JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 78, NO. 7, 2021

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Coronary Computed Tomographic Angiography for Complete Assessment of Coronary Artery Disease

JACC State-of-the-Art Review

Patrick W. Serruys, MD, PhD,[a,b,*] Hironori Hara, MD,[a,c,*] Scot Garg, MD, PhD,[d] Hideyuki Kawashima, MD,[a,c] Bjarne L. Nørgaard, MD, PhD,[e] Marc R. Dweck, MD, PhD,[f] Jeroen J. Bax, MD, PhD,[g] Juhani Knuuti, MD, PhD,[h] Koen Nieman, MD, PhD,[i] Jonathon A. Leipsic, MD,[j] Saima Mushtaq, MD,[k] Daniele Andreini, MD, PhD,[k,l] Yoshinobu Onuma, MD, PhD[a]

ABSTRACT

Coronary computed tomography angiography (CTA) has shown great technological improvements over the last 2 decades. High accuracy of CTA in detecting significant coronary stenosis has promoted CTA as a substitute for conventional invasive coronary angiography in patients with suspected coronary artery disease. In patients with coronary stenosis, CTA-derived physiological assessment is surrogate for intracoronary pressure and velocity wires, and renders possible decision-making about revascularization solely based on computed tomography. Computed tomography coronary anatomy with functionality assessment could potentially become a first line in diagnosis. Noninvasive imaging assessment of plaque burden and morphology is becoming a valuable substitute for intravascular imaging. Recently, wall shear stress and perivascular inflammation have been introduced. These assessments could support risk management for both primary and secondary cardiovascular prevention. Anatomy, functionality, and plaque composition by CTA tend to replace invasive assessment. Complete CTA assessment could provide a 1-stop-shop for diagnosis, risk management, and decision-making on treatment. (J Am Coll Cardiol 2021;78:713–736) © 2021 by the American College of Cardiology Foundation.

Patients with chest pain who have a nondiagnostic electrocardiogram (ECG) and a normal troponin commonly undergo noninvasive testing (exercise ECG, stress echocardiography, single-photon emission computed tomography [SPECT]/positron emission tomography [PET], stress cardiac magnetic resonance [CMR] and so on) (**Figure 1**) (1). Based on the results of these

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Department of Cardiology, National University of Ireland, Galway (NUIG), Galway, Ireland; [b]NHLI, Imperial College London, London, United Kingdom; [c]Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [d]Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom; [e]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [f]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom; [g]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [h]Heart Center, Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland; [i]Department of Radiology and Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA; [j]Department of Medicine and Radiology, University of British Columbia, Vancouver, British Columbia, Canada; [k]Centro Cardiologico Monzino, IRCCS, Milan, Italy; and the [l]Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy. *Drs Serruys and Hara contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 19, 2021; revised manuscript received June 2, 2021, accepted June 3, 2021.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2021.06.019

ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease

AUC = area under the curve

CABG = coronary artery bypass grafting surgery

CTA = computed tomography angiography

CTP = computed tomography perfusion

FFR = fractional flow reserve

ICA = invasive coronary angiography

LAP = low-attenuation plaque

LMCAD = left main coronary artery disease

PCI = percutaneous coronary intervention

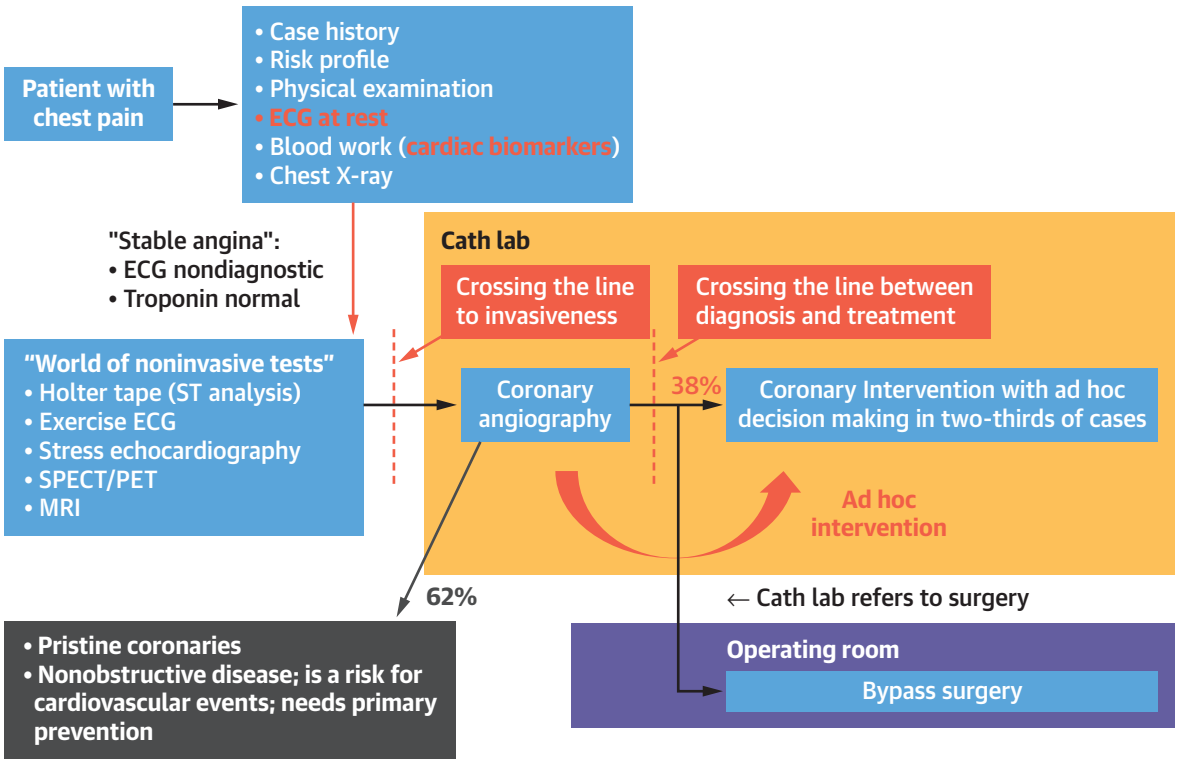
noninvasive investigations, their physician will take the decision to proceed with invasive coronary angiography (ICA). Ultimately, the physician in charge of this ICA may perform an "ad hoc" subsequent revascularization, which has been reported to occur in approximately one-third of cases (2). In two-thirds of cases, this ICA will not be followed by revascularization because pristine coronary arteries or nonobstructive coronary artery disease (CAD) have been found through a simple visual inspection of the major epicardial vessels.

What is the future vision? Coronary computed tomography angiography (CTA) may in the future play a pivotal role as a "1-stop-shop" in the screening, diagnosis, decision making, and treatment planning (**Figure 2**) (3). Conceivably, CTA could become extremely beneficial for our patients and cost-effective for our health economies (4). This 1-stop-shop could potentially provide the physician with noninvasive angiography, fractional flow reserve (FFR), perfusion with hyperemia, plaque burden, high-risk plaque, inflammation, wall motion analysis, myocardial scar and fibrosis, percent myocardium at risk, and risk scores such as the Leaman score (3). After this complete noninvasive assessment by CTA, patients' therapy decisions can be safely guided and

HIGHLIGHTS

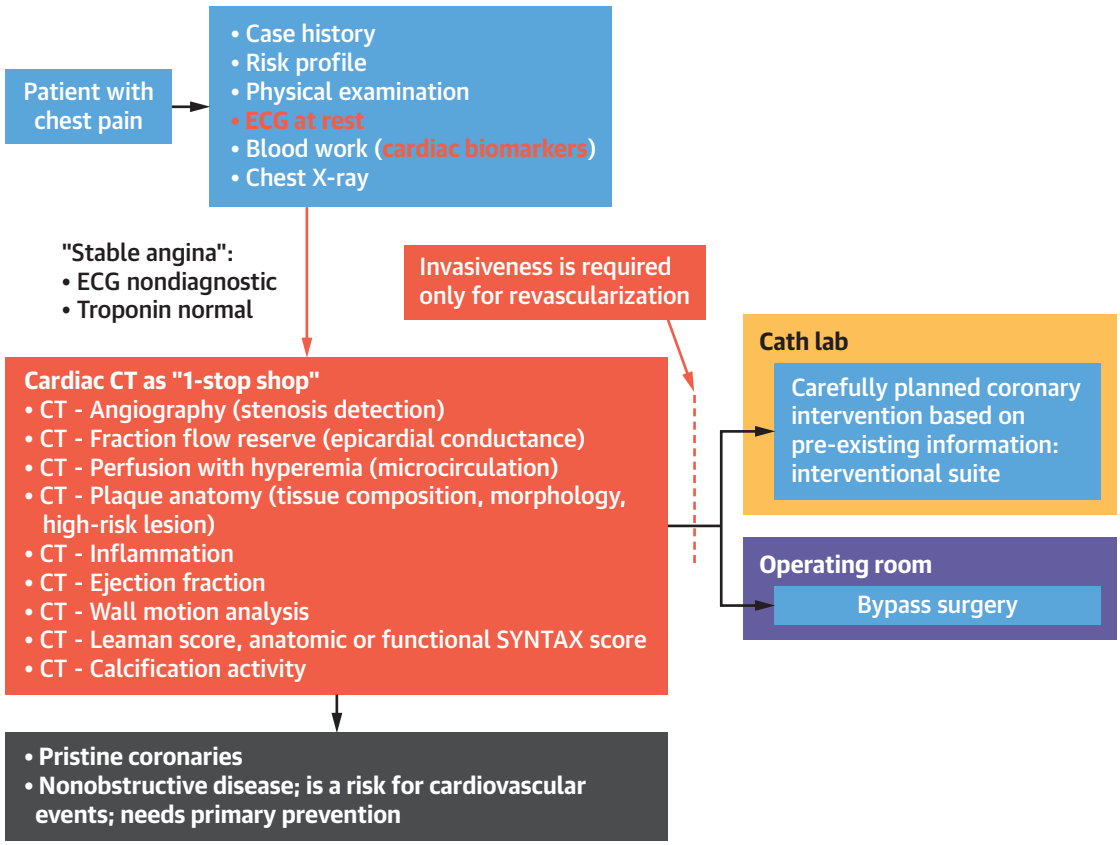
- CTA has become a primary method for diagnosis of coronary artery disease.
- Noninvasive plaque imaging can provide information previously obtained only by intravascular imaging.
- CTA-derived physiological assessments of epicardial conductance and myocardial resistance are surrogates for catheter-based intracoronary pressure and velocity measurements.

FIGURE 1 The Chest Pain Pathway Today



Patients with chest pain who have a nondiagnostic electrocardiogram (ECG) and a normal troponin commonly undergo noninvasive testing. Based on the results of noninvasive investigations, their physician will take the decision to proceed with invasive coronary angiography. Cath Lab = catheterization laboratory; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

FIGURE 2 Future Vision for the Chest Pain Pathway



Cardiac computed tomography (CT) angiography as a "1-stop-shop" increases quality and effectiveness of medicine. Abbreviations as in **Figure 1**.

only patients who need invasive therapy will cross 1 line of invasiveness: toward percutaneous coronary intervention (PCI) in the catheterization laboratory or coronary artery bypass surgery (CABG) in the operating room (5,6). In patients with nonobstructive CAD, which remains a risk for cardiovascular events, sophisticated assessment such as plaque characterization will be performed for primary prevention.

Most evidence has been derived from patients with chronic coronary syndrome. CTA also has been applied to patients with non-ST-segment elevation ACS (NSTEACS), which is defined as patients with acute chest discomfort but no persistent ST-segment elevation that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudonormalization of T waves, or normal ECG (7) (see the section "CTA and Plaque Analysis in Suspected ACS Patients"). When there is a low-to-intermediate likelihood of CAD, and when cardiac troponin and/or ECG are normal or inconclusive, CTA is recommended in the 2020 European Society of Cardiology (ESC) NSTEACS guidelines (Class I/Level of Evidence: A) as an alternative to ICA to exclude acute coronary syndrome (ACS) (7). To date, the evidence in the acute setting, especially for physiological and plaque assessment, is limited. If trials for ACS patients, such as the RAPID-CTCA (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA; NCT02284191) study, provide additional evidence, CTA as a "1-stop-shop" will be more widely applied.

CTA, THE ANATOMICAL APPROACH: A SUBSTITUTE FOR INVASIVE ANGIOGRAPHY

Prospective multicenter studies have demonstrated the diagnostic accuracy of CTA, with a sensitivity between 85% and 99% and a specificity between 64% and 92%, in patients with suspected but unconfirmed CAD (**Table 1**) (8-15). In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, CTA

TABLE 1 Diagnostic Accuracy on Computed Tomography Angiography

Study/First Author (Ref. #)	Year	N Patients	Sensitivity	Specificity	PPV	NPV	Accuracy
ACCURACY (8)	2008	230	95	83	64	99	NA
Meijboom et al. (9)	2008	360	99	64	86	97	88
NIMISCAAD (10)	2009	327	94	88	91	91	91
CORE-64 (11)	2012	273	91	87	90	88	NA
EVINCI (12)	2015	475	91	92	83	96	91
Budoff et al. (13)	2017	77	85	90	81	92	NA
PICTURE (14)	2017	230	92	78	82	90	NA
VERDICT (15)	2020	1,023	97	72	91	88	89
Andreini et al. (17): Patients with atrial fibrillation	2017	83	95	98	95	98	96
Andreini et al. (18): patients with heart rate ≥80 beats/min	2018	40	100	82	100	82	90

NA = not available; NPV = negative predictive value; PPV = positive predictive value.

demonstrated high concordance with subsequent ICA for identification of patients with angiographically significant disease without left main coronary artery disease (LMCAD). In 92.2% of patients (1,593 of 1,728), the findings of at least single-vessel disease without LMCAD on CTA were confirmed by ICA, with only 4.9% having no anatomically significant CAD (16). Relevant technological advancements have boosted the diagnostic accuracy for detecting a significant coronary artery stenosis (≥50% luminal narrowing), even in patients with atrial fibrillation and/or a high heart rate (**Table 1**) (17,18). Knuuti et al. (19) have reported the performance of noninvasive tests to rule-in and rule-out significant coronary stenoses in patients with stable angina in a meta-analysis. CTA had a sensitivity of 97%, a specificity of 78%, and substantial positive and negative likelihood ratios (4.44 and 0.04, respectively), that closely compete with the performance of PET. The best performance for ruling-out CAD was obtained with CTA, whereas the best performance for ruling-in CAD was obtained with PET. As supported by the high accuracy of CTA, randomized trials demonstrated that the rates of major cardiovascular events were similar between the CTA followed by ICA if positive for obstructive CAD and direct ICA in patients with suspected CAD (20,21).

The CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry confirmed the predictive performance of CTA for midterm all-cause mortality in >23,000 patients (22). Both nonobstructive and obstructive CAD diagnosed by CTA were associated with higher rates of mortality, compared with the absence of CAD (22). In 16,949 patients who had new-onset symptoms and received CTA in the Western Denmark Heart Registry, nonobstructive CAD and no CAD were detected in 9,305 and 4,900 patients, respectively. Nonobstructive CAD was highly associated with adverse cardiovascular events (late coronary revascularization procedure >90 days after CTA, myocardial infarction [MI], and all-cause death) at 3.5 years, compared with no CAD (adjusted HR: 1.28 [95% confidence interval (CI): 1.01-1.63]) (23). In other words, nonobstructive coronary arteries are major "troublemakers." Recently, this observation was confirmed in the SCOT-HEART (Scottish Computed Tomography of the Heart Trial) and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trials (**Table 2**), where as many heart attacks were observed in patients with nonobstructive CAD as those with obstructive CAD (24,25). Importantly, patients with a comparable plaque burden carried similar risk for downstream major cardiovascular events regardless of whether they had nonobstructive or obstructive CAD (26). The identification of nonobstructive plaque is an important advantage of CTA that is missed by ischemia-based imaging assessments and should prompt consideration of preventative medical therapies.

CTA IMAGING FOR PHYSIOLOGY: A SUBSTITUTE FOR INTRACORONARY PRESSURE-WIRE

Current revascularization guidelines recommend physiological assessment of stenotic lesions with treatment targeted at only functionally significant lesions (27). In the ESC guidelines, noninvasive functional testing using stress echocardiography, SPECT, PET, or CMR imaging is the preferred approach to provide hemodynamic information about detected coronary stenoses. FFR or instantaneous wave-free ratio (iwFR) are recommended as invasive functional tests because of the multiple randomized controlled trials—DEFER, FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2), DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation), and iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) studies—which support pressure wire-derived physiological assessment (28-30). However, according to data from the VA CART Program in the United States, wire-derived FFR is still used in <20% of patients with intermediate lesions, with significant site-level variation (31). These findings suggest that the main reasons for underutilization of wire-derived FFR are a lack of interest from operators in the technique itself,

concerns relating to the small risks associated with the technique, and the fact that it can be time-consuming, can be costly, and can cause patients discomfort through the use of hyperemic agents (31,32).

CTA-DERIVED FFR

Noninvasive CTA-derived physiological assessments could be an alternative (33). FFR_{CT} analysis by HeartFlow Inc automatically performs lumen centerline assessment, luminal boundary determination, and myocardial mass assessment. The automated results generated by deep learning methods are then inspected and corrected by trained analysts, following which, FFR is calculated using a finite element mesh model and computational fluid dynamics methods based on solving the Navier-Stokes equation for flow velocity and pressure (**Figure 3**) (34).

The diagnostic performance of anatomical and functional CTA for detecting hemodynamically significant CAD has been reported in a meta-analysis consisting of 6,400 vessels (35). In this meta-analysis, invasive FFR was used as a reference for detecting hemodynamically significant CAD. Although the specificity of CTA (61%) remains moderate for the detection of a hemodynamically significant stenosis, the specificities of FFR_{CT} (n = 2,432) and its combined use with CTA (n = 362) were high (78% and 80%, respectively). In patients with 3-vessel disease (3VD) in the SYNTAX II trial, FFR_{CT} was shown to be accurate (area under the curve [AUC] = 0.85), with iwFR as the reference (36). In a meta-analysis, the AUCs of CTA-derived FFR at the patient and vessel level were 0.90 and 0.91, respectively, which are higher than those of CTA (0.76 at patient level and 0.73 at vessel level), in the identification of an obstructive stenosis as identified by FFR (37). In the PACIFIC (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CCTA With Invasive Coronary Angiography) trial, the FFR_{CT} substudy compared the diagnostic performance of FFR_{CT}, SPECT, and PET for diagnosing ischemia using FFR as the reference: the AUCs of FFR_{CT}, SPECT, and PET were 0.92, 0.75, and 0.91 at the patient level, and 0.94, 0.70, and 0.87 at the vessel level, respectively, although analyzability of FFR_{CT} was 75% (157 patients in 208 patients) at the patient level and 83% (505 vessels in 612 vessels) at the vessel level (38). FFR_{CT} (AUC = 0.94) showed the highest diagnostic performance for vessel-specific ischemia, compared with SPECT (AUC = 0.70; $P < 0.001$) and PET (AUC = 0.87; $P < 0.001$), when the vessels were interpretable (83%) by CTA.

Clinical outcomes were investigated in the large prospective ADVANCE (Assessing Diagnostic Value of Noninvasive FFR-CT in Coronary Care) registry, which enrolled 5,083 clinically stable symptomatic patients diagnosed with CAD on CTA. No death or MI occurred within 90 days in patients with an FFR_{CT} >0.80 (n = 1,529). The prognostic value of FFR_{CT} has been confirmed up to 5 years in several studies and registries (39-42).

Recently, the randomized ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) and ISCHEMIA trials have created a substantial therapeutic dilemma in clinical practice. In the ORBITA trial, patients with stable angina and severe (≥70%) single-vessel stenoses were randomized to PCI or a sham procedure (43). PCI did not increase exercise time at 6 weeks after the procedure, despite both anatomically (84.4% area reduction) and hemodynamically (FFR = 0.69 and iwFR = 0.76) severe coronary stenoses. Importantly, the trial design only kept patients blinded to the actual performed procedure (PCI or sham) during the 6-week study period, and after this time, 85% of patients randomized to the sham arm chose to have PCI (44). The ISCHEMIA trial randomized 5,179 patients with moderate or severe ischemia to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy, or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed (45). Compared with the conversative strategy, the invasive strategy significantly improved angina-related health status at 3, 12, and 36 months (differences of Seattle Angina Questionnaire summary scores: 4.1 points [95% CI: 3.2-5.0 points], 4.2 points [95% CI: 3.3-5.1 points], and 2.9 points [95% CI: 2.2-3.7 points], respectively) (46). However, at 5 years, the primary endpoint of death from cardiovascular causes, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest was not significantly different between the 2 groups (invasive group 16.4% vs conservative group 18.2%, difference −1.8% [95% CI: −4.7% to 1.0%]) (45). These trials may support a strategy of initial optimal medical therapy in patients with at least moderate ischemia. However, patients with LMCAD were excluded in these trials, and CTA is still required for anatomical risk stratification. Given the added costs of FFR_{CT}, one approach might be to restrict FFR_{CT} to patients with ongoing symptoms despite optimal medical therapy, in whom assessment of borderline obstructive lesions are necessary for appropriate revascularization.

TABLE 2 Randomized Controlled Trials Evaluating the Utility of CTA

First Author/Study, Year (Ref. #)	Objective	Design	CT Method	Study Population
Min et al., 2012 (119)	Utility of CTA in CCS	CTA vs functional imaging by myocardial perfusion SPECT	CTA by 64-detector row scanner	Stable suspected angina
SCOT-HEART, 2015 (24,120)	Utility of CTA in CCS	CTA vs standard of care	CTA by 64- or 320-detector row scanner	Stable suspected angina
PROMISE, 2015 (49)	Utility of CTA in CCS	CTA vs functional test	CTA by ≥64-detector row scanner	Nonurgent suspected angina
CAPP, 2015 (121)	Utility of CTA in CCS	CTA vs exercise stress ECG	CTA by 64-detector row scanner	Stable suspected angina
CRESCENT, 2016 (122)	Utility of CTA in CCS	Calcium score + CTA vs functional testing	Calcium score = 0 and pretest probability ≤70%: CTA not performed	Stable suspected angina
Dewey et al., 2016 (20)	Utility of CTA in CCS	CTA vs ICA	CTA by 320-detector row scanner	Suspected coronary artery disease because of atypical chest pain
IAEA-SPECT/CTA, 2017 (123)	Utility of CTA in CCS	CTA vs functional testing by stress myocardial perfusion imaging	CTA by ≥64-detector row scanner	Symptomatic patients with an intermediate likelihood of CAD or asymptomatic patients at intermediate-high risk of coronary events
CAT-CAD, 2018 (124)	Utility of CTA in CCS	CTA vs ICA	CTA by dual-source scanner	Stable suspected angina
CONSERVE, 2019 (21)	Utility of CTA in CCS	CTA vs ICA	NA	Stable suspected angina
CARE-CCTA, 2019 (125)	Utility of CTA in CCS	CTA vs myocardial perfusion SPECT	CTA by 64-detector row scanner	Stable suspected angina with 10%-90% pretest probability of CAD
RESCUE, 2020 (126)	Utility of CTA in CCS	CTA vs myocardial perfusion SPECT	CTA by ≥64-detector row scanner	Stable suspected angina
IMAGE-HF 1C, 2020 (127)	Utility of CTA in heart failure	CTA vs ICA	CTA by ≥64-detector row scanner	Heart failure of unknown etiology
Goldstein et al., 2007 (128)	Utility of CTA in ACS	CTA vs standard of care	CTA by 64-detector row scanner	Suspected ACS at low risk
Chang et al., 2008 (129)	Utility of CTA in ACS	CTA vs standard of care	CTA by 64-detector row scanner	Low-to-high risk for ACS
Miller et al., 2011 (130)	Utility of CTA in ACS	CTA vs standard of care	CTA by 64-detector row scanner	Suspected ACS without cardiac enzyme elevation
CT-STAT, 2011 (131)	Utility of CTA in ACS	CTA vs myocardial perfusion SPECT	CTA by 64- or 320-detector row scanner	Suspected ACS at low-to-intermediate risk
ROMICAT-II, 2012 (132)	Utility of CTA in ACS	CTA vs standard of care	CTA by ≥64-detector row scanner	Suspected ACS
ACRIN PA 4005, 2012 (133)	Utility of CTA in ACS	CTA vs standard of care	CTA by ≥64-detector row scanner	Suspected ACS at low-to-intermediate risk
CATCH, 2013 (134,135)	Utility of CTA in ACS	CTA vs standard of care	CTA by 320-detector row scanner	Suspected ACS
CT-COMPARE, 2014 (136)	Utility of CTA in ACS	CTA vs exercise stress ECG	CTA by 64- or 128-detector row scanner	Low-to-intermediate risk for ACS
Levsky et al., 2015 (137)	Utility of CTA in ACS	CTA vs myocardial perfusion SPECT	CTA by 64-detector row scanner	Suspected ACS
BEACON, 2016 (138)	Utility of CTA in ACS	CTA vs standard of care	CTA by ≥64-detector row scanner	Suspected ACS
Levsky et al., 2018 (139)	Utility of CTA in ACS	CTA vs stress echocardiography	CTA by 64-detector row scanner	Low-to-intermediate risk for ACS
CARMENTA, 2019 (95)	Utility of CTA in NSTEMI	Routine clinical care vs CMR first vs CTA first	CTA by second-generation dual-source scanner	Suspected NSTEMI

3VD = 3-vessel disease; ACRIN-PA 4005 = CT Coronary Angiography Versus Traditional Care for Low-Risk ED Patients With ACS; ACS = acute coronary syndrome; AUC = area under the curve; BEACON = Better Evaluation of Acute Chest Pain with Computed Tomography Angiography; CAPP = Cardiac CT for the Assessment of Pain and Plaque; CAT-CAD = Computed Tomography as the First-Choice Diagnostics in High Pre-Test Probability of Coronary Artery Disease; CCS = chorionic coronary syndrome; CMR = cardiovascular cardiac magnetic resonance; CONSERVE = Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization; CRESCENT = Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease; CTA = computed tomography angiography; CT-COMPARE = CT Coronary Angiography Compared to Exercise ECG; CTP = computed tomography perfusion; CT-STAT = Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment; ECG = electrocardiogram; FFR = fractional flow reserve; IAEA-SPECT/CTA = Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease; ICA = invasive coronary angiography; IMAGE-HF = Imaging Modalities to Assist with Guiding therapy and the Evaluation of patients with Heart Failure; LMCAD = left main coronary artery disease; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RESCUE = Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations; ROMICAT-II = Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II; SAQ = Seattle Angina Questionnaire; SPECT = single-photon emission computed tomography.

Continued on the next page

TABLE 2 Continued

N Patients	Country	Primary Endpoint and Other Clinically Relevant Endpoints	Results
180 (91 vs 89)	United States	Near-term angina-specific health status	Both arms improved angina-specific health status comparably at an average of 55 days
4,146 (2,073 vs 2,073)	United Kingdom	Certainty of diagnosis of angina caused by coronary heart disease at 6 weeks Death from coronary heart disease or nonfatal MI at 5 y	Reclassification of the diagnosis of angina caused by coronary heart disease: 23% vs 1%; $P < 0.0001$ 2.3% vs 3.9%; HR: 0.59 (0.41-0.84); $P = 0.004$
10,003 (4,996 vs 5,007)	United States and Canada	Death, nonfatal MI, hospitalization for unstable angina, or major procedural complications	3.3% vs 3.0% (a median follow-up of 25 months); adjusted HR: 1.04 (0.83-1.29); $P = 0.75$
500 (250 vs 250)	United Kingdom	The change of the SAQ score at 3 months	Difference of angina stability: −11.1 (−17.4 to −4.8: CTA better); $P = 0.001$; quality of life: −5.7 (−10.3 to −1.2: CTA better); $P = 0.014$
350 (242 vs 108)	Netherlands	Absence of chest pain complaints at 1 y	39% vs 25%; $P = 0.012$
340 (168 vs 172)	Germany	Major procedural (CTA or ICA) complication occurring within 48 h Cardiac death, stroke, MI, unstable angina, or revascularization	0.6% vs 0.0%; $P = 1.00$ 4.2% vs 3.7% (a median follow-up of 3.3 y); $P = 0.86$
303 (152 vs 151)	Brazil, Czech Republic, India, Mexico, Slovenia, Turkey	Additional noninvasive testing or ICA within 6 months	27.7% vs 16.8%; adjusted OR: 2.0 (1.1-3.6); $P = 0.023$
120 (60 vs 60)	Poland	Rate of ICA ICA not leading to revascularization	35% vs 98%; $P < 0.001$ 8% vs 70%; $P < 0.001$
1,631 (823 vs 808)	North America, East Asia, Europe, India	Death, MI, unstable angina, stroke, urgent and/or emergent revascularization or cardiac hospitalization at 1 y	4.6% vs 4.6%; $P = 0.99$
903 (460 vs 443)	Korea	Total cost Death, ACS, cerebrovascular accident, revascularization, stent thrombosis, or significant bleeding at 1 y	$4,514 vs $5,208; $P = 0.043$ 4.6% vs 5.4%; $P = 0.455$
1,050 (518 vs 532)	United States, Germany, the Netherlands	Cardiac death, MI, or revascularization	HR: 1.03 (0.61-1.75); (median follow-up of 16.2 months); $P = 0.19$
253 (124 vs 129)	Canada, Finland	Total cost at 12 months	C$7,611 vs C$8,482; $P = 0.310$
197 (99 vs 98)	United States	Test complications Time from randomization until completion of testing interpretation	0.0% vs 0.0%; $P =$ NA 3.4 h vs 15.0 h; $P < 0.001$
266 (133 vs 133)	Korea	Admission Death, MI, or target vessel revascularization at 1 month	41% vs 50%; $P = 0.14$ 0.0% vs 0.8%; $P =$ NA
60 (30 vs 30)	United States	Total cost at 90 days	$10,134 vs $16,579; $P = 0.144$
699 (361 vs 338)	United States	Time from randomization to when test results were called to emergency department physicians	2.9 h vs 6.3 h; $P < 0.001$
1,000 (501 vs 499)	United States	Length of stay in the hospital	23.2 h vs 30.8 h; $P < 0.001$
1,370 (908 vs 462)	United States	Cardiac death or MI within 30 days in patients with a negative CTA examination Death or MI at 30 days	0.0% (0/640) 1.10% vs 1.08%; difference 0.02% (−5.6% to 5.7%)
600 (299 vs 301)	Denmark	Cardiac death, MI, hospitalization for unstable angina, late symptom-driven revascularization, or readmission for chest pain	11% vs 16% (a median follow-up of 18.7 months); $P = 0.04$
562 (322 vs 240)	Australia	Diagnostic performance for ACS Hospital cost at 30 days	AUC 0.97 vs 0.87; $P = 0.22$ A$2,193 vs A$2,704; $P < 0.001$
400 (200 vs 200)	United States	ICA not leading to revascularization within 1 y	7.5% vs 10%; $P = 0.44$
500 (250 vs 250)	The Netherlands	The number of patients requiring revascularization within 30 days	9% vs 7%; $P = 0.40$
400 (201 vs 199)	United States	Hospitalization rate Median emergency department length of stay for discharged patients Median hospital length of stay	19% vs 11%; $P = 0.026$ 5.4 h vs 4.7 h; $P < 0.001$ 58 h vs 34 h; $P = 0.002$
207 (69 vs 68 vs 70)	The Netherlands	Proportion of patients referred to ICA during initial hospitalization	100% vs 66% ($P = 0.001$ vs routine care) vs 87% ($P < 0.001$ vs routine care)

TABLE 2 Randomized Controlled Trials Evaluating the Utility of CTA

Study/First Author, Year (Ref. #)	Objective	Design	CT Method	Study Population
CRESCENT II, 2018 (60)	Utility of CTA and CTP in CCS	Calcium score + CTA + CTP vs functional test	Calcium score = 0 and pretest probability ≤80%: CTA not performed Calcium score >0 or pretest probability >80%: CTA performed CTA detected >50% stenosis: CTA + dynamic CTP performed	Stable suspected angina
CATCH-2, 2018 (61)	Utility of CTA and CTP in CCS	CTA+CTP vs CTA	CTA/CTP by 320-detector row scanner	Hospitalization caused by acute chest pain and ACS ruled out
Yu et al., 2020 (140)	Utility of CTA and CTP in CCS	CTA + CTP vs CTA	CTA/CTP by third-generation dual-source scanner	Stable suspected angina at intermediate risk
SYNTAX III REVOLUTION, 2018 (141)	CTA and FFR_{CT} for decision making on revascularization	Decision making on revascularization by CTA vs ICA	CTA and FFR_{CT} by 256-detector row scanner	Chronic stable angina or stabilized ACS with de novo 3VD and/or LMCAD

Continued on the next page

COST-EFFECTIVENESS OF FFR_{CT}

Diagnosis solely based on noninvasive imaging is not only beneficial for the patient from a medical point of view, but it is also cost effective from a societal perspective. In the United States, CTA ($301) with FFR_{CT} ($1,500) is $1,138 cheaper than ICA ($2,838) with FFR ($101) (39,47). In the United Kingdom, according to the National Institute for Health and Care Excellence (NICE) guidance updated in 2021, the cost of CTA (£290) with FFR_{CT} (£700) is also lower than ICA (£2,369) with FFR (48).

The prospective, randomized PROMISE trial compared an anatomical testing strategy with CTA (n = 4,996) with a functional testing strategy (n = 5,007) in patients with stable chest pain, with ICA showing nonobstructive CAD assessed as a secondary endpoint (49). In the anatomical testing group, 609 patients underwent an ICA, and among them 311 (51.1%) received revascularization. ICA was performed in 406 patients in the functional-testing group, and revascularization was performed in 158 patients (38.9%). In the PROMISE trial, FFR_{CT} was retrospectively calculated in 181 patients with CTA and ICA, and 50 patients (27.7%) had an FFR_{CT} >0.80, which suggested that FFR_{CT} could additionally reduce unnecessary ICA (50). The PLATFORM (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts) trial prospectively compared usual care to FFR_{CT}-guided evaluation in stable, symptomatic patients with suspected CAD. In 58% (112 of 193) of patients, scheduled ICA was no longer required following their $FFR_{CT,}$ which was associated with lower costs (39).

NICE advocates CTA as the first-line test for patients with CAD with a potential increase in CTA by 400% (4,51). In the 2019 ESC guidelines, CTA along with noninvasive functional imaging was given a Class I, Level of Evidence: B recommendation as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD could not be excluded by clinical assessment alone (52). NICE have also suggested that the selective use of FFR_{CT} may lead to cost savings of £391/patient/year and a reduction in ICA by 60% (48,53). Experts in the field raised the following question in the *European Heart Journal*: "Should NICE guidelines be universally accepted?" and the final conclusion was "in favor of CTA provided that FFR_{CT} and high-risk plaque are properly evaluated" (54).

CT PERFUSION IMAGING

Ischemia can be noninvasively detected by assessing myocardial perfusion, as performed using stress CMR and nuclear imaging (**Figure 4**). Computed tomography perfusion (CTP) imaging can be performed by a static or dynamic CTP acquisition method. Static CTP imaging is based on acquisition of a single phase during the first-pass of contrast agent in the myocardium, with scan timing critical for detecting the perfusion abnormality (55). Perfusion defects on the stress images are identified by comparing contrast enhancement against remote myocardium, and defects are subsequently compared with the rest images (often the coronary CT angiogram) to distinguish reversible ischemia from permanent scar (56). Dynamic CTP is based on repeated rapid CT scans during intravenous contrast medium injection, and is used to obtain a quantitative evaluation of myocardial perfusion and myocardial blood flow (56). This acquisition is associated with a higher radiation dose; however, myocardial blood flow calculated from

TABLE 2 Continued

N Patients	Country	Primary Endpoint and Other Clinically Relevant Endpoints	Results
268 (130 vs 138)	Netherlands	ICA without an ESC Class I indication for revascularization among all patients at 6 months ICA with an ESC Class I indication for revascularization among patients with ICA	1.5% (2/130) vs 7.2% (10/138); $P = 0.035$ 88% (15/17) vs 50% (10/20); $P = 0.017$
600 (300 vs 300)	Denmark	Frequency of revascularization among patients referred for ICA at 60 days Frequency of patients referred for ICA	48% (20/41) vs 50% (42/89); $P = 0.85$ 14% (41/300) vs 30% (89/300); $P < 0.0001$
250 (125 vs 125)	China	ICA not leading to revascularization within 3 months	10.8% (4/37) vs 50.0% (29/58); $P < 0.0001$
223	Italy, Belgium, Germany, France, Switzerland	Agreement between heart teams on revascularization strategy Change of revascularization strategy by FFR_{CT}	93%; Cohen's kappa 0.82 7% (14/196 patients in whom FFR_{CT} was available)

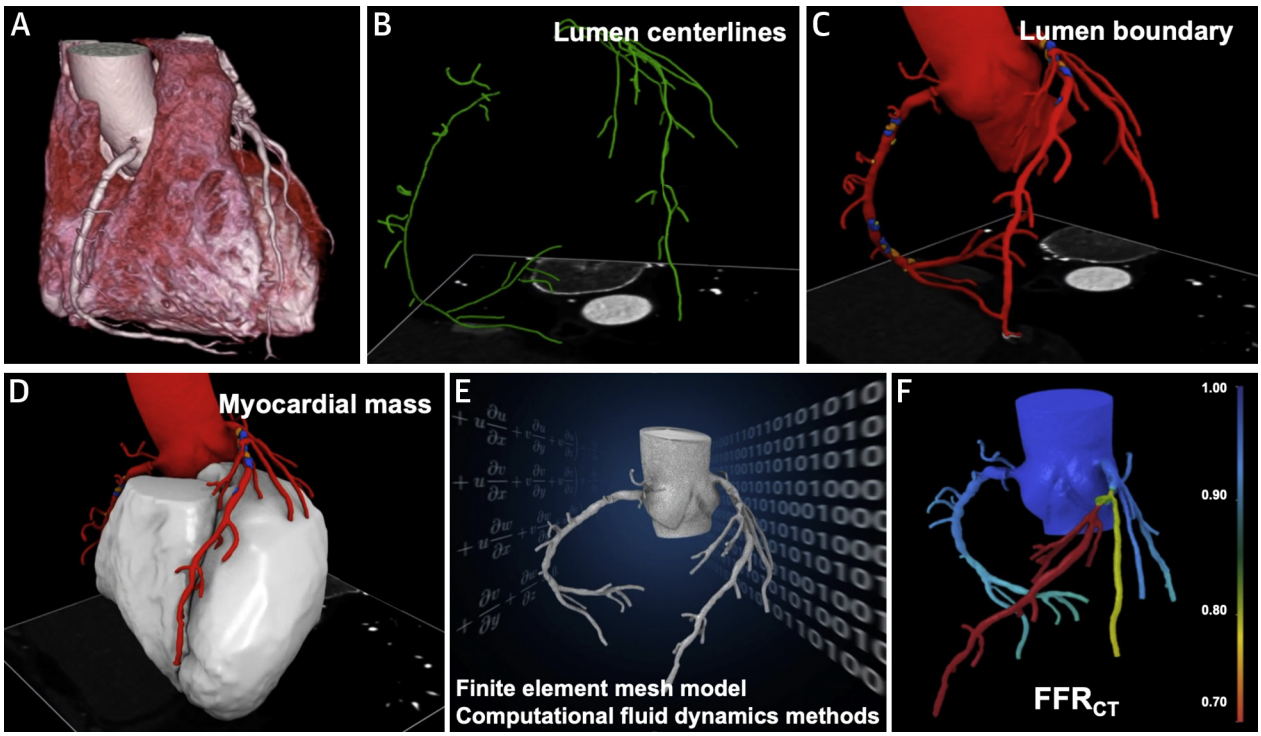
changes in myocardial contrast enhancement (time-attenuation curves) can be helpful to diagnose myocardial ischemia in cases of multivessel disease where extensive but balanced ischemia may be underestimated (56,57). CTP imaging can assess the microcirculation by the attenuation difference between the endocardium and epicardium in patients with nonobstructive CAD (58). More specifically, decreased attenuation in the endocardium compared with the epicardium is associated with microvascular dysfunction, which correlates with cardiovascular risk (59).

The diagnostic accuracy of CTP has been improved with advancements in CT technology regardless of the method of acquisition. A recent meta-analysis demonstrated that CTP and its combined use with CTA had good sensitivities (81% and 82%, respectively) and excellent specificities (86% and 88%, respectively) for the detection of hemodynamically significant CAD when invasive FFR was used as the reference standard (35). The CRESCENT II trial (**Table 2**) randomized patients with stable chest pain to a tiered cardiac CT protocol, including perfusion imaging if the CTA showed coronary stenosis (n = 130), or standard care based on stress testing (n = 138). ICA was performed in 17 and 20 patients, respectively, and the comprehensive cardiac CT approach resulted in a higher diagnostic yield of subsequent ICA with an ESC Class I indication for revascularization (88% [15 of 17] vs 50% [10 of 20]; $P = 0.017$) (60). The CATCH-2 (Cardiac CT in the Treatment of Acute Chest Pain 2) trial (**Table 2**) randomized 600 patients to CTA (n = 300) or CTA with adenosine perfusion (n = 300) and came to the conclusion that CTP reduces the need for invasive examination (30% [n = 89] vs 14% [n = 41]; $P < 0.0001$) (61).

One question is whether CT with myocardial perfusion assessment during hyperemia induced by adenosine is a better alternative to CTA-derived FFR. Only a few studies have compared the 2 using invasive FFR as the reference (**Table 3**). In the prospective CTP registry, assessment of invasive FFR, CTA, static CTP, and CTA-derived FFR (using cFFR [Siemens Healthcare]) were available in 72 patients with 138 vessels (62). CTP combined with CTA demonstrated similar diagnostic performance to CT-derived FFR combined with CTA (AUC = 0.91 vs 0.92, respectively) for the detection of a hemodynamically significant stenosis in the per-vessel analysis. Similarly, Coenen et al. (63) prospectively performed CTA, dynamic CTP, and CTA-derived FFR (using cFFR) before ICA with FFR measurement in 74 patients (142 vessels) with known or suspected CAD, and showed that CTP combined with CTA had a similar diagnostic performance to CT-derived FFR combined with CTA (AUC = 0.83 vs 0.80, respectively). The PERFECTION (Comparison Between Stress Cardiac Computed Tomography Perfusion Versus Fractional Flow Reserve Measured by Computed Tomography Angiography in the Evaluation of Suspected Coronary Artery Disease) study confirmed the equivalent diagnostic performance of CTA plus CTP and CTA plus FFR_{CT} (AUC = 0.92 vs 0.93, respectively) (64).

It is important to consider the strengths and weaknesses of CTP and CTA-derived FFR in clinical practice. In contrast to a conventional CTA with postprocessing FFR_{CT}, CTP needs specific image acquisition, requiring 2 consecutive scans, higher doses of radiation, and the infusion of a hyperemic agent. The pretest probabilities recommended in the ESC guidelines are based on age, sex, and the nature of the symptoms (typical, atypical, nonanginal, and dyspnea), and were internally validated by ICA and FFR in 15,815 symptomatic patients (52,65). These pretest probabilities were externally validated and appear to be well calibrated in the SCOT-HEART trial and the Western Denmark Heart

FIGURE 3 Fractional Flow Reserve by Computed Tomography



(A) 3-dimensional volume rendering technique image. **(B to E)** After automatic lumen centerline assessment **(B)**, luminal boundary determination **(C)**, and myocardial mass assessment **(D)**, Fractional flow reserve (FFR) value is calculated using finite element mesh model and computational fluid dynamics methods **(E)**. **(F)** Fractional flow reserve by computed tomography (FFR$_{CT}$) is provided as a color-coded 3D map.

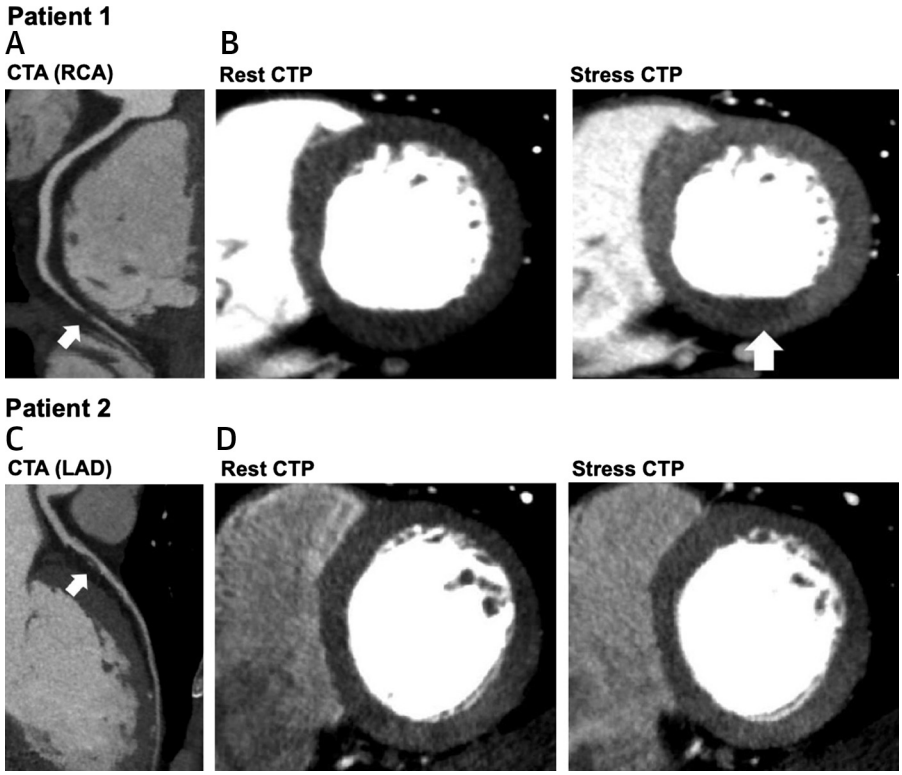
Registry data (66,67). In pooled data of more than 40,000 symptomatic patients, incorporation of 5 additional clinical risk factors (family history, smoking, dyslipidemia, hypertension, and diabetes) improved the prediction of obstructive CAD (68). When considering CTP, the pretest probabilities of obstructive CAD may justify the type of CT acquisition, either CTA or CTA with CTP.

CTA-derived FFR does not require additional scans or the use of stressors. In 2017, the large international radiation dose survey demonstrated a considerable reduction in radiation exposure with CTA over the last decade (69). Notably, although the radiation dose for a CTA with or without CTA-derived FFR is now 2-5 mSV, it is still more than 5 mSv for dynamic CTP (57,70,71). In addition, static CTP may mask balanced ischemia when a patient has 3VD. However, the performance of CTP is not usually influenced by the quality of CTA imaging (motion artifact, severe calcification, stenting, and so on), which is a limitation to the use of FFR$_{CT}$. The ADVANTAGE study enrolled 150 patients with coronary stents (72). At a patient level, when ICA was used as the reference standard, diagnostic accuracy was significantly higher with CTP than with CTA (86.7% vs 76.7%; $P = 0.02$). Invasive FFR was performed in 36 coronary stenoses in 36 patients and at a vessel level, when FFR was used as the reference standard, diagnostic accuracy was again significantly higher with CTP than with CTA (75.0% vs 30.5%; $P = 0.003$).

CTA IMAGING FOR DECISION MAKING BETWEEN PCI AND CABG

In the SYNTAX III REVOLUTION trial, 2 heart teams were randomized: one only had access to the ICA, whereas the other only had access to the CTA for the decision making between PCI and CABG in patients with LMCAD or 3VD (Table 2). Each heart team made a decision about treatment based on the SYNTAX score II: a combination of the anatomic SYNTAX score and comorbidities (73), and an agreement between the 2 heart team's decision was observed in 92.8% with a Cohen's kappa of 0.82. When FFR$_{CT}$ was integrated into the decision-making process,

FIGURE 4 CTP Imaging



(A and B) Patient 1. **(A)** Stenosis with ≥50% in right coronary artery (RCA) **(arrow). (B)** A corresponding perfusion deficit (most reversible **[arrow]**) in inferior wall. **(C and D)** Patient 2. **(C)** Stenosis with ≥50% in left anterior descending artery (LAD) **(arrow). (D)** Rest and stress images did not show perfusion deficit in anterior wall. Reproduced with permission from Magalhães et al. (118). CTA = computed tomography angiography; CTP = computed tomography perfusion.

the recommended treatment between PCI and CABG and the vessel to be revascularized were changed in 7% and 12% of patients, respectively, compared with CTA assessment (74).

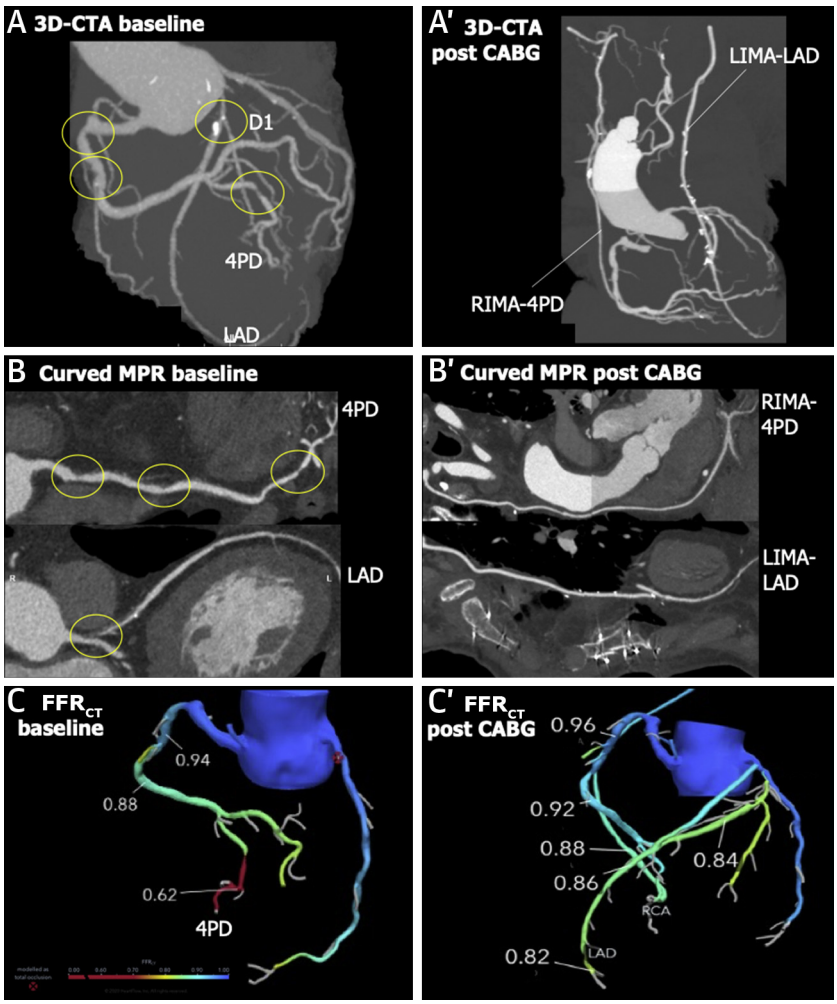
In the ongoing FASTTRACK CABG trial (Safety and Feasibility Evaluation of Planning and Execution of Surgical Revascularization Solely Based on Coronary CTA and FFRCT in Patients With Complex Coronary Artery Disease; NCT04142021) trial (6) the surgeon may or may not decide to plan and execute the CABG solely based on CTA with FFR_{CT} without viewing ICA (feasibility assessment). Thirty days after surgery, graft patency will be used as proof of the safety of the CTA modality of assessment (**Figure 5**). If the FASTTRACK CABG trial proves the feasibility and safety of noninvasive imaging guidance for CABG, then in the

TABLE 3 CTA vs CTA-Derived FFR vs CTP

	N		Methods			AUC at Vessel Level			*P* Value		
Study/First Author (Ref. #)	Patients	Vessels	CTA-Derived FFR	CTP	Significant Stenosis	CTA	CTA + CTA-Derived FFR	CTA+CTP	CTA vs CTA + CTA-Derived FFR	CTA vs CTA + CTP	CTA + CTA-Derived FFR vs CTA + CTP
Prospective CTP registry (62)	72	138	cFFR	Static	FFR ≤0.80	0.86	0.92	0.91	0.004	0.004	NA
Coenen et al. (63)	74	142	cFFR	Dynamic	FFR ≤0.80	0.70	0.80	0.83	0.001	<0.001	NA
PERFECTION (64)	147	NA	FFR_{CT}	Static	%DS >80% or FFR <0.80	0.89	0.93	0.92	<0.001	<0.001	0.128

Abbreviations as in Table 2.

FIGURE 5 A Case of FASTTRACK CABG



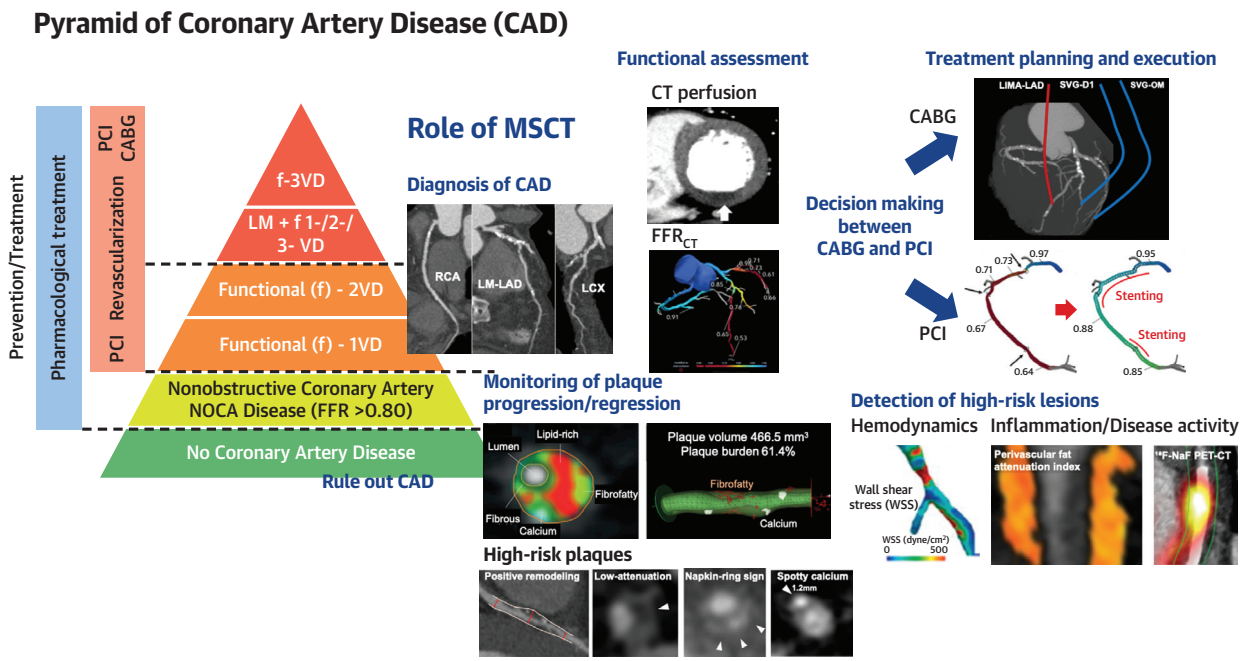
(A to C) Baseline. **(A)** 3D-CTA (maximum intensity projection [MIP]) image. **(B)** Curved multiplanar reconstruction (MPR) images in RCA and LAD. **Yellow circles** indicate the significant stenoses, and an **orange circle** indicates the occlusion. **(C)** FFR_{CT} findings. FFR_{CT} indicates flow-limiting lesions at the distal RCA and total occlusion at the proximal LAD. **(A′ to C′)** 30-day follow-up post-coronary artery bypass graft (CABG). **(A′)** 3D-CTA image. Left internal mammary artery (LIMA)-LAD and right internal mammary artery (RIMA)-4 posterior descending artery (4PD) were grafted. **(B′)** Curved MPR images in LIMA-LAD and RIMA-4PD. All grafts were patent. **(C′)** FFR_{CT} findings. The post-CABG FFR_{CT} values in RCA and LAD were 0.86 and 0.82, respectively. Abbreviations as in Figures 3 and 4.

future, the surgeon may, can, and will operate safely on the most complex patients of the CAD pyramid with the sole guidance of CTA and FFR_{CT} (Central Illustration).

CTA-BASED PLAQUE EVALUATION: A SUBSTITUTE FOR INTRAVASCULAR IMAGING

ATHEROMA VOLUME. Software applications for plaque characterization by CTA are becoming more sophisticated. The software makes it possible to quantify total plaque volume and assess the burden of different plaque types including calcific, noncalcific, and low-attenuation plaque (LAP) (Figure 6). Conte et al. (75) reported an excellent correlation for total plaque volume quantification between IVUS and 256-slice CTA. In the PARADIGM (Progression of Atherosclerotic Plaque Determined By Computed Tomographic Angiography Imaging) study, plaque assessment by CTA demonstrated that statins promoted the conversion of unstable plaques to stabilized calcified plaques, decreased the progression of noncalcified plaques, and reduced the total plaque burden (76). In the assessment of plaque distribution,

CENTRAL ILLUSTRATION The Pyramid of Coronary Artery Disease and the Diagnostic Role of Multislice Computed Tomography



Serruys, P.W. et al. J Am Coll Cardiol. 2021;78(7):713–736.

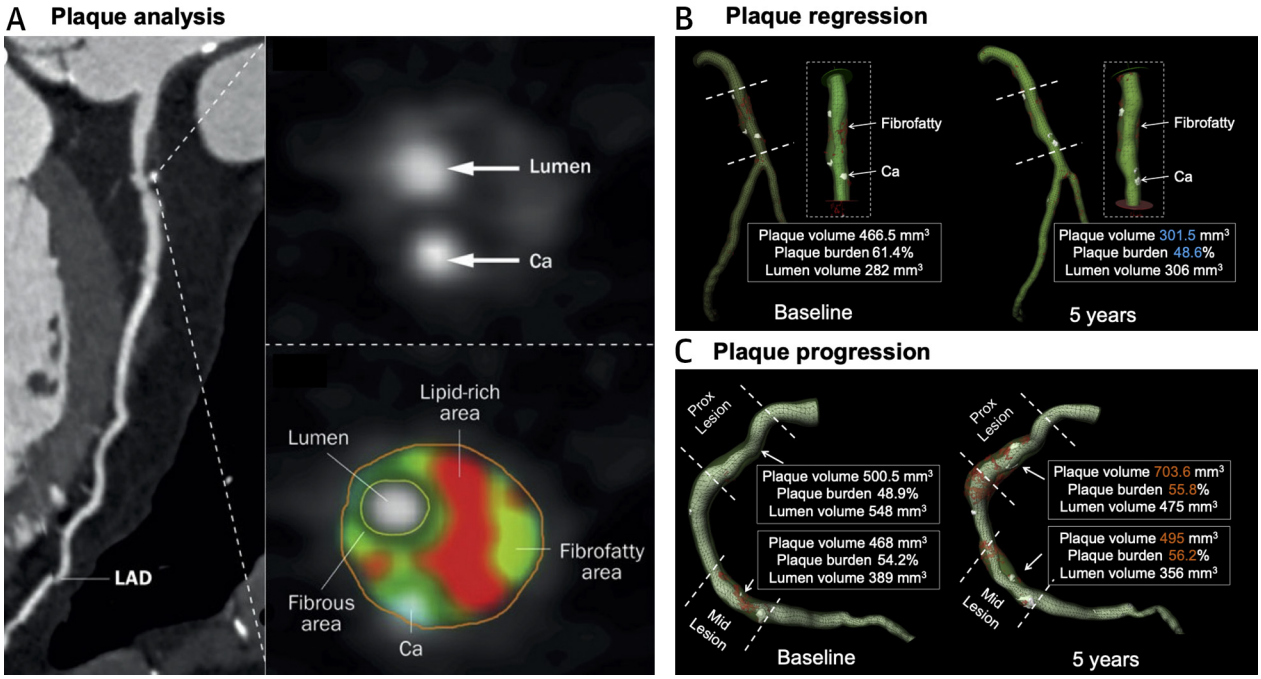
Main role of multislice computed tomography (MSCT) may vary as a function of the disease severity. **(Red)** The decision making, treatment planning, and execution of revascularization strategies (percutaneous coronary intervention [PCI] or coronary artery bypass grafting surgery [CABG]) for patients with complex coronary artery disease (left main and/or 3-vessel disease) can be based on MSCT anatomic and functional assessment, and in the future, CABG could be guided solely by noninvasive information (5,6). **(Orange)** If a surgeon can perform CABG with the sole guidance of MSCT in the most complex patients, then patients with 1- or 2-functionally significant vessel disease should be referred directly to PCI without prior invasive coronary angiography. **(Yellow)** Patients with nonobstructive coronary artery without functional compromising alteration of the epicardial coronary conductance (fractional flow reserve >0.80) could benefit from pharmacological treatment. The MSCT allows for detection of high-risk lesions and monitoring of plaque progression or regression. **(Green)** The MSCT rules out coronary artery disease in patients with normal coronary anatomy and epicardial conductance. CAD = coronary artery disease; CT = computed tomography; FFR = fractional flow reserve; LIMA = left internal mammary artery; NOCA = normal coronary anatomy; VD = vessel disease.

atherosclerotic burden varied across the epicardial coronary arteries, with a significantly lower plaque volume, especially for low-density plaque, in the left circumflex when compared with the left anterior descending artery and right coronary artery (77). In terms of predictive value, the impact of baseline total atheroma volume on nonobstructive lesions progressing to obstructive lesions was significant (adjusted HR: 1.04 [95% CI: 1.02-1.07]; $P < 0.05$) (78). More importantly, plaque volume, particularly noncalcified plaque volume, was a stronger predictor of cardiovascular events compared with lumen stenosis and clinical risk profile in the CAPIRE (Coronary Atherosclerosis in Outlier Subjects: Protective and Individual Risk Factor Evaluation) study (79). In the SCOT-HEART trial, the burden of low-attenuation coronary plaque was the strongest predictor of future MI outperforming cardiovascular risk scores, luminal stenosis severity, coronary calcium scores, and total plaque volume (80).

Based on the accuracy of plaque volume assessments on CTA and their association with cardiovascular events, plaque volume measured by CTA has been used as a surrogate endpoint in clinical trials. In the EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy) trial the primary endpoint of change in LAP volume measured by CTA was significantly reduced with the combination of icosapent ethyl and statins (n = 31) compared with placebo and statins (n = 37) over 18 months (−17% vs +109%) (81).

VULNERABLE PLAQUE. Plaque assessment on CTA helps predict the risk of adverse cardiac events.

FIGURE 6 Plaque Assessment



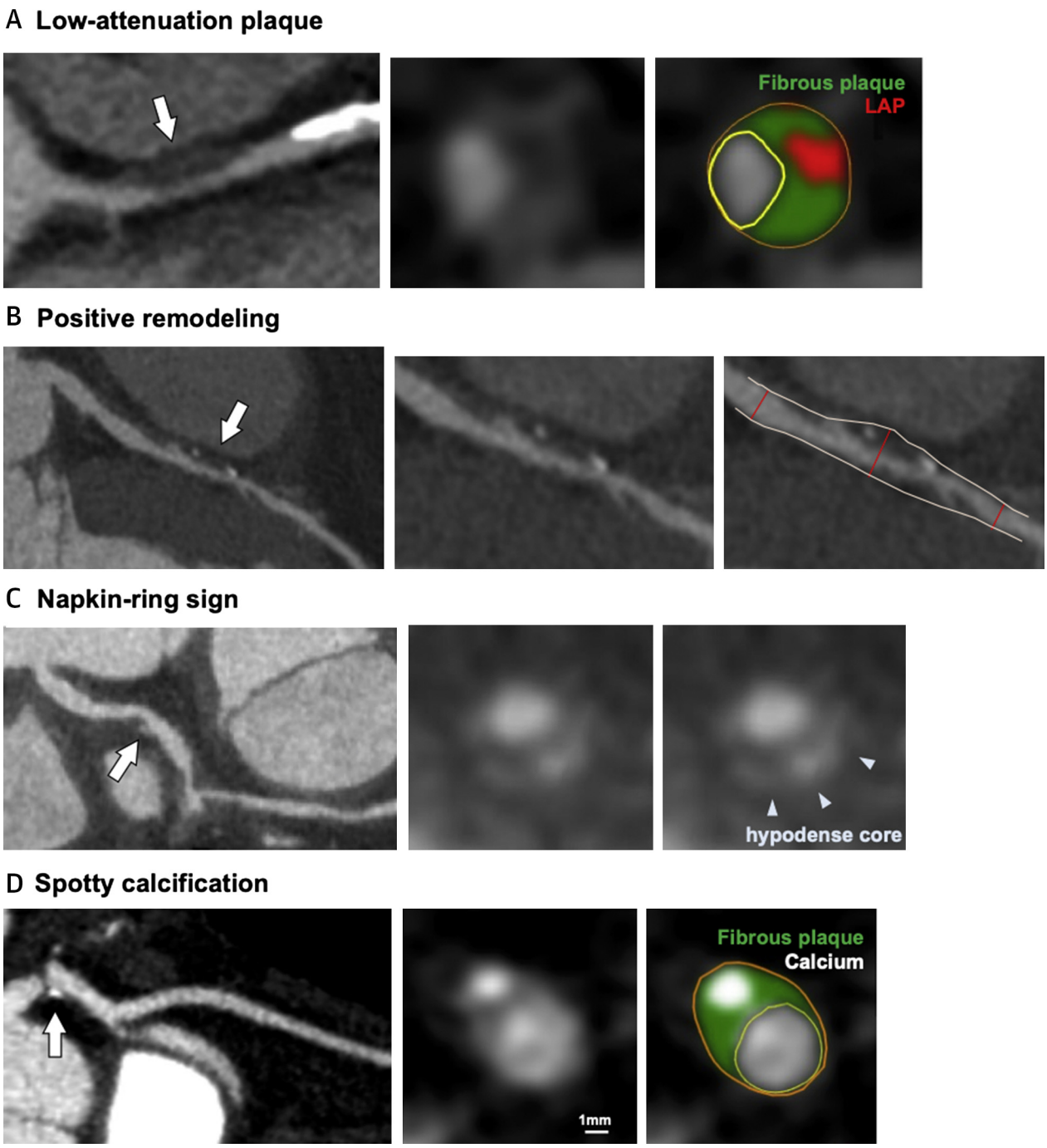
(A) Plaque characterization by coronary CTA. **(B and C)** Plaque volume regression **(B)** and progression **(C)** over 5 years. Ca = calcium; other abbreviations as in **Figure 4**.

Motoyama et al. (82,83) reported that high-risk plaques with positive remodeling and/or LAP (**Figure 7**) were associated an increased risk of presenting with ACS over the short (2.3 years) and medium-term (4.1 years). Substudies of large trials confirmed the impact of high-risk plaques. In the PROMISE trial, the presence of high-risk plaque (positive remodeling, LAP, spotty calcification, or napkin-ring sign) (**Figure 7**) was associated with higher rates of major adverse cardiac events (death, MI, or hospitalization for unstable angina) at 25 months in 4,415 patients with stable symptoms (6.4% vs 2.4%, unadjusted HR: 2.73 [95% CI: 1.89-3.93]) (25). In the SCOT HEART study, 1 or more high-risk plaques (positive remodeling, LAP, or napkin-ring sign) was associated with higher rates of coronary heart disease related death or MI at 5 years in 1,769 patients with stable chest pain (4.1% vs 1.4%; unadjusted HR: 3.01 [95% CI: 1.61-5.63]) (84). Quantification of the LAP burden provided an even more powerful prediction for MI than the more simplistic identification of individual lesions (80). Among these 2 trials, only the PROMISE trial demonstrated a significant association between high-risk plaque and adverse events in patients without a significant stenosis. However, in a long-term study with a median follow-up of 98 months (n = 245), positive remodeling, LAP, plaque burden of more than 0.7, or the napkin ring sign were significantly associated with higher rates of cardiac death or ACS even in absence of a diameter stenosis >50% (85). In the 3V FFR-FRIENDS (Clinical Implication of 3-vessel Fractional Flow Reserve) study, CTA and FFR in all vessels were performed in 299 patients (772 vessels) with 3VD (>30% stenosis), and the number of high-risk plaque characteristics was associated with adverse cardiac outcomes in deferred lesions (FFR >0.80) (86).

Conversely, the ICONIC (Incident Coronary Syndromes Identified by Computed Tomography) study demonstrated that 31% of culprit lesions in ACS had high-risk plaque characteristics, and 52% of non-ACS patients with high-risk plaque features experienced an ACS during 3.4 years of follow-up (87). In terms of primary prevention, high-risk plaques are associated with adverse cardiac events; however, not all high-risk plaques cause ACS. Nevertheless, it can be inferred that patients with high-risk plaques should receive intensive medical treatment to prevent plaque progression and rupture.

COMBINATION OF ANATOMY AND PLAQUE CHARACTERIZATION. The segment involvement

FIGURE 7 Features of Vulnerable Plaques



(A) Low-attenuation plaque (LAP) (plaque with <30 HU) confirmed by the color coding of the plaque analysis software (**red color** shows the LAP component). **(B)** Positive remodeling. In this case, positive remodeling index is 2.2 (27.5 mm^2 [lesion plaque area]/12 mm^2 [reference lumen area]). **(C)** Napkin-ring sign is represented by a hypodense core surrounded by fibrotic tissue, which appears as a hyperdense ring around the core (see **arrowheads**). **(D)** Spotty calcifications are represented by small calcified nodules with length <3 mm. **White arrows** indicate the lesions with vulnerable plaques.

FIGURE 8 CT Leaman Score and Leiden CTA Risk Score

A

CT Leaman Score

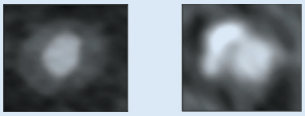
Localization of the Coronary Plaques			
Coronary Segments	Right Dominance	Left Dominance	Balanced
RCA			
RCA proximal	1	0	0.5
RCA mid	1	0	0.5
RCA distal	1	0	0.5
PDA	1	NA	0.5
PL branch	0.5	NA	NA
Left main	5	6	5.5
LAD			
LAD proximal	3.5	3.5	3.5
LAD mid	2.5	2.5	2.5
LAD distal	1	1	1
1st diagonal	1	1	1
2nd diagonal	0.5	0.5	0.5
LCX			
LCX proximal	1.5	2.5	2
Intermediate branch	1	1	1
1st obtuse marginal	1	1	1
2nd obtuse marginal	1	1	1
LCX distal	0.5	1.5	1
PL branch	NA	0.5	0.5
PDA	NA	1	NA

×

Type of Plaque

- Noncalcified and mixed plaques: 1.5
- Calcified plaques: 1

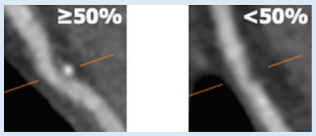
Noncalcified Calcified



×

Degree of Stenosis

- Obstructive (≥50% stenosis): 1
- Nonobstructive (<50% stenosis): 0.615



The CT-Leaman score **(A)** and Leiden CTA risk score **(B)** are calculated by weighting for localization × type of plaque × stenosis severity. LCX = left circumflex; PL = postero-lateral.

Continued on the next page

score, which is the total number of segments with plaque, and the segment stenosis score obtained by grading the stenosis severity of each segment with plaque were developed in 2007, and they are both significantly associated with 2-year all-cause mortality (segment involvement score: adjusted HR: 1.16 [95% CI: 1.05-1.28]; $P = 0.004$, and segment stenosis score: adjusted HR: 1.52 [95% CI: 1.09-2.14]; $P = 0.01$) (88).

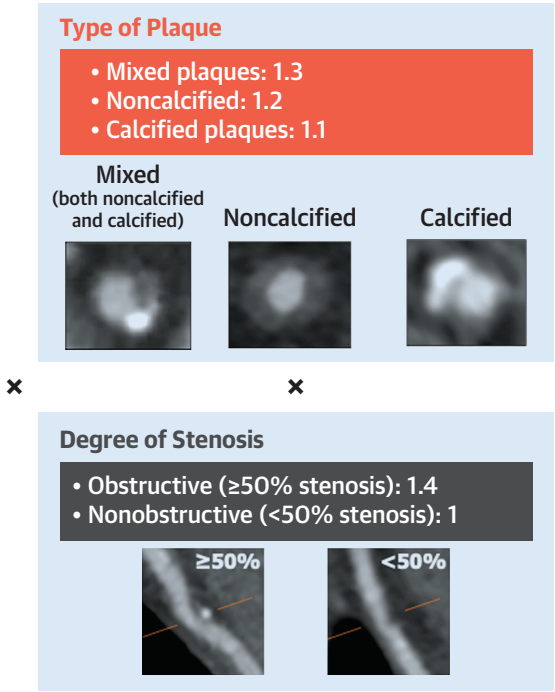
Type of plaque and its location has also been included in CTA-derived scoring systems. The Leaman score takes into account the proximal or distal location of plaque in the coronary circulation (89). The CT-Leaman score integrated the type of plaque (calcified plaque or noncalcified plaque) and the degree of stenosis (>50% or <50%) with location of the coronary plaque, to reflect the coronary atherosclerotic burden (**Figure 8A**) (90,91). The key observation from a single-center prospective registry including 1,304 consecutive patients undergoing CTA for suspected CAD was that patients with a CT-Leaman score >5 without obstructive stenoses had similar hard cardiac event (cardiac death or ACS)-free survival compared with those patients with obstructive stenoses (78.6% vs 77.6%) (91). In the CONFIRM registry, the 5-year prognostic value of the CT-Leaman score was significant in patients without obstructive stenoses (92). The Leiden CTA risk score is similar to the CT-Leaman score (**Figure 8B**). In this score, the location of coronary plaque, the type of plaque (calcified plaque, noncalcified plaque, or mixed) and the degree

FIGURE 8 Continued

B

Leiden CTA Risk Score

Localization of the Coronary Plaques		
Coronary Segments	Right Dominance	Left Dominance
RCA		
RCA proximal	1	0
RCA mid	1	0
RCA distal	1	0
PDA	1	0
PL branch	0.5	0
Left main	5	6
LAD		
LAD proximal	3.5	3.5
LAD mid	2.5	2.5
LAD distal	1	1
1st diagonal	1	1
2nd diagonal	0.5	0.5
LCX		
LCX proximal	1.5	2.5
Intermediate branch	1	1
obtuse marginal	1	1
LCX distal	1	1.5
PL branch	0.5	0.5
PDA	0	1



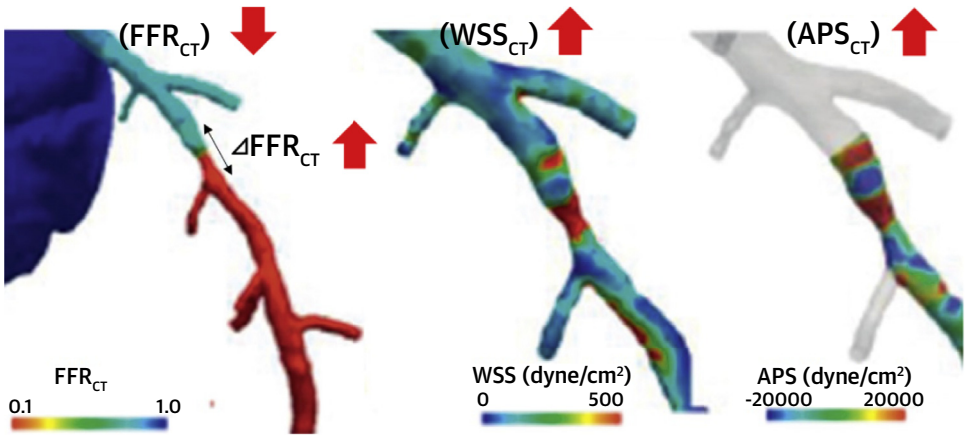
of stenosis (>50% or <50%) have been integrated (93). Higher Leiden CTA risk score was associated with 5-year all-cause mortality or MI in the derivation cohort (Leiden University Medical Center) (2.6% in score 0-5, 10.7% in score 6-20, and 19.2% in score >20; log-rank $P < 0.001$) and the external validation cohort (the CONFIRM registry) (6.2% in score 0-5, 16.9% in score 6-20, and 25.7% in score >20; log-rank $P < 0.001$).

CTA AND PLAQUE ANALYSIS IN SUSPECTED ACS PATIENTS

Recently, the utility of CTA and additional assessments have been investigated in patients with NSTEACS. A subanalysis of the VERDICT trial (Very EaRly vs Deferred Invasive evaluation using Computerized Tomography) demonstrated that CTA had a high diagnostic accuracy, with a sensitivity of 97% to rule out clinically significant CAD in patients with NSTEACS (15). Consistent with this performance, CTA was equivalent to ICA for the prediction of 4-year clinical outcomes, even though CTA assessment was only confined to stenosis severity, without consideration of high-risk plaque characteristics or coronary flow (94).

In the 2020 ESC NSTEACS guidelines, "CTA is recommended as an alternative to ICA to exclude ACS when there is a low-to-intermediate likelihood of CAD, and when cardiac troponin and/or ECG are normal or inconclusive (Class I/Level of Evidence: A)" (7). For NSTEMI patients, an early invasive strategy within 24 hours is recommended (Class I; Level of Evidence: A). Of note, the impact of CTA before ICA on clinical outcomes in NSTEMI patients was evaluated in the CARMENTA (the role of initial CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography in non-ST-elevation myocardial infarction patients) trial (**Table 2**) (95), wherein compared with routine care, a

FIGURE 9 Adverse Hemodynamic Characteristics



The internal stress in the plaque should be balanced with the total external stress acting on the plaque (ie, traction). Axial plaque stress represents the axial component of the traction vector. The large pressure gradient over the lesion induces force imbalance locally and elevates delta fractional flow reserve, wall shear stress (WSS), and axial plaque stress (APS), which can be potentially associated with the risk of plaque rupture. Thus, low FFR$_{CT}$ (≤0.80), high delta FFR$_{CT}$ (change in fractional flow reserve by computed tomography [FFR$_{CT}$] across the lesion, ≥0.06), high WSS (≥154.7 dyne/cm^2), and high APS (≥1,606.6 dyne/cm^2) are introduced as adverse hemodynamic characteristics. Reproduced with permission from Nicol et al. (98).

CTA-first strategy significantly reduced ICA rates by 34% ($P < 0.001$), without increasing the rate of the safety endpoint of major adverse cardiac events or procedure-related complications at 1 year (16% in CTA-first strategy vs 23% in routine clinical care; $P = 0.288$). In this trial, median times to revascularization were 52 house (interquartile range: 40-145 hours) and 72 hours (interquartile range: 28-141 hours) ($P = 0.977$) in the routine clinical care and CTA-first strategy, respectively, which were longer than the recommended 24-hour time window. Considering the ESC guidelines, the CARMENTA trial suggested that in NSTEMI patients, there was a benefit to having a CTA before ICA, especially if the CTA could be done within 24 hours.

Plaque analysis has been performed in suspected ACS patients. The presence of high-risk plaque on CTA, defined as positive remodeling (remodeling index >1.1), the presence of LAP, the napkin ring sign, or spotty calcium, increased the likelihood of ACS in patients presenting to the emergency department with acute chest pain and a normal initial ECG and troponin (96). Therefore, plaque analysis could support the diagnosis in the acute setting.

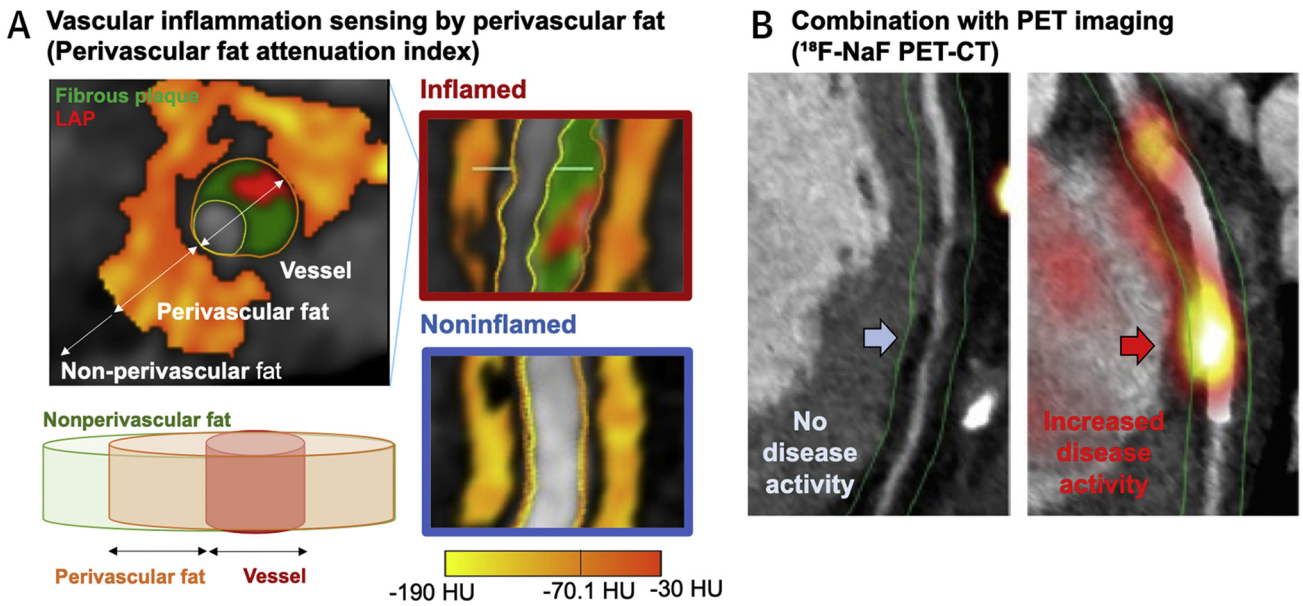
HEMODYNAMIC ASSESSMENT

Recently, in the EMERALD (Exploring the Mechanism of Plaque Rupture in Acute Coronary Syndrome Using Coronary CT Angiography and Computational Fluid Dynamic) trial, noninvasive hemodynamic assessment was used to improve the identification of high-risk plaques that resulted in ACS (**Figure 9**) (97,98). Classical adverse plaque characteristics defined as positive remodeling, LAP, spotty calcification, and the napkin-ring sign, in combination with hemodynamic characteristics defined as low FFR$_{CT}$, high delta FFR$_{CT}$ (change in FFR$_{CT}$ across the lesion), high wall shear stress, and high axial plaque stress, showed a significantly higher risk for subsequent ACS than plaques without classical adverse plaque characteristics/hemodynamic characteristics (HR: 11.75 [95% CI: 2.85-48.51]; $P = 0.001$) or with either adverse plaque characteristics or hemodynamic characteristics alone (HR: 3.22 [95% CI: 1.86-5.55]; $P < 0.001$). Although this was a retrospective study, the prospective ongoing EMERALD II study (NCT03591328) will validate the incremental value for risk prediction of hemodynamic parameters over plaque characteristics.

INFLAMED PLAQUE AND CALCIFICATION ACTIVITY

Inflammation is a key factor for the development and progression of atherosclerotic plaques (99). Vascular inflammation changes the structure of perivascular adipose tissue, triggering lipolysis and inhibiting adipogenesis. This causes a gradient of adipocyte size in the first few millimeters around

FIGURE 10 Inflamed Plaque and Disease Activity



(A) Coronary plaque inflammation can be detected by perivascular fat attenuation index. Inflammation was detected in a lesion with low-attenuation plaque (LAP). **(B)** Calcification activity can be detected by ^{18}F-NaF positron emission tomography (PET)-computed tomography (CT). Reproduced with permission from Kwiecinski et al. (113).

the inflamed coronary arterial wall and changes CT attenuation in these regions (100,101). In that way coronary inflammation can be detected indirectly and noninvasively by assessing the perivascular fat CT attenuation index (**Figure 10A**). When the perivascular fat has an attenuation above −70.1 HU the perivascular fat is considered inflamed, whereas noninflamed perivascular fat has an attenuation below −70.1 HU (100). In the CRISP-CT (Cardiovascular Risk Prediction using Computed Tomography) study, the impact of inflamed pericoronary fat on cardiac mortality was substantial (102). In patients without inflamed pericoronary fat, high-risk plaques were not associated with cardiac mortality, whereas inflamed pericoronary fat significantly affected cardiac mortality, even in patients without high-risk plaques (103). Inflammation in perivascular fat may identify the "vulnerable" patient before the development of "vulnerable plaques." In terms of prevention of cardiac events, inflammation could be a target (104). In patients with psoriasis, biologic therapy (antitumor necrosis factor-α, anti-interleukin 17, or anti-IL-12/23 therapy) significantly reduced C-reactive protein from 2.2 mg/L (95% CI: 0.8-5.5 mg/L) to 1.3 mg/L (95% CI: 0.7-3.7 mg/L) ($P = 0.03$) and perivascular fat attenuation index from −71.22 HU (95% CI: −75.85 to −68.11 HU) to −76.09 HU (95% CI: −80.08 to −70.37 HU) ($P < 0.001$) after 1 year of treatment (105). Perivascular fat attenuation index might be useful to monitor cardiac risk, with the important advantage that this index does not require additional tests other than CTA.

On the other hand, a post hoc analysis of 199 patients demonstrated that perivascular fat attenuation indexes were similar between patients with elevated (>3 mg/L) high-sensitive C-reactive protein (hs-CRP) and normal (≤3 mg/L) hs-CRP (−69.8 ± 10.3 vs −70.0 ± 12.0; $P = 0.953$), although LAP and the napkin-ring sign were more commonly observed in patients with elevated hs-CRP (14.1% vs 2.6%; $P = 0.001$, and 35.9% vs 19.4%; $P = 0.007$, respectively) (106). In another post hoc analysis including 540 patients, there was no significant association between hs-CRP and perivascular fat attenuation index ≥70.1 HU (OR: 1.066 [95% CI: 0.962-1.182]; $P = 0.223$) (107). Although hs-CRP is an independent predictor for cardiovascular events, there was no good correlation between perivascular fat CT attenuation index and hs-CRP (108). Prospective, large, multicenter cohorts with long-term follow-up are warranted to confirm the utility of perivascular fat CT attenuation index for risk stratification.

In principle, vascular inflammation can also be assessed in combination with CT using the PET tracer ^{18}F-fluorodeoxyglucose (109). However, its application to the coronary arteries is limited caused by significant myocardial uptake (110). Alternatively, ^{18}F-sodium fluoride (NaF) detects active microcalcification, enabling the detection of culprit lesions in patients presenting with an acute MI, and plaques with adverse characteristics as defined with IVUS or OCT (**Figure 10B**) (110,111). More generally, coronary ^{18}F-NaF provides an assessment of disease activity in the coronary arteries, predicting disease progression as well as powerful prediction of MI in recent studies of patients with advanced coronary atherosclerosis (112,113). To confirm the predictive value of ^{18}F-NaF PET-CT, the prospective PREFFIR (Prediction of Recurrent Events With 18F-Fluoride; NCT02278211) study is ongoing in 700 patients with a recent MI and proven multivessel CAD.

THE PYRAMID OF CAD AND THE DIAGNOSTIC ROLE OF CTA

A heart team discussion considering individual cardiac and extracardiac characteristics is recommended to decide the treatment of patients with complex CAD (27), and numerous tools have been developed to support this decision making, such as the SYNTAX score II 2020 (73,114,115). Coronary anatomy is essential in this process, and ICA has conventionally documented coronary anatomy and facilitated calculation of the SYNTAX score. Additional noninvasive or invasive physiological assessments are also required to document the hemodynamic impact of the stenoses. Coronary anatomy and physiology can be evaluated using only CTA; consequently, ICA could be skipped for patients who need surgery. If the ongoing FASTTRACK CABG trial demonstrates the feasibility of planning and executing CABG solely diagnosed and guided by CTA and FFR_{CT}, then the interventional cardiologist should have no reluctance in intervening on patients whose coronary anatomy is known in advance, together with the stenotic lesion's functionality and plaque composition, even before entering the "catheterization laboratory", now upgraded into "an interventional suite" (116).

Patients with cardiac symptoms but without any significant stenoses in their coronary arteries—the nonobstructive coronary artery syndrome—are challenging to manage and are major "troublemakers," and should receive intensive primary prevention. Notably, analysis of plaque morphology, inflammation, and calcification activity may allow us to monitor disease activity, regression, or progression.

CONCLUSIONS

Noninvasive coronary imaging by CTA has become a cost-effective first line technique in the diagnosis of patients with chest pain. In the ongoing DISCHARGE (Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease; NCT02400229) trial, 3,546 patients with a low-to-intermediate pre-test probability (10%-60%) of suspected CAD and a clinical indication for ICA because of stable chest pain will be randomized to either CTA or ICA, with subsequent management based on the findings, and decided by local heart teams in line with European society guidelines (117). Although the primary outcome is major adverse cardiovascular events, the study will also evaluate the cost-effectiveness of CTA. The functional assessment of physiological epicardial conductance and myocardial resistance by means of FFR_{CT} could further boost the diagnostic capacity of this technique. Decision making between pharmacological treatment, PCI, and CABG based solely on noninvasive imaging will become a reality. Nonobstructive CAD can be diagnosed by noninvasive CT imaging and become a vital target for prevention based on lifestyle modification with/without aggressive pharmacological treatment.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Serruys has received personal fees from Biosensors, Micel Technologies, Sinomedical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside of the submitted work. Dr Hara has received a grant for studying overseas from Japanese Circulation Society, a grant-in-Aid for JSPS Fellows, and a grant from Fukuda Foundation for Medical Technology. Dr Nørgaard has received unrestricted research support from HeartFlow Inc. Dr Knuuti has received consultancy fees from GE Healthcare and AstraZeneca; and has received speaker fees from GE Healthcare, Bayer, Lundbeck, Boehringer Ingelheim, and Merck, outside of the submitted work. Dr Nieman has received unrestricted institutional research support from Siemens Healthineers, Bayer, and HeartFlow Inc; and has served as a consultant for Siemens Medical Solutions USA. Dr Leipsic has served as a consultant to and holds stock options in HeartFlow and Circle CVI; and has served on the Speakers Bureau of GE Healthcare and Philips. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Patrick W. Serruys, Interventional Medicine and Innovation, National University of Ireland, Galway (NUIG), University Road, Galway H91 TK33, Ireland. E-mail: patrick.w.j.c.serruys@gmail.com. Twitter: @hara_hironori.

REFERENCES

1. Serruys PW, Chichareon P, Modolo R, et al. The SYNTAX score on its way out or … towards artificial intelligence: part II. *EuroIntervention*. 2020;16(1):60–75.

2. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362(10):886–895.

3. Becker CR. Cardiac CT: a one-stop-shop procedure? *Eur Radiol*. 2006;16(Suppl 7):M65–M70.

4. Moss AJ, Williams MC, Newby DE, Nicol ED. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease. *Curr Cardiovasc Imaging Rep*. 2017;10(5):15.

5. Sonck J, Miyazaki Y, Collet C, et al. Feasibility of planning coronary artery bypass grafting based only on coronary computed tomography angiography and CT-derived fractional flow reserve: a pilot survey of the surgeons involved in the randomized SYNTAX III Revolution trial. *Interact Cardiovasc Thorac Surg*. Published online March 28, 2019. https://doi.org/10.1093/icvts/ivz046

6. Kawashima H, Pompilio G, Andreini D, et al. Safety and feasibility evaluation of planning and execution of surgical revascularisation solely based on coronary CTA and FFR(CT) in patients with complex coronary artery disease: study protocol of the FASTTRACK CABG study. *BMJ Open*. 2020;10(12), e038152.

7. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289–1367.

8. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52(21):1724–1732.

9. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52(25):2135–2144.

10. Marano R, De Cobelli F, Floriani I, et al. Italian multicenter, prospective study to evaluate the negative predictive value of 16- and 64-slice MDCT imaging in patients scheduled for coronary angiography (NIMISCAD-Non Invasive Multicenter Italian Study for Coronary Artery Disease). *Eur Radiol*. 2009;19(5):1114–1123.

11. Arbab-Zadeh A, Miller JM, Rochitte CE, et al. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. *J Am Coll Cardiol*. 2012;59(4):379–387.

12. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging*. 2015;8(3):e002179.

13. Budoff MJ, Kalia N, Cole J, Nakanishi R, Nezarat N, Thomas JL. Diagnostic accuracy of Visipaque enhanced coronary computed tomographic angiography: a prospective multicenter trial. *Coron Artery Dis*. 2017;28(1):52–56.

14. Budoff MJ, Li D, Kazerooni EA, Thomas GS, Mieres JH, Shaw LJ. Diagnostic Accuracy of Noninvasive 64-row Computed Tomographic Coronary Angiography (CCTA) Compared with Myocardial Perfusion Imaging (MPI): The PICTURE Study, A Prospective Multicenter Trial. *Acad Radiol*. 2017;24(1):22–29.

15. Linde JJ, Kelbæk H, Hansen TF, et al. Coronary CT angiography in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:453–463.

16. Mancini GBJ, Leipsic J, Budoff MJ, et al. Coronary CT angiography followed by invasive angiography in patients with moderate or severe ischemia-insights from the ISCHEMIA Trial. *J Am Coll Cardiol Img*. 2021;14(7):1384–1393.

17. Andreini D, Pontone G, Mushtaq S, et al. Atrial fibrillation: diagnostic accuracy of coronary CT angiography performed with a whole-heart 230-μm spatial resolution CT scanner. *Radiology*. 2017;284(3):676–684.

18. Andreini D, Mushtaq S, Pontone G, et al. Diagnostic performance of coronary CT angiography carried out with a novel whole-heart coverage high-definition CT scanner in patients with high heart rate. *Int J Cardiol*. 2018;257:325–331.

19. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018;39(35):3322–3330.

20. Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ*. 2016;355:i5441.

21. Chang HJ, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. *J Am Coll Cardiol Img*. 2019;12(7 Pt 2):1303–1312.

22. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol*. 2011;58(8):849–860.

23. Nielsen LH, Bøtker HE, Sørensen HT, et al. Prognostic assessment of stable coronary artery disease as determined by coronary computed tomography angiography: a Danish multicentre cohort study. *Eur Heart J*. 2017;38(6):413–421.

24. Newby DE, Adamson PD, Berry C, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379(10):924–933.

25. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol*. 2018;3(2):144–152.

26. Mortensen MB, Dzaye O, Steffensen FH, et al. Impact of Plaque Burden Versus Stenosis on Ischemic Events in Patients With Coronary Atherosclerosis. *J Am Coll Cardiol*. 2020;76:2803–2813.

27. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165.

28. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015;36(45):3182–3188.

29. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376(19):1824–1834.

30. Gotberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376(19):1813–1823.

31. Parikh RV, Liu G, Plomondon ME, et al. Utilization and outcomes of measuring fractional flow reserve in patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2020;75(4):409–419.

32. Adjedj J, Guillon B. FFR-guided revascularization in stable "intermediate" lesions: room for improvement and good reasons to do so. *J Am Coll Cardiol*. 2020;75(4):420–421.

33. Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. *J Am Coll Cardiol Intv*. 2020;13(14):1617–1638.

34. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol*. 2013;61(22):2233–2241.

35. Celeng C, Leiner T, Maurovich-Horvat P, et al. Anatomical and functional computed tomography for diagnosing hemodynamically significant coronary artery disease: a meta-analysis. *J Am Coll Cardiol Img*. 2019;12(7 Pt 2):1316–1325.

36. Collet C, Miyazaki Y, Ryan N, et al. Fractional flow reserve derived from computed tomographic angiography in patients with multivessel CAD. *J Am Coll Cardiol*. 2018;71(24):2756–2769.

37. Zhuang B, Wang S, Zhao S, Lu M. Computed tomography angiography-derived fractional flow reserve (CT-FFR) for the detection of myocardial ischemia with invasive fractional flow reserve as reference: systematic review and meta-analysis. *Eur Radiol*. 2020;30(2):712–725.

38. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73(2):161–173.

39. Douglas PS, De Bruyne B, Pontone G, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM study. *J Am Coll Cardiol*. 2016;68(5):435–445.

40. Nørgaard BL, Terkelsen CJ, Mathiassen ON, et al. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2018;72(18):2123–2134.

41. Patel MR, Nørgaard BL, Fairbairn TA, et al. 1-year impact on medical practice and clinical outcomes of FFR(CT): The ADVANCE Registry. *J Am Coll Cardiol Img*. 2020;13(1 Pt 1):97–105.

42. Ihdayhid AR, Norgaard BL, Gaur S, et al. Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary CT angiography. *Radiology*. 2019;29(2):343–351.

43. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31–40.

44. Al-Lamee R, Howard JP, Shun-Shin MJ, et al. Fractional flow reserve and instantaneous wave-free ratio as predictors of the placebo-controlled response to percutaneous coronary intervention in stable single-vessel coronary artery disease. *Circulation*. 2018;138(17):1780–1792.

45. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382(15):1395–1407.

46. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med*. 2020;382(15):1408–1419.

47. Shaw LJ, Nicol E. Lesion-specific ischemia with noninvasive computed tomographic angiography: superior to conventional stress testing? *JAMA Cardiol*. 2017;2(7):717–719.

48. National Institute for Health and Care Excellence (NICE). HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. *Medical Technologies Guidance 32*. 2021. Accessed July 1, 2021. https://www.nice.org.uk/guidance/mtg32.

49. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372(14):1291–1300.

50. Lu MT, Ferencik M, Roberts RS, et al. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE Trial. *J Am Coll Cardiol Img*. 2017;10(11):1350–1358.

51. National Institute for Health and Care Excellence (NICE). *Chest pain of recent onset: assessment and diagnosis*. 2016. Accessed July 1, 2021. https://www.nice.org.uk/guidance/cg95.

52. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407–477.

53. National Institute for Health and Care Excellence (NICE). HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. *Medical Technologies Guidance 32*. 2017. Accessed July 1, 2021. https://www.nice.org.uk/guidance/mtg32.

54. Hecht HS, Shaw L, Chandrashekhar YS, Bax JJ, Narula J. Should NICE guidelines be universally accepted for the evaluation of stable coronary disease? A debate. *Eur Heart J*. 2019;40(18):1440–1453.

55. Rossi A, Merkus D, Klotz E, Mollet N, de Feyter PJ, Krestin GP. Stress myocardial perfusion: imaging with multidetector CT. *Radiology*. 2014;270(1):25–46.

56. Danad I, Szymonifka J, Schulman-Marcus J, Min JK. Static and dynamic assessment of myocardial perfusion by computed tomography. *Eur Heart J Cardiovasc Imaging*. 2016;17(8):836–844.

57. Conte E, Sonck J, Mushtaq S, et al. FFR(CT) and CT perfusion: a review on the evaluation of functional impact of coronary artery stenosis by cardiac CT. *Int J Cardiol*. 2020;300:289–296.

58. Kühl JT, George RT, Mehra VC, et al. Endocardial-epicardial distribution of myocardial perfusion reserve assessed by multidetector computed tomography in symptomatic patients without significant coronary artery disease: insights from the CORE320 multicentre study. *Eur Heart J Cardiovasc Imaging*. 2016;17(7):779–787.

59. Echavarría-Pinto M, Collet C, Escaned J, Piek JJ, Serruys PW. State of the art: pressure wire and coronary functional assessment. *EuroIntervention*. 2017;13:666–679.

60. Lubbers M, Coenen A, Kofflard M, et al. Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease: the multicenter, randomized CRESCENT-II Trial. *J Am Coll Cardiol Img*. 2018;11(11):1625–1636.

61. Sørgaard MH, Linde JJ, Kühl JT, et al. Value of myocardial perfusion assessment with coronary computed tomography angiography in patients with recent acute-onset chest pain. *J Am Coll Cardiol Img*. 2018;11(11):1611–1621.

62. Yang DH, Kim YH, Roh JH, et al. Diagnostic performance of on-site CT-derived fractional flow reserve versus CT perfusion. *Eur Heart J Cardiovasc Imaging*. 2017;18(4):432–440.

63. Coenen A, Rossi A, Lubbers MM, et al. Integrating CT myocardial perfusion and CT-FFR in the work-up of coronary artery disease. *J Am Coll Cardiol Img*. 2017;10(7):760–770.

64. Pontone G, Baggiano A, Andreini D, et al. Stress computed tomography perfusion versus fractional flow reserve CT derived in suspected coronary artery disease: the PERFECTION Study. *J Am Coll Cardiol Img*. 2019;12(8 Pt 1):1487–1497.

65. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2019;20(11):1198–1207.

66. Bing R, Singh T, Dweck MR, et al. Validation of European Society of Cardiology pre-test probabilities for obstructive coronary artery disease in suspected stable angina. *Eur Heart J Qual Care Clin Outcomes*. 2020;6(4):293–300.

67. Winther S, Schmidt SE, Rasmussen LD, et al. Validation of the European Society of Cardiology pre-test probability model for obstructive coronary artery disease. *Eur Heart J*. 2020;42(14):1401–1411.

68. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol*. 2020;76(21):2421–2432.

69. Stocker TJ, Deseive S, Leipsic J, et al. for the PROTECTION VI Investigators. Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the PROspective multicenter registry on radiaTion dose Estimates of cardiac CT angIOgraphy iN daily practice in 2017 (PROTECTION VI). *Eur Heart J*. 2018;39(41):3715–3723.

70. Williams MC, Stewart C, Weir NW, Newby DE. Using radiation safely in cardiology: what imagers need to know. *Heart*. 2019;105(10):798–806.

71. Pontone G, Baggiano A, Andreini D, et al. Dynamic stress computed tomography perfusion with a whole-heart coverage scanner in addition to coronary computed tomography angiography and fractional flow reserve computed tomography derived. *J Am Coll Cardiol Img*. 2019;12(12):2460–2471.

72. Andreini D, Mushtaq S, Pontone G, et al. CT perfusion versus coronary CT angiography in patients with suspected in-stent restenosis or CAD progression. *J Am Coll Cardiol Img*. 2020;13(3):732–742.

73. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381(9867):639–650.

74. Andreini D, Modolo R, Katagiri Y, et al. Impact of fractional flow reserve derived from coronary computed tomography angiography on heart team treatment decision-making in patients with multivessel coronary artery disease: insights from the SYNTAX III REVOLUTION Trial. *Circ Cardiovasc Interv*. 2019;12(12):e007607.

75. Conte E, Mushtaq S, Pontone G, et al. Plaque quantification by coronary computed tomography angiography using intravascular ultrasound as a reference standard: a comparison between standard and last generation computed tomography scanners. *Eur Heart J Cardiovasc Imaging*. 2020;21(2):191–201.

76. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM Study. *J Am Coll Cardiol Img*. 2018;11(10):1475–1484.

77. Bax AM, van Rosendael AR, Ma X, et al. Comparative differences in the atherosclerotic disease burden between the epicardial coronary arteries: quantitative plaque analysis on coronary computed tomography angiography. *Eur Heart J Cardiovasc Imaging*. 2021;22(3):322–330.

78. Lee SE, Sung JM, Andreini D, et al. Differences in progression to obstructive lesions per high-risk plaque features and plaque volumes with CCTA. *J Am Coll Cardiol Img*. 2020;13(6):1409–1417.

79. Andreini D, Magnoni M, Conte E, et al. Coronary plaque features on CTA can identify patients at increased risk of cardiovascular events. *J Am Coll Cardiol Img*. 2020;13(8):1704–1717.

80. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). *Circulation*. 2020;141(18):1452–1462.

81. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41(40):3925–3932.

82. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54(1):49–57.

83. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66(4):337–346.

84. Williams MC, Moss AJ, Dweck M, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART Study. *J Am Coll Cardiol*. 2019;73(3):291–301.

85. Conte E, Annoni A, Pontone G, et al. Evaluation of coronary plaque characteristics with coronary computed tomography angiography in patients with non-obstructive coronary artery disease: a long-term follow-up study. *Eur Heart J Cardiovasc Imaging*. 2017;18(10):1170–1178.

86. Lee JM, Choi KH, Koo BK, et al. Prognostic implications of plaque characteristics and stenosis severity in patients with coronary artery disease. *J Am Coll Cardiol*. 2019;73(19):2413–2424.

87. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71(22):2511–2522.

88. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50(12):1161–1170.

89. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation*. 1981;63(2):285–299.

90. de Araújo Gonçalves P, Garcia-Garcia HM, Dores H, et al. Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden. *Int J Cardiovasc Imaging*. 2013;29(7):1575–1584.

91. Mushtaq S, De Araujo Gonçalves P, Garcia-Garcia HM, et al. Long-term prognostic effect of coronary atherosclerotic burden: validation of the computed tomography-Leaman score. *Circ Cardiovasc Imaging*. 2015;8(2):e002332.

92. Andreini D, Pontone G, Mushtaq S, et al. Long-term prognostic impact of CT-Leaman score in patients with non-obstructive CAD: Results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study. *Int J Cardiol*. 2017;231:18–25.

93. van Rosendael AR, Shaw LJ, Xie JX, et al. Superior risk stratification with coronary computed tomography angiography using a comprehensive atherosclerotic risk score. *J Am Coll Cardiol Img*. 2019;12(10):1987–1997.

94. Kofoed KF, Engstrom T, Sigvardsen PE, et al. Prognostic value of coronary CT angiography in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2021;77(8):1044–1052.

95. Smulders MW, Kietselaer B, Wildberger JE, et al. Initial imaging-guided strategy versus routine care in patients with non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2019;74(20):2466–2477.

96. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol*. 2014;64(7):684–692.

97. Lee JM, Choi G, Koo BK, et al. Identification of high-risk plaques destined to cause acute coronary syndrome using coronary computed tomographic angiography and computational fluid dynamics. *J Am Coll Cardiol Img*. 2019;12(6):1032–1043.

98. Nicol ED, Norgaard BL, Blanke P, et al. The future of cardiovascular computed tomography: advanced analytics and clinical insights. *J Am Coll Cardiol Img*. 2019;12(6):1058–1072.

99. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105(9):1135–1143.

100. Antonopoulos AS, Sanna F, Sabharwal N, et al. Detecting human coronary inflammation by imaging perivascular fat. *Sci Transl Med*. 2017;9(398):eaal2658.

101. Antoniades C, Antonopoulos AS, Deanfield J. Imaging residual inflammatory cardiovascular risk. *Eur Heart J*. 2020;41(6):748–758.

102. Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet*. 2018;392(10151):929–939.

103. Oikonomou EK, Desai MY, Marwan M, et al. Perivascular fat attenuation index stratifies cardiac risk associated with high-risk plaques in the CRISP-CT Study. *J Am Coll Cardiol*. 2020;76(6):755–757.

104. Ridker PM. Clinician's guide to reducing inflammation to reduce atherothrombotic risk: JACC review topic of the week. *J Am Coll Cardiol*. 2018;72(25):3320–3331.

105. Elnabawi YA, Oikonomou EK, Dey AK, et al. Association of biologic therapy with coronary inflammation in patients with psoriasis as assessed by perivascular fat attenuation index. *JAMA Cardiol*. 2019;4(9):885–891.

106. Dai X, Deng J, Yu M, Lu Z, Shen C, Zhang J. Perivascular fat attenuation index and high-risk plaque features evaluated by coronary CT angiography: relationship with serum inflammatory marker level. *Int J Cardiovasc Imaging*. 2020;36(4):723–730.

107. Sugiyama T, Kanaji Y, Hoshino M, et al. Determinants of Pericoronary Adipose Tissue Attenuation on Computed Tomography Angiography in Coronary Artery Disease. *J Am Heart Assoc*. 2020;9(15):e016202.

108. Ridker PM, MacFadyen JG, Glynn RJ, Bradwin G, Hasan AA, Rifai N. Comparison of interleukin-6, C-reactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: secondary analyses from the Cardiovascular Inflammation Reduction Trial. *Eur Heart J*. 2020;41(31):2952–2961.

109. Tarkin JM, Joshi FR, Rudd JH. PET imaging of inflammation in atherosclerosis. *Nat Rev Cardiol*. 2014;11(8):443–457.

110. Joshi NV, Vesey AT, Williams MC, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet*. 2014;383(9918):705–713.

111. Lee JM, Bang JI, Koo BK, et al. Clinical relevance of (18)F-sodium fluoride positron-emission tomography in noninvasive identification of high-risk plaque in patients with coronary artery disease. *Circ Cardiovasc Imaging*. 2017;10(11):e006704.

112. Doris MK, Meah MN, Moss AJ, et al. Coronary (18)F-fluoride uptake and progression of coronary artery calcification. *Circ Cardiovasc Imaging*. 2020;13(12), e011438.

113. Kwiecinski J, Tzolos E, Adamson PD, et al. Coronary (18)F-sodium fluoride uptake predicts outcomes in patients with coronary artery disease. *J Am Coll Cardiol*. 2020;75(24):3061–3074.

114. Takahashi K, Serruys PW, Fuster V, et al. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation. *Lancet*. 2020;396(10260):1399–1412.

115. Qintar M, Humphries KH, Park JE, et al. Individualizing revascularization strategy for diabetic patients with multivessel coronary disease. *J Am Coll Cardiol*. 2019;74(16):2074–2084.

116. Collet C, Sonck J, Leipsic J, et al. Implementing coronary computed tomography angiography in the catheterization laboratory. *J Am Coll Cardiol Img*. Published online November 19, 2020. https://doi.org/10.1016/j.jcmg.2020.07.048

117. Napp AE, Haase R, Laule M, et al. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. *Eur Radiol*. 2017;27(7):2957–2968.

118. Magalhães TA, Kishi S, George RT, et al. Combined coronary angiography and myocardial perfusion by computed tomography in the identification of flow-limiting stenosis - The CORE320 study: an integrated analysis of CT coronary angiography and myocardial perfusion. *J Cardiovasc Comput Tomogr*. 2015;9(5):438–445.

119. Min JK, Koduru S, Dunning AM, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. *J Cardiovasc Comput Tomogr*. 2012;6(4):274–283.

120. SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385(9985):2383–2391.

121. McKavanagh P, Lusk L, Ball PA, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. *Eur Heart J. Cardiovasc Imaging*. 2015;16(4):441–448.

122. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J*. 2016;37(15):1232–1243.

123. Karthikeyan G, Guzic Salobir B, Jug B, et al. Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: an international, multicenter, randomized controlled trial (IAEA-SPECT/CTA study). *J Nucl Cardiol*. 2017;24(2):507–517.

124. Rudziński PN, Kruk M, Kępka C, et al. The value of coronary artery computed tomography as the first-line anatomical test for stable patients with indications for invasive angiography due to suspected coronary artery disease: CAT-CAD randomized trial. *J Cardiovasc Comput Tomogr*. 2018;12(6):472–479.

125. Lee SP, Seo JK, Hwang IC, et al. Coronary computed tomography angiography vs. myocardial single photon emission computed tomography in patients with intermediate risk chest pain: a randomized clinical trial for cost-effectiveness comparison based on real-world cost. *Eur Heart J Cardiovasc Imaging*. 2019;20(4):417–425.

126. Stillman AE, Gatsonis C, Lima JAC, et al. for the RESCUE Investigators. Coronary computed tomography angiography compared with single photon emission computed tomography myocardial perfusion imaging as a guide to optimal medical therapy in patients presenting with stable angina: the RESCUE Trial. *J Am Heart Assoc*. 2020;9(24), e017993.

127. Chow BJW, Coyle D, Hossain A, et al. Computed tomography coronary angiography for patients with heart failure (CTA-HF): a randomized controlled trial (IMAGE-HF 1C). *Eur Heart J Cardiovasc Imaging*. Published online June 26, 2020. https://doi.org/10.1093/ehjci/jeaa109

128. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol*. 2007;49(8):863–871.

129. Chang SA, Choi SI, Choi EK, et al. Usefulness of 64-slice multidetector computed tomography as an initial diagnostic approach in patients with acute chest pain. *Am Heart J*. 2008;156(2):375–383.

130. Miller AH, Pepe PE, Peshock R, et al. Is coronary computed tomography angiography a resource sparing strategy in the risk stratification and evaluation of acute chest pain? Results of a randomized controlled trial. *Acad Emerg Med*. 2011;18(5):458–467.

131. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011;58(14):1414–1422.

132. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012;367(4):299–308.

133. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366(15):1393–1403.

134. Linde JJ, Kofoed KF, Sørgaard M, et al. Cardiac computed tomography guided treatment strategy in patients with recent acute-onset chest pain: results from the randomised, controlled trial: CArdiac cT in the treatment of acute CHest pain (CATCH). *Int J Cardiol*. 2013;168(6):5257–5262.

135. Linde JJ, Hove JD, Sørgaard M, et al. Long-term clinical impact of coronary CT angiography in patients with recent acute-onset chest pain: the randomized controlled CATCH trial. *J Am Coll Cardiol Img*. 2015;8(12):1404–1413.

136. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG–a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). *Int J Cardiol*. 2014;177(3):867–873.

137. Levsky JM, Spevack DM, Travin MI, et al. Coronary computed tomography angiography versus radionuclide myocardial perfusion imaging in patients with chest pain admitted to telemetry: a randomized trial. *Ann Intern Med*. 2015;163(3):174–183.

138. Dedic A, Lubbers MM, Schaap J, et al. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. *J Am Coll Cardiol*. 2016;67(1):16–26.

139. Levsky JM, Haramati LB, Spevack DM, et al. Coronary computed tomography angiography versus stress echocardiography in acute chest pain: a randomized controlled trial. *J Am Coll Cardiol Img*. 2018;11(9):1288–1297.

140. Yu M, Shen C, Dai X, et al. Clinical outcomes of dynamic computed tomography myocardial perfusion imaging combined with coronary computed tomography angiography versus coronary computed tomography angiography-guided strategy. *Circ Cardiovasc Imaging*. 2020;13(1), e009775.

141. Collet C, Onuma Y, Andreini D, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*. 2018;39(41):3689–3698.

KEY WORDS coronary computed tomography angiography, coronary physiology, coronary plaque