The status of coronary CT angiography (CCTA) with regards to its use in current clinical practice, based on the extensive body of research material now available, is reviewed. Current further needs and deficiencies that require to be addressed in the future, to allow easier implementation of CCTA into clinical workflow are also discussed.

CORONARY STENOSIS ASSESSMENT BY CCTA

Since the introduction of CCTA many studies and multicentre trials have been performed to assess the accuracy of CCTA to detect coronary stenosis ≥50% luminal diameter stenosis compared to invasive quantitative coronary angiography (QCA). CCTA is currently considered the best non invasive test for detection of coronary stenosis compared to exercise treadmill.

Exercise stress test, stress echo as well as nuclear single photon emission CT (SPECT) imaging. Based on results of several meta-analyses, we know that CCTA has the highest negative predictive value (NPV) of usually >98% (range 83–98%) and highest sensitivity usually >90% (range 81–91%) compared to these other non invasive tests [1]. The high sensitivity and high NPV of these results means that CCTA can be used to detect and exclude ≥50% obstructive stenosis. We also know that CCTA has a relatively low positive predictive value (PPV) for detection of stenosis ≥50%, ranging from 61–92%, and this means an excessive rate of false positive CTA findings as coronary stenosis tends to be overestimated by CTA. This potentially decreases the value of CTA as it may result in an increase in follow up tests including invasive coronary angiography and this can be considered a weakness of CTA for clinical use.

Most of the reported studies and multicentre trials were performed in expert academic centers, often using consensus of 2 expert readers, unlimited time to analyse the images as well as exclusion of uninterpretable segments from analysis so in daily clinical practice one should not expect such good results. Similarly the very high NPV of CCTA means that one should be able to confidently exclude significant coronary stenosis ≥50% by CCTA. However if image quality is suboptimal due to motion (e.g., irregular or fast heart rates in spite of beta-blockade) or increased noise (e.g., very obese patients) then the NPV is reduced. The presence of calcified plaques also has a significant effect on PPV and NPV results and is discussed further in this review.

In clinical practice, to guide further management, clinicians require quantification of coronary stenosis when coronary artery disease (CAD) is present on CTA, not just detection of stenosis ≥50% or to rule out presence of CAD. There have been far fewer studies on quantification of stenosis and most studies have shown...
that CCTA compared to QCA can only estimate diameter stenosis within ±25% with wide limits of agreement, with approximately 90% probability (~2 standard deviations) [2]. More recent studies using newer scanners has shown similar results [3]. Details of methods of quantification of coronary stenosis by CTA have been described previously [4]. We also know that visual estimation of stenosis severity is as accurate as manual measurements. It was recommended that readers of CCTA scans use a visually based multitiered grading approach to evaluate coronary stenosis. Authors reported that a 49% diameter stenosis lesion on CCTA can be considered virtually exclusive of 70% stenosis at invasive coronary angiography [5].

Using a tiered grading system is still the current recommended method for grading stenosis severity and the terminology is used in the recommended Coronary Artery Disease Reporting and Data System (CAD-RADS) standardised reporting system [6]. Further management of the patient can be based on CAD-RADS classification and presence of symptoms e.g., stable chest pain, acute chest pain [troponin negative, normal electrocardiogram (ECG)]. For example a CAD-RADS 3 classification with maximum coronary stenosis 50–69% seen on CCTA is considered moderate stenosis and the recommendation is for further cardiac functional testing to be performed with symptom guided pharmacological treatment. CAD-RADS classification has now also been shown to have prognostic value [7].

At the same the clinician should be aware of the possibility of false negative results resulting from a CCTA scan. Missing a significant or severe stenosis on CCTA has a much greater impact on patient outcome than a false positive result.

False negative results can be related to presence of motion artifacts, image noise and poor contrast enhancement e.g., in very obese patients, small vessel size, as well as presence of calcified plaques [8]. Calcified plaques are well known to be associated with overestimation of luminal narrowing, especially with calcified plaque >90 degree arc in cross section [9]. Calcified plaques have been associated with significant false negative findings [10].

In a paper assessing the impact of calcium characteristics on the accuracy of CCTA compared to intravascular ultrasound (IVUS), it was found that false positives or IVUS lumen area underestimation occurred, not just with large volume calcifications and calcium arc >47 degrees, but also with smaller arteries <2.9 mm lumen diameter [11]. The authors felt that artifacts caused by moderate calcium deposits may turn into critical diagnostic errors. In this study, IVUS lumen area overestimation by CTA resulting in false negative results occurred in 8% of cases and was associated with less dense and smaller calcifications.

The main reason for CTA overestimating or underestimating degree of coronary stenosis compared to invasive coronary angiography, especially in the presence of calcified plaques, is related to spatial resolution as the difference is spatial resolution is up to 5 times (CCTA spatial resolution of 9 line pairs/mm compared to invasive coronary angiography spatial resolution of 50 line pairs/mm). Even with current generations of CT scanners, detector collimator width, which largely determines spatial resolution of a CT scanner, has remained unchanged for several years (0.50–0.625 mm depending on the CT vendor). A new high resolution scanner has been recently become available with detector collimator width of 0.25 mm but with scan range of only 4 cm and initial clinical results have been reported [12]. There appears to be technical difficulty related to producing narrower detector collimator widths <0.5 mm and one of these relates to increased radiation dose.

Potential solutions to improving acquisition and post processing data when calcified plaques are present, as well as suggested methods to improve reporting results in the presence of calcified plaques, by assessing the arc or amount of cross-sectional lumen occupied by calcium on the CCTA images, has been previously discussed [13].

In essence, if the CCTA result shows no significant or severe stenosis, e.g., CAD-RADS 2 or 3 classification, especially in the presence of small calcifications and a vessel diameter <3 mm, further management must be guided by one's clinical judgement. In a symptomatic patient the possibility of a false negative result may need to be excluded. American College of Cardiology guidelines on appropriate use of diagnostic catherization [14], for example, considers the use of invasive coronary angiography to be in the uncertain but not inappropriate use category, in a symptomatic patient with lesion <50% with partly calcified and non-calcified plaques.

Current indications for performing CCTA in symptomatic patients such as those with abnormal treadmill ECG tests; stable chest pain; acute chest pain with negative cardiac enzymes and no ECG changes are all considered appropriate indications under Society of Cardiovascular Computed Tomography (SCCT) 2010, Asian Society of Cardiovascular Imaging (ASCI), European Society of Cardiology (ESC) and National Institute for Health and Core Excellence (NICE) guidelines and will not be discussed further in this paper. For asymptomatic patients for primary prevention, use of calcium scoring for risk prediction is well established but use of CCTA is still currently considered an inappropriate test following SCCT 2010 and ASCI 2010 guidelines. However there are several prognostic studies showing increased major adverse cardiac events (MACE) in asymptomatic patients found to have CAD on CCTA [15,16].

In summary we now know that CTA has high accuracy for detection of coronary stenosis; modest accuracy for quantification of stenosis and clinical management can be guided by CAD-RADS score result. However the false negative rates may be higher than reported in the literature and one should always be guided by the patients symptoms and one's clinical judgement if the...
CTA result show lesions <50% stenosis, especially in presence of small calcified plaques. In the future there is a possibility that performing CTA in asymptomatic patients may be considered an appropriate indication but more clinical trials regarding outcomes following medical therapy will be needed. Will the CT vendors design new types of scanners e.g., using photon counting detectors, to improve spatial resolution of scanners from current designs but without an increase in radiation dose exposure?

CCTA FOR DIAGNOSIS OF HEMODYNAMICALLY SIGNIFICANT CORONARY STENOSIS (MYOCARDIAL ISCHEMIA)

We have known for some time that CCTA identified stenosis ≥50% is a poor predictor of reversible ischemia detected by myocardial perfusion SPECT imaging (MPI). An abnormal MPI result is seen in only approximately half the patients, while those with CTA stenosis <50% usually have a normal MPI result [17]. The PPV of CCTA to detect myocardial ischemia ranges from 29–44% [17]. This is probably related to overestimation of stenosis by CCTA.

We also know that the contrast enhanced coronary artery contains information that is related to coronary blood flow and contrast gradients in a segment of coronary stenosis can be assessed by different methods to assess for the functional significance of the stenosis. Corrected contrast opacification and transluminal attenuation gradient (TAG) are methods that can be used [18]. However these methods appear to show limited incremental value for evaluation of haemodynamic stenosis [18].

CT myocardial perfusion (CTP) can also be performed with pharmacological stress agents such as adenosine or dipyramidal. They can be performed as static CTP scans using single energy or dual energy or as dynamic CTP scans [19-21].

The use of computational fluid dynamics has allowed the assessment of functional flow reserve (FFR) in coronary arteries using data from the CCTA. This development has caused great interest when first released in 2010. It has led to many studies on its diagnostic accuracy as well as effect on patient outcomes but will not be further reviewed or discussed here.

In a recent metanalysis of functional CT accuracy for diagnosing hemodynamically significant CAD using FFR as the reference standard, it was shown that anatomic CCTA used alone had the highest sensitivity of 87% but limited specificity of only 61% [22]. However CTA combined with CTP scans as well as CTA combined with FFR-CT had high sensitivity and high specificity (82%, 88% and 76%, 80%, respectively). As both methods show the substantial value of functional CT, it was recommended that these methods be integrated into the clinical workflow before revascularisation is recommended. The true diagnostic performance of TAG was indeterminate due to the limited number of studies performed. The same metanalysis also showed that dynamic CTP compared to static CTP studies has higher sensitivity but lower specificity compared to FFR as the reference standard.

In view of these results, the question is why are CTP studies not more widely performed outside academic centres? This is likely related to issues related to the complexity of the CTP technique with technical difficulties to perform CTP studies with regards to workflow, patient pre selection, scheduling and patient preparation issues as well as CT room occupancy time needed to perform the study. The cost of adenosine can also be an issue. Reading the scans is also not easy with artifacts common present and false positive results are not uncommon. Possibility to quantify myocardial blood flow is however helpful. Dynamic CTP studies seem to be more popularly performed compared to static scans, which are usually performed on volume scanners. However the radiation dose associated with dynamic CT scans is an issue even when using low 70–80 Kvp scans [22].

Most of the publications on FFR-CT are based on computational fluid dynamics analysis provided by Heartflow (FFRCT). However there are some practical limitations associated with use of this software which hinder its use in daily clinical practice, although it has US Federal Drug Administration (FDA) approval. These include high cost of using the software, which is performed on a supercomputer (approximately USD 1400 per case, not including the cost of the CCTA scan); offsite location of the company in the USA raises issues with regards to patient data privacy and data transfer internationally which is prohibited in some countries, as well as the turnaround time required to get the results.

Currently there are 3 CT vendors developing onsite software which would allow FFR-CT to be performed on their onsite workstations. The first published reports were several years ago, showing good diagnostic performance in comparison with invasive FFR [23]. The methods used to perform FFR-CT by each vendor are not always transparent, but include using alternative boundary conditions and reduced order fluid models as well as a recently released open software model that can be used on any vendors CT scanners using a new computational fluid dynamics algorithm [24,25]. In the metanalysis mentioned earlier, that included 2 CT vendors onsite software, compared with offsite FFR-CT it was found that there was no significant difference in sensitivity and specificity for detection of functional stenosis compared with FFR [22]. Artificial intelligence (AI) and machine learning (ML) has recently been used to improve ease of use of FFR-CT software [26].

Some advantages of having onsite software for FFR-CT is reduced costs, maintaining patient data privacy and relatively shorter processing time, which is performed at the point of care. However it is currently unknown why none of the software developed...
by 2 CT vendors, which have been in development for several years, and have upgraded versions, are still considered works in progress and we keenly await FDA approval for their use at more onsite locations.

In summary we know that functional CT information combined with anatomical CTA is more accurate for diagnosing myocardial ischemia. However CTA+TAG, CTA+CTP, and CTP+FFR-CT are not easily performed, data post processing is complex, and interpretation of the data can also be difficult. These methods are not readily available for clinical use in most non academic sites. We also know that results using both CTA+CTP combined, appears to be as good as CTA+FFR-CT. What we do not know is if FFR-CT will become the preferred method over CTP due to the much higher radiation doses associated with CTP, especially with dynamic CTP protocols. We also do not know when onsite FFR-CT software, which will likely include use of AI and ML, will become easily available.

**CCTA OF ATHEROSCLEROTIC PLAQUE**

Detection of atherosclerotic plaque in coronary arteries has been studied for many years and in a metaanalysis done some time ago it was shown that CCTA has high sensitivity of 90% and specificity of 92% compared to IVUS for detection of atherosclerotic plaque [27]. Many prognostic trials and studies, including long term studies, have also been performed on the association of atherosclerotic plaque seen on CCTA scans with MACE and mortality such as CONFIRM, ISCHEMIA, PROMISE, SCOT-HEART, etc. Most of these trials were conducted on symptomatic patients and will not be discussed further in this review.

We also know that CCTA can be used to identify high risk plaque or vulnerable plaque. It was reported that having 2 high risk features such as plaque density <30 Hounsfield unit and presence of positive remodelling resulted in a hazard ratio for increased MACE at 27 months follow up [28]. Other high risk plaque features previously reported include presence of small spotty calcifications and “napkin ring” sign. Plaque metrics such as plaque density, size, length, volume, remodelling index, can be obtained using automated software (quantitative CT, QCT) available on all CT vendors workstations or from 3rd party software providers. Using QCT has shown good correlation with IVUS but use of QCT software can be time consuming and complex in patients with multiple atherosclerotic lesions. The accuracy of plaque assessment by CCTA has been recently reviewed [29]. Using AI and ML has also been shown to be helpful for faster analysis [30].

There have also been many prognostic studies assessing plaque burden. In one study, it was shown that large plaque burden together with presence of high risk plaque showed a higher risk of MACE (hazard ratio 3.8 vs. 2) at 4 years follow up [31]. In a study where serial follow up CCTA was performed one year after initial CTA, patients who showed plaque progression, on the second CTA scan, especially if associated with high risk plaque, were found to have increased risk of ACS on follow up to 7 years [32]. In follow up of patients treated by statins, plaque regression can also be documented [33].

We can use this information regarding presence of atherosclerotic plaque on the CCTA, for risk management or risk stratification of patients, in additional to traditional clinical CAD risk factors.

Calcium scoring has been well established as a tool for further management of asymptomatic patients in primary prevention care and will not be discussed in this review. We can use the CCTA information using the CAD classification based on invasive coronary angiography results e.g., number of vessels diseased and if there is vessel stenosis present. The CAD-RADS score can also be used to risk stratify symptomatic patients [7].

There are more complex scoring systems that can also be used for symptomatic patients such as CONFIRM score, CT Leaman score and a recently reported Leiden CTA score [34,35]. These scores are complex and difficult to easily implement into an everyday clinical workflow or report.

The segmental stenosis score (SSS) was first proposed in 2007 and is a semi quantitative method of assessing plaque burden which may be more practical [36]. It grades plaque severity and number of affected segments of vessels based on a modified 16 segment American Heart Association model to yield a score from 0 to 48. A long term 7 year prognostic study using SSS <5 and >5 showed significant event free differences with SSS >5 having poorer prognosis [37]. A large study using SSS >4 showed significant improved event free survival in patients with SSS >4

### Table 1. CAD staging by CCTA (after Arbab-Zadeh and Fuster [39])

<table>
<thead>
<tr>
<th>CAD stage</th>
<th>0-Normal</th>
<th>1-Mild</th>
<th>2-Moderate</th>
<th>3-Severe</th>
<th>4-Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTA criteria</td>
<td>No plaque</td>
<td>&lt;30% stenosis in 1–2 vessels</td>
<td>30–49% stenosis in 1–2 vessels</td>
<td>≥50% stenosis in 1–2 vessels</td>
<td>≥50% stenosis in 2 vessels +proximal LAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or &lt;30% stenosis in 3 vessels</td>
<td>Or 30–49% stenosis in 3 vessels</td>
<td>Or ≥50% in 3 vessels Or ≥50% in left main</td>
<td></td>
</tr>
</tbody>
</table>

**CAD:** coronary artery disease, **CCTA:** coronary CT angiography, **LAD:** left anterior descending artery
treated with statins and aspirin at 1500 days [38].

A recent review concluded that overall CAD plaque burden is the main determinant of patient outcome in stable CAD and that too much emphasis has been placed on detection and treatment of high risk plaque (HRP) or vulnerable plaque [39]. The authors proposed a new method of CAD staging based on CTA results that can be easily implemented in clinical practice although no prognostic studies are yet available using this method of risk stratification (Table 1). The clinical role of atherosclerotic plaque seen on CCTA imaging has been recently reviewed as well [40].

In summary we know that CCTA can be used to detect plaque as well as to characterise plaque and identify HRP. Plaque quantification using automated software can be done but is complex and time consuming in the presence of multi-vessel disease. Follow up CTA scans for plaque progression and plaque regression can be done and used for prognostication. What we currently do not know is if CTA for plaque detection and quantification in asymptomatic patients will be considered an appropriate indication for CCTA as we need more outcome studies with medical therapy included. We also do not know how much help AI and ML algorithms will be to improve ease of use of QCT software. Due to the difficulty of easily generating risk scores using QCT, in the meantime, should the use of SSS (>5 being significant) or the newly proposed CAD stage score be more widely implemented into daily clinical practice to improve risk stratification of patients? We also do not currently know when is an ideal time to perform follow up serial CTA scans, if at all.

CONCLUSION

This review paper attempts to summarise our current state of knowledge with regards to use for CCTA for quantification of stenosis, functional CT combined with anatomical CTA to assess for hemodynamically significant stenosis and presence of myocardial ischemia as well as CCTA for evaluation of atherosclerotic plaque. The incorporation of the results into a practical method for risk management and risk stratification of patients to guide further management was also discussed. CCTA has been more widely performed for more than 12 years and there have been many technological improvements and long term outcome studies that have resulted during this period. We still have gaps in our knowledge that need to be addressed by more new technological innovations and more multicentre long term outcome studies.

Conflicts of Interest
The author has no potential conflicts of interest to disclose.

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