

## The value of multi-slice-computed tomography coronary angiography for risk stratification

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**Multi-slice-computed tomography coronary angiography (CTA) provides direct non-invasive anatomic assessment of the coronary arteries allowing for early identification of coronary artery disease (CAD). This information is useful for diagnosis of CAD, particularly the rule out of CAD. In addition, early identification of CAD with CTA may also be useful for risk stratification. The purpose of this review is to provide an overview of the current literature on the prognostic value of CTA and to discuss how the prognostic information obtained with CTA can be used to further integrate the technique into clinical practice. Non-invasive anatomic assessment of plaque burden, location, composition, and remodeling using CTA may provide prognostically relevant information. This information has been shown to be incremental to the Framingham risk score, coronary artery calcium scoring, and myocardial perfusion imaging. Characterization of atherosclerosis non-invasively has the potential to provide important prognostic information enabling a more patient-tailored approach to disease management. Future studies assessing outcome after CTA-based risk adjustments are needed to further understand the value of detailed non-invasive anatomic imaging.**

**Key Words:** Unstable atherosclerotic plaque • computed tomography (CT) • coronary artery disease • diagnostic and prognostic application

### INTRODUCTION

The introduction of multi-slice-computed tomography coronary angiography (CTA) has changed the field of non-invasive imaging. In addition to existing functional imaging techniques assessing myocardial perfusion and wall motion, CTA currently provides direct non-invasive anatomic assessment of the coronary

arteries. This allows for detection of coronary artery disease (CAD) at an earlier stage compared to functional imaging,<sup>1</sup> which may have important implications for the diagnosis as well as prognosis of CAD. For diagnosis, numerous studies support the use of CTA for rule out of the presence of CAD with a high accuracy.<sup>2-8</sup> As a result the technique is increasingly used as a gatekeeper for further diagnostic testing. In addition, data are emerging that early identification of CAD with CTA may be useful for risk stratification. Since the first publications on the prognostic value of CTA in 2007 a number of studies have been published providing further insight into the potential value of non-invasive anatomic imaging for risk stratification.<sup>8-21</sup> The purpose of this review is to provide an overview of the literature on the prognostic value of CTA and to discuss how the prognostic information obtained with CTA can be used to further integrate the technique into clinical practice.

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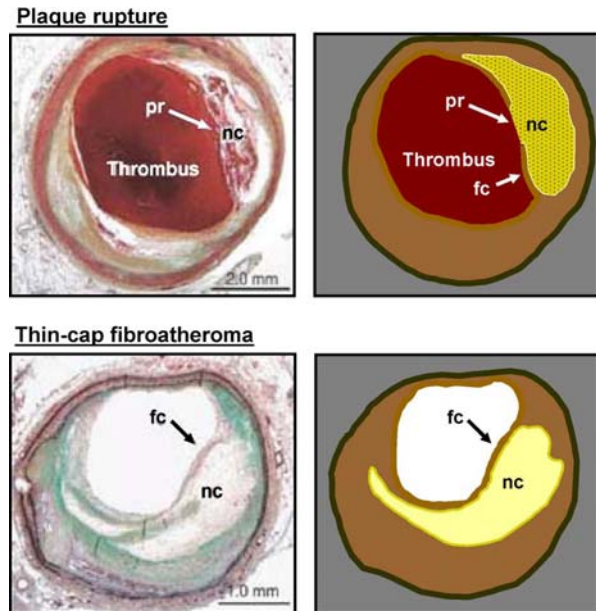
### ACCURACY FOR RISK STRATIFICATION

#### Shift From Stenosis To Atherosclerosis

Diagnostic accuracy studies assessing the value of CTA have determined its ability to identify the

presence or absence of significant stenosis ( $\geq 50\%$  luminal narrowing).<sup>3,22-26</sup> This threshold is important from a diagnostic point of view, as it can identify a cause for the patient's complaints as well as a treatment target for revascularization. Furthermore, patients with a significant stenosis on CTA may have worse outcome as compared to patients without significant CAD.<sup>14,15,18,20</sup> Indeed, an annualized event rate for the occurrence of all cause mortality and myocardial infarction ranging between approximately 1% and 5%<sup>14,15,18,20</sup> has been observed in patients with significant CAD compared to approximately 0-2% in patients without significant CAD. However CTA can further differentiate patients as having non-significant CAD or completely normal coronary arteries. This is important as the presence of non-significant CAD may not necessarily be considered benign.<sup>27-29</sup> Indeed, myocardial infarction and unstable angina are frequently caused by lesions deemed to be non-significant prior to the event.<sup>30-33</sup> In line with this notion, the presence of non-significant CAD on CTA has been associated with an increased annualized event rates up to 1.5%,<sup>14,18,20</sup> compared to a very low annualized event rates of  $<0.7\%$  in patients with completely normal coronary anatomy.<sup>8-10,12-14,18,20,34</sup> Accordingly, classification of patients as having normal anatomy, non-significant CAD, or significant CAD may allow straightforward and reliable risk stratification. However, it is conceivable that the prognostic information may be refined by further characterization of the observed atherosclerosis on segmental or plaque level. Potentially, such analysis may include identification of certain characteristics of lesions that may have a higher likelihood to cause thrombotic occlusion of the vessel and subsequent coronary events.

In the past, numerous histological studies have addressed the mechanism underlying coronary occlusion, thereby identifying three major causes, namely plaque erosion, the presence of calcified nodules and, in the majority of cases, plaque rupture.<sup>35</sup> In the setting of plaque rupture, the underlying plaque at the site of thrombus formation has been typically characterized as a lesion with a large lipid-rich atheromatous necrotic core, with a ruptured thin fibrous cap and expansive remodeling. These findings have subsequently led to the hypothesis that plaque rupture is caused by rupture of the thin fibrous cap overlying a lesion with a large lipid-rich atheromatous necrotic core (Figure 1). In addition to morphological characteristics of the plaque, the presence of inflammation, as reflected by macrophages and lymphocytes infiltration, also plays an important role. An overview of morphological plaque characteristics associated with vulnerability is provided in Table 1.<sup>36</sup> Due to its ability to visualize the vessel wall, CTA may allow



**Figure 1.** Thin capped fibroatheroma as a cause of plaque rupture. The *top panel* shows a histological specimen of a ruptured plaque. As can be observed in the specimen, the lumen is completely occluded by a large thrombus. The underlying plaque contains a large necrotic core (nc) and is covered by a thin fibrous cap (fc) which has ruptured (pr). These findings have subsequently led to the hypothesis that plaque rupture is caused by rupture of the thin fibrous cap of thin capped fibroatheroma plaques. A histological specimen of a thin capped fibroatheroma can be observed in the *bottom panel*. The plaque is characterized by a large necrotic atheromatous core (similar to the necrotic core observed in sites of plaque rupture), covered by a thin non-ruptured fibrous cap. Adapted and reprinted with permission from Jain et al.<sup>78</sup>

**Table 1.** Morphological markers of plaque vulnerability

Plaque
Plaque cap thickness
Plaque lipid core size
Plaque stenosis
Color
Collagen content versus lipid content, mechanical stability
Calcification burden and pattern
Pan arterial
Total coronary calcium burden
Total arterial burden of plaque including peripheral

Based on the table from Naghavi et al.<sup>36</sup>

non-invasive identification of several characteristics associated with vulnerability including plaque burden, location, composition, and remodeling.<sup>37-48</sup>

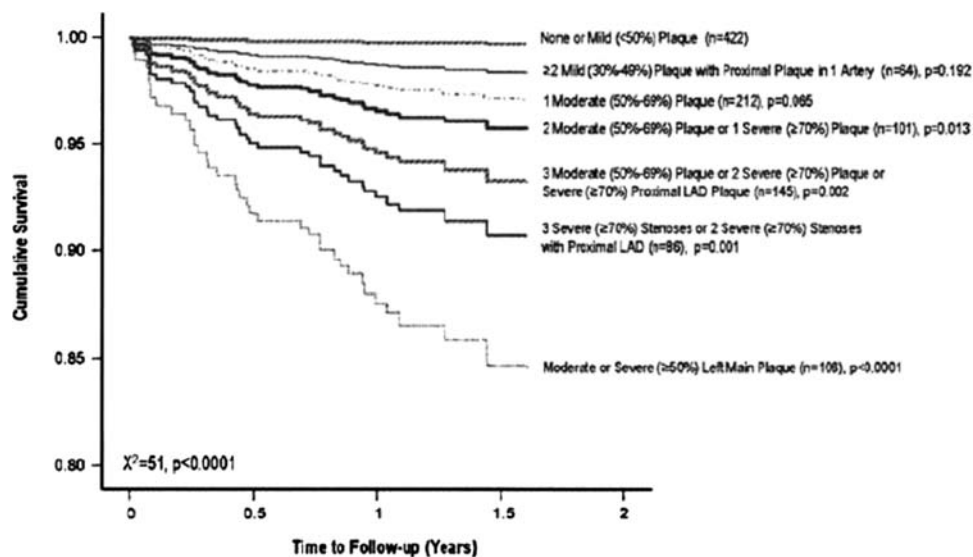
### Non-invasive Characterization of Atherosclerosis with CTA

**Plaque burden and location.** By combining plaque extent and severity throughout the coronary system, plaque burden can be either assessed quantitatively or semi-quantitatively with CTA by summation of the number of diseased and significantly diseased vessels or segments. Although plaque burden in itself does not directly imply plaque vulnerability, an increase in plaque burden is associated with an increased risk for vulnerable plaques. Several studies have attempted to create models of plaque burden using a modified AHA segment model of the coronary artery tree. In the study by Pundziute et al,<sup>8</sup> increased number of segments with plaque as well as increased number of segments with significant stenosis were independent predictors of events when corrected for baseline clinical variables. Using similar scoring methods, other studies have also observed a higher risk for events in patients with increased number of segments with atherosclerosis.<sup>10,16</sup> Min et al observed that a segmental involvement score allowed good differentiation between patients with a low and high risk for future events. In patients with more than five segments involved, an absolute event rate of 8.4% was observed compared to 2.5% in patients with a score  $\leq 5$ .<sup>16</sup> In a next step, the extent and severity of atherosclerosis throughout the coronary artery tree was incorporated into the segmental severity score. Each coronary segment was graded according to stenosis severity (absent to severe plaque (0-3)) and the scores for all segments were combined. When using this

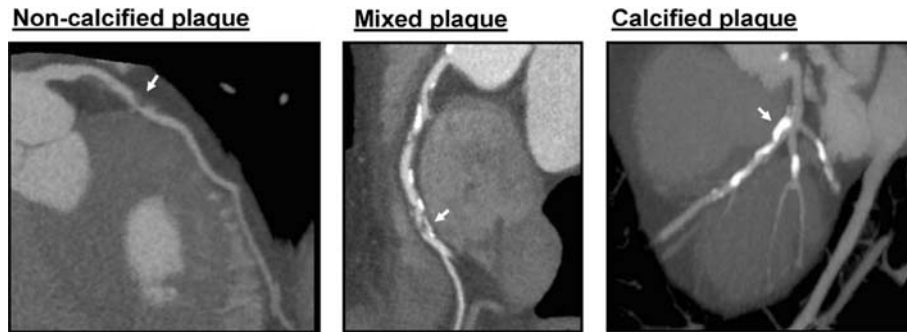
segmental severity score an absolute event rate of 6.6% was observed in patients with a score  $>5$  compared to 1.6% in patients with a score  $\leq 5$ .

In addition to plaque burden, plaque location should be considered as well, as vulnerable plaques are most often observed in proximal segments of the coronary artery tree.<sup>49</sup> The presence of proximal lesions is therefore associated with an increased risk of vulnerable plaques. Furthermore, plaque rupture in a proximal segment also increases the risk of a major cardiac event, due to the larger volume of myocardium that is at risk. Indeed, Pundziute et al<sup>8</sup> observed that the presence of left main plaque or proximal LAD plaque was an important independent predictor of events associated with a high event rate. Likewise, in the study by Min et al<sup>16</sup> the presence of any left main stenosis was also an independent predictor of events. Subsequently, the authors created a modified version of the Duke coronary artery score by combining both plaque burden and location into a single predictive model. As illustrated in Figure 2, events rates paralleled increasing disease severity as determined with this hierarchic model.

**Plaque remodeling and plaque composition.** To some extent, CTA allows assessment of plaque composition. A differentiation can be made between non-calcified plaques having low attenuation, calcified plaques with high attenuation, and mixed plaques with both non-calcified and calcified elements (Figure 3).<sup>47</sup> Furthermore, plaque remodeling, a marker of vulnerability, can also be appreciated (Figure 4). In retrospective studies comparing observations on CTA

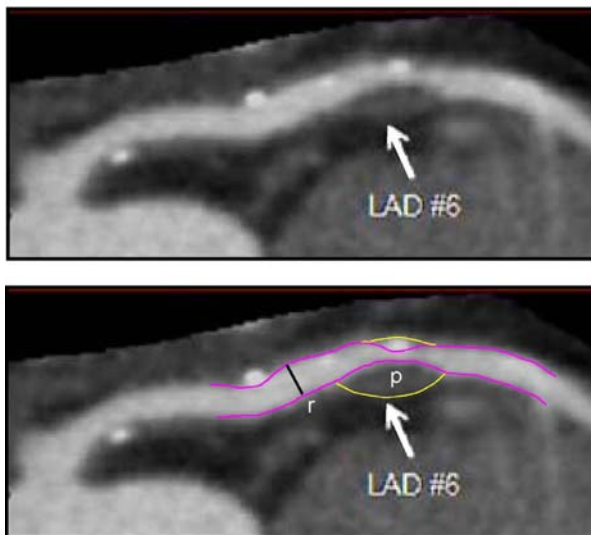


**Figure 2.** Prognostic value of CTA. Cumulative survival curves illustrating the risk of events in each category of the Duke Prognostic Coronary Artery Disease Index. The risk of events increases with increasingly higher disease severity categories. Reprinted with permission from Min et al.<sup>16</sup>



**Figure 3.** Plaque composition assessed with CTA. Curved multi-planar reconstructions showing three distinct plaque characteristics observed on CTA with non-calcified plaque (*arrow, left panel*), mixed plaque (*arrow, mid-panel*), and calcified plaque (*arrow, right panel*). CTA, Multi-slice computed tomography coronary angiography.

### Positive remodeling



**Figure 4.** Example of a positively remodeled plaque. A multi-planar reconstruction of the left anterior descending coronary artery. In the proximal section of the vessel a large plaque can be observed between the lumen (*purple line*) and the vessel wall (*yellow line*). The diameter of the vessel at the plaque site is clearly larger compared to the diameter at the reference section (*r*), indicating positive remodeling (*p*). Adapted and reprinted with permission from Motoyama et al.<sup>17</sup> LAD, Left anterior descending artery.

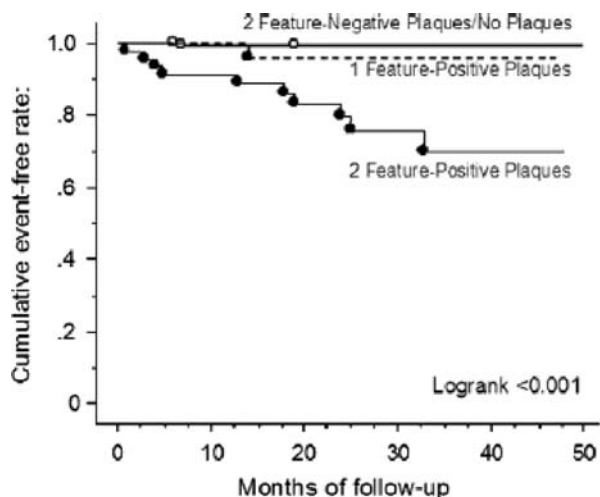
between patients presenting with stable CAD and patients with suspected acute coronary syndrome (ACS), more outward plaque remodeling, non-calcified plaque, and mixed plaque were observed in the latter.<sup>41,50,51</sup> In subsequent prognostic investigations these characteristics have been further studied. Pundziute et al<sup>8</sup> assessed the prognostic value of different plaque characteristics and observed that increased number of segments with mixed plaques was an independent predictor of events. Non-calcified plaque however has also been associated

with an increased risk for events. Both the number of segments with mixed plaques as well as the number of segments with non-calcified plaque were independent predictors of events in a recent study by Van Werkhoven et al.<sup>20</sup> Furthermore, the presence of substantial non-calcified plaque burden was demonstrated to provide incremental prognostic value over the presence of significant stenosis on CTA. In a recent study by Motoyama et al<sup>17</sup> the concept of plaque morphology was investigated more extensively in 1059 patients during an average follow up of 27 months. The authors assessed the presence of two plaque characteristics, low attenuation plaque and positive remodeling, and recorded the occurrence of ACS during follow-up. In patients with a normal CTA study no events occurred. In patients with atherosclerosis but without either high-risk plaque feature (e.g., absence of both low-attenuation plaque tissue and positive remodeling) the event rate was 0.49% whereas in patients with plaques positive for 1 high-risk feature (either low attenuation or positive remodeling) the event rate increased to 3.7%. Finally, the majority of events occurred in patients with both high-risk plaque features. In these patients an event rate as high as 22.2% was observed (Figure 5). Accordingly, these findings may provide a proof of concept for the assessment of plaque composition on CTA for risk stratification.

## INTEGRATION INTO CLINICAL PRACTICE

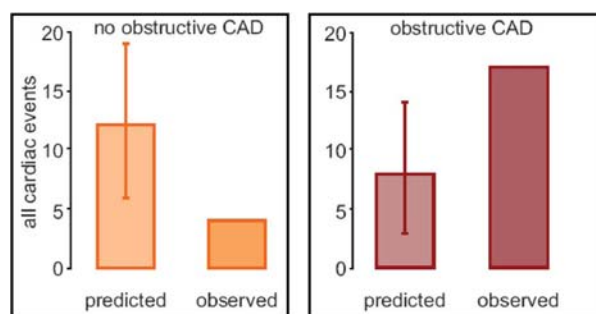
### Relation to Existing Tools for Risk Stratification

As outlined above, several investigations have demonstrated the feasibility of CTA for risk stratification. An important question however remains whether the technique provides incremental prognostic information to existing risk stratification methods. To a large extent, prognosis is determined using baseline clinical



**Figure 5.** Prognostic value of low-attenuation plaque and plaque remodeling features. Survival curves illustrating the prognostic value of 2 plaque features (low-attenuation plaque and remodeling) associated with acute coronary syndrome. The event rate increased in patients with 1 feature positive plaques and was highest in patients with both high risk features. Reprinted with permission from Motoyama et al.<sup>17</sup>

characteristics. To this end the Framingham score is widely used and provides an estimate of the risk of developing adverse coronary events.<sup>52</sup> The disadvantage of this method is that it is a population-based screening tool, whereas CTA may provide a more patient-specific approach. In a recent investigation by Hadamitzky et al<sup>15</sup> the value of risk stratification with CTA was compared to the Framingham risk score in a population of 1256 patients during an average follow-up of 18 months. Figure 6 illustrates the difference between the predicted risk based on the Framingham risk score and the observed risk according to findings on CTA. In patients without obstructive CAD, the observed

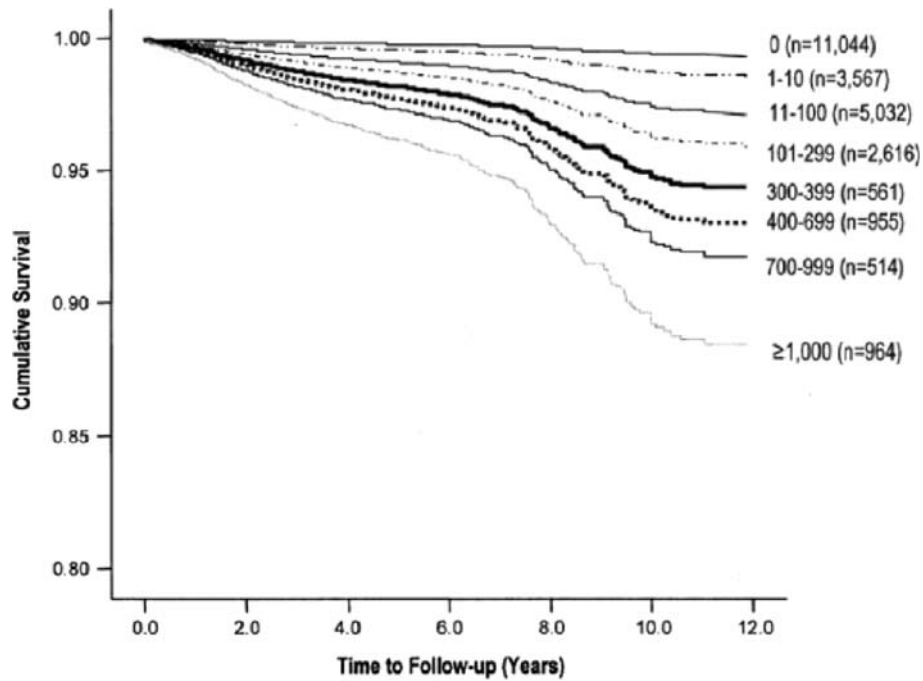


**Figure 6.** Prognostic value of CTA in addition to the Framingham risk score. In patients without obstructive CAD, the observed risk was significantly lower than predicted by the Framingham risk score. In contrast significantly more events were observed in patients with obstructive CAD compared to the predicted event rate. Reprinted with permission from Hadamitzky et al.<sup>15</sup> CAD, Coronary artery disease.

risk was significantly lower than predicted by the Framingham risk score. In contrast significantly more events were observed in patients with obstructive CAD compared to the predicted event rate. CTA may therefore further refine risk stratification over conventional risk assessment alone.

Of note, the incremental value of atherosclerosis over traditional risk assessment has been shown in the past for coronary artery calcium scoring (Figure 7).<sup>53-56</sup> Based on numerous trials, coronary artery calcium scoring—performed either by electron beam computed tomography or CT—has been accepted as a robust tool for prognostification, especially in asymptomatic individuals.<sup>57</sup> In addition, the technique may be used in symptomatic patients to identify the presence and the extent of atherosclerosis.<sup>58</sup> However, the technique can only provide an estimate of total calcified plaque burden, and does not provide any information on the stenosis severity nor the presence and extent of non-calcified plaque burden. An important advantage of CTA therefore is the additional information on stenosis severity and plaque composition. In a study by Ostrom et al<sup>18</sup> the incremental value of non-invasive coronary angiography with electron-beam-computed tomography over coronary calcium was assessed. The authors demonstrated that CTA-derived plaque burden, defined as the number of non-significantly or significantly diseased vessels, had independent and incremental value in predicting all-cause mortality independent of age, gender, conventional risk factors, and coronary artery calcium score. Similar findings were recently reported by Rubinshtein et al.<sup>19</sup> In a more recent study the incremental prognostic value of both stenosis severity and plaque composition on CTA over the coronary artery calcium score was determined.<sup>21</sup> In addition to stenosis severity the number of segments with non-calcified plaque as well as the number of segments with mixed plaque was shown to be independently associated with increased risk for events. Accordingly, it appears that non-invasive measures of plaque extent, severity, and composition not only provide improved diagnostic information but also incremental prognostic information over coronary artery calcium scoring.

Although risk stratification using non-invasive anatomic imaging is gaining momentum, traditionally functional imaging has been used extensively for this purpose. Particularly myocardial perfusion imaging is an established and important technique for prognosis. Patients with a normal perfusion have a very low event rate compared to increased event rates in patients with abnormal perfusion.<sup>59-65</sup> Comparative studies between CTA and myocardial perfusion imaging have shown that CTA provides complementary information to myocardial perfusion imaging when regarding the diagnosis of



**Figure 7.** Prognostic value of coronary calcium scoring. Cumulative survival curves illustrating the event rate in increasingly higher calcium score categories. Reprinted with permission from Budoff et al.<sup>54</sup>

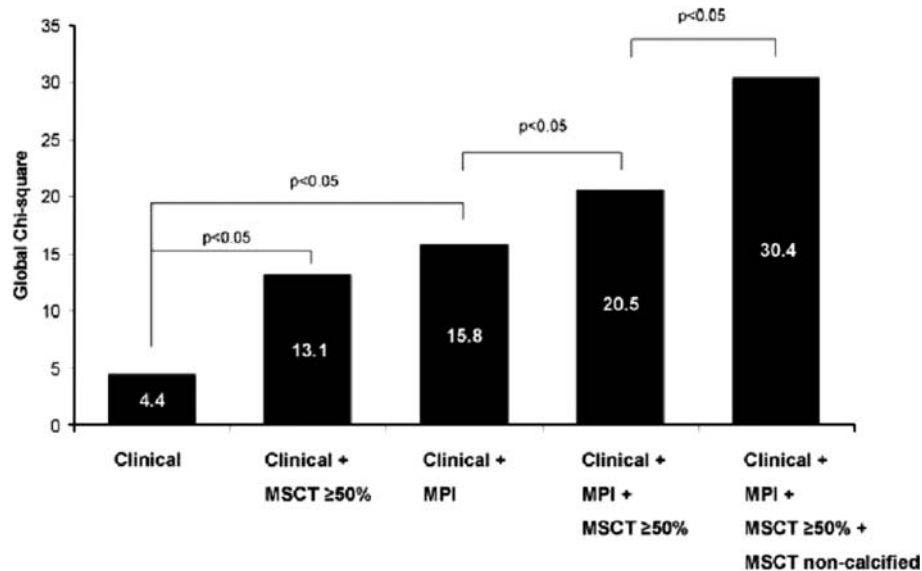
CAD.<sup>66-69</sup> The added value of this complementary information for risk stratification was recently determined.<sup>20</sup> Several CTA variables were able to provide prognostic information independent of myocardial perfusion imaging. On a patient level the presence of significant CAD ( $\geq 50\%$  stenosis) was identified as a robust independent predictor. In addition to stenosis severity, plaque composition was shown to further enhance risk stratification, as illustrated in Figure 8.

### Patient Populations

**Symptomatic populations.** CTA has been proposed for diagnosis of significant CAD in symptomatic patients presenting with an intermediate pre-test likelihood for significant stenosis. Based on the diagnostic accuracy of CTA for the detection of significant CAD on conventional coronary angiography, the comparative studies between CTA and myocardial perfusion imaging, and the limited prognostic data at the time, an algorithm has been proposed which integrates the use of these techniques for the diagnosis and management of this patient population (Figure 9).<sup>70</sup> The algorithm separates patients into three strategies for management: first, patients with normal coronary anatomy can be safely discharged, secondly patients with non-flow limiting atherosclerosis requiring medical treatment and

aggressive risk factor modification and finally patients with a flow-limiting stenosis requiring further evaluation with conventional coronary angiography with potential revascularization. The currently available outcome data support that the discharge of patients with a normal CTA study is safe as low events rates have been confirmed in these patients.<sup>8-10,12-14,18,20,34</sup> However in patients with atherosclerosis regardless of stenosis severity, assessment of plaque extent, composition, location, and remodeling may further improve risk stratification. As indicated by initial data, this information can be valuable both in patients with or without ischemia.<sup>20</sup>

CTA is currently not recommended for diagnosis in other populations than those with an intermediate pre-test likelihood for significant CAD. It is however conceivable that in the future CTA may be used in other populations with the purpose of risk stratification. In symptomatic patients with a low pre-test likelihood for significant stenosis, non-invasive imaging is generally not indicated for diagnosis. However assessment of atherosclerosis can be useful in identifying patients at increased risk of future events. As shown by Henneman et al, the prevalence of atherosclerosis in patients with a low pre-test likelihood is approximately 40% which illustrates that, although the pre-test likelihood for significant stenosis is low, atherosclerosis is nevertheless present in a large proportion of these patients. In patients



**Figure 8.** Incremental prognostic value of CTA over MPI. Bar graph illustrating the incremental prognostic value (depicted by Chi-square value on the y axis) of CTA. The addition of CTA provides incremental prognostic information to baseline clinical variables and MPI. Furthermore, the addition of non-calcified plaque on CTA results in further incremental prognostic information over baseline clinical variables, MPI, and significant CAD ( $\geq$ 50% stenosis) on CTA. Reprinted with permission from Van Werkhoven et al.<sup>20</sup> CAD, Coronary artery disease; CTA, multi-slice computed tomography coronary angiography; MPI, myocardial perfusion imaging.

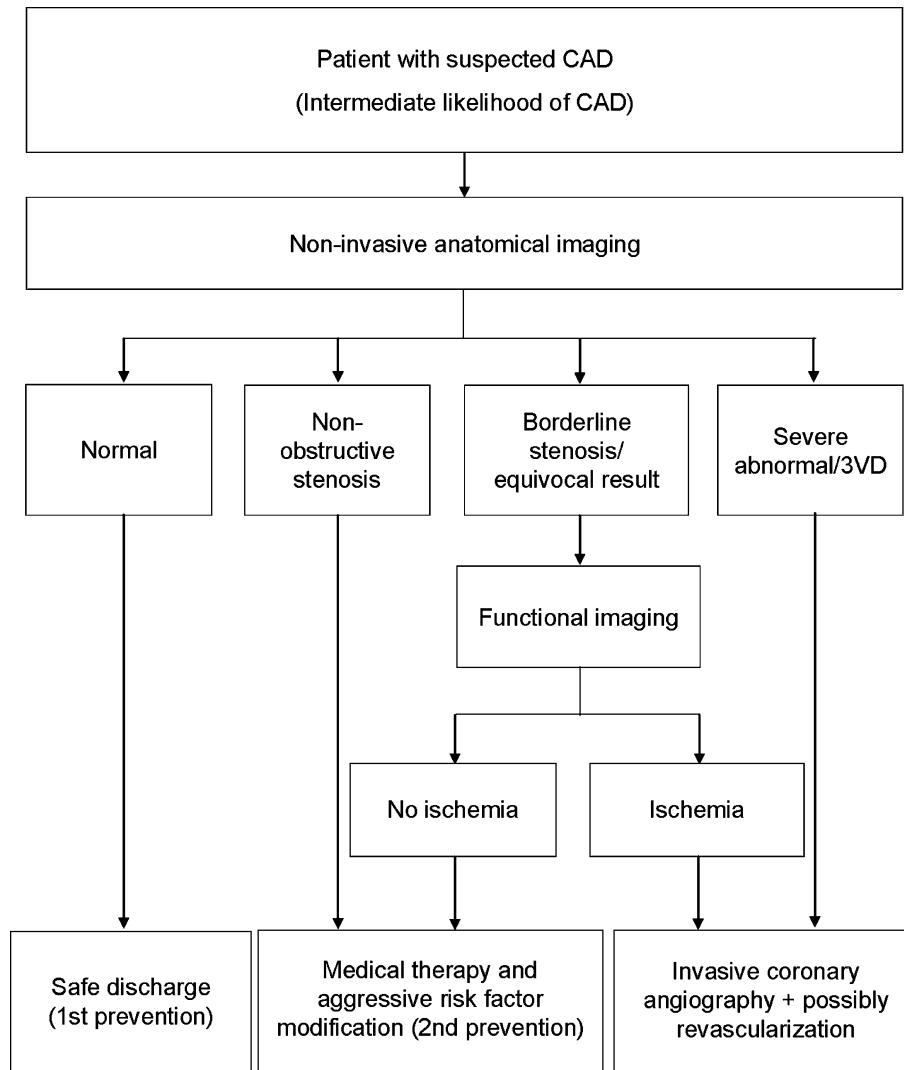
with a high pre-test likelihood for significant stenosis, functional data may be more relevant than CTA to determine need for revascularization. However, CTA can potentially be used as a second line test for risk stratification as the anatomic information has been shown to provide incremental prognostic information to myocardial perfusion imaging alone.<sup>20</sup>

**Asymptomatic populations.** Although only limited data are available in asymptomatic patient populations it is possible that CTA is valuable for risk stratification in these patients. On the one hand, CTA can be used to identify patients with severe CAD, such as triple vessel disease or left main disease, and who may benefit from aggressive intervention. On the other hand, CTA can be performed to document atherosclerosis for long-term risk assessment. In a recent study in 1000 asymptomatic individuals undergoing CTA the prevalence of atherosclerosis was reported to be 22%.<sup>11</sup> During a follow-up of 17 months, coronary events (unstable angina and revascularization) occurred in 15 (1.5%) individuals, all of which had atherosclerosis on CTA. However, the majority of events were revascularizations, triggered by the CTA results. In combination with the low overall event rate, these observations indicate the limited value of screening for atherosclerosis with CTA in this population. Accordingly, CTA is currently not acceptable as a general screening tool and CS testing or truly non-invasive approaches may be

preferable. However, as proposed by Naghavi et al<sup>36</sup> non-invasive coronary angiography may potentially be used as a downstream test in the workup of asymptomatic individuals with high-risk characteristics, following home- or office-based screening (Figure 10). Through selection of high-risk patients with truly non-invasive techniques only a small subgroup of high-risk patients remains in which further non-invasive and subsequent invasive imaging may be beneficial. Future studies will need to determine the value and feasibility of such a screening strategy.

## LIMITATIONS

Although the available data support the potential clinical relevance of assessment of plaque characteristics on CTA, accurate quantification of plaque remains challenging, while requiring optimal image quality. Leber et al<sup>44</sup> have reported on the accuracy of 64-slice CTA to classify and quantify plaque volumes in the proximal coronary arteries as compared to intravascular ultrasound. CTA, detected calcified and mixed plaque with high accuracy (95 and 94%, respectively) but accuracy was lower for non-calcified lesions (83%). When regarding plaque volume, non-calcified plaque and mixed plaque volumes were systematically underestimated whereas calcified plaque volume was overestimated by CTA. Novel software packages aimed at



**Figure 9.** Algorithm illustrating the sequential use of CTA and functional imaging in patients with an intermediate pre-test likelihood. Reprinted with permission from Schuijf et al.<sup>70</sup> CTA, Multi-slice computed tomography coronary angiography.

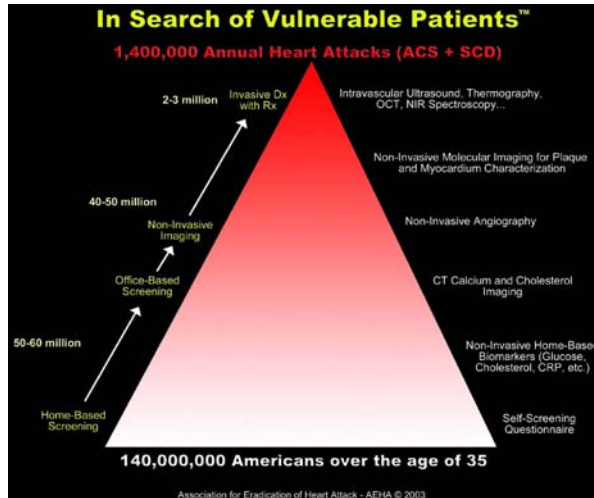
assessing plaque volume and plaque composition are currently being developed and may improve not only accuracy but also reproducibility of measurements.

In addition, the radiation dose remains a cause of concern for CTA. Currently traditional 64-slice CTA protocols are still associated with high radiation exposure, although the radiation dose of CTA has recently decreased substantially.<sup>71-74</sup> Importantly, low-dose CTA with prospective ECG triggering has recently been shown to reduce radiation burden while maintaining image quality and a high diagnostic accuracy.<sup>75,76</sup> Currently, the radiation burden with these novel acquisition techniques is approaching the level of diagnostic catheterization or even lower.<sup>77</sup>

## CONCLUSION

Non-invasive anatomic assessment of plaque burden, location, composition, and remodeling using CTA may provide prognostically relevant information, incremental to not only the Framingham risk score, but also to other imaging approaches as coronary artery calcium scoring and myocardial perfusion imaging. Thus, non-invasive characterization of atherosclerosis has the potential to provide a more patient-tailored approach to disease management. Future studies assessing outcome after CTA-based risk adjustments are needed to further understand the value of detailed non-invasive anatomic imaging.





**Figure 10.** Potential screening algorithm for the identification of vulnerable plaque in asymptomatic individuals. An example of an algorithm with potential usefulness in the workup of high-risk patients, to identify the presence of plaques with vulnerable characteristics. At the *bottom* of the pyramid, individuals are selected for further non-invasive evaluation with CS testing and CTA based on home-based screening questionnaires and biomarker assessment. At the *top* of the pyramid a small subgroup remains warranting further invasive assessment. Ideally such an algorithm can be used to identify a subgroup of the general asymptomatic populations in need of aggressive primary prevention strategies. Reprinted with permission from Naghavi et al.<sup>36</sup> CS, Calcium score; CTA, multi-slice computed tomography coronary angiography.

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