Coronary Computed Tomography Angiography as a Gatekeeper to Coronary Revascularization: Emphasizing Atherosclerosis Findings Beyond Stenosis

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Abstract

Purpose of Review Coronary computed tomography angiography (CCTA) is the optimal non-invasive test to rule out coronary artery disease (CAD). Decisions to perform coronary revascularization have traditionally been based upon ischemia testing. This review summarizes the latest observations and trials evaluating the suitability of CCTA to select patients for invasive coronary angiography (ICA) and subsequent revascularization.

Recent Findings Recent data shows that beyond stenosis, whole-heart quantification and characterization of coronary atherosclerotic plaque improves the estimation of myocardial ischemia. This comprehensive evaluation of the coronary artery tree has greater diagnostic accuracy for invasive fractional flow reserve (FFR) than conventional stress tests. Further, clinical trials have demonstrated that the performance of CCTA in patients with a clinical indication for ICA results in more effective patient care and significantly lower costs.

Summary Besides the excellent ability to rule out CAD, recent data shows that quantification and characterization of the coronary artery tree results in high accuracy for ischemia and that CCTA-guided care to select patients for ICA and revascularization is effective. Trials evaluating revascularization based on CCTA findings may be needed.

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Abbreviations

CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
FFR	Fractional flow reserve
FFR-CT	Fractional flow reserve derived from computed tomography
HU	Hounsfield units
ICA	Invasive coronary angiography
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
QCA	Quantitative coronary angiography

Introduction

Coronary computed tomography angiography (CCTA) is a rapidly evolving technology and multiple trials have demonstrated its effectiveness as a primary test in patients with

suspected coronary artery disease (CAD). Due to the direct, multiplanar, and isovoxel visualization of coronary atherosclerosis, it can reliably exclude coronary heart disease as the cause of chest pain and risk stratify individuals for future major cardiac events based on the overall burden of observed coronary plaque [1, 2]. CCTA has been considered an optimal diagnostic modality primarily in patients with a low to intermediate likelihood of obstructive CAD. However, contemporary data is coming out in support of its utility for individuals at higher risk [3]. Coronary plaques that possess a combination of ≥ 50% stenosis with a large burden of low-attenuation plaque and other high-risk plaque features are more likely to be ischemic and to receive benefit from revascularization [4, 5]. Detailed quantification of coronary atherosclerosis allows for objective and reproducible dimensions of coronary plaque, lumen, and vessel, and this extensive evaluation has demonstrated improved prognostication of events over and above visual CCTA reading and to potentially more precisely estimate myocardial ischemia [6, 7]. The current review summarizes the latest insights into the application of CCTA to rule in patients for CAD and describes coronary plaque features that may aid decision-making with regard to downstream invasive coronary angiography (ICA) and revascularization.

Coronary CTA to Detect Hemodynamically Significant Atherosclerosis

CCTA allows for the anatomic assessment of CAD. However, the relationship between coronary anatomic stenosis and its hemodynamic consequences—i.e., myocardial ischemia—remains complex because of discrepancies between both. For example, merely 50% of obstructive coronary lesions by CCTA or ICA are known to cause ischemia [8, 9]. To date, invasive fractional flow reserve (FFR) is considered the gold standard for determining lesion-specific ischemia and can help distinguish lesions that will and will not benefit from revascularization [10].

Recently, a detailed analysis of coronary arteries with CCTA has improved the identification of FFR positive lesions and vessels, compared to the assessment of maximal stenosis alone [7, 11]. Ischemia is best defined as the inadequate supply of oxygen relative to the demand of the myocardium, which is the result of the inability of coronary arteries to dilate in reaction to stressors (e.g., adenosine, exercise) [12]. Luminal narrowing is an important determinant, but there is a complex interplay of various factors beyond stenosis. A lipid-rich necrotic core, oxidative stress, and vascular inflammation have all been related to the inability of coronary arteries to vasodilate, and therefore cause a drop in FFR [12].

To this end, a post hoc analysis of the PACIFIC (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography with Invasive Coronary Angiography) trial investigated the association between coronary plaque characteristics as assessed with 256-slice CCTA and its hemodynamic consequences [4]. In this single-center study from the Netherlands, 208 patients with suspected stable CAD (ages 58 ± 9 years, 63% males) were prospectively enrolled to undergo CCTA, $[^{15}O]H_2O$ positron emission tomography (PET), and ICA with FFR interrogation of all major epicardial arteries. The primary endpoint was defined non-invasively (i.e., impaired hyperemic myocardial blood flow with PET) as well as invasively (i.e., FFR ≤ 0.80 or quantitative coronary angiography (QCA) > 90% diameter stenosis if an FFR value was unobtainable) on a per-vessel basis. Coronary plaques were analyzed for adverse characteristics (e.g., morphology, burden) in a qualitative and quantitative manner and included the following features: low-attenuation plaque < 30 Hounsfield units (HU), positive remodeling ≥ 1.1, spotty calcification < 3 mm, napkin ring sign, stenosis severity, plaque length, volume, and area. Several observations were obtained from this comprehensive study. First, by employing the non-invasive endpoint as the reference standard, a gradual reduction in hyperemic myocardial blood flow was observed with an increasing amount of adverse coronary plaque characteristics. Further, in multivariable regression analysis including stenosis severity as a covariate, it was demonstrated that positive remodeling and non-calcified plaque volume < 150 HU remained independent predictors of an impaired hyperemic myocardial blood flow as assessed with PET. Secondly, adverse coronary plaque features were examined with the invasive endpoint as the reference standard. Likewise, positive remodeling, non-calcified plaque volume, low-attenuation plaque, and spotty calcification were independently associated with a reduced FFR. Thus, stenosis severity $p \leq 0.001$ for both, positive remodeling ($p = 0.004$ and $p = 0.007$), and non-calcified plaque volume ($p < 0.001$ and $p = 0.010$) were independently associated with both the non-invasive and invasive endpoints, respectively. For ischemia by FFR, the area under the receiver-operating characteristics curve (AUC) for stenosis severity was 0.86; for stenosis severity plus non-calcified plaque volume was 0.89 (vs. former $p < 0.001$); and for the latter plus positive remodeling was 0.90 (vs. former $p = 0.044$). Hence, in summary, it was shown that a comprehensive CCTA evaluation incorporating adverse coronary plaque features was superior to a traditional approach of stenosis severity alone for the prediction of a detrimental downstream myocardial perfusion.

Similar results were obtained from the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial, which also studied the association between coronary plaque features and ischemia as part of a post hoc analysis [11]. Additionally, in this trial, the performance of fractional flow reserve derived from computed tomography (FFR-CT) was evaluated. FFR-CT applies computational fluid dynamics to the anatomic information provided by CCTA to compute

FFR non-invasively. In this prospective multicenter study across 8 countries, 254 patients with suspected stable CAD (ages 64 ± 10 years, 64% males) underwent CCTA ≤ 60 days prior to scheduled, non-emergent, clinically indicated ICA. The primary endpoint was lesion-specific ischemia, which was defined as FFR ≤ 0.80 measured ≥ 20 mm distal to the stenosis within a vessel. Coronary lesions were evaluated for composition (e.g., calcified, non-calcified) and high-risk plaque features (e.g., low-attenuation plaque volume < 30 HU, positive remodeling ≥ 1.1, spotty calcification < 3 mm). In total, 484 vessels were interrogated with FFR; obstructive lesions were present in 239 (49%) vessels and of this portion 83 (35%) were considered ischemic. Moreover, in all vessels—e.g., with non-obstructive and obstructive lesions—an inverse relationship was observed between all compositional plaque volumes and FFR. In addition, in multivariable analysis, only a low-attenuation plaque volume ≥ 30 mm^3 was associated with ischemia independent of other coronary plaque features (RR 4.3; 95% CI, 2.0–9.2; $p < 0.001$). For ischemia, AUC for stenosis > 50% was 0.71 (95% CI, 0.67–0.76), for stenosis >50% plus low-attenuation plaque volume ≥ 30 mm^3 0.79 (95% CI, 0.74–0.84; vs. former $p < 0.001$), and for the latter plus FFR-CT ≤ 0.80 was 0.90 (95% CI, 0.87–0.93; vs. former $p < 0.001$). Thus, compared to stenosis severity alone, diagnosis of ischemia improved with the addition of coronary plaque features and FFR derived from CCTA. These two findings were in line with observations from other cohorts [13, 14]. As a consequence, CCTA with its ability to fully quantify coronary atherosclerosis—i.e., not only coronary plaque but also the vessel wall to assess positive remodeling and the lumen to assess luminal narrowing—could refine the diagnosis of myocardial ischemia and the selection of patients for ICA with subsequent revascularization (Fig. 1).

Coronary CTA to Select Patients for ICA and Revascularization

An important aim of non-invasive coronary testing performed in patients with suspected CAD is to identify those with flow-limiting coronary lesions that may benefit from revascularization [10, 15]. Previous data from the USA of 398,978 patients undergoing elective ICA from 2004 until 2008 showed that only 37.6% of the patients had ≥ 70% stenosis, 41.0% had $\geq$ 50% stenosis, and 39.2% had no stenosis defined as < 20% luminal narrowing. Importantly, 83.9% underwent previous non-invasive testing which was positive in 68.6% of the patients. These data are obtained in an era where functional testing, as compared to anatomical testing with CCTA, was performed much more frequently, as advocated by the guidelines [16]. The cause of this low yield of ICA after stress testing is multifactorial, but important determinants are the low prevalence of disease in the study population resulting in suboptimal specificity, artifacts mimicking perfusion defect in myocardial perfusion imaging, and the presence of microvascular dysfunction which is associated with coronary atherosclerosis but less amenable to revascularization [17].

The high concordance of CCTA with ICA for stenosis quantification provides the potential to reduce this rate of normal and non-obstructive ICA [18, 19]. Early observational

Quantitative CCTA   **ICA**

Fig. 1 Case example of a patient with a hemodynamically significantly diseased left anterior descending artery (LAD) demonstrating an invasive fractional flow reserve of 0.53. Quantitative coronary computed tomography angiography (CCTA, left panel) demonstrates severe outward remodeling as a result of a build-up of non-calcified plaque. Two cross-sectional analyses demonstrate the large cross-sectional plaque burden mainly consisting of fibrous (i.e., dark green, plaque with 131–350 HU) and fibro-fatty tissue (i.e., light green, plaque with 31–130 HU). Invasive coronary angiography (ICA, right panel) shows anatomical similarities with the two previous modalities. The yellow arrow in the panels indicates the lesion with the minimal luminal area of the vessel
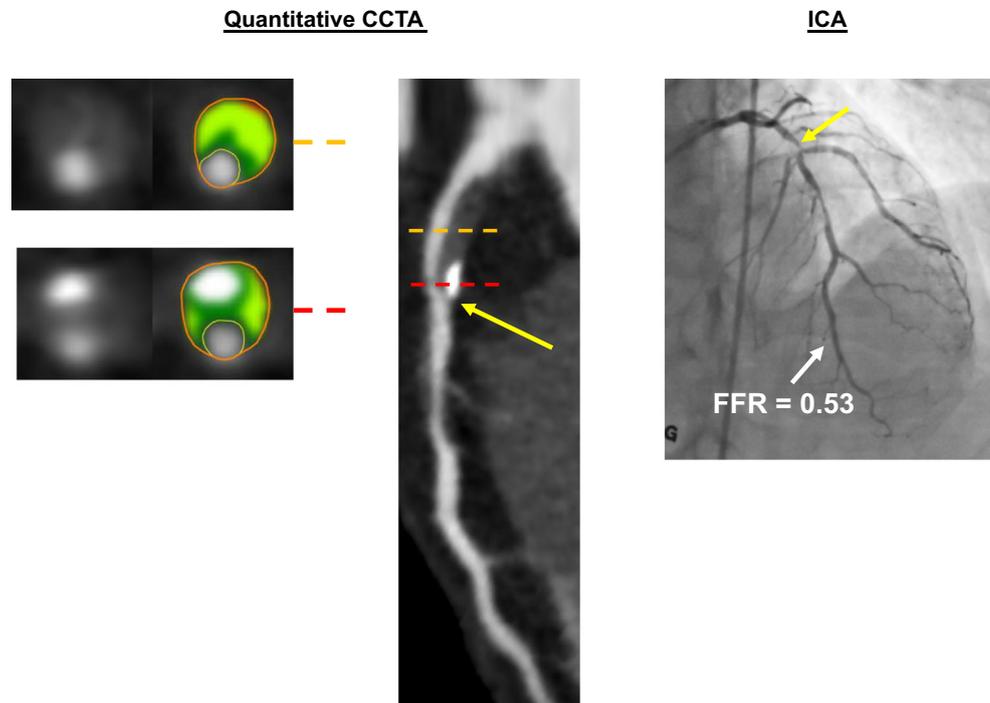
data from the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) registry demonstrated the excellent rule-out ability of CCTA when no to minimal CAD was observed, and high revascularization rates when patients were referred for ICA after the detection of anatomically severe CAD [20]. Among 15,207 patients, absence of CAD was associated with ICA referral in 2.5% of patients during a mean follow-up of 2.3 years and patients with three-vessel obstructive CAD underwent ICA in 69.4% with revascularization in 66.8%.

The recent CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial randomized 1,611 patients to either direct ICA or CCTA, with ICA performed at the discretion of the local physician informed by the CCTA findings [21]. Eligible patients had suspected but no known CAD and a class II indication for non-emergent ICA based upon the ACC/AHA guidelines [22]. All patients in the direct referral group underwent ICA and only 23% of the CCTA-guided arm underwent follow-up ICA. Moreover, patients in the CCTA-guided arm underwent only slightly more additional stress testing during follow-up (14% vs. 11%, $p = 0.04$). The absence of $\geq 50\%$ stenosis on ICA was significantly lower in the CCTA-guided arm (25% vs. 61%, $p < 0.001$); the rates of percutaneous coronary intervention (PCI) were lower in the CCTA-guided arm (11% vs. 15%, $p < 0.001$); and major cardiovascular event rates (i.e., primary outcome of the study, defined as death, myocardial infarction, unstable angina, stroke, and urgent and/or emergent cardiac admission or revascularization) were similar (4.6% vs. 4.6%) at median follow-up of 1 year. Consequently, 57% of lower costs were observed in the CCTA-guided arm ($2,755 vs. $1,183). These findings are a step forward to perform CCTA not only in low to intermediate risk patients, but also in more high-risk patients already referred for ICA (i.e., rule-in). Importantly, only 25% of the patients in the CCTA-guided arm had < 50% stenosis, which was substantially lower than the previously reported 59% in the National Cardiovascular Data Registry from the USA [23]. Comparable findings were reported by Dewey et al., who randomized 340 symptomatic patients from one center with a clinical indication for ICA to either direct ICA or CCTA [24]. Only 14% of the CCTA arm were sent for ICA, which was associated with obstructive CAD in 75% compared to 15% in the direct referral group. Similar findings were observed in the PLATFORM (Prospective Longitudinal Trial of FFR-CT: Outcome and Resource Impacts) study, in which a subgroup of 380 patients was referred for non-emergent ICA [25, 26]. In total, 187 patients were allocated to receive CCTA with additional FFR-CT measurements. Again, the CCTA/FFR-CT-guided group could prevent ICA referral in 60.6% and only 12.4% of ICA did not show obstructive CAD compared to 73.3% in the direct referral group without worsened outcomes at 1-year follow-up. Summarizing the use of CCTA as a gatekeeper resulted in fewer unnecessary ICAs, a higher yield of

obstructive CAD at ICA and lower PCI rates with its consequent cost savings, without affecting event rates.

However, comparisons between CCTA and ICA suggest that CCTA may overestimate stenosis severity. This may be due to blooming artifacts that may occur in heavily calcified lesions, motion artifacts, as well as the usage of different reference points for evaluation of luminal size in plaques that have positive remodeling. This has raised concerns about downstream increases in ICA referral and revascularization rates [27]. A meta-analysis that included randomized clinical trials comparing functional testing with CCTA in stable and unstable patients with suspected CAD, demonstrated that patients were 33% more likely to undergo ICA and 86% more likely to undergo revascularization post CCTA. Both the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) [28] and SCOT-HEART (Scottish Computed Tomography of the Heart) [2] trials, that only included patients with stable chest pain, also demonstrated a 70% increase in revascularization at approximately 2 years of follow-up [27]. However, CCTA is more sensitive for CAD than functional imaging which can only detect the consequences of severe atherosclerosis leading to myocardial ischemia. As such, more CCTA studies will be abnormal than functional tests, which may prompt physicians to treatment with revascularization [29]. An inherent concern of this approach is that CCTA only detects anatomical stenoses that are not necessarily functionally significant, which is key to guiding revascularization and reducing adverse coronary events [10]. In the recent SCOT-HEART trial, 4,146 patients with stable chest pain were randomized to either standard care by their cardiologist or standard care added with CCTA [1]. The primary result of this study was a significant reduction in coronary heart disease death and non-fatal myocardial infarction (2.3% vs. 3.9%, $p = 0.004$) at 5 years of follow-up. Also, interesting patterns of ICA referral and revascularization were revealed. At approximately 2 years of follow-up, a trend was observed towards more revascularization in the CCTA arm (11.2% vs. 9.7%, $p = 0.061$) with a 42% prevalence of $\geq 50\%$ stenosis. However, at 5 years, revascularization was performed equally often in both arms (13.5% vs. 12.9%) and beyond the first year after randomization post hoc analysis showed lower rates of revascularization in the CCTA arm (HR 0.59; 95% CI, 0.38–0.90). This can be explained by the more accurate diagnosis of coronary heart disease followed by revascularization within the first year, but this hypothesis needs more confirmation from other studies.

ICA referrals in the aforementioned studies were based upon visual interpretation of CCTA, which is likely guided by maximal stenosis [30]. More data arises that besides maximal stenosis, overall plaque burden, high-risk plaque features, or percent atheroma volume can refine the diagnosis of ischemia and improve prediction of acute coronary syndromes [4, 6]. Important subgroups of patients are those with

non-obstructive CAD (i.e., < 50%) who demonstrate ischemia in 10–15%, but also those with obstructive disease that do not show ischemia [4, 7]. With the evolving technology in quantitative automated plaque software, a comprehensive anatomical evaluation of the coronary plaque, lumen, and vessel is soon foreseeable, with more precise evaluation of coronary atherosclerosis and improved selection of patients for revascularization.

Conclusion

CCTA is effective as the first test in patients with suspected CAD. It rules out CAD to prevent further coronary testing, estimates overall plaque burden which is strongly related to future events, and demonstrates lower rates of normal and non-obstructive ICA compared to functional testing. Importantly, these findings have been observed in higher risk cohorts. The quantitative CCTA evaluation of coronary atherosclerosis, focusing on high-risk plaque features, improves the ability to rule in patients for CAD and consequently select those likely to have ischemic arteries that benefit from revascularization. Future research should improve our understanding of the relationship between CCTA detected coronary atherosclerosis and ischemia.

Compliance with Ethical Standards

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