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SCCT 2021 Expert Consensus Document on Coronary Computed Tomographic Angiography: A Report of the Society of Cardiovascular Computed Tomography

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1. Introduction: scope of the document

Cardiac computed tomography (CT) has changed rapidly since the last major guideline from SCCT.[1] While there have been significant advances in technology, the most gratifying part has been the development of a robust evidence base for the use of cardiac CT in diagnoses of heart disease, prognostication and modulating therapy (both medical and interventional). Such a systematic development of knowledge base has not been the usual practice for any other imaging modality before widespread clinical acceptance in the past. It is no surprise that major guideline bodies have started to endorse incorporation of cardiac CT more definitively than before, and some, like the NICE guidelines in the UK,[2] have even given it first line status. While CTA has been shown to be very good for prognosticating risk, excluding significant coronary artery disease (CAD) in stable patients with chest pain and has high sensitivity for the identification of significant coronary stenoses, it is somewhat less robust in specificity and positive predictive accuracy, leading to the development of value added CT angiography (CTA) strategies like fractional flow reserve derived from CT (CT-FFR) and CT perfusion (CTP); these have arrived into the clinical arena since the last guidelines and, more importantly, have produced a large volume of scientific data showing significant clinical utility. Finally, some questions that often arise in regular clinical practice lack robust trial based evidence and a considered expert opinion might help the clinician make appropriate decisions in everyday practice. It is thus clear that an updated scholarly compendium of recent data is needed to bridge the knowledge gap since the last iteration of the SCCT guideline documents. This SCCT consensus statement summarizes current evidence, updates previous recommendations, addresses key questions regarding the use of CTA in multiple different cardiac scenarios and brings together the collective corpus of literature in the form of definitive recommendations. CTA in acute coronary syndromes will be presented in a separate document. The Expert Consensus recommendations are summarized in Table 1 and Fig. 1.

2. Evidence base

2.1. Diagnostic accuracy

2.1.1. Introduction—Since the recognition that coronary artery stenoses can produce chest pain, the imperative has been to identify through noninvasive testing both the patients whose chest pain is ischemic in etiology, and, with a view towards revascularization, the arteries and specific stenoses that are responsible for the ischemia. To fulfill this need, testing has evolved from simple exercise treadmill test (ETT) to (a) Measures estimating myocardial blood flow changes: myocardial perfusion imaging by single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), (b) Measures detecting the functional consequence of reduced myocardial blood flow: stress echocardiography (SE), (c) Anatomic Imaging: CTA, and finally (d). Combination of anatomic coronary imaging coupled with physiology or perfusion: CTA derived fractional flow reserve (FFR_{CT}) and CTP. How these modalities compare with each other has important implications for diagnostic strategies.

The gold standard for determining ischemia has also evolved from percent diameter stenosis (DS) on invasive coronary angiography (ICA) to more physiologic measures, such as

invasive fractional flow reserve (FFR) that better reflect coronary blood flow and inducible ischemia. Using DS as a reference standard often provides an inaccurate assessment of ischemia. For instance, when compared to invasive FFR ≤0.80, the sensitivity of ICA is 69%, and the specificity is 67%.[3] Although invasive FFR was initially validated by functional noninvasive testing (SPECT and SE), this method has become a universally accepted gold standard by virtue of its strong association with outcomes.[4–6] Nonetheless, %DS continues to be used much more often than invasive FFR before percutaneous coronary intervention (PCI), - In the ALKK Registry in Germany, FFR was performed in only 3.3% of 40,160 patients undergoing ad hoc PCI from 2010 to 2013.[7] There has been an increase in invasive FFR use in the US, from 8.1% in 2010 to 30.8% in 2014, in a registry of 397,737 patients undergoing nonacute PCI.[8] Consequently, the noninvasive imaging modalities will be compared to both %DS and FFR. The best level of evidence is provided by meta-analyses, which will serve as the basis for comparisons, with the exception of 2 recent single center studies not included in meta-analyses. The meta-analyses included patients with and without confirmed CAD and did not draw distinctions between them.

2.1.2. Diagnostic performance of functional imaging and CTA compared to >50% diameter stenosis by ICA—

The National Cardiovascular Data Registry[9] suggested that functional testing is suboptimal for detecting significant coronary stenoses. Of the 661,063 patients undergoing elective catheterization, 64% had testing before the invasive coronary angiogram (ICA); of those, only 51.9% were abnormal. The percentages of patients with <50% DS on subsequent ICA ranged from 55 to 56% after an abnormal exercise treadmill test (ETT), stress echocardiography (SE), single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI); for resting CTA, the percentage was 30%. In the oldest report, Fleischmann et al. evaluated 5874 patients in 41 studies from 1990 to 1997, and reported sensitivity and specificity of 85% and 77% for SE and 87% and 64% for SPECT, with 52% and 71% for exercise ECG.[10] DeJong et al. (Table 2A), in a meta-analysis of 5088 patients in 51 studies from 2000 to 2011 evaluated MRI, SE and SPECT with >50%DS by ICA as reference.[11] MRI was the most sensitive and specific (91% and 80%), with SE (87% and 72%) and SPECT (83% and 77%) roughly similar. Jaarsma et al. (Table 2B), reported on SPECT, MRI and positron emission tomography (PET) in 141 per-patient studies and 70 per-vessel studies.[12] Per-patient diagnostic odds ratio (DOR) was highest for PET (36.47) followed by MRI (26.42) and SPECT (16.31). In per-vessel analysis, PET and MRI were equal (24.74 and 24.11), while SPECT was lowest (11.75). In a meta-analysis limited to 26 studies in which CTA was compared to either ETT or SPECT in the same group of patients, Nielsen et al.[13] (Table 2C) reported CTA sensitivities of 95–99%, specificities of 68–93% and DOR of 128–728. Corresponding ranges for ETT were 65–70%, 24–60% and 0.7–4 and for SPECT were 67–73%, 48–52% and 2–4. It is important to understand that available meta-analyses are also challenged by the small numbers of patients in some of the individual reports, potential referral bias, and often include a mixture of newer and older technology (e.g., planar and SPECT imaging). Finally, in a paper published too recently for meta-analysis inclusion, 391 symptomatic patients, 52% with intermediate and 46% with high risk pre-test probability, who were scheduled for ICA, underwent both CTA and SPECT with >50%DS by ICA as reference.[14] Sensitivity, specificity, positive and negative predictive values were 0.92, 0.75,

0.84 and 0.87 for CTA and 0.62, 0.68, 0.74 and 0.55 for SPECT. AUC was significantly higher for CTA (0.91 versus 0.69, $p < 0.001$.

2.1.3. Diagnostic performance of functional imaging and CTA compared to FFR—

There have been several recent meta-analyses of the correlation between noninvasive testing and Invasive FFR ≤0.80. Takx et al.[15] (Table 3A) compared multiple myocardial perfusion imaging modalities to FFR in 2048 patients and 4721 vessels in 37 studies. They reported the highest areas under the receiver operator characteristic curve (AUC) per patient for CTP (0.93), PET (0.93) and MRI (0.94) compared to SPECT (0.82) and SE (0.83). Similarly, the highest per vessel sensitivities were for MRI (89%), CTP (88%) and PET (84%) compared to SE (69%) and SPECT (74%). Specificities were similar for all modalities, ranging from 79% for SPECT to 87% for PET, with 80% for CTP and 84% for SE and MRI.

A second meta-analysis, analyzing 3798 patients and 5323 vessels in 23 studies, by Danad et al.,[3] (Table 3B), excluded studies in which <75% of vessels were evaluated by FFR, included CTA >50% diameter stenosis and ICA >50%DS and excluded PET, for which there were not sufficient numbers after excluding studies with <75% of vessels having invasive FFR. Sensitivity was highest for CTA and MRI in both per patient (90%) and per vessel (91%) analyses. SPECT sensitivity was the lowest of the functional tests for both patients (70%) and vessels (57%) while SE was also suboptimal (77%). ICA sensitivity was dramatically lower (69%) than for CTA even though both depict coronary anatomy. Specificity was highest for MRI for both per patient (94%) and per vessel analysis (85%), followed by the other 2 functional modalities of SPECT and SE in the 75–78% range. CTA specificity was remarkably lower (39%) than both the functional tests and ICA (66%). The likelihood ratios and AUC reflect these differences; MRI was superior for both positive and negative likelihood ratios and AUC. CTA negative likelihood was excellent as well but had the lowest per patient and per vessel positive likelihood ratio and AUC. Comparison of the anatomical modalities indicates that %DS is overestimated by CTA and under-estimated by ICA, explaining the higher sensitivity and lower specificity for CTA.

A third meta-analysis of all the functional imaging modalities with considerably more patients, by Dai et al.[16] (Table 3C) of 74 studies, included CTFFR and CTP and excluded solely anatomic CTA. As before, CTP, CTFFR CMR and PET had superior per patient sensitivity (88–90%), specificity (84–87%) and DOR (41–57). The 2 most frequently performed functional imaging modalities of SE and SPECT were the least accurate: 69% and 78% sensitivity, 77% and 79% specificity, and 7.40 and 13.40 DOR.

Finally, in the PACIFIC trial, a single center study of 208 patients who underwent CTA, SPECT, PET and ICA with FFR, CTA was 90% sensitive, 60% specific and 74% accurate, compared to 87%, 84% and 85% for PET and 57%, 94% and 77% for SPECT.[17]

CT has 2 additional advantages in diagnosis and management of chronic stable CAD. It can prognosticate very well[18–22], and has the unique ability to identify adverse coronary plaque characteristics that portend adverse risk[23–33] and might even influence the occurrence of ischemia [(34)]. Some of the newer value added technologies like CT-FFR and CTP [(35,36)]

have now been shown to improve the accuracy of CAD diagnosis over and above CTA alone.

Addition of physiologic studies to anatomic information in the same CT scan improve test performance.[35,36] The meta-analysis by Gonzalez et al., of 1535 patients in 18 studies, compared CTA, CTP and CT-FFR.[35] Per patient sensitivities were similar (90–94%), but specificities (43%, 77% and 72%) and DOR (9.17, 63.42 and 24.34) were lowest for CTA without a functional imaging component. Per-vessel results were much less disparate, with sensitivities of 89%, 83% and 83%, specificities of 65%, 76% and 77%, and virtually identical DOR of 19.78, 20.10 and 18.21. A more recent meta-analysis (5330 patients) comparing CTA, CTP and CT-FFR also showed improved efficacy for diagnosing hemodynamically significant CAD compared with CTA alone with higher vessel level, pooled specificity with CTP (0.86; 95% confidence interval [CI]: 0.76 to 0.93), and CT-FFR_{CT} (0.78; 95% CI: 0.72 to 0.83) than that of CTA (0.61; 95% CI: 0.54 to 0.68); addition of either $FFR_{CT,}$ or CTP to CTA improved specificities (0.80–0.92) and superior diagnostic accuracy for CTP, FFR_{CT}, and combined CTA and CTP, compared with CTA. On-site FFR performed as well as off-site FFR and dynamic CTP was more sensitive (0.85 vs. 0.72), but less specific (0.81 vs. 0.90) than static CTP.[36]

With few exceptions, these meta-analyses represent a compilation of prospective and retrospective single center studies with their implicit biases and general lack of direct inter-modality comparisons in the same group of patients. Nonetheless, they offer the most comprehensive evaluation by virtue of their large numbers, and the similarities of the findings irrespective of the inclusion criteria for the meta-analyses.

2.1.4. General conclusions

- **a.** With ICA >50%DS as the reference, CTA, MRI and PET are the most sensitive and specific modalities; SPECT and SE are less sensitive and specific.
- **b.** With invasive FFR ≤0.80 as the reference, CTA, MRI and PET are the most sensitive and MRI and PET are the most specific. CTA is the least specific but CT-FFR and CTP increase the specificity to the level of MRI and PET without loss of sensitivity. SPECT and SE are the least sensitive.
- **c.** These accuracy data should inform the suspected ischemia decision making process, which will also be strongly affected by the availability and expertise of the imaging centers, as well as by outcome and cost studies, some of which are already available after short term analysis.
- **d.** While proceeding to testing was predicated upon estimating pre test probability, the current practice patterns pose some challenges – patients are at lower risk than before and the percentage of positive tests is declining. Models for predicting pre test probability, derived from older data perform sub optimally[37,38] and therefore require an update.[39] There is now a strong movement towards dispensing wth this completely as formulated in the NICE guidelines.

e. Adding non CT modalities for myocardial perfusion (which have better specificity) to CTA (which has excellent sensitivity) is an attractive strategy to minimize the disadvantages of each technique but this has not worked out very well in practice; hybrid cardiac imaging improves diagnostic specificity but with only modest improvement in overall diagnostic performance.

2.2. Prognostic value and comparison with functional testing

The prognostic value of CTA has now been established in both large registry studies and more recent randomized controlled trials. This increasing depth of evidence highlights that CTA provides prognostic information for patents with all levels of cardiovascular risk. In addition, both normal and abnormal CTA results provide important information that can alter downstream investigations and management and influence subsequent outcomes. Our knowledge of the utility of CTA has moved beyond confirmation of diagnostic accuracy, with comparative effectiveness studies now underpinning the prognostic benefit of CTA in large randomized populations. The identification of both obstructive and non-obstructive coronary artery disease by CTA provides important information in patients with both stable chest pain and acute symptoms.

Registry studies have established the excellent prognostic value of a normal CTA, both for short-term outcomes and longer term mortality.[40–44] Previous analysis of stress myocardial perfusion imaging (MPI) identified that a normal study is associated with a low risk of subsequent major adverse cardiovascular events, equating to less than a 1% annual risk for patients without comorbidities.[45] Similarly, a meta-analysis of patients 122,721 patients in 165 studies identified that a normal CTA (without plaque) in patients with suspected or known coronary artery disease (CAD) was associated with a low risk of subsequent events, which is below an annual event rate of 1%.[46] This low event rate was maintained after correction for the underlying population event risk and the proportion of patients with CAD.[46] After correction, the event rate for a normal CTA was similar to that of a normal SPECT, ETT, CMR, PET or stress echocardiogram.[46] Indeed, a normal CTA is associated with an excellent prognosis extending beyond 5 years.[40–44] There is now data showing that a normal CTA strongly predicts event free survival even over a 10 year follow up.[47]

The identification of both obstructive and non-obstructive CAD is associated with worse prognosis in patients undergoing CTA. The COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry found that both the presence and severity of CAD was important in predicting subsequent events.[48,49] The presence of obstructive disease and number of vessels involved were predictive of mortality at 2 years in 23,854 patients without known CAD undergoing CTA.[48] Other registry and cohort studies have identified a similar impact on subsequent outcomes based on the presence and severity of obstructive CAD.[40,42,50,51] A meta-analysis of 25,258 patients with suspected or known CAD in 21 studies identified a similar long term (>2.5 years) prognostic value for CTA and stress MPI in the prediction of death and non-fatal myocardial infarction.[52] Registry studies have also shown that CTA provides incremental prognostic information over cardiovascular risk factors[48,49,51,53,54] and, in some sub-groups, over coronary artery calcium score (CACS).[51,55,56] The PROMISE

(PRO-spective Multicentre Imaging Study for Evaluation of chest pain) trial assessed stable symptomatic outpatients referred for non-invasive investigation for suspected CAD.[57] The 10,003 participants were randomized to anatomical testing with CTA or functional testing with exercise electrocardiography, stress echocardiography or SPECT.[57] After 25 months of follow-up there was no difference between the two groups in the primary outcome of mortality, myocardial infarction, hospitalization for unstable angina and major complications of procedures or diagnostic testing.[57] However, subsequent assessment of this study identified that the discriminatory ability to predict subsequent events was higher for CTA than functional testing (c-index 0.72; 95% CI 0.68 to 0.76 versus 0.64; 0.59 to 0.69; p = 0.04), mostly due to the ability of CTA to detect prognostically important non-obstructive disease.[18] A methodical description of the extent of CAD on CTA allows finer evaluation of the prognostic value of different levels of CAD. Application of the CAD-RADs classification to the CONFIRM database[19] showed a graded decrease in event free survival with more severe disease (5-year event-free survival of 95% with CAD-RADS 0–69.3% for CAD-RADS 5). An analysis of the PROMISE study[20] showed that increasing severity (CAD-RADs score) continued to have additional prognostic value over and above CAC and ASCVD scores.

In addition to the presence and severity of coronary artery stenosis, CTA can provide additional information on plaque burden and adverse coronary artery plaque characteristics. Semi-quantitative assessment of plaque burden such as the CT-Leaman score[21] or segment involvement score can provide additional stratification of patients with non-obstructive coronary artery disease that is an independent predictor of subsequent prognosis. In the Partners registry, among 3242 patients evaluated with CTA, patients with non-obstructive plaque involving at least 4 segments had the same risk of hard cardiovascular events as those who had obstructive CAD[22] Moreover, treatment of such individuals with extensive plaque was associated with a reduction in cardiovascular events[22] which is supported by other data showing that plaques can be stabilized with various therapies. Quantitative assessment of plaque characteristics is also associated with subsequent outcomes in multiple studies.[23–25] In a study looking at serial CTAs, the percent atheroma volume (PAV) at baseline was the strongest predictor of progression of non-obstructive disease to obstructive lesions.[25] The non calcified component of plaque is important: while not different from patients with low vs. high clinical risk (based on number of risk factors), high volume of noncalcified plaque is one of the strongest parameters for predicting ACS in patients with extensive CAD.[24] Not surprisingly, an increased total, non-calcified or low-density plaque volume is associated with a significant increase in cardiac mortality in >5 years follow-up, independent of the segment involvement score.[23] Similar data are seen in high risk groups like asymptomatic diabetic subjects.[26] A composite inclusion of plaque volume, location and composition, might be advantageous for prognostication.[27]

Adverse coronary artery plaque characteristics (also known as high risk plaques or vulnerable plaques) include the presence of positive remodeling, spotty calcification, low attenuation plaque and the ‘napkin ring’ sign.[28,29] and these predict adverse outcomes including acute coronary events.[30–32] Motoyama et al. identified that the presence of positive remodeling or low attenuation plaque was an independent predictor of subsequent acute coronary syndromes in patients undergoing CTA.[28] In the PROMISE

study the presence of positive remodeling, low attenuation plaque or the napkin-ring sign was associated with an increased rate of major cardiovascular events, independent of cardiovascular risk score and the presence of significant stenosis.[31] In the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial the presence of positive remodeling and or low attenuation plaque was associated with an increased rate of myocardial infarction or coronary heart disease death.[32] However, at 5 years the presence of adverse plaque was not an independent predictor of events compared to coronary artery calcium score. This suggests that adverse plaque features are a predictor of increased risk in the short-term but that plaque burden is a more important predictor of longer-term prognosis.[32] Future quantitative assessment of adverse coronary artery plaque characteristics may provide more precise risk assessment.

Thus, a normal CTA is associated with a prognosis similar to, or better than a normal functional imaging assessment. The presence, extent, and severity of coronary artery disease on CTA is strongly associated with prognosis in patients with stable and acute chest pain. Additional characteristics including plaque volume and adverse coronary artery plaque characteristics can provide information on prognosis, over and above the assessment of stenosis severity.

2.3. Randomized controlled trials of coronary computed tomography angiography in patients with stable chest pain

There have been five randomized controlled trials of coronary computed tomography angiography (CTA) in patients with stable chest pain (Table 4) that have been performed in Europe and North America with important differences in study populations and design. Most trials have undertaken head-to-head comparisons with functional testing (predominantly exercise electrocardiography, myocardial perfusion imaging or stress echocardiography). These trials assessed the effect of CTA on diagnosis, risk stratification, clinical management (invasive coronary angiography and coronary revascularization), symptoms and clinical outcomes.

2.3.1. Diagnosis—CTA is a diagnostic test and its accuracy has been established for the diagnosis of coronary artery disease (see section 2.1). It is important to distinguish between its diagnostic accuracy for atherosclerosis, obstructive coronary artery disease and angina pectoris due to coronary artery disease. Clearly, the latter also relies on the patient history and the clinical context. The SCOT-HEART,[33,58] Cardiac CT for the Assessment of Pain and Plaque (CAPP),[59] the Computed Tomography versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT 1),[60] and CRESCENT II[62] and Min et al.[61] trials directly assessed the influence of CTA on the diagnosis of stable chest pain that was suspected to be due to coronary artery disease. All studies found that CTA was superior to functional testing or standard of care, with the SCOT-HEART trial reporting a 2-fold increase in diagnostic certainty compared to standard of care. Whilst the frequency of the diagnosis of coronary artery disease rose in all trials, the diagnosis of angina pectoris due to coronary heart disease tended to fall in the SCOT-HEART trial perhaps reflecting the absence of obstructive disease in those who were initially presumed to have angina.

2.3.2. Clinical management—The effect of CTA on subsequent clinical management is highly dependent on the population studied. In the SCOT-HEART,[63] CAPP[59] and CRESCENT[60] trials, the study population consisted of patients specifically referred for the evaluation of chest pain suspected to be due to coronary artery disease, with a high prevalence of obstructive coronary artery disease. In these trials, rates of invasive coronary angiography were either reduced or unchanged. However, documentation of obstructive coronary artery disease was more frequent at the time of invasive coronary angiography, which led to a modest increase in coronary revascularizations in the short term trials. In the 5 year follow up of the SCOT-HEART trial, the apparent early increases in coronary angiography and coronary revascularization were offset by later reductions in both invasive angiography and coronary revascularization; by 5 years there was no difference in these procedures. Indeed, beyond the first year, CTA was associated with less invasive coronary angiography (hazard ratio, 0.70; 95% CI, 0.52 to 0.95; p = 0.022) and coronary revascularization (hazard ratio, 0.59; 95% CI, 0.38 to 0.90; p = 0.015).[58] This suggests that the right patients are identified early and treated more promptly, thereby preventing progression of disease and avoiding later reinvestigation and revascularization.

2.3.3. Symptoms—Both the CAPP and the CRESCENT trials[59,60] were designed to assess the influence of CTA on angina symptoms in comparison to a functional testing strategy. They reported reduced levels of angina after 12 months of follow-up. Similar improvements in symptoms were seen in the SCOT-HEART trial, especially in those demonstrated to have normal coronary arteries or those with obstructive disease who underwent coronary revascularization.[64]

2.3.4. Clinical outcomes—The SCOT-HEART and PROMISE trials were sufficiently large to assess the impact of CTA on hard clinical outcomes.[57,58,65] The PROMISE trial had a large composite clinical outcome that included all-cause mortality as well as coronary events (myocardial infarction and unstable angina). Although there was no difference in this primary outcome, CTA appeared to be associated with a lower rate of death or myocardial infarction at 12 months. Meta-analysis has reported reduced rates of myocardial infarction with CTA (hazards ratio, 0.69 [95% confidence intervals, 0.49 to 0.98]) but no effect on overall mortality.[66] Similar reductions in myocardial infarction have also been reported in a large (n = 86,705) observational Danish registry (hazards ratio, 0.71 [95% confidence intervals, 0.61 to 0.82]).[67] The 5-year outcome data from the SCOT-HEART trial have now confirmed these earlier promising results: hazard ratios were 0.59 (p = 0.004) for CTA compared to standard of care for the primary endpoint of death from CAD or nonfatal myocardial infarction and 0.60 for nonfatal myocardial infarction alone, without overall differences in ICA or revascularization.[58,68]

2.4. Cost effectiveness of CTA

We define in this guideline use of the term cost effectiveness to include the cost consequences of CTA use as well as comparisons of costs associated with CTA-guided strategies of care.[69] There have been numerous decision analytic models which have explored the cost effectiveness of CTA as compared to functional testing strategies of care in the evaluation of acute, low risk and stable chest pain syndromes. For this guideline,

we will highlight evidence available from high quality clinical trials and large multicenter registries.[70]

Following CTA-detection of obstructive CAD, there have been concerns regarding an increasing rate of downstream invasive coronary angiography (ICA). Early reports noted higher rates of post-CTA use of ICA but more recent data support a more selective referral of patients to ICA following index CTA testing. In a report from the CONFIRM registry (n = 15,207 symptomatic patients), follow-up rates of ICA were low over 3 years of follow-up for patients with normal (2.5%) and mild CAD (8.3%), defined as a stenosis 1–49%.[71] By comparison, for patients with obstructive CAD, use of ICA occurred promptly within 3 months of follow-up and occurred in 44%, 53%, and 69%, respectively of patients with 1-, 2-, and 3-vessel CAD. Overall, in the PROMISE trial, a relatively low rate of ICA use was reported for patients randomized to CTA (12%) as compared to the functional testing (8%) arms of the trial.[57] Evidence is not available to judge the appropriateness of ICA use, as post-CTA use of stress testing or additional documentation of ischemia prior to ICA referral is not available. A synthesis of this evidence supports a relatively low rate of referral to ICA, notably for those patients without any obstructive CAD.

Many of the recent randomized clinical trials also include economic sub-studies that have been synthesized in a recent review (Table 5).[60,72–77] Importantly, for these analyses, comparisons of cost differences are valid given the documentation of similar rates of 2–3 year rates of major adverse events.[57,33] From the PROMISE trial, near term costs at ≤90 days and cumulative costs through 3-years of follow-up were aggregated. Within the near-term, there were no differences in cost between patients randomized to CTA as compared to functional testing, with a mean difference in cost of $254.[72] Within 90 days, there was a notable but not significantly higher use of ICA and revascularization. When aggregated through 3 years of follow-up, the differences in cost by randomization to CTA as compared to functional testing did not yield significant differences.

Through 3 years of follow-up, the difference in costs by randomized test strategy in PROMISE was non-significant (Δ = $627); with similar findings for stress nuclear, echocardiography, and ECG testing. These longer-term cost findings identify the importance of follow-up testing patterns to reflect the cost-consequences of a given index procedure.[69] Results from the SCOT-HEART trial revealed slightly higher costs associated with randomization to CTA, with cost differences of $462. Importantly, the induced costs did not result from additional outpatient or inpatient services or medication use.[76] Several reports have noted higher use of anti-platelet and statin therapy following CTA but that has not translated into significantly higher costs associated with medications.[67,72,76] Importantly, medication use appears to be targeted to higher risk patients, more often with evidence of obstructive CAD or to those with evidence of atherosclerosis.

Additional cost analyses are available from the CRESCENT trial whereby referral to exercise electrocardiography was associated with a higher rate of additional diagnostic testing; nearly half of patients in the stress testing arm had induced diagnostic testing procedures as compared to only 1 in 4 in the CTA arm of the CRESCENT trial ($p < 0.0001$).[60] This higher rate of diagnostic testing following exercise electrocardiography was

associated with a 16% higher cost of care. Additional cost savings were achieved in the CTA arm of the CRESCENT trial as nearly 42% of this arm had a 0 CAC score and did not undergo follow-up CTA, per the selective testing protocol whereby only those with detectable CAC proceeded to CTA. The randomized trial evidence supports the conclusion that costs associated with a CTA strategy are similar to those following stress testing, with only minimal differences through 2–3 years of follow-up.

Additional relevant data are provided by the cost effectiveness analysis employed in the UK's NICE guidance document on stable chest pain[78] which identified the lowest cost per correct diagnosis of obstructive CAD.[79] The rate of detection of obstructive CAD was higher for CCTA than for all other diagnostic testing approaches.[9,80] In a recent review, a synthesis of available randomized trial data revealed that concordance between CTA and ICA detected obstructive CAD was demonstrably higher than that of stress testing (71% of 1047 patients undergoing ICA versus 53% of 819 patients undergoing ICA).[70] As such, in the NICE cost effectiveness analysis, CTA had the lowest cost per correct diagnosis and was projected to save the National Health Service approximately £16 million each year by excluding CAD with a high negative predictive value.[78] Moreover, an index testing approach with CTA allows for a selective use of higher cost stress testing in a smaller proportion of patients with stable chest pain.

2.5. Plaque characterization

Pathologic studies have demonstrated that the acute coronary events, including sudden death, myocardial infarction and unstable angina, in a majority of cases result from acute coronary thrombosis secondary to rupture of plaques. These plaques demonstrate large plaque and necrotic core burden, positive remodeling and thin inflamed fibrous caps, and these characteristics have been referred to as high risk plaque (HRP) features. It has been proposed that noninvasive identification of atherosclerotic lesions with HRP features in stable patients should help predict the likelihood of adverse outcomes. It is therefore important to identify HRP for prevention of major adverse coronary events (MACE). Such thinking could be of clinical value because relief of luminal stenosis alone does not prevent the likelihood of acute events.

Intracoronary imaging modalities, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have confirmed the histopathological observations and allowed assessment of HRP features in vivo. Whereas IVUS has demonstrated the presence of large plaque burden, echolucent necrotic core, and positive remodeling, OCT has successfully measured the fibrous cap thickness in vivo. Noninvasive imaging with CTA offers the most convenient basis of identification of the HRP characteristics and can be used to predict plaques that could cause acute events.[28,30,31,81,82] Two CTA characteristics have demonstrated the best association with clinical outcomes up to 10 years of follow-up, and include the presence of low-attenuation plaques (LAP) with <30 HU density and positive remodeling (PR) of ≥110%. The plaques with these two CTA characteristics were called 2-feature-positive plaques (2-FPP); 22.5% of 2-FPP resulted in an acute event over a 2-year follow-up. On the other hand, 2-feature-negative plaques (2-FNP) were associated with benign outcomes with less than 0.5% resulting in acute events (Fig. 2). Multiple other

adverse plaque characteristics have been suggested, such as the presence of circumferential necrotic cores (napkin-ring sign) and spotty calcification.

The positive predictive value of HRP characteristics is increased with greater magnitude and number of HRP features and also with the interval progression of HRP features.[28,30,81,83] The larger the LAP volume and more expansive the PR, the greater is the likelihood of plaque rupture. HRP resulting in events demonstrated 2-fold greater expansive remodeling compared to HRP that did not produce MACE; eventful HRP demonstrated 126% remodeling against 113% remodeling of uneventful HRP. The LAP volume was 20 mm^3 in plaques resulting in events compared to 1.1 mm^3 in the HRP which did not end up in MACE. Plaques with the napkin ring sign contain large necrotic cores and, although infrequent, they are closely associated with OCT-verified thin fibrous caps and future MACE. Furthermore, quantitatively greater extent of adverse plaque characteristics are associated with both increased and earlier events.

Although it has been tacitly believed that (invasive) angiographically-verified minimally obstructive HRP are usually the precursors of adverse outcomes, studies in which the angiograms were done within 3–6 months of the events revealed more significantly stenotic coronary lesions, reported as wellby the PROSPECT study.[83] Therefore, the plaques must progress or enlarge (often causing significant luminal compromise) before they rupture and result in an acute event. This phenomenon was observed in serial CTA of almost 450 patients wherein the plaque progression was an important determinant of adverse outcome.[84] It is believed that the few plaques which are associated with adverse events despite relatively mild luminal stenosis usually harbor huge necrotic cores and substantial positive remodeling and could contribute to the hemodynamic turbulence in the luminal flow.[85] It is also being proposed that HRP characteristics influence the physiology of coronary flow and closely correlate with invasively measured FFR,[86–88] and may constitute the basis of hard events. The resolution of HRP features could influence FFR[89,90] and probably the likelihood of events. This might explain why PCI may not be superior to maximal guideline directed medical therapy for the prevention of hard outcomes.[91]

2.6. Functional significance

2.6.1. CT derived FFR

Physiologic Basis of CAD Severity.: Current standards for determining the physiologic severity of CAD are invasive fractional flow reserve (FFR) and non-invasive coronary flow reserve (CFR).[92] Both derive from experimentally defined CFR, stenosis pressure flow fluid dynamic equations, pharmacologic stress, integrated anatomic dimensions to predict pressure gradient or relative stenosis flow reserve and FFR. Evolution from experimental to clinical applications paralleled advancing invasive and non-invasive technologies, and were validated clinically using pressure flow velocity wires, and quantitative positron emission tomography (PET).[93] PET and/or MRI allow assessment of coronary flow reserve (CFR), coronary flow capacity (CFC), and stress MBF myocardial blood flow cc/min/g (MBF. On the other hand, functional assessment can be made using angiograms, including CTA measurements of FFR (FFR_{CT}), quantitative coronary angiogram FFR (FFR_{QCA}), quantitative flow ratio (QFR), and stenosis flow reserve (SFR). CT-FFR chiefly reflects the

degree of stenosis but is also affected by the size of the coronary arteries[94] as well as the mass of ventricular myocardium subtended by the stenosis bearing vessel[95] and both these parameters can be accounted for by CT, which may make this parameter more meaningful.

The relative merits of these metrics depend on personal preference and available technology for invasive versus non-invasive, or directly measured physiology versus anatomy-based calculations. However, two universal characteristics provide objective comparisons and insights into the final criteria of patient benefit. The first is testretest precision defined by the standard deviation of repeat serial measurements in the same subject at the same time. The second is the imprecision of the critical threshold of any metrics in relation to the net benefit of revascularization strategy over medical therapy. Substantial literature shows the utility of CT-FFR.[96–98]

Inclusion of FFR_{CT}.: This metric involves an integration of computational fluid dynamics, in addition to the anatomical data from coronary CTA, to allow the calculation of a 3-dimensional pressure map (Fig. 3). To facilitate FFR_{CT}, CTA should be performed according to best practice guidelines with heart rate control and administration of sublingual nitroglycerin. Not all CTA examinations are of adequate quality for FFR_{CT} analysis, with artifacts related to misalignment and motion resulting in a higher likelihood of erroneous FFR_{CT} analysis. In clinical practice, 4–10% of CTA examinations are of insufficient quality for analysis.

There have been numerous diagnostic accuracy studies assessing FFR_{CT} compared to invasive FFR. The most recent is the PACIFIC sub-study which showed FFR_{CT} to be the most accurate modality for the discrimination of lesion specific ischemia, with significant improvement in accuracy compared to CTA, SPECT and PET alone.[92] The area under the receiver operating characteristic curve (AUC) for identification of ischemia-causing lesions was 0.94 in comparison with coronary CTA (0.83, $p < 0.01$), SPECT 0.70, $p < 0.01$ and PET (0.87, $p < 0.01$). The diagnostic accuracy of 46% for FFR_{CT} in the “grey zone” of 0.70–0.80[99] has raised concerns, although the FFR_{CT}sensitivity of 87% for invasive FFR values of 0.70–0.80 (92) may be reassuring.

In addition to accuracy data there is growing evidence of clinical utility; the recently published 90-day outcome data from the ADVANCE (Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care) registry with over 5000 subjects undergoing FFR_{CT}, demonstrated significant changes to clinical management, with more refined determination of revascularization versus medical management. Building on the 90 day experience,[97] the 1 year clinical outcomes of the ADVANCE registry were recently published highlighting the good prognosis associated with a negative FFRct (>0.80) with significantly lower CV death and MI rate amongst those participants as compared to those with a positive FFR_{CT}.[96] Moving beyond outpatient testing for stable CAD, CTA/FFRct to guide decision making in more complicated CAD was evaluated recently in both the SYNTAX II and III trial as an aide to guide complex coronary revascularization. The SYNTAX II study demonstrated that FFR_{CT} may enable improved treatment decision making in patients with complex multivessel CAD compared to CTA alone. The findings highlighted the ability of CTA with FFR_{CT} to generate a non-invasive functional Syntax score that correlates with the

invasive gold standard. Introducing the derived functional data appears to moderate the disease overestimation based on anatomy alone, with good correlation between the invasive and noninvasive functional Syntax score, allowing decision making regarding complex revascularization and safe deferral at one year. Subsequently, the SYNTAX III Revolution trial[100] randomized heart teams to determine revascularization treatment decisions based upon invasive coronary angiography vs CTA with FFR_{CT} as needed. It documented a high correlation between the two, with a Cohen's Kappa of 0.82. In clinical practice FFR_{CT} is also being evaluated in a randomized controlled trial in the UK comparing it to NICE guided standard of care for patients with stable chest pain and will be followed by a larger international trial evaluating FFR_{CT} against traditional testing algorithms in the outpatient setting. These trials will be important for better definition of the clinical role of FFR_{CT}. At present, FFR_{CT} is a reasonable option for informing downstream ICA and treatment planning in patients with moderate to severe single and multivessel disease (30–90% severity) with a limited role in patients with ≥50% left main stenosis or critical triple vessel disease.[101,102] Other approaches reporting similar results, e.g., machine learning without utilizing computational fluid dynamics,[103] have been reported but have not yet received approval. On site techniques might improve adoption of CT-FFR more widely but these are still under development for routine clinical use.[104–106]

2.6.2. CT myocardial perfusion—Similar to other more established modalities, it is possible to use CT to image myocardial enhancement during hyperemia and identify functionally significant CAD (Fig. 4). Static perfusion protocols acquire a single set of images during the first pass of contrast medium through the myocardium and allow for qualitative differentiation of normal and hypo-perfused myocardium. Static perfusion imaging can be performed on most CT systems, and the radiation dose is comparable to a regular CT angiogram. A number of single and multi-center studies have shown that static perfusion imaging has incremental value over CTA for the detection of hemodynamic CAD.[107–114] Because dual-energy CT offers better differentiation of tissues and contrast-enhancement, these systems may provide more accurate static perfusion imaging.[115,116] For dynamic perfusion imaging a series of (low-dose) datasets is acquired during the passage of contrast medium, from which quantitative perfusion parameters can be derived. Dynamic perfusion imaging requires either a 2nd/3rd generation dual-source or wide-detector CT system for complete myocardial coverage in 1 or 2 acquisitions, and is associated with a higher radiation exposure than static perfusion imaging. Dynamic perfusion imaging correlates well with other functional tests and provides incremental value over CTA alone for the detection of functionally significant CAD.[117–120] Meta-analyses indicate at least comparable diagnostic accuracy for CT-based perfusion imaging compared to other perfusion imaging modalities[15] and perhaps a slightly higher accuracy for dynamic compared to static perfusion imaging,[121,122,123] although, no head-to-head comparison has been performed in the same cohort. There are practical advantages to a so-called stress-rest protocol, i.e. lingering contrast from CTA can be avoided by performing the perfusion scan first, yet a rest first protocol makes more sense from a clinical point of view by allowing deferral of the perfusion scan in case of a normal CTA or one showing clearly nonobstructive lesions. In one randomized study, the use of dynamic perfusion imaging after a positive CTA removed the need for noninvasive downstream testing and avoided negative

invasive angiograms compared to standard care based on functional testing.[62] A more recent study using modern scanners with whole heart coverage showed that adding stress CTP to coronary CTA better identified functionally significant CAD with only a small additional radiation dose.[124]

Dynamic CTP allows quantification of myocardial blood flow and this has an incremental value over CTA for diagnosis as well as risk stratification of patients with stenosis on CTA.[125] Calculation of stress myocardial blood flow ratio (SFR) might improve specificity and diagnostic accuracy of CTA.[126] Head-to-head comparisons of varying combinations of perfusion imaging and CT-FFR techniques as well as meta-analyses of independent cohorts, suggest comparable performance and potentially complementary value of both functional CT applications when added to coronary CTA.[62,127,128]

Studies in patients with stable angina referred to invasive coronary angiography based on coronary CTA, FFR_{CT} and CMR yielded similar overall diagnostic accuracy. FFR_{CT}, had high sensitivity for predicting revascularization but CMR had higher specificity.[129] It is important to remember that test performance for all these value added CT modalities depends on the substrate being studied. For example, while FFR_{CT} was more sensitive for diagnosis than SPECT, the overall diagnostic accuracy of FFR_{CT} and SPECT were comparable for hemodynamically significant stenosis in these patients with stable angina referred to angiography.[130]

Although CT-FFR offers practical advantages to both patients and imagers, perfusion imaging remains a potentially valuable alternative particularly when CT-FFR is not available or technically not possible (e.g., suboptimal CTA quality, prior revascularization). In addition, it can be combined with other measures like CT derived delayed enhancement to obtain additional prognostic information.[131]

Combining physiology through FFR_{CT} and stress-CTP, with anatomy during a CTA study is an evolving area and future studies will provide more granular data about its best use. There is clinical study evidence for some of these approaches while others like TAG have not borne out in terms of clinical utility.[132] At this stage early head to head studies[133] show that both provide clinically meaningful increases in specificity, positive predictive value, and diagnostic accuracy over regular CTA, and FFR_{CT} and stress-CTP, despite some differences in performance are largely comparable.

2.7. Coronary artery bypass grafts

CTA is highly accurate for the assessment of coronary artery bypass graft patency. The 2010 multi-societal Appropriate Use Criteria (AUC) defined coronary CTA as “Appropriate” for the evaluation of coronary artery bypass graft (CABG) patency in patients with ischemic symptoms.[134] The very high diagnostic accuracy of 64-slice coronary CTA was demonstrated in a recent meta-analysis that evaluated a total of 2482 grafts. Therein, the sensitivity and specificity for the presence of any CABG stenosis >50% were 0.98 (95% CI, 0.97–0.99) and 0.98 (95% CI, 0.96–0.98) with an area under the curve of 0.99.[135] Importantly, the accuracy was consistent regardless of graft conduit type (arterial vs. venous). Recent studies suggest that CTA performed using state-of-the art scanners (faster

gantry rotation, larger Z-axis coverage, advanced detectors) may have even higher overall diagnostic accuracy (96%).[136]

While CTA is highly accurate for bypass grafts, relatively large structures with minimal calcification and motion, the evaluation of native coronary arteries in patients with prior CABG can be challenging, due to the diffuse, severe nature of underlying CAD in many CABG patients. For example, the sensitivity for detection of stenosis ≥50% in recipient and nongrafted vessels is typically lower (83–90%) in patients with CABG than in patients without prior CABG.[137,138] Importantly, the performance of cardiac CTA to identify "protected" and "unprotected" territories, as defined by the combination of graft and native vessel patency using coronary CTA, has been shown to have important prognostic implications.[139] The decision to perform coronary CTA may depend on the clinical question. If graft patency is the primary goal of the study, coronary CTA is clearly an appropriate and well-validated study. If evaluation of native coronary arteries is the clinical question, then careful attention to image acquisition to ensure optimal image quality using CTA is crucial and functional testing should be considered. CT is also very helpful in planning for CABG, especially during reoperations where retrosternal adhesions and location of the LIMA become important for safe outcomes.[140]

2.8. Coronary stents

PCI with intracoronary stent implantation is the most commonly performed technique for coronary revascularization worldwide and post PCI symptoms are frequently encountered. According to current stable chest pain guidelines, functional ischemic testing is generally the preferred method to evaluate symptomatic patients with prior coronary stenting due, in part, to well-documented imaging challenges posed by intracoronary stents when utilizing coronary CTA.[2,141,142] Factors known to negatively impact the accuracy of coronary CTA in patients with stents include motion and beam hardening artifacts, volume averaging related to stent struts and superimposed calcified plaque that limit lumen visualization in stented segments, and the frequent presence of extensive, calcified, coronary atherosclerosis of non-stented segments. Accordingly, the 2010 multi-societal Appropriate Use Criteria (AUC) defined coronary CTA as "Appropriate" (A) only in asymptomatic patients with prior left main coronary stent implantation ≥3 mm in diameter. Among symptomatic patients, coronary CTA was considered "Uncertain" (U) when nominal stent diameter is ≥ 3 mm and "Inappropriate" (I) in stents <3 mm or of unknown diameter.[134]

The accuracy of 64-slice coronary CTA to detect potentially flow-limiting stenosis (≥50% lumen diameter) within stented segments is generally lower as compared to non-stented segments. Blooming of metallic stent struts has been shown to obscure up to 55% of the lumen within the stented segment, depending on strut thickness, design and image acquisition and reconstruction parameters.[143] A recent updated meta-analysis assessed per-stent accuracy of ≥64 slice coronary CTA for the detection of in-stent restenosis ≥50% on ICA, across 35 studies involving 2656 patients (4131 stents).[144] The study demonstrated a per-stent sensitivity, specificity, and positive and negative likelihood ratios (LR+ and LR−) of 0.90 (95% CI, 0.85–0.94), 0.94 (95% CI, 0.91–0.96), LR+ 14.0 (95% CI, 9.6–20.3) and

LR− 0.10 (95% CI, 0.07–0.17), suggesting that coronary CTA is accurate for assessing most stents.

There are important limitations in the evidence supporting the use of CCTA in patients with stents. In the meta-analysis, the authors demonstrated that overall accuracy (especially sensitivity) was significantly reduced by[1] stent strut thickness ≥100 μm,[2] stent diameter <3.0 mm,[3] scans performed at heart rates ≥65 bpm and[4] bifurcation stents. The authors did not report the percentage of non-diagnostic stents or per-patient accuracy and the results were limited by high heterogeneity and publication bias. Prior studies have suggested that up to 11% of stents may be deemed non-evaluable.[145] Further, studies were performed across a large number of CT platforms, with a minority of patients (11 studies, n = 961) scanned using dual source (n = 380) or ≥64 slice scanners. Finally, most studies used filtered back projection reconstruction as opposed to modern iterative reconstruction.

Numerous advances in CT technology appear to have significantly improved the diagnostic accuracy of coronary CTA for stent imaging. Specifically, improvements in scanner temporal resolution and detector coverage, development of model-based iterative reconstruction algorithms, improvements to detector and electric circuit design, and the maturation of imaging protocols have been shown to improve the visualization of stented and non-coronary segments.[146–150] As a result, many providers feel increasingly comfortable assessing stents in proximal coronary segments using contemporary scanners, particularly in patients with known stent diameter ≥3.0 mm in whom good heart rate control can be achieved. In such patients, the use of a tube potential ≥100 kVp, sharp reconstruction kernel, model-based iterative reconstruction and very thin slice reconstructions may significantly improve diagnostic accuracy, especially when imaging contemporary stents. Further, most current generation drug-eluting stents have struts <100 μm.

Advances in the area of spectral, high-definition and photon-counting CT techniques are promising technologies that will likely further improve the evaluation of intracoronary stents using coronary CTA. Highlighting this potential, two recent phantom-based studies, using third-generation dual source[151] or 128-slice spectral detector[152] imaging, demonstrated that compared to conventional polychromatic reconstructions, lumen visualization within stents was significantly improved using mono-energetic reconstructions >130 keV. Finally, the addition of physiologic information during CTA might significantly increase the number of patients with evaluable information and improve diagnostic accuracy while assessing coronary stents. For example, The diagnostic accuracy of CTP was significantly higher than that of coronary CTA (75% vs. 30.5%; $p < 0.001$) and was very high compared to invasive coronary angiography when both CTA and CTP were concordant.[153]

3. Guidelines and pre-test probability

3.1. 2016 NICE guidelines

Risk determination and the calculation of pre-test probability (PTP) of obstructive CAD have been the bedrock of chest pain guidelines for the last 25 years,[154] but, controversially, have been removed from the most recent 2016 UK National Institute for Healthcare Excellence (NICE) guidelines for the assessment of chest pain of recent onset.[2] The

previous (2010) NICE chest pain guideline, based on a modified Diamond and Forrester (DF) score,[155] recommended no further investigations for PTP <10%, coronary artery calcium scoring (CACS) for PTP 10–29%, functional imaging for PTP 30–60% and ICA for PTP 61–90%. Since the publication of the 2010 NICE guidelines, the American College of Cardiology (ACC) guideline was updated in 2012[141,156] and European Society of Cardiology (ESC) guidelines were updated in 2013[142] and 2019[157] (see 3.2) ([1] in 3.2)) In these the CAD consortium probability score in the 2013 ESC guideline was used as the basis of PTP assessment but with refinement and incorporation of additional population specific data. In the 2012 ACC guidelines the modified DF was refined using data from the 1979 Coronary Artery Surgery Study (CASS) registry and contemporaneous data from the Duke Databank for Cardiovascular Disease. The ESC guidelines used additional data from the European CAD consortium to underpin their PTP recommendations.[158]

In 2016 the NICE guideline group was tasked with updating the 2010 guidelines using very similar methodology and an anatomic gold standard.[2] The 2016 process looked at 15 validated PTP models, diagnostic accuracy comparing non-invasive investigations to ICA, and the costs for each modality. Further modeling against disease prevalence was undertaken.[2] Ultimately the 2016 guidelines recommended CTA (on a ≥64-slice CT scanner) in all patients with typical or atypical anginal symptoms (or ECG findings consistent with significant CAD in the absence of symptoms) as the first line test, regardless of PTP. Functional imaging was recommended only in those with equivocal CTA, or with known CAD, while ICA was recommended as a third-line investigation or when the functional imaging was non-diagnostic.[2]

Ultimately the combination of the strongest negative predictive value of CTA, compared to the gold standard (at both 50% and 70% thresholds), and a comparable positive predictive value compared with alternative modalities, in conjunction with being the least costly investigation, demonstrated that CTA was the most cost-effective first line investigation at all levels of disease prevalence (25%, 45% and 75%). NICE predicted that uptake of their guidelines would save the NHS up to $20 million dollars annually. Early validation of NICE's 2016 approach against the SCOT-HEART dataset strongly supported the use of CTA as the first line investigation.[159]

When comparing patients who met the criteria versus those outside the guideline there was a significant reduction in events in the NICE cohort and, importantly a significant reduction in downstream ICA, compared with no improvement in outcome and an increase in ICA utilization in those who were outside the guidelines.[159] Furthermore, a comparison of the guidelines in the SCOT-HEART and PROMISE populations identified the superiority of the NICE guidelines, with a c-statistic for the identification of obstructive coronary artery disease of 0.634 in the SCOT-HEART population, compared to 0.594 for the ESC guidelines and 0.560 for ACC guidelines.[37]

NICE also published additional recommendations regarding HeartFlow FFR_{CT} in 2017,[160] following a detailed review of the literature by a separate NICE Medical Technology Assessment Committee (MTAC). The conclusion of the MTAC was that FFRCT was a robust and scientifically valid adjunct to CTA and that if incorporated into the 2016 chest

pain of stable onset guidelines had the potential to save a further £9 million savings within 5 years, due to a reduction in the need for downstream ICA.[160]

3.2. 2019 ESC guidelines

The 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[157] retained the use of PTP which was based on more contemporary data,[161] resulting in PTP values approximately one-third of those in previous guidelines. The guideline recommended (Class l) coronary CTA or non-invasive functional imaging as the initial test to evaluate chest pain, depending on the PTP as well as test availability, local expertise and other patient characteristics that influence test performance. In patients with a low clinical CAD likelihood, CTA was the first choice. In addition, coronary CTA was recommended (Class lla) as an alternative to invasive angiography in the setting of an equivocal or non-diagnostic functional imaging test.

4. Clinical indications for coronary CTA

4.1. Stable chest pain

The above data support the accuracy of CTA for the non-invasive evaluation of the presence, extent, and severity of CAD. Importantly, when compared to functional testing techniques, the use of CTA is associated with increased use of preventive medical therapies and a significant reduction in the rate of incident myocardial infarction.[66,68,162–164] Review of the data supports a relatively low rate of referral to ICA, notably for those patients without any obstructive CAD, without an increased likelihood of undergoing coronary revascularization in the only long term trial.[162] The collective data strongly support the achievement of outcomes by CTA which are at least comparable to functional testing, without increasing costs.

There is a paucity of data relating to CTA accuracy in patients with known CAD who have not had coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), in whom double or triple vessel disease is more likely than in patients without known CAD. In the study discussed in section 2.1, in a high risk population of 391 patients, 38% of whom had known CAD, CTA was superior to SPECT[14]. Individual vessel CTA analysis is unaffected by the limitations of stress imaging, i.e., the best perfused area would be classified as the normal reference area in SPECT even if supplied by a significantly narrowed vessel, and sufficient stress may not be achieved to evoke ischemia in multiple distributions for both SPECT and SE.

4.1.1. Stable chest pain – No known CAD—It is appropriate to perform CTA as the first line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g. dyspnea on exertion, jaw pain).

It is appropriate to perform coronary CTA following a non-conclusive functional test, in order to obtain more precision regarding diagnosis and prognosis, if such information will influence subsequent patient management.

Coronary CTA is rarely appropriate in very low risk symptomatic patients, such as those <40 years of age who have “non-cardiac symptoms (e.g. chest wall pain, pleuritic chest pain).

4.1.2. Known CAD (see 4.3 and 4.4 for patients with CABG and stents)—It is appropriate to perform CTA as a first line test for evaluating patients with known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g. dyspnea on exertion, jaw pain).

4.1.3. Functional imaging—It may be appropriate to perform CT derived FFR and CT myocardial perfusion Imaging to evaluate the functional significance of intermediate stenoses on CTA (30–70% diameter stenosis).

4.2. Asymptomatic high risk subjects

It may be appropriate to perform CTA in selected asymptomatic high risk individuals, especially in those who have a higher likelihood of having a large amount of non-calcified plaque. The presence of predominantly non-calcified plaque is more prevalent in young individuals (age<45–50 years) who have risk factors such as diabetes, HIV, smoking, or a strong family history of premature ASCVD. Other high risk groups include patients with inflammatory conditions (e.g. SLE, RA, or psoriasis), familial hypercholesterolemia, or those working in high hazard occupations. Testing of such asymptomatic individuals should be performed in the context of shared decision making, if there is uncertainty regarding the patient’s need, or benefit for medical therapies. (i.e. statin therapy, PCSK9 inhibitors).

4.3. Asymptomatic low or intermediate risk

It is rarely appropriate to perform CTA in low or intermediate risk asymptomatic subjects.

4.4. Coronary artery bypass grafts

It is appropriate to perform CTA for evaluation of patients with prior CABG, particularly if graft patency is the primary objective.

4.5. Coronary stents

It is appropriate to perform coronary CTA in symptomatic patients with a stent diameter ≥3.0 mm. Measures to improve accuracy of stent imaging should be utilized, to include strict heart rate control (goal <60 bpm), iterative reconstruction, sharp kernel reconstruction, and mono-energetic reconstructions (when available). Protocols to optimize stent imaging should be developed and followed. It may also be appropriate to perform coronary CTA in symptomatic patients with stents <3.0 mm, especially those known to have thin stent struts (<100 μm) in proximal, non-bifurcation locations. The best results are likely to be achieved with the newest generation CT scanners.

4.6. Preoperative evaluation

4.6.1. Noncoronary cardiac surgery—In patients undergoing non-coronary cardiac surgery, invasive angiography is recommended in most patients over the age of 40 years. The diagnostic yield of invasive angiography is generally low, and stress testing may be difficult

to perform and interpret in the presence of valvular disease or heart failure. The performance of cardiac CT in this context has been investigated extensively and confirms that CT angiography can rule out CAD accurately in the majority of patients.[165,166] According to a recent meta-analysis, ≥64-slice CT had a sensitivity of 93% and specificity of 90% for the detection of angiographic CAD.[165] Because of age and associated atherosclerotic burden, the ability to rule out CAD is lower in patients with aortic stenosis compared to those with other non-coronary condition. CTA may have particular advantages when invasive angiography is associated with increased risk, such as in patients with mobile vegetations on the aortic valve or acute aortic dissection. In the context of transcatheter aortic valve implantation cardiac CTA are routinely performed. Although many scans will show extensive coronary calcification, CAD can be ruled out reliably in a proportion of scans performed for procedure planning.[167,168] Prior to percutaneous pulmonary valve implantation, cardiac CT may be helpful to assess the proximity of the coronary arteries to anticipate compression by the valvular device.

It is appropriate to perform CTA for coronary artery evaluation prior to noncoronary cardiac surgery as an equivalent alternative to invasive angiography in selected patients, e.g., low-intermediate probability of CAD, younger patients with primarily non-degenerative valvular conditions.

4.6.2. Noncardiac surgery—Cardiac events are a major contributor to peri-operative mortality for non-cardiac surgery. Although debates about the benefit of cardiovascular screening and revascularization before non-cardiac surgery continue, the 2014 guidelines support exercise testing or pharmacological stress testing for patients with an elevated risk of peri-procedural adverse events if it will change management.[169] Coronary disease detected by CT conveys incremental prognostic value over clinical risk stratification.[170,171] While CTA might be considered an alternative to stress testing for ruling out CAD in selected cases, its value remain uncertain for patients with an expectedly high atherosclerotic disease burden (undergoing high-risk vascular procedures). The 2014 guidelines currently do not recommend CTA, for lack of data.[169]

It is appropriate to perform CTA as an alternative to other noninvasive tests for evaluation of selected patients prior to noncardiac surgery.

4.6.3. Bypass graft localization prior to redo cardiac surgery—Patients with prior CABG are at increased risk for injury of patent grafts – especially the LIMA – and other retrosternal structures during re-sternotomy. Cardiac CT can accurately localize patent grafts to map their proximity or adhesion to the chest wall. This knowledge better prepares the surgeon, who may change the surgical approach or establish peripheral cannulation for cardiopulmonary bypass before re-entry if the risk of injury to the grafts or other retrosternal structures is deemed high. A reduction in re-entry trauma and better clinical outcome has been observed when pre-operative imaging was performed.[172–174]

It is appropriate to perform CTA to visualize grafts and other structures prior to re-do cardiac surgery.

4.7. Ischemic versus non-ischemic cardiomyopathies

Cardiac computed tomography is increasingly used in the evaluation of ischemic and non-ischemic cardiomyopathies.[175] In this context, cardiac CT offers an ability to evaluate the coronary arteries, quantify cardiac chamber size and function, detect morphological abnormalities of the heart, and identify various patterns of late enhancement which may aid diagnose several different types of non-ischemic cardiomyopathies.

Given the important need of excluding obstructive CAD in patients who present with a new undifferentiated cardiomyopathy, coronary CTA (CTA) is especially helpful in patients with cardiomyopathy in whom there is a need to exclude obstructive CAD. While traditionally invasive angiography has been used for this purpose, several studies have demonstrated a very high diagnostic accuracy of CTA among patients who present with a new cardiomyopathy or left bundle branch block.[176,177] While coronary CTA is especially helpful for excluding obstructive CAD, the identification of obstructive CAD, when present, provides useful data for patient management decisions. In patients who have non-ischemic cardiomyopathy who are unable to undergo cardiac MRI, cardiac CT can also be used to perform delayed enhancement imaging. Such imaging is often performed 7–10 minutes after the administration of intravenous contrast, and can be used to detect various patterns of late enhancement.[178–180]

Coronary CTA is useful for excluding coronary artery disease in patients with suspected non-ischemic cardiomyopathy. In patients with cardiomyopathy, cardiac CT can also provide information on chamber size, function, and morphology.

In selected patients who have non-ischemic or ischemic cardiomyopathy and who cannot undergo cardiac MRI, late enhancement CT imaging may be performed for detecting infiltrative heart disease or scar. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for ablation therapy)

4.8. Myocardial viability

Viability imaging with CT relies on the same science that has pharmacokinetic and biological principles that make MRI viability testing feasible. Iodine-based CT contrast agent, like gadolinium-based agents, is an extracellular contrast agent and accumulates in areas of increased extracellular volume in the equilibrium phase.[181] Normally the myocardium has modest global extracellular volume resulting in washout of the iodine after first past perfusion. In the setting of regional scar following infarction, the regional extracellular volume increases and iodine, like gadolinium, pools in this region during the equilibrium phase. The accumulation of contrast offers the opportunity to identify areas of regional areas of infarction that would be higher in attenuation, having trapped the iodinated contrast medium. Unfortunately, when compared with MRI, CT suffers from inferior contrast resolution and a lower contrast to noise ratio[182] although recent developments in spectral imaging may change this limitation.

In standard single energy CT, beyond using a greater amount of contrast material, there are a limited number of ways to optimize scar detection without using a greater amount of contrast material. Some investigators have noted improved conspicuity using low tube

potential scanning with 100 or even 80 kVp settings but these protocols are highly limited in larger patients and those with implanted devices owing to the inability of lower energy scanning to penetrate such patients and resultant increased noise[183,184] as well as device related artifacts. In general, delayed enhancement CT studies are best viewed as thick (5 or 10 mm) multiplanar reformations with a narrow window width and level (e.g., width, 200 HU; level, 100 HU)[185] or as maximum intensity projections. Dual energy CT with its ability to enable improved tissue characterization offers the potential for more accurate scar detection but the evidence evaluating this technique is modest to date.[186]

A number of studies[187–192] have compared the diagnostic performance of CT delayed enhancement using MRI as the gold standard. These studies suggest that CT can characterize acute and chronic infarctions yielding contrast enhancement patterns similar to first-pass perfusion and delayed enhancement MRI. On first pass CTA examinations, short axis thick (8mm) minimum intensity projections with narrow window width are used to detect areas of hypoattenuation in a coronary artery distribution to suggest perfusion abnormalities or acute/subacute infarction. These findings may be particularly helpful in the acute setting for infarct detection and to some extent adjudicate the severity of an anatomical stenosis. There are also data that suggest that infarct size quantified on delayed enhancement CT correlates fairly well with MRI. Regarding the identification of remote infarctions, CT offers very distinct features that when identified connote a high specificity for infarction. Chronic MI have reduced capillary density and show a temporally consistent evolution with fatty metaplasia suggestion an infarct at least 12 months of age and calcification with remodeling suggesting an older infarct typically at least 3 years old.[193] In the setting of fatty metaplasia, marked thinning and calcification viability is considered unlikely.

It may be appropriate to perform late enhancement CT imaging for the evaluation of myocardial viability in selected patients who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for revascularization).

It is appropriate to report prior myocardial infarction when its features are evident.

It is appropriate to report remote myocardial infarction when fatty metaplasia or calcification are present in a coronary artery distribution in the context of CAD.

4.9. Cardiac transplant patients

Coronary allograft vasculopathy (CAV) is a progressive disorder that complicates cardiac transplantation.[194] Its hallmark is diffuse and concentric intimal hyperplasia involving the epicardial coronary arteries and their branches. The diagnosis of CAV is often difficult as patients are commonly asymptomatic and this diagnosis has traditionally relied on non-invasive ischemia testing, ICA and the gold standard of intravascular imaging.[194–196] Historically, CAV would not manifest until late in its course, commonly with end stage findings of heart failure. Consequently, yearly screening to detect CAV has been recommended.

The role of CTA as a surrogate for ICA has been explored over the last decade. A recent meta –analysis, including 13 studies and 615 patients undergoing >16 slice MDCT, documented a high diagnostic performance of CTA for the diagnosis of CAV when compared to ICA.[197] On a patient-based analysis for the detection of any CAV (>luminal irregularities) or significant CAV (stenosis ≥50%), CTA analysis yielded weighted sensitivity of 97% and 94%, specificity of 81% and 92%, negative predictive value (NPV) of 97% and 99%, a positive predictive value (PPV) of 78% and 67%, with overall diagnostic accuracies of 88% and 94%, respectively. When using IVUS as the gold standard, CTA displayed lower diagnostic accuracy, largely driven by lower sensitivity. Patient-based analysis of 64-slice CTA versus IVUS showed a mean weighted sensitivity and specificity of 81% and 75% to detect CAV (intimal thickening >0.5 mm), whereas the PPV and NPV were 93% and 50%, respectively. In view of these results there is growing clinical use of CTA in surveillance of patients for the development of CAV, thereby sparing patients annual ICA. This approach should be taken with caution and is very much dependent on local site expertise and capacity, and the status of kidney function.

It may be appropriate to perform CTA as an alternative to invasive coronary angiography for the screening of patients for coronary allograft vasculopathy in the selected clinical practice settings.

4.10. Coronary anomalies

CTA was recognized early in its evolution as a suitable test for evaluation of anomalous coronary arteries in adults[198–200] because of its strengths compared to the alternatives. ICA does visualize the coronary lumen very well at high spatial and temporal resolutions, but has two major drawbacks. First, it is a projection modality that usually does not allow 3D demonstration of the anatomy and, secondly, it will not show the relationship of the coronary arteries to the surrounding structures as well as CT or MRI, which is a critical component of the evaluation. Several studies have been performed to evaluate the prevalence of coronary anomalies and utility of CTA for classifying anomalies and guiding treatment. Cheezum et al. found a prevalence of 1.7% of anomalous coronary artery originating from the opposite sinus of Valsalva (ACAOS) in a study of 5991 consecutive patients, 45% of which were discovered incidentally(213). They found the following CTA derived features to be of importance and to predict subsequent revascularization: slit-like narrowing of the origin of the anomalous vessel, interarterial course, intramural course, narrowing of proximal anomalous vessel of >5.4 mm in length[201] Opolski et al. found in a study of 8522 consecutive subjects a prevalence of less than 1% (0.84) of ACAOS.[202] Only right coronary arteries arising from the left coronary sinus showed presence of significant interarterial compression and malignant ACAOS type; compression was correlated with symptoms at follow-up.[202]

The ACC, in conjunction with SCCT and other imaging societies, recognized early on that assessment of coronary anomalies is considered an appropriate indication for CTA, receiving the highest appropriate use score available on their scale.[134] The ACR – NASCI – SPR practice parameter for performance and interpretation of cardiac CT mandates that patient

selection for coronary CT angiography be based on evidence-based clinical algorithms and includes suspected coronary anomaly on prior echocardiography or cardiac MRI.[203]

It is appropriate to perform CTA for the evaluation of coronary anomalies.

4.11. Coronary evaluation on aortic aneurysm/dissection and PE studies

Operating on the principle that all relevant cardiovascular findings in the field of view on noncontrast chest CT examinations should be evaluated and reported, the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology recommended that coronary artery calcium scoring by quantitative or semiquantitative analysis should be part of every non-contrast chest CT analysis and report, whether gated or non-gated, even though it had not been requested by the referring physician.[204] Similarly, since the coronary arteries are in the field of view of every contrast chest CTA, they may be evaluated by electrocardiographically (EKG) gating a single phase prospective acquisition. The most appropriate clinical scenarios are aortic dissection, and pulmonary embolus (in men >45 years and women >55 years) since the CTA's are infrequently positive (<15%), and do not provide an explanation for the presenting symptoms for which, because of its prevalence, coronary artery disease may be the culprit.[205] Similarly, aortic aneurysm CTA's, whether for initial diagnosis, surveillance or post repair, are candidates for coronary artery analysis.

From the technical perspective, gated acquisition of a single phase (75% for heart rate <65 bpm and 40% for heart rate >65 bpm) will improve the quality of the CTA and minimize motion artifacts which may be interpreted as aortic dissections and facilitate evaluation for embolus in the smaller pulmonary artery branches; depending on the scanner technology there may be no associated increase in contrast volume or radiation dose. Acquisition of only a single phase may result in inability to evaluate all coronary segments if there is motion artifact but this problem is inherent in all prospective single phase studies. Immediate interpretation of the coronary arteries is indicated in dissection and PE studies and may be problematic outside of normal working hours depending on the training of the interpreting physician.

It is appropriate to use EKG gating for CTA performed for aortic dissection and aneurysm CTA, as well as pulmonary embolus studies in men >45 years and women >55 years, and analyze and report the coronary arteries.

4.12. Atrial fibrillation pulmonary vein isolation, cardioversion, embolic stroke

Guidelines have uniformly recommended transesophageal echocardiography (TEE) for the evaluation of the left atrium/left atrial appendage (LA/LAA) for the presence of thrombus prior to cardioversion and pulmonary vein isolation, and of the entire heart for embolic sources in the setting of cryptogenic stroke. Review of the relevant literature suggests appropriate changes featuring an important role for CTA.[206]

The sensitivity of TEE for LAA thrombus using a surgico-pathological reference standard is 93–100%, with 99–100% specificity.[207] CTA has been validated by comparison to TEE. A meta-analysis was performed of 19 studies with 2955 patients in which both CTA and TEE were obtained within 7 days to rule out LA/LAA thrombi before PVI or cardioversion

for AF and likelihood of stroke.[208] For the entire population, the sensitivity, specificity and accuracy for detection of thrombus by TEE were 96%, 92% and 99% respectively, with PPV of 41% and NPV of 94%. However, in 753 patients with delayed imaging from 30 to 180 seconds after contrast injection, the sensitivity, specificity, and accuracy were nearly 100% and the PPV increased to 92%. The results were very similar for the 1836 PVI patients. There were no significant differences between studies with and without EKG gating. Those cases which demonstrate complete resolution on delayed imaging are routinely reported as “slow flow” and are thought to represent the equivalent of spontaneous echo contrast SEC), with partial resolution on delayed imaging consistent with a combination of SEC and thrombus.

The effectiveness of delayed imaging in the clinical practice of ablation for atrial fibrillation and atrial flutter was studied by Bil-chik et al. in 320 ablation patients who underwent nongated CTA with delayed imaging 40 seconds after contrast injection, with TEE only after abnormal or equivocal CTA findings but not after normal CTA studies.[209] Using intracardiac echocardiography (ICE) as the reference standard, the sensitivity and NPV of CTA were 100%. With equivocal CTA results classified as negative, the specificity and PPV were also 100%; when classified as positive the specificity was 98%. Patients with normal CTA had neither thrombus on ICE nor procedure-related stroke or TIA. TEE was performed in 57.5% prior to implementation of the protocol. These findings persisted across all levels of stroke risk and CHA2DS2-VASc score.

Despite their comparable results, TEE and CTA have some unique non-overlapping capabilities that may dictate their use in specific situations. TEE should be performed when long term prognostic markers of emptying velocity, SEC, valvular disease and systolic and diastolic function are required. CTA is indicated when coronary artery analysis, achieved by EKG gating, is sought. For PVI, CTA is preferred since the LAA has already been imaged by the PVI CTA study. In the setting of cryptogenic stroke, better valvular visualization renders TEE the preferred study. For LAA occlusion, a combination of CTA and TEE appears to be the best strategy.[210] CTA should be performed in patients with relative or absolute contra-indications to TEE, and TEE is the preferred test in patients with contrast anaphylaxis or renal dysfunction. As part of shared decision making, patient preference should be the deciding factor when TEE and CTA are equally viable alternatives.

CTA with a limited delayed image (60–90 sec) to ensure complete LAA opacification is an appropriate alternative to TEE when the primary aim is to exclude LA/LAA thrombus and in patients where the risks associated with TEE outweigh the benefits. In all situations CTA and TEE should be discussed with the patient in the setting of shared decision making.

5. Decision making

5.1. Medical versus invasive treatment

A central aim of evaluation for CAD is to identify patients who need appropriate revascularization to improve prognosis or symptoms not responding to medical therapy, as well as those that can be managed with medical therapy alone (Fig. 5). Stress testing has been the traditional method of evaluating for CAD but it has many limitations. It is not

very accurate, especially in the current milieu of low prevalence of CAD among the tested population[80] and the imprecision of pretest probability paradigms used to refer to stress testing.[37–39,211] It is important that we refine non-invasive stress testing for CAD.

Stenosis severity still remains the primary arbiter of therapeutic decisions, but more and more data now suggest that anatomy coupled with a physiologic correlate is a better or even possibly, a necessary way for optimal decision-making. The most optimum testing pathway would ideally lead to the specific pool of patients needing guideline-based intervention and would improve outcomes. An increasing body of evidence suggests that CTA, especially when used along with its newer value-added iterations (CT-FFR and CTP) might have advantages that would make it the first line test in many situations.

5.1.1. Role of CTA for guiding further non-invasive evaluation—Choosing CTA as the first line test for symptomatic CAD results in a significant reduction in cardiovascular death and MI over the course of 5 years, with more apporpriate preventive therapy[58,76] compared to stress testing, and this difference in favor of CTA[33], there are some important nuances. Following CTA there is more detection of CAD without necessarily needing significantly more invasive catheterization and the yield of catheterization procedures is improved, in terms of actionable CAD. There are more revascularizations following CTA in the short-term but not the long-term, and the total cost of either strategy is largely similar or slightly higher with CTA. CTA shows non-obstructive CAD and is more prognostic than functional testing in contemporary patients with stable chest pain[17,58,76] and this difference in favor of CTA is greater in high risk patients e.g. diabetics.CTA reduces the need for further non-invasive testing and could thus be considered an optimum first test compared to other current stress testing paradigms.

CTA facilitates decision making by dividing patients into multiple informative categories. This characteristic was an integral part of the ISCHEMIA trial[91] by excluding patients with <50% diameter stenosis and significant LM disease from randomization to medical versus interventional treatment. A good format for decision making can be based on CAD-RADS classification.[212] This classification is easy to use, well standardized and has significant prognostic value in its sub-sets.[18,213] Those with a negative CTA or demonstration of non-obstructive CAD would exclude flow limiting CAD with high certainty and avoid downstream testing. A CTA with non-obstructive anatomy excludes the need for further downstream testing since there is no need for revascularization. However, such a CTA finding should prompt adequate preventive or disease modifying therapy and CTA seems to allow for more appropriate use of statins and anti-platelet therapies better than when using non CTA methods for CAD diagnosis.[67,76] CTA can act as an excellent gate-keeper for subsequent decision making in this group and indeed the finding of non-obstructive disease can change preventive management in both non ER[58] and ER[214] settings. This also extends to women with chest pain, a group that has traditionally been under treated – CTA reclassifies more women into the non-CAD category, appropriately decreases down-stream testing, results in similar preventive therapies in both men and women and, more importantly, equal benefit in terms of risk reduction.[215] Combining CTA and FFR_{CT} may allow for even more uniform down-stream interventions and narrow the differences between revascularization rates between men and women[216], unlike what happens after usual stress

testing imaging. Newer data seem to suggest that CTA can help personalizing preventive medicine better.[217] For example, statin effects for reducing ASCVD events, when aiming for the 2018 ACC/AHA and 2019 ESC treatment targets, are highly contingent upon CAD severity; the NNT in 6 years to prevent 1 ASCVD event varied considerably with the severity of CAD, ranging from >230 in patients with no CAD to <10 in patients with 3-vessel disease.

1. CAD with clearly surgical anatomy – CAD-RADS 4B: A CTA showing significant LMCA disease, or 3 vessel disease, especially if associated with LV dysfunction, involving the proximal LAD or in a diabetic patient, identifies subsets known to benefit from surgical revascularization. This group does not usually need further non-invasive testing and operative decisions can be taken after invasive coronary angiography.

2. CAD that is clearly not a surgical anatomy but might benefit from intervention: A positive CTA in the CAD-RADS class 4A or class 5 category is of sufficient concern and should lead to consideration for angiography (with invasive FFR or iFR as needed) which might be indicated under the right clinical scenarios.

    a. CAD-RADS class 4A: if the lesion involves a significant sized vessel in the 3 major proximal arteries subtending a significant sized bed (e.g. proximal LAD)

    b. CAD-RADS class 5: if there are optimum conditions and a clinical indication for CTO interventions.

3. A positive CTA in non-surgical anatomy categories not known to clearly benefit from intervention or revascularization: this includes CAD-RADS class 3 patients where the worst stenosis is in the 50–69% range: A positive CTA has low positive predictive value in this group and recent data show that CT-FFR might also perform less than optimally in this range.[99] Testing in real-world studies might have different performance characteristics but at least 1 study of such patients with intermediate CAD[218] also showed variable agreement between CT-FFR and invasive FFR (55% when CT-FFR was between 0.76 and 0.80, >80% when invasive FFR was less than 0.75, and approaching 100% in patients with very severely reduced FFR). One may, therefore, need further testing in certain circumstances for confirming CAD that needs intervention. This should be tempered by the fact that once the anatomy is known and high-risk substrates are excluded (which CTA can confidently accomplish), patients with CAD-RADS 3 should first be treated medically, with subsequent testing as well as an invasive approach reserved for the patient who remains symptomatically unresponsive to medical therapy. The very recent ISCHEMIA Trial[91] provided robust evidence for this approach.

5.1.2. Options for downstream noninvasive testing after an inconclusive CTA

—CAD RADs recommends using additional non-invasive testing in certain situations after CTA. Downstream testing in this situation can be multiparametric CTA testing that provides additional physiologic information (e.g. CT-FFR or CTP) or non CTA based physiologic

testing (nuclear myocardial perfusion imaging, CMR or stress echo). There is very little literature to guide the choice of noninvasive functional testing following an indeterminate or intermediate stenosis on CTA. Comparative studies looking at the ability of various testing modalities for diagnosing CAD in the general stress testing population are plentiful but have a number of limitations.[219] While meta-analysis[3] show that CMR and PET have the highest accuracy and combinations of CTA + CT-FFR or CTP improve diagnostic accuracy, these pathways add to the cost, radiation and may not readily available. In addition, the choice of second line testing remains heavily dependent on local expertise and patient suitability for a given test. Finally, these should be considered only after exhausting medical therapy in patients with coronary anatomy that clearly does not need immediate surgical intervention.

5.1.3. Role of multi parametric CTA testing or sequential CT—CTA can provide much more than anatomy through newer strategies using CT-FFR and CTP, which can improve decision-making (both diagnostic and therapeutic) by improving the specificity and positive predictive value (its main limitation). More robust data is needed to demonstrate that this approach is logistically feasible and cost effective when used routinely. CAC is a good discriminator of risk, better than myocardial perfusion imaging[220], and adding CAC into the diagnostic algorithm for CAD patients is attractive. Most stable CAD patients with events have measurable CAC; a smaller proportion have abnormal stress tests results that are specific for CV events.[220] Any non-zero CAC by itself is better than a positive functional stress test in terms of sensitivity (84% vs. 43%, $p < 0.001$) while functional testing is more specific (79% vs. 35%, $p < 0.001$) for predicting adverse events. Using higher cutoffs for CAC improves specificity but decreases sensitivity. Two randomized controlled trials, CRESCENT I[60] and CRESCENT II,[62] have used a protocol where CAC was the first measurement and only a positive CAC necessitated proceeding to CTA. This approach was found to have similar 1-year outcomes as the routine strategy of stress testing in the CRESCENT I study. CRESCENT II showed using a similar approach but proceeded to CTP if both CAC and CTA were positive. This strategy was associated with better outcomes, and more appropriate angiography (fewer invasive angiograms without a class I indication for revascularization) than routine stress testing. Studies with longer follow-up are needed before routine implementation.

5.1.4. Role of CTA in guiding invasive evaluation—Ideally, ICA should be offered to only those patients who will benefit from an intervention, either surgical or percutaneous; high quality non-invasive testing should be able to decide who undergoes ICA. Unfortunately, many of the angiograms done in current practice scenarios are normal or non-obstructive, even in those referred after a positive stress test. CTA appears to be an excellent gatekeeper for angiographic referral – using value added CTA methods like CT-FFR and CTP improves this even further. In the PLATFORM study,[221] CT-FFR reduced the rate of finding no obstructive disease on invasive angiogram from 73% to 12% and decreased referral to angiography by 61%. Other studies also confirm the utility of CT-FFR in precluding the need for invasive angiography.[222,223] ICA can be safely deferred when CT-FFR shows a lack of lesion-specific ischemia; no MACE were seen in the year after avoiding angiography after CT-FFR in the PLATFORM study[224] and initial estimates show that this was cost effective.[69] The ADVANCE FFR_{CT} registry confirmed this safety in the

real world practice.[96] In CRESCENT II,[62] adding CTP when CTA revealed a >50% stenosis resulted in far fewer invasive angiograms without a class I indication for revascularization. Thus, CTA has excellent ability to optimize downstream angiography use and is likely to find an increasing role in this manner.

6. Summary

Coronary artery disease is the most important etiology of chest pain in clinical practice, has significant prognostic implications and is eminently treatable. Moreover, CAD is highly prevalent and may exist in various forms, extending from the presence of non-obstructive plaque to flow limiting disease to complete obstruction of a vessel. Not only the presence, but the location and extent of stenosis, the composition of the plaque underlying the stenosis, its physiologic effect and the health of the distal bed, all determine hard outcomes (death or MI). Thus, identifying the presence of CAD is a critical part of cardiac practice requiring significant investment in time and resources. A plethora of non-invasive testing options are available for evaluating patients presenting with chest pain that could be related to ischemic heart disease but there is significant controversy about what is the most optimal testing strategy.[225] Consistent with past paradigms for CAD, these have all focused mainly on identifying flow limiting disease that could cause ischemia. Broadly, these can be divided into those assessing anatomy, those assessing physiology and those that can combine some characteristics of both anatomy and physiology. While there is a significant body of evidence for each strategy and current randomized controlled trials (albeit, with all their limitations as pragmatic studies) have not found a consistent difference in major outcomes with one strategy or the other, they are not equivalent. There is already evidence that some strategies influence hard outcomes through advantages other than revascularization (e.g., better titration of preventive medical therapy after seeing an atherosclerotic plaque with CTA vs. physiologic testing) and future studies may show intrinsic advantages of one strategy over the others.

In general, CTA has the advantage of reducing cardiovascular mortality and myocardial infarction. It visualizes the stenosis and the atheromatous plaque as opposed to making an educated guess about its presence, as with physiologic testing. CTA has excellent sensitivity for identifying flow limiting disease and has very high negative predictive value, making it the strongest test to rule out flow limiting CAD, especially in patients with low to intermediate risk. It has the best evidence so far for decreasing the number of procedures in patients in whom a decision to define coronary anatomy with invasive catheterization was already taken based on other non-invasive criteria. Moreover, deferring ICA in this manner has been shown to be safe. Using CTA as the first test for stable chest pain syndromes also reduces non-productive ICA (patients where ICA does not show CAD that needed a class I indicated intervention) with a slightly increased rate of diagnostic catheterization. This has led to the NICE guidelines recommending of CTA as the first line test in patients without known CAD who present with typical or atypical chest pain.

CTA has lower specificity and positive predictive value, which places it in the same diagnostic performance band as most tests using stress imaging. However, the newer value-added modalities of CTA (CT-FFR and CTP) may significantly minimize this disadvantage.

A reasonably strong body of evidence supports the use of CT-FFR for the diagnosis of CAD in patients presenting with stable chest pain syndromes and this results in diagnostic rates comparable to invasive FFR. Early data from studies using CT perfusion seem to suggest a similar gain in diagnostic accuracy. It is likely that a suite of CTA based testing (CAC, CTA, FFR-CT, CTP in some combination), often needing only a small increment in time, effort, contrast agent or radiation, is likely to elevate its positive predictive value to the best of breed range. Tiered testing as in CRESCENT I and II has shown distinct advantages in early discharge and safe outcomes in small randomized control trial settings. However, robust evidence-based recommendations await well conducted prospective studies in this arena. Hybrid strategies involving both CTA and PET are also in development to improve the predictive value of a positive CTA.

CTA also has a unique advantage possessed by no other testing, based as they are on identifying a flow limiting stenosis indirectly through an ischemic response. It provides a look at the plaque extent and nature even if there is no flow limiting lesion; multiple studies show that it is better at parsing out future risk than physiologic testing. Through its ability to visualize calcified and non-calcified plaque, it identifies the majority of patients with future events in prospectively tested cohorts, far better than by identifying flow limiting stenosis by any test. It also promotes better initiation and maintenance of preventive therapy (use of guideline directed medication like statins and anti-platelet therapy) and may thus reduce future hard events without a difference in revascularization rates. It has a small cost in terms of dye load and radiation but many centers are already using protocols to decrease both[226] and newer strategies are likely to significantly minimize this risk further.

Thus, CTA is a robust test that, in addition to reducing myocardial infarction and cardiovscular mortality, serves as a gatekeeper invasive testing, is cost effective and better allocates the use of high cost downstream testing as well. The data support the widespread use of CTA as the first line test in the assessment of patients without known CAD who present with stable chest pain.

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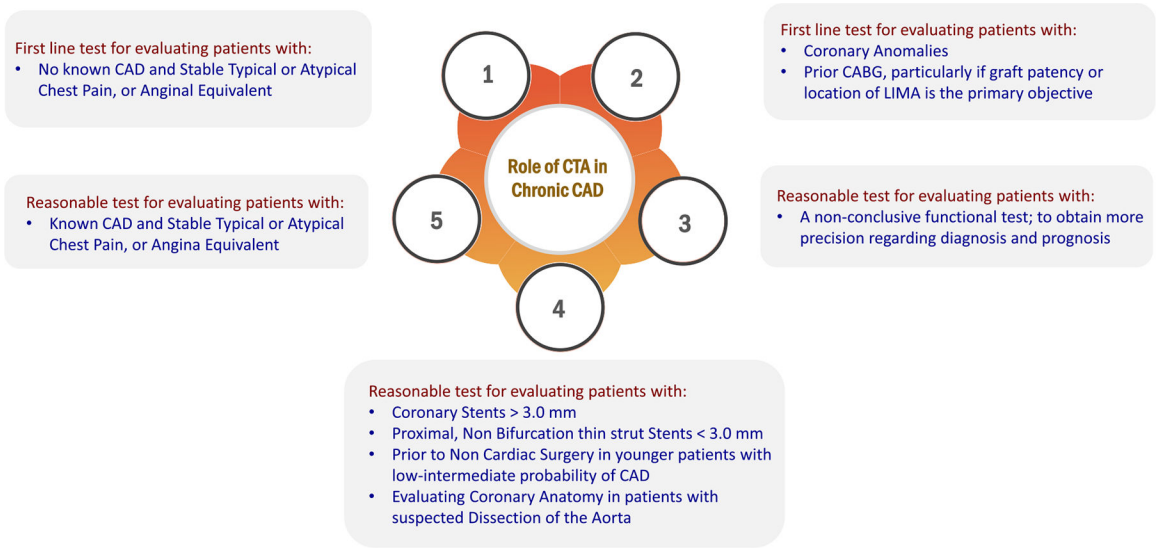
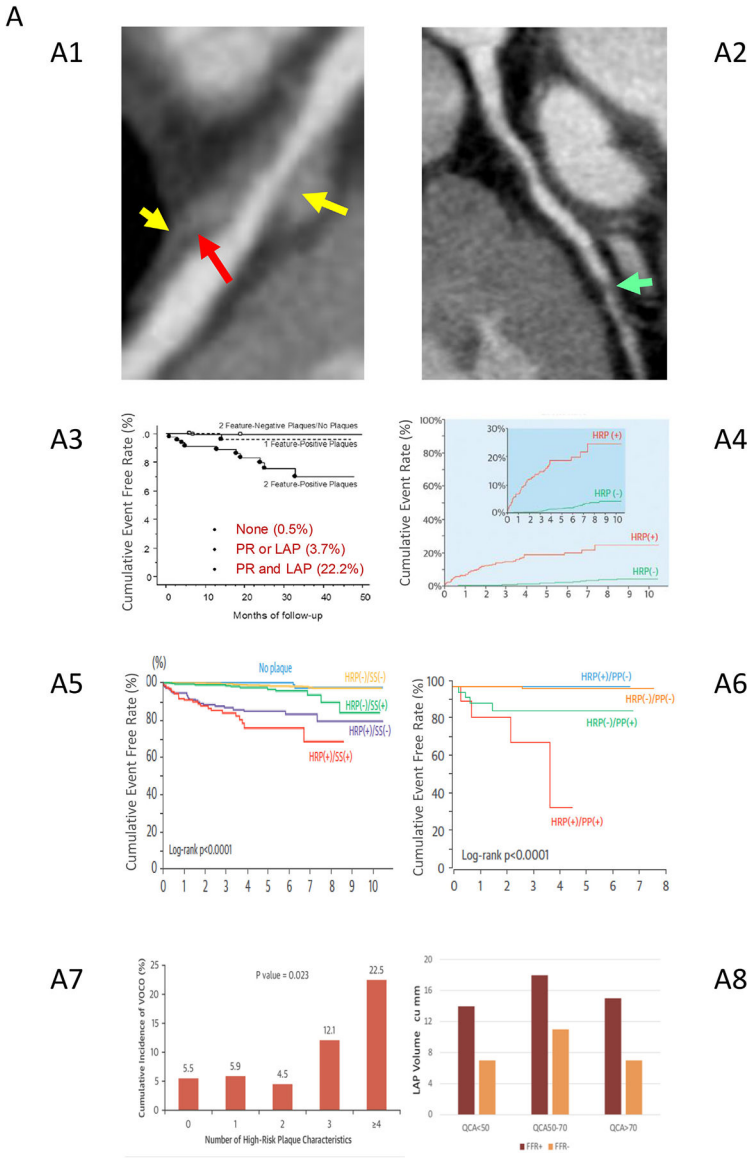


Fig. 1.
Central Illustration Role of CTA in chronic CAD. Also please see Table 1.



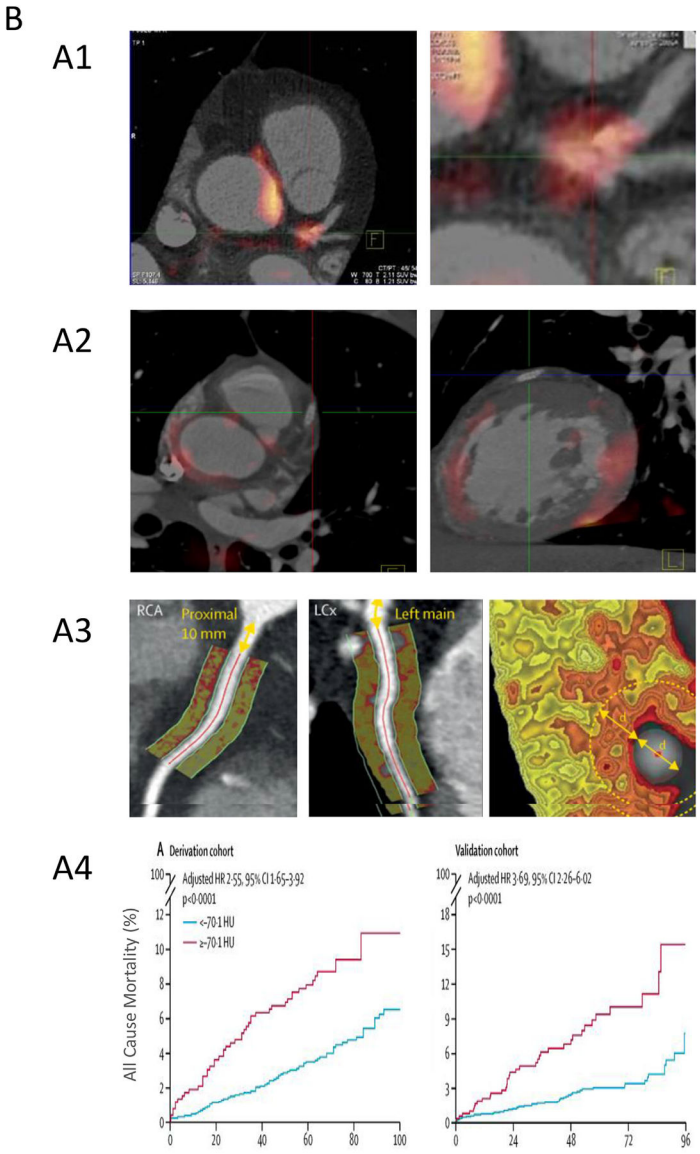


Fig. 2. CT angiography for detection of high-risk plaques.

(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 significant stenosis 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).

(B) Potential indicators of inflammation by CTA as a complementary feature for identification of plaque vulnerability. It can be detected either by simultaneous PET imaging

with F-18 FDG (that targets macrophage infiltration) (A1 & A2), or by fat attenuation index of perivascular fat (that represents lower prevalence of adipocytes consequent to greater cytokines in neointima) (A3 & A4). Modified from Motoyama et al. JACC 2007, Motoyama et al. JACC 2009, Lee et al. JACC 2019 Ahmadi et al. JACC-Imaging 2018, Rogers et al. JACC-Imaging 2010, Antoniades et al. Lancet 2018.

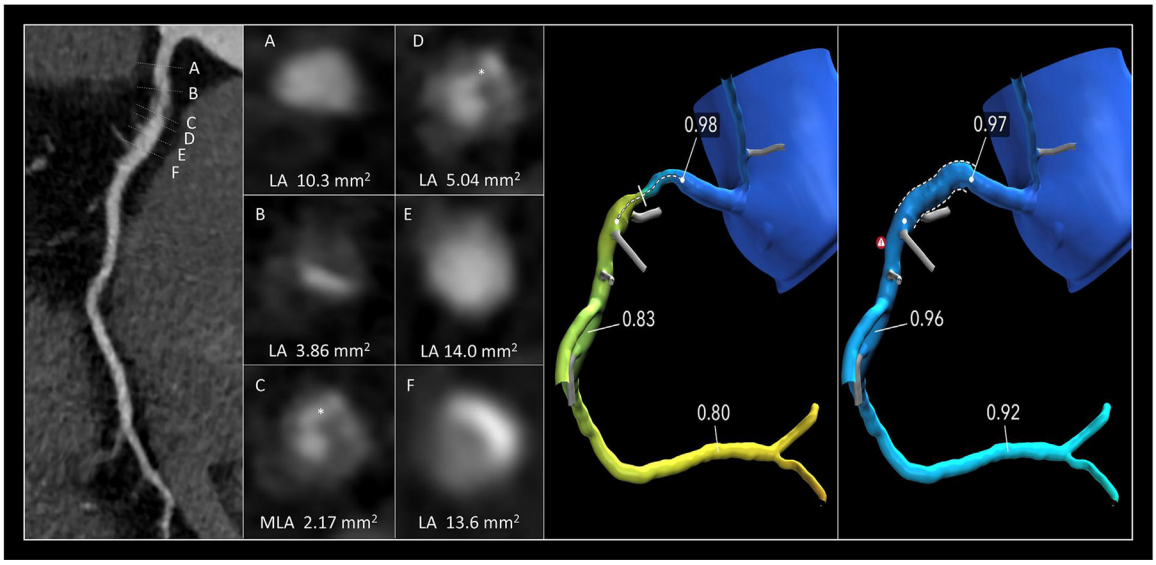


Fig. 3.

CT-based assessment of FFR in a complex coronary lesion. A 47-year-old male, a smoker with dyslipidemia, presented with ST-elevation myocardial infarction in the left anterior descending artery territory, and was treated by primary PCI. He had a non-culprit lesion in the right coronary artery (RCA). A coronary computed tomography angiography was acquired in the context of the precise PCI plan study (P3 - NCT03782688). The left panel shows a multiplanar reconstruction of an RCA with severe stenosis and high-risk in the proximal segment of the vessel. The cross-section B, C and D show positive remodelling, low attenuation plaque and plaque rupture (white star). The FFRCT model confirmed the hemodynamic significance of the lesion with a pressure gradient across the stenosis of 0.15 FFRCT units and distal FFRCT of 0.80. In the right panel, the results of the FFRCT Planner are shown after the virtual implantation of 18-mm long stent. The results show complete functional revascularization with a predicted FFR post-PCI of 0.92.

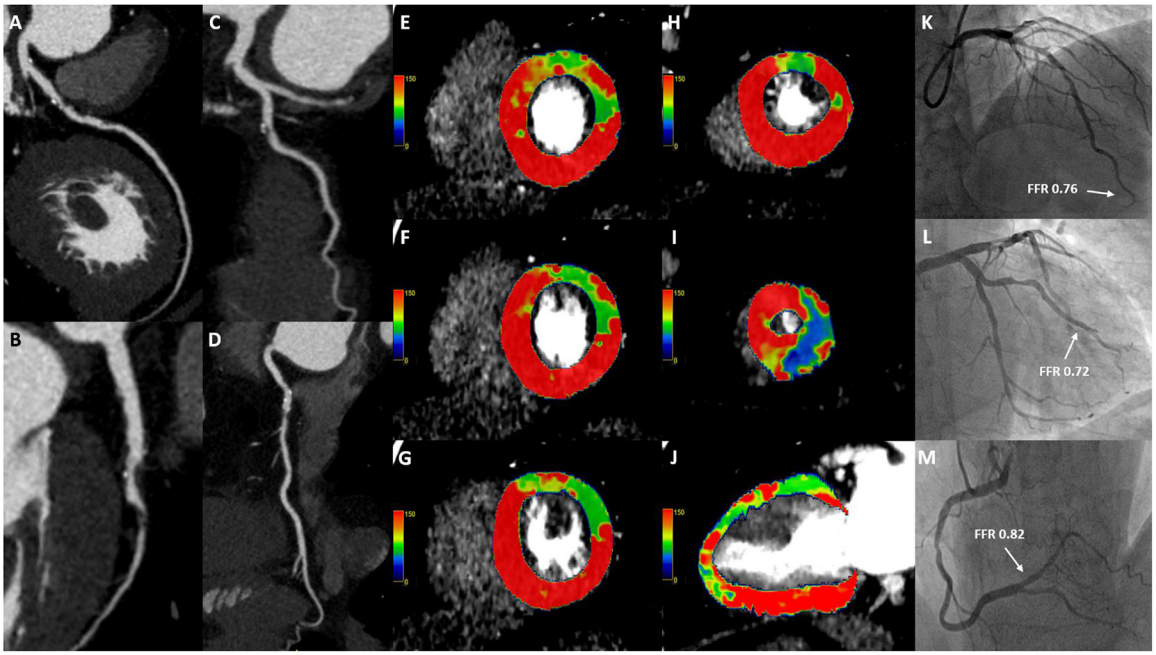


Fig. 4.

75 y/o man known for hypertension and dyslipidemia, with recent onset of atypical chest pain and abnormal T waves in anterolateral leads. Panels A, B, C, D: Rest coronary CTA shows severe stenosis of mid LAD (Panel A), subtotal occlusion of second diagonal (B), severe stenosis of first obtuse marginal (C) and moderate stenosis of RCA (D). Panels E to J: Dynamic Stress-CTP, short axis view (E to I) and 2-chamber long axis view (J), show reduced MBF of anterior and anterolateral walls. Panel K, L, M: Invasive coronary angiogram shows severe mid LAD stenosis with positive invasive FFR (panel K), severe obtuse marginal stenosis with positive invasive FFR (Panel L), and moderate RCA stenosis with negative invasive FFR (Panel M). CTA: coronary computed tomography angiography; LAD: left anterior descending artery; D2: second diagonal branch; OM: obtuse marginal branch; RCA: right coronary artery; CTP: computed tomography perfusion; MBF: myocardial blood flow; ICA: invasive coronary angiography; FFR: fractional flow reserve. [Courtesy of Dr A. Baggiano and Dr G. Pontone].

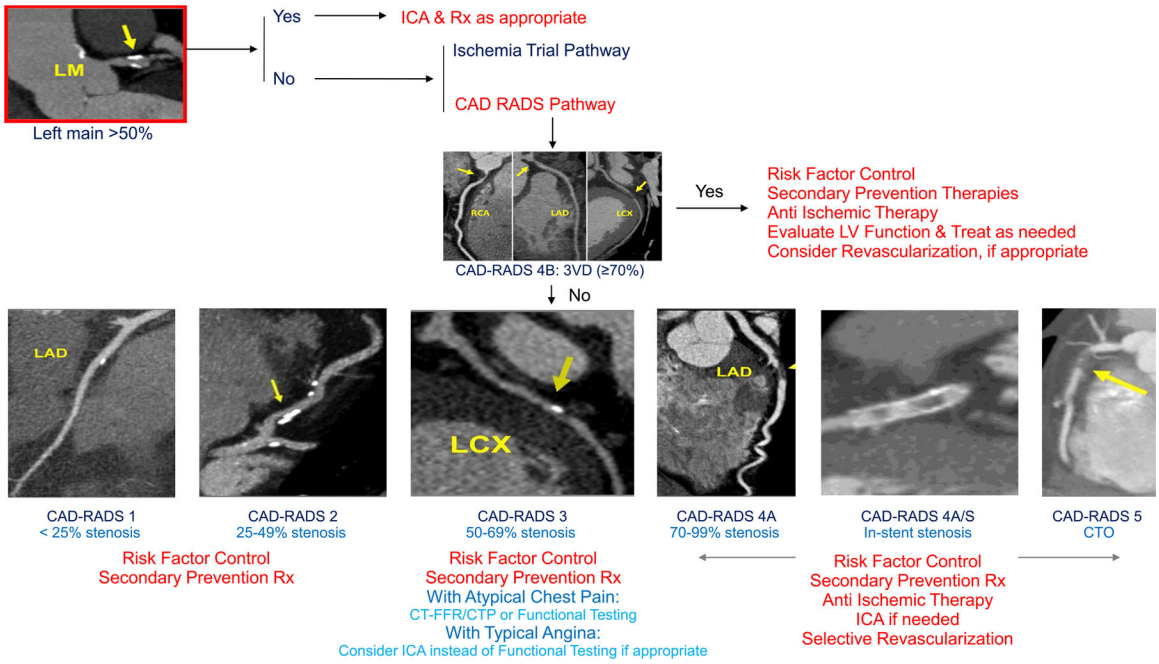


Fig. 5.

Conceptual diagram outlining the use of CTA in diagnosis, downstream testing and management of chronic stable CAD. Images from the SCCT Statement on CAD-RADS.

Table 1

SCCT coronary CTA expert consensus recommendations.

Evaluation of Stable Coronary Artery Disease: Coronary CTA in Native Vessels
• It is appropriate to perform CTA as the first line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g., dyspnea on exertion, jaw pain).
• It is appropriate to perform CTA as a first line test for evaluating patients with known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g., dyspnea on exertion, jaw pain).
• It is appropriate to perform coronary CTA following a non-conclusive functional test, in order to obtain more precision regarding diagnosis and prognosis, if such information will influence subsequent patient management.
• It is recommended to perform CTA as the first line test when considering evaluation for revascularization strategies using the ISCHEMIA Trial.
• It may be appropriate to perform CTA in selected asymptomatic high risk individuals, especially in those who have a higher likelihood of having a large amount of non-calcified plaque
• It is rarely appropriate to perform coronary CTA in very low risk symptomatic patients, e.g., <40 years of age with non-cardiac symptoms (chest wall pain, pleuritic chest pain).
• It is rarely appropriate to perform CTA in low- and intermediate risk asymptomatic patients.
Evaluation of Stable Coronary Artery Disease: Coronary CTA Post Revascularization
• It is appropriate to perform coronary CTA in symptomatic patients with intracoronary stent diameter ≥3.0 mm. Measures to improve accuracy of stent imaging should be utilized, to include strict heart rate control (goal <60 bpm), iterative reconstruction, sharp kernel reconstruction, and mono-energetic reconstructions (when available). Protocols to optimize stent imaging should be developed and followed.
• It may be appropriate to perform coronary CTA in symptomatic patients with stents <3.0 mm, especially those known to have thin stent struts (<100 mm) in proximal, non-bifurcation locations.
• It is appropriate to perform CTA for evaluation of patients with prior CABG, particularly if graft patency is the primary objective.
• It is appropriate to perform CTA to visualize grafts and other structures prior to re-do cardiac surgery.
Evaluation of Stable Coronary Artery Disease: Coronary CTA with FFR or CTP
• It may be appropriate to perform CT derived FFR and CT myocardial perfusion Imaging to evaluate the functional significance of intermediate stenoses on CTA (30e90% diameter stenosis) particularly in the setting of multivessel disease to help guide ICA referral and revascularization treatment planning. LM stenosis≥50% and severe triple vessel disease should undergo invasive coronary angiography.
• Adding FFRCT and stress-CTP to CTA increases specificity, positive predictive value, and diagnostic accuracy over regular CTA.
• FFRCT and stress-CTP may be largely comparable in diagnostic utility. CTP is a potentially valuable alternative particularly when CT-FFR is technically difficult (e.g., suboptimal CTA quality, prior revascularization).
Evaluation of Stable Coronary Artery Disease: Coronary CTA in Other Conditions
• It is appropriate to perform CTA for coronary artery evaluation prior to noncoronary cardiac surgery as an equivalent alternative to invasive angiography in selected patients, e.g., low-intermediate probability of CAD, younger patients with primarily non-degenerative valvular conditions.
• CTA may be considered an appropriate alternative to other noninvasive tests for evaluation of selected patients prior to noncardiac surgery.
• It is appropriate to perform CTA to exclude coronary artery disease in patients with suspected non-ischemic cardiomyopathy.
• It may be appropriate to perform late enhancement CT imaging to detect infiltrative heart disease or scar in selected patients who have non-ischemic or ischemic cardiomyopathy and who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for ablation therapy).

- It may be appropriate to perform CTA as an alternative to invasive coronary angiography for the screening of patients for coronary allograft vasculopathy in selected clinical practice settings.
- It is appropriate to perform CTA for the evaluation of coronary anomalies.
- It is appropriate to EKG gate aortic dissection and aneurysm CTA, as well as pulmonary embolus studies in men >45 years and women >55 years, and analyze and report the coronary arteries.
- CTA with a limited delayed image (60e90 sec) is an appropriate alternative to TEE when the primary aim is to exclude LA/LAA thrombus and in patients where the risks associated with TEE outweigh the benefits. In all situations CTA and TEE should be discussed with the patient in the setting of shared decision making.
- It may be appropriate to perform late enhancement CT imaging for the evaluation of myocardial viability in selected patients who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for revascularization).

Reporting on CTA: Coronary and Non Coronary Information

- The CAD-RADs reporting is recommended.
- It is appropriate to report prior myocardial infarction when its features are evident on CTA.
- It is appropriate to report remote myocardial infarction when fatty metaplasia or calcification within an area of infarction are present.

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Table 2

Meta-analyses of the diagnostic performance of functional imaging and CCTA with ICA >50%DS as reference standard[a].

A. MRI, SE and SPECT

		Sensitivity	Specificity	PLR	NLR	DOR
MRI (n = 2970)	Overall	91%	80%	4.43	0.12	37.69
	Suspected	90%	86%	6.61	0.12	54.70
	CAD>50%	89%	79%	4.25	0.13	31.84
	CAD>70%	91%	82%	4.97	0.11	46
SE (n = 795)	Overall	87%	72%	3.08	0.18	16.94
	Suspected	88%	89%	8.35	0.13	62.76
	CAD>50%	86%	74%	3.28	0.19	17.59
	CAD>70%	90%	65%	2.58	0.15	17.04
SPECT (n = 1323)	Overall	83%	77%	3.56	0.22	15.84
	Suspected	83%	79%	3.88	0.21	18.15
	CAD>50%	81%	81%	4.15	0.24	17.24
	CAD>70%	85%	66%	2.53	0.22	11.42

B. SPECT, MRI and PET

	No. of studies	Sensitivity	Specificity	DOR
Patient				
SPECT	105	88%	61%	15.31
MRI	27	89%	76%	26.42
PET	11	84%	81%	36.47
Territory				
SPECT	46	69%	79%	11.75
MRI	17	84%	83%	24.11
PET	7	77%	88%	24.74

C. CCTA, XECG and SPECT

	No. studies	Sensitivity	Specificity	PPV	NPV	DOR
CCTA vs ETT	7					
CTA		98%	87%	85	97.5	221

C. CCTA, XECG and SPECT

	No. studies	Sensitivity	Specificity	PPV	NPV	DOR
ETT		67%	46%	41	72	2
CCTA vs ETT (ICA in all)	5					
CCTA		99%	88%	89%	99%	728
ETT		68%	39%	50%	51%	1.2
CCTA vs ETT (inconclusive excluded)	4					
CCTA		98%	68%	75%	97%	128
ETT		70%	60%	49.5%	78%	4
CCTA vs ETT (intention to diagnose)	3					
CCTA		95%	93%	93%	96%	192
ETT		65%	24%	32%	55%	0.7
CCTA vs SPECT	5					
CCTA		99%	71%	91%	95.5%	172
SPECT		73%	48%	80%	33%	2
CCTA vs SPECT (ICA in all)	2					
CCTA		99%	74%	91%	96%	228
SPECT		67%	52%	78%	38%	

Abbreviations: AUC = area under receiver operator characteristic curve, CAD = coronary artery disease.

DOR = diagnostic odds ratio, CTA = coronary computed tomographic angiography, MRI = stress magnetic resonance imaging, NLR = negative likelihood ratio, NPV = negative predictive value, PET = positron emission tomography, PLR = positive likelihood ratio, PPV = positive predictive value, SE = stress echocardiography, SPECT = single photon emission computed tomography myocardial perfusion imaging, XECG = exercise electrocardiogram.

[a]Reprinted with permission of Oxford Academic from Hecht et al. Eur Heart J 2019:40;1440–1453

Table 3

Meta-analyses of the diagnostic performance of functional imaging and CCTA with FFR ≤0.80 as reference standard[a].

A. CTP, SPECT, SE, MRI, PET						
Index test	**N**	**Sensitivity**	**Specificity**	**PLR**	**NLR**	**AUC**
Patients						
CTP	316	88%	80%	3.79	0.12	0.93
SPECT	533	74%	79%	3.13	0.39	0.82
SE	177	69%	84%	3.68	0.42	0.83
MRI	798	89%	84%	6.29	0.14	0.94
PET	224	84%	87%	6.53	0.14	0.93
Vessels						
CTP	1074	78%	86%	5.74	0.22	0.91
SPECT	924	81%	84%	3.76	0.47	0.83
SE	NA	–	–	–	–	–
MRI	1830	83%	89%	8.27	0.16	0.95
PET	870	83%	89%	7.43	0.15	0.95

B. CCTA, SE, FFRCT, ICA, MRI, and SPECT							
Index test	**N**	**Sensitivity**	**Specificity**	**PLR**	**NLR**	**DOR**	**AUC**
Patients							
CCTA	694	90%	39%	1.54	0.22	6.91	0.57
FFR_{CT}	609	90%	78%	3.34	0.16	21.94	0.94
SPECT	110	70%	78%	3.40	0.40	9.06	0.79
SE	115	77%	75%	3.00	0.34	9.51	0.82
MRI	70	90%	94%	10.31	0.12	92.15	0.94
ICA	954	69%	67%	2.52	0.46	5.46	0.79
Vessels							
CCTA	2085	91%	51%	2.09	0.17	13.15	0.85
FFR_{CT}	1050	83%	78%	4.02	0.22	19.15	0.92
SPECT	470	57%	75%	2.34	0.55	4.72	0.74
SE	NA	–	–	–	–	–	–

MRI	371	91%	85%	6.16	0.11	73.53	0.97
ICA	3196	71%	66%	2.26	0.45	5.34	0.76

C. CMR, FFR_{CT}, CTP, DSE, PET and SPECT

Index test	N	Sensitivity	Specificity	PLR	NLR	DOR	AUC
Patient							
MRI	1054	88%	84%	5.62	0.14	40.69	0.91
FFRct	662	90%	75%	3.60	0.14	25.87	0.90
CTP	532	88%	87%	6.97	0.14	49.88	0.94
DSE	359	69%	77%	2.96	0.40	7.40	0.78
PET	609	90%	84%	6.00	0.12	56.59	0.92
SPECT	1142	78%	79%	3.76	0.28	13.52	0.85
Vessel							
MRI	3260	87%	89%	8.15	0.14	57.93	0.94
FFR_{CT}	2782	86%	83%	5.10	0.17	29.37	0.89
CTP	1444	89%	89%	7.82	0.13	61.98	0.94
DSE	94	62%	87%	4.66	0.44	10.51	0.86
PET	2017	86%	88%	7.15	0.17	42.39	0.92
SPECT	1288	72%	79%	3.45	0.36	9.71	0.83

D. CCTA, CTP and FFRCT

Index test	N	Sensitivity	Specificity	PLR	NLR	DOR	PPV	NPV
Per patient								
CCTA	1039	92%	43%	1.64	0.19	9.17	57%	87%
CTP	187	94%	77	3.85	0.09	63.42	83%	92%
FFR_{CT}	662	90%	72%	3.70	0.16	24.34	70%	90%
Per vessel								
CCTA	1239	89%	65%	2.66	0.17	19.78	48%	94%
CTP	264	83%	76%	3.68	0.22	20.10	61%	91%
FFR_{CT}	714	83%	77%	3.76	0.23	18.21	63%	91%

Abbreviations: CTA = coronary computed tomographic angiography CTP = CT perfusion DOR = diagnostic odds ratio FFR = fractional flow reserve FFR_{CT} = fractional flow reserve by computed tomography ICA = invasive coronary angiography MRI = stress magnetic resonance imaging NA = not available NLR = negative likelihood ratio NPV = negative predictive value PET = positron emission tomography PLR = positive likelihood ratio PPV = positive predictive value SE = stress echocardiography SPECT = single photon emission computed tomography myocardial perfusion imaging.

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Table 4

Randomized controlled trials of coronary computed tomography angiography in patients with stable chest pain.

Trial	Population Size	Comparison	Primary Outcome	Principal Finding	Invasive Coronary Angiography	Obstructive Coronary Heart Disease[a]	Coronary Revascularization	Myocardial Infarction
SCOT-HEART 1.7 Years[33]	4146	SOC + CTA *vs* SOC	Diagnostic Certainty	Increased diagnostic certainty	409/2073 (20%) *vs* 401/2073 (19%)	283/2072 (14%) *vs* 230/2073 (11%)	233/2073 (11%) *vs* 201/2073 (10%)	26/2073 (1.3%) *vs* 42/2073 (2.0%)
SCOT-HEART 4.8 Years[58]	4146	SOC + CTA *vs* SOC	Composite Clinical Outcome	Reduced coronary heart disease death or non-fatal MI	491/2073 (24%) *vs* 502/2073 (24%)	–	279/2073 (14%) *vs* 267/2073 (13%)	48/2073 (2.3%) *vs* 81/2073 (3.9%)
PROMISE 2.1 Years[57]	10,003	CTA *vs* Functional	Composite Clinical Outcome	No difference in clinical outcome	609/4996 (12%) *vs* 406/5007 (8%)	439/4996 (9%) *vs* 193/5007 (4%)	311/4996 (6%) *vs* 158/5007 (3%)	30/4996 (0.6%) *vs* 40/5007 (0.8%)
CAPP[59]	500	CTA *vs* ETT	Symptoms of chest pain	Less symptoms at 3 and 12 months with CTA	51/245 (21%) *vs* 66/243 (27%)	83/245 (34%) *vs* 70/243 (29%)	37/245 (15%) *vs* 19/243 (8%)	–
CRESCENT[60]	350	CAC/CTA *vs* Functional	Symptoms of chest pain	Less symptoms at 12 months with CTA	29/239 (12%) *vs* 12/108 (11%)	21/239 (9%) *vs* 7/108 (7%)	21/239 (9%) *vs* 7/108 (7%)	–
Min et al.[61]	180	CTA *vs* Myocardial Perfusion Imaging	Symptoms of chest pain	No difference in symptoms	12/86 (14%) *vs* 7/87 (8%)	–	7/86 (8%) *vs* 1/87 (1%)	–

[a]At the time of invasive coronary angiography. SOC, standard of care; CTA, coronary computed tomography angiography; ETT, electrocardiogram exercise tolerance test; CAC, coronary artery calcium score.

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Table 5

Examples of cost analyses from recent RCTs in stable ischemic heart dissease.

Trial Acronym	Target population	Near-Term Δ Cost	Long-Term Δ Cost	Overall Cost Findings
PROMISE[57]	n = 9504	Δ $254 at 90-days (p = NS)	Δ $627 at 3-years (p = NS)	3-Year Cumulative Costs were $7213 for CTA vs. $6586 for Functional Testing (p = NS)
SCOT-HEART[58]	N = 4146	Index Cost $342 Higher for CTA (p < 0.001)	$462 at 6-months higher for CTA (p < 0.0001)	6-Month Cumulative Costs were $1900 for CTA vs. $1438 for SC (p < 0.0001); When Excluding Index CTA Cost - No Differences in Downstream Costs: Δ $89 (p = 0.27)
CRESCENT[60]	N = 350	Index Cost $164 Higher for Selective CTA	€71 at 1-year higher for Exercise ECG (p < 0.0001)	1-Year Cumulative Costs were €369 for CTA vs. €440 for Exercise ECG (p < 0.0001)

Abbreviation: p = NS: p value not statistically significant.

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