Noninvasive Imaging Risk Stratification with Computed Tomography Angiography for Coronary Artery Disease

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KEYWORDS

• Coronary stenosis • Coronary imaging • Computed tomography • Cardiovascular risk

KEY POINTS

- The role of Coronary Computed Tomography Angiography (CTA) for the diagnosis and prognosis assessment in coronary artery disease (CAD) still needs definition.
- CTA use is currently indicated for the exclusion of CAD in low-risk patients and in special settings, as coronary total occlusions and bypass grafts.
- Intermediate-risk patients may benefit of the assessment of the ischemic power of coronary lesions of the fusion of functional and anatomic data from CTA.
- Further definition of the impact of CTA as a gatekeeper test before invasive coronary angiography is still warranted.

BACKGROUND

In recent years, the evolution in imaging technology has improved the evaluation of coronary artery disease (CAD). Coronary computed tomography angiography (CTA) has emerged among imaging methods for its high accuracy in visualizing the lumen and wall of the coronary vessels, including a variety of examinations with different degrees of complexity and radiation exposure, from calcium score to the traditional contrast-mediated angiography and even allowing the fusion of anatomic and functional information in the assessment of obstructive coronary stenoses.[1–3]

Although invasive coronary angiography remains the gold standard for the diagnosis and treatment of CAD, previous large-scale registries have shown that almost two-thirds of patients undergoing invasive angiography appear to have normal or nonobstructive disease.[4]

Therefore, a stepwise strategy based on a noninvasive stratification of the patients according to the risk of CAD, and subsequent selective invasive approach in patients with documented ischemia, is currently suggested in guidelines,[5] being associated with similar effectiveness but increased safety, preventing the complications associated with the invasive angiography.

However, the definition of the most accurate diagnostic algorithms comprising CTA as a first-line strategy for ruling out CAD and the correct management of the patients according to the results of imaging tests is still debated,[6] requiring further dedicated studies.

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CURRENT INDICATIONS FOR CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY: THE DEFINITION OF CLINICAL LIKELIHOOD

Clinical evaluation is still the initial diagnostic management of patients with suspected obstructive CAD, aiming at the identification of symptoms and at the definition of a pretest clinical risk of obstructive CAD.

This initial assessment, or clinical likelihood, according to guidelines, is generally based on patients' sex, age, and geographic region. However, the key point in the evaluation of patients with suspected coronary disease is the presence of symptoms that suggest angina.[7] The definition of pretest probability of CAD according to the most recent European Society of Cardiology guidelines is shown in **Fig. 1**.[5] In addition to this primary assessment, cardiovascular risk factors, which are often incorporated in several available scores,[8,9] should be considered in the global evaluation of the cardiovascular risk.

Thus, asymptomatic patients with low pretest probability of CAD (<15%) should generally not undergo further testing.[9] However, in specific settings, as in patients with several cardiovascular risk factors, the assessment of calcium score by coronary CTA has emerged as the most accurate imaging tool for ruling out CAD.[10] Coronary calcium is an early marker of atherosclerotic disease, and coronary calcifications are quickly and easily evaluated by computed tomography (CT) with low radiation exposure and no need for contrast agents.[11] The Agatston score is the most widely used calcium score, and an Agatston score of zero in asymptomatic patients is associated with an excellent prognosis.

Shaw and colleagues[12] showed that an Agatston score of 0 accurately predicted the 15-year overall mortality with an absolute events rate of 3%, and more recent studies found a low prevalence of obstructive CAD (<5%) and low risk of death or nonfatal MI (<1% annual risk) in the absence of coronary calcium. However, coronary calcium imaging does not exclude coronary stenosis caused by a noncalcified atherosclerotic lesion, and although the negative predictive value of a zero calcium score for excluding severe stenosis (on CTA) was 99.5%,[13] in patients with a marked increase of calcium score (>400), an abnormal myocardial perfusion single-photon emission CT (SPECT) was observed only in 31% to 46% of patients.[14–16] The identification of coronary calcium can influence the subsequent management of the patient, allowing a direct second-level complete CTA examination with contrast medium but also an earlier introduction of preventive measures, such as statin therapy and lifestyle modifications[17–19]

Nevertheless, this stepwise approach to CTA is considered but not recommended in guidelines[20] and the protocols for the management of the diagnostic process in asymptomatic patients with incidental detection of coronary calcium are still poorly defined.

In contrast, although patients with a high pretest probability of CAD are better to undergo directly invasive coronary angiography offering the possibility of treatment in the same procedure, further noninvasive testing represents the most appropriate strategy in presence of symptoms and an intermediate probability (15%–85%) of CAD.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY IN SUSPECT OBSTRUCTIVE CORONARY ARTERY DISEASE

For patients with suspected angina and an intermediate pretest probability of CAD, guidelines[5] recommend the use of either a noninvasive functional test of ischemia or anatomic imaging. Debate is still open, attempting to define the strategy that offers the best risk stratification and prognostic benefit. In patients with known CAD, research in ischemia is needed, especially because patients with stents and prior coronary artery bypass grafts are not optimal candidates for CTA.

The recent publication of the data derived from 2 large multicenter randomized controlled trials[21,22] and 2 smaller randomized trials[23,24] significantly

	Angina		Atypical/Dyspnea		Nonanginal	
Age (y)	Men	Women	Men	Women	Men	Women
40–49	22%	X	X	X	X	X
50–59	32%	X	17%/20%	X	X	X
60–69	44%	16%	26%/27%	X	22%	X
>=70	52%	27%	34%/32%	19%	24%	X

Fig. 1. Pretest (PTP) of obstructive coronary artery disease according to age, sex, and the nature of symptoms. Only patients with PTP greater than or equal to 15% and potential indication to coronary CTA are shown.

favored the use of coronary CTA among other imaging modalities in patients with no history of CAD, leading to the present indication as the first-line strategy (class Ia) in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.

The PROMISE[23] (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial randomly assigned more than 10,000 patients to an initial strategy of anatomic testing with the use of coronary CTA or to functional testing. Over a median follow-up of 2 years, there were similar outcomes in the coronary CTA and functional testing groups of patients.[25] More patients in the coronary CTA than in the functional group underwent coronary angiography early after testing (12.2 vs 8.1%) but also 50% of patients previously classified as having an intermediate likelihood of obstructive CAD were reclassified to a low (<15%) risk after CTA evaluation, pointing to a good negative predictive value and prognostic impact of coronary CTA.

The Scottish computed tomography of the heart (SCOT-HEART)[21] trial assessed the use of coronary CTA in a large population of more than 20,000 patients, randomized to standard care or standard care plus CT. At 5 years follow-up, the use of imaging significantly reduced the coronary mortality, without increasing the rate of coronary angiography or coronary revascularization.

Similar results were reported in a subsequent meta-analysis, including the PROMISE[22] and other 2 studies, but not the 5-year SCOT-HEART results,[25] where patients undergoing CTA had a significant reduction in the annual rate of myocardial infarction ($P = .038$) but no difference in all-cause mortality. Most acute ischemic events occur because of the complication of non–flow-limiting plaques,[26] which might be underestimated by the use of a functional test, because they do not induce ischemia, therefore delaying those pharmacologic measures that could prevent major cardiovascular events.[27] In SCOT-HEART, patients assigned to CTA were more likely than patients assigned to standard care alone to have commenced preventive and antianginal therapies and to have undergone earlier coronary revascularization, although only the overall differences in pharmacologic prescribing persisted over 5 years.[21,28] This finding could suggest that CTA can guide the early selection of appropriate patients for both invasive coronary angiography and revascularization and also that earlier onset of treatment in the CTA group prevented downstream longer-term disease progression, whereas the unrecognized disease in the standard care group underwent only more delayed management, often after the occurrence of a major ischemic event.[29]

Therefore, although functional testing is very effective for risk prediction but is unable to exclude CAD, coronary CTA has shown a 94% to 99% sensitivity and a 64% to 83% specificity for the identification of coronary stenosis,[30] with a 97% to 99% negative predictive value to rule out anatomic CAD. Moreover, the exclusion of CAD by coronary CTA offers the unique opportunity to reassure the patients of presenting a very low risk of adverse cardiac events extending over the following 5 years, often referred to as a warranty period. Initial prognostic studies have estimated that the rate of myocardial infarction or cardiac death remains less than 1% per year for at least 8 years,[2] thus potentially avoiding unnecessary downstream hospital visits and investigations,[31] whereas the severity of CAD, as defined by coronary CTA, clearly affected the long-term outcomes, as shown in **Fig. 2**.[31]

However, the anatomic evaluation of coronary lesions presents some limitations, and mainly for nonthigh (50%–90%) stenoses. Coronary obstructions detected by visual inspection are not necessarily functionally significant, and assessing the ischemic power of a lesion represents a key point for establishing the indications for revascularization, even with invasive coronary angiography. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME-2) trial,[32] among patients with stable CAD, PCI was superior to medical therapy alone in the reduction of the primary composite end point at 5 years, when PCI was guided by fractional flow reserve (FFR) to assess the functional ischemic effect of a lesion. Similar conclusions were confirmed by Johnson and colleagues[33] in a subsequent patient-level meta-analysis.

However, the technical limitations of coronary CTA should be acknowledged.[34] For example, irregular heart rate and the presence of extensive coronary calcifications are associated with increased nondiagnostic quality of coronary CTA. To obtain good-quality scans, patients should be in sinus rhythm with a heart rate less than 65 beats per minute and should have good breath holding and collaboration capabilities. In addition, in patients with renal failure, CTA may not be an appropriate choice because of the contrast medium that is needed.[35]

The progressive evolution of CT imaging, allowing high-quality examinations to be obtained with lower radiation exposure and increased accuracy, has partially overcome these technical issues. In the SCOT-HEART trial, the positive results of CTA were confirmed despite the inclusion of those

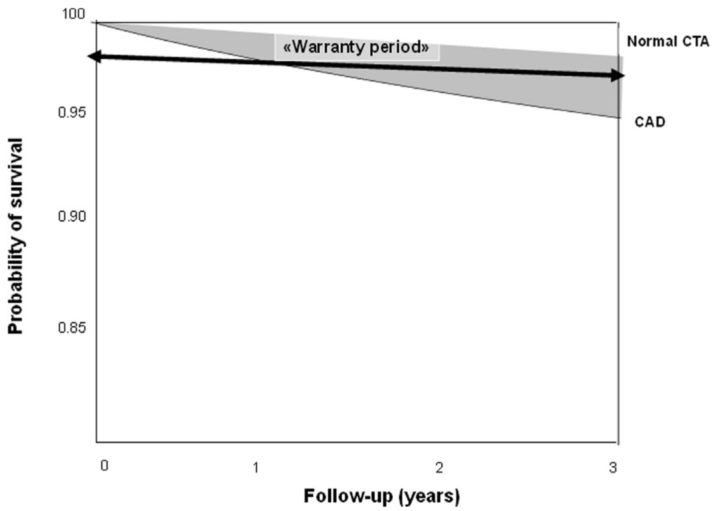

Fig. 2. Unadjusted all-cause 3-year Kaplan-Meier survival by the maximal per-patient presence of normal coronary arteries or obstructive CAD.

patients generally representing the pitfalls of CTA, such as those in atrial fibrillation, with higher body mass index or coronary calcium level.[28]

However, a more tailored approach should be considered in the selection of the noninvasive tests, accounting for the clinical characteristics of the patients and the features of the test, attempting to apply it in those settings where the usefulness of its application is maximal.[5,6] Combination strategies, with the use of multiple noninvasive tests, should be considered in equivocal cases, because both anatomic and functional information are generally required in order to proceed to coronary revascularization (**Fig. 3**).

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY IN SPECIAL SETTINGS

The pressing need for both anatomic and functional data for the assessment of coronary obstructions has led to the progressive development of hybrid technologies, combining the visualization of the coronary vessel by CTA with the evaluation of myocardial ischemia and perfusion. In particular, hybrid imaging with nuclear cardiology imaging (PET or SPECT) combines the high negative predictive value of coronary CTA with one of the most sensitive and specific functional tests.[36] Benz and colleagues[37] showed that a matched combination of a reversible perfusion defect on SPECT in a territory supplied by a coronary artery with CAD on CTA was independently associated with an improved outcome compared with medical therapy alone. In contrast, patients with unmatched findings did not benefit from early revascularization, irrespective of the presence or absence of high-risk CAD.

Another recent acquisition in CT technology is the noninvasive calculation of FFR noninvasively (FFRCT), based on the application of computational fluid dynamics to model and predict FFR from conventionally acquired CTA, without requiring further exposure to radiation or contrast media.[38] Three large multicenter studies (NXT, DISCOVER-FLOW [Diagnosis of Ischemia-Causing Stenoses Obtained Viat Noninvasive Fractional Flow Reserve], and DeFACTO,[39–41]) have compared the accuracy of FFRCT with invasive FFR measurements, and reported sensitivities of between 88% and 90% and specificities between 54% and 90%.[42,43] A meta-analysis of the 3 trials concluded that FFRCT has a pooled sensitivity similar to coronary CTA (0.89 vs 0.89 at per-patient analysis; 0.83 vs 0.86 at per-vessel analysis) but improved specificity (0.71 vs 0.35 at per-patient analysis; 0.78 vs 0.56 at per-vessel analysis),[44] leading to a reduction in the number of unnecessary invasive angiographies.[2]

Another unique opportunity that recently emerged for coronary CTA is the identification of high-risk plaques. An important advantage of coronary CTA is that, in addition to the identification of coronary artery stenosis, it can also assess plaque characteristics, which can be in the form of visual assessment, or more recently using software capable of semiautomated quantitative and qualitative assessment of the plaque.[45] More detailed visual assessment includes the identification of adverse features, including positive remodeling, low-attenuation plaque, spotty calcification, and the so-called napkin-ring sign. These features are associated with markers of histologic vulnerability[46] and with prognosis in several studies, being more frequently observed in patients experiencing

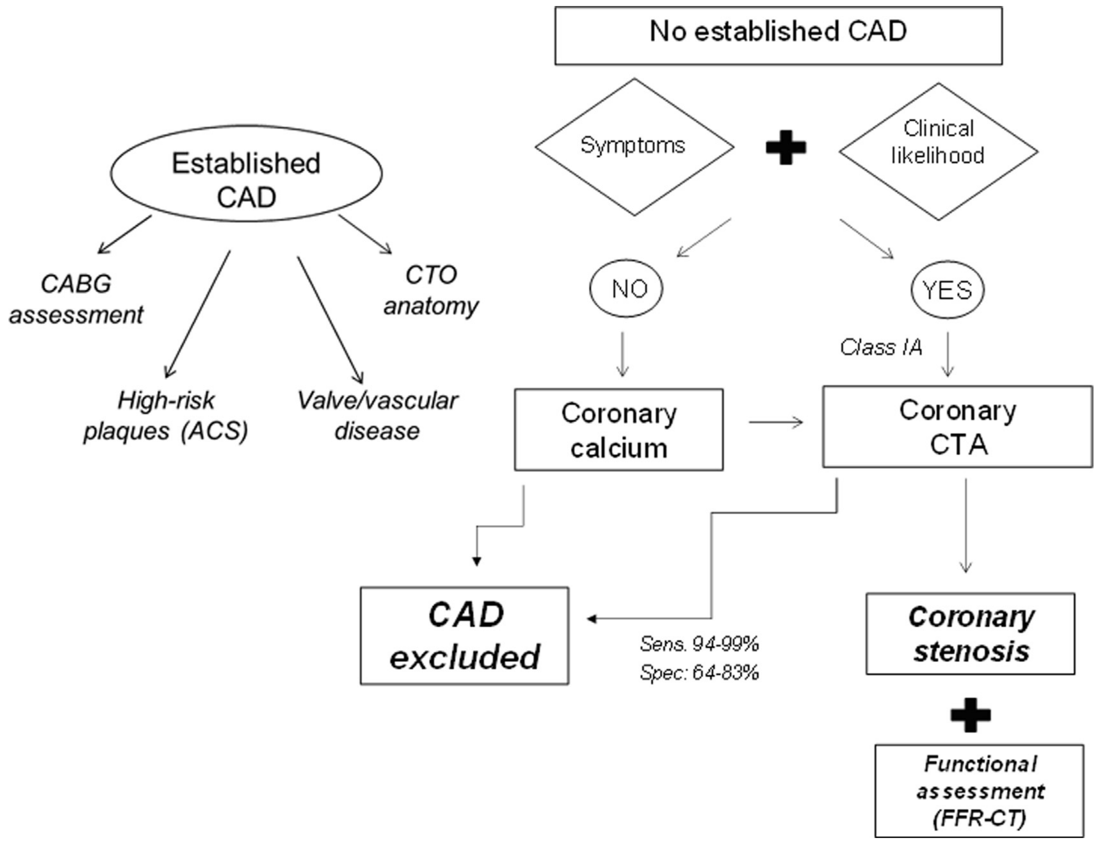

Fig. 3. Proposed tailored approach for CAD risk stratification using a stepwise approach. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CTO, chronic total occlusion.

a future acute coronary syndrome.[47,48] The largest study on this topic was reported by Motoyama and colleagues,[49] which included 3158 patients followed up for 4 years. They found that positive remodeling or low-attenuation plaque was associated with an increased likelihood of acute cardiovascular events. Similarly, in the PROMISE trial, high-risk plaques were associated with an increased risk of death, myocardial infarction, or hospitalization for unstable angina at 2 years.[50]

In effect, adverse plaques are frequently identified on coronary CTA, ranging from 15% of patients in the stable population of the PROMISE trial[50] to the 35% in the Multicenter Study to Rule Out Myocardial Infarction by Cardiac Computed Tomography (ROMICAT-II).[51] In the latter study, among 1000 patients admitted to the emergency department with symptoms suggestive of acute coronary syndromes, incorporating coronary CTA into a triage strategy improved the efficiency of clinical decision making, compared with a standard evaluation in the emergency department, allowing the time of hospitalization to be shortened, especially when combined with high-sensitivity troponin.

In addition, a special mention is needed about the role of coronary anatomy in certain special subsets of patients with established cardiovascular disease, where the tridimensional imaging offered by coronary CTA compared with invasive angiography can provide useful information for the assessment of CAD and planning of interventions.

In effect, the progressive increase of the indication to the percutaneous reopening of chronic coronary occlusions has led to the need to face more and more complex lesions, where the information provided by the coronary CTA can help in the procedural success.[52] Coronary CTA can feature the coronary course and connections with collaterals, the extent of calcification, vessel tortuosity, stump morphology, presence of multiple occlusions, and lesion length. Previous studies have suggested that the procedural success in chronic total occlusions was larger in patients in whom preprocedural CTA was performed.[53]

In addition, the progressive aging of the population has led to the increase of comorbidities, such as renal failure and aortic stenosis, where the possibility of performing multiple anatomic evaluations with a smaller amount of contrast medium can render CTA more advantageous compared with invasive angiography, especially among special subsets of patients, such as those who need aortic valve treatment[54] or patients with prior bypass grafting.[55] CTA of coronary bypass is more demanding from a technical point of view, because it requires a larger scan range (12.5–22.0 cm) and consequently a longer breath hold, and the nondynamic nature of CTA makes the assessment of competitive flow or vasospasm in the arterial graft difficult. Also, arterial grafts pose some limitations to CTA study, as does the presence of metallic clips in mammary artery and, particularly, in radial artery grafts, which interfere with the visualization of lesions.

In contrast, invasive evaluation of grafts can be challenging and exposes patients to large contrast volumes in addition to rare complications such as injury to the graft vessel during catheter engagement. In addition, coronary artery bypass grafts are more amenable to CTA imaging, because of their larger diameters and lower pulsatile movements along the cardiac cycle than native arteries and their relative freedom from calcification, therefore rendering noninvasive assessment a promising opportunity for these patients.

SUMMARY

The availability of imaging technologies for the assessment of CAD, both in elective settings and in emergency room departments, and the options to combine functional and anatomic information, allow clinicians to stratify cardiovascular risk by noninvasive methods. Coronary CTA has recently emerged as the most accurate and effective technique for the exclusion of CAD, whereas different tests could be more appropriate for specific subsets of patients. However, the contests where the different noninvasive tests could provide the greatest advantages still lack a unique definition. Therefore, future large randomized trials are needed in order to draw tailored diagnostic and therapeutic pathways, allowing the assessment of cardiovascular risk to be individualized and the outcome benefits maximized.

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