Imaging of coronary atherosclerosis by computed tomography

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Modern computed tomography (CT) systems afford sufficient spatial and temporal resolution for imaging of the heart and coronary arteries. The detection of coronary artery calcium (CAC) is relatively straightforward and it is applied to detect and quantify subclinical coronary atherosclerosis even in asymptomatic individuals. A large body of evidence has accumulated that uniformly attests to a high predictive value of CAC for future cardiac events. More complex data acquisition protocols, which require higher spatial and temporal resolution, specific patient preparation, and the intravenous injection of contrast agent, allow to perform coronary CT angiography (CTA). With CTA, the presence of luminal stenoses and, given sufficient image quality, calcified as well as non-calcified atherosclerotic plaque can be visualized. Initial studies have shown that certain plaque characteristics, such as positive remodelling or very low CT attenuation, are associated with plaque vulnerability. So far, the available clinical data are not sufficient to draw specific conclusions as to the risk–benefit ratio of contrast-enhanced coronary CTA for risk prediction, especially for asymptomatic individuals. Hence, CTA is currently not recommended for risk stratification purposes. However, the technology of coronary CTA continues to evolve at a rapid pace and clinical applications for plaque imaging and characterization may become possible in the future.

Keywords
Computed tomography • Atherosclerosis • Plaque • Coronary calcium

Introduction
Imaging of the heart and coronary arteries requires high spatial and temporal resolution. Until fairly recently, computed tomography (CT) imaging did not have sufficient temporal resolution to visualize the rapidly moving heart. However, the introduction of electron beam computed tomography in the early 1990s followed by the development of multi-detector CT (MDCT) scanners substantially improved the ability to perform CT imaging of cardiac structures, including the coronary arteries. Multi-detector CT technology continued to evolve rapidly. Sixty-four-slice CT systems are now considered the minimum prerequisite for high-quality cardiac and coronary artery imaging, and further developments include systems with even more detector rows (up to 320 slices) as well as systems with two tubes and detectors (‘dual source CT’) which further improve image quality beyond 64-slice CT. Under certain prerequisites, most importantly a low and stable heart rate, MDCT allows relatively robust visualization of the heart and coronary arteries.

Coronary calcium
In the coronary arteries, calcifications occur almost exclusively in the context of atherosclerosis.1,2 The only exception are patients with advanced chronic kidney disease, in whom medial (non-atherosclerotic) calcification of the coronary artery wall may occur in addition to atherosclerotic calcification. Not every visualize coronary atherosclerotic plaque is of tremendous interest for purposes of risk stratification. Computed tomography offers two ways of assessing coronary atherosclerosis. In CT scans performed without injection of contrast agent (calcium screening), coronary calcium can be detected and quantified. In scans performed during intravenous injection of contrast agent and with more refined imaging protocols (coronary CT angiography), it is also possible to detect non-calcified plaque components and, to some degree, to perform characterization of such plaque. The following review covers the current data and potential applications for both of these investigations.

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Atherosclerotic coronary plaque is calcified, but within a coronary artery, the amount of coronary calcium roughly correlates to the extent of atherosclerotic plaque burden.\cite{1,2} Calcification is neither a sign of stability nor instability of an individual plaque, and its presence or absence is not closely associated with the likelihood of an individual lesion to rupture and cause an event.\cite{3} Some researchers assume calcium to be a sign of previous plaque haemorrhage, while this is disputed by others.\cite{4} Plaques with healed ruptures usually contain calcium, whereas plaques with erosions (a less frequent mechanism of acute coronary syndromes) are often not calcified.\cite{5} Although, therefore, the relationship between calcium and the potential mechanisms that may lead to acute coronary syndromes is not clearly established, the fact that coronary calcium, as detected and quantified by CT, is correlated with the presence and amount of coronary atherosclerotic plaque makes coronary calcium an interesting tool for risk stratification purposes.

In the overwhelming majority of patients with acute coronary syndromes, some coronary calcium can be detected, and the amount of calcium in these patients is substantially greater than in matched control subjects without coronary artery disease.\cite{6–7}

It is important to note that in spite of the relationship between coronary calcification and coronary plaque burden, there is only a weak correlation between the amount of coronary calcium and the angiographic severity of luminal stenosis. Even large amounts of coronary calcium are not necessarily associated with the presence of significant coronary artery stenoses. Although the absence of coronary calcium makes the presence of significant luminal obstruction relatively unlikely, it is not absolutely impossible and a ‘zero’ calcium score cannot be used to rule out coronary artery stenoses in symptomatic individuals, especially when they present at young age and with acute symptoms.\cite{8,9}

**Detection of coronary calcium**

Electron beam computed tomography and MDCT with electrocardiogram gating are equally accurate for detection and quantification of coronary artery calcium (CAC).\cite{10,11} Images are acquired without injection of contrast and at a relatively low radiation dose (about 0.7–3.0 mSv, Figure 1). The amount of calcium is quantified using the so-called Agatston score. Several large reference data sets are available that describe the distribution of ‘Agatston scores’ found in the population, stratified by age and gender.\cite{6,13–15} Volume and mass scores are alternative methods to quantify coronary calcium but they are not widely used. Interscan variability for calcium scores can be high, especially for patients with small amounts of calcium. A study of 3355 individuals found an average variability of 20% for the Agatston score and 18% for calcified plaque volume.\cite{11}

**Clinical significance of coronary calcium**

Several cohort studies have shown that the presence of coronary calcium demonstrated by CT in asymptomatic individuals is a prognostic parameter with high predictive power regarding the development of hard cardiac events during the following 3–5 years.\cite{6,18–26} Similarly, calcium is associated with total mortality.\cite{27} Several meta-analyses demonstrated that a calcium score of 0 is associated with an extremely low mid-term risk of future myocardial infarction or death due to coronary heart disease (as low as 0.03% per year).\cite{24,28} However, even relatively small amounts of coronary calcium confer an elevated risk. One recently published large population-based trial demonstrated a three-fold risk for hard cardiovascular events in 508 individuals with an ‘Agatston score’ between 1 and 10 when compared with 3415 individuals with the absence of detectable calcification.\cite{29} More pronounced calcium is associated with higher risk: in the same patient population, a calcium score between 1 and 100 was associated with a ‘hazard ratio’ for major coronary events of 3.89 (when compared with individuals without calcium), a score between 101 and 300 with a ‘hazard ratio’ of 7.1, and a score of more than 300 with a ‘hazard ratio’ of 6.8 (Table 1).\cite{25} Similar to several previous trials, this study confirmed that coronary calcium provides incremental prognostic information beyond traditional risk factors. In receiver-operating characteristic analyses for prediction of coronary events,
the ‘area under the curve’ for risk factors alone was 0.79, whereas it was 0.83 when coronary calcium was added (P < 0.006). When assessing the predictive value of coronary calcium in low-, intermediate-, and high-risk populations (based on the Framingham risk score), it was shown that in all risk groups, the presence and amount of coronary calcium allowed further stratification. Furthermore, several studies demonstrated that coronary calcium allows better risk stratification than other markers of risk, such as C-reactive protein or intima–media thickness.

Interestingly, there is an influence of ethnicity both on the prevalence of coronary calcification and on the predictive power of coronary calcium, with African-Americans being at highest risk when high calcium scores are present. The extent of progression is associated with severity of non-coronary atherosclerosis, and shows a genetic association. One study reported a higher coronary artery disease event rate in individuals who displayed more rapid progression of calcification. A number of trials have evaluated the influence of lipid-lowering therapy on the progression of coronary calcium, but they have reported conflicting results. Currently, no sufficiently strong data are available to support the use of repeated calcium scans for guiding the intensity of risk factor modification. Together with the relatively high measurement variability especially for small amounts of calcification, this currently prevents clinical applications of repeat coronary calcium scanning.

Clinical implications

In summary, coronary calcium is closely associated with coronary atherosclerosis and the predictive value of coronary calcium concerning the occurrence of future cardiovascular disease events in asymptomatic individuals is widely accepted. However, it is less clear that which patients or individuals will profit from having a coronary calcium scan performed. The ‘Appropriateness Criteria’ for cardiac CT and magnetic resonance imaging, published in 2006 by the American College of Cardiology and several other American organizations, list coronary calcium screening as an ‘uncertain’ indication for patients with intermediate and high Framingham risk. The most recent European Guidelines on Cardiovascular Disease prevention, published in 2007, state that ‘Although calcium scanning is widely applied today, it should not be used uncritically as a screening method’. Other consensus statements support a potential role of coronary calcium assessment for further risk stratification in patients with intermediate Framingham or PROCAM risk. Clinical decision-making could potentially be altered by coronary artery calcium measurement in patients initially judged to be at intermediate risk (10–20% in 10 years). The accumulating evidence suggests that asymptomatic individuals with an intermediate Framingham Risk Score may be reasonable candidates for testing using coronary artery calcium as a potential means of modifying risk prediction and altering therapy.

In patients at high or very low risk, it is currently assumed that coronary calcium imaging will not be clinically reasonable since the result is unlikely to influence treatment decisions (‘... the current literature on coronary artery calcium does not provide support for the concept that high-risk asymptomatic individuals can safely be excluded from medical therapy for coronary heart disease even if coronary artery calcium score is 0’). Unselected ‘screening’ or patient self-referral is uniformly not recommended. Future research should be directed towards the identification of patient populations who will benefit from coronary calcium imaging as far as prognosis is concerned.

Coronary computed tomography angiography

Coronary CT angiography (coronary CTA) permits visualization of the coronary artery lumen and detection of coronary artery stenoses. In addition, non-stenotic coronary atherosclerotic plaques can be depicted. In contrast to ‘calcium screening’, coronary CTA also allows visualization and, to some extent, quantification and characterization of non-calcified plaque deposits. However, all of this requires excellent image quality without artefacts. In addition, image acquisition for coronary CTA is substantially more elaborate than coronary calcium imaging. Intravenous injection of contrast agent is required (~60–100 mL). Data acquisition protocols as well as hardware must provide for extremely high spatial and temporal resolution (which may bring about a relatively high radiation exposure). In addition, image quality is strongly dependent on heart rate and it is usually required to lower the patients’ heart rate to <65 b.p.m., preferably even <60 b.p.m. This is usually achieved by administrating β-blockers. The need for strict heart rate control may not be as important for more recent scanner generations.

Coronary computed tomography angiography: detection of coronary artery stenoses

Coronary CTA offers high accuracy for the detection and especially for ruling out coronary artery stenoses (Figure 2). However, as outlined above, patients have to be somewhat selected. Sinus rhythm and the ability to follow breath-holding commands are a prerequisite and a low heart rate and the absence of severe obesity improve accuracy. In two recent multicentre trials, coronary CTA was reported to have a sensitivity of 95–99%, specificity of 64–83% and negative predictive value of 97–99% to identify patients with at least one coronary artery stenosis among individuals at low to intermediate risk for coronary artery disease. Typically, the positive predictive value is lower (64 and 86% in the above-named trials), which is due to a tendency to overestimate stenosis degree in coronary CTA as well as the fact that image artefacts often result in false-positive interpretations. Coronary CTA performs best in patient groups who are not at high likelihood of coronary artery disease. A multicentre study of 291 patients with 56% prevalence of coronary artery stenoses, as well as 20% of patients with previous myocardial infarction and 10% with prior revascularization demonstrated a sensitivity of only 85% and specificity of 90%. Ruling out obstructive coronary artery stenoses by coronary CTA has prognostic value: several cohort studies have demonstrated extremely low rates of clinical events after coronary CTA had ruled out coronary
artery stenoses in patients with stable angina pectoris or acute chest pain.59 – 64

Coronary computed tomography angiography: assessment of coronary atherosclerotic plaque

Beyond the detection of coronary artery stenoses, coronary CTA can demonstrate coronary atherosclerotic plaque. Calcified plaque can be detected just as in non-enhanced scans, and more importantly, if image quality is high, non-calcified plaque components can also be visualized (Figure 3). To a certain degree, plaque characterization is possible.

Plaque detection and quantification

The accuracy of coronary CTA to detect non-calcified coronary plaque is not well known. In several small studies that compared CT with intravascular ultrasound (IVUS), sensitivities and specificities for the detection of coronary artery segments with plaque have been reported to vary between 80 and 90%.65– 70 In other studies, it has been shown that there is a close correlation between CT and IVUS for plaque cross-sectional area, volume of single plaques, and plaque volume per coronary segment.65,68– 74 However, while correlation coefficients typically were high ($r \approx 0.9$) and always significant, the variability of measurements between CT and IVUS was always substantial, and limits of agreement were typically large. The difficulty to accurately quantify plaque dimensions by CT is easily explained by the fact that the spatial resolution of CTA, as impressive as the obtained images may often be, is relatively limited at about 0.5 mm. Plaques may hence be difficult to depict accurately, especially when their thickness is relatively low.

The difficulty to accurately quantify plaque dimensions by CT also becomes obvious when studying interobserver variability for plaque quantification. Using the same data set, two different observers typically achieve $\sim 30\%$ variability for plaque volume quantification.68,69,75,76 Interobserver variability is dependent on image quality. In one study of 41 patients, the variability was $17 \pm 10\%$ for the left anterior descending coronary artery, which was visualized with the least amount of artefact, whereas it was $29 \pm 13\%$ for the left circumflex and $32 \pm 10\%$ for the right coronary artery.76 In single studies, coronary CTA has been used to study the progression of coronary plaque volume over time. In 50 selected patients with very high image quality, and limited to the left main and left anterior descending coronary artery, Schmid et al. showed that the average annualized rate of progression of non-calcified plaque volume was $22 \pm 25\%$ (whereas the rate of progression for coronary calcium was $38 \pm 50\%$). Only 16%
of patients showed regression of plaque volume. \textsuperscript{77} Burgstahler et al. \textsuperscript{78} were able to demonstrate that statin therapy may reduce the amount of non-calcified plaque in a group of 27 individuals (whereas it did not affect the amount of coronary calcium), but this observation has so far not been verified.

It must be noted that all studies which evaluated the accuracy of coronary CTA for plaque detection and quantification used heavily pre-selected patients and were performed in very experienced laboratories. Hence, accuracies for plaque identification and quantification in ‘real life’ will most probably be lower.

**Plaque characterization**

Beyond detection, the characterization of coronary atherosclerotic plaque is possible to a certain extent (Figure 4). Obviously, CT is able to differentiate calcified, partly calcified, and non-calcified plaque (for non-calcified plaque, often the term ‘soft’ plaque is used, but it lacks scientific justification). The aim of further characterization is to identify parameters that will be associated with increased plaque ‘vulnerability’.

To a certain extent, the CT attenuation of non-calcified plaques may contribute towards plaque characterization. Computed tomography density within ‘fibrous’ plaques is usually higher than within ‘lipid-rich’ plaques [mean attenuation values have been reported in a range between 11 and 99 Hounsfield units (HU) for ‘lipid-rich’ plaque vs. 77–121 HU for ‘fibrous’ plaque; Table 2]. \textsuperscript{69,70,79–84} However, the variability of density measurements within plaque types is large \textsuperscript{82} and some studies did not even find any significant difference in CT attenuation between plaque types. \textsuperscript{69} Furthermore, density measurements within coronary plaques are heavily influenced by the contrast attenuation in the adjacent lumen \textsuperscript{85} and by image reconstruction parameters such as slice thickness and reconstruction kernel. \textsuperscript{86} Therefore,

![Figure 4](image)

**Figure 4** Various types of coronary atherosclerotic plaque demonstrated by coronary computed tomography angiography. In all cases, the proximal right coronary artery is shown in the form of a ‘curved multiplanar reconstruction’. (A) Proximal right coronary artery (arrows) without any detectable plaque. (B) Proximal right coronary artery with calcified plaque (large arrows). Non-calcified plaque is not detectable. (C) Proximal right coronary artery with both calcified and non-calcified plaque (sometimes referred to as ‘mixed plaque’). Two large arrows point at plaques that contain calcified and non-calcified components. A small arrow indicates a completely non-calcified plaque. (D) Proximal right coronary artery with exclusively non-calcified plaque (arrows). Calcified plaque is not present.
accurate classification of plaque composition by measuring the CT attenuation is currently not reliably possible. However, based on studies performed in patients after acute coronary syndromes, it has been speculated that the identification of very low CT densities (below 30 HU) within a plaque may be associated with a higher predisposition towards rupture. Other plaque features which were demonstrated in patients who underwent CT imaging of the coronary arteries after acute coronary syndromes included a predominance of non-calcified plaque as well as pronounced positive remodelling, the assessment of which by CTA seems to correlate well with IVUS.

Table 2  Computed tomography attenuation values found in lipid-rich and fibrous plaques in various studies (HU, Hounsfield units)

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Lipid-rich plaque</th>
<th>Fibrous plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroeder et al.</td>
<td>IVUS</td>
<td>14 ± 26</td>
<td>91 ± 21</td>
</tr>
<tr>
<td>Becker et al.</td>
<td>Histology</td>
<td>47 ± 9</td>
<td>—</td>
</tr>
<tr>
<td>Carrascosa et al.</td>
<td>IVUS</td>
<td>58 ± 43</td>
<td>121 ± 34</td>
</tr>
<tr>
<td>Pohle et al.</td>
<td>IVUS</td>
<td>11 ± 12</td>
<td>90 ± 27</td>
</tr>
<tr>
<td>Sun et al.</td>
<td>IVUS</td>
<td>12 ± 15</td>
<td>32 ± 130</td>
</tr>
<tr>
<td>Petranovic et al.</td>
<td>IVUS</td>
<td>99 ± 28</td>
<td>—</td>
</tr>
</tbody>
</table>

Figure 5 Longitudinal reconstruction of the proximal left anterior descending coronary artery. A plaque with pronounced positive remodelling is visualized by computed tomography angiography (arrow). The total vessel area (lumen plus plaque) is substantially larger than for normal vessel segments proximal or distal to the lesion. The insert shows a cross-section of the plaque. The large arrow indicates the contrast-enhanced lumen, whereas the small arrows indicate the eccentric non-calcified plaque.

Prognostic implications of plaque detection by coronary computed tomography angiography

Similar to the detection and quantification of coronary calcium, one would expect that the detection and further characterization of non-calcified plaque should provide prognostic information concerning the occurrence of future acute coronary syndromes. Indeed, surrogate markers of plaque burden have been shown to be predictive of overall mortality in two other large trials. Ostrom et al. demonstrated that the presence of non-obstructive plaque in all three coronary arteries was associated with increased mortality (risk ratio 1.77 when compared with individuals without any detectable plaque). The presence of non-obstructive plaque in only one or two coronary vessels was not associated with an increased risk. Min et al. could demonstrate that the presence of coronary atherosclerotic plaque in at least five coronary artery segments in symptomatic patients was associated with increased mortality when compared with patients with detectable plaque in less than five segments. In a landmark study, Motoyama et al. could demonstrate that beyond the mere assessment of plaque burden, specific plaque parameters may be associated with a particularly high risk. In 1059 patients who were followed over a mean period of 2.3 years after having undergone coronary CTA, they clearly showed that plaques with positive remodelling and low CT attenuation were at particularly high risk for causing future cardiovascular events.

Is coronary CTA, which allows to identify non-calcified plaque components, a better predictor of risk than the measurement of coronary calcium? Intuitively, one would assume this to be the case, but this has so far only been demonstrated in a single study. The actual clinical utility of coronary CTA for risk stratification purposes is very uncertain, especially when considering extending the currently available findings to a ‘screening’ situation. The above-named trials which demonstrated a prognostic value of coronary CTA were all retrospective analyses of individuals in whom CT was performed for a clinical reason, so most likely the populations mainly consisted of symptomatic patients. Because of the low overall event rate, predicting acute coronary syndromes in asymptomatic individuals is substantially more difficult. In fact, a trial of 1000 middle-aged asymptomatic Korean
special measures to minimize the dose are implemented.\[97,98\] are than calcium scans. Average effective doses for coronary CTA usually associated with substantially higher radiation exposure over a 17-month follow-up period.\[96\]

A further concern is the fact that coronary CTA, as opposed to coronary calcium, requires the injection of contrast agent and is intensely scientific interest, the clinical use of coronary CTA to rule out coronary artery stenoses, quality may not be sufficient achieved. However, such data sets will often have relatively high noise levels, and while they may be appropriate to detect or rule out coronary artery stenoses, quality may not be sufficient for accurate plaque detection and characterization. While of intense scientific interest, the clinical use of coronary CTA to detect plaque in asymptomatic individuals for purposes of risk stratification is therefore currently not considered an ‘appropriate’ indication and is uniformly discouraged.\[47,105\]

**Summary**

In summary, CT imaging of the coronary arteries has tremendous potential to provide uniquely valuable information concerning coronary atherosclerosis. Both for risk stratification of an individual and for obtaining new information on the disease process itself, the ability to directly visualize coronary atherosclerotic lesions is of great potential. Coronary calcium measurements are relatively clearly established as a way to obtain prognostic information, which may most likely be useful for further risk stratification of asymptomatic individuals at intermediate risk based on traditional risk factor assessment. As image quality of coronary CTA shows continuous improvement, the amount of detailed information that can be obtained from a coronary CT angiogram will undoubtedly increase and even better characterization of coronary atherosclerosis will become possible. Along with new acquisition and post-processing algorithms which will allow imaging with lower radiation doses, the constant evolution of CT hardware witnessed during the past years can be expected to continue and most likely contrast-enhanced CTA will eventually contribute meaningfully to risk stratification of specific individuals.

Obviously, sound clinical trials that demonstrate a benefit of integrating coronary artery imaging by CT into patient management will be the optimal form of evidence to turn coronary CTA into a widely accepted clinical tool.

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