Cardiac CT angiography in current practice: An American society for preventive cardiology clinical practice statement☆ ☆

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A B S T R A C T

In this clinical practice statement, we represent a summary of the current evidence and clinical applications of cardiac computed tomography (CT) in evaluation of coronary artery disease (CAD), from an expert panel organized by the American Society for Preventive Cardiology (ASPC), and appraises the current use and indications of cardiac CT in clinical practice. Cardiac CT is emerging as a front line non-invasive diagnostic test for CAD, with evidence supporting the clinical utility of cardiac CT in diagnosis *and* prevention. CCTA offers several advantages beyond other testing modalities, due to its ability to identify and characterize coronary stenosis severity and pathophysiological changes in coronary atherosclerosis and stenosis, aiding in early diagnosis, prognosis and management of CAD. This document further explores the emerging applications of CCTA based on functional assessment using CT derived fractional flow reserve, peri-coronary inflammation and artificial intelligence (AI) that can provide personalized risk assessment and guide targeted treatment. We sought to provide an expert consensus based on the latest evidence and best available clinical practice guidelines regarding the role of CCTA as an essential tool in cardiovascular prevention – applicable to risk assessment and early diagnosis and management, noting potential areas for future investigation.

1. Introduction

This document presents an expert consensus of the state of the art and emerging applications of cardiac computed tomography (CT). The topic of this document was approved by the American Society for Preventive Cardiology (ASPC) Manuscript Committee. The writing group comprises experts in the field of cardiac CT and preventive cardiology. Indications related to coronary artery calcium (CAC) and non-contrast CT scanning is addressed in a parallel paper being developed by a separate writing group. For CT angiography (CTA), each author reviewed the current evidence and conducted literature searches on specific topics. Based on the available evidence, they drafted a manuscript summarizing the current utility and indications of cardiac CT. This draft was circulated among all co-authors of the writing committee and each section was carefully reviewed until a consensus was reached. Then the paper was submitted to the ASPC for external peer review and approval.

This paper is not intended to provide technical details about acquisition or performance of the technology. Cardiac computed tomographic angiography (CCTA) is now a mature technology that has seen great advances since the earliest applications in 1995 using electron beam technology. The current technique requires intravenous contrast administration (usually 50–80 cc/study), a breath hold of 5–10 s and acquisition gated to the electrocardiogram to allow for diastolic acquisition of images. The entire procedure is usually performed in approximately 15 min, as a non-invasive method to acquire complete three-dimensional images of the heart (Fig. 1) using sub-millimeter slices of data. The x-ray tube has become more powerful over time, allowing for more detectors to work simultaneously for image acquisition. Since the earliest single slice images[1], the ability to acquire simultaneous images with one rotation of the gantry has allowed for markedly reduced radiation doses, contrast requirements and breath hold durations [2]. Further improvements, including advances in CT software algorithms,
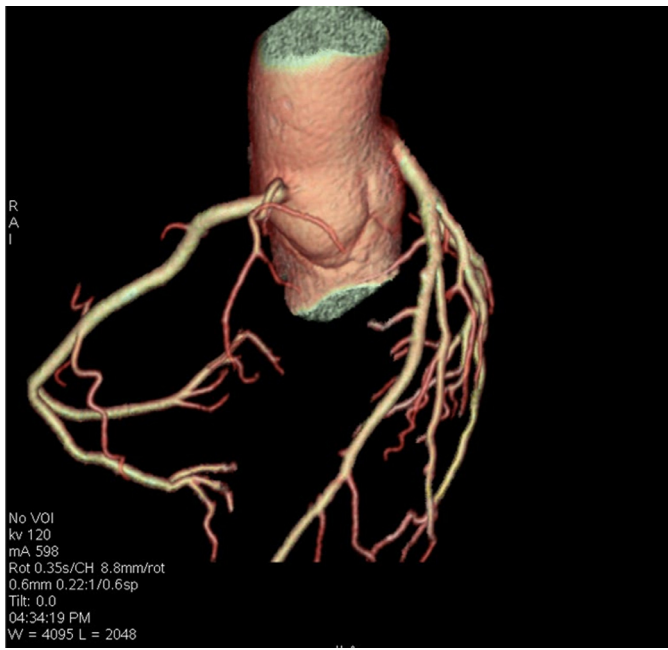
Fig. 1. Three dimensional, volume rendered image of the coronary arteries revealing largely normal vessels. The negative predictive power exceeds 99% for obstructive disease.

workstation processing and hardware, such as slip-ring technology and multidetector arrays, have provided improved image quality and better reproducibility. Currently, the minimum requirements for CCTA performance are 64 detector systems, and scanner rows with up to 640 detectors are now available. For technical and acquisition protocols, please see "SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography" for a comprehensive overview of CCTA performance [3].

1.1. Pathophysiology of atherosclerosis

Atherosclerosis is a maladaptive, inflammatory disease of arteries whose development and progression is pathophysiologically highly orchestrated and influenced by both genetic and environmental factors [4]. It is the response to retention of the apoB containing lipoproteins that is maladaptive, with inflammation playing an important role. When evaluating a patient's atherosclerotic disease burden, there will generally be a continuum of disease, extending from fatty streaks and soft lipid rich plaque, and on to histologically more complex plaques that can be fibrotic, harbor a necrotic core, or have a calcified surface.

Endothelial dysfunction results in reductions in nitric oxide production, increased adhesion molecule and endothelin-1 expression, increased cell proliferation, formation of a more thrombogenic surface, and alterations in gap junction function [5]. Apoprotein B (apoB)-containing lipoproteins (e.g., intermediate-density lipoproteins and low-density lipoproteins [LDL]) bind to scavenger receptor-B1 (SR-B1) and activin receptor-like kinase 1 (ALK1) and undergo transcytosis into the subendothelial space [6,7].

Monocytes in the subendothelial space differentiate into resident macrophages in response to monocyte colony stimulating factor. When presented with oxidized lipids and phospholipids, the macrophages initiate lipid scavenging via SR-A1 and CD36 [8]. As the lipid-loading of macrophages continues, they become foam cells (lipid-laden macrophages) secondary to the enlarging of cytosolic lipid inclusion bodies [9].

As foam cell formation progresses, the excess internalized lipid becomes toxic and the macrophage undergoes apoptosis with production of apoptotic bodies [10,11]. However, as the pace of foam cell develop-

ment and progression increases, the phagocytic capacity of macrophages in the forming lesion is exceeded, and there is a net deposition of released lipid and apoptotic cellular debris, with increased inflammation and the formation of fatty streaks and early atherosclerotic plaques [12,13]. Secondary to the migration of smooth muscle cells from the media, a fibrous cap comprised of collagen, elastin, and variable cellularity (smooth muscle cells, macrophages) develops [14]. More advanced lesions can encapsulate a necrotic core, which renders them more inflamed, architecturally less stable, and more prone to rupture [15]. Atherosclerotic plaques can also undergo calcification (osteogenesis) subsequent to activation of such osteogenic factors as osteonectin, bone morphogenetic protein, and osteocalcin [16]. Plaques that have not yet undergone fibrosis or osteogenesis have some plasticity since a variety of therapeutic interventions can result in plaque regression.

The initial evolution of an atherosclerotic plaque is often accompanied by arterial wall reorganization so as to preserve luminal diameter and blood flow [17]. This is achieved via positive or "Glagovian" remodeling, such that plaque volume enlarges in an outward direction, resulting in arterial wall ectasia [18]. Such plaques may be "invisible" at time of coronary angiography, but apparent on CCTA. During later stages of plaque progression there is increasing luminal obstruction and reduced blood flow ultimately resulting in myocardial ischemia. Plaque rupture or erosion with formation of overlying thrombus and sudden luminal obstruction is etiologic for acute coronary syndromes (ACS) [19].

1.2. Correlation of CCTA plaque to Histology and IVUS

Not only does CCTA provide excellent coronary artery images with high accuracy for detecting obstructive coronary artery disease (CAD)[20], and better outcomes for stable chest pain patients than stress testing[21,22], but it can also identify atherosclerotic plaque components and high-risk plaque (HRP) features [23]. Low attenuation plaque (LAP) on CCTA correlates closely with the necrotic core on IVUS, positive remodeling and spotty calcification to a lesser degree, are associated with the development of ACS [24]. Measures of plaque volume for multiple subtypes are derived by establishing density ranges (Hounsfield Units- HU) for noncalcified and calcified plaques: low attenuation −50 to 50 HU, non-calcified 50 HU to 130 HU, fibrotic 131 HU to 350 HU, and calcified >350 HU. Total plaque volumes are easily measured. Plaque characterization has been provided by at least 5 different software programs and has been utilized in an ever-increasing number of scientific publications. Their utility, as with any new tool, depends on their validation by accepted gold standards, which in this case are intravascular ultrasound (IVUS), histology and optical coherence tomography (OCT) [25]. Relevant HRP data are summarized in Central illustration A2.

1.3. Clinical CCTA in acute syndromes

There are numerous randomized trials comparing the use of CCTA compared to stress testing in the evaluation of symptomatic patients presenting to the Emergency Department with initial negative troponin values and deemed at low ACS risk[26–31]. Trial findings support that CCTA reduces the time to diagnosis and fosters early discharge, without any differences in major CAD events, such as death, acute myocardial infarction (MI), repeat emergency department (ED) visits or re-hospitalization for ACS, over near-term follow-up of ~1–6 months as compared with the standard diagnostic approaches with stress testing[26–34]. Additionally, CCTA is generally more accurate for the identification of patients with obstructive CAD who warrant subsequent invasive coronary angiography [35–38]. Longer term outcome data are available; from a prospective randomized outcome trial comparing radionuclide stress myocardial perfusion imaging and CCTA, the 40-month major CAD events were similar between CCTA and stress myocardial perfusion SPECT imaging ($p = 0.29$) [39]. By comparison, from the Cardiac-CT in the Treatment of Acute Chest Pain trial, the hazard ratio

for CAD events at ~18 months was 0.62 (95% CI: 0.40–0.98, p = 0.04) for CCTA versus a standard care approach [40].

As CAC scanning is an integral part of almost every CCTA done, it is possible to stop at the non-contrast CAC scan and not proceed to CCTA in lower risk CP patients. Data reveal that ~ half of patients scanned in the ED have a 0 CAC score [41–44]. In some cases, CAC may then be followed by CCTA for those with detectable scores >0, with such an approach reducing unnecessary testing in ~60% of patients [45]. From one report, the rate of ACS was directly proportional across a range of CAC scores from <1% for patients with a 0 score to >40% for patients with CAC scores >400 [46,47]. Long term follow up re-affirms this approach, as the absence of CAC in a prospective study was associated with a very low risk of future cardiac risk events, with an annual event rate <1% over 7 years [48]. This approach has been adopted by the recent AHA/ACC Chest Pain guidelines, endorsing this algorithm for low risk chest pain patients [49].

Two recent trials have focused on the utility of CCTA in higher risk patients with non-ST elevation ACS. From the Very Early Versus Deferred Invasive Evaluation Using CT in Patients With Acute Coronary Syndromes (VERDICT) trial, CCTA when promptly performed within ~2.5 h of the non-ST elevation ACS (NSTEACS) diagnosis was highly accurate with a negative and positive predictive value of 91% and 88%, respectively; and similarly accurate as when testing was performed within 2–3 days of initial diagnosis [50]. These findings extend prior trials results and support CCTA use in higher risk patients but also use very early on following the NSTEACS diagnosis to identify patients not requiring further invasive evaluation. When integrated with the VERDICT trial, such a strategy of early CCTA would foster prompt discharge of patients without obstructive CAD. Most recently, in the updated 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain, CCTA received the highest class I, level of evidence A recommendation, as the first line test for evaluation of acute chest pain in intermediate-high risk patients with no known CAD [49].

1.4. CCTA in stable coronary artery disease

In this section, we summarize evidence that anatomic assessment with CCTA in patients with suspected CAD improves clinical outcomes as compared with stress testing, discuss the plausible mechanisms by which these benefits are achieved, and explore potential future applications of CCTA in stable CAD patients.

CCTA has emerged as a powerful diagnostic imaging modality in the initial evaluation of stable patients with symptomatic CAD, with promising insights from multiple clinical trials, including SCOT-HEART (Scottish Computed Tomography of the HEART), PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), CON-SERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization), CAPP (Cardiac CT for the Assessment of Pain and Plaque) and a study by Min et al [21,51-54]. To this effect, a "CCTA-first strategy" for evaluation of stable chest pain in low to intermediate risk patients is currently endorsed by major guideline committees and international societies. In 2016, the National Institute of Health and Care Excellence (NICE) in the UK updated their guidelines to incorporate CCTA as the "first test for low risk stable chest pain patients without known history of CAD."[55]. This was closely followed by the European Society of Cardiology Clinical Practice guidelines on Chronic Coronary Syndromes, where they acknowledged the role of CCTA as a "first line tool for evaluation of chronic coronary syndromes for low to intermediate risk patients, with a class I, level of evidence B recommendation."[56]. Most recently, in the updated 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain, CCTA received the highest class I, level of evidence A recommendation, as the first line test for evaluation of stable chest pain in intermediate-high risk patients with no known CAD [49].

As an initial diagnostic test for low-risk patient with chest pain potentially due to suspected CAD, the major strengths of CCTA over functional testing are its ability to effectively rule out obstructive CAD and determine the anatomic burden of atherosclerosis.

Unlike stress testing, CCTA has been well established as an effective gatekeeper for invasive coronary angiography in clinical practice, enriching the diagnostic yield of referral for obstructive CAD [52]. A comprehensive meta-analysis that compared the diagnostic accuracy of CCTA and functional testing in stable CAD showed the superiority of CCTA, where sensitivity to identify obstructive CAD (defined as at least ≥50% stenosis on ICA) was 98% for CCTA vs. 67% for exercise electrocardiography and 99% for CCTA vs. 73% for single-photon emission computed tomography (SPECT) (P = 0.001) [57]. Most recently, in the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, blinded CCTA was used to exclude participants who had obstructive left main (LM) disease and those who did not have obstructive CAD. Among participants with at least moderate ischemia on stress testing who underwent CCTA, 8% were excluded because of obstructive LM disease and 21% were excluded because of the absence of obstructive disease [58]. In a follow-up analysis of ISCHEMIA, Mancini et al. reported high rates of concordance of CCTA findings with invasive coronary angiography [59].

CCTA allows for comprehensive, anatomic assessment of atherosclerotic disease burden that plays a pivotal role in improved risk stratification and can guide risk-based decisions in management, such as early initiation of preventive therapy vs revascularization for severe LM disease or multi vessel disease [60,61]. The landmark SCOT-HEART trial examined the diagnostic utility of CCTA in addition to standard of care in stable CAD (4146 patients, median follow-up of 4.8 years), and the premise of the trial was to understand the impact of anatomic assessment by CCTA in clarifying the diagnosis of angina and how it influenced further management and clinical outcomes [62]. SCOT-HEART demonstrated that addition of CCTA to standard of care resulted in a nearly 2-fold increase in diagnostic certainty of angina (primary endpoint) compared with standard of care alone [63]. In a 5-year follow-up, SCOT-HEART found a significant reduction in rate of death from CAD or non-fatal MI with use of CCTA in addition to standard of care vs standard of care alone (hazard ratio (HR), 0.59; 95% confidence interval [CI], 0.41 to 0.84; P = 0.004) [21]. The presumed mechanism of the observed benefits was initiation of evidence-based preventive medications in patients with nonobstructive disease detected on CCTA (atherosclerosis that does not cause ischemia, therefore not detectable with stress testing). Notably, patients in the CCTA group were more likely to be started on lipid lowering, anti-hypertensive, anti-platelet, and anti-anginal medications (19.4% vs. 14.7%, HR 1.40, 95% CI 1.19–1.65) [64]. The PROMISE trial, a comparative effectiveness trial of CCTA vs functional testing enrolled 10,003 patients with stable chest pain, and demonstrated noninferiority of CCTA over functional testing, after a follow-up of 25 months [51]. Although no differences were found between testing strategies regarding the primary outcome, the rate of MI and death at 12 months was significantly lower in patients who underwent CCTA (HR 0.66, p = 0.049). As compared with the SCOT-HEART 5-year follow-up, the neutral results are thought to be related to shorter follow-up (minimum follow up was reduced during the trial to 1 year) and low statistical power, since a majority (approximately 90%) of patients on recruitment had atypical or non-anginal symptoms, likely leading to lower than anticipated event rates [65].

The superior prognostic value of anatomy as compared with stress testing has been shown in COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and ISCHEMIA, where the severity and extent of CAD predicted adverse CV outcomes including death and MI, while the severity of ischemia did not [66,67]. In ISCHEMIA, increasing severity of CCTA-defined anatomic disease correlated strongly with risk of adverse events. On the contrary, increasing severity of ischemia was not associated with higher risk of adverse events. Similarly, CCTA had a higher discriminatory ability to predict

adverse events than functional testing in PROMISE (c-index, 0.72; 95% CI, 0.68–0.76 versus 0.64; 95% CI, 0.59–0.69; *P* = 0.04) [68]. Furthermore, in a long-term follow-up of patients with stable CAD in CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry), anatomic extent of CAD on CCTA was associated with a higher risk of major adverse CV events, beyond traditional CV risk factors [69].

The mounting evidence from these studies further builds on the potential role of CCTA in management of stable CAD in higher risk patient subgroups. In a secondary analysis of PROMISE after 25 months of median follow-up, CCTA imaging was associated with significantly fewer adverse CV outcomes (1.1% versus 2.6%, HR 0.38, 95% CI 0.18–0.79) in participants with diabetes, with higher rates of statin use in the CCTA group in comparison with the functional testing group [68,70]. Similarly, CCTA imaging was associated with a significantly reduced risk of the primary endpoint in participants with diabetes in SCOT-HEART (HR 0.36, 95% CI 0.15–0.87), even larger than the overall cohort (HR 0.59, 95% CI 0.41–0.84) [21].

CCTA in stable CAD therefore improves risk stratification beyond stress testing, with the added benefits of being able to identify patients with no obstructive disease who might demonstrate ischemia on a stress test, and patients with obstructive left main (LM) disease who would benefit from revascularization and who cannot be identified reliably by stress testing alone. In the context of the overall results of ISCHEMIA, the safety of a conservative strategy using a CCTA-based approach after exclusion of LM disease highlights its emergent role as a noninvasive tool to identify appropriate patients with stable angina who prefer initial conservative management. Table 1

With the recent updates to American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Diagnosis and Management of Patients with Stable Chest Pain[49], we are encouraged to see United Healthcare, the nation's largest commercial health insurer, modify its reimbursement policies to cover CCTA as a first line test to evaluate stable chest pain in low-intermediate risk patients [71]. Based on the accumulating evidence supporting the use of CCTA in stable CAD, providers should consider CCTA as an alternative to stress testing as an initial test for evaluation of stable chest pain. Future research is needed to evaluate the utility of serial CCTA to optimize management of stable CAD.

1.5. Role of CCTA in women and sex differences in plaque

Despite women having a similar or higher prevalence of angina than men,[72] among symptomatic individuals, women are more likely to have no CAD or non-obstructive disease, compared with men [73,74]. Nevertheless, non-obstructive CAD is highly prognostic in women and associated with increased risk of future major adverse cardiovascular outcomes (MACE) and should not be ignored [75,76]. In the CONFIRM registry, the presence of non-obstructive CAD on CCTA was associated with an approximate 2-fold increased risk for MACE, with similar prognostic value for women and men [76]. Furthermore, the presence of non-obstructive LM disease was actually associated with a greater relative risk in women than in men [77]. Additionally among patients in the CT arm of the PROMISE trial, the presence of high-risk plaque (defined as positive remodeling, low CT attenuation, or napkin ring sign) conferred a greater relative risk for MACE in women compared with men even after adjusting for severity of obstructive disease [78].

In a registry of patients who had undergone serial CCTA scans, progression of atherosclerosis between scans was more common in men than women, but progression was associated with increased risk of MACE for both sexes [79]. This may be related to sex differences in the composition of plaque and its progression. In one registry of patients undergoing serial CCTAs, women had less total and non-calcified plaque volume at baseline compared to men [80]. Furthermore women had slower progression of non-calcified plaque volume and were less likely

Table 1
CT Acquisition Improvements and Their Effects on Radiation Dose.

CT Acquisition Improvements	Effect on Radiation Dose
CT Scanner Technology	Wide-area detector (256-slice and greater) or high pitch with dual x-ray tubes can cover the entire heart in one prospective scan with a significant reduction in dose
Tube potential (kVp) reduction	Use of lower tube voltage decreases the dose by the square of the kVp reduction
Tube current (mAs) modulation	Tube current is at maximum during the cardiac phase when coronary anatomy is best visible and decreased during other phases resulting in significant dose reduction
Prospective ECG-gated scan protocol	The X-ray beam is turned on for only a short portion of the cardiac phase when coronary anatomy is best visible with significant dose reduction
Decreased scan length	Tightening the scan length to include only the required portions of the cardiac anatomy avoids unnecessary exposure
Iterative reconstruction	New data are generated during post-processing by compensating for image noise and interpretability. Dose reduction is seen by enhancing the quality of images obtained at higher noise levels
Patient preparation	Adequate heart rate control prior to scanning increases the ability to scan prospectively or apply tube current modulation without image degradation

to develop high risk plaques than men; however women had greater calcified plaque progression [80].

Mechanisms for MACE in the setting of non-obstructive CAD include plaque erosion with subsequent thrombus formation, endothelial dysfunction, coronary micro-vasospasm or impaired vasodilation. In women with ischemia with non-obstructed coronary arteries (INOCA) who had undergone coronary angiography, intravascular ultrasound (IVUS) revealed the presence of coronary plaque in nearly 80% of women with 73% having positive remodeling;[81] In other words, plaque is highly prevalent in women with INOCA which makes non-invasive detection of coronary plaque such as through CCTA attractive so that preventive interventions (e.g., statins, ARBs) can be implemented.

At a given age, women have lower prevalence of coronary plaque than men, but since women have smaller coronary arteries, they might be more symptomatic at a lower plaque burden. There might be a sex specific plaque signature with men being more likely to have a larger lipid core, greater calcification with higher CAC score, thicker fibrous cap, and more obstructive CAD, whereas women have smaller vessels, lower plaque volume, smaller necrotic core, lower calcification and lower CAC score, and more ischemia with non-obstructive CAD [82].

As women have smaller coronary arteries but also lower myocardial mass, this results in a higher coronary volume to myocardial mass (V/M) ratio in women than men for same degree of coronary stenosis [83]. This translates to women being less likely to have an abnormal fractional flow reserve by CT (FFR-CT) of ≤0.80 compared to men for a similar degree of obstructive stenosis [83]. Some of these differences likely lead to sex differences in referral for revascularization.

The Society of Cardiac Computed Tomography (SCCT) has put forth an expert consensus statement about the use of CCTA in women,[84] so this topic will be only briefly reviewed here. It should be noted that among patients with stable chest pain, women might preferentially benefit from CCTA due to higher rates of normal scans which can lead to fewer downstream testing. In the PROMISE trial, the event rates of MACE for women with a negative CCTA were similar to that of women with a negative stress test [85]. On the other hand, women with an abnormal CCTA had higher MACE rates than women with an abnormal stress test, suggesting that women might particularly benefit from a CCTA-guided approach for its better prognostic value [85]. In contrast, in men in that same trial the prognostic value of an abnormal CCTA and abnormal stress test were similar [85]. This should further be put in the context that the radiation exposure for contemporary CCTA is low and much lower than for a nuclear stress test. In the SCOT-HEART trial of patients with stable chest pain, a CCTA-guided approach for management was superior to the usual standard care approach in women, to a similar degree as men (p interaction for sex 0.57), with the benefit likely driven by the initiation of more preventive therapies (i.e., statins and aspirin) in the CCTA-guided arm [21].

Among patients with moderate to severe ischemia on stress testing who underwent CCTA as part of screening for enrollment in ISCHEMIA trial, those found to have no obstructive disease were predominantly women (66% female) vs those who were found to have obstructive disease being predominantly male (26% female). Those without obstructive disease were enrolled in the CIAO-ISCHEMIA registry and underwent a repeat stress echo and angina questionnaire at 1 years' time [86]. It should be noted that the INOCA patients had a similar degree of both angina and ischemic echocardiographic wall motion abnormalities as those with obstructive disease. Furthermore, change in ischemia over time was not correlated with change in angina, emphasizing the point that ischemia and angina are not always well correlated [86].

In sum, plaque is prognostic in women and women might benefit even more from a CCTA-guided approach for management of chest pain. Coronary microvascular dysfunction may be present in the absence of obstructive disease. Preventive care is warranted for all at-risk women.

1.6. Correlation with functional imaging

Although invasive coronary angiography remains the "gold standard" for many clinicians, functional imaging with measurement of parameters that quantitate coronary blood flow at rest and/or stress, or coronary flow reserve (CFR), has been shown to be superior to anatomic imaging alone [87]. This anatomic mode of assessing the impact of CAD remains despite the longstanding literature consistently indicating its limitations.

Iskandrian et al.[88] in 1993 published that major adverse cardiac events are predicted better by SPECT than by visually analyzed coronary angiograms, and that there was no incremental prognostic value of angiographic data over the SPECT perfusion data, thereby making non-invasive perfusion imaging a better "gold standard" for patient management. Schachinger et al.[89] confirmed that provocative testing with intracoronary acetylcholine to demonstrate flow limiting endothelial dysfunction was superior for predicting patient outcomes to coronary angiography ("lumenography") showing no obstructive stenoses, presumed to represent a low risk finding.

Hachamovitch et al.[90] found in an observational study that patients with smaller degrees of reversible ischemia on functional imaging had a survival advantage with no revascularization (referred to as "medical therapy" although the content of medical therapy was not documented), while those with larger amounts of ischemia (>12% of the myocardium) were more likely to benefit from revascularization. In women with symptomatic chest pain, "false positive" noninvasive functional studies, judged by a negative invasive coronary angiogram, were more likely to have adverse cardiovascular outcomes despite absence of angiographic findings if they had impaired coronary vasomotor response to acetylcholine [91]. In fact, the study of invasive FFR in the 2009 FAME trial similarly confirmed the prognostic usefulness of physiologic assessment to document ischemia prior to performing revascularization to improve outcomes [92]. Unfortunately, the prospective ISCHEMIA Trial[93] failed to demonstrate this benefit, so utility of functional testing is more strongly for intermediate to high risk chest pain patients in the new CP Guidelines [49].

Measurement of the ratio of hyperemic to baseline blood flow, CFR with rubidium-82 or nitrogen-13-ammonia PET perfusion imaging has proven superior to myocardial perfusion indices alone in predicting cardiovascular events. This superiority is likely based on the ability of CFR to identify at-risk ischemic patients with either microvascular disease or balanced reduction in blood flow due to multivessel CAD [94–96]. Specifically, a normal CFR has the ability to recategorize the patient's future adverse cardiovascular event risk, whether the perfusion scan is normal or abnormal [94].

Collectively, given concordance of invasive FFR, FFR-CT and PET CFR, these studies have influenced the American College of Cardiology[97] and European Society of Cardiology[98] guidelines for revascularization, with a class I recommendation for functional imaging in patients with an intermediate probability of CAD prior to revascularization. However, in many medical centers invasively and noninvasively derived coronary anatomy drives management based on anatomic features, such as percent diameter stenosis (Fig. 2). While this technique may continue to be uniquely useful when used as a technical guide for intervention, e.g., how to intervene, based on the size and length of a given stenosis. Functional assessment should be more routinely performed during PET myocardial perfusion imaging, CTA and invasive coronary angiography.

1.7. Fractional flow reserve by coronary CTA

Evidence to date suggest that lesion-specific ischemia assessed by FFR can influence clinical management, guide revascularization, and provide clinical outcome benefit in patients with stable CAD, unlike traditional stress testing. The FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) and FAME 2 trials demonstrated
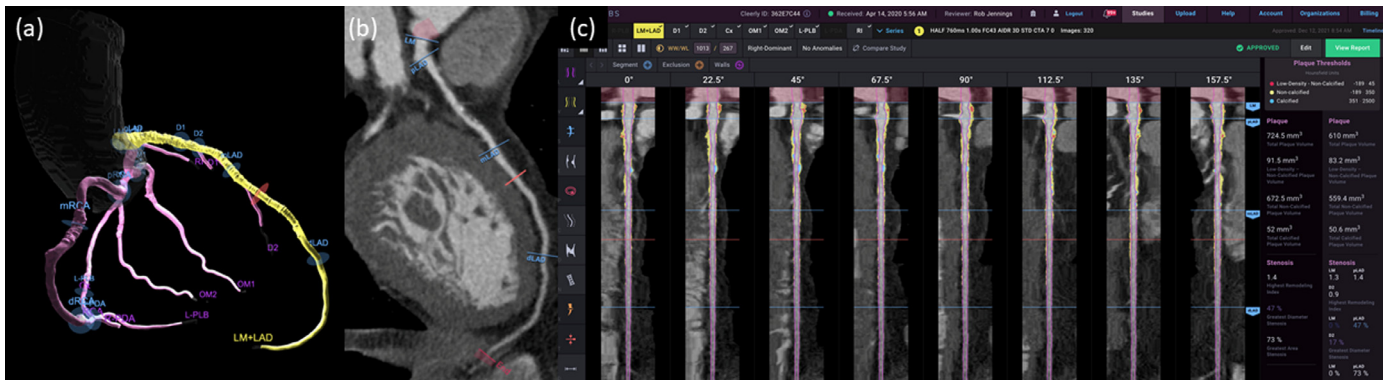
Fig. 2. Coronary CT angiogram of the left anterior descending artery (LAD) demonstrated (a) topologically in volume rendered technique, (b) visually in curved multiplanar reformat, and (c) quantitatively in straightened multiplanar reformat across different 3D views. This patient demonstrates high atherosclerotic plaque burden that is comprised primarily of non-calcified (yellow and red) rather than calcified plaque (blue).The ability to visualize both stenosis and plaque makes this modality unique among non-invasive imaging tests.

significant reduction in MACE with FFR-guided percutaneous coronary intervention (PCI) for stenosis with FFR ≤0.80 (ischemic zone) compared with no-FFR/angiography only strategy for PCI or GDMT alone [99,100].

FFR_{CT} computed from non-invasive coronary CT angiography provides data on hemodynamic significance that can characterize lesion specific physiology, and makes it possible to complement the anatomic assessment provided by CCTA. This technology available currently in clinical practice, was originally developed by HeartFlow (Redwood City, California, USA) and involves a novel, post-processing technique of computational fluid dynamics simulating hyperemia which is applied to the standard set of mages acquired routinely by CCTA [101]. Currently, FFR_{CT} from HeartFlow is the only technique for functional assessment on CCTA approved by Food and Drug Administration and NICE, in the United States and United Kingdom, respectively. Other vendors are developing parallel or competing methods, but not yet approved for clinical use.

Prior multicenter trials including DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve), DEFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) and NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps), have shown a high diagnostic performance of FFR_{CT} against invasive FFR (gold standard) [102–104]. FFR_{CT} has shown to have a superior diagnostic performance over CCTA alone, without a compromise in its sensitivity and potentially overcome limitations related to high coronary calcium score [104–106]. A recent sub analysis of the PACIFIC trial showed higher diagnostic performance of FFR_{CT}, with significant improvement in accuracy for discrimination of lesion specific ischemia compared to CTA, SPECT and PET alone. Area under the receiver-operating characteristic curve (AUC) for identification of ischemia-causing lesions was higher with FFR_{CT} (0.94), when compared to coronary CTA (0.83; p < 0.01), SPECT (0.70; p < 0.01), and PET (0.87, $p < 0.01$), on a per-vessel basis, respectively [107].

Apart from the excellent diagnostic performance, there is extensive evidence to establish the clinical utility of FFR_{CT} as a safe and feasible, non–invasive alternative to ICA in management of stable CAD. Studies such as PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts) and RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) have shown that the additional information of functional significance of coronary lesions provided by FFR_{CT}, can effectively guide clinical decisions regarding invasive coronary angiography deferral, revascularization planning and adjudication of PCI targets, enriching the diagnostic and therapeutic yield of referral to catheterization laboratory [108,109]. Data from the prospective ADVANCE (Assessing

Diagnostic Value of Non-invasive FFRCT in Coronary Care) registry of patients with clinically stable, symptomatic CAD, demonstrated that addition of FFR_{CT} was associated with significant modifications in the clinical management pathway, leading to meaningful changes in treatment recommendations including determination of revascularization versus medical management [110].

There is growing evidence in favor of the prognostic value of FFR_{CT} from observational studies, and results from multiple ongoing prospective, randomized on the impact of FFR_{CT} on clinical outcomes trials in FORECAST (Fractional Flow Reserve Derived from Computed Tomography Angiography in the Assessment and Management of Stable Chest Pain) and PRECISE (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization), are eagerly awaited. Most recently, the ADVANCE FFR_{CT} Registry demonstrated favorable prognosis in patients with a negative FFR_{CT}, with lower rates of CV death or MI and less revascularization. At 1 year follow up, the rates of adverse events including CV death or MI, was higher in patients with FFR_{CT} ≤0.80 compared with those who had an FFR_{CT} >0.80 (25 [0.80%] vs. 3 [0.20%]; RR: 4.22; $p = 0.01$) [111]. These findings complement the results from a hypothesis-generating post-hoc analysis of the PROMISE trial, that showed that FFR_{CT} ≤0.80 was a significant predictor of revascularization or MACE [112].

In addition to the clinical utility of FFR_{CT} in the outpatient management of stable CAD, there is an increasingly potential role for application of FFR_{CT} in clinical decision making, procedural planning and guiding complex revascularization in complicated, multivessel CAD, as highlighted in the SYNTAX trials. The SYNTAX II score demonstrated strong correlations between FFR_{CT} and invasive coronary angiography, suggesting the usefulness and feasibility of a non-invasive CCTA/FFR_{CT} based strategy in guiding treatment and procedures in patients with complex CAD [113]. The SYNTAX III trial demonstrated that in patients with 3-vessel coronary artery disease, physiologic assessment with FFR_{CT} changed heart team's treatment decisions in 7% of the patients, informed procedural planning including CABG (coronary artery bypass grafting) and modified selection of target vessels for revascularization in 12% of the patients [114].

In sum, FFR_{CT} is a novel, non-invasive method that uses computational fluid dynamics for determining lesion-specific ischemia and has made it possible to provide a combination of detailed anatomic and precise coronary physiology data in a 'one-stop shop', making it a promising, transformative tool in the management of CAD. Results from ongoing, multicenter, randomized trials will further inform us on the clinical use of FFR_{CT} and its adoption in routine clinical practice. The 2021 AHA/ACC Chest Pain guidelines also recommend incorporation into use, with a 2A recommendation which states "For intermediate-risk patients with acute chest pain and no known CAD, with a coronary artery steno-

Fig. 3. A 62 year old man with atypical chest pain. Computed tomographic angiography reveals severe atherosclerosis (mostly calcified plaque) without obstructive disease. The image demonstrates the ability to visualize the lumen clearly despite high calcium burdens.

sis of 40% to 90% in a proximal or middle coronary artery on CCTA, FFR-CT can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization."[49].

1.8. Tracking atherosclerosis over time

CCTA is especially effective in quantitative and qualitative plaque assessment, and is now considered in many studies to be the imaging modality of choice in monitoring changes in coronary plaque. The utility by preventive cardiology physicians to measure the effects of individual therapies or global approaches in a given patient to track atherosclerosis to assess if the process has become quiescent is unique to CCTA. It has been used in many clinical trials which have demonstrated the benefits of several therapeutic agents and has excellent correlation with previously used invasive imaging modalities[115]. As compared with IVUS and other invasive techniques, it is safer, easier, less cumbersome, and dramatically less costly for coronary plaque analysis.

To date, advancement in CCTA technology has made it feasible to identify coronary stenosis and define plaque characteristics on cardiac CT. Several features of CT imaging, including excellent spatial resolution (0.3–0.6 mm), temporal resolution (80 ms), cardiac volume coverage, slice thickness and reconstruction algorithms have enabled us to capture high quality images[116] and advances in plaque quantification now allow for serial assessment of plaque quantity, including noncalcified and calcific plaque (Fig. 3). Noncalcified plaque is further classified into low attenuation plaque (LAP), fibrous or fibrofatty plaque based on Hounsfield unit (HU) attenuation thresholds.

Serial CCTA studies such as PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) and EVAPORATE (Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy) have described beneficial effects of anti-atherosclerotic therapies on progression of coronary atherosclerotic burden and characteristics, which offer mechanistic correlations to improvement in clinical outcomes [117]. These findings highlight the potential of using serial CCTA to monitor response to therapy and adjust intensity of preventive interventions accordingly [118,119]. Beyond therapeutics, CCTA has been utilized to study dietary interventions. The DISCO–CT trial evaluated the effect of lifestyle changes on plaque progression. In this study Hen-

zel et al. recruited 92 patients with nonobstructive CAD (2 segments with atheroma <70% stenosis on baseline CTA) and randomized them to optimal medical therapy (OMT) versus OMT plus DASH (Dietary Approach to Stop Hypertension) diet and physical activity [120]. Patients underwent CCTA at baseline and 67±14 weeks later. They showed a significant difference in the reduction of non-calcified plaque (NCP) volume, with greater reductions in the treatment arm ($p = 0.04$).

In the prospective, multinational PARADIGM study of 1255 patients undergoing CCTA who were versus were not treated with statin medications, statins were associated with a slower progression of atherosclerosis that was accompanied by an increase in CP and a decrease in NCP [119]. These results suggest a greater rate of plaque transformation from NCP to CP, a finding associated with a significant reduction in 8-year MACE. Similar to the effects of statins on CCTA-identified atherosclerosis, other salutary medical therapies also reduce NCP and slow plaque progression, including icosapent ethyl, PCSK9 inhibitors, colchicine, diet and others [117,120,121]. Together these findings suggest 2 goals to atherosclerosis imaging and treatment to improve patient survival:[1] slow or stop the progression of atherosclerosis, and[2] transform NCPs into CPs (i.e., turn CT-based dark plaques brighter).

Importantly, in all cases, when plaque volumes decreases on CCTA with a certain intervention, those interventions have demonstrated improvement in clinical outcome studies (e.g.,- statins, icosapent ethyl, colchicine),[122–124] and when interventions increase atherosclerosis on CCTA (e.g., testosterone),[125] outcome studies have demonstrated increased CV events[126]. Thus, CCTA plaque changes may provide important surrogate information related to outcomes, allowing smaller studies to be performed with serial CCTA to test the potential for CV event reduction.

Given low achievable radiation and high reproducibility, CCTA now permits quantification not only plaque burden but also allows for further distinction of plaque components and identification of vulnerable plaques. Application of these findings continue to extend the prospect of coronary CCTA in evaluation and management of atherosclerotic CAD in clinical practice.

1.9. Peri-coronary inflammation and other non-coronary metrics

In this section, we summarize the non-coronary metrics including peri-coronary inflammation that can be evaluated on CCTA which provides useful information for further risk assessment. Inflammation is known to play a major role in the development and progression of atherosclerosis [4]. Perivascular adipose tissue (PVAT), the epicardial adipose tissue (EAT) around the coronary vasculature, is believed to have an active role in coronary atherogenesis by the release of pro-inflammatory mediator into the coronary vasculature ("outside to inside" signaling) via vasocrine signaling through the shared vasa vasorum with the coronary vasculature and paracrine signaling due to the lack of fascia separating the coronary vasculature and surrounding adipose tissue [127]. However, recent studies have demonstrated that inflammatory cytokines released locally from inflamed vasculature diffuse into the surrounding PVAT and lead to lipolysis in the surrounding adipose tissue and suppression of adipogenesis ("inside to outside" signaling) which results in increased intracellular and extracellular fluid content, decreased lipid content, and poorly differentiated smaller adipocytes [128]. As a result, the PVAT is pathophysiologically different from the rest of the EAT (non-PVAT) which do not undergo these inflammatory changes.

CCTA has good spatial resolution and volumetric acquisition, therefore is considered as gold standard for the assessment of EAT. Adipose tissue is detected within the range of −30 to −190 Hounsfield units (HU) on CT imaging. Traditionally, PVAT was assessed quantitatively on CCTA using measures such as the PCAT thickness, area, and volume. Routinely PVAT volume was assessed by manual tracing of the adipose tissue surrounding the coronary segment in axial planes at every 3–5 mm intervals; however, recent development of software such as QFAT have

automated PVAT volume assessment [129]. Studies have shown PCAT volume to have a positive association with CAC progression, ischemia, coronary stenosis, high-risk plaque features,[130] and adverse cardiovascular events [131–133]. However, among individuals with high risk characteristics, there was a negative association between PVAT volume and obstructive coronary artery disease which is thought to be due to reduced fat content in the PVAT due to inflammatory changes [134].

Advances in CCTA technology have enabled qualitative evaluation of the inflammatory changes in PVAT which serves as a novel imaging marker of coronary atherosclerosis. The aqueous and lipid changes in PVAT result in a gradient in the CT attenuation of the PCAT, with the more aqueous and smaller adipocytes (-30 HU) closer to the coronaries and larger adipocytes (-190 HU) farther away. Though PVAT attenuation is a better indicator of peri-coronary inflammation when compared with quantitative assessment, there is significant variability in the mean PVAT attenuation due to variation in the normal reference for various coronary segments, technical parameters such as tube voltage and reconstruction algorithms, and underlying conditions such as obesity and insulin resistance. Therefore, perivascular fat attenuation index (FAI), a weighted PVAT attenuation gradient obtained using AI algorithms was developed by Antonopoulos et al., which has an excellent accuracy for detection of peri-coronary inflammation as assessed by 18-F-fluorodeoxyglucose on cardiac PET imaging [135]. Both PVAT attenuation and perivascular FAI were associated with flow limiting lesions, culprit lesions, myocardial infarction, cardiac mortality, and all-cause mortality [136–139]. Individuals with a high perivascular FAI (≥-70.1 HU; vs low perivascular FAI) were found to have a hazards ratio (HR) of 9.04 (95% CI, 3.35–24.40) and 5.62 (95% CI, 2.90–10.88) for cardiovascular mortality among participants with known CAD in United States and Germany, respectively in the CRISP CT study (Non-invasive Detection of Coronary Inflammation using Computed Tomography and Prediction of Residual Cardiovascular Risk) [139]. Moreover, addition of perivascular FAI to the risk prediction model has demonstrated significant increase in risk discrimination and substantial improvement in net reclassification index among both the cohorts [139].

1.10. Cardiac computed tomography angiography and artificial intelligence

Artificial intelligence (AI) has been applied in multiple contexts across cardiovascular medicine to include therapeutic discovery, precision disease stratification, and integration of multi-omic data [140,141]. To address the estimated 20–40% of patients who experience cardiovascular events and sudden death in previously undiagnosed CAD, AI methods applied to CCTA may allow for enhanced prevention approaches [142–145]. This may enable care to move upstream that allows for precise identification and quantification of early atherosclerosis. Machine learning (ML), as a subfield of AI allows complex algorithms to perform tasks that mimic human intelligence that include convolutional neural networks, recurrent neural networks, support vector machines and decision tree techniques [140].

ML models that integrate atherosclerosis identified by CCTA and CAC with clinical parameters are beneficial in enabling improved risk prediction. Current risk stratification models based on historical cohorts apply a limited selection of clinical findings [146]. While these models have been validated for population level prediction, they may overestimate risk and misclassify patients on an individual patient level. Nakanishi, et al. derived a supervised ML model that applied non-contrast CT metrics with 46 clinical variables and provided superior risk prediction (AUC 0.85) when compared to guideline directed atherosclerotic cardiovascular disease risk scoring (AUC 0.82) from CAC or CAC alone (AUC 0.78) [147]. Motwani, et al. used LogiBoost modeling of 25 clinical variables and 44 reader determined parameters of coronary atherosclerosis severity and found that the ML model (AUC 0.79) outperformed Framingham risk (AUC 0.61) and CCTA scoring (0.64) for predicting 5 year mortality [148]. Van Rosendael, et Al. found from the multi-center CONFIRM registry that a machine learned risk score in combination with

coronary segment stenosis and plaque composition from readers had higher AUC (0.77) vs conventional CCTA risk scores (AUC 0.68 – 0.70) [149].

AI may be considered to enhance identification of CCTA adverse atherosclerotic plaque characteristics (APC) that enable improved application of personalized preventive therapies. Beyond coronary artery stenosis, an advanced understanding of atherosclerosis defined by CCTA has allowed for comprehensive evaluation of plaque composition that predict events [150–152]. AI improves upon legacy semi-automated approaches that are time consuming and require high expertise which limits clinical uptake. Prior studies have evaluated human input of CCTA plaque features, while recent studies have evaluated individual aspects of AI-enabled plaque quantification,[153,154] with validation to a ground truth of expert readers, invasive angiography and invasive fractional flow reserve [155]. Choi AD, et al. has found that AI can achieve 98% agreement with expert readers for CAD-RADS category on a per-patient and 99% of vessels on a per-vessel basis with >95% sensitivity for detection of obstructive stenosis [155]. Griffin WF, et al. has found that AI can achieve agreement with quantitative coronary angiography with AUC of 0.90 for ≥ 50% and 0.95 for ≥ 70% stenosis agreement while providing detailed quantitative APC evaluation to include total plaque burden, non-calcified and calcified plaque volumes in obstructive and non-obstructive stenosis [156].

The future investigation of preventive therapies on plaque progression, medication response, or medication non-response may be guided by AI-guided plaque quantification. Recent data have found that therapies such as statins and icosapent ethyl have linked clinical outcomes with a quantifiable CCTA derived APC phenotype [117,119,157]. The advent of multiple agents that have varying levels of evidence of plaque inhibition such as PCSK9 inhibition, colchicine, novel oral anticoagulants and biologic therapies present future opportunities to evaluate the response or non-response to these therapies through AI guided APC imaging [158–160].

It is important to note that ML and AI solutions should be validated in multicenter clinical trials against appropriate ground truth standards in order to ensure accuracy, precision, and generalizability [144]. In addition, the effect of individualized preventive therapies that is guided by the identification of AI-identified CCTA adverse plaque characteristics require study in future prospective randomized trials [161].

2. Radiation dose in coronary CTA

Coronary CTA has come under intense scrutiny for the associated radiation dose exposure to the patient. Considering an annual exposure to an effective dose of ≤3 mSv in background radiation from natural sources, the annual population-based rates of receiving >3 and >20 mSv (the upper limit of average occupational exposure over 5 years) are 89.0/1000 and 3.3/1000 cases, respectively [162]. Acute awareness of these data in the past decade has spurred the development and refinement of cardiac CT technology and scanning protocols to minimize dose exposure to patients.

While numerous measures of dose are available in clinical imaging, the effective dose is the most useful to compare radiation dose between modalities, and is defined as the sum of the weighted organ-absorbed doses. Effective dose is calculated by multiplying the dose-length product by a k-factor, which is 0.014 mSv.mGy^{-1}.cm^{-1} per the European Commission guidelines and the American Association of Physicists in Medicine for chest CT scans in adults [163].

The PROTECTION series of studies give us an understanding of the rapid evolution of technology and its adoption in clinical practice, with a 78% reduction in the median dose-length product (DLP) from 2007 to 2017 (885 [IQR 560–1239] to 195 [IQR 110–338], *p*<0.001) without a significant deterioration of image quality (Fig. 1) [164]. While these results may be largely attributed to increased awareness of dose reduction protocols, scanner technology has improved greatly during this time

with possibility of obtaining coronary CTA scans with sub-millisievert doses given appropriate equipment and training.

3. Improvements in CT acquisition

The latest CT scanners have higher gantry rotation speed and pitch, greater number of detector panel rows, and improved performance of the x-ray tubes with shorter scan times [165]. With this advancement, the entire heart can be included in one prospective scan ("single heartbeat acquisition"). The additional adoption of meticulous scanning protocols to decrease dose include tube potential reduction, tube current modulation, and iterative reconstruction [166]. Scan protocols can be modified to heart rate and rhythm as well as body mass index to further fine-tune the dose exposure to the patient. Patient selection and preparation are important considerations in dose reduction strategies. Appropriate use of CCTA as well as adequate heart-rate lowering allows for the successful application of scan protocols (Table 1).

4. Cost/Reimbursement

CCTA is reimbursed by almost all major payors. Most notably, United Health Care **in the 2020 Policy**, "United will reimburse for Coronary CT Angiograms when ordered to evaluate stable chest pain in members with low and intermediate risk for coronary artery disease (CAD) as first-line testing. Computed tomographic angiography (CTA) is expected to replace the need for other functional stress testing in this population."[167]. Other payors that have favorable policies include Aetna, Blue Shield, Humana and every Medicare local coverage decision broadly covers CCTA. With the incorporation in the new guidelines[49], even wider access is expected. The NICE Guidelines from the United Kingdom did an extensive cost-effectiveness analysis and found that CCTA dominated over every other strategy (nuclear first, treadmill first, no testing, cardiac catheterization) across a very broad range of pre-test probabilities [55,118].

5. Use of CCTA in asymptomatic persons

For decades, the field of cardiology has emphasized non-invasive cardiac imaging for the evaluation of the etiology of a patient's symptoms that are suggestive of "significant" CAD. In this paradigm, the definition of "significant" has relied upon the presence of myocardial ischemia as an indirect measure for the concomitant presence of high-grade coronary stenoses that may be targets for coronary revascularization[93]. The survival benefit for individuals undergoing CCTA in SCOT-HEART[22] call for a revisitation of the clinical question (or questions) being addressed by non-invasive CHD imaging. In this regard, the SCOT-HEART trial provides important contemporary data to inform this target as atherosclerosis, as medical therapy was the sole factor associated with improved outcomes in SCOT-HEART, and speaks directly to the role of CCTA in prevention of heart attacks.

In the multicenter international CONFIRM registry, Hadamitzky and colleagues developed and validated a 3-year risk score for MACE [168]. In this CONFIRM risk score, the contribution of atherosclerosis significantly outweighed clinical risk factors and stenosis severity for the prediction of future MACE. These results are unsurprising, given that most MIs are caused by non-high-grade coronary stenoses that are expectedly non-ischemic, as described by Ambrose more than 30 years ago using invasive coronary angiography studies [169]. Identical findings have been observed for individuals undergoing non-invasive CCTA, as reported in the multicenter ICONIC registry [170]. Given that the majority of individuals who will suffer MI do not experience any antecedent symptoms prior to their event, whether the evaluation of MI risk should be expanded to asymptomatic individuals also remains a topic of high interest [171].

In the context of preventive cardiology, CCTA has been studied in several large populations of asymptomatic individuals for its potential benefit to guide treatment decision making and improve patient outcomes. The sole randomized controlled trial to date – FACTOR-64 – evaluated 900 patients with diabetes mellitus who did versus did not undergo CCTA imaging and were followed for 4 years [172]. At follow-up, a 20% reduction in MACE events was seen in the CCTA arm, but was not statistically significant (HR 0.80 [95%CI, 0.49–1.32];$P = 0.38$). Similarly, the CONFIRM long-term registry of 1226 patients undergoing CCTA and followed for 6 years, CCTA did not provide incremental prognostic benefit above and beyond CAD risk factors and coronary artery calcium scoring (CACS) [173].

Yet in both FACTOR-64 and CONFIRM, CCTAs were solely interpreted for angiographic stenosis, with no measures of atherosclerotic plaque burden or composition provided. This omission may have significantly reduced the precision of prognostication, as atherosclerosis is not a single disease entity but possesses many characteristics that may differentiate risk and guide therapy, including plaque burden, composition, vascular remodeling, location, diffusivity and so on. Several of these features were evaluated in the ICONIC study, which identified lower density non-NCP burden to be the strongest discriminator of future ACS risk on both a per-patient and per-lesion level. Conversely, a survival benefit was observed in patients with highly dense calcified plaque (CP) [170,174].

Notably, recently completed and ongoing clinical trials may address these goals in either direct or indirect fashion. In the largest population-based study performed to date, 25,182 people aged 50–64 years underwent CCTA as part of the Swedish Cardiopulmonary Bioimage Study (SCAPIS) [175]. From this asymptomatic population, the prevalence of any CCTA-identified atherosclerosis was 42.1%, underscoring a vast epidemic of CHD for which CCTA can pinpoint individuals with obstructive and silent disease who may benefit from more aggressive medical treatment and lifestyle interventions. To determine whether we can alter the natural history of CHD, the SCOT-HEART 2 Trial has initiated enrollment of 6000 asymptomatic people in Scotland (clinicaltriasl.gov NCT03920176) to determine whether CCTA-based screening is associated with diagnostic and treatment decision changes in patients as compared to standard of care, which includes probabilistic cardiovascular risk scoring.

As we await studies, a judicious approach to use of CCTA in asymptomatic populations is to target high-risk populations that are currently missed by traditional ASCVD risk factor scoring.

The best case for CCTA in asymptomatic individuals would include family history of premature ASCVD, diabetes, smokers, human immunodeficiency virus infection in highly activating anti-retroviral therapy, South Asian descent with strong family history, and many others.

6. Clinical recommendations

For preventive cardiology, CCTA in asymptomatic persons to determine presence of subclinical atherosclerosis may be useful as an alternative to CAC in certain clinical settings (e.g., young persons, familial hypercholesterolemia, diabetes)

Preferred test for low-intermediate and intermediate chest pain evaluations, both stable and acute

As an initial test to evaluate chest pain one can confirm the diagnosis of obstructive CAD, rule out obstructive left main stenosis, and identify nonobstructive CAD leading to initiation of preventive interventions

Women may preferentially benefit from CCTA due to lower prevalence of coornary disease

In patients with low probability of obstructive CAD, such as cardiomyopathy or valve disease, may preclude need for invasive angiography

Functional assessment may be added (i.e., FFR-CT) when physiological significance of stenosis is unclear

Coronary artery calcium is useful in low probability chest pain to rule out obstructive CAD
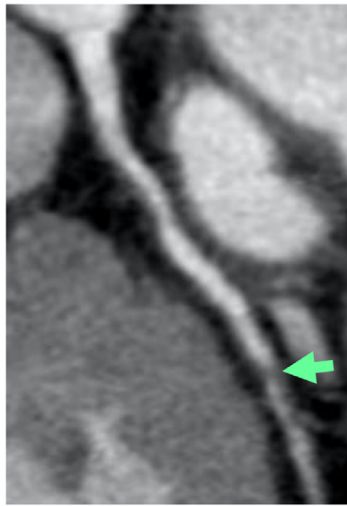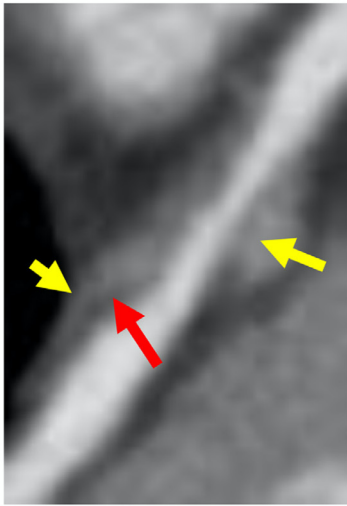
Central Figure Legend: (A1) Presence of positive remodeling (yellow arrows) and low attenuation plaques (LAP, red arrow) are the most important determinants of plaque vulnerability. (A2) Stable plaques lack both these features. Major adverse cardiac events by the presence of 1 or both features in a follow up of — patients for 2 years (A3), and 300 patients for up to 10 years. (A4) Patients with HRP had 45 and 10 folds higher likelihood of adverse outcomes, respectively. Presence of obstructive disease over and above HRP features (A5) and interval progression in plaque magnitude (A6) increased the likelihood of adverse events further. Greater number of adverse plaque characteristics were associated with greater of adverse outcomes (A7) and the HRP characteristics were associated with abnormal fractional flow reserve regardless of luminal stenosis (A8). (Reprinted with permission of Elsevier from [1].)
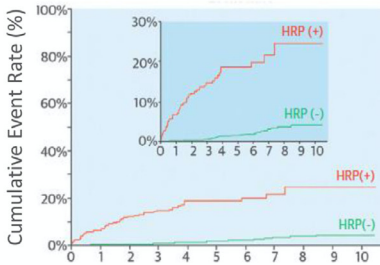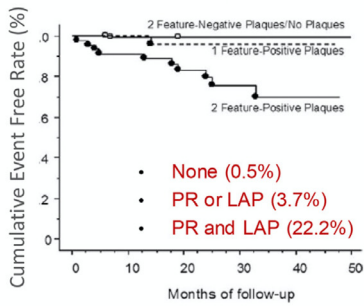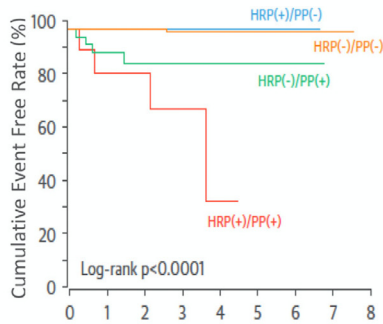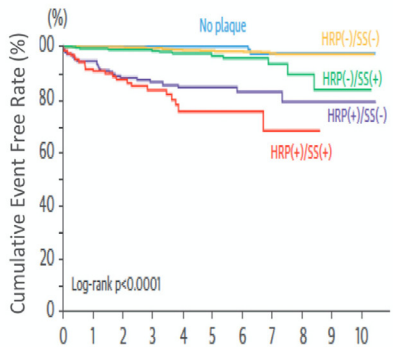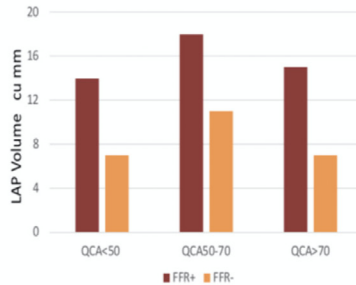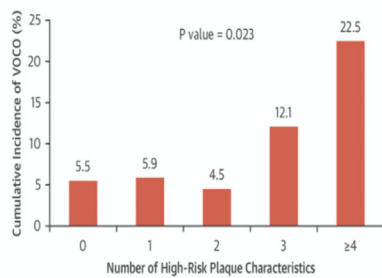
Serial CCTA imaging may be useful to monitor response to preventive therapies

6.1. Limitations

Many of the observations and results of studies discussed highlight the fact that CCTA can identify risk better than other modalities. However, there is limited evidence that by intervening on the patients so identified, we have reduced their risk. This is suggested as one of the benefits of this strategy in several of the randomized trials noted above, but not proven as the sole or primary reason for risk reduction with CCTA compared with other testing algorithms.

7. Conclusions

The evolution of CCTA has been dramatic over the last 25+ years, now becoming the preferred test in a number of situations. New AHA/ACC, United Kingdom and European guidelines strongly advocate for the first-line use of CCTA in low-intermediate risk acute chest pain patients, and a majority of stable chest pain evaluations. The addition of functional capabilities (ie FFR-CT) further expand the utility of CCTA to simultaneously evaluate both anatomy and function. The ability to visualize non-obstructive atherosclerosis further advances this test, allowing for earlier initiation of preventive therapies than functional testing, which typically requires a severe stenosis to be present to detect disease. CCTA plaque analysis will play an increasingly important role in noninvasively defining the natural history of CAD, evaluating the effects of treatment, and providing an automated assessment of cardiac risk in large populations, and will largely replace currently utilized invasive IVUS and OCT.Further validation from large scale clinical trials, including PROMISE, SCOT-HEART and ISCHEMIA, continue to bolster the clinical utility of test. While evidence continues to accrue on the true value of this test, fortunately, advances in image quality, acquisition, post-processing and radiation dose reduction, will further allow for wider use. Future directions will include potential use in asymptomatic cohorts for screening, as well as in younger patients, not previously feasible due to radiation concerns.

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