

**WJR 6<sup>th</sup> Anniversary Special Issues (2): CT**

## Coronary plaque imaging by coronary computed tomography angiography

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Author contributions: Sato A analyzed the data and wrote the paper.

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Received: December 27, 2013 Revised: February 9, 2014

Accepted: April 17, 2014

Published online: May 28, 2014

### Abstract

Coronary computed tomography angiography (CTA) has become the useful noninvasive imaging modality alternative to the invasive coronary angiography for detecting coronary artery stenoses in patients with suspected coronary artery disease (CAD). With the development of technical aspects of coronary CTA, clinical practice and research are increasingly shifting toward defining the clinical implication of plaque morphology and patients outcomes by coronary CTA. In this review we discuss the coronary plaque morphology estimated by CTA beyond coronary angiography including the comparison to the currently available other imaging modalities used to examine morphological characteristics of the atherosclerotic plaque. Furthermore, this review underlies the value of a combined assessment of coronary anatomy and myocardial perfusion in patients with CAD, and adds to an increasing body of evidence suggesting an added diagnostic value when combining both modalities. We hope that an integrated, multi-modality imaging approach will become the gold standard for noninvasive evaluation of coronary plaque morphology and outcome data in clinical practice.

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**Key words:** Coronary computed tomography angiog-

raphy; Coronary plaque; Vulnerable plaque; Clinical outcome

**Core tip:** With the development of technical aspects of coronary computed tomography angiography (CTA), clinical practice and research are increasingly shifting toward defining the clinical implication of plaque morphology and patients outcomes by coronary CTA. In this review we discuss the coronary plaque morphology estimated by CTA beyond coronary angiography including the comparison to the currently available other imaging modalities used to examine morphological characteristics of the atherosclerotic plaque. We hope that an integrated, multi-modality imaging approach will become the gold standard for noninvasive evaluation of coronary plaque morphology and outcome data in clinical practice.

Sato A. Coronary plaque imaging by coronary computed tomography angiography. *World J Radiol* 2014; 6(5): 148-159 Available from: URL: <http://www.wjgnet.com/1949-8470/full/v6/i5/148.htm> DOI: <http://dx.doi.org/10.4329/wjr.v6.i5.148>

### INTRODUCTION

For the past decade, invasive coronary angiography (ICA) has been used as the gold standard for the diagnosis of coronary narrowing and clinical decision making for coronary interventions. However, coronary angiography has several limitations, including the substantial interpretation variability of visual estimates and assessment of lesion severity for diffuse atherosclerotic lesions and intermediate-severity lesions<sup>[1-3]</sup>. The recent advent of multidetector computed tomography (MDCT) has greatly improved the image quality, and may therefore allow more precise evaluation of coronary stenosis<sup>[4-6]</sup>. Multicenter studies have confirmed the accuracy of 64-slice MDCT for directly

**Table 1** Respective pros and cons of multi-detector computed tomography and coronary angiogram for analysis of coronary artery disease

	Pros	Cons
MDCT	It can be performed with short examination times, and is generally available and easily performed It is a noninvasive character, and contributes important information of plaque morphology and characterization in the arterial wall Calcium score	Study population was limited to selected patients chosen for good CTA image quality with absence of motion artifacts or severe calcification Quantitative measurement of plaque morphology is slightly limited
CAG	Serial MDCT plaque imaging Excellent image quality can be observed with absence of artifacts Degree of luminal stenosis can be measured by QCA Gold standard for the diagnosis of coronary narrowing and clinical decision making for coronary interventions	Radiation exposure, which is currently between 9 and 1 mSv for a retrospectively gated MDCT coronary angiogram Contrast medium is used It is an invasive character, and contributes no plaque morphologic information Substantial interpretation variability of visual estimates and assessment of lesion severity for diffuse atherosclerotic lesions and intermediate-severity lesions Catheterization costs are expensive. Contrast medium is used

MDCT: Multi-detector computed tomography; CTA: Computed tomography angiography; CAG: Coronary angiogram; QCA: Quantitative coronary angiography.

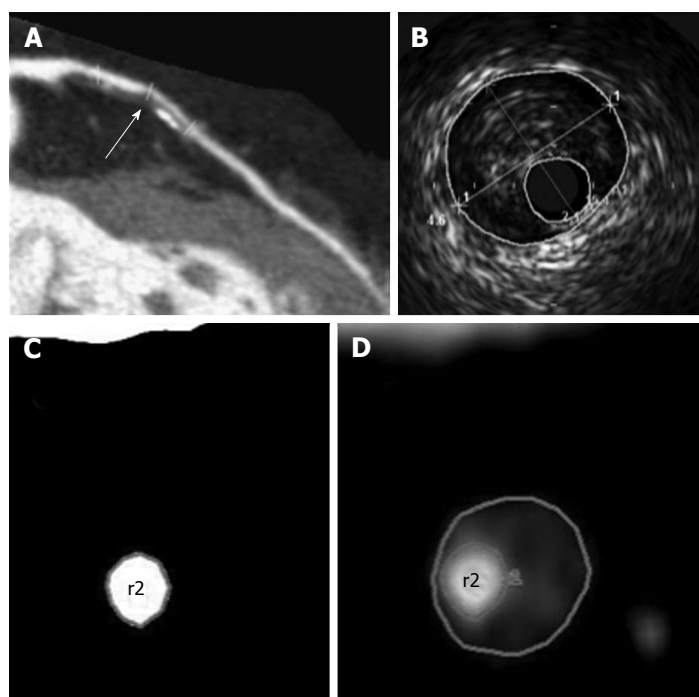
visualizing and detecting coronary artery stenoses in patients with suspected coronary artery disease (CAD)<sup>[7-10]</sup>. Furthermore, the introduction of 256-slice, 320-detector scanner, and dual-source computed tomography (DSCT) developed to significantly improve faster scan times, wider volume coverage, and high spatial resolution<sup>[11]</sup>. With the improvement of technical aspects of coronary computed tomography angiography (CTA), clinical practice and research are increasingly shifting toward defining the clinical implication of plaque morphology and patients outcomes by coronary CTA (Table 1). In this review, we discuss the coronary plaque morphology estimated by CTA beyond coronary angiography including the comparison to the currently available other imaging modalities used to examine morphological characteristics of the atherosclerotic plaque.

### Coronary plaque imaging

With the development of MDCT, it is possible not only to detect coronary artery stenosis but also to evaluate coronary plaque quality and quantity such as can be done with intravascular ultrasound (IVUS) and optical coherence tomography (OCT)<sup>[12,13]</sup>. Leber *et al*<sup>[14]</sup> demonstrated that 64-slice CTA-derived measurements showed good correlations with IVUS for lumen and plaque area determinations using individually adapted window settings, although their ability to quantify the grade of a luminal obstruction was limited by the significant trends toward overestimation of the lumen area and underestimation of the plaque area. Our group published that the lumen cross-sectional area (CSA) and percent area stenosis of 32 de novo coronary lesions measured by CTA were closely correlated to those obtained by IVUS (Figure 1); however the lumen CSA measured by CTA was systematically overestimated and percent area stenosis was slightly underestimated<sup>[15]</sup>. Voros *et al*<sup>[16]</sup> conducted a meta-analysis to assess the accuracy of coronary CTA against IVUS regarding coronary vessel and plaque sizes, as well

as the accuracy of computed tomography (CT) to detect any plaque compared with IVUS. This meta-analysis confirmed that coronary CTA slightly overestimated luminal area, presumably because of partial volume effects that lead to overestimation of the size of very bright structures (such as the contrast-enhanced lumen), whereas plaque area volume, and area stenosis measurements are similar between CT and IVUS. For plaque characterization, it has been shown that CT-derived attenuation values are different in calcified and noncalcified plaques. They also demonstrated that low-density noncalcified plaques, the presumed lipid-rich plaques on CT, correlated best with the sum of necrotic core plus fibro-fatty tissue by IVUS/virtual histology<sup>[17]</sup>. Kashiwagi *et al*<sup>[13]</sup> revealed that plaque with vascular remodeling and low CT attenuation values had the MDCT morphological features of thin cap fibroatheroma (TCFA) observed by OCT, and a ring-like enhancement observed by MDCT was one important sign of TCFA. Motoyama *et al*<sup>[18]</sup> showed that the CT characteristics of plaques associated with acute coronary syndrome (ACS) include positive vascular remodeling, low plaque density, and spotty calcification. Presence of all 3 [*i.e.*, positive remodeling (PR), non-calcified plaque measuring < 30 Hounsfield units (HU), and spotty calcification] showed a high positive predictive value, and absence of all 3 showed a high negative predictive value, for the culprit plaques associated with ACS. Coronary CTA is able to successfully characterize ruptured plaques as low-attenuation plaque with PR. However, Ozaki *et al*<sup>[19]</sup> demonstrated that CTA fails to characterize lesions at risk of intact fibrous cap-ACS which are often referred to as plaque erosions and responsible for up to one-third of culprit lesions in ACS patients.

The introduction of DSCT marked another technological improvement of MDCT in cardiac imaging, as the temporal resolution was further increased from 165 ms to 83 ms, thus eliminating the need to control the heart rate during the scan by use of  $\beta$ -blockers. Studies comparing



**Figure 1** The window settings for the lumen and outer vessel boundary by computed tomography angiography are the same as those for intravascular ultrasound imaging<sup>[19]</sup>. A: A curved multiplanar reconstructed CTA image reveals a significant stenosis in the left anterior descending artery (arrow); B: An IVUS cross-section reveals a lumen area of 2.1 mm<sup>2</sup> and a vessel area of 15.4 mm<sup>2</sup>; C: The cross-sectional CTA images show the luminal CSA of 2.1 mm<sup>2</sup>; D: Vessel CSA of 15.4 mm<sup>2</sup>. CTA: Computed tomography angiography; IVUS: Intravascular ultrasound; CSA: Cross-sectional area.

DSCT with single-source CT demonstrated that DSCT maintains high diagnostic accuracy in the diagnostic examination of a wide range of patient subsets, *e.g.*, patients with higher and even irregular heart rates<sup>[20]</sup>. Westwood *et al*<sup>[21]</sup> showed the systematic review of the accuracy of dual-source cardiac CT for detection of arterial stenosis in some or all difficult to image patients. The pooled, per-patient estimates of sensitivity were 97.7% (95%CI: 88.0%, 99.9%) and 97.7% (95%CI: 93.2%, 99.3%) for patients with arrhythmias and high heart rates, respectively. The corresponding pooled estimates of specificity were 81.7% (95%CI: 71.6%, 89.4%) and 86.3% (95%CI: 80.2%, 90.7%), respectively. In patients with high coronary calcium scores, previous bypass grafts, or obesity, only per-segment or per-artery data were available. Sensitivity estimates remained high (> 90% in all but one study), and specificities ranged from 79.1% to 100%. We showed the table summarizing various studies reporting analysis of coronary plaque by MDCT (Table 2).

### Non-culprit coronary plaques imaging

Approximately 6% of PCI patients will have clinical plaque progression requiring non-target lesion percutaneous coronary intervention (PCI) by 1 year, and greater CAD burden confers a significantly higher risk for clinical plaque progression<sup>[22]</sup>. The prospect study showed that on multivariate analysis, nonculprit lesions associated with recurrent events were more likely than those not associated with recurrent events to be characterized by a plaque burden of 70% or greater (HR = 5.03; 95%CI: 2.51-10.11;  $P < 0.001$ ) or a minimal luminal area of 4.0 mm<sup>2</sup> or less (HR = 3.21; 95%CI: 1.61-6.42;  $P = 0.001$ ) or to be classified on the basis of radiofrequency intravascular ultrasonography as thin-cap fibroatheromas (HR = 3.35; 95%CI: 1.77-6.36;  $P < 0.001$ )<sup>[23]</sup>. Our group showed

that the number of coronary plaques in non-culprit lesions on CTA images was more significantly observed in acute myocardial infarction (AMI) patients than in stable angina pectoris patients with normal myocardial perfusion imaging (MPI)<sup>[24]</sup>. Specifically, non-calcified, mixed, and vulnerable plaques were more significantly observed in AMI patients than in SAP patients (Figure 2). Leber *et al*<sup>[25]</sup> found that non-calcified plaques contribute to a higher degree to the total plaque burden in AMI than in SAP. In addition, 64-slice CTA enabled the visualization of lipid cores and spotty calcifications that are frequently associated with plaque ruptures<sup>[14]</sup>. We suggested that all three major coronary arteries in patients with AMI were extensively diseased and have multiple vulnerable plaques that could potentially cause another occurrence of ACS, although the natural course of vulnerable plaque development and disruption has not yet been clearly established<sup>[24]</sup>. Recent studies have demonstrated that metabolic syndrome was associated with an increasing risk of cardiovascular disease<sup>[26]</sup>. Furthermore, IVUS study has shown that metabolic syndrome is associated with lipid-rich plaques that contribute to the increasing risk of plaque vulnerability<sup>[27]</sup>. Within the AMI group, the number of PR and low attenuation plaque was significantly higher in patients with metabolic syndrome than in those without the syndrome. This finding might explain the mechanism of metabolic syndrome contributing to the increased risk of cardiovascular events<sup>[24]</sup>. We showed the table comparing various imaging for analysis of coronary vulnerable plaque (Table 3).

### Coronary plaque characteristics on MDCT and slow-flow phenomenon/cardiac troponin T elevation

Cardiac biomarker troponin T (cTnT) is sensitive and specific for detection of myocardial damage. Porto *et al*<sup>[36]</sup>

**Table 2 Various studies reporting analysis of coronary plaque by multi-detector computed tomography**

Ref.	n	Imaging techniques	Major findings
Leber <i>et al</i> <sup>[12]</sup>	59	64-detector	The mean plaque areas and the percentage of vessel obstruction measured by IVUS and 64-slice CT were 8.1 mm <sup>2</sup> vs 7.3 mm <sup>2</sup> ( $P < 0.03$ , $r = 0.73$ ) and 50.4% vs 41.1% ( $P < 0.001$ , $r = 0.61$ ), respectively
Kashiwagi <i>et al</i> <sup>[13]</sup>	105	64-detector	Vascular remodeling and low CT attenuation values had the MDCT morphological features of TCFA observed by OCT, and a ring-like enhancement was one important sign of TCFA
Leber <i>et al</i> <sup>[14]</sup>	46	16-detector	The MDCT-derived density measurements within coronary lesions revealed significantly different values for hypoechoic (49 HU $\pm$ 22), hyperechoic (91 HU $\pm$ 22), and calcified plaques (391 HU $\pm$ 156, $P < 0.02$ )
Sato <i>et al</i> <sup>[15]</sup>	102	64-detector	Lumen CSA and percent area stenosis of coronary lesions were closely correlated to those obtained by IVUS, however the lumen CSA measured by CTA was systematically overestimated and percent area stenosis was slightly underestimated
Voros <i>et al</i> <sup>[17]</sup>	60	64-detector	Low-density noncalcified plaques, the presumed lipid-rich plaques on CT, correlated best with the sum of necrotic core plus fibro-fatty tissue by IVUS/virtual histology
Motoyama <i>et al</i> <sup>[18]</sup>	71	16, 64-detector	Presence of positive remodeling, non-calcified plaque < 30 HU, and spotty calcification showed a high positive predictive value for with ACS
Ozaki <i>et al</i> <sup>[19]</sup>	66	16, 64-detector	CTA fails to characterize lesions at risk of intact fibrous cap-ACS which are often referred to as plaque erosions
Sato <i>et al</i> <sup>[24]</sup>	226	64-detector	Number of coronary plaques in non-culprit lesions was more significantly observed in AMI patients than in SAP patients with normal MPI. Non-calcified, mixed, and vulnerable plaques were more significantly observed in AMI patients than in SAP patients
Leber <i>et al</i> <sup>[25]</sup>	15	4-detector	Non-calcified plaques contribute to a higher degree to the total plaque burden in AMI than in SAP
Schroeder <i>et al</i> <sup>[41]</sup>	32	16-detector	Mean CT density of 14-47 HU was found in lipid-rich plaque
Pohle <i>et al</i> <sup>[43]</sup>	32	16-detector	The mean CT attenuation within plaque that corresponded to hyper-echogenic appearance in IVUS was 121 $\pm$ 34 HU ( $n = 76$ ). The mean CT attenuation within plaque that corresponded to hypo-echogenic appearance was 58 $\pm$ 43 HU ( $n = 176$ , $P < 0.001$ )
Pundziute <i>et al</i> <sup>[44]</sup>	100	64-detector	In multivariate analysis, significant predictors of events were the presence of CAD, obstructive CAD, obstructive CAD in LM/LAD, number of segments with plaques, number of segments with obstructive plaques, and number of segments with mixed plaques
Pundziute <i>et al</i> <sup>[45]</sup>	50	64-detector	TCFA on virtual histology IVUS were most prevalent in mixed plaques, suggesting a higher degree of vulnerability of these mixed plaques

IVUS: Intravascular ultrasound; CT: Computed tomography; MDCT: Multi-detector computed tomography; OCT: Optical coherence tomography; CTA: Computed tomography angiography; HU: Hounsfield units; CSA: Cross-sectional area; AMI: Acute myocardial infarction; SAP: Stable angina pectoris; MPI: Myocardial perfusion imaging; TCFA: Thin-cap fibroatheromas; CAD: Coronary artery disease; LAD: Left anterior descending artery.

**Table 3 Characteristics of various imaging modalities for analysis of coronary vulnerable plaque**

Modalities	Characteristics of vulnerable plaque
MDCT	Low-attenuation, positive remodeling, spotty calcification <sup>[18]</sup>
	Ring-like enhancement <sup>[13]</sup> , napkin-ring sign <sup>[28,29]</sup>
IVUS	Low echoic, positive remodeling, spotty calcification <sup>[30]</sup>
	Echo signal attenuation <sup>[31]</sup>
OCT	Lipid-rich plaque by a signal-poor region with a diffuse border <sup>[32]</sup>
	TCFA (large lipid core and a thin fibrous cap < 65 $\mu$ m) <sup>[33]</sup>
	Macrophages imaging <sup>[34]</sup>
Angioscopy	Intensive yellow plaque, presence of thrombus <sup>[35]</sup>

MDCT: Multi-detector computed tomography; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; TCFA: Thin-cap fibroatheroma.

found that the cause of periprocedural myocardial necrosis after PCI was the impairment of flow in coronary side branches and distal embolization of atheromatous or thrombotic materials. Therefore, pre-PCI plaque composition may have an impact on myocardial injury/infarction during PCI. However, there are few published data regarding the relation between pre-PCI plaque composition by MDCT and post-PCI cardiac biomarker levels (Table 4).

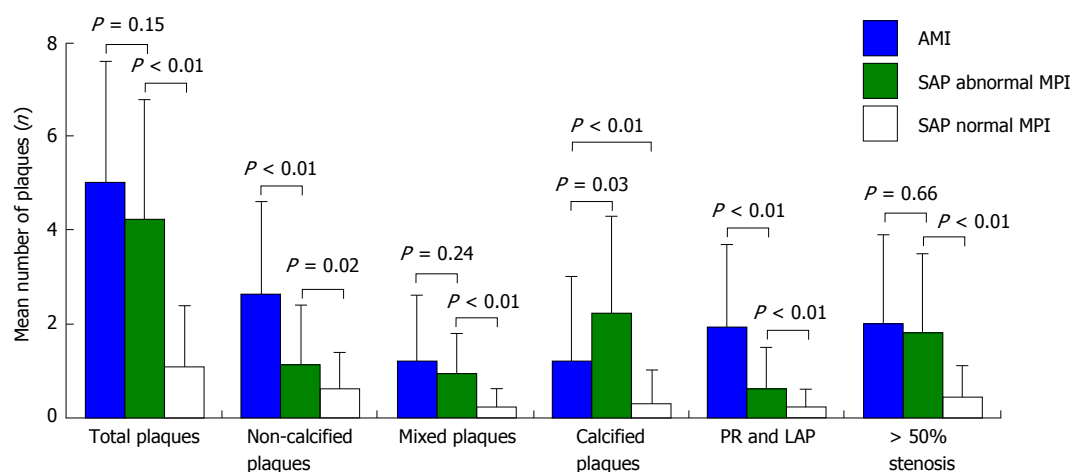
**Table 4 Coronary plaque characteristics on multi-detector computed tomography and slow-flow phenomenon/cardiac troponin T elevation**

Ref.	Minimum CT value (HU)	Positive remodeling index	Calcification	Ring-like appearance
Nakazawa <i>et al</i> <sup>[37]</sup>	67.0 $\pm$ 10.1	N/A	N/A	55.60%
Uetani <i>et al</i> <sup>[38]</sup>	< 50	1.10 $\pm$ 0.21	37.70%	N/A
Watabe <i>et al</i> <sup>[39]</sup>	43 (26.5-75.7)	1.20 $\pm$ 0.18	Spotty (50%)	31.00%
Kodama <i>et al</i> <sup>[40]</sup>	23.5 (9.5-40)	1.5 (1.3-1.8)	CPC (63%)	10.00%

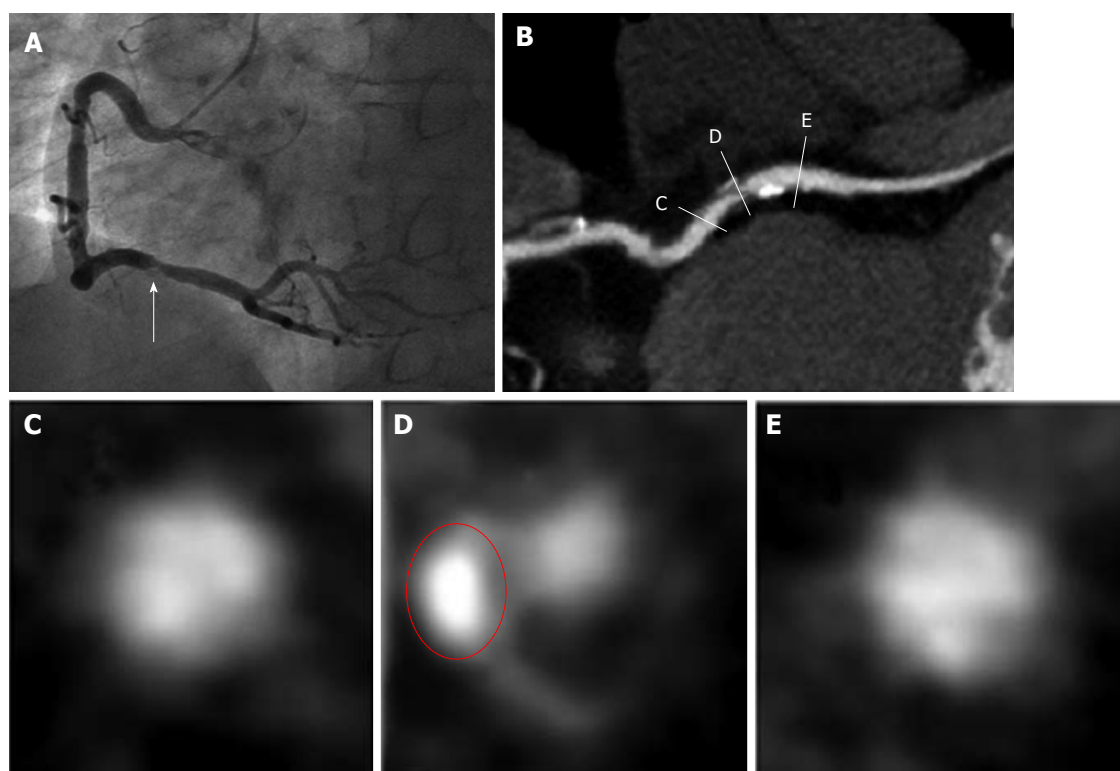
CT: Computed tomography; HU: Hounsfield units; CPC: Circumferential plaque calcification; N/A: Not available.

Nakazawa *et al*<sup>[37]</sup> reported that patients who experienced transient no-reflow during PCI had lower plaque CT density values in culprit lesions. Uetani *et al*<sup>[38]</sup> demonstrated that post-procedural myocardial injury was associated with the volume and fraction of low-attenuation plaques by MDCT. Our group showed that CT attenuation value of < 55 HU was associated with post-PCI cTnT elevation<sup>[39]</sup>. While in earlier studies, a mean CT density of 14-47 HU was found in lipid-rich plaque<sup>[41,42]</sup>, Pohle *et al*<sup>[43]</sup> showed a mean density of 58 HU (median 53) and Leber *et al*<sup>[14]</sup> reported that a low CT density value (49  $\pm$  22 HU) is considered to correspond to soft plaque identified on





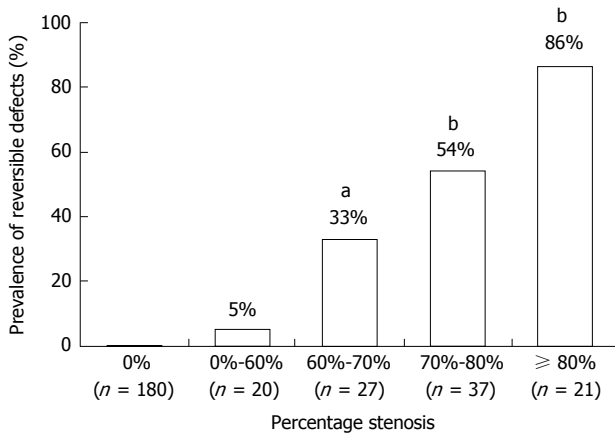
**Figure 2** Mean number of the coronary plaques in the non-culprit segments of the acute myocardial infarction and stable angina pectoris patients<sup>[24]</sup>. AMI: Acute myocardial infarction; SAP: Stable angina pectoris; MPI: Myocardial perfusion imaging; PR: Positive remodeling; LAP: Low-attenuation plaques.



**Figure 3** The computed tomography characteristics of a culprit lesion in the 52-year-old male patient with post-percutaneous coronary intervention troponin T elevation  $\geq 3 \times$  the upper limit of normal<sup>[31]</sup>. Coronary angiogram (A) and multiplanar reconstructed image (B) show severe stenosis in the mid right coronary artery. Cross-sectional images show the proximal reference (C), culprit lesion (D), and distal reference (E). The lesion has positive remodeling (remodeling index 1.28), spotty calcification, and low CT density (16 HU). Red circle indicates area of spotty calcification. CT: computed tomography; HU: Hounsfield units.

IVUS. This difference most likely results from the natural course of atherosclerotic plaque or slice thickness and contrast medium concentration that affect plaque density measurements. It will be possible to use our cutoff point of CT attenuation value  $< 55$  HU for prediction of post-PCI cTnT elevation clinically. PR and spotty calcification were also significant predictors of post-PCI cTnT elevation. Furthermore, presence of all 3 CT characteristics (CT attenuation value  $< 55$  HU, remodeling index  $> 1.05$ , and spotty calcification) showed a high positive predictive

value (PPV) of 94%, and their absence showed a high negative predictive value (NPV) of 90% (Figure 3). Kodama *et al*<sup>[40]</sup> demonstrated that CTA-verified circumferential plaque calcification (CPC) with low-attenuation plaque and PR were determinants of slow-flow phenomenon (SF) during PCI. The conditional logistic regression analysis revealed that CPC, plaque density, and dyslipidemia were the predictors of SF, with CPC being the strongest (OR = 79; 95%CI: 8-783,  $P < 0.0001$ ). A previous study exploring potential prognostic predictors of cardiovascular events



**Figure 4** Prevalence of reversible defects evaluated by single-photon emission tomography in the study groups defined according to the percentage stenosis obtained by computed tomography angiography<sup>[15]</sup>. Numbers under the bars represent the number of vessels. <sup>a</sup> $P = 0.018$ , <sup>b</sup> $P < 0.0001$  vs percentage stenosis of 0%-60%.

on MDCT showed that mixed lesions were associated with adverse events on follow-up<sup>[44]</sup>. Thin-cap fibroatheromas on virtual histology IVUS were most prevalent in mixed plaques, suggesting a higher degree of vulnerability of these mixed plaques on MDCT<sup>[45]</sup>. These data suggest that it would be worthwhile to consider the identification of these vulnerable plaques by MDCT before PCI. If the plaque has the characteristics of low plaque density, PR, and spotty calcification, a plan for prevention of post-PCI cTnT elevation can be made before the PCI procedure.

### Coronary CTA and nuclear MPI

Stress nuclear MPI using single-photon emission tomography (SPECT) is an established method for assessment of the functional significance of coronary stenosis and delivers valuable information for risk stratification<sup>[46]</sup>. Disagreement between CTA  $\geq 50\%$  stenosis and reversible MPI defects is common<sup>[47]</sup>. CTA and MPI are measuring two different things, vessel patency and perfusion, respectively. Only 50% of obstructed vessels with  $\geq 50\%$  luminal narrowing by CTA show abnormal MPI<sup>[48]</sup>. We previously indicated that 64-slice CTA alone was not always sufficient to assess the functional significance of anatomic stenoses, especially stenoses of intermediate grade (Figure 4). When stenosis severity by CTA was  $< 60\%$ , ischemia was seldom observed, and when stenosis severity was  $\geq 80\%$ , ischemia was common. For intermediate stenosis severity values of 60%-80%, the prevalence of reversible defects was difficult to determine, given CTA's current spatial resolution<sup>[15]</sup>. We also demonstrated that combined CTA and stress nuclear MPI provide improved diagnostic accuracy for the noninvasive detection of CAD in comparison with that of 64-slice CTA alone. One hundred thirty symptomatic patients with suspected CAD underwent both 64-slice CTA and stress thallium-201 MPI before ICA. Of 390 arteries in 130 patients, 54 (14%) were nonevaluable by CTA due to severe calcifications, motion artifacts, and poor opacifica-

tion. All nonevaluable arteries were considered positive. The sensitivity, specificity, PPV and NPV were 95%, 80%, 69%, and 97%, respectively, for CTA alone and 94%, 92%, 85%, 97%, respectively, for CTA with stress nuclear MPI for all nonevaluable arteries on CTA. Per-patient analysis showed a significant increase in specificity and PPV<sup>[49]</sup>. The results of hybrid SPECT/CTA imaging have provided a marked increase in specificity and PPV to detect hemodynamically significant coronary lesions compared to those of 16-slice CTA alone<sup>[50]</sup>. Cardiac 3D SPECT/CT fusion imaging has been shown to provide additional information about hemodynamic relevance and facilitates lesion interpretation by allowing exact allocation of perfusion defects to the subtending coronary artery<sup>[51]</sup>. Pazhenkottil *et al*<sup>[52]</sup> demonstrated that the impact of hybrid SPECT/CT imaging in 318 consecutive patients. Referral to revascularization was higher in patients with matched abnormalities (41%), compared with those with unmatched abnormalities (11%) or those with normal studies (0%).

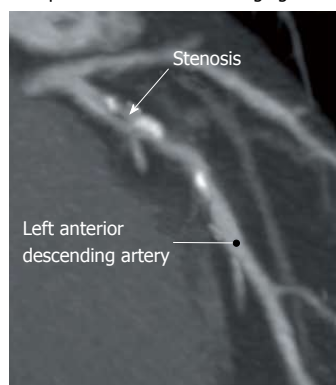
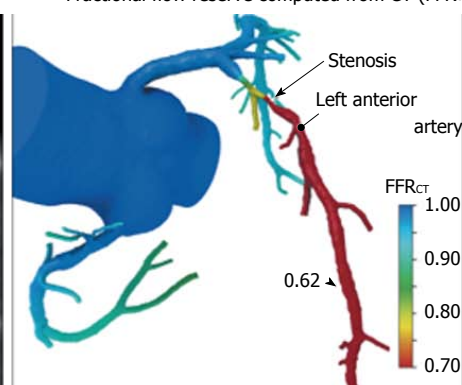
Available clinical experience points toward tailoring the initial diagnostic approach according to the pretest probability of the patient<sup>[53]</sup>. In low-to-intermediate likelihood patients, CTA may well be the best initial test due to its high NPV; however, in intermediate-to-high probability patients, CTA's low PPV may result in unnecessary radiation exposure, and stress nuclear MPI might be a better first-line test. In fact, the high diagnostic accuracy of stress nuclear MPI may argue in favor of stress nuclear MPI as the initial test. From the present study, we cannot definitely conclude which is the better first-line test, and we acknowledge that further head-to-head comparisons between the two modalities are required.

Recently, the addition of physiologic measures of coronary flow by fractional flow reserve (FFR) to anatomic-based assessment of stenosis severity by ICA to guide decisions of coronary revascularization improves event-free survival in a manner that is long-lived and cost-effective<sup>[54,55]</sup>. Ko *et al*<sup>[56]</sup> demonstrated that FFR compared with combinations of coronary CTA and CT myocardial perfusion imaging findings in 86 myocardial perfusion territories. The FFR is lowest in patients who have both stenosis  $\geq 50\%$  on coronary CTA and myocardial perfusion abnormalities and highest in patients with no significant stenosis and no myocardial perfusion defects. Among patients with discrepant results, FFR correlates better with myocardial perfusion abnormalities than with angiographic stenosis.

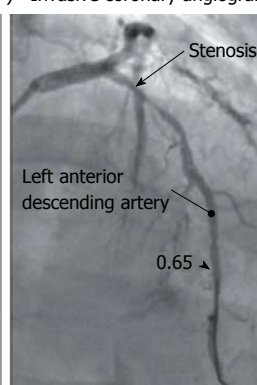
Min *et al*<sup>[57]</sup> demonstrated that use of noninvasive FFR<sub>CT</sub> plus CT among stable patients with suspected or known CAD was associated with improved diagnostic accuracy and discrimination *vs* CT alone for the diagnosis of hemodynamically significant CAD when FFR determined at the time of ICA was the reference standard (Figure 5). On a per-patient basis, diagnostic accuracy, sensitivity, specificity, PPV, and NPV of FFR<sub>CT</sub> plus CT were 73% (95%CI: 67%-78%), 90% (95%CI: 84%-95%), 54% (95%CI: 46%-83%), 67% (95%CI: 60%-74%), and

**A Study patient with ischemia**

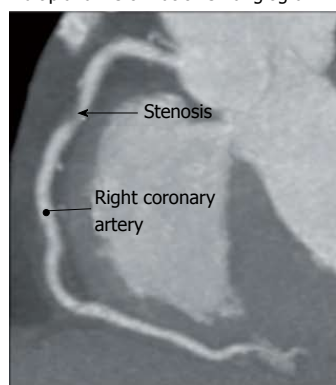
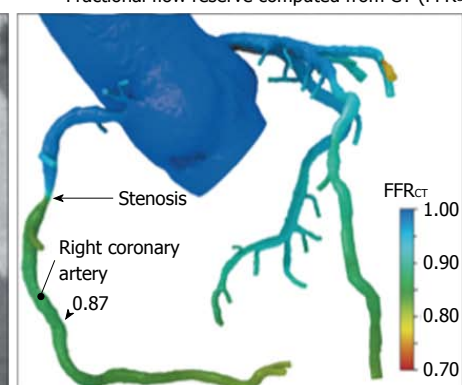
Multiplanar reformat of CT angiogram

Fractional flow reserve computed from CT (FFR<sub>CT</sub>)

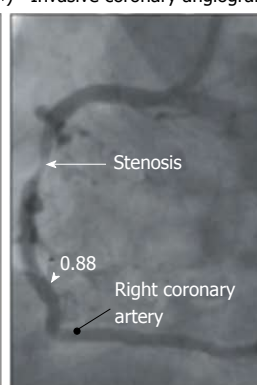
Invasive coronary angiogram

**B Study patient without ischemia**

Multiplanar reformat of CT angiogram

Fractional flow reserve computed from CT (FFR<sub>CT</sub>)

Invasive coronary angiogram



**Figure 5** One patient (A) has ischemia and the other patient (B) does not have ischemia<sup>[49]</sup>. A: Multiplanar reformat of a computed tomography (CT) angiogram demonstrating obstructive stenosis of the proximal portion of the left anterior descending artery (LAD) and a computed fractional flow reserve (FFR<sub>CT</sub>) value of 0.62, indicating vessel ischemia. Invasive coronary angiogram demonstrates obstructive stenosis of the proximal portion of the LAD and measured fractional flow reserve (FFR) values of 0.65, indicating vessel ischemia; B: CT angiogram demonstrating obstructive stenosis of the mid portion of the right coronary artery (RCA) and an FFR<sub>CT</sub> value of 0.87, indicating no vessel ischemia. Invasive coronary angiogram demonstrates obstructive stenosis of the mid portion of the RCA and a measured FFR value of 0.88, indicating no vessel ischemia.

84% (95%CI: 74%-90%), respectively. Compared with obstructive CAD diagnosed by CT alone [area under the receiver operating characteristic curve (AUC), 0.68; 95%CI: 0.62-0.74], FFR<sub>CT</sub> was associated with improved discrimination (AUC, 0.81; 95%CI: 0.75-0.86;  $P < 0.001$ ).

The CORE320 study compared the combination of CT perfusion (CTP) and coronary artery assessment with SPECT imaging and conventional coronary angiography<sup>[58]</sup>. Sixteen centers enrolled 381 patients who underwent combined CTA-CTP and SPECT/MPI prior to conventional coronary angiography. The patient-based diagnostic accuracy defined by the AUC of integrated CTA-CTP for detecting or excluding flow-limiting CAD was 0.87 (95%CI: 0.84-0.91). In patients without prior myocardial infarction, the AUC was 0.90 (95%CI: 0.87-0.94) and in patients without prior CAD the AUC for combined CTA-CTP was 0.93 (95%CI: 0.89-0.97). For the combination of a CTA stenosis  $\geq 50\%$  stenosis and a CTP perfusion deficit, the sensitivity, specificity, positive predictive, and negative predictive values (95%CI) were 80% (72%-86%), 74% (68%-80%), 65% (58%-72%), and 86% (80%-90%), respectively. For flow-limiting disease defined by ICA-SPECT/MPI, the accuracy of CTA was significantly increased by the addition

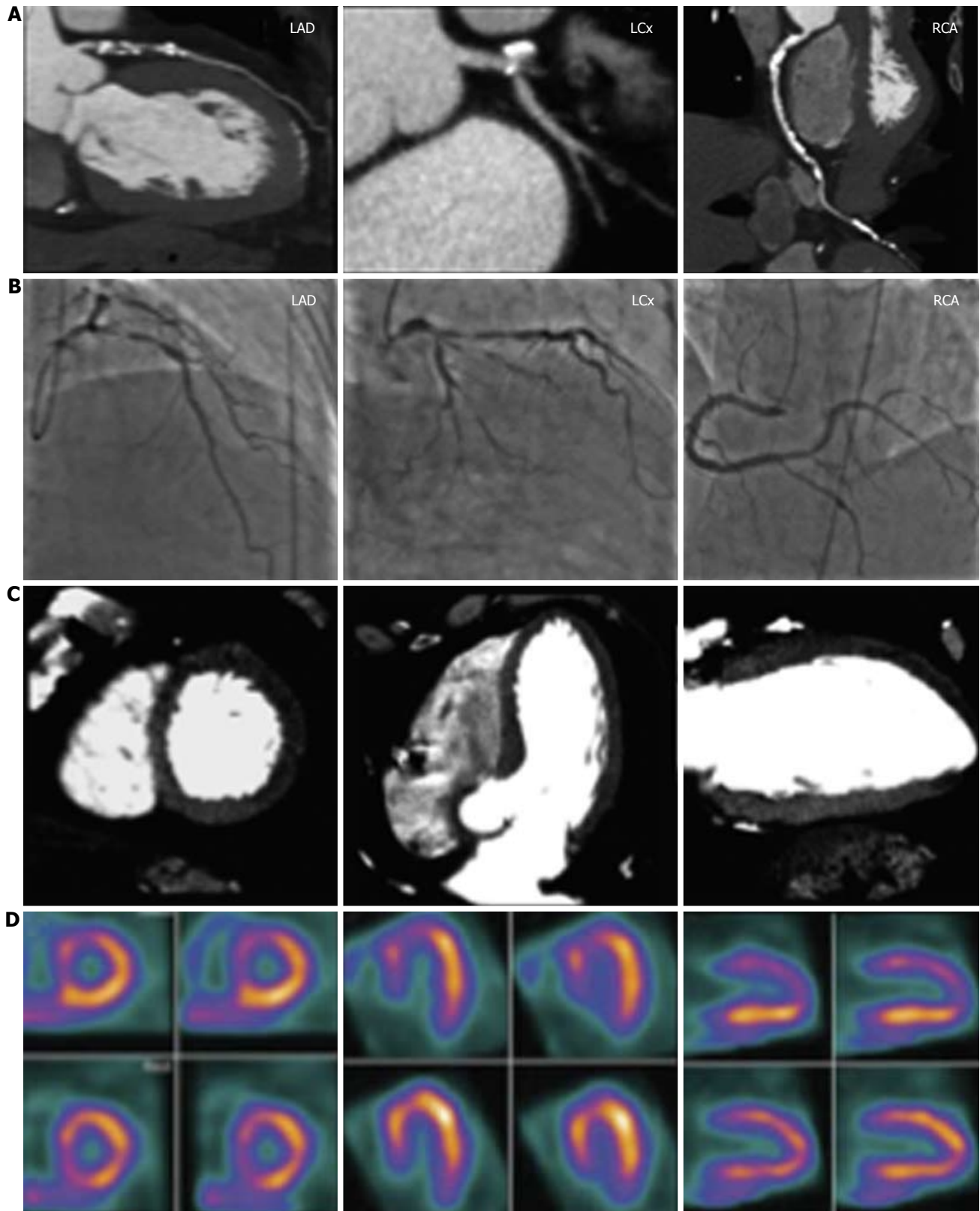
of CTP at both the patient and vessel levels (Figure 6).

Recent advances in the development of noninvasive imaging techniques have enabled quantification of vessel wall inflammation with <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT). The post hoc analysis in the dal-PLAQUE study demonstrated the possible role of FDG-PET especially in relationship of serum inflammatory biomarkers with plaque inflammation assessed by FDG PET/CT. They showed a positive correlation between baseline serum myeloperoxidase (MPO) and baseline carotid arterial wall (target) to background (blood) of the most diseased segment (TBR<sub>mds</sub>). This relation remained present at 3-mo follow-up and was independent of traditional risk factors. This study is the first to investigate the relationship between MPO and vessel wall <sup>18</sup>F-FDG uptake<sup>[59]</sup>. Longitudinal studies will be needed to investigate whether vessel wall inflammation measured by <sup>18</sup>F-FDG PET/CT is predictive for future cardiovascular events.

### Prognostic value of CTA in symptomatic and asymptomatic individuals

Currently, the main clinical advantage of CTA appears to be related to its high NPV. The ability to rule out sig-





**Figure 6** A complete CORE320 imaging data set for a 64-year-old male without prior history of coronary artery disease with chest pain symptoms<sup>[50]</sup>. The left anterior descending coronary artery revealed a 96% diameter stenosis by computed tomography angiography (CTA) (row A) and an 85% diameter stenosis by invasive coronary angiography (ICA) (row B). The computed tomography myocardial perfusion (CTP) (row C) study revealed a mild defect in the distal anteroseptal wall, and moderate defects in the basal anteroseptal, the basal anterior, the distal anterior, and apical walls, while the single photon emission computed tomography (SPECT) (row D) study revealed moderate defects in the distal anterior, the distal anteroseptal, the basal anteroseptal and apical walls. The left circumflex artery revealed an 87% diameter stenosis by CTA, a 79% diameter stenosis by ICA, mild defects in the distal inferoseptal and distal inferolateral walls, and moderate defects in the distal anterolateral and distal anterior walls by CTP, and a moderate defect in the distal anterior wall by SPECT. The right coronary artery revealed a 60% diameter stenosis by CTA, a 77% diameter stenosis by ICA, a mild defect in the distal inferoseptal wall by CTP, and no myocardial perfusion defects by SPECT.



nificant CAD in symptomatic patients with a low pre-test likelihood of disease makes CT a useful tool to diagnose many patients with acute chest pain who are often at a low risk of actually ACS. Recently, several randomized large trials have evaluated clinical value of coronary CTA for chest pain triage in the emergency department. Litt *et al*<sup>[60]</sup> demonstrated that among the 908 of 1370 patients with acute chest pain to undergo coronary CT angiography, 640 could be immediately discharged after negative findings on a CT scan, and none died or had a myocardial infarction within 30 d. As compared with patients receiving traditional care, patients in the coronary CTA group had a higher rate of discharge from the emergency department (49.6% *vs* 22.7%), a shorter length of stay (median, 18.0 h *vs* 24.8 h;  $P < 0.001$ ), and a higher rate of detection of coronary disease (9.0% *vs* 3.5%). Hoffmann *et al*<sup>[61]</sup> demonstrated that among the randomized 1000 low-risk acute chest pain patients in a multicenter trial, 501 patients underwent coronary CTA as a first triage test. After early coronary CTA, as compared with standard evaluation, the mean length of stay in the hospital was reduced by 7.6 h ( $P < 0.001$ ) and more patients were discharged directly from the emergency department (47% *vs* 12%,  $P < 0.001$ ). No patient with negative findings on CT experienced AMI, and only 23 MI occurred in the entire patient cohort (plus 52 cases of unstable angina).

The use of coronary CTA has been advocated as a potentially valuable atherosclerotic imaging tool for risk stratification<sup>[62,63]</sup>. Several studies have explored the prognostic value of coronary CTA, primarily limited to symptomatic populations<sup>[64,65]</sup>. Recent article by Hadamitzky *et al*<sup>[66]</sup> add a new data on CCTA that predict both death and myocardial infarction as well as need for subsequent revascularizations out to 5 years. CCTA imaging may be a valuable tool in the assessment of long-term prognosis in patients with suspected CAD. Atherosclerosis imaging such as coronary artery calcium scoring (CACS) or carotid intimal-medial thickness for individuals without chest pain syndrome has been advocated recently for use by professional consensus guidelines<sup>[67]</sup>. Furthermore, CACS has been demonstrated to improve risk re-stratification above and beyond global risk scores that combine traditional CAD risk factors<sup>[68,69]</sup>. However, in a large international multicenter study of individuals without chest pain syndrome, the additional risk-predictive advantage by coronary CTA is not clinically meaningful compared with a risk model based on CACS. At present, the application of coronary CTA for risk assessment of individuals without chest pain syndrome should not be justified<sup>[70]</sup>.

## CONCLUSION

With further improvements in CT technology, coronary CTA become accurate detection of coronary plaques in clinical practice. Assessment of both coronary stenosis and perfusion has great potential application to further advance the evaluation of patients with CAD. In low-to-intermediate likelihood patients, CTA may well be

the best initial test due to its high NPV; however, in intermediate-to-high probability patients, CTA's low PPV may result in unnecessary radiation exposure, and stress nuclear MPI might be a better first-line test. The choice of the optimal first line-test remains a question that is not answered in this review. This review underlies the value of a combined assessment of coronary anatomy and myocardial perfusion in patients with CAD, and adds to an increasing body of evidence suggesting an added diagnostic value when combining both modalities. We hope that an integrated, multi-modality imaging approach will become the gold standard for noninvasive evaluation of coronary plaque morphology and outcome data in clinical practice.

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