Coronary artery disease (CAD) is the major cause of morbidity and mortality worldwide. More than 50% of CAD deaths occur in previously asymptomatic individuals at intermediate cardiovascular risk, highlighting the need of more accurate individual risk assessment to decrease cardiovascular events. Cardiac computed tomography (CCT) has emerged as a valuable technique for risk stratification in asymptomatic subjects and in symptomatic patients without known CAD. The absence of coronary artery calcium (CAC) identifies asymptomatic subjects at very low cardiac risk and is reasonable in intermediate risk individuals, in whom CAC measurement reclassifies a substantial number of subjects to different risk categories. In symptomatic patients with suspected CAD, detection of non-obstructive or obstructive CAD by CCT angiography is associated with increased all-cause mortality, and provides incremental risk stratification to CAC. Further studies are needed to assess the impact of CCT on clinical outcomes and its cost-effectiveness in different clinical settings.

Keywords
- Cardiovascular risk
- Coronary artery disease
- Cardiovascular imaging
- Coronary calcium score
- Coronary CT angiography

Introduction

Coronary artery disease (CAD) is the first cause of mortality worldwide and affects the majority of individuals older than 60 years of age.1 Myocardial infarction (MI) represents the first clinical manifestation of CAD in 50–65% of previously asymptomatic patients and approximately 35% of unheralded MIs are fatal.

These considerations sustain the growing interest for improvement of risk assessment in asymptomatic and in symptomatic subjects with suspected CAD to guide risk profile management and improve prognosis. In particular, in the past decades, several imaging risk markers have been proposed to further reclassify asymptomatic intermediate risk subjects in whom appropriate management of risk factors is still debated.2

Therefore, the aim of this review will be to summarize current evidence and future perspectives on the role of cardiac computed tomography (CCT) for cardiovascular risk stratification in clinical practice.

Prognostic value of coronary artery calcium

Coronary artery calcium for risk stratification in asymptomatic patients

Major scientific associations currently consider the amount of coronary artery calcium (CAC) measured by electron beam or multi-detector CCT using the Agatson scoring method (CACS) reasonable for risk stratification in asymptomatic subjects at intermediate risk.4,5 The largest registry of CAC testing in 25,253 asymptomatic patients demonstrated incremental prognostic value of CACS above and beyond age, gender, ethnicity, and cardiac risk factors, with 10-year adjusted survival of 99.4% for a CACS of 0 and 87.8% for a score >1000 (P < 0.001).6 Similar findings were reported by the prospective Multi-Ethnic Study of Atherosclerosis (MESA)7 that enrolled 6722 subjects without history or symptoms of CAD, belonging to 4 ethnic groups, which were
followed up for 3.8 years. In this study, a CACS between 101 and 300 was associated with a 7.7 increased risk of coronary events, whereas a CACS >300 increased the risk of a factor of 9.67. The area under the receiver-operating-characteristic curves for predicting coronary events was significantly increased when CACS was added to Framingham risk scores. Recently, Sarwar et al. reviewed the prognostic value of CAC in more than 85,000 symptomatic and asymptomatic individuals collected from 49 studies with a mean follow-up of 51 months. In this large cohort of patients, only 0.56% of 64,873 asymptomatic subjects with no CAC experienced CE, compared with 4.14% of asymptomatic subjects with any evidence of CAC. Interestingly, the CE rate was also quite low (1.8%) in symptomatic subjects with no CAC compared with symptomatic individuals with any CAC (8.99%).

However, the clinical value of any new risk marker is currently best assessed by the quantification of subjects that, using the new marker, are reclassified in different risk categories compared with the original risk classification from risk charts. In this regard, a recent analysis of the MESA population reporting 5660 asymptomatic subjects showed that the probability of identifying subjects with substantial CAC is very low in patients with FRS <5% but steadily increases for higher FRS categories, with a prevalence of CACS >300 in 24% of subjects at intermediate risk. This indicates that about a quarter of intermediate risk subjects would be reclassified to high-risk stratum adding CACS to conventional risk evaluation. The Heinz Nixdorf Recall Study reported a cohort of 4129 subjects without CAD undergoing CACS and followed up for 5 years. Using CACS <100 to identify low-risk and CACS >400 to identify high-risk subjects, 21.7% of intermediate risk subjects (FRS from 1 to 2% per year) were reclassified. Similarly, in the Rotterdam Study, 2028 elderly asymptomatic subjects were followed up for 9.2 years. Using CACS <50 to identify low risk and >615 to identify high-risk elderly subjects, 52% of subjects at intermediate risk were correctly reclassified in a different risk category. However, reclassification studies are retrospective and, therefore, do not still provide definitive evidence on how this approach will change patient management in clinical practice.

The complementary value of CACS to inflammatory risk markers has also been investigated in several studies, widely demonstrating that CACS is more accurate than C-reactive protein (CRP) in risk stratification and in prediction of CAD events.

In summary, CACS provides incremental risk stratification in intermediate risk asymptomatic subjects, reclassifying a sizable number in more accurate risk categories.

### Does screening for coronary artery calcium improve clinical outcome?

The effects of CAC scoring on cardiovascular risk profile were recently reported by Rozanski et al. in a prospective randomized trial assessing the impact of CAC scanning on conventional risk factors modification in 2137 asymptomatic volunteers followed for 4 years. A significant higher reduction in systolic blood pressure, serum LDL cholesterol levels, and waist circumference were observed in subjects who underwent CAC scanning compared with those who did not, without increased downstream use of medical testing. In a recent study, van Kempen et al. evaluated the cost-effectiveness of adding CACS to conventional risk evaluation in symptomatic elderly subjects at intermediate risk for CAD. In this study, the model that included CACS resulted in more cost-effective compared with the model that included only conventional risk evaluation recommended by guidelines or to the model in which all subjects were treated with statins. However, due to the higher number of men reclassified at high risk by CACS, compared with women, cost effectiveness was shown in men but not in women.

Thus, these findings suggest that a strategy of CAC scanning may prompt adoption of healthy life-style changes or drug therapy implementation leading to improvement of cardiovascular risk profile and, potentially, to more favourable clinical outcome.

### Prognostic value of coronary CT angiography

#### Prognostic role of coronary CT angiography in known or suspected coronary artery disease

Most data on risk stratification using coronary CT angiography (CCTA) apply to symptomatic patients with known or suspected CAD. In this population, the recent CONFIRM study provided relevant evidence in a very large patient population. This international multicentre registry reported all-cause mortality over a follow-up of 2.3 years in a cohort of 24,775 patients undergoing ≥64-detector CCTA, all of them without known CAD. In this study, both obstructive (HR: 2.60) and non-obstructive (HR: 1.60) CAD were associated with increased mortality. A stepwise increase in mortality was observed for progressive severity of CAD, reaching HR of 3.70 in patients with three-vessel or left main disease. Notably, the absence of CAD was associated with the annualized mortality rate of 0.28%. In the CONFIRM study, about two-thirds of patients had an intermediate pre-test likelihood of CAD and 34% was asymptomatic (Table 1).

However, limitations of the CONFIRM study also need to be considered. First, the study only reported all-cause mortality, whereas the prognostic power for cardiovascular endpoints would have been also relevant. Additionally, as for data coming from registries, the impact of uncontrolled therapeutic changes or revascularization as a consequence of CCTA findings cannot be excluded. Of note, however, the same authors further confirmed the prognostic value of non-obstructive CAD in a prospective study from two independent centres enrolling 2583 symptomatic subjects without haemodynamically significant CAD. In this study, the presence of any non-obstructive plaque was associated with 1.98 hazard ratio for all-cause mortality, after adjustment for cardiovascular major risk factors. For patients with non-obstructive plaques in all three major coronary arteries, a 4.75 hazard ratio was observed, whereas plaque composition (calcified, non-calcified, or mixed) was not associated to risk. In a different clinical setting, Kristensen et al. recently reported, in 312 patients suffering acute coronary syndrome (ACS) and followed up for 16 months, that the extent of non-obstructive coronary
Coronary computed tomography

Table 1  Coronary CT angiography studies in symptomatic subjects without known coronary artery disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Objective of the study</th>
<th>Length of follow-up</th>
<th>Main findings</th>
<th>Predictive accuracy of CCTA findings (% of patients with events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min et al.(^{24})</td>
<td>1127</td>
<td>Prognostic</td>
<td>15.3 + 3.9 months</td>
<td>Obstructive CAD associated with all-cause mortality</td>
<td>NA                  NA         NA</td>
</tr>
<tr>
<td>Ostrom et al.(^{32})</td>
<td>2538</td>
<td>Prognostic</td>
<td>78 + 12 months</td>
<td>Obstructive CAD associated with all-cause mortality</td>
<td>1.3                3.0       8.0</td>
</tr>
<tr>
<td>van Werkhoven et al.(^{23})</td>
<td>432</td>
<td>Prognostic</td>
<td>670 days</td>
<td>Obstructive and non-obstructive CAD associated with composite of all-cause death, MI, ACS</td>
<td>0.8                2.1       5.9</td>
</tr>
<tr>
<td>Russo et al.(^{34})</td>
<td>441</td>
<td>Prognostic</td>
<td>31.9 + 14.8 months</td>
<td>Obstructive and non-obstructive CAD associated with cardiac death, nonfatal MI, unstable angina</td>
<td>0.9                3.9       8.1</td>
</tr>
<tr>
<td>Schmermund et al.(^{33})</td>
<td>706</td>
<td>Prognostic</td>
<td>3.2 years</td>
<td>Non-obstructive CAD associated with composite of all-cause death, MI, stroke, revascularization</td>
<td>1.0                4.0       14.0</td>
</tr>
<tr>
<td>Min et al.(^{17})</td>
<td>13 978</td>
<td>Prognostic</td>
<td>2.3 + 1.1 years</td>
<td>Obstructive and non obstructive CAD associated with all-cause mortality</td>
<td>0.6                *        *</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; MI, myocardial infarction; ACS, acute coronary syndrome; NA, not available.

*3.1% of patients had obstructive or non-obstructive CAD.

plaques but not CACS was associated with the increased risk of recurrent ACS. Taken together, these findings point to the prognostic value of non-obstructive CAD over a large spectrum of patients, in primary and secondary prevention. Yet, the clinical impact and cost-effectiveness of CCTA screening (in consideration of its growing availability and radiation burden reduction) in large population groups with suspected or known CAD will deserve appropriate evaluation in prospective studies.

An additional relevant finding of the CONFIRM study was the substantial overestimation of pre-test likelihood of CAD prevalence using current guidelines-endorsed algorithms based on the age, gender, and symptoms typicality,\(^{19}\) raising concerns on current indications for CAD testing in clinical practice. Similarly, Genders et al.\(^{20}\) observed that the Diamond–Forrester model considering the age, sex, and type of chest pain to estimate the probability of obstructive CAD in patients between 30 and 70 years old overestimated the prevalence of CAD.

Coronary CT angiography also provides information on plaque characteristics and morphology that have been investigated as prognostic parameters.\(^{21}\) Motoyama et al.\(^{22}\) reported that, in 1059 patients with suspected or known CAD, lesions exhibiting positive vessel remodelling and low-attenuation characteristics at CCTA were associated with a 22.2% risk of developing ACS over a follow-up of 27 months, as opposed to 0.5% risk of patients showing neither vessel remodelling nor low-attenuation plaques. Notably, all patients developing ACS in the study had culprit lesions <75% stenotic. Yet, despite the pathophysiologic relevance of these findings, the low predictive value observed (one of five patients with both positive remodelling and low attenuation plaques developing ACS) makes the impact of these findings on clinical management of patients uncertain. Along the same line, van Werkhoven et al.\(^{23}\) reported that the presence of any plaque or partially calcified plaque at CCTA was independently associated with CE in patients with suspected CAD, whereas, in 1127 patients with chest pain studied at a single centre, Min et al.\(^{24}\) reported an increase in the mortality rate from 1.4% for calcified plaque to 3.3% for partially calcified and to 9.6% for non-calcified plaques in patients with intermediate FRS. Thus, data on plaque quantification and characterization appear promising for risk stratification of symptomatic patients with suspected CAD, but further improvement in reproducibility and accuracy will be needed to assess the clinical value of these information.

**Coronary CT angiography for screening of asymptomatic subjects (Table 2)**

The role of CCTA for risk stratification of asymptomatic subjects is still uncertain and has been investigated in very few studies. In 2007, Romeo et al.\(^{25}\) reported a cohort of 168 asymptomatic subjects with >1 risk factor and an inconclusive or unfeasible non-invasive stress test, who underwent CCTA and invasive coronary
angiography. Unknown CAD had a prevalence of 27% in the whole population, which raised to 36% in diabetic patients, but no follow-up was reported. Similarly, in a population of 93 asymptomatic diabetic patients undergoing CCTA, Iwasaki et al. reported a 33.3% prevalence of significant CAD compared with 16.1% of non-diabetic patients, whereas Scholte et al. observed a prevalence of 26% obstructive CAD in asymptomatic diabetic patients. However, although these studies consistently demonstrate a prevalence of occult obstructive CAD in about one of three adult type II diabetic patients, lack of functional evaluation of stenotic lesions and of follow-up prevents a clear definition of the prognostic value and clinical relevance of these observations. These limitations also apply to the observation of Neefjes et al. which reported a 26% prevalence of occult CAD in 101 asymptomatic subjects affected by familial hypercholesterolaemia. In fact, data on the prognostic value of occult CAD in asymptomatic high-risk subjects are quite scanty. Choi et al. followed up for 17 months a population of 1000 middle-aged asymptomatic South Korean subjects who underwent CCTA. In this study, unknown CAD had a prevalence of 22% and was associated with a higher incidence of CE that, however, were mainly represented by myocardial revascularizations driven by the CCTA findings. More recently, the impact of CCTA on patient and physician behaviour was investigated by McEvoy et al. in 1000 asymptomatic subjects followed up for 18 months. In this study, 21.5% of asymptomatic subjects showed coronary atherosclerosis and 5% significant stenosis. Detection of occult CAD was associated with a significant increase in statin and aspirin use at 90 days and 18 months, but also of invasive testing. Yet, no difference in the event rate was observed between subjects screened with CCTA compared with a matched control group of subjects not undergoing CCTA. Thus, these findings indicate that a careful cost-effectiveness analysis is needed to assess the value of CCTA in asymptomatic subjects, and that, as reported by guidelines, CCTA is currently not recommended in asymptomatic subjects.

**Does coronary CT angiography provide incremental prognostic value to CACS?**

Several studies evaluated the complementary value of CCTA and CACS for risk stratification. Ostrom et al. in 2538 symptomatic patients, observed that the burden of CAD detected by CCTA provided the independent and incremental value in predicting all-cause mortality over traditional risk factor and CACS. Schmermund et al. confirmed these data, reporting that CCTA provided more accurate risk stratification compared with CACS in patients with mild-to-moderate atherosclerosis. Similar findings were also reported by Russo et al. in patients with the intermediate-to-high prevalence of cardiovascular risk factors and suspected CAD, undergoing CCTA and CACS. Over a mean follow-up of 31.9 months, patients with normal coronary arteries had an annualized cardiac event rate of 0.88%. Compared with a baseline clinical risk

<table>
<thead>
<tr>
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<th>Predictive accuracy of CCTA findings (% of patients with events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romeo et al.</td>
<td>168</td>
<td>Prevalence of CAD</td>
<td>NA</td>
<td>13% CAD prevalence in non-diabetic patients, 36% CAD prevalence in diabetic patients</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>1000</td>
<td>Prognostic</td>
<td>17 + 2 months</td>
<td>Obstructive CAD associated with composite of cardiac death, ACS, revascularization</td>
<td>0 * §</td>
</tr>
<tr>
<td>Iwasaki et al.</td>
<td>425</td>
<td>Prevalence of CAD</td>
<td>NA</td>
<td>16.1% CAD prevalence in non-diabetic patients, 33.3% significant CAD prevalence in diabetic patients</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Scholte et al.</td>
<td>70</td>
<td>Prevalence of CAD</td>
<td>NA</td>
<td>26% CAD prevalence in diabetic patients</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Min et al.</td>
<td>7009</td>
<td>Prognostic</td>
<td>2.3 + 1.1 years</td>
<td>Obstructive and non-obstructive CAD associated with all-cause mortality</td>
<td>0.6 § §</td>
</tr>
<tr>
<td>McEvoy et al.</td>
<td>2000</td>
<td>Management of patients, prognosis</td>
<td>18 months</td>
<td>CCTA associated with increased drugs prescription and invasive tests. No difference on outcome between CCTA and non-CCTA managed patients</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Neefjes et al.</td>
<td>227</td>
<td>Prevalence of CAD</td>
<td>10 + 8 years</td>
<td>26% obstructive CAD prevalence in subjects affected by familial hypercholesterolaemia</td>
<td>NA NA NA</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; ACS, acute coronary syndrome; CCTA, coronary CT angiography; NA, not available.

*7.0% of patients had obstructive or non-obstructive CAD; §3.1% of patients had obstructive or non-obstructive CAD.

Table 2 Coronary CT angiography studies in asymptomatic subjects without known coronary artery disease
model, CACS added incremental prognostic power. Detection of non-obstructive or obstructive CAD by CCTA significantly increased the prognostic power, compared with a baseline clinical risk model and a model, including also CACS. Finally, a meta-analysis, including 7335 patients, confirmed that the detection and extent of CAD at CCTA are strong predictors of CE in symptomatic subjects, independent of CAC and other cardiovascular risk factors. Very recently, an analysis of the CONFIRM population reported 10,037 symptomatic subjects undergoing CCTA and CACS, followed up for 2.1 years. Fifty-one per cent of these patients had CACS of 0, and among them there was a 13% prevalence of non-obstructive and a 1.4% prevalence of obstructive (70% stenosis) CAD. Although no difference in all-cause mortality was observed in patients with 0 CACS, irrespective of obstructive CAD, the composite endpoint of mortality, MI, or late revascularization occurred more frequently (3.9%) in patients with significant (>50%) stenosis and 0 CACS compared with those with CACS of 0 and no obstructive CAD (0.8%), and CACS did not add incremental prognostic information to CCTA.

To summarize, CCTA provides incremental prognostic value to CACS in symptomatic subjects without known CAD, but the prevalence of significant CAD in patients with CACS of 0 is low and cost-effectiveness of CCTA in these patients remains undetermined.

### Combination of coronary CT angiography with functional imaging for risk stratification

Anatomic imaging does not predict the functional significance of atherosclerotic lesions, making hybrid anatomic and functional imaging more accurate for identifying functionally significant CAD. It has been observed that in symptomatic patients undergoing hybrid myocardial perfusion and CCTA imaging, up to 69% of coronary stenosis >50% do not determine inducible ischaemia, whereas abnormal perfusion defects may occur in patients without detectable coronary atherosclerosis at CCTA. Thus, since both the extent of inducible ischaemia and coronary anatomy provide independent prognostic information, it is conceivable that predicting prognosis would be enhanced by complementary evaluation of coronary anatomy and myocardial perfusion, with potential implications for management of patients with CAD. Yet, the value of hybrid imaging for risk stratification has not been extensively investigated. In a recent study, Pazenhenkotil et al. reported 318 patients at intermediate pre-test likelihood of CAD undergoing myocardial perfusion scintigraphy and CCTA for evaluation of suspected CAD. During a follow-up of 60 days, the revascularization rate was 41% in patients showing significant stenosis at CCTA with concordant reversible perfusion defects, whereas the revascularization rate was significantly reduced to 11% in subjects showing unmatched CCTA and perfusion findings. No invasive coronary angiography was performed in patients showing normal CCTA and myocardial scintigraphy. Interestingly, at 2.8 years follow-up, the incidence of cardiac death or MI was significantly higher in patients with functionally significant stenosis (matched CCTA and scintigraphic findings) compared with patients with normal anatomic and functional findings. These preliminary observations further fuel the interest for hybrid imaging that will represent an area of relevant clinical research for the near future.

### Conclusions

CACS is a reasonable risk stratification tool in asymptomatic intermediate-risk patients, and the absence of CAC identifies subjects at very low risk of cardiovascular events (<1% per year). Coronary CT angiography provides independent prognostic information in symptomatic patients with known or suspected CAD that are incremental to CACS.

### Conflict of interest

None declared.

### References


