

# Defining the *non-vulnerable* and *vulnerable* patients with computed tomography coronary angiography: evaluation of atherosclerotic plaque burden and composition

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Received 6 November 2015; accepted after revision 13 January 2016; online publish-ahead-of-print 21 February 2016

The shift from coronary plaque stability to plaque instability remains poorly understood despite enormous efforts and expenditures have been assigned to the study of the subject. On the other hand, there have been serious advances in imaging helping us to characterize *non-vulnerable patients*. The latter has much more value in the clinical decision-making process since it provides high certainty that the patient's probability of a future acute event is low and treatment decisions should be made accordingly. Although coronary plaque rupture is still recognized as the main source of acute thrombotic events, numerous studies have shown that the prediction of events on an individual basis is far more complex and demands a more open approach aimed at characterizing patient risk rather than assessing the risk of thrombosis of a single plaque. Computed tomography coronary angiography (CTCA) has the ability to evaluate non-invasively the extent, burden, severity, and characteristics of coronary artery disease (CAD) and has a close relationship to intravascular ultrasound. On the basis of an excellent negative predictive value with an annualized event rate of ~0.20% assessed over more than 6000 patients, thus providing a 5-year warranty period, CTCA has been identified as the finest non-invasive tool to exclude CAD. This means that CTCA is able to reliably characterize the non-vulnerable patient. Conversely, in the past few years, several studies have attempted to establish CTCA-derived predictors of acute coronary syndromes, both from a lesion level and a patient level basis with very low positive predictive value, thus questioning the vulnerable patient/plaque concept.

**Keywords** coronary • atherosclerosis • imaging • computed tomography

## Introduction

The pathophysiology of coronary atherosclerosis (CA) has undergone significant changes in paradigms during the past decades related to plaque development, growth, and destabilization. Numerous studies have established that CA is a highly prevalent and ubiquitous disease that can initiate at very young age in certain conditions, but that also has an unexpected natural history.<sup>1,2</sup> Indeed, the shift from coronary plaque stability to plaque instability remains poorly understood despite enormous efforts and expenditures have been assigned to the study of the subject by the industry, the National Institutes of Research, independent investigators, and other funding sources.<sup>3</sup>

The search for the identification of single high-risk atherosclerotic plaques has been fuelled by the attractive possibility to treat plaques before they disrupt or evolve to luminal thrombosis.<sup>4</sup>

Notwithstanding, although coronary plaque rupture is still recognized as the main source of acute thrombotic events, numerous studies have shown that the prediction of events on an individual basis is far more complex and demands a more open approach aimed at characterizing patient risk rather than assessing the risk of thrombosis of a single plaque.

Computed tomography coronary angiography (CTCA) has emerged during the past decade as an accurate and robust non-invasive imaging tool that allows the assessment of the presence and severity of coronary artery disease (CAD). One distinctive feature of

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CTCA is its ability to evaluate the vessel wall aside from the lumen. As such, it can portray the extent, burden, and severity of CAD. For that reason, CTCA has a closer relationship to intravascular ultrasound (IVUS) rather than to invasive coronary angiography (ICA).<sup>5</sup>

The presence of an underlying state of vulnerability in vascular lesions, involving a triad of endothelial lesion, impairment of blood flow and a pro-thrombotic condition, has been suggested as early as two centuries ago by Rudolf Virchow.<sup>6</sup> It is paradoxical therefore that during the first decade of the 21<sup>st</sup> century the pathophysiology of acute coronary syndromes (ACS) seemed to be mostly reduced to the search of a single culprit vulnerable plaque purportedly prone to plaque disruption and subsequent local acute thrombosis, which was meant to become the solitary responsible of future adverse coronary events (Figure 1).<sup>7</sup>

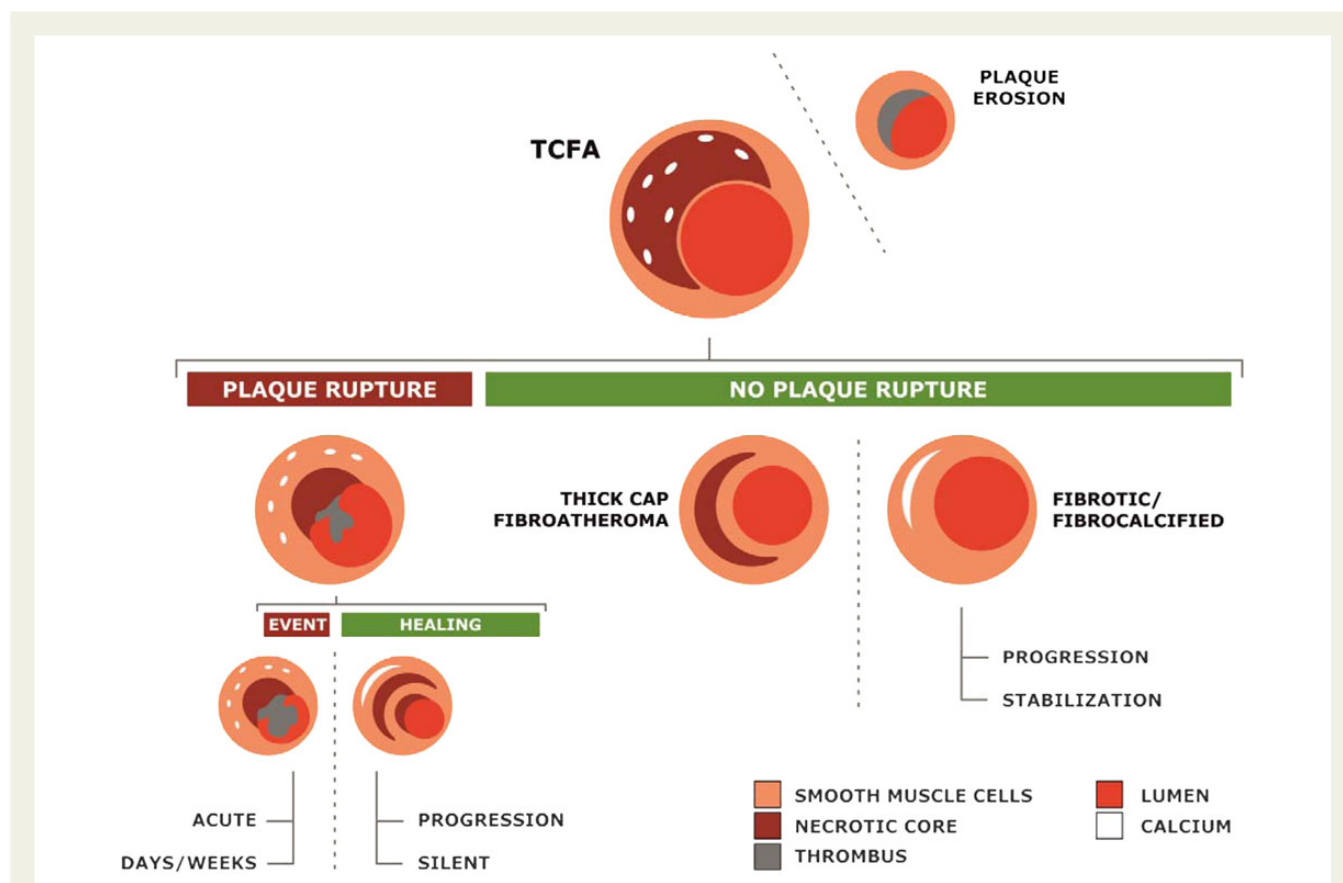
## Plaque characterization with CTCA: positive remodelling and low-attenuation plaques

On the basis of an excellent negative predictive value with an annualized event rate of ~0.20% assessed over more than

6000 patients, thus providing a 5-year warranty period, CTCA has been identified as the finest non-invasive tool to exclude CAD.<sup>8–11</sup> This means that CTCA is able to reliably characterize the *non-vulnerable* patient.

One of the most attractive points for non-invasive imaging with CTCA is the ability to, unlike invasive imaging, target at primary prevention. Further, a number of studies have explored the characteristics of plaques in ACS by means of CTCA. It is worth mentioning that post-processing techniques including the use of a soft reconstruction kernel might improve the visualization of low-density plaques.

Moreover, CTCA has emerged as a tool with great potential for the assessment of thin-cap fibroatheroma lesions (TCFAs), the most frequent substrate of plaque rupture and subsequent acute thrombotic coronary occlusion.<sup>12–15</sup> CT attenuation values (Hounsfield units, HU) are clearly different for calcified and non-calcified plaques. Indeed, plaques with large ( $\geq 10\%$  of plaque area) necrotic cores have significantly lower attenuation values compared with plaques with  $< 10\%$  necrotic core ( $41 \pm 26$  vs.  $93 \pm 38$  HU,  $P < 0.0001$ ).<sup>16</sup> Nevertheless, a significant overlap of mean CT densities exists between plaques with necrotic core areas in the range between these values. Pathological studies have established that the



**Figure 1** Natural history of thin-cap fibroatheroma (TCFA). As depicted in the graph, despite roughly 60% of acute thrombotic occlusions have TCFA as the underlying substrate, almost 40% of occlusions have plaque erosions as substrate, that typically are plaques with no identifiable feature. TCFAs are a relatively common finding, and only a portion of these lesions undergo plaque rupture. Furthermore, most plaque ruptures have a silent course or are related to stable angina due to plaque progression. Only a portion of plaque ruptures lead to events, with a delay of days to weeks in half of the patients.

size of necrotic cores in TCFA ranges from 1.6 to 1.7 mm<sup>2</sup>, with a length ranging from 2 to 17 mm; whereas in rupture plaques the size ranges from 2.2 to 3.8 mm<sup>2</sup> and the length from 2.5 to 22 mm.<sup>17</sup> Accordingly, CTCA has enough resolution to assess the size and characteristics of necrotic cores. Furthermore, using combined IVUS and computational simulation models Ohayon *et al.* have shown a high correlation between necrotic core thickness and fibrous cap stress. Indeed, the authors found that the necrotic core thickness outweighed area for predicting plaque rupture.<sup>18</sup> These findings are warranted to be explored by CTCA in future studies.

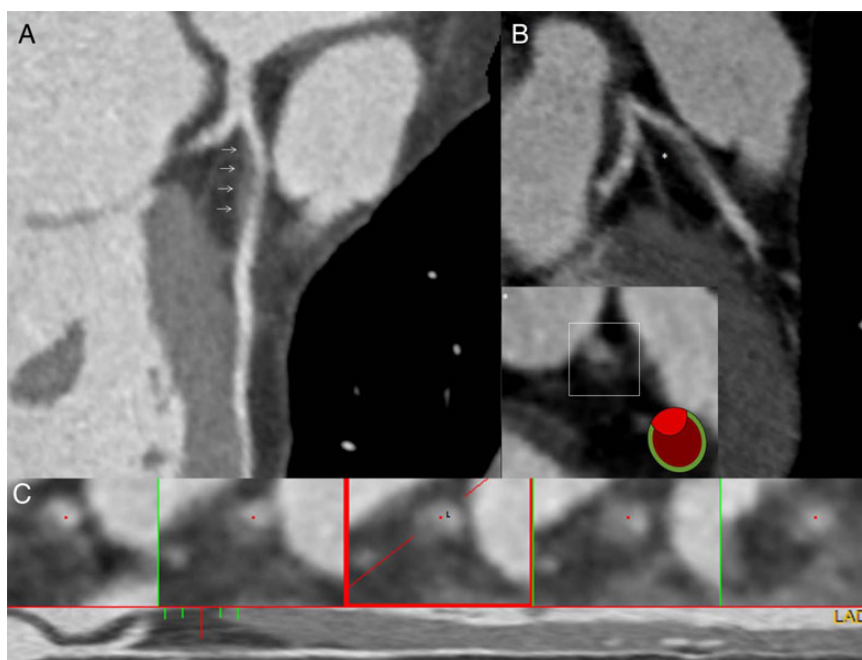
The main CTCA features related to high-risk plaques are: (1) positive remodelling, PR [remodelling index (RI)  $\geq 1.1$ ]; (2) low-attenuation plaque, LAP (<30 HU); (3) napkin-ring sign, NRS (description below); and (4) spotty calcifications, SCs (<3 mm). Examples of these are portrayed in Figures 2–5.

Several studies have established that TCFA, as well as plaque ruptures and healed plaque ruptures, are non-uniformly distributed throughout the coronary tree.<sup>12,19–22</sup> Most of these lesions are located within the proximal segments of the left anterior descending (LAD) and left circumflex arteries, whereas they are more widely distributed in the right coronary artery (RCA). Such proximal clustering of high-risk plaques further favours detection by CTCA (Figures 2, 3 and 5). Moreover, two out of the three major vulnerable plaque criteria (PR and necrotic core) can be measured and/or closely inferred with CTCA. Particularly, as long as there is no

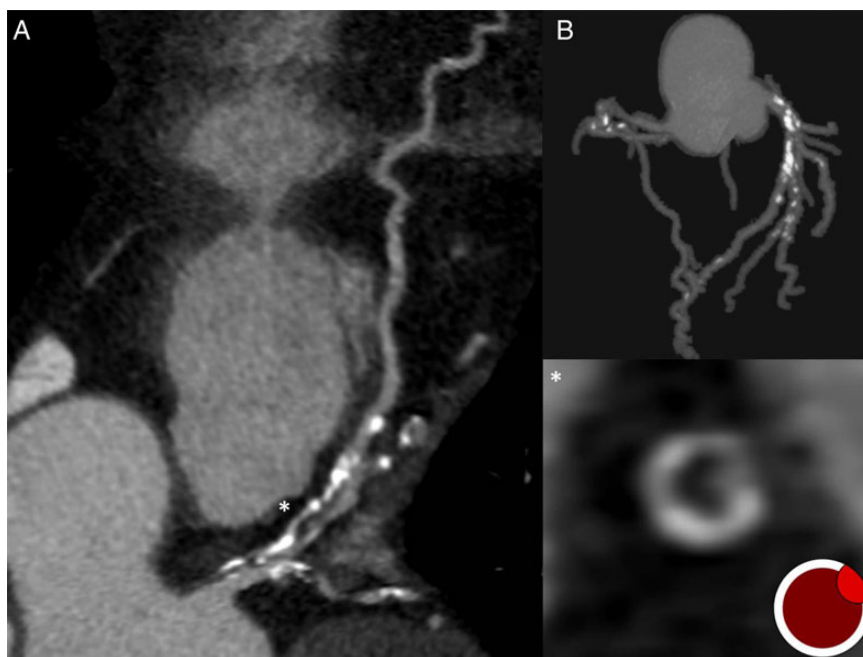
underlying severe calcification, CTCA enables accurate measurement of vessel size and thus of remodelling pattern.<sup>23,24</sup>

The presence of PR is based on the RI, which is calculated as the vessel size at the site of maximal narrowing divided by the vessel size of the reference site. An RI of  $\geq 1.1$  has been identified as the optimal threshold to identify PR compared with IVUS (Figure 2).<sup>24</sup> In numerous *ex vivo* and *in vivo* studies, PR has been associated with the extent of lipidic-necrotic core.<sup>25</sup> Accordingly, acquaintance of the remodelling pattern by CTCA can accurately become a reliable surrogate of plaque composition. Furthermore, plaque ruptures commonly occur at sites of significant plaque accumulation related to PR.<sup>26</sup>

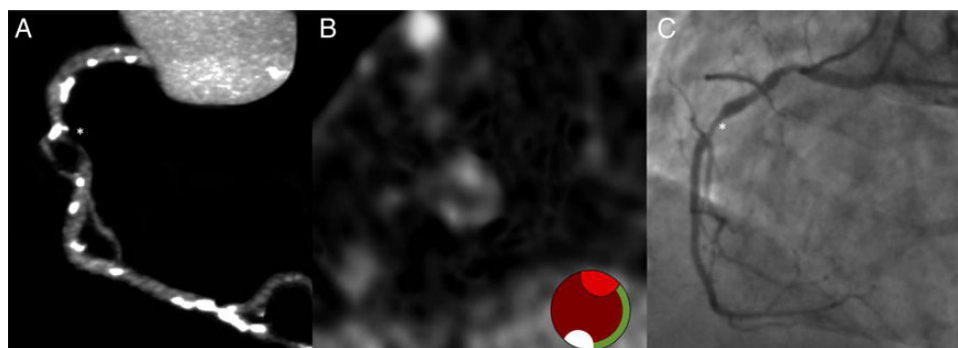
One of the first studies in this regard found significantly larger plaque area and PR in culprit lesions of patients with ACS compared with patients with stable CAD.<sup>27</sup> In the same line, Motoyama *et al.* reported that culprit lesions of patients with ACS commonly had PR, LAP, and SCs (Figure 4).<sup>28</sup> The same group extended such preliminary findings in much larger populations. In the first of these studies, the combined presence of both PR and LAP conferred an increased risk of developing ACS compared with patients without these features (both features positive: 22.2%; one feature positive: 3.7%; both features negative: 0.5%).<sup>29</sup> And in the most recent and largest study ( $n = 3158$ ), the presence of these high-risk plaques was an independent predictor of events, although with a low positive predictive value (16%).<sup>30</sup> In this study, after a mean follow-up of



**Figure 2** A 43-year-old male, active, without coronary risk factors, and with anterior wall ischaemia assessed with SPECT. CTCA depicts an eccentric non-calcified lesion (arrows) at the proximal LAD artery, with PR and NRS. (A) A curved multiplanar reconstruction, (B) a multiplanar maximum intensity projection reconstruction, and (C) a longitudinal view of the LAD. An orthogonal cross-sectional area at the site of maximal stenosis (\*) shows a plaque with moderate stenosis (red lumen in graph), with a low-attenuation core (brown in graph) and a peripheral rim of higher-attenuation tissue but lower than 130 HU. These findings are characteristic of NRS. The patient had also a mild non-calcified lesion at the mid-RCA, with overall non-extensive CAD by all scores (calcium score 0, SIS 2/16, SSS 3/48, Duke prognostic CAD index 2/6, 3-vessel plaque 0/1, any left main plaque 0/1, and a CT-Leaman score of 4.5).



**Figure 3** LAD artery with diffuse mixed atherosclerosis (A). Three-dimensional maximum intensity reconstruction (B) demonstrated the presence of extensive CAD (SIS larger than 4; since 8 segments are involved: left main coronary artery, proximal, mid, and distal LAD, first and second diagonal branches, proximal circumflex, and mid-RCA). The presence of a severe stenosis (asterisk) at the proximal LAD, with PR and low-attenuation core ( $<30$  HU, brown in graph). Peripheral calcification is observed (white in graph), possibly related to a healed plaque rupture.



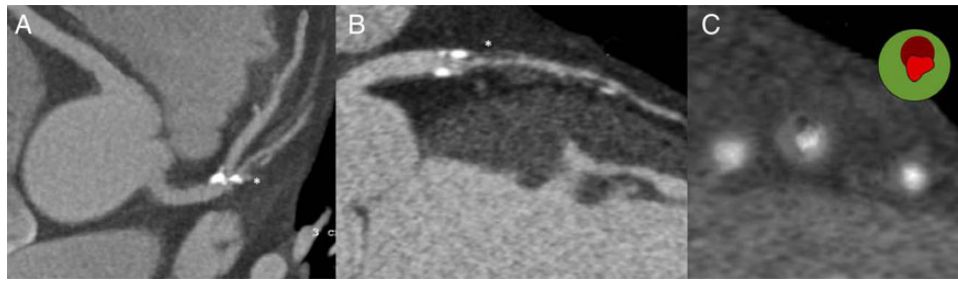
**Figure 4** Patient with extensive CAD (SIS 9/16, SSS 21/48, Duke prognostic CAD index 5/6, 3-vessel plaque 1/1, any left main plaque 1/1, and a CT-Leaman score of 20.2). Maximum intensity projection (A) of the RCA, showing multiple calcifications and a severe stenosis (asterisk) at the mid-RCA. The orthogonal cross-sectional area shows at the site of maximum stenosis (B) shows a mixed plaque, with a low-attenuation core ( $<30$  HU, brown in graph), a SC at 7 o'clock (white in graph), and rim of higher attenuation (green in graph, 'napkin-ring' sign). The invasive angiography is depicted (C).

$3.9 \pm 2.4$  years, plaque progression detected by CTCA was identified as an independent predictor of ACS.<sup>30</sup>

Furthermore, using optical coherence tomography (OCT) as reference standard, Kashiwagi *et al.* demonstrated the ability of CTCA to discriminate between TCFA and non-TCFA lesions.<sup>13</sup> In this study, PR identified by CTCA was identified more frequently in the TCFA group than in the non-TCFA group (76 vs. 31%,

$P < 0.0001$ ), and the attenuation values of culprit plaques in the TCFA group were lower than that in the non-TCFA group ( $35.1 \pm 32.3$  vs.  $62.0 \pm 33.6$  HU,  $P < 0.001$ ).

CTCA lacks the sufficient spatial resolution to measure fibrous plaque thickness, which can be accurately estimated by means of OCT.<sup>31</sup> It is noteworthy though that IVUS does not have enough resolution either, and that such limitation has not impaired its ability



**Figure 5** Multiplanar reconstructions (A and B) showing a mixed plaque with severe stenosis (asterisk) at the proximal intermediate branch. The orthogonal cross-sectional area (C) shows a non-calcified plaque with a very low-attenuation core next to the lumen at 12 o'clock.

to detect *in vivo* surrogates of TCFA.<sup>32</sup> Indeed, Sato *et al.* showed that the fibrous cap thickness measured by OCT was highly related to the presence of PR and LAP assessed by CTCA, with a mean cap thickness of  $76 \pm 24 \mu\text{m}$  with the presence of both features, of  $154 \pm 51 \mu\text{m}$  with one feature present, and of  $192 \pm 49 \mu\text{m}$  with none present ( $P < 0.001$ ).<sup>33</sup>

The NRS has been defined as a plaque with a low-attenuation core surrounded by a rimlike area of higher attenuation (but less than 130 HU) (Figures 2 and 4), and has been identified as a consistent finding in high-risk plaques.<sup>34,35</sup> The pathophysiology of this finding remains unsettled, although it might be related to diverse high-risk features such as intraplaque haemorrhage, contrast enhancement of the vasa vasorum, microcalcifications, or even healed ruptures.<sup>14</sup> Indeed, the same group has established in a more recent study including heart donors that the NRS has a high specificity and positive predictive value for the detection of advanced atherosclerotic lesions, with an area under the receiver-operating characteristic curve of 0.77 for the detection of advanced lesions and TCFA.<sup>36</sup>

Kashiwagi *et al.* found that TCFA, aside from higher RIs and lower CT attenuation values, had more often NRS (44% in the TCFA group vs. 4% for the non-TCFA group).<sup>13</sup> Furthermore, a recent prospective study including 1.174 plaques in 895 patients who underwent CTCA found that after a mean follow-up of 2.3 years, PR (HR 5.3,  $P < 0.001$ ), LAP (HR 3.8,  $P = 0.007$ ), and the NRS (HR 5.6,  $P < 0.0001$ ) were identified as significant independent predictors of ACS.<sup>37</sup>

The NRS shows promise to emerge as a more specific marker of high-risk plaques, since it is less prevalent than the other high-risk features, and might appear as a better predictor of events. It is noteworthy that in the study of Otsuka *et al.*, PR, LAP, and NRS were identified in 1.0, 0.8, and 0.4% of the assessed plaques, respectively. Furthermore, 41% of the events occurred in plaques with underlying NRS.<sup>37</sup> Notwithstanding, the reported frequency of NRS remains highly variable, from 0.4 to 22%.<sup>38</sup> Along this line, IVUS-derived studies have reported a higher prevalence of TCFA, particularly within the 30-mm proximal LAD arteries (up to 24%).<sup>39,40</sup> Moreover, in a very recent study using OCT as reference standard, PR and LAP predicted TCFA with macrophage infiltration, whereas SC and the NRS did not.<sup>41</sup> Of note, OCT has been recently under scrutiny for TCFA detection since there are many OCT artefacts that are the source of misclassification and misinterpretation of plaque types.

## Computational fluid dynamics-based CT applications

Although it lies beyond the scope of this review, another worth-mentioning aspect of CTCA related to plaque characterization involves the recent developments in computational fluid dynamics (CFD)-based CT applications such as fractional flow reserve (FFR)-CT and endothelial shear stress-CT. Briefly, these applications have emerged mainly as a response to the weak relationship between the degree of stenosis of a given lesion and the underlying downstream haemodynamical significance. Three multicentre prospective studies have been published in this regard, suggesting that FFR-CT (based on complex post-processing of conventional CTCA) might improve the diagnostic accuracy of CTCA to detect lesion-specific ischaemia.<sup>42–44</sup> In parallel, by means of CFD, a number of flow parameters including endothelial and wall shear stress, which until recently required advanced catheter-based techniques, can be calculated using CTCA. Such CT-based 3D models are not only validated but also have been recently related to atherosclerotic plaque characteristics.<sup>45,46</sup>

## Atherosclerotic plaque burden assessment with CTCA

The ability of CTCA to evaluate the vessel wall positions the technique as more closely related to IVUS than to ICA. Furthermore, IVUS interrogations are related to a 2% incidence of vasospasm and hardly ever include the three major epicardial coronary arteries, usually excluding the distal segments as well as secondary branches.<sup>22,47</sup> On the contrary, CTCA has the capacity to assess the presence and extent of plaque throughout the whole coronary tree, only excluding segments smaller than 1.5 mm.

In a meta-analysis, Voros *et al.* found that CTCA had an excellent diagnostic accuracy for the detection of plaques compared with IVUS (area under receiver-operating characteristic curve of 0.94), with similar plaque area, volume, and per cent area stenosis, and a slight overestimation of luminal area. The latter was possibly attributed to partial volume effects of the contrast-enhanced lumen.<sup>5</sup>

As mentioned above, most acute thrombotic lesions have TCFA lesions as substrate. Since pathologic studies reported that 80% of TCFA have a per cent area stenosis lower than 75%, which

corresponds to a <50% diameter stenosis, it can be inferred that plaques responsible for future coronary events might be large but are often non-obstructive.<sup>48</sup> Advanced plaque composition imaging has provided modest incremental prognostic value over established risk predictors such as atherosclerotic plaque burden. Indeed, in the largest prospective clinical study aimed to explore the natural history of CAD with three-vessel IVUS in patients with ACS (PRO-SPECT), the risk of AMI or sudden death related to TCFA was

remarkably low.<sup>49</sup> On opposite, atherosclerotic plaque burden has been strongly and systematically linked to the risk of cardiovascular events.<sup>50–52</sup>

CTCA has the ability to portray the global extent or burden of CA. Several CAD scores have been proposed in this regard (Tables 1 and 2). Briefly, Maddox et al. have described seven categories of CAD extent: normal; one-, two-, and three-vessel non-obstructive CADs; and one-, two-, and three-vessel obstructive CADs.<sup>53</sup>

**Table 1** CTCA variables related to risk stratification, discriminated by conventional (routine) reading, atherosclerotic burden assessment, and high-risk characteristics

CTCA variables		
Conventional reading	Atherosclerotic burden	High-risk characteristics
Severity (none, mild, moderate, or severe)	SIS ( $\leq$ or $>$ 4)	NRS
Coronary artery calcium scoring (zero, $<$ or $\geq$ 75% percentile)	SSS	LAP
Basic morphology (calcified, non-calcified, mixed)	Total plaque volume	PR
	Total non-calcified plaque	SC
	Total plaque burden	
	Three-vessel plaque	
	Any LMCA plaque	
Risk stratification		
Lesion based	Patient based	
Severity	Calcium scoring	
Morphology (including length)	SIS	
NRS <sup>a</sup>	SSS	
LAP ( $<$ 30 HU)	Total plaque volume	
PR (RI $>$ 1.1)	Three-vessel plaque	
SC ( $<$ 3 mm)	Any LMCA plaque	
	CT-Leaman score	
	CT-SYNTAX score	

LMCA refers to left main coronary artery.

<sup>a</sup>NRS defined as plaque with a low-attenuation core surrounded by a rimlike area of higher attenuation (but less than 130 HU).

**Table 2** Atherosclerotic burden CTCA scores

Modified Duke prognostic CAD index

(1) <50% stenosis; (2)  $\geq$ 2 non-obstructive stenoses (including one artery with proximal disease or one artery with 50–69% stenosis); (3) two vessels with stenoses 50–69% or one vessel with  $\geq$ 70% stenosis; (4) three-vessel disease with stenoses 50–69%, or two vessels  $\geq$ 70%, or proximal LAD stenosis  $\geq$ 70%; (5) three-vessel disease with stenoses  $\geq$ 70% or two-vessel disease  $\geq$ 70% with proximal LAD; (6) left main stenosis  $\geq$ 50%

SIS

The total number of segments involved irrespective of the degree of stenosis, ranging from 0 to 16.

SSS

Each coronary segment is graded based on the degree of coronary stenosis (0 = no plaque, 1 = mild, 2 = moderate, 3 = severe). Subsequently, the scores of all segments are summed leading to total score ranging from 0 to 48.

CT-LeSc

This score uses three sets of weighting factors using a 18-segment coronary model: (1) localization of plaques, accounting for dominance [i.e. multiplication factors: left main (right dominance  $\times$ 5, left dominance  $\times$ 6), LAD proximal  $\times$ 3.5, LAD mid  $\times$ 2.5, and LAD distal  $\times$ 1]; (2) type of plaque, with a multiplication factor of 1 for calcified plaques and of 1.5 for non-calcified and mixed plaques; and (3) degree of stenosis, with a multiplication factor of 0.615 for non-obstructive (<50% stenosis) and a multiplication factor of 1 for  $\geq$ 50% lesions.

Binary scores

Presence or absence of:

Three-vessel plaque

Any left main coronary artery plaque

Moreover, the atherosclerotic burden can also be classified according to the modified Duke prognostic CAD index, segment involvement score (SIS), segment stenosis score (SSS), CTCA-adapted Leaman score (CT-LeSc), CT-SYNTAX score, and binary scores (Table 2), all providing further prognostic information.<sup>51,54</sup>

The prognostic value of non-obstructive CAD assessed by CTCA has been nicely addressed in the large (currently more than 32,000 patients) international multicentre CONFIRM registry that demonstrated worse survival rates in patients with non-obstructive CAD compared with patients with normal coronary arteries.<sup>8</sup> Lin *et al.*, in a cohort of 2583 symptomatic patients, also reported a two-, three-, and six-fold increment in the mortality risk among patients with (non-obstructive) involvement of one, two, or three vessels.<sup>55</sup>

Furthermore, the prognostic value of the atherosclerotic burden extension assessed by means of the SIS has been consistently established in different populations, showing that a SIS larger than five segments was related to a significantly higher rate of hard events.<sup>10,51</sup>

Importantly, Bittencourt *et al.* recently reported in a large cohort of 3,242 patients with long-term (median 3.6 years) follow-up that the presence of non-obstructive but extensive CAD defined as a SIS >4 segments (Figure 3) conferred an increased risk of myocardial infarction or cardiovascular death, with similar rates of events compared with patients with obstructive disease but with a SIS ≤4.<sup>56</sup> On the contrary, of the 1,301 patients with normal CTCA within this cohort, only 1.0% suffered events (0.04% myocardial infarctions per year). In this study, the addition of the presence and severity (Model 2) to a clinical stratification model (Model 1) provided a significant improvement for the prediction of cardiovascular death or myocardial infarction (global  $\chi^2$  from 23.5 to 46.6;  $P < 0.001$ ). Moreover, adding the presence of extensive (SIS > 4) or non-extensive (SIS ≤ 4) obstructive or non-obstructive CAD to Model 2 provided additional incremental predictive value (global  $\chi^2$  from 46.6 to 53.4;  $P < 0.001$ ).<sup>56</sup> Similarly, it has recently been demonstrated that patients with non-obstructive CAD but with a high CTCA-Leaman score (>5) have a similar hard-event rate than patients with obstructive CAD but a low CTCA-Leaman score.<sup>57</sup>

Versteylet *et al.* recently reported on 1650 patients who underwent CTCA and were followed up for a mean 26 months. In this study, conventional reading analysis [CACS, degree of stenosis (no lesion, mild, moderate, severe), and plaque characterization (calcified, non-calcified, or partially calcified)] could not discriminate between controls and patients who had an ACS. In contrast, semi-automated plaque quantification (total plaque volume, total non-calcified volume, non-calcified percentage, and plaque burden) provided an incremental prognostic value over clinical risk profile and conventional reading (area under the curve 0.64 vs. 0.79,  $P < 0.05$ ).<sup>58</sup>

Finally, in a very recent study, Park *et al.* reported the results of a multicentre study that included 407 lesions evaluated with invasive FFR and CTCA, evaluating the relationship between atherosclerotic plaque characteristics (APC) (including aggregate plaque volume, lesion length, PR, LAP, and SC) and the presence of lesion-specific ischaemia. In this study, only 55% of lesions classified as obstructive (>50% stenosis) had abnormal invasive FFR, whereas 17% of lesions classified as non-obstructive were actually functionally significant (abnormal invasive FFR). Interestingly, the per cent aggregate plaque volume (measured from the ostium to the distal end of the lesion,

and divided by the total vessel volume) was an independent predictor of lesion-specific ischaemia independently from the severity of obstructive lesions. Furthermore, all abovementioned APC provided significant incremental risk prediction beyond coronary stenosis. Of note, the authors demonstrated a strong association between the number (particularly ≥ 2 APC) and type of APC and lesion-specific ischaemia even among non-obstructive lesions. Particularly, at multivariate analysis, PR was the strongest independent predictor of ischaemia in both obstructive lesions [OR 3.6 (95% CI 1.8–7.2),  $P < 0.001$ ] and, more importantly, in non-obstructive lesions [OR 10.5 (CI 95% 3.1–36.4),  $P < 0.001$ ].<sup>59</sup> Similarly, Naya *et al.* reported that the extent of CA assessed by the modified Duke CAD index and the number of coronary segments with mixed plaque were associated with decreased myocardial flow reserved as assessed by <sup>82</sup>Rb myocardial perfusion positron emission tomography.<sup>60</sup>

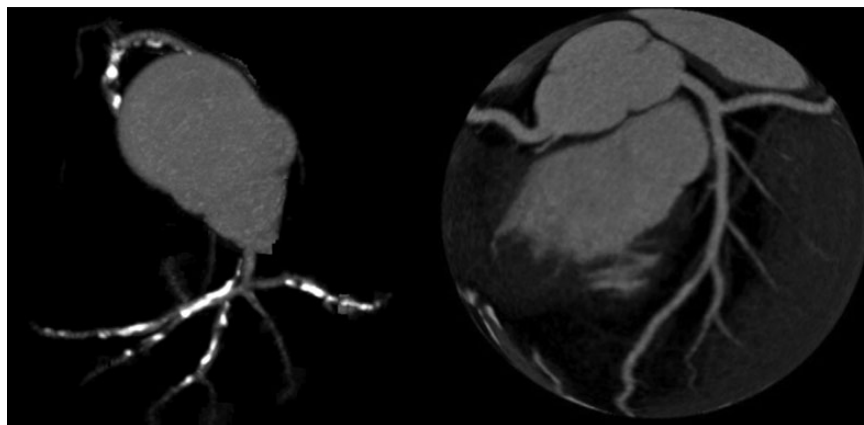
The CONFIRM registry has demonstrated that the identification of non-obstructive CAD does not lead to an increase in revascularization rates.<sup>61</sup> In turn, identification of non-obstructive CAD by CTCA leads to an increase in the utilization of preventive cardiovascular medical therapies including improvement in blood pressure and cholesterol levels.<sup>62</sup> In this regard, intriguing findings from a recent study including 2839 patients showed that among those with non-obstructive but extensive CAD (SIS > 4), statin use after was associated with a significant reduction in death or myocardial infarction.<sup>63</sup>

Finally, a recent study has described the prognostic value of the CT-based SYNTAX score, although it should be acknowledged that this score has been developed for the prediction of complications related to revascularization procedures of patients with multiple-vessel CAD.<sup>64</sup> Accordingly, calculation of this score is not only much more challenging than the aforementioned scores, but also probably targets a population of few interest for primary prevention (Figure 6).

## Technical considerations and limitations

With the current available scanners, CTCA can be performed with an ~70% radiation exposure reduction and comparable image quality by means of prospectively electrocardiogram (ECG)-gated scan protocol ( $3.5 \pm 2.1$  mSv).<sup>65</sup> Furthermore, in patients with heart rates lower than 60 bpm, CTCA using the high-pitch mode (dual-source CT) can be achieved at sub-millisievert doses ( $0.9 \pm 0.1$  mSv), with preserved diagnostic accuracy.<sup>66</sup> These effective radiation doses are significantly lower than those of myocardial perfusion studies using single-photon emission computed tomography, which depend on the protocol, camera, and tracer used, but are usually higher than 7 mSv.<sup>67</sup>

Coronary calcification endures as a major limitation of CTCA since it is commonly related to overestimation of the stenosis severity due to a number of technical issues including blooming and beam hardening effects. The generation of artefacts adjacent to calcified plaques might mimic non-calcified plaques and thus lead to an overestimation of plaque volume. Dual-energy CTCA, by means of monochromatic evaluation, that has recently emerged as a novel



**Figure 6** Examples of two patients with atypical chest pain and discordant functional assessment. On the left, a 70-year-old male with hypertension, hypercholesterolaemia, and previous smoking as coronary risk factors; with abnormal exercise ECG but without evidence of ischaemia by myocardial perfusion imaging. The CTCA showed evidence of extensive (SIS 13/16, SSS 28/48, Duke prognostic CAD index 5/6, 3-vessel plaque 1/1, any left main plaque 1/1, and a CT-Leaman score of 25.2) and severe CAD. On the right, a 42-year-old male with stress, obesity, and hypercholesterolaemia as risk factors; with abnormal exercise ECG but without evidence of ischaemia by myocardial perfusion imaging. The CTCA showed a completely normal coronary tree.

approach might potentially offer a more accurate assessment of CA and plaque characterization since it mitigates or might even solve some of the aforementioned limitations related to the polychromatic nature of X-rays.<sup>68,69</sup>

Finally, the extent of intraluminal contrast opacification, related to iodine delivery rate, acquisition parameters, and reconstruction algorithms has an impact on plaque characterization. Consequently, this should be accounted for since LAP thresholds might differ according to the adjacent iodine concentration.<sup>70</sup> Other obvious limitations include patients with respiratory or cardiac (arrhythmia) motion artefacts and the risk of contrast-induced nephropathy in high-risk patients, though very rare at currently low iodinated contrast doses.

## Calcium scoring

A large body of evidence has established coronary artery calcification (CAC), a hallmark of atherosclerosis, as an independent predictor of events with incremental prognostic value over traditional risk stratification algorithms.<sup>52,71,72</sup> Furthermore, CAC progression has been associated with a higher incidence of events.<sup>73</sup> Both *ex vivo* and IVUS studies have shown that CAC is closely related to atherosclerotic plaque burden.<sup>74–76</sup> Nonetheless, the extent of CAC is not strongly related to the degree of luminal stenosis on a per lesion basis.<sup>76,77</sup> Indeed, despite CAC is commonly associated to advanced stages of atherosclerosis and to a more stable phenotype, it has also been shown that calcifications can be present in early stages of CAD. Particularly, most TCFA lesions show microcalcifications within the necrotic core or at the periphery.<sup>12</sup>

CAC assessment by multidetector CT is associated to a very low effective radiation dose ( $\sim 1.0$  mSv), and it has been extensively validated as an independent predictor of major adverse cardiac events and total mortality in asymptomatic patients, providing a

significant incremental value over traditional risk factors and functional studies.<sup>78–81</sup>

A number of absolute CAC score thresholds have been defined for risk prediction ranging from very low risk to very high risk of events (CAC 0, 1–99, 100–399, 400–999, and  $\geq 1000$ ), being asymptomatic individuals with CAC  $> 400$  at a similar risk of events than patients with established CAD.<sup>79–81</sup> Nevertheless, the close relationship between CAC and age mandates an assessment according to age and sex. In fact, Leber *et al.* have shown that CAC above the 75th percentile is associated with significantly higher rates of cardiovascular death and myocardial infarction than patients with CAC scores below the 75th percentile.<sup>82</sup>

The *non-vulnerable* patient is an asymptomatic and possibly even symptomatic patient with the absence of calcifications (CAC zero), and these patients have a utterly low incidence of events at long-term follow-up.<sup>72,76</sup> Of note, a large body of evidence renders the absence of calcification a 5-year safety window, with a 0.10% annual risk of events.<sup>71,80,83–87</sup>

Notwithstanding, the absence of calcium does not rule out the presence of plaque. Indeed, CAC zero in symptomatic patients should lead to a cautious interpretation due to a number of factors. Firstly,  $\sim 30\%$  of acute coronary thromboses, particularly in young women and in smokers, are attributed to plaque erosion.<sup>88,89</sup> Secondly, SCs can be occasionally undetected by the 3-mm slices that are routinely used for CAC assessment by MDCT.

As mentioned above, CTCA is so far aimed at the assessment of symptomatic patients and at secondary prevention. Indeed, in the recently published FACTOR-64 randomized trial that involved asymptomatic patients with diabetes, the use of CTCA to screen for CAD did not reduce the rate of events at 4 years.<sup>90</sup> In turn, CAC scoring targets primary prevention.

Finally, there is ongoing debate regarding the prognostic value of CTCA compared with CAC in asymptomatic patients. Recently, a



**Table 3** CTCA thresholds for patient-based risk stratification

CTCA variables	Thresholds	Low risk (non-VP)	High risk (VP)
Coronary artery calcium score	0, 1–99, 100–399, ≥400	0	≥400/>75th percentile
SIS	0/16	<5	≥5
Three-vessel plaque	0/1	0	1
Any left main plaque	0/1	0	1
CT-Leaman score	0 <sup>a</sup>	≤5	>5
Duke CAD prognostic index	1/6	1	≥4

As depicted, low- and high-risk patients are clearly identified with CTCA, whereas the positive predictive value of intermediate risk patients remains to be established.

<sup>a</sup>The maximum level of the CT-Leaman score depends on the coronary anatomy. VP refers to vulnerable patient.

sub-analysis of the CONFIRM registry reported that CTCA has incremental value over clinical risk scores only among patients with moderately high CAC (between 100 and 400). Interestingly, among patients with non-obstructive CAD, CAC extent was directly related to an increased incidence of all-cause mortality.<sup>91</sup>

## Conclusions

In summary, as discussed above, the past decades have witnessed a blind pursuit of vulnerable plaques allegedly being adjudicated as the cause of almost all acute thrombotic complications. We believe that this is clearly an unrealistic oversimplification of a much more complex disease. CTCA has the ability to identify atherosclerotic plaque characteristics that might refine risk stratification both from a patient basis and from a lesion basis (Table 1), thus possibly aiding the revitalization of the fading vulnerable patient/plaque concept. Notwithstanding, the reported prevalence of high-risk plaques remains highly variable and the positive predictive value relatively low. Accordingly, and given the mounting prognostic evidence in this regard, the search of vulnerable patients based on CTCA (Table 3) data might appear so far as a better approach.

**Conflict of interest:** None declared.

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