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Clinical applications of cardiac computed tomography: a consensus paper of the European Association of Cardiovascular Imaging—part II

Left running head: G. Pontone *et al.*

Short title : Clinical applications of Cardiac computed tomography AQ1

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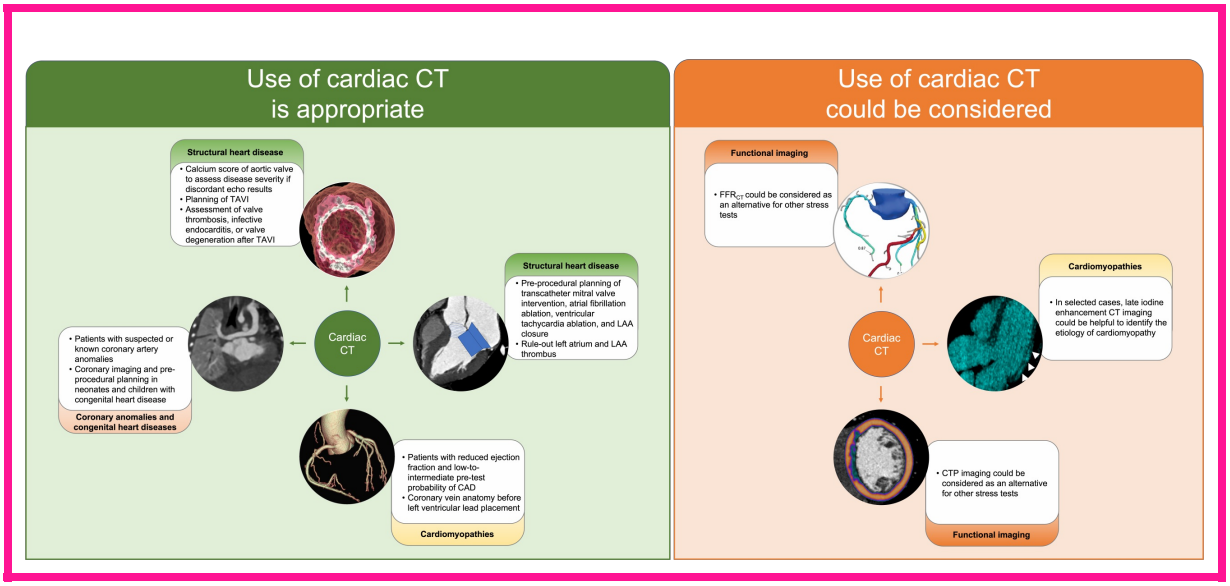
Abstract

Cardiac computed tomography (CT) was initially developed as a non-invasive diagnostic tool to detect and quantify coronary stenosis. Thanks to the rapid technological development, cardiac CT has become a comprehensive imaging modality which offers anatomical and functional information to guide patient management. This is the second of two complementary documents endorsed by the European Association of Cardiovascular Imaging ~~(EACVI)~~ aiming to give updated indications on the appropriate use of cardiac CT in different clinical scenarios. In this article, emerging CT technologies and biomarkers, such as CT-derived fractional flow reserve, perfusion imaging, and pericoronary adipose tissue attenuation, are described. In addition, the role of cardiac CT in the evaluation of atherosclerotic plaque, cardiomyopathies, structural heart disease, and congenital heart disease is revised. AQ4

Clinical applications of cardiac CT. {Comment by Author: Is the font size too small? Is it readable in the PDF file?} For more details, please refer to Table 1 which summarizes the main applications of cardiac CT. CAD, coronary artery disease; CT, computed tomography; CTP, computed tomography perfusion; FFR_{CT}, CT-derived fractional flow reserve; LAA, left atrial appendage; TAVI, transcatheter aortic valve implantation. AQ14



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Keywords: Coronary computed tomography angiography (CCTA)Cardiac computed tomographyMyocardial

ischaemiaFractional flow reserveFFR_{CT}CT perfusion imagingPlaque imagingStructural heart diseaseRadiomicsArtificial intelligenceCardiomyopathy{**Comment by Author:** In order to be consistent with the part I of this manuscript, please do not use a capital font for the first letter of each keyword. Please modify the keywords as follows: coronary computed tomography angiography - cardiac computed tomography - myocardial ischaemia - fractional flow reserve - FFR_{CT} - CT perfusion imaging - plaque imaging - structural heart disease - radiomics - artificial intelligence - cardiomyopathy

} AQ5

Introduction AQ6

This is the second of two complementary documents released by the European Association of Cardiovascular Imaging (EACVI) to provide recommendations on the evolving clinical applications of cardiac computed tomography (CT). The aim of this second document is to summarize the available evidence on coronary atherosclerotic plaque imaging, computational fluid dynamics, and perfusion imaging techniques as well as pericoronary adipose tissue (PCAT) attenuation, radiomics, and artificial intelligence. Finally, the key findings for a standardized coronary CT angiography (CCTA) report are described. AQ7

Methodology

The topic of this document was approved by the EACVI Scientific Document Committee. The writing committee comprised acknowledged experts in the field of cardiac CT. The writing committee discussed and approved the table of contents. This includes either well established applications of cardiac CT, or novel tools which have shown promising results for a potential implementation in the clinical arena. The evidence-based literature was searched in the electronic databases Medline/PubMed, Embase, and the Cochrane Library and afterwards reviewed by G.P. and A.R., with the restriction to English language. Both retrospective and prospective studies were considered eligible. Case reports, letters to the editor, and comments were excluded. The final decision on inclusion was reached by consensus between the two screening authors. Based on the collected data, the screening authors wrote the first draft of the article which was then circulated among all co-authors. Thereafter, each section was carefully reviewed by the entire writing committee until a consensus was reached for each potential application of cardiac CT. Thus, this consensus ~~statement~~document reports the current and emerging clinical applications of cardiac CT agreed by the panel of experts and grounded on the best available evidence at present, as summarized in *Table 1* and in *Graphical Abstract*.

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Table 1 EACVI key-points on the clinical applications of cardiac CT

Plaque imaging and standardized CCTA report

- Reporting total Agatston calcium score and the corresponding risk category is appropriate (when available) as a surrogate of total plaque burden. The coronary calcium risk categories are as follows: no coronary calcium, minimal: 1–9 calcium score, mild : 10–99 calcium score, moderate: 100–299 calcium score, severe: ≥300 calcium score.
- Reporting the severity of luminal stenoses, location, and extent of the coronary plaque is appropriate.
- The following grading of luminal stenosis severity (percentage stenosis) is appropriate: no stenosis, minimal: <25%; mild: 25–49%; moderate: 50–69%; severe: 70–99%; occlusion.
- For patients presenting with coronary atherosclerotic plaque, description of plaque composition (i.e. calcified, non-calcified, and partially calcified) and reporting of adverse plaque characteristics are appropriate.
- For patients presenting with coronary atherosclerotic plaque, reporting the overall plaque burden is appropriate. This can be provided by visual assessment as mild, moderate, or severe plaque burden (sub-optimal method) or by semi-quantitative approaches such as the segment involvement score (SIS).
- The use of the CAC-DRS (Coronary Artery Calcium—Data and Reporting System) and CAD-RADS (Coronary Artery Disease—Reporting And Data System) systems for standardized coronary calcium and CCTA report has been suggested by the Society of Cardiac Computed Tomography (SCCT) since they provide information on disease severity considering the presence, burden and location of both non-obstructive and obstructive plaque.

Pericoronary adipose tissue

- Limited data prevent recommendation on the role of PCAT attenuation/FAI.

~~Fractional flow reserved derived from~~ CT-derived fractional flow reserve (FFR_{CT})

- FFR_{CT} could be considered to assess functional significance of moderately obstructive lesions if CCTA image quality is adequate and the results are likely to change patient management.

Myocardial perfusion imaging with CT

- CTP could represent an alternative for other stress tests to evaluate myocardial ischaemia although its exact clinical role remains to be determined.

Structural heart disease

- CT calcium score of the aortic valve is appropriate to assess disease severity in patients with discordant echocardiographic measurements.
- Cardiac CT is appropriate prior to TAVI to assess the size of aortic annulus and its distance from the coronary ostia, the anatomy and dimensions of the aortic root, and the distribution of annular and sub-annular calcifications.
- Cardiac CT is appropriate prior to TAVI to select the optimum vascular access route.
- In the absence of obstructive CAD on CCTA, catheterization could be avoided.
- Post-TAVI cardiac CT is appropriate when there is concern of valve thrombosis, infective endocarditis, or structural valve degeneration.
- Cardiac CT is appropriate for pre-procedural planning of transcatheter mitral valve intervention.
- Cardiac CT is appropriate for pre-procedural planning of atrial fibrillation and ventricular tachycardia ablation.
- Cardiac CT with delayed acquisition (60–90 s) is appropriate as an alternative to ~~transoesophageal echocardiography~~TOE to rule-out left atrium and LAA thrombosis.
- Cardiac CT is appropriate for pre-procedural planning of LAA closure.

Cardiomyopathies

- CCTA is appropriate in patients with reduced ejection fraction and low–intermediate pre-test probability of CAD.
- In selected cases when echocardiography and/or CMR are unavailable or not interpretable, cardiac CT could be helpful for the evaluation of cardiac volumes, ejection fraction, and regional wall motion abnormalities.
- In selected cases when CMR is unavailable or not interpretable, late iodine enhancement CT imaging could be helpful to identify the aetiology of cardiomyopathy.
- Cardiac CT is appropriate in the evaluation of coronary vein anatomy before left ventricle lead placement.
- Limited data prevent recommendation on the role of CT-derived ECV for the detection of diffuse fibrosis.
- Limited data prevent recommendation on the role of ~~detection of~~ late iodine CT enhancement imaging for myocardial scar detection and localization before CRT.

Coronary anomalies and congenital heart disease • Cardiac CT is appropriate in patients with suspected or known coronary artery anomalies. • Cardiac CT could be indicated in neonates and children with suspected or known congenital heart diseases in the presence of complex anatomy, extra-cardiac findings, CMR incompatible device, or poor CMR image quality. • Cardiac CT is appropriate in neonates, children, and adult patients for coronary artery imaging. • Cardiac CT is appropriate in neonates, children, and adult patients to plan interventional and surgical procedures.
Coronary anatomy in aortic dissection, aortic aneurysms, and pulmonary embolism scans • ECG-triggered CT angiography is appropriate in patients presenting with symptoms of aortic dissection and pulmonary embolism to allow for the evaluation of coronary arteries (depending on the CT technology available and the training of the interpreting physician). • ECG-triggered CT angiography is appropriate at the first diagnosis and follow-up after repair of thoracic aortic aneurysm to allow for the evaluation of coronary arteries (depending on the CT technology available and the training of the interpreting physician).

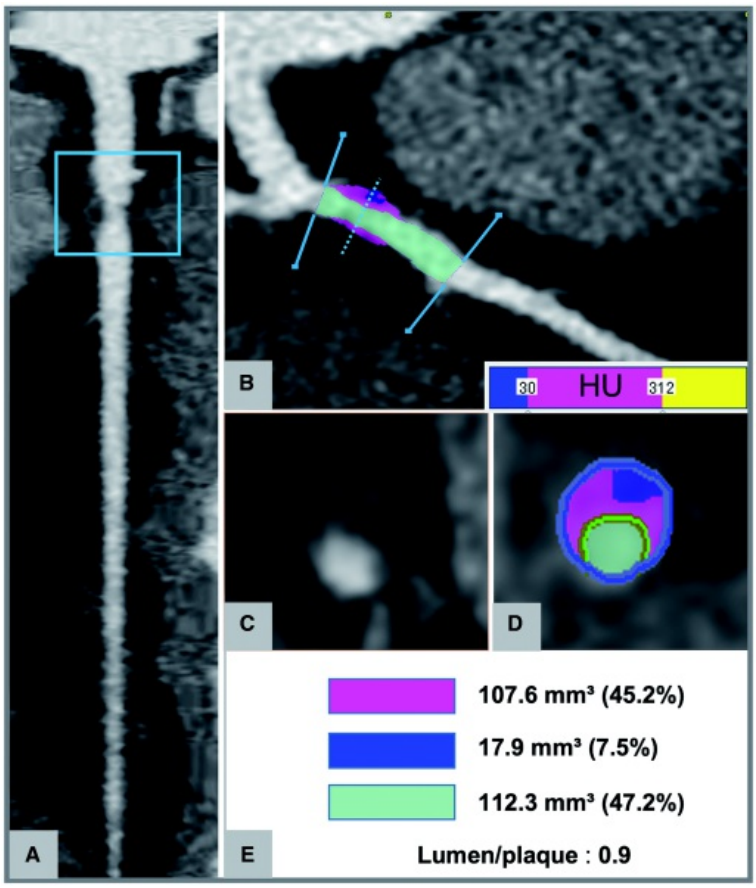
CAD, coronary artery disease; CAC-DRS, Coronary Artery Calcium—Data and Reporting System; CAC -RADS, Coronary Artery Disease—Reporting And Data System; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; CT, computed tomography; CTP, computed tomography perfusion; ECG, electrocardiogram; ECV, extracellular volume; FAI, fat attenuation index; FFR_{CT}, computed tomography-derived fractional flow reserve; LAA, left atrial appendage; PCAT, pericoronary adipose tissue; TAVI, transcatheter aortic valve implantation; TOE, transoesophageal ecocardiography.

Plaque imaging with CT

Rationale

CCTA is the only non-invasive tool capable of robustly imaging the coronary atherosclerotic plaque that leads to myocardial infarction (MI) as well as stable angina pectoris. CCTA therefore can directly assess the disease process driving coronary artery disease (CAD): from plaque detection and characterization to identification of adverse plaque features, quantification of atherosclerotic plaque burden and assessment of stenosis severity as shown in *Figure 1*.

Figure 1 Plaque characterization and quantitative assessment using semi-automated software. (*A–E*) Plaque of the proximal LAD. Straight (*A*) and curved (*B*) MPRs demonstrate a non-calcified plaque of the proximal LAD. The cross-section (*C*) shows a low-attenuation component of the plaque associated with positive remodelling and a rim of higher attenuation corresponding to the ~~(~~napkin-ring sign~~)~~. The semi-automate software delineates inner (green) and outer (blue) vessel walls and automatically identifies components with attenuation <30 HU (blue), 31–312 HU (pink), and >312~~3~~ HU (yellow~~, D~~). The lumen is highlighted in light blue (*B* and ~~–~~*D*). Quantitative data on area stenosis severity and volume of plaque subcomponents are provided in (*E*). ~~CT, computed tomography;~~ HU, Hounsfield unit; LAD, left anterior descending artery; MPR, multiplanar reconstruction.



Non-obstructive plaque

An advantage of CCTA is its ability to image and quantify non-obstructive atherosclerotic plaque, a stage of the disease missed by conventional stress perfusion imaging techniques and stress echocardiography. Multiple studies have highlighted the prognostic importance of non-obstructive plaque detection. In the ICONIC (Incident Coronary Events Identified by Computed Tomography) ~~(ICONIC)~~ study, 75% of culprit lesions identified by invasive coronary angiography (ICA) were non-obstructive on antecedent CCTA.[1] In the SCOT-

HEART (Scottish CoCOmputed Tomography of the HEARTHeart Trial) (SCOT-HEART) and PROMISE (ProROspective Multicenter Imaging Study for Evaluation of Chest Pain) (PROMISE) trials, as many subsequent myocardial infarctionsMIs were observed in patients with non-obstructive as obstructive CAD.[2,3] Although more prospective data are needed, given its prognostic importance, non-obstructive plaque may be used to guide the prescription of statin and aspirin therapy.

Plaque burden

CT calcium scoring has provided a surrogate of coronary plaque burden for many years, however advances in CCTA software technology mean that quantification of both calcified and non-calcified coronary plaque is now possible. The approach can be either semi-quantitative, in terms of number of segments involved by atherosclerosis [segment involvement score (SIS), segment stenosis score (SSS), or CT adapted Leaman score],[4,5] or quantitative through plaque burden quantification by semi-automated/automated software.[6] Although such quantitative approach is attractive and has shown good correlation with the invasive evaluation by intravascular ultrasound,[7] it is still time-consuming and requires validation, standardization, and automation before being implemented in routine clinical care. Moreover, since none of the currently used quantitation algorithms have been validated, the accuracy of these quantitative plaque measurements has not been definitely established.

Adverse plaque characteristics

CCTA can also characterize plaque type. Most simply, coronary plaques can be categorized into calcified, non-calcified, and partially calcified by visual assessment.[8] A further step in plaque analysis consists in the visual identification of adverse plaque[9,10] which include low-attenuation plaque (LAP), a marker of a large necrotic core, positive remodelling (PR), spotty calcification, and the napkin-ring sign[11] as defined in *Table 2*. Adverse plaque features have been correlated with worse prognosis and can be used to identify patients at increased probability of developing a future acute event. As such, the PROMISE trial demonstrated that the presence of adverse plaque was associated with 70% increase of death, myocardial infarctionMI, and hospitalization for unstable angina after 2 years follow-up.[12] In line with this, the SCOT-HEART trial showed that patients with adverse plaque characteristics had a three-fold increased rate of major cardiovascular events (MACE) at 5 years. However, this elevated risk was not independent of plaque burden as assessed by CT calcium score.[13] A recent meta-analysis reported that the napkin-ring sign was associated with the highest risk of future MACE (HR: 5.06), followed by LAP (HR: 2.95) and PR (HR: 2.58).[14] Spotty calcification showed the lowest correlation with MACE (HR: 2.25),[14] likely due to its high prevalence and therefore low specificity.[15] *Table 3* summarizes the major studies reporting on the association between adverse plaque features and MACE.[10,12,16–22] Furthermore, the EMERALD (Exploring the Mechanism of plaque Rupture in Acute coronary syndrome using coronary CT Angiography and computational fluid Dynamics) (EMERALD) study demonstrated that integrating adverse haemodynamic plaque characteristics (i.e. haemodynamic forces acting on plaques like fractional flow reserve (FFR) derived byfrom CCTA and its change across the lesion, wall shear stress, and axial plaque stress) {Comment by Author: Should be the square brackets used here?} to adverse plaque features improves the identification of culprit lesions for future acute coronary syndrome (ACS)[23]. Importantly, in all the studies the number of adverse plaques greatly exceeded the number of clinical events, highlighting that only a small

minority of these adverse plaques causes a ~~myocardial infarction~~MI.[12,13,24,25] However, at the patient level, subjects with a tendency to develop such lesions consistently appear to be at high risk. The next level is to consider not only the presence of high-risk plaques but their burden. In a sub-study of the SCOT-HEART trial, Williams *et al.*[21] demonstrated that patients with total LAP burden >4% had five times higher risk of developing fatal or ~~non-fatal myocardial infarction~~nonfatal MI and that this risk prediction was independent of calcium score~~s~~ as well as cardiovascular risk factors and the presence of luminal stenoses. Similarly, the ICONIC study showed that necrotic and fibro-fatty plaque volumes were higher in the ACS patients as compared to controls.[11] Further work is required to confirm the prognostic utility of the LAP burden in different patient populations and to streamline methods for quantification.

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Table 2 Definitions of adverse plaque characteristics~~HRP features and corresponding CT appearance~~

HRP feature	Definition
Low attenuation plaque	Presence of a central area within the plaque characterized by low CT attenuation <30 HU.[10]
Positive remodelling or remodelling index (RI)	Presence of an outer vessel diameter which is >10% of the diameter of the reference normal segment within the same vessel (RI >1.1).[10]
Spotty calcification	Small focal calcifications <3 mm diameter in any direction.[10]
Napkin-ring sign	Central area of low CT attenuation that is apparently in contact with the lumen and is surrounded by a rim of higher attenuation.[11]

CT, computed tomography; HU, Hounsfield unit; RI, remodelling index.

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Table 3 {**Comment by Author:** Something went wrong with the formatting in the PDF file. Please check and correct according to the original table.} **Selection of studies ~~that investigated~~investigating the prognostic value of qualitative adverse plaque characteristic detected by CCTA**

Trial	Motoyama *et al.*[10]	Motoyama *et al.*[18]	Nadjiri *et al.*[19]	Feuchtner *et al.*[16]	Ferencik *et al.*[12]	Finck *et al.*[17]	Williams *et al.*[21]	Senoner *et al.*[20]	Yamamoto *et al.*[22]
Study design	Retrospective, observational study	Retrospective, observational study	Retrospective, observational study	Prospective, observational study	RCT	Prospective, observational study	RCT	Prospective, observational study	Prospective, observational study

Trial	Motoyama *et al.*[10]	Motoyama *et al.*[18]	Nadjiri *et al.*[19]	Feuchtner *et al.*[16]	Ferencik *et al.*[12]	Finck *et al.*[17]	Williams *et al.*[21]	Senoner *et al.*[20]	Yamamoto *et al.*[22]
Sample size	1059	3158	1168	1469	4415	1615	~~1764~~1769	1430	2083
Population	Suspected or known CAD	Suspected or known CAD	Suspected CAD	Suspected CAD, low to intermediate pre-test probability	Suspected CAD	Suspected CAD	Suspected CAD	Suspected CAD, low to intermediate pre-test probability	Suspected CAD
Follow-up (years)	2.3	3.9	5.7	7.8	2.1	10.5	4.7	10.5	2
~~MACE~~Primary end point	ACS	ACS	Cardiac death, ~~myocardial infarction~~ MI, unstable angina, and coronary revascularization	STEMI, NSTEMI, unstable angina	Death from any cause, ~~myocardial infarction~~ MI, and hospitalization for unstable angina	Cardiac death ~~and~~or ~~non-fatal myocardial infarction~~ nonfatal MI	Fatal or ~~non-fatal myocardial infarction~~ nonfatal MI	~~ACS~~Fatal and nonfatal MACE	Cardiac death, non-fatal acute coronary syndrome, and coronary revascularizati >3 months after indexed CCTA
Rate of ~~MACE~~primary end point (%)	1.4	2.8	3.9	2.8	3.0	3.1	2.3	3.9	3.5
Plaque feature	LAP, PR	LAP, PR	PR, NRS, SC	LAP, NRS, SC	LAP, PR, NRS	LAP, NRS, SC	LAP	LAP, PR, NRS, SC	LAP, PR, NRS, SC

Trial	Motoyama *et al.*[10]	Motoyama *et al.*[18]	Nadjiri *et al.*[19]	Feuchtner *et al.*[16]	Ferencik *et al.*[12]	Finck *et al.*[17]	Williams *et al.*[21]	Senoner *et al.*[20]	Yamamoto *et al.*[22]
Adjusted hazard ratio (95% CI) {Comment by Author: If possible the value of the hazard ratio (e.g. 22.79) and the corresponding confidence interval (e.g. 6.91-75.17) should stay in one line.}	LAP and/or PR: 22.79 (6.91–75.17)	• LAP and/or PR: 13.13 (3.80–82.66) {Comment by Author: No bullet point.}	• PR: 1.04 (0.95–1.1) • NRS: 1.4 (0.6–2.9) • SC: 1.07 (0.5–2.2)	• LAP: 4.5 (1.4–14.8) • NRS: 7.0 (2.0–13.6) • SC: 2.6 (1.1–6.5)	• At least one high risk feature present: 1.72 (1.13–2.62) {Comment by Author: No bullet point.}	• LAP: 1.29 (0.40–4.15) • NRS: 2.25 (1.09–4.65) • SC: 2.35 (0.94–5.90)	LAP: 1.60 (1.10–2.34)	• LAP: 4.00 (1.52–10.52) • PR: 0.56 (0.18–1.75) • NRS: 4.11 (1.77–9.52) • SC: 1.40 (0.65–2.98)	• ≥2 adverse • ~~C~~charac 1.95 (1.13–3.34) {Comment by Author: No bullet point.}

ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; LAP, low-attenuation plaque; MACE, major adverse cardiovascular events; MI, myocardial infarction; NRS, napkin-ring sign; NSTEMI, non-ST elevation myocardial infarction; PR, positive remodelling; RCT, randomized clinical trial; SC, spotty calcification; STEMI, ST elevation myocardial infarction.

Progression of CAD and effect of medications

Several studies demonstrated the ability of CCTA in monitoring the effects of anti-atherosclerotic medications on plaque volume and compositions.[26–28] As such, *Table 4* summarizes the results of ~~some~~selected studies which investigated the impact of statins on coronary plaque burden by using serial CCTA scans.[6,29–35] In particular, the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) ~~(PARADIGM)~~ study is a multicentre prospective registry, which included patients who underwent repeat CCTA with a median follow-up time of 3.8 years.[36] Lee *et al.*[6] demonstrated that in patients on statin treatment non-calcified plaques showed slower progression over time and increased conversion to calcified plaque compared with statin naïve subjects. Of note, patients with diabetes experienced more plaque progression, in terms of disease burden and adverse plaque features, than those without diabetes.[37] Overall, total plaque burden (defined as plaque volume/vessel volume) was the strongest predictor of progression from non-obstructive to obstructive lesions after adjustment for drug use including statin.[38]

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Table 4 Selection of studies ~~that investigated~~investigating the effect of statins using serial CCTA

Trial	Inoue *et al.*[30]	Zeb *et al.*[35]	Lo *et al.*[33]	Ausher *et al.*[29]	Li *et al.*[32]	Lee *et al.*[6]	Lee *et al.*[31]	van Rosendael *et al.*[34]
Study design	Prospective, non-randomized study	Retrospective, observational study	Randomized, double-blind, placebo-controlled study	Prospective, open label, randomized clinical trial	Prospective, observational study	Multinational, observational registry	Multinational, observational registry	Multinational, observational registry
Sample size	32	100	40	96	206	1255	654	857
Population	Suspected CAD	Suspected CAD	Patients with HIV with no prior history of CAD	AMI	Suspected CAD	Suspected or known CAD	Suspected or known CAD	Suspected or known CAD
Therapy	Fluvastatin vs. control	Statin vs. no statin	Atorvastatin vs. placebo	~~Rosuvastatin vs. simvastatin~~ Intensive vs. standard statin therapy	Intensive vs. moderate vs. no statin	Statin vs. no statin	Statin vs. no statin	Statin vs. no statin
Follow-up time	12 months ~~(median)~~	406 days ~~(mean)~~	12 months	360 days ~~(median)~~	18 months	3.8 years ~~(mean)~~	3.9 years ~~(mean)~~	3.2 years ~~(median)~~
Quantitative plaque parameter	Total PV, LAP	Total PV, NCP, LAP	Total PV, NCP	Total PV, dense calcium volume	Total PV, LAP	Annualized changes in total PAV, calcified PAV	Annualized changes in normalized total PV and calcified PV	LAP, fibro-fatty plaque volume

Trial	Inoue *et al.*[30]	Zeb *et al.*[35]	Lo *et al.*[33]	Ausher *et al.*[29]	Li *et al.*[32]	Lee *et al.*[6]	Lee *et al.*[31]	van Rosendael *et al.*[34]
Treatment effect	tTot {**Comment by Author:** Please change the text of this cell to: Statin therapy was associated with decrease in plaque and necrotic core volume}al PV:h−15.0 vs. +4.0 mm^{3}tLAP: −3.6 vs +0.2 mm^3 Statin therapy was associated with decrease in plaque and necrotic core volume	Total {**Comment by Author:** Please change the text of this cell to: Statin therapy was associated with lower progression of LAPs and NCPs} PV:−33.3 vs. +31.0 mm^3(P < 0.001)LAP:−12.2 vs. +5.9 mm^3(P < 0.001)NCP: −47.7 vs. 13.8 mm^3 (P < 0.001) Statin therapy was associated with lower progression of LAPs and NCPs	Total PV: {**Comment by Author:** Please change the text of this cell to: Statin therapy reduced NCP volume and adverse plaque characteristics} −0.8 vs. +12 mm^3(P = 0.002)NCP:−8.2 vs. +6.7 mm^3(P = 0.003) Statin therapy reduced NCP volume and adverse plaque characteristics	Total PV: {**Comment by Author:** Please change the text of this cell to: Intensive statin therapy increased dense calcium volume}+43.5 vs. +19.1 mm^3(P = 0.570)Dense calcium volume:=11.1 vs. −0.4 mm^3(P < 0.001) Intensive statin therapy increased dense calcium volume	Total PV: {**Comment by Author:** Please change the text of this cell to: Statin therapy induced regression of LAP}−16.4 vs. −0.1 vs. +12.3 mm^3(P < 0.001)LAP:−7.1 vs. −2.8 vs. +0.9 mm^3(P < 0.001) Statin therapy induced regression of LAP	PAV:+1.7 vs. +2.0 mm^3/year(P = 0.02)Calcified PAV:+1.2 vs. +0.9 mm^3/year(P < 0.001) Statin therapy was associated with slower progression of disease and increased plaque calcifications	Total PV: {**Comment by Author:** Please change the text of this cell to: Statin therapy was associated with only calcified PV progression} +20.3 vs. +13.0 mm^3/year (P < 0.001) Calcified PV: +13.8 vs. +6.0 mm^3/year (P < 0.001) Statin therapy was associated with disease progression limited to calcified PV	Statin therapy was associated with larger decrease of LAP and fibro-fatty plaque volume

Trial	Inoue *et al.*[30]	Zeb *et al.*[35]	Lo *et al.*[33]	Ausher *et al.*[29]	Li *et al.*[32]	Lee *et al.*[6]	Lee *et al.*[31]	van Rosendael *et al.*[34]

~~P-values are shown only if comparison between treated group and control group was provided in the original article.~~

AMI, acute myocardial infarction; CAD, coronary artery disease; HIV, human immunodeficiency virus; LAP, low-attenuation plaque; NCP, non-calcified plaque; PAV, percentage atheroma volume; PV, plaque volume.

Standardized CCTA report

Standardization of CCTA reporting is recommended to assure an effective communication of the results to the referring physician. A complete overview of the different sections of a standardized cardiac CT report is presented in Supplementary data online, *Figure S1*. A section providing the evidence which supports the use of coronary calcium in clinical care is presented in the part 1 of this consensus document.

Key points

- Reporting total Agatston calcium score and the corresponding risk category is appropriate (when available) as a surrogate of total plaque burden. The coronary calcium risk categories are as follows: no coronary calcium, minimal: 1–9 calcium score, mild : 10–99 calcium score, moderate: 100–299 calcium score, and severe: ≥300 calcium score.[39]
- Reporting the severity of luminal stenoses, location, and extent of the coronary plaque is appropriate.
- The following grading of luminal stenosis severity (percentage stenosis) is appropriate: no stenosis, minimal: <25%; mild: 25–49%; moderate: 50–69%; ~~and~~ severe: 70–99%; occlusion.[40]
- For patients presenting with coronary atherosclerotic plaque, description of plaque composition (i.e. calcified, non-calcified, and partially calcified) and reporting of adverse plaque characteristics are appropriate.
- For patients presenting with coronary atherosclerotic plaque, reporting the overall plaque burden is appropriate. This can be provided by visual assessment as mild, moderate, or severe plaque burden (sub-optimal method) or by semi-quantitative approaches such as the SIS.
- The use of the Coronary Artery Calcium—Data and Reporting System (CAC-DRS)[41] and Coronary Artery Disease—Reporting And Data System (CAD-RADS)[42] systems for standardized coronary calcium and CCTA report has been suggested by the Society of Cardiac Computed Tomography (SCCT) since they provide information on disease severity considering the presence, burden, and location of both non-obstructive and obstructive plaque.

Pericoronary adipose tissue

Rationale

Inflammation is a key factor in the development and progression of atherosclerosis.[43] In the presence of vascular inflammation, the release of pro-inflammatory cytokines triggers lipolysis in the PCAT and blocks the differentiation of adipocytes thereby increasing the water/lipid ratio[44] and PCAT attenuation. A recent study reported that PCAT values increased across three distinct stages of CAD (no disease vs. stable CAD vs. ~~myocardial infarction~~MI) independently of age, gender, risk factors, and coronary plaque burden.[45]

The fat attenuation index (FAI) captures changes in PCAT attenuation around standardized segments of the coronary arteries on CT images. FAI is measured by using dedicated software which considers local anatomy, biological factors, scan settings, and reconstruction parameters.[46,47] Of note, few studies demonstrated that FAI is a dynamic value which is affected by anti-inflammatory and disease-modifying therapies.[48–50]

Prognostic value

In a *post hoc* analysis of outcome data from the CRISP-CT (Cardiovascular risk prediction using CT) ~~(CRISP-CT)~~ study, an adjusted FAI value of >−70.1 ~~HU~~Hounsfield unit was derived to identify patients at higher risk of all-cause mortality, cardiac mortality, and ACS.[46]

Despite these promising results, evaluation of PCAT attenuation/FAI is still considered a research tool. Further work is required to assess where measurements are best made and whether it provides clinical value above and beyond direct CT assessments of coronary plaque.

Key points

- Limited data prevent recommendation on the role of PCAT attenuation/FAI.

Functional assessment of coronary stenoses with CT

Rationale

Documentation of myocardial ischaemia and the haemodynamic impact of luminal stenoses might help patient selection for elective invasive procedures, particularly in patients with recalcitrant symptoms and borderline obstructive stenoses.

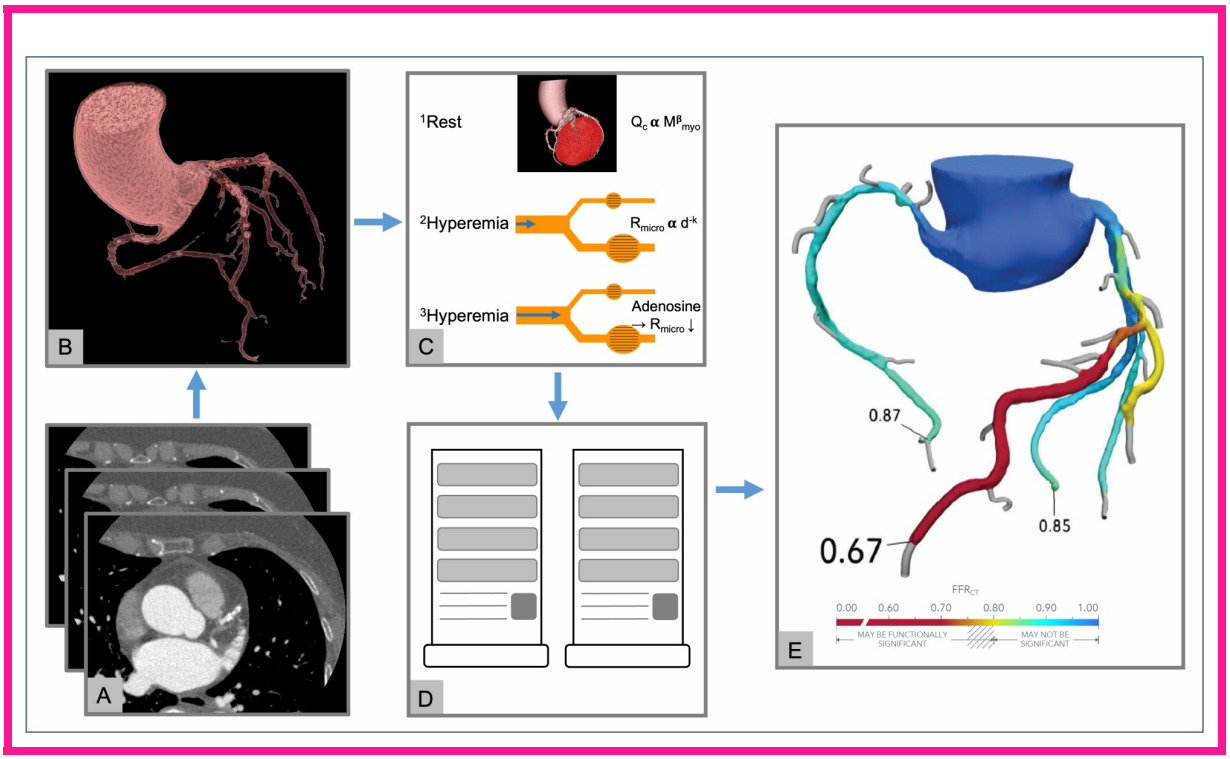
FFR derived from CT {Comment by Author: Subheading (blue in the PDF file). Please change the title to:CT-derived FFR}

Technique {Comment by Author: Detailed subheading (black in the PDF file).}

At the present time, invasive FFR is widely used during ~~invasive angiography~~ICA to evaluate the haemodynamic significance of a coronary stenosis.[51,52] Nevertheless, FFR can be estimated non-invasively by applying computational fluid dynamics to anatomic image data extracted from CCTA, without the need for additional imaging, modification of acquisition protocols, or administration of additional medications[53] as detailed in *Figure 2*. Currently, the only technology for CT-derived FFR~~FFR derived from CT~~ (FFR_{CT}) approved for clinical use requires off-site analysis in a central core laboratory (Heartflow, Redwood City, CA, USA). Meanwhile, multiple ~~CT-FFR~~ applications have been developed allowing on-site analysis on a regular workstation with

shorter computational time, although none of these are commercially available.[54,55]

Figure 2 ~~CT-derived~~ FFR_{CT}. (*A*–*E*) Calculation of FFR_{CT} by using computational fluid dynamics principles. (*A* and *B*) Standard rest CCTA images (*A*) are used to create a 3-dimensional~~D~~ anatomic model of the coronary arteries (*B*). (*C*) A physiological model of the coronary microcirculation is derived according to the following principles: [1]resting coronary flow is proportional to myocardial mass; [2]microvascular resistance is inversely proportional to vessel size; and [3]microvascular resistance is reduced to simulate maximal hyperaemia. (*D* and *E*) An off-site supercomputer is used to compute coronary blood flow by applying the physical laws of fluid dynamics (*D*) and calculated FFR_{CT} throughout the entire coronary tree (*E*). ~~FFR, fractional flow reserve;~~ FFR_{CT}, ~~CT~~CT-derived fractional flow reserve.



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Diagnostic accuracy {Comment by Author: Detailed subheading (black in the PDF file).}

A recent meta-analysis reported a pooled sensitivity of 85% and a pooled specificity of 75% of FFR_{CT} at vessel level (n = 1247) in the detection of haemodinamically significant lesions as defined by invasive FFR.[56] *Table 5* summarizes the results of the major prospective studies investigating the feasibility and diagnostic accuracy of FFR_{CT} against invasive FFR in patients with chronic stable angina.[57–64] The NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next steps) trial showed improved specificity of FFR_{CT} for the detection

of haemodynamically significant stenoses at the patient level compared with 50% stenosis on CCTA (79% vs. 34%, respectively).[60] Moreover, the PACIFIC (Comparison of Cardiac Imaging Techniques for Diagnosing Coronary Artery Disease) trial compared FFR_{CT} vs. single-photon emission computed tomography ~~(SPECT)~~ and positron emission tomography ~~(PET)~~ demonstrating the highest diagnostic accuracy of FFR_{CT} for the detection of vessel specific ischaemia, provided CCTA images were evaluable by FFR_{CT}.[57] Indeed, inadequate CCTA image quality is still a considerable limitation of FFR_{CT} with a rejection rate of FFR_{CT} in contemporary cohorts, ranging from 2.9% to 8.4% due to motion and slab artefacts.[65] Diagnostic accuracy of FFR_{CT} is not as good in patients with extensive coronary calcium,[66] multi-vessel disease post ST myocardial infarction,[67] and FFR_{CT} values ranging between 0.7 and 0.8—the borderline lesions where it most likely to be used.[68]

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Table 5 Major studies evaluating the diagnostic performance ~~at vessel level of CT-derived FFR~~of FFR_{CT} at vessel level with FFR ≤ 0.80 as reference standard

Trial	DISCOVER-FLOW[58]	DeFACTO[59,64]	NXT[60]	PACIFIC[57]	Coenen *et al.*[62,63]	Ko *et al.*[54]	Li *et al.*[55]
Study design	Prospective, multicentre. international study	Prospective, multicentre. international study	Prospective, multicentre. international study	Prospective, single-centre study	Prospective/retrospective, multicentre. international study	Prospective, single-centre study	Retrospective, two-centre study
Company	HeartFlow	HeartFlow	HeartFlow	HeartFlow	Siemens	Canon	Pulse Medical
Name of CT-derived FFR	FFR_{CT}	FFR_{CT}	FFR_{CT}	FFR_{CT}	~~c~~CT-FFR	CT-FFR	CT-QFR
Technique	C F D ~~(blood modelled as Newtonian fluid)~~	C F D ~~(blood modelled as Newtonian fluid)~~	C F D ~~(blood modelled as Newtonian fluid)~~	C F D ~~(blood modelled as Newtonian fluid)~~	Machine learning approach	C F D ~~(blood modelled as non-Newtonian fluid)~~	CFD
Patients, *n*	103	252	254	157	351	30	134
All lesions							
Vessels, *n*	159	407	484	505	525	58	156
AUC (95% CI)	0.90[a]	N/A	0.93 (0.91–0.95)	0.94 (0.92–0.96)	0.84 (0.80-0.87)	0.88 (0.76–1.0)	0.92[a]
Sensitivity (95% CI)	87 (76–95)	80 (73–86)	84 (75–89)	90 (84–95)	81 (75–86)	77 (51–92)	87[a]
Specificity (95% CI)	82 (73–89)	61 (54–67)	86 (82–89)	86 (82–89)	76 (71–81)	86 (71–95)	86[a]
PPV (95% CI)	73 (61–83)	N/A	61 (53–69)	65 (57–73)	70 (64–76)	73 (48–89)	82[a]

Trial	DISCOVER-FLOW[58]	DeFACTO[59,64]	NXT[60]	PACIFIC[57]	Coenen *et al.*[62,63]	Ko *et al.*[54]	Li *et al.*[55]
NPV (95% CI)	92 (84–96)	N/A	95 (93–97)	96 (92–98)	85 (81–90)	89 (73–95)	90[a]
Intermediate lesions							
Vessels, *n*	47	150	N/A	N/A	144[b]	N/A	N/A
Definition of intermediate lesions	50–69% DS	30–70% DS	N/A	N/A	25–69% DS	N/A	N/A
AUC (95% CI)	N/A	~~NA~~0.79 (0.72-0.87)	N/A	N/A	N/A	N/A	N/A
Sensitivity (95% CI)	66[a]	74 (57–88)	N/A	N/A	87 (76–94)	N/A	N/A
Specificity (95% CI)	88[a]	67 (58–75)	N/A	N/A	59 (47–70)	N/A	N/A
PPV (95% CI)	66[a]	41 (29–54)	N/A	N/A	62 (51–72)	N/A	N/A
NPV (95% CI)	88[a]	90 (81–95)	N/A	N/A	85 (73–93)	N/A	N/A

AUC, area under curve; CFD, computational fluid dynamics; CI, confidence interval; CT, computed tomography; DeFACTO, Determination of Fractional Flow Reserve by Anatomic Computed Tomography Angiography; DISCOVER-FLOW, Diagnosis of Ischaemia-Causing Stenoses Obtained Via Non-invasive Fractional Flow Reserve; DS, diameter stenosis; FFR, fractional flow reserve; FFR_{CT}, ~~computed tomography~~CT-derived fractional flow reserve; N/A, not~~a~~ available; NPV, negative predictive value; NXT, Analysis of Coronary Blood Flow Using CT Angiography: Next Steps; PACIFIC, Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography; PPV, positive predictive value; QFR, quantitative flow ratio.

[a] 95% confidence intervals not reported in the original study.

[b] CFD technique.

~~DISCOVER-FLOW, Diagnosis of Ischaemia-Causing Stenoses Obtained Via Non-invasive Fractional Flow Reserve; DeFACTO, Determination of Fractional Flow Reserve by Anatomic Computed Tomography Angiography; FFR_{CT}, computed tomography derived fractional flow reserve; NXT, Analysis of Coronary Blood Flow Using CT Angiography: Next Steps; PACIFIC, Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography.~~

Prognostic utility {Comment by Author: Detailed subheading (black in the PDF file).}

Several follow-up studies have demonstrated both the prognostic value and clinical utility of FFR_{CT}.[69–73] The 5 years follow-up of the NXT trial showed that a FFR_{CT} value of 0.8 or less was independently associated with MACE.[69] In particular, each 0.05 unit decrease of FFR_{CT} correlated with greater incidence of the primary endpoint.[69] The PROSPECT (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impact) ~~(PLATFORM)~~ study compared two consecutive cohorts of patients with recent onset of chest pain evaluated with CCTA/FFR_{CT} vs. usual care. The cohort that underwent CCTA and FFR_{CT} had a lower

number of ICA performed, a lower rate of non-obstructive CAD for those who were invasively investigated, and an overall lower cost compared with usual care.[70] Furthermore, the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) ~~(ADVANCE)~~ registry investigated the real-world utility of FFR_{CT} showing that the prospective implementation of FFR_{CT} after positive CCTA affected management recommendations in ~ 67% of the patients. Only 2.6% of cases required further non-invasive diagnostic testing after FFR_{CT}.[73] The randomized FORECAST (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain) ~~(FORECAST)~~ trial demonstrated that a strategy guided by CCTA and selective FFR_{CT} in patients with chronic coronary syndrome was comparable with standard clinical care in terms of cost and clinical outcomes, whilst reducing the number of ICA.[74]

Revascularization decision-making

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The role of FFR_{CT} has been also investigated in patients with complex CAD. In this context, the anatomical Syntax Score (SS) is commonly used to grade the severity and complexity of CAD on ICA and to help the heart team in decision-making between percutaneous coronary intervention ~~(PCI)~~ and coronary artery by-pass graft ~~(CABG)~~.[75,76] The SYNTAX (Synergy Between PCI With TAXus and Cardiac Surgery) ~~(SYNTAX)~~ II trial demonstrated the feasibility of deriving functional SS from CCTA and FFR_{CT} with comparable results against ICA with pressure-wire assessment.[75] Furthermore, the SYNTAX III trial reported that decision-making based on non-invasive functional SS was in high agreement with the decisions derived from the invasive approach.[77] Adding the functional information provided by FFR_{CT} to the anatomic data of CCTA changed the heart team recommendation in 7% of the cases and modified selection of vessel for revascularization in 12%.[78] Future developments in novel post-processing software, which allows for the non-invasive recalculation of FFR_{CT} after the virtual stent implantation, are waited.[79]

Key points

- ~~FFRCT~~FFR_{CT} could be considered to assess functional significance of moderately obstructive lesions if CCTA image quality is adequate and the results are likely to change patient management.

Myocardial perfusion imaging with CT

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Technique

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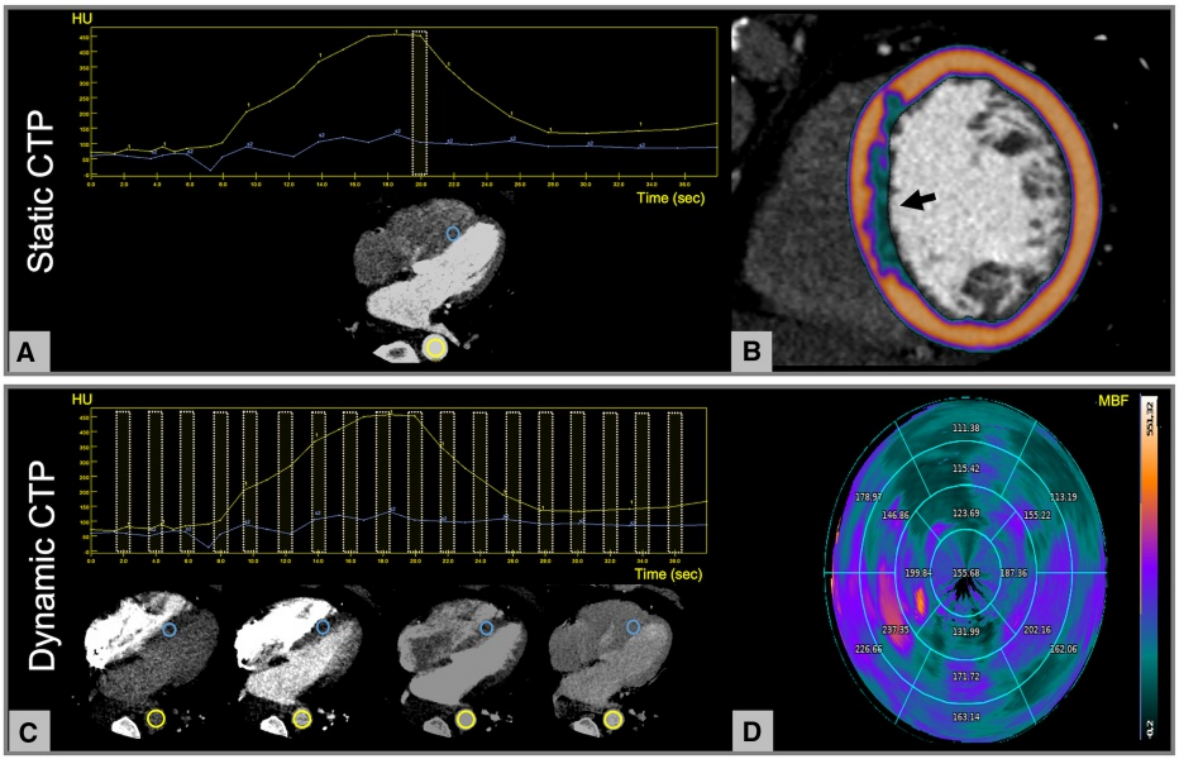
Myocardial perfusion imaging by computed tomography (CTP) allows for the evaluation of the distribution of myocardial blood flow (MBF) into the myocardium during rest and hyperaemia, thus providing information on the presence of myocardial ischaemia. Static perfusion protocols require the acquisition of a single set of images

during the maximum myocardial enhancement, with either a single-energy or dual-energy approach.[80] Dynamic perfusion protocols consist of multiple acquisitions over time of the same cardiac volume in order to evaluate the wash-in and wash-out of contrast material from the myocardium. This allows the construction of time-attenuation curves and, through the application of specific mathematical models, the quantification of MBF in each voxel of the myocardium.[81] Examples of CTP acquisition protocols are shown in *Figure 3*. While for static CTP the effective dose is comparable with a regular CCTA with an average value of 5.93 mSv, the average radiation exposure of dynamic CTP is higher with an average value of 9.23 mSv.[82] Nevertheless, new developments in CT hardware and software and tailored acquisition protocols appear promising in terms of dose reduction.[83] At the present time there is no standardization regarding acquisition protocols and imaging analysis for CTP imaging.

Figure 3 CTP imaging during pharmacological stress. (*A* and *B*) Static CTP consists of a single acquisition of the entire heart at the time of maximum myocardial enhancement as shown by the yellow dotted box in (*A*). The image assessment is qualitative and relies on the visual comparison between the hypo-perfused area and a normal (remote) region of the myocardium. In this example, a colour-coded map representing the myocardial distribution of HU has been overlayed to the myocardium showing a subendocardial perfusion defect of the septum (*B*). (*C* and *D*) Dynamic CTP protocols are based on the acquisition of serial CT datasets of the whole myocardium at different time points, which allows the construction of time attenuation curves of the descending aorta (yellow circle) and the myocardium (blue circle, *C*). ~~Myocardial blood flow~~MBF is calculated in absolute terms for each single voxel of the myocardium by applying dedicated mathematical models to the time-attenuation curves. A representative polar map of the MBF (mL/100g/min) distribution based on 17-segment AHA model is shown in (*D*) demostrating ~~a mildly~~ reduced perfusion in the anterior and antero-lateral walls of the left ventricle. The numbers indicate the average perfusion value for each myocardial segment. AHA, American Heart Association; CT, computed tomography; CTP, CT perfusion; HU, Hounsfield unit; MBF, myocardial blood flow.



Diagnostic accuracy {Comment by Author: Detailed subheading (black in the PDF file).}

A selection of studies reporting on feasibility and diagnostic performance of static and dynamic CTP are summarized in *Tables 6 and 7*, respectively.[83–96] In a recent meta-analysis including 697 patients and 2118 corresponding vessels CTP presented a sensitivity of 81% and a specificity of 86% in the detection of

functionally significant coronary stenoses as defined by FFR ≤0.80.[97] In particular, CTP improved the diagnostic accuracy of CCTA alone by decreasing the number of false positive findings either in patients with suspected CAD[97] or in patients with previous coronary stent implantation.[98] Dynamic CTP has shown to have higher sensitivity but lower specificity than static CTP (85% vs. 72% and 81% vs. 90%, respectively).[97]

Table 6 Selection of the available studies evaluating the diagnostic performance of single-energy static CTP

Trial	Bettencourt *et al.*[84]	Rochitte *et al.*[85]	Cury *et al.*[86]	George *et al.*[95]	Magalhaes *et al.*[96]	Pontone *et al.*[83]
Study design	Prospective, single-centre study	Prospective, multicentre, international study	Randomized, multicentre, multivendor study	Prospective, multicentre, international study	Prospective, multicentre, international study	Prospective, single-centre study
Sample size	101	381	110	381	381	147
Clinical setting	Stable CAD	Stable CAD	Stable CAD	Stable CAD	Stable CAD	Stable CAD
CT scanner	64-slice CT	320-slice CT	Multivendor	320-slice CT	320-slice CT	256-slice CT
Reference standard	FFR ≤ 0.80 or LM disease or vessel occlusion on ICA	QCA ≥ 50% and SPECT	SPECT	QCA	QCA ≥ 50% and SPECT	QCA > 80% and/or invasive FFR ≤0.80
Level of analysis	Vessel (*n* = 303)	Vessel (*n* = 1143)	Patient (*n* = 110)	Vessel (*n* = 1143)	Vessel (*n* = N/A)	Vessel (*n* = 432)
Sensitivity (95% CI)	55 (46–61)	61 (55–67)[a]	90 (71–100)	78 (73–82)	58 (51–64)[a]	92 (87–97)[a]
Specificity (95% CI)	95 (93–97)	83 (80–86)[a]	84 (77–91)	62 (58–67)	86 (83–88)[a]	95 (92–97)[a]
PPV (95% CI)	78 (66–88)	52 (45–58)[a]	36 (17–55)	58 (53–63)	55 (48–61)[a]	87 (81–92)[a]
NPV (95% CI)	87 (84–89)	88 (85–90)[a]	99 (97–100)	81 (76–85)	87 (84–90)[a]	97 (95–99)[a]

[a] CCTA + CTP.

CAD, coronary artery disease; CI, confidence interval; CT, computed tomography; FFR, fractional flow reserve; ICA, invasive coronary angiography; LM, left main; NPV, negative predictive value; PPV, positive predictive value; QCA, quantitative coronary angiography; SPECT, single-photon emission computed tomography.

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Table 7 Selection of the available studies evaluating the diagnostic performance of dynamic CTP

Trial	Huber *et al.*[87]	Rossi *et al.*[88]	Coenen *et al.*[89]	Pontone *et al.*[90]	Alessio *et al.*[91]	de Kneght *et al.*[92]	Nous *et al.*[93]	Kitagawa *et al.*[94]
Study design	Prospective, single-centre study	Prospective, two-single-centre study	Prospective, two-single-centre study	Prospective, single-centre study	Prospective, single-centre study	Prospective, single-centre study	Prospective, multicentre, international study	Prospective, multicentre study
Sample size	32	80	74	85	34	93	~~114~~123	157
Clinical setting	Suspected and stable CAD	Suspected and stable CAD	Suspected and stable CAD	Suspected and stable CAD	Suspected and stable CAD	Suspected and stable CAD	Suspected and stable CAD	Suspected or known CAD
CT scanner	256-slice CT	128-slice dual source CT (second generation)	128-slice dual source CT (second generation)	256-slice CT	256-slice CT	128-slice dual source CT (second generation)	128-slice dual source CT (third generation)	128-slice dual source CT (second and third generation)
Reference standard	ICA > 75% and/or invasive FFR ≤0.75	QCA > ~~8~~90% and/or invasive FFR ≤0.75	Invasive FFR ≤0.80	~~ICA~~ QCA ≥80% and/or invasive FFR ≤0.80	PET	Q C A ~~>~~≥ 80% and/or invasive FFR ≤0.80	QCA > 90% and/or invasive FFR ≤0.80	ICA >90% and/or FFR <0.80
Level of analysis	Patient	Vessel (n = 210)	Vessel (n = 142)	Vessel (n = 255)	N/A	Vessel (n = 218)	Vessel (n = 289)	Vessel (n=442) **AQ15**
Cut-off value of MBF {**Comment by Author:** Please do not use bullet points in all cells of this row}	• Absolute MBF = • 1.64 mL/g/min	• Absolute MBF = • 78 mL/100 mL/min	• ~~Absolute~~ Relative MBF = • 0.71 ~~(index)~~	• Absolute MBF = • 101 mL/100 mL/min	N/A	• Relative MBF = • 0.72 ~~(index)~~	• Absolute MBF = • 142 mL/100 mL/min	• Relative MBF = • 0.76

Trial	Huber *et al.*[87]	Rossi *et al.*[88]	Coenen *et al.*[89]	Pontone *et al.*[90]	Alessio *et al.*[91]	de Kneght *et al.*[92]	Nous *et al.*[93]	Kitagawa *et al.*[94]
Sensitivity (95% CI)	75 (56–89)	88 (74–95)	73 (61–86)	73 (63–83)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}	75[a]	84 (77–89)	84 (75–92)	73 (64–81)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}
Specificity (95% CI)	100 (94–100)	90 (82–95)	68 (56–80)	86 (81–91)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}	71[a]	88 (82–92)	89 (85–93)	72 (67–77)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}
PPV (95% CI)	100[a]	77 (61–87)	67 (55–80)	87 (81–92)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}	NA	67 (54–79)	73 (63–83)	47 (42–53)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}
NPV (95% CI)	90[a]	95 (90–98)	74 (63–85)	72 (62–82)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}	NA	95 (90–97)	94 (91–97)	89 (85–92)[a] {Comment by Author: Please change the superscript a with b in each cell where it is present}

~~a CCTA + CTP.~~ [a] 95% CI not reported in the original study; [b] CCTA + CTP

CAD, coronary artery disease; CI, confidence interval; CT, computed tomography; FFR, fractional flow reserve; ICA, invasive coronary angiography; MBF, myocardial blood flow; N/A, not~~n~~ available; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; QCA, quantitative coronary angiography.

With regard to dynamic CTP, a wide range of CT-derived MBF cut-off values ~~have~~has been reported by different groups, preventing the identification of a standardized threshold. The implementation of indexed MBF values, in which the ischaemic myocardium was normalized to either the remote myocardium or the 75th percentile of MBF, improved the diagnostic performance of CTP in selected cohorts.[89,99,100]

CTP vs. FFR_{CT}~~C~~ {Comment by Author: Detailed subheading (black in the PDF file).} ~~T-derived FFR~~

Several studies have reported a comparable diagnostic performance of dynamic CTP and FFR_{CT} as well as other stress imaging modalities in the detection of functionally significant coronary lesions.[89,90,101] Although FFR_{CT} may have practical advantages in terms of acquisition protocol and dose saving, ~~perfusion imaging by CT~~CTP imaging may be useful when the value of FFR_{CT} is in the 'grey area' (i.e. 0.74–0.85)[89] or when FFR_{CT} cannot be calculated due to technical reasons (i.e. sub-optimal image quality, diffuse coronary calcifications).

Prognostic value {Comment by Author: Detailed subheading (black in the PDF file).}

At the present time, data on the prognostic value of CTP is still scarce.[102–106]

Clinical utility {Comment by Author: Detailed subheading (black in the PDF file).}

The multicenter prospective randomized CRESCENT (~~Comprehensive~~ Comprehensive Cardiac CT Versus Exercise Testing in Suspected Coronary Artery Disease) II ~~(CRESCENT)~~ trial demonstrated that a comprehensive cardiac CT protocol including dynamic CTP is an efficient alternative to standard functional testing in patients with stable angina. At 6 months follow-up the rate of ICA with a European Society of Cardiology (ESC) class I indication for revascularization was higher in the cardiac CT group without increasing overall catheterization rate and with a lower rate of additional non-invasive testing.[107] The results of the multicentre, randomized controlled CTP-PRO (impact of stress Cardiac computed Tomography myocardial Perfusion on downstream resources and PROgnosis in patients with suspected or known CAD: A multicentre international study) study will provide further insights in to the cost-effectiveness of a CCTA+CTP strategy vs. usual care in intermediate–high risk patients with suspected or known CAD.[108]

Key points

- CTP could represent an alternative for other stress tests to evaluate myocardial ischaemia although its exact clinical role remains to be determined.

Structural heart disease

Rationale

Cardiac CT has become crucial in the diagnosis of structural heart disease as well as in the selection of patients for interventional procedures, pre-procedural planning, device sizing, and post-procedural follow-up as shown in *Figures 4 and 5*. Specific protocols for the preparation, acquisition, and interpretation of cardiac CT in patients with structural heart diseases are reported in detail elsewhere.[109–112]

Figure 4 Role of cardiac CT in patients with aortic valve stenosis. (*A–E*) Overview of the applications of cardiac CT in patients with aortic valve stenosis. (*A* and *B*) Diagnostic work-up of aortic valve stenosis. The severity of aortic valve stenosis can be estimated by the calcium load of aortic valve calculated according to the Agatston method on non-enhanced cardiac CT (*A*). In addition, CCTA can be used for CAD evaluation. In this example, curves MPRs show diffuse calcifications of RCA, LAD, and LC~~x~~X (*B*). (*C* and *D*) Pre-procedural planning, device selection, and access sites prior to TAVI. Cardiac CT provides information on aortic root and thoracic aorta measurements (*C*), aortic annulus sizing with determination of maximum (white), and minimum (red) diameters, area (purple), and perimeter (orange, *C1*), as well as distance of the coronary ostia from the aortic valve plane (*C2*). In addition, CT allows the assessment of abdominal aorta and peripheral vascular access. In this case, a transfemoral vascular approach has been evaluated (*D*) with sizing of maximum and minimum diameters of the left femoral artery (*D1*). (*E*) Follow-up after TAVI. Cross-section (*E1*) and volume rendering (*E2*) of the prosthetic valve show an example of a patient with HALT (~~arrow heads~~arrowheads). CAD, coronary artery disease; CCTA, computed tomography coronary angiography; CT, computed tomography; HALT, hypo-attenuated leaflet thickening; MPR, multiplanar reconstruction; LAD, left anterior descending coronary artery; LCX~~x~~, left circumflex coronary artery; RCA, right coronary artery; TAVI, transcatheter aortic valve implantation.

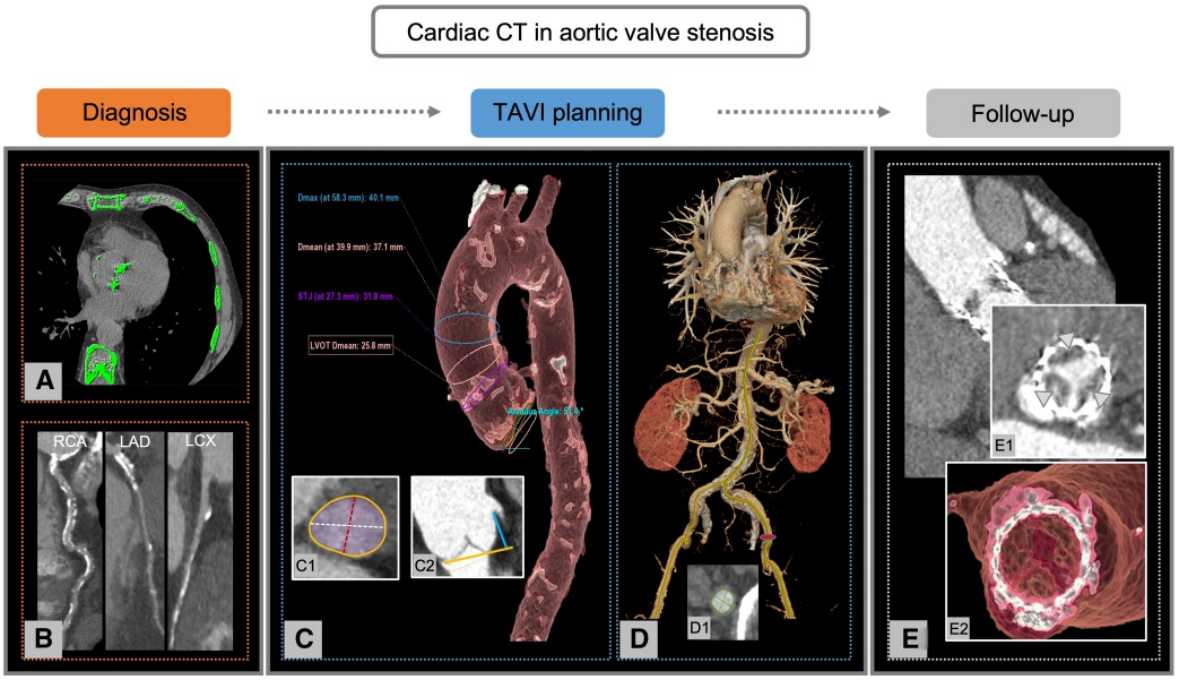
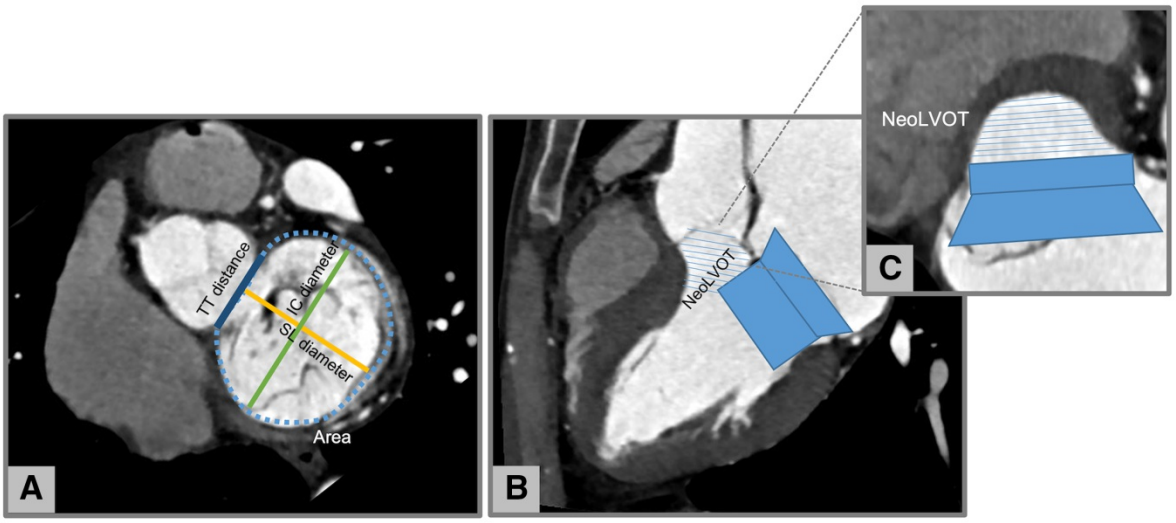


Figure 5 Neo LVOT assessment in native mitral regurgitation with CT. (*A*) Measurement of mitral annulus size: area, SL, IC, and TT diameters. (*B*) Virtual valve implantation ~~of TMVR~~ and identification of the neo LVOT (*C*). Images by courtesy of Antonio Esposito and Anna Palmisano, San Raffaele IRCCS, Milan (Italy). CT, computed tomography; IC, inter-commissural; LVOT, left ventricular outflow tract; SL, septal–lateral; TT, trigone to trigone~~; TVMR, transcatheter mitral valve repair~~.



Aortic valve stenosis

Diagnosis of aortic valve stenosis

CT calcium score of the aortic valve can be quantified on non-enhanced, electrocardiogram (ECG)-triggered cardiac CT by using the Agatston method[113] allowing for flow-independent assessments of aortic stenosis severity when echocardiography measurements are discordant as recommended in the recent ESC heart valve guidelines.[114,115] Sex-specific thresholds for differentiating moderate from severe aortic stenosis have been proposed (≥2065 Agatston for men and ≥1274 for women) and validated in a large international study, demonstrating excellent agreement with concordant echocardiography and providing powerful prognostic information.[116]

Diagnostic work-up before transcatheter aortic valve implantation

Cardiac CT is the preferred imaging modality to select patients suitable for transcatheter aortic valve implantation (TAVI) allowing for more precise measurements of the aortic annulus than 2D echocardiography, thereby optimizing the sizing and selection of the aortic valve prostheses.[117] As a consequence, a CT-guided approach resulted in better patient outcomes and less paravalvular regurgitation rate than echocardiography.[118,119] In addition, CT provides ancillary information on the distance of the coronary ostia from the aortic valve plane, the number and length of aortic cusps, aortic root and ascending aorta dimensions, optimal fluoroscopic projection[109,110] as well as the grade and distribution of annular and sub-annular calcifications.[120,121] Finally,

CT offers information regarding the optimal vascular access route providing detail on vessel size, tortuosity, course, calcifications, and stenosis which are the main determinants of vascular complications during the procedure.[109,110] The information provided by cardiac CT in the context of TAVI is summarized in *Figure 4*.

The assessment of CAD and comorbidities is another fundamental step in the diagnostic work-up of patients undergoing TAVI.[122,123] A recent meta-analysis including 1275 patients reported a sensitivity of 95% and a specificity of 65% for CCTA in the detection of obstructive CAD in TAVI candidates.[124] As such, the 2021 ESC guidelines for the management of valvular heart disease suggested that CCTA could be used to rule-out CAD in patients at low risk of atherosclerosis thanks to its high negative predictive value.[125] *Table 8* reports a selection of the major studies investigating the diagnostic performance of CCTA for pre-TAVI coronary assessment.[126–133]

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Table 8 Major studies evaluating the diagnostic performance ~~at patient-level~~ of CCTA at patient level for the detection of obstructive CAD (coronary stenosis ≥ 50%) in TAVI candidates

Trial	Pontone *et al.*[131]	Andreini *et al.*[126]	Hamdan *et al.*[127]	Harris *et al.*[128]	Opolski *et al.*[130]	Matsumoto *et al.*[129]	Rossi *et al.*[132]	Strong *et al.*[133]
~~Patients,~~ Sample size ~~n~~	60	325	115	100	475	60	140	200
Prevalence of obstructive CAD (%)	43	~~30~~N/A	43	~~74~~73	57	40	41	34
Sensitivity (95% CI)	88 (76–100)	89[a]	96[a]	98 (92–100)	98 (95–99)	91[a]	91 (81–96)	100 (94–100)
Specificity (95% CI)	88 (77–99)	90[a]	73[a]	55 (35–74)	37 (30–44)	58[a]	54 (44–65)	42 (33–50)
PPV (95% CI)	85 (72–99)	80[a]	~~96~~72[a]	85 (76–92)	67 (62–72)	59[a]	58 (48–68)	47 (44–51)
NPV (95% CI)	91 (81–100)	95[a]	~~72~~96[a]	93 (69–99)	94 (86–98)	91[a]	90 (78–95)	100 (92–100)
Coronary stents included	+	+	+	+	+	-	-	-
CABG included	+	+	+	+	+	-	-	-

[a] 95% confidence intervals not reported in the original study.

CABG, coronary artery by-pass graft; CAD, coronary artery disease; CI, confidence intervals; N/A, not available; NPV, negative predictive value; PPV, positive predictive value.

Post-procedural follow-up

Although cardiac CT is not routinely performed after TAVI, its use is advocated when there is concern regarding valve thrombosis, infective endocarditis, or structural degeneration. Regarding endocarditis, CT is particularly helpful in the detection of aortic root abscesses and pseudoaneurysms. In patients with valve thrombosis, cardiac CT allows for the detection of hypoattenuating leaflet thickening and restricted leaflet motion, which are often signs of leaflet thrombus.[134]

Mitral valve disease

Diagnosis of mitral valve disease

CT has shown promising results in identifying the aetiology,[135,136] in detecting mitral valve prolapse,[137] and in quantifying the regurgitation volume by a combined approach with echocardiography.[138]

Diagnostic work-up before percutaneous mitral valve interventions

Thanks to the recent advancements in percutaneous mitral valve interventions, CT is playing an increasing role in the ~~preprocedural~~pre-procedural work-up of patients with mitral valve disease, helping determine device suitability[111,139] as demonstrated in *Figure 5*. Specifically, cardiac CT has been used to evaluate the mitral annulus size and geometry, the relationship of the mitral valve with the circumflex coronary artery and the distribution of mitral annular calcifications.[111] Pre-procedural CT based simulation has shown to be helpful in identifying patients at higher risk for post-implant left ventricular outflow tract obstruction.[140,141] Ancillary information that can be further extracted from CT images are the optimal fluoroscopic view for the percutaneous procedure[142] and the appropriate access point for the transapical puncture.[143]

Atrial fibrillation

In the context of atrial fibrillation, cardiac CT has been widely used in the pre-procedural planning of catheter ablation, providing detailed anatomic delineation of left atrium and pulmonary veins.[144] In addition, delayed imaging (60–90 s) with CT has been proposed as an alternative method to rule out left atrial appendage (LAA) thrombus thanks to its high sensitivity of 100% and specificity of 99%.[145] Of note, anatomic features of the left atrium as detected on cardiac CT have been correlated with patient outcomes following cryoablation.[146]

LAA closure

Nowadays cardiac CT is considered a valid alternative to the reference standard transoesophageal echocardiography (TOE) for pre-procedural planning prior to LAA closure.[112] Thanks to its high isotropic spatial resolution and 3D datasets, cardiac CT is ideal for the evaluation of LAA morphology and dimensions, as well as its relationship with surrounded structures, thereby guiding appropriate device selection.[112] In addition, CT appears a promising alternative to TOE for exclusion of LAA thrombus before the procedure[145] and for device surveillance after LAA closure.[147]

Key points

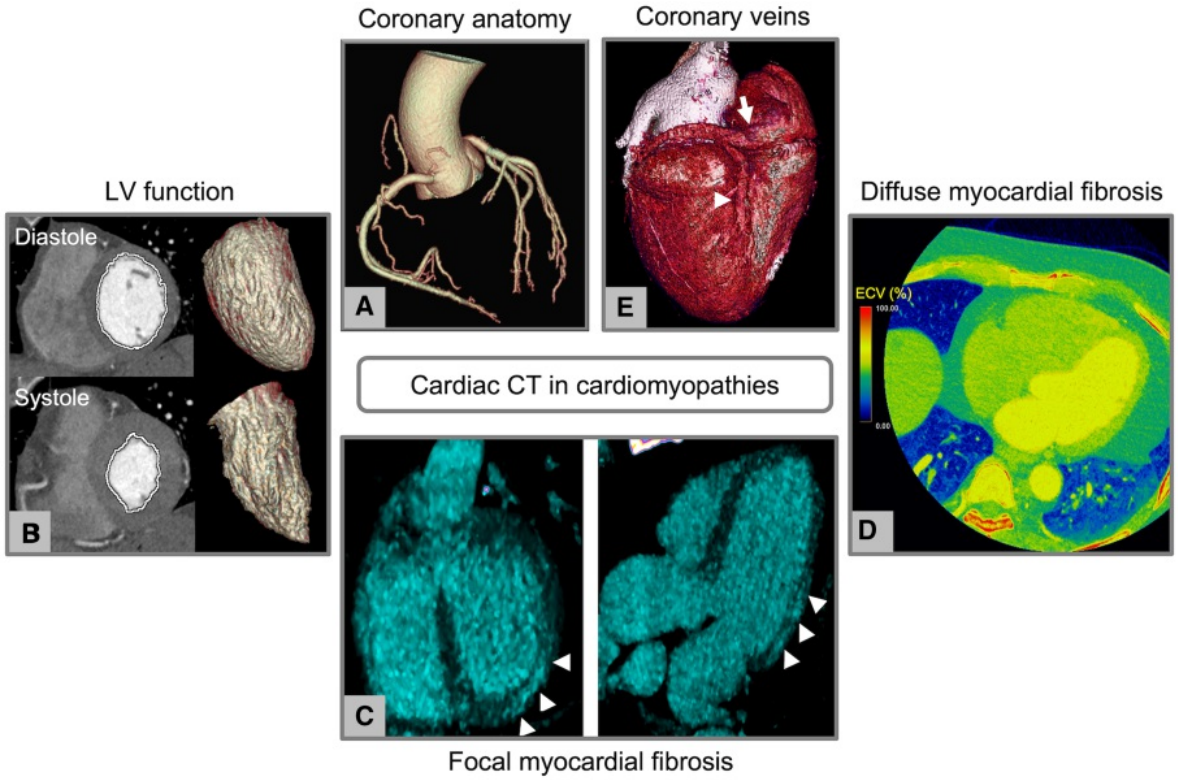
- CT calcium score of the aortic valve is appropriate to assess disease severity in patients with discordant echocardiographic measurements.
- Cardiac CT is appropriate prior to TAVI to assess the size of aortic annulus and its distance from the coronary ostia, the anatomy and dimensions of the aortic root, and the distribution of annular and sub-annular calcifications.
- Cardiac CT is appropriate prior to TAVI to select the optimum vascular access route.
- In the absence of obstructive CAD on CCTA, catheterization could be avoided.
- Post-TAVI cardiac CT is appropriate when there is concern of valve thrombosis, infective endocarditis, or structural valve degeneration.
- Cardiac CT is appropriate for pre-procedural planning of transcatheter mitral valve intervention.
- Cardiac CT is appropriate for pre-procedural planning of atrial fibrillation and ventricular tachycardia ablation.
- Cardiac CT with delayed acquisition (60–90 s) is appropriate as an alternative to TOE to rule-out left atrium and LAA thrombosis.
- Cardiac CT is appropriate for pre-procedural planning of LAA closure.

Cardiomyopathies

Rationale

Cardiac CT can be helpful in the setting of cardiomyopathies as shown in *Figure 6*.

Figure 6 Cardiac CT ~~for~~in cardiomyopathies. (*A*–*E*) Overview of the potential information derived from cardiac CT in patients with cardiomyopathies. (*A*) Evaluation of coronary anatomy; (*B*) functional assessment with calculation of ventricular volumes and ejection fraction; (*C*) identification of focal myocardial fibrosis with late iodine enhancement technique (arrowheads); (*D*) assessment of diffuse fibrosis using extracellular volume measurement; and (*E*) assessment of the coronary venous system prior to cardiac resynchronization therapy (arrow, coronary sinus; arrowhead, posterior interventricular vein). CT, computed tomography.



Functional evaluation

Cardiac CT can reliably quantify cardiac volumes and ejection fraction of left and right ventricle, with excellent accuracy compared with the reference standard cardiac magnetic resonance (CMR).[148–151] A retrospectively ECG-gated acquisition throughout the cardiac cycle is required, hence leading to an average radiation dose of ~10 mSv in men and 11 mSv in women.[150] ECG-tube current modulation is often implemented to minimize radiation exposure.

CAD assessment

Current ESC guidelines on acute and chronic heart failure recommend CCTA in patients with low—intermediate pre-test probability of CAD or in those with an equivocal non-invasive stress test in order to exclude the diagnosis of CAD (Class IIa).[152]

Focal and diffuse fibrosis

While CMR is the imaging ~~modalities~~modality of choice for cardiomyopathy phenotyping and risk assessment,[153] cardiac CT may alternatively be used in patients with CMR contraindications. Late iodine CT enhancement imaging has shown good agreement with CMR in the localization and pattern recognition of myocardial fibrosis in patients with heart failure.[154–157] Most recently, the feasibility of extracellular volume (ECV) calculation, which is a surrogate marker of diffuse myocardial fibrosis, has been also demonstrated using different CT technologies and CT protocols.[158–160] Several studies demonstrated a good correlation between CT-derived ECV and CMR-derived ECV in heart failure patient cohorts.[161–163] Furthermore, when compared with healthy subjects, CT-derived ECV was significantly higher in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, sarcoidosis, and amyloidosis.[159] Currently, no studies on the prognostic role of CT-derived ECV are available in patients with cardiomyopathies.

Treatment planning before cardiac resynchronization therapy

Cardiac CT can visualize accurately the coronary venous system which can be helpful for left ventricle lead implantation before cardiac resynchronization therapy (CRT), particularly in cases where the coronary sinus has previously proved difficult to intubate.[164] Little data are available on the role of cardiac CT for the assessment of scar location[165] and of phrenic nerve anatomy in relation to target veins[166] before CRT.

Key points

- CCTA is appropriate in patients with reduced ejection fraction and low–intermediate pre-test probability of CAD.
- In selected cases when echocardiography and/or CMR are unavailable or not interpretable, cardiac CT could be helpful for the evaluation of cardiac volumes, ejection fraction, and regional wall motion abnormalities.
- In selected cases when CMR is unavailable or not interpretable, late iodine enhancement CT imaging could be helpful to identify the aetiology of cardiomyopathy.
- Cardiac CT is appropriate in the evaluation of coronary vein anatomy before left ventricle lead placement.
- Limited data prevent recommendation on the role of CT-derived ECV for the detection of diffuse fibrosis.
- Limited data prevent recommendation on the role of ~~detection of~~ late iodine CT enhancement imaging for myocardial scar detection and localization before CRT.

Coronary anomalies

CCTA provides detailed information on coronary artery architecture and relationship to the surrounding cardiac structures, with superior ability to ICA.[167] In particular, CCTA is highly accurate in the detection of anomalous coronary arteries and in the classification of high-risk anatomic features (i.e. slit-like ostium, inter-arterial course, intramural course and acute take-off angle) which have been associated with an increased risk of myocardial ischaemia, ventricular arrhythmias and sudden cardiac death.[168]

Congenital heart disease

Cardiac CT is increasingly used for the initial diagnosis of congenital heart diseases (CHD) in neonates and children as demonstrated in *Figure 7*.[169] Cardiac CT offers precise anatomical and functional information of cardiac structures, great vessels, and associated abnormalities of lung parenchyma.[169–171] Moreover, rapid acquisition allows for minimal motion artefacts, reducing the need for sedation whilst preserving image quality. In addition, thanks to evolving technical developments and implementation of tailored protocols, radiation dose can be substantially reduced.[172] Beyond diagnosis, cardiac CT is becoming a common tool to plan interventional and surgical procedures and to evaluate postoperative anatomy and complications as shown in *Figure 8*.[171] Due to the complexity and heterogeneity of CHD, specific training and expertise are essentials in this setting.[172]

Key points

- Cardiac CT is appropriate in patients with suspected or known coronary artery anomalies.
- Cardiac CT could be appropriate in neonates and children with suspected or known CHD in the presence of complex anatomy, extra-cardiac findings, CMR incompatible device, or poor CMR image quality.
- Cardiac CT is appropriate in neonates, children, and adult patients for coronary artery imaging.
- Cardiac CT is appropriate in neonates, children, and adult patients to plan interventional and surgical procedures.

Figure 7 Cardiac CT in neonate with suspected congenital heart disease. (*A*–*C*) Ten-day-old female patient with partial anomalous pulmonary venous return and a small muscular VSD. Images by courtesy of Francesco Bianco, Ospedale Riuniti Ancona, Ancona (Italy). Ao, aorta; CT, computed tomography; La, left atrium; Lv, left ventricle; PVs, pulmonary veins; Rv, right ventricle; VSD, ventricular septal defect.

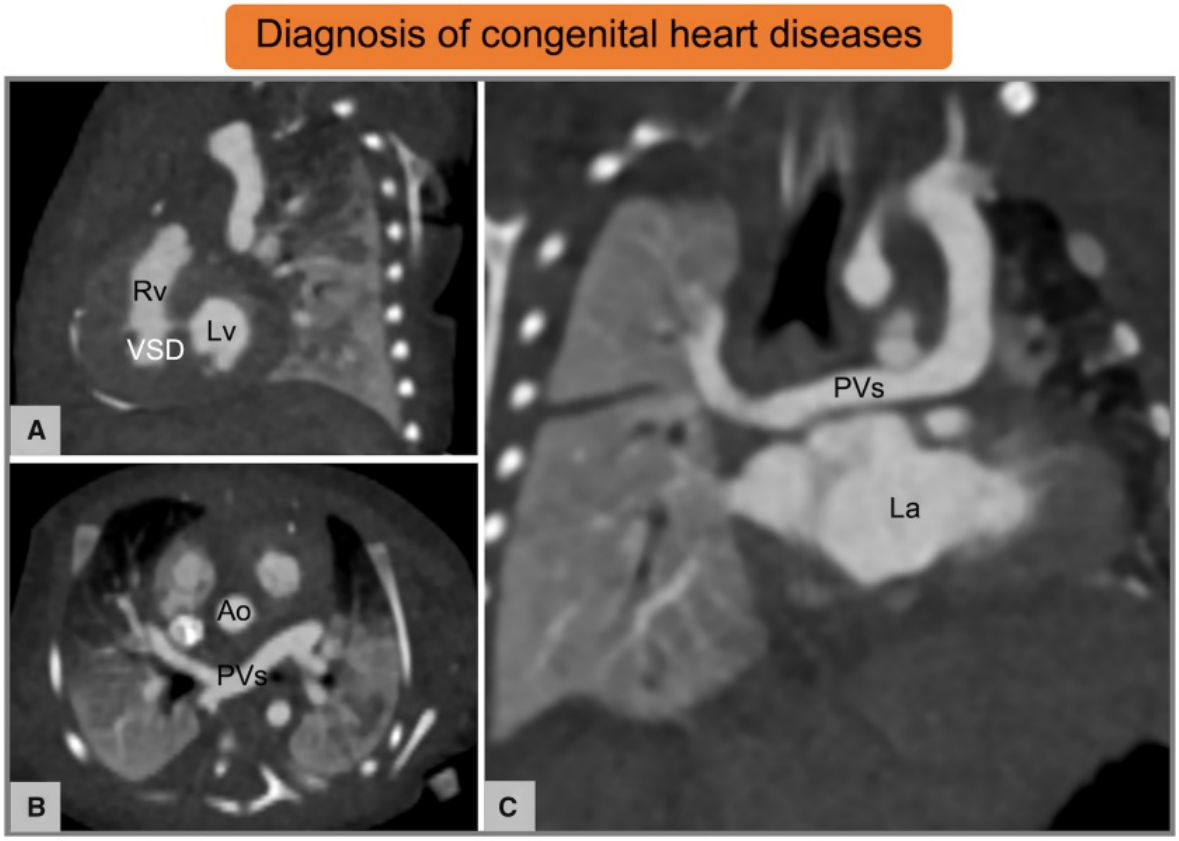
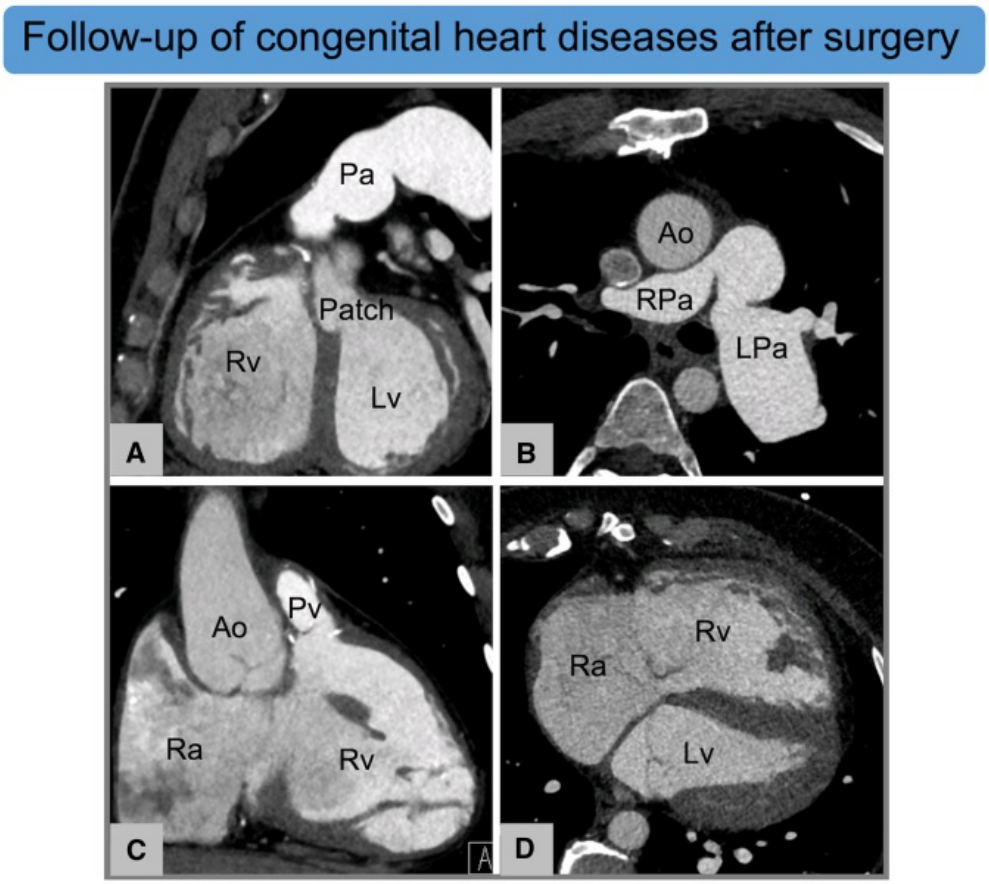


Figure 8 Cardiac CT for the postoperative follow-up of congenital heart disease. (*A–D*) Thirty-one-year-old male with repaired Tetralogy of Fallot, postsurgical LPa aneurism and Rv dilatation. Ventricular septal defect has been repaired by using a patch (*A*). Images by courtesy of Francesco Bianco, Ospedale Riuniti Ancona, Ancona (Italy). Ao, aorta; CT, computed tomography; LPa, left pulmonary artery; Lv, left ventricle; Pa, pulmonary artery; Pv, pulmonary vein;: Ra, right atrium; ~~RC, right coronary artery;~~ Rpa, right pulmonary artery; Rv~~V~~, right ventricle.



Evaluation of coronary anatomy in aortic dissection, aortic aneurysms, and pulmonary embolism scans

Since scans performed for aortic dissection and pulmonary embolism have been reported to be positive only in ~~<15%~~a small proportion of patients, evaluation of coronary arteries could be beneficial to explain the presenting symptoms.[173] In addition, if aortic dissection is the final diagnosis, knowledge of coronary atherosclerotic burden is essential to decide for concomitant coronary artery by-pass surgery. Similarly, thoracic aortic aneurisms are often associated with CAD[174] and, therefore, coronary evaluation is critical also in this category of patients.

Performing a single-phase, ECG-triggered CT angiography can improve image quality, thus allowing for the evaluation of coronary arteries as well as facilitating the detection of pulmonary emboli in small branches and a more accurate estimation of ascending aorta diameters.{Comment by Author: Please delete reference 173 from here}[173] Nevertheless, an obstacle to the implementation of this approach is the requirement of a specific training for the interpreting physician.

Key points

- ECG-triggered CT angiography is appropriate in patients presenting with symptoms of aortic dissection and pulmonary embolism to allow for the evaluation of coronary arteries (depending on the CT technology available and the training of the interpreting physician).
- ECG-triggered CT angiography is appropriate at the first diagnosis and follow-up after repair of thoracic aortic aneurysm to allow for the evaluation of coronary arteries (depending on the CT technology available and the training of the interpreting physician).

Radiomics and artificial intelligence

Rationale

The amount of imaging data has increased dramatically in recent years and so therefore has the quantitative information that can be extracted from them. The traditional image analysis approach based on visual assessment and interpretation of radiological images guided by previous training and experience may not capture all the information contained within these scans. In this context, radiomics and artificial intelligence (AI) techniques have been used at different levels, from image post-processing to diagnosis and prognosis. Although a detailed overview of the basic principles of radiomics and AI techniques is beyond the aim of this article, a brief explanation of these novel methods is provided in *Table 9*.[175–177]

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Table 9 Radiomics and data analytic methods applied to cardiac imaging

Technique	Definition 175-177 {Comment by Author: These indicate references}
Radiomics	Process by which quantitative features describing the texture and spatial complexity of the tissue are extracted from CT images.

Technique	Definition[175-177] {Comment by Author: These indicate references}
Machine learning	Sub-division of artificial intelligence, which uses computer algorithms to learn from data analysis, without being programmed for that specific task. Differently from conventional multivariable analysis based on probability theory, it derives pure statistical models to detect non-linear relationships between a large number of potential predictor variables.
Deep learning	Sub-division of machine learning, which uses deep neural networks to solve difficult problems.

CT, computed tomography.

Image post-processing

Deep learning (DL) methods have been investigated to improve the fully automated segmentation of different cardiac structures. Validated applications include quantification of coronary calcium[178] and epicardial adipose tissue,[179] where ~~deep learning~~DL techniques demonstrate good agreement with corresponding manual assessments. Similarly, on-site computation of FFR_{CT} based on machine learning (ML) showed equal performance to FFR_{CT} derived from the conventional computed flow dynamics approach in the detection of haemodynamically significant stenoses while reducing processing time.[62]

Diagnosis

Radiomics and ML algorithms have been used to optimize the extraction of information from cardiac CT images to facilitate CAD diagnosis. Examples of this application include automated stenosis grading,[180] plaque phenotyping,[181,182] CAD-RADS classification,[183] detection of lesion-specific ischaemia,[184] and identification of the napkin-ring sign.[181]

Prognosis

The accuracy of ML algorithms to predict adverse outcome has been evaluated in several studies.[185,186] In a recent study including 66 636 asymptomatic patients ~~from the CONSORTIUM population~~, Nakanishi *et al.*[185] demonstrated that a ML model including clinical variables, coronary calcium score, and CT variables extracted from non-contrast acquisition was superior to Atherosclerotic Cardiovascular Disease score and coronary calcium score alone in the prediction of cardiovascular and CAD death.

Key points

- Several AI algorithms, mainly involved in automated image segmentation, have been already implemented in the clinical routine.

Summary

In recent years, developments in CT technology have increased dramatically the amount of information that can be derived from cardiac CT. CCTA offers unrivalled information about coronary atherosclerotic plaque, with its ability to identify, characterize, and quantify coronary atherosclerosis allowing for accurate patient risk stratification and monitoring of treatment effect. Emerging technologies, such as ~~CT perfusion~~CTP imaging and computational flow dynamics, have overcome some of the limitations of CCTA, thus improving the identification of patients who might benefit from coronary revascularization. In near future, the next generation of randomized clinical trials will likely incorporate cardiac CT features extracted using radiomics or artificial intelligence-based models. These are likely to expand yet further the clinical applications of cardiac CT described in this consensus ~~statement~~document.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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References AQ10

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