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Coronary CT angiography in coronary artery disease: Opportunities and challenges

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Review article

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ABSTRACT

Coronary CT angiography is widely recognised as a reliable imaging modality for the diagnosis of coronary artery disease. Coronary CT angiography not only provides excellent visualisation of anatomical changes in the coronary artery with high diagnostic value in the detection of lumen stenosis or occlusion, but also offers quantitative characterisation of coronary plaque components. Furthermore, coronary CT angiography allows myocardial perfusion imaging with diagnostic value comparable to the reference standard method. Coronary CT angiography-derived haemodynamic analysis has the potential to evaluate functional significance of coronary lesions. This review article aims to provide an overview of clinical applications of coronary CT angiography in coronary artery disease.

Key Words
Coronary artery disease, coronary computed tomography angiography, diagnosis, clinical applications

Implications for Practice:

1. What is known about this subject?
Coronary CT angiography is a widely available imaging technique for the diagnosis of coronary artery disease.

2. What new information is offered in this case study?
This review provides an overview of current status of coronary CT angiography with a focus on the diagnostic value, quantitative assessment of coronary plaques as well as its roles in patient management and treatment strategy guidance.

3. What are the implications for research, policy, or practice?
Coronary CT angiography is developing rapidly over the last decades and its role in coronary artery disease continues to evolve. A good understanding of these clinical applications will assist clinicians to use this technique judiciously.

Introduction

Coronary computed tomography angiography (CCTA) has become a routine imaging modality for the diagnosis of coronary artery disease (CAD) due to its high diagnostic accuracy, less invasiveness and wide availability.[1-5] Rapid developments in multislice CT scanning techniques have enabled the CCTA to be performed in a low-dose protocol with radiation dose similar to that of invasive coronary angiography.[6-8] Some recent studies have shown that radiation dose associated with CCTA can be further lowered to 0.1-0.4mSv, which is equivalent to that of routine chest radiography.[9,10] In addition to the anatomical assessment of coronary lumen stenosis, CCTA allows for quantitative assessment of coronary plaque morphological features. This is clinically important as coronary lumen stenosis does not always translate to functional significance, as plaque components instead of degree of lumen stenosis play a critical role in predicting cardiac events and guiding patient management through identification of high-risk plaques. Furthermore, CCTA shows high diagnostic value in identifying myocardial ischaemic changes by providing functional assessment of CAD. Despite these promising outcomes, there are still some challenges to be resolved, especially the limited diagnostic value of CCTA in highly calcified plaques. This review article provides a comprehensive overview of the current developments of CCTA in CAD, with a focus on the diagnostic value and functional assessment of CCTA in CAD. Challenges of CCTA are discussed, and future directions are highlighted.

Diagnostic value of CCTA in CAD

CCTA has been confirmed as a reliable imaging modality in the diagnosis of CAD with high diagnostic accuracy. It is well known that the diagnostic performance of CCTA has been significantly improved from early generation of 4-slice CT to 64- and post 64-slice CT. This is mainly due to the improved spatial and temporal resolution of multi-slice CT scanners, which enable detection of coronary artery and its side branches with high resolution: isotropic spatial resolution of 0.4x0.4x0.4mm^3, and temporal resolution of up to 75ms. The spatial resolution of current CCTA imaging technique is close to that of invasive coronary angiography (ICA), which is 0.2mm.[11] The newly introduced high-definition CT scanner with substantially improved in-plane spatial resolution of 0.23mm further improved diagnostic value of CCTA.[12] Pontone et al. compared the diagnostic value of high spatial resolution (0.23mm) with standard spatial resolution (0.625mm) CCTA in patients at high risk for CAD by using ICA as the reference method.[13] Their results showed that overall agreement between CCTA and ICA was significantly improved in the analysis of calcified coronary plaques for high resolution CCTA when compared to the standard CCTA. The temporal resolution of current multi-slice CT scanners is still inferior to that of ICA, which is 10-20ms.[11] Hence, heart rate control is still necessary in most of the patients to ensure acquisition of cardiac CT images with acceptable diagnostic quality.

Currently, 64-slice CT has become a widely available technique in most of the public hospitals and private practices, while 128-, 256- and 320-slice CT scanners are also increasingly used in many clinical centres. Table 1 shows the diagnostic value of CCTA in CAD, according to several systematic reviews and meta-analyses of diagnostic value of CCTA with use of 64-slice and 320-slice scanners.[14-22] As shown in Table 1, CCTA has high diagnostic sensitivity of more than 93 per cent and specificity of more than 86 per cent at per-patient assessment. It is well-known that CCTA has a very high negative predictive value (>95 per cent), thus it can be used as a gatekeeper to reliably exclude patients with suspected CAD.

Quantitative assessment of coronary plaques by CCTA

It has become well established that plaque composition is a key determinant of plaque stability.[23] Progressive increasing worldwide use of CCTA has demonstrated that CCTA has the potential to revolutionise how patients are risk-stratified by identifying rupture-prone, non-calcified or predominant non-calcified coronary plaques accurately and reliably. As our understanding of plaque histology has improved, there has been an increasing interest in the ability of CCTA to identify particularly the high-risk or vulnerable plaques.[24,25] According to the SCCT (Society of Cardiovascular Computed Tomography) criteria of subdividing plaques into calcified, predominant calcified, non-calcified, predominant non-calcified and partially calcified types, CCTA shows excellent inter and intra-observer agreement, and high capability to quantify and distinguish plaque types.[26-30]

Intravascular ultrasound (IVUS) is the gold standard for characterisation of coronary plaque composition. However, it is an invasive procedure which is not commonly performed in routine clinical practice and thus may be limited to research studies. CCTA as a less-invasive imaging modality has been reported to have comparable diagnostic value with IVUS in the assessment of plaque features. Studies based on head to head comparison between CCTA and IVUS reported the high diagnostic accuracy of CCTA with good correlation with IVUS for quantitative assessment of coronary plaques.[31,32] The ATLANTA (Assessment of Tissue Characteristics, Lesion Morphology, and Hemodynamics by Angiography With Fractional Flow Reserve, Intravascular Ultrasound and Virtual Histology, and Non-invasive Computed Tomography in Atherosclerotic Plaques) study was a prospective, single-centre study comparing CCTA with IVUS/VH (virtual histology) in 50 patients who underwent ICA examinations.[33] Results showed a significant correlation between CCTA and IVUS/VH for quantitative assessment of plaque geometric, compositional, lumen area and vessel area measurements. A large retrospective study by Motoyama et al. has shown the promising role of CCTA plaque characterisation for predicting acute cardiac events in more than 1000 patients with suspected or known CAD with a mean follow-up of 27 months. Researchers found that plaques with positive vascular remodelling and containing large areas of low attenuation are associated with a higher risk of acute coronary syndrome when compared with patients without these characteristics (22.2 per cent versus 0.5 per cent).[27]

In their meta-analysis of 17 articles comparing CCTA with IVUS with regard to the diagnostic accuracy of CT in detecting coronary plaques, Gao et al. observed a good weighted sensitivity of 92 per cent and specificity of 93 per cent for CCTA in the detection of any type of coronary plaque as compared with IVUS, and a good positive and negative predictive value (>84 per cent) for diagnosis of any plaque in a wide range of pre-test probabilities. Authors suggested that CCTA could serve as a non-invasive alterative to IVUS for detecting coronary plaques.[34] This is confirmed by another meta-analysis comparing CCTA with IVUS for quantitative assessment of coronary plaques.[35] Results showed that CCTA is accurate for the quantification of coronary plaques with mean sensitivity and specificity being 93 per cent and 92 per cent to detect any plaque when compared to IVUS. Our experience of using 3D virtual intravascular endoscopy (VIE) for visualisation of coronary plaques has demonstrated the potential value of this novel technique for plaque characterisation and intraluminal appearances[36,37] (Figure 1), although further studies should be conducted to correlate VIE findings with IVUS analysis. The reader is referred to some excellent reviewing articles on the CCTA in coronary plaque quantification.[37-40]

Functional assessment of CCTA in CAD

It is well known that anatomical coronary stenosis by CCTA is not necessarily associated with functional significance.[41] Therefore, detection of myocardial ischaemic changes caused by coronary plaques is more important than anatomical assessment of lumen stenosis since patients with decreased myocardial perfusion will benefit from revascularisation, thus, reducing adverse cardiac events. Myocardial CT perfusion imaging has been increasingly used in clinical practice with promising results reported based on single centre and multicentre experiences.[42-46] Furthermore, improvement of the diagnostic value of myocardial CT perfusion imaging has been achieved by a combination of CCTA and myocardial CT perfusion for detection of myocardial ischemia.[46,47] George et al. in their prospective, multicentre study comprising 381 patients from 16 centres demonstrated the high diagnostic value of myocardial CT perfusion imaging when compared with single photon emission computed tomography (SPECT) perfusion.[45]

On per-patient and per-vessel analysis, the sensitivity of myocardial CT perfusion imaging was significantly higher than that of SPECT, which was 88 per cent and 78 per cent, 62 per cent and 54 per cent ($p<0.05$), respectively. The specificity of SPECT imaging was significantly higher than that of CT perfusion imaging, which was 67 per cent and 81 per cent, 55 per cent and 62 per cent at per-patient and vessel analysis ($p<0.05$), respectively. The area under the receiver operating characteristic curve (AUC) for myocardial CT perfusion imaging was significantly higher than that for SPECT imaging at per-patient and per-vessel analysis, with corresponding values being 0.78 and 0.74, 0.69 and 0.69 ($p<0.05$), respectively. Despite these promising reports, SPECT, as the reference method for functional assessment of coronary stenosis is regarded as the first line diagnostic test for the diagnosis and prognosis of patients with CAD as there is insufficient evidence to recommend CCTA as the first line test.[48,49] Table 2 compares the characteristics between myocardial perfusion SPECT and myocardial CT perfusion imaging in the diagnostic evaluation of CAD.

Recently, investigation of diagnostic performance of non-invasive fractional flow reserve (FFR) derived from CCTA (FFR_{CT}) has attracted a lot of interest. Computation of FFR_{CT} is performed by computational fluid dynamics (CFD) modelling after segmentation of coronary arteries and left ventricular myocardium. Calculation of the FFR_{CT} ratio is acquired by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure, and this can be measured during CFD simulations. An FFR of ≤0.80 is currently used as a cut off value to determine hemodynamic coronary stenosis responsible for myocardial ischemia (Figures 2 and 3).[50,51]

Clinical validation of FFR_{CT} is based on a direct comparison to measured FFR during ICA. Currently, three multicentre trials are available in the literature, namely DISCOVER-FLOW DeFACTO and NXT trials investigating the diagnostic value of FFR_{CT} in CAD.[52-54] The reported sensitivity and specificity of FFR_{CT} ranged from 86–90 per cent to 54–79 per cent, on a per-patient analysis, while on a per-vessel analysis, the sensitivity and specificity of FFR_{CT} ranged from 84 per cent to 86-88 per cent, respectively. Several systematic reviews and meta-analyses of FFR_{CT} in comparison with CCTA with invasive FFR as the reference method also supported the statement that FFR_{CT} was more accurate for diagnosing myocardial ischemia due to coronary lesions.[55-57] Despite these promising results of FFR_{CT} in the detection of flow-limiting coronary stenosis, more multicentre trials need to be performed to compare the clinical impact of FFR_{CT} guided-treatment versus standard diagnostic evaluation on clinical outcomes, costs and quality of life in patients with suspected coronary artery disease.

Challenges of CCTA and future directions

There are some limitations with CCTA which need to be addressed so that its clinical efficacy will be further enhanced. First, although CCTA allows a comprehensive assessment of coronary plaques regarding lumen changes and plaque characterization and composition, its ability to differentiate vulnerable or unstable plaques from those which are stable is still inferior to IVUS or optical coherence tomography.[58-61] Therefore, differentiation of lipid-rich content from fibrous content with CCTA remains challenging due to considerable overlap in the attenuation values of lipid and fibrous tissue. Second, extensive coronary artery calcification (coronary calcium score >400) still limits the diagnostic accuracy of CCTA in CAD, in particular, reducing the sensitivity to some extent due to high rate of false positive results. It has been reported that highly calcified plaques (high calcium in the plaques) significantly lowered the specificity of CCTA to between 18 per cent and 44 per cent if no image post-processing was implemented.[62-65]

With use of iterative reconstruction (IR) and other image processing algorithms, the specificity and positive predictive values (PPV) were improved due to suppressing the blooming artefacts from high calcium scores.[66-69] Although IR has been confirmed to significantly reduce radiation dose and improve image quality when compared to the conventional image reconstruction of filtered back projection in CCTA, most recent studies have shown the negative impact of IR techniques on coronary artery calcium scores which could change patient's risk stratification in up to 31 per cent patients.[70-72] Thus, use of image processing algorithms could be an effective approach for diagnostic assessment of calcified coronary plaques. This is confirmed by our recent study with specificity and positive predictive value significantly improved for CCTA diagnosis of calcified plaques when compared to the conventional approach (66 per cent and 57 per cent vs. 33 per cent and 41 per cent for CCTA with and without use of image processing) (Figure 4).[68] Despite these improvements, the specificity is still moderate, and more studies are needed to further enhance CCTA diagnostic performance. Another approach to improve diagnostic performance of CCTA in calcified plaques is to use the high definition CT scanner with substantially improved in-plane spatial resolution of 0.23 mm, therefore, reducing beam hardening and blooming artefacts due to heavy calcification in coronary plaques.[12] Pontone et al. reported that at a segment-based analysis, the specificity and PPV were 98 per cent and 91 per cent for high resolution CCTA, which is significantly higher than the 95 per cent and 80 per cent for standard CCTA (0.625 mm spatial resolution). Significant improvement was found with high resolution CCTA in the analysis of calcified plaques when compared to the standard CCTA,[13] although further studies are needed to confirm its clinical value.

Clinical applications of CCTA in CAD have undergone a paradigm shift from test performance to assessment of end clinical outcomes. This is represented by some randomised controlled trials available in the recent literature, including FACTOR-64 Randomized Clinical Trial, PROMISE Clinical Trial, PLATFORM Clinical Trial and SCOT-HEART trial.[73-76] Table 3 summarises key findings of these four multicentre trials. As shown in the table, clinical value of CCTA is controversial as FACTOR-64 and PROMISE trials concluded that CCTA did not improve clinical outcomes as compared with functional testing or did not reduce all-cause mortality. While in the SCOT-HEART trial, CCTA was found to change treatment strategy which was associated with reduction in fatal and non-fatal myocardial infarction. According to the PLATFORM Trial, authors concluded that use of CCTA/FFR_{CT} can be more effectively triage patients than the use care approach for invasive procedures since ICA was cancelled in 61 per cent of patients based on the results of CCTA/$FFR_{CT.}$[77]

Summary and conclusion

Coronary CT angiography has developed as reliable less-invasive imaging modality in the diagnosis of coronary artery disease. Tremendous progress has taken place over the last decades in cardiac CT imaging, owing to the evolution of CT scanning technology, which allows coronary CT angiography to serve as a potential alternative to invasive coronary angiography. In addition to anatomical assessment of coronary lumen stenosis and quantification of coronary plaques, functional evaluation of significance of coronary stenosis is also improving which is manifested by promising results of myocardial CT perfusion imaging. Coronary CT angiography-derived haemodynamic studies and FFR_{CT} shows improved clinical outcomes in the diagnostic evaluation of patient-specific lesions. Multicentre trials have confirmed the clinical value of coronary CT angiography for reduction of cardiac mortality and improvement of patient outcomes, although more studies based on long-term follow-up are required to further validate its clinical applications. With more research being conducted using advanced cardiac CT imaging techniques, there is no doubt that coronary CT angiography continues to play an important role in the early detection and diagnosis of coronary artery disease and prevention of major adverse cardiac events through improving treatment strategy.

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PEER REVIEW

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CONFLICTS OF INTEREST

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None

Table 1: Diagnostic value of coronary CT angiography in coronary artery disease according to systematic reviews and meta-analyses

Type of CT scan	First author	No. of articles in the analysis	Patient-based sensitivity (95% CI)	Patient-based specificity (95% CI)
64-slice coronary CT angiography	Abdulla et al.[14]	27 studies	97.5% (96–99)	91% (87.5–94)
	Stein et al.[15]	23 studies	98% (96–98)	88% (85–89)
	Mowatt et al.[16]	28 studies	99% (97–99)	89% (83–94)
	Sun et al.[17]	15 studies	97% (94–99)	88% (79–97)
	Guo et al.[18]	24 studies	98% (99–99)	87% (83–90)
	Salavati et al.[19]	25 studies	99% (97–99)	89% (84–92)
320-slice coronary CT angiography	Gaudio et al.[20]	7 studies	95.4% (88.8–98.2)	94.7% (89.1–97.5)
	Li et al.[21]	10 studies	93% (91–95)	86% (82–89)
	Sun and Lin[22]	12 studies	96.3 (92.9–99.8)	86.4% (77.8–94.9)

Table 2: Characteristics of cardiac SPECT and CCTA (modified from Trzaska et al.[48])

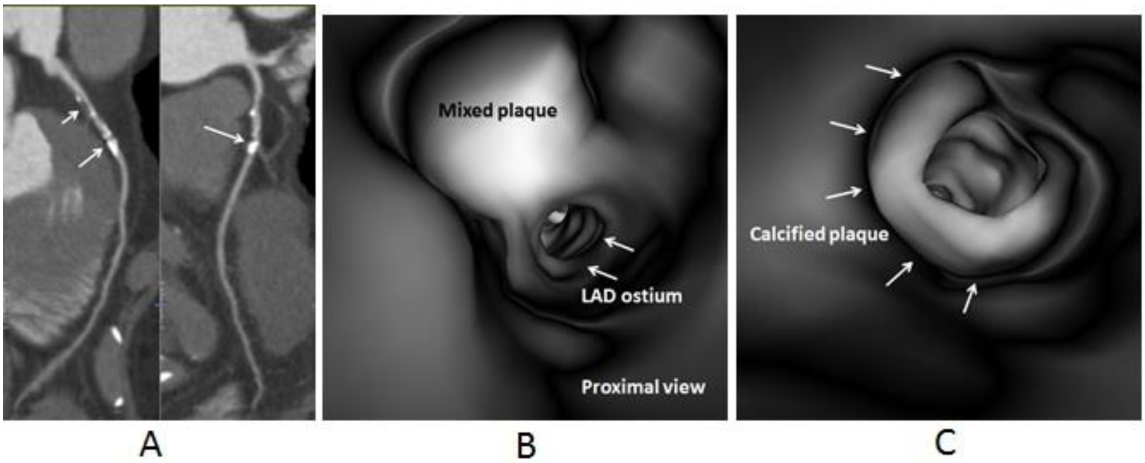
Characteristics	Myocardial CT perfusion imaging	Myocardial perfusion SPECT
Diagnostic accuracy	Yes	Yes
Prognostic value	Yes	Yes
Impact on patient management	Uncertain	Yes
Assessment of response to therapy	Uncertain	Yes
Contribution to better outcomes	Uncertain	Yes
Widespread availability	Yes	Yes
Applicable in a wide spectrum of patients	No	Yes
Low radiation dose to patients	Yes	Yes
Cost-effectiveness	Yes	Yes

Table 3: Summary of four multi-centre clinical trials with regard to coronary CT angiography in coronary artery disease

Clinical trials	Study population and design	Key findings
FACTOR-64 trial[73]	900 patients with type 1 or 2 diabetes without symptoms of CAD from 45 clinics and practices were randomly assigned to CAD screening with CCTA (n=452) or standard diabetic care (n=448). The mean follow-up for both groups was 4.0 years. The primary outcome was all cause mortality with secondary outcome being ischemic adverse cardiovascular events.	No significant differences were found between the CCTA and control groups in terms of primary event rates (6.2% vs. 7.6%, p=0.38) and second end points of cardiovascular events (4.4% vs. 3.8%, p=0.68). Results showed that CCTA did not offer advantage in reducing heart and coronary artery disease outcomes, thus, it is not recommended as a screening tool in this population.
PROMISE trial[74]	10,003 symptomatic patients from 193 clinical sites were assigned to anatomical testing with use of CCTA (n=4,996) or functional testing (n=5,007). The primary endpoint was a composite of major adverse cardiac events, while secondary endpoints included invasive cardiac catheterization that did not show obstructive CAD and cumulative radiation exposure. The median follow-up was 25 months.	CCTA did not reduce the incidence of the cardiac events when compared with functional testing (3.3% vs. 3.0%, p=0.75). CCTA was associated with fewer cardiac catheterization showing no obstructive CAD as compared with functional testing (3.4% vs. 4.3%, p=0.02). At 12 months' follow-up, the risk of death or non-fatal myocardial infarction was significantly lower in CCTA group than in the functional testing group (p=0.049). Overall radiation dose was significantly higher in CCTA group than in the functional test group (12.0mSv vs. 10.1mSv, p<0.001). Over a mean follow-up of 2 years, CCTA as an initial strategy was not associated with better clinical outcomes than functional testing.
PLATFORM trial[75]	584 patients with recent onset chest pain from 11 clinical sites were assigned to undergo either the planned usual care testing (n=287) or CCTA/FFR$_{CT}$ testing (n=297). The 90-day follow-up visits were reported in this study to determine the cardiac event rates with primary endpoint being rate of invasive coronary angiography and secondary endpoints of	Non-obstructive CAD was found at invasive coronary angiography in 12% of the patients in the CCTA/FFR$_{CT}$ group, which is significantly lower than that observed in the usual care group (73%) (p<0.0001). No significant differences were found in cardiac events between these two groups (p=0.95). The use of CCTA/FFR$_{CT}$ can be more effectively triage patients than the use care approach for invasive procedures since invasive

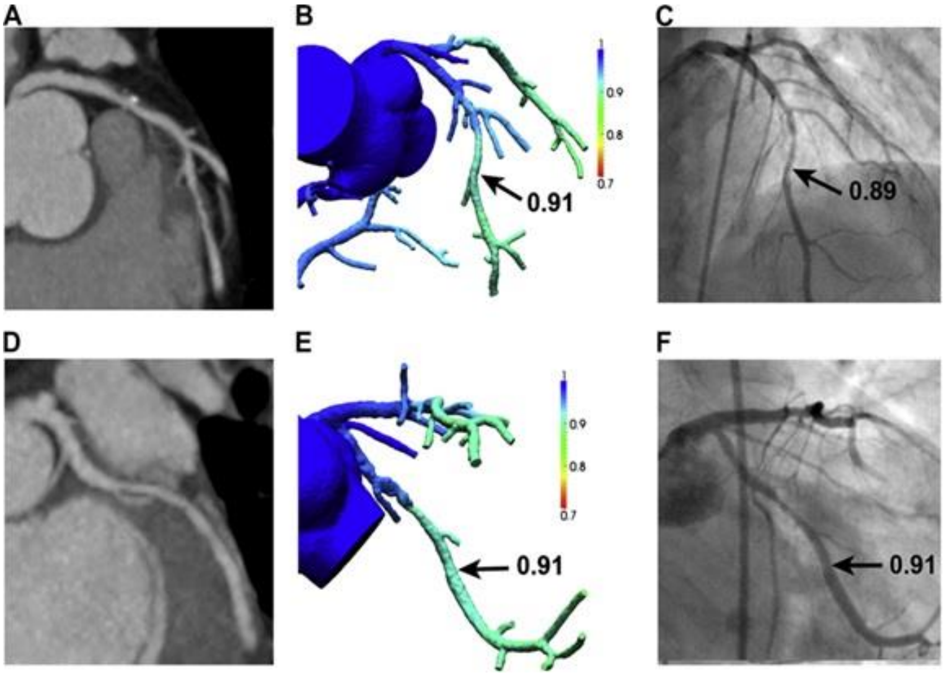
	adverse cardiovascular events.	coronary angiography was cancelled in 61% patients based on the results of CCTA/FFR_{CT}.
SCOT-HEART trial[76]	4,146 patients with suspected angina from 12 cardiology clinics were randomly assigned to receive standard care plus CCTA (n=2,073) or standard care alone (n=2,073). The mean follow-up for both groups was 1.4 years. The primary endpoint was percentage of patients diagnosed with angina secondary to CAD at six weeks, and long-term outcomes were adverse cardiac events.	CCTA increased certainty and frequency of the diagnosis of CAD at six weeks when compared with standard care ($p<0.0001$). This was translated into increased certainty but no effect on frequency of diagnosis of angina due to CAD for primary endpoints. CCTA was associated with 38% reduction in cardiac death and non-fatal myocardial infarction. Addition of CCTA to clinical care changed the treatment strategies.

Figure 1: 3D virtual intravascular endoscopy of coronary plaques



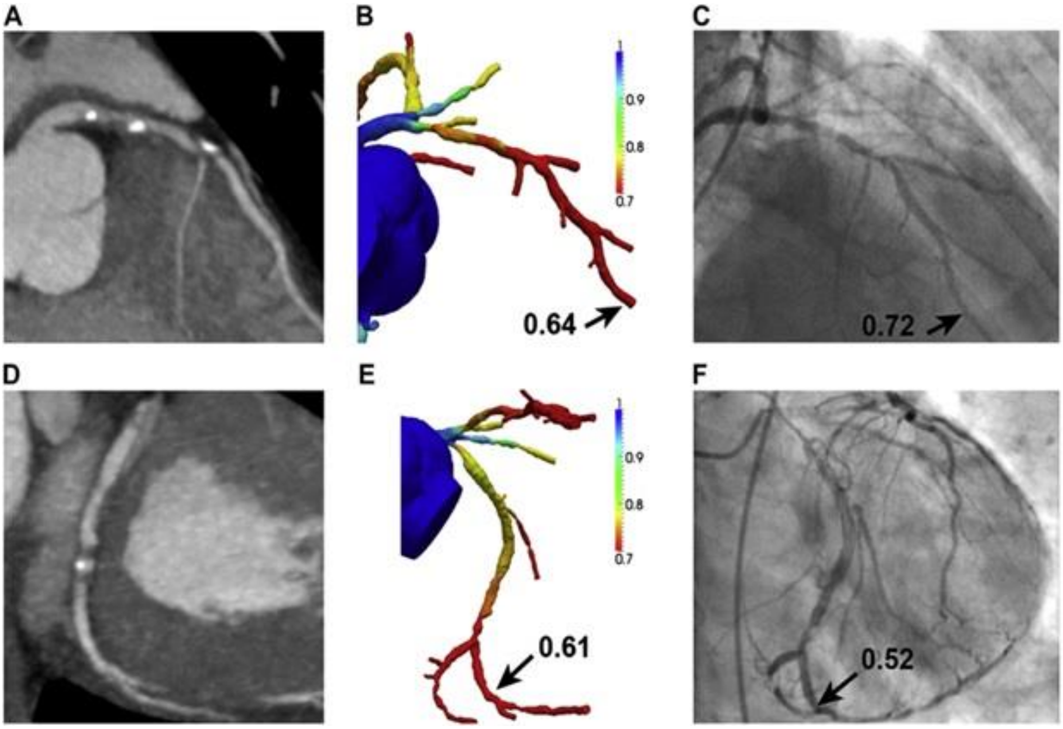
Virtual intravascular endoscopy (VIE) visualisation of mixed and calcified plaques in a 75-year-old man with coronary artery disease. A Curved planar reformation shows mixed plaque (short arrow) and calcified plaque (long arrows) in the proximal segment of left anterior descending coronary artery (LAD). B Close VIE view of the mixed plaque. C VIE view of the calcified plaque at LAD with significant lumen stenosis. Reprinted under the terms of open access article from reference.[37]

Figure 2: Fractional flow reserve (FFR) derived from CT angiography (FFR$_{CT}$) results for 66-year-old man with multi-vessel coronary artery disease but no lesion-specific ischemia



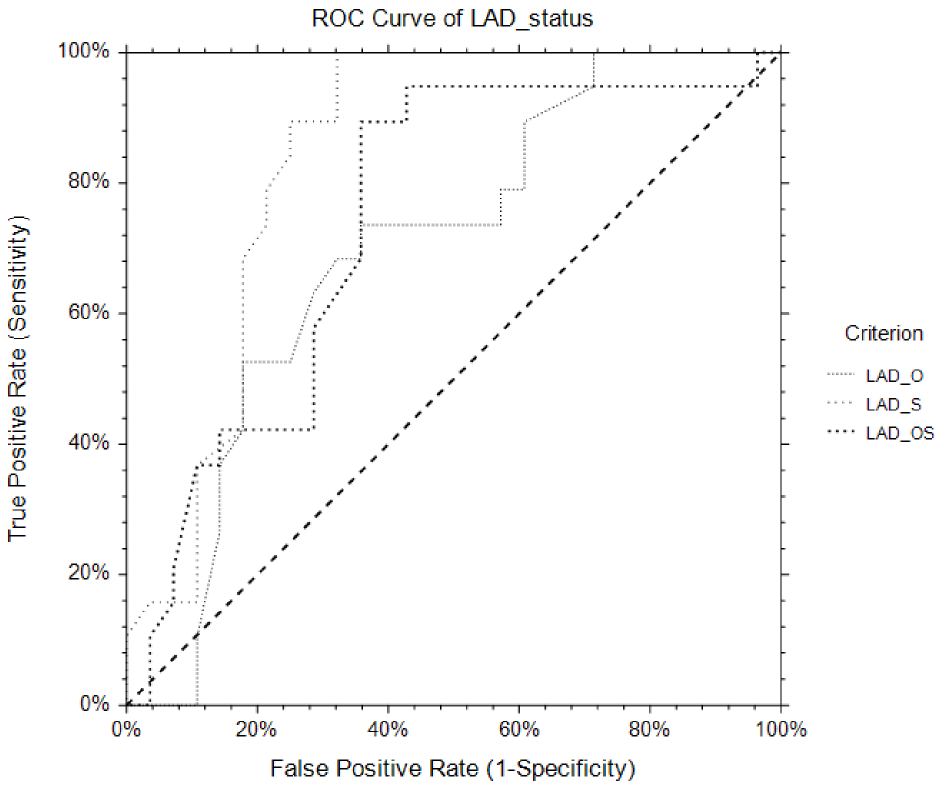
(A) Coronary computed tomography angiography (CCTA) demonstrating stenosis in the left anterior descending coronary artery (LAD). (B) FFR$_{CT}$ demonstrates no ischemia in the LAD, with a computed value of 0.91. (C) Invasive coronary angiography (ICA) with FFR also demonstrates no ischemia in the LAD, with a measured value of 0.89. (D) CCTA demonstrating stenosis in the left circumflex coronary (LCx) artery. (E) FFR$_{CT}$ demonstrates no ischemia in the LCx, with a computed value of 0.91. (F) ICA with FFR also demonstrates no ischemia in the LCx, with a measured value of 0.91. Reprinted with permission.[50]

Figure 3: FFR$_{CT}$ results for 66-year-old man with multi-vessel CAD and lesion-specific ischemia



(A) Coronary CT Angiography (CCTA) demonstrating stenosis in the left anterior descending coronary artery (LAD). (B) FFR$_{CT}$ demonstrates ischemia in the LAD, with a computed value of 0.64. (C) Invasive coronary angiography (ICA) with FFR also demonstrates ischemia in the LAD, with a measured value of 0.72. (D) CCTA demonstrating stenosis in the left circumflex (LCx). (E) FFR$_{CT}$ demonstrates ischemia in the LCx, with a computed value of 0.61. (F) ICA with FFR also demonstrates ischemia in the LCx, with a measured value of 0.52. Reprinted with permission.[50]

Figure 4: Use of image post-processing algorithms in CCTA for visualisation of calcified coronary plaques



	AUC		
LAD_O	0.697 ± 0.078	0.001	0.111
LAD_S	0.841 ± 0.059	0.003	
LAD_OS	0.740 ± 0.075		

Areas under the curve (AUCs) by receiver-operating characteristic curve analysis demonstrate significant improvements in diagnostic performance of coronary CT angiography (CCTA) with use of image sharpen (CCTA_S) when compared to the original (CCTA_O) and smooth algorithms (CCTA_OS) in the detection of significant coronary stenosis at the left anterior descending coronary artery. Reprinted under the terms of open access article from reference.[68]