascular bed, without the need for additional imaging, modification of image acquisition protocols, additional radiation doses, or medication administration. Preliminary data show that the addition of functional information, using FFR_{CT} data, enables to cut down on the use of ICA, the main driver of costs within the area of CAD (38).

CTCA as gatekeeper to ICA?

Although guidelines recommend the selective referral to ICA based on the results of prior noninvasive stress testing, this approach is not widespread. Currently up to one-third of nonemergent ICAs are being performed in the absence of any sort of noninvasive functional evaluation (39). Even when stress testing is applied more rigorously, up to 40% of ICAs detect normal coronary arteries (40). In a recent study, comparing different noninvasive cardiac imaging tests as gate-keeper versus upfront ICA, ICA was still performed in about 80% of patients in the noninvasive groups (41). The probable explanation is that the use of ICA is driven by ongoing symptoms, in spite of having a normal stress test result. In other words, the characterisation of a patient as low risk is often insufficient to allay concerns of the clinician and/or patient. As a corollary, new strategies are needed to increase the diagnostic yield of cardiac catheterisation in routine clinical practice (40).

Cardiac CT may effectively fill this need as it reliably provides the clinician with essential information, previously unavailable when using noninvasive stress tests. As already alluded to, CTCA easily identifies individuals with nonobstructive CAD, who are at risk of incident myocardial infarction and ischemic cardiac death, and could therefore help to implement effective preventive measures (e.g., statin therapy) in patients with (subclinical) evidence of CAD (16). Unlike stress testing, CTCA is also reliable for the identification and exclusion of high-risk (left main or 3-vessel) CAD (42,43). Real-world data provide ammunition to the view that CTCA serves as an effective gatekeeper to

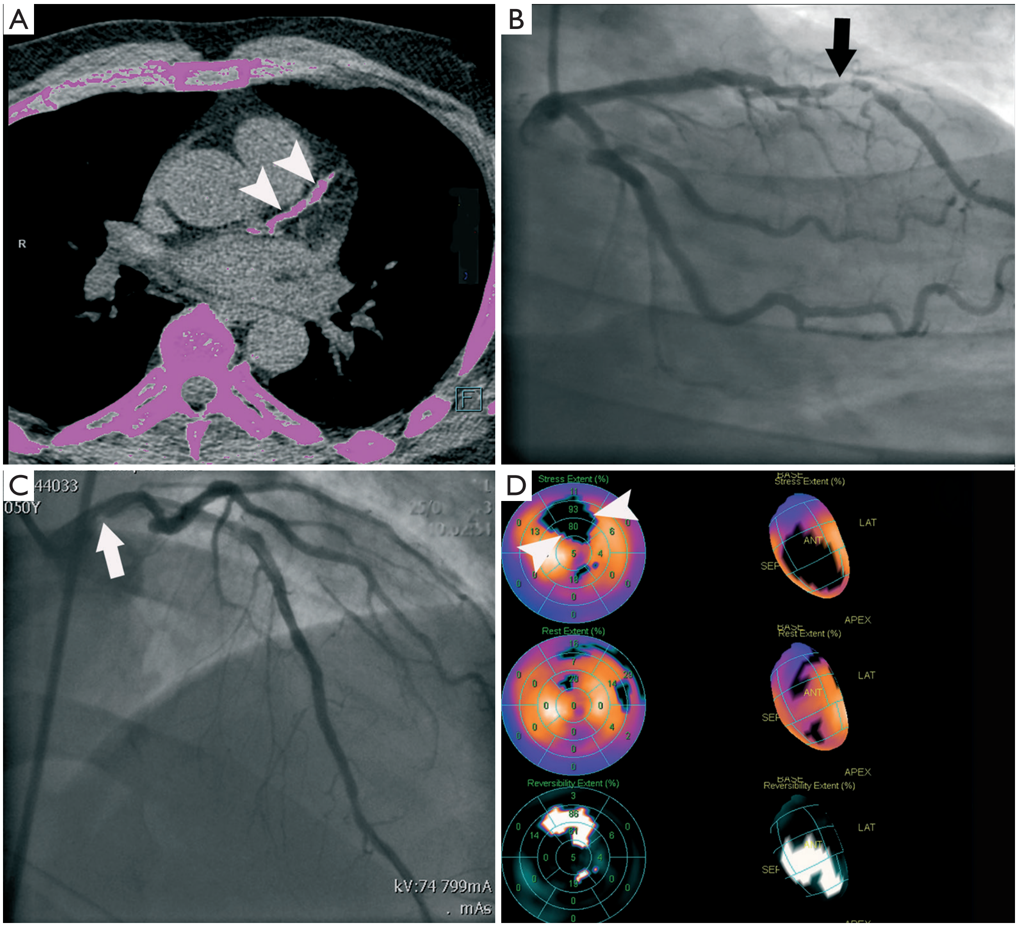

Figure 1 A 50-year-old man presents to the outpatient clinic for a cardiac check-up. He is asymptomatic but shows several cardiac risk factors, including medically treated familial hypercholesterolemia, sedentary life style and a family history of coronary artery disease (CAD). Notably, his younger brother underwent coronary artery bypass graft surgery at the age of 42. When performing a bicycle exercise test, he demonstrates a good exercise capacity of 275 Watts but develops significant depression of the ST-segment up to 1.8 mm at maximal exercise. He subsequently underwent CT coronary angiography to allow better assessment of his coronary risk. A contrast scan was not performed because of the presence of extensive coronary calcifications, notably in the left anterior descending (LAD) territory (A, arrowheads), with a total Agatston calcium score of 1680. In the presence of such extensive calcifications, the likelihood of finding angiographically significant CAD becomes high and it was therefore proposed to proceed with invasive coronary angiography. He demonstrated angiographic disease of the three coronary arteries, including a subtotal stenosis (B, black arrow) of the mid LAD and a 50% stenosis of the left main coronary artery (LMCA) (C, white arrow). Because of proof of ischemia based on the findings of the exercise test and the central localization of the stenosis in the mid LAD, a percutaneous coronary intervention (PCI) with stenting was performed. After stenting of the LAD stenosis, measurement of the fractional flow reserve (FFR) in the LAD turned out to be abnormal (value of 0.79) with an important focal gradient at the level of the LMCA. In addition, single-photon emission computed-tomography performed 2 weeks after stenting demonstrated persistent extensive (summed difference score of 10) and reversible ischemia in the anterior wall (D, arrowheads). Five weeks after the first procedure, a successful PCI of the LMCA was performed. His clinical condition 4 years later is excellent and he demonstrates no residual signs of ischemia on repetitive electrocardiographic exercise testing.

ICA, by demonstrating a reduction in the use of ICA as low as 12% over a 2-year post-test period (5,44).

Conclusions

Over the past two decades CTCA has matured into a valuable diagnostic test in today's patient care. However, many other noninvasive tests are available for assessing the individual with possible CAD and it is anticipated that the emphasis will be placed more than ever on cost-effectiveness of diagnostic testing strategies. The use of CTCA as gatekeeper to ICA looks promising and is further being tested in prospective multicenter studies. Information obtained from functional tests will remain necessary to guide referral for ICA and coronary revascularisation decisions. In any case, it has become clear that the emergence of CTCA has changed existing clinical practice and will have a central role in the future referral pattern of patients to the cathlab. Notably in this respect is the design of the ongoing ISCHEMIA trial (ClinicalTrials.gov number NCT01471522). This prospective large-scale study randomizes 8000 patients with ischemia to an invasive strategy in addition to optimal medical therapy (OMT) versus a non-invasive approach of OMT, with catheterisation and possible revascularisation being reserved for those patients whose medical therapy fails. Acknowledging the limitations of stress testing, all patients will undergo CTCA before ICA to exclude significant left main CAD and confirm obstructive CAD prior to randomization.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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