

Cardiac computed tomography: from anatomy to function

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Ischaemic heart disease (IHD) is one of the world's leading causes of morbidity and mortality. Likewise, the diagnosis and risk stratification of patients with coronary artery disease (CAD) have always been based on the detection of the presence and extent of ischaemia by physical or pharmacological stress tests with or without the aid of imaging methods (e.g. exercise stress, test, stress echocardiography, single-photon emission computed tomography, or stress cardiac magnetic resonance). These methods show high performance to assess obstructive CAD, whilst they do not show accurate power to detect non-obstructive CAD. The introduction into clinical practice of coronary computed tomography angiography, the only non-invasive method capable of analyzing the coronary anatomy, allowed to add a crucial piece in the puzzle of the assessment of patients with suspected or chronic IHD. The current review evaluates the technical aspects and clinical experience of coronary computed tomography in the evaluation of atherosclerotic burden with a special focus about the new emerging application such as functional relevance of CAD with fractional flow reserve computed tomography (CT)-derived (FFR_{ct}), stress CT perfusion, and imaging inflammatory makers discussing the strength and weakness of each approach.

General considerations

Ischaemic heart disease (IHD) is one of the world's leading causes of morbidity and mortality.

It is therefore of great importance to identify the best diagnostic and therapeutic approach to prevent its costs in human, health and economic terms.

Until the introduction of coronary angiography and angioplasty, the study and treatment of IHD were solely based on the manifestations and indirect consequences of pathology, without being able to directly visualize the affected vessels and without the possibility to directly treat the lesions responsible for the symptoms.

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The introduction of invasive coronary angiography and, subsequently, coronary angioplasty, has revolutionized the possibilities of diagnosis and therefore of early treatment of coronary artery lesions, significantly improving patients' prognosis and quality of life.

Likewise, the diagnosis and risk stratification of patients with coronary artery disease (CAD) has always been based on the detection of the presence and extent of ischaemia by physical or pharmacological stress tests with or without the aid of imaging methods (e.g. exercise stress, test, stress echocardiography, SPECT or stress CMR). These methods show high performance to assess obstructive CAD, whilst they do not show accurate power to detect non-obstructive CAD.¹ Indeed, treating ischaemia is clearly crucial for symptom relief in patients with angina; but whether treating inducible ischaemia reduces the risk of MI is much more controversial. Initial data based on retrospective studies demonstrated that a moderate or severe grade of inducible ischaemia could predict the patient's outcome properly.² When data based on larger prospective trial, such as the COURAGE trial, became available, the direct comparison between the relative utility of anatomical and ischaemic burden of CAD for predicting outcomes showed a net result in favour of the anatomical evaluation (performed with invasive angiography in the specific case).³ Similar results were provided by a substudy of the landmark ISCHEMIA trial, which showed that ischaemia severity was not associated with increased mortality after adjusting for CAD severity. The increasing severity of CAD was instead independently associated with increased risk of death (HR: 2.72) and myocardial infarction (HR: 3.78) when comparing the most vs. least severe CAD subgroup.⁴

The introduction into clinical practice of coronary computed tomography angiography (CCTA), the only non-invasive method capable of analyzing the coronary anatomy, allowed to add a crucial piece in the puzzle of the assessment of patients with suspected or chronic IHD.

The introduction of cardiac computed tomography angiography

The first publications regarding the use of computed tomography (CT) to study the heart date back to the late 70s and the first years of the 80s.^{5,6} At that time, however, due to the presence of heavy artefacts from cardiac motion and the lack of powerful X-ray tubes, the focus of the research was shifted on the study of cardiac morphology and the detection of MI complications. In the upcoming years, the availability of new CT technologies (such as multidetector arrays and, in recent years, wide detector and dual source CT systems) has paved the way to the introduction in the everyday clinical routine practice of cardiac CT as a reliable and safe tool to assess the heart and, even most importantly, the coronary arteries.

The introduction of CCTA has represented a cornerstone in the cardiological clinical practice, as it offers, among the multiple imaging methods available to study the heart, the unique possibility of reliably visualizing the coronary artery tree without the need of an invasive procedure. This feature has important advantages, because it permits to detect CAD also in its non-obstructive form, allowing a pharmacological and/or invasive approach tailored on the effective burden of CAD of the single patient.

Nowadays, the current European clinical practice Guidelines, on the basis of previous landmark trials,⁷ have upgraded the role of CCTA to Class I indication as the initial test to rule-out CAD in patients with low-to-intermediate pre-test probability, equalling its position to the one of the other functional imaging tests.¹

Indeed, new tools are contributing to enrich the anatomical analysis beyond the simple luminal stenosis grading, as in the case of plaque characterization or epicardial and pericoronary adipose tissue quantification. Moreover, in the setting of patients with known CAD or with a history of previous revascularizations, the performance of a pure anatomical assessment can be more limited. In this context, CCTA is the only non-invasive imaging method that offers the opportunity to integrate a functional study on top of a complete anatomical coronary description, by the use of CT-derived FFR or stress CT perfusion.

In the present review, we will summarize the current evidence in Literature supporting the use of CCTA as a unique diagnostic and prognostic tool in IHD, since it allows a comprehensive study of CAD, from anatomy to function.

Coronary artery calcium score

Coronary artery calcium score (CAC score) represents one of the most useful imaging-screening tool available in cardiovascular medicine.

The acquisition and reconstruction settings of CAC imaging have been progressively standardized. CT scans are acquired in basal conditions only, with ECG triggering in late diastole, with a standard tube voltage setting of 120 kV, that should not be changed to avoid biases in measuring calcium attenuation and Hounsfield Units (HU) values.⁸ An example of CAC scoring is shown in [Figure 1](#).

Detecting and measuring coronary calcium, in fact, is not a mere radiological collateral finding, but it is nowadays considered a specific marker of atherosclerosis. Therefore, CAC score can be applied to improve risk stratification for CV events both in asymptomatic and symptomatic patients, on top of traditional cardiovascular (CV) risk factors and clinical scores.

Large, population-based cohort studies have contributed to establish CAC score as an important risk stratification tool in asymptomatic patients; the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective multicentre study, confirmed the prognostic potential of CAC score over traditional CV risk factors across more than 6000 people with a wide distribution in terms of age (from 45- to 84-years-old), ethnicity and sex.⁹

For what concerns symptomatic patients, the last European Society of Cardiology (ESC) Guidelines on chronic coronary syndromes proposed the use of CAC score as one of the determinants of the clinical likelihood of obstructive CAD on top of a clinical score based on age, sex and nature of symptoms.¹

In line with ESC Guidelines indication, Winther *et al.*¹⁰ developed, on a large cohort of more than 40 000 symptomatic patients, two models of assessment of pre-test likelihood of CAD: one weighted on age, gender, chest pain characteristics and CV risk factors and the second that included the CAC score on top of the first clinical model. The two risk-assessment tools were validated on a large and heterogeneous population of more than 15 000

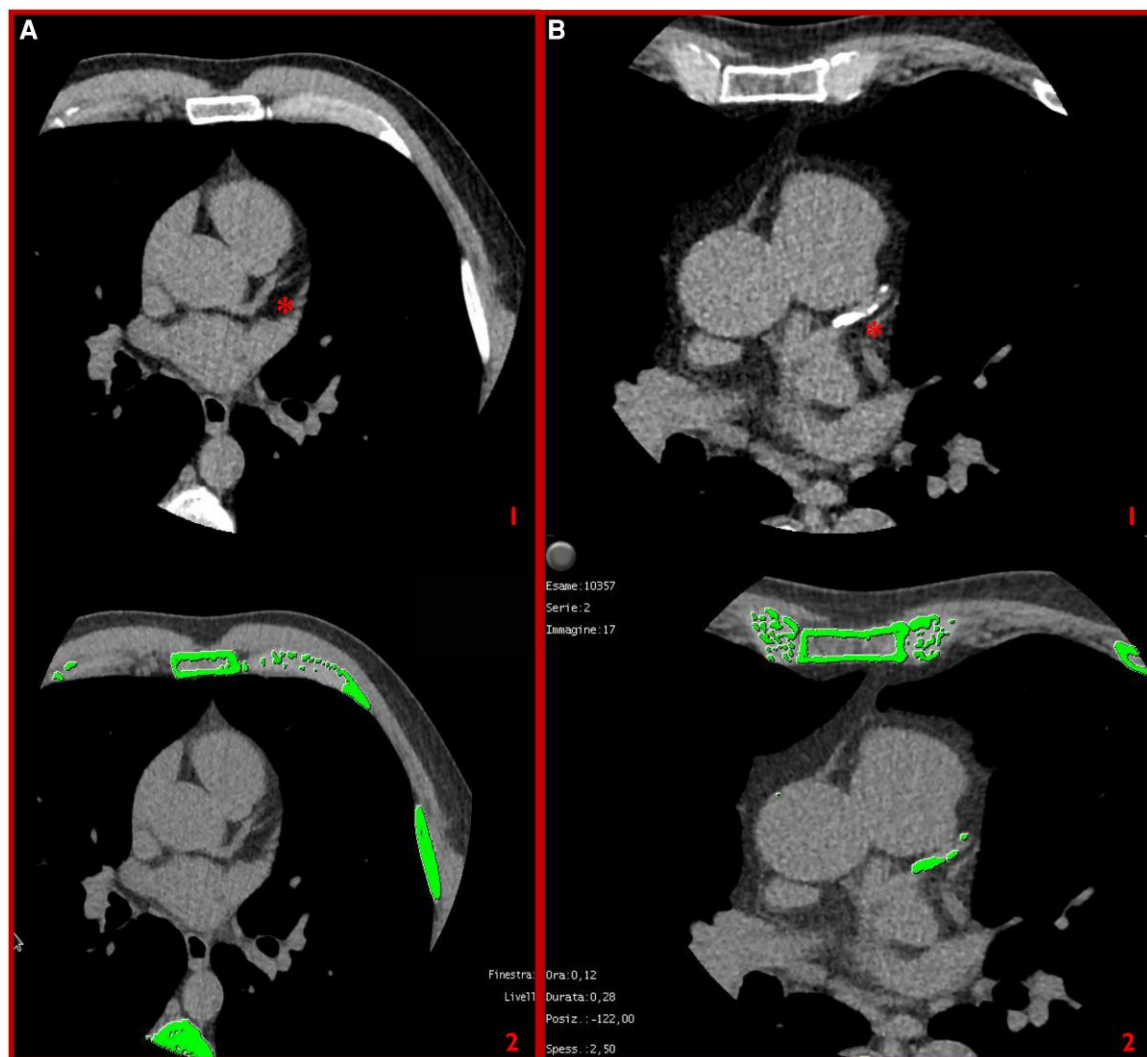


Figure 1 Panel A shows the axial CT scan¹ and the semiautomatic CAC scoring application² of a 54-year-old man with a complete absence of CAC, agatston score 0. Panel B the axial CT scan¹ and the semiautomatic CAC scoring application² of a 63-year-old man with heavy calcifications on the LAD artery, Agatston score 1120. CAC, coronary artery calcium; LAD, left anterior descending.

patients with the evidence that CAC score-empowered risk stratification clearly overperformed the diagnostic power of the clinical-based model (AUC 84.9 vs. 74.9, respectively).

Finally, despite not being validated in any guideline indication, evidence is growing supporting a role of CAC score, on top of clinical risk stratification tools, to guide aspirin and statin primary prevention therapy.¹¹ In particular, the presence of a completely negative calcium score (namely Agatston score = 0) has a very high negative predictive value and correlates with a high probability of not having clinical events in the following 5 years.¹² CAC score is therefore able to reclassify in lower risk categories patients who, according to current clinical risk scores, would have benefited from primary prevention drug therapy.¹¹

Anatomical CT analysis

The assessment of coronary luminal stenosis (namely the degree and localization) is currently the most common method of quantification of CAD in everyday clinical

practice and portends a defined prognostic role.¹³ After reconstructing the branches of the coronary tree, many clinical software allow a rapid quantification of the percentage of luminal stenosis, thus allowing the referring physicians to classify the coronary heart disease according to the CAD-RADS system.¹⁴ However, evidence is growing in the Literature to support a more comprehensive analysis of coronary artery disease, especially through tools that provide a comprehensive evaluation of the atherosclerotic plaque and the structures surrounding it, such as pericoronary fat [pericoronary adipose tissue (PCAT)].

Plaque imaging

CCTA has rapidly advanced beyond the anatomical assessment of the luminal stenosis and is nowadays able to offer a complete anatomical assessment of the atherosclerotic plaque.

As aforementioned, the extension and degree of luminal stenosis provides important prognostic information. However, a solid body of evidence has gained in the last

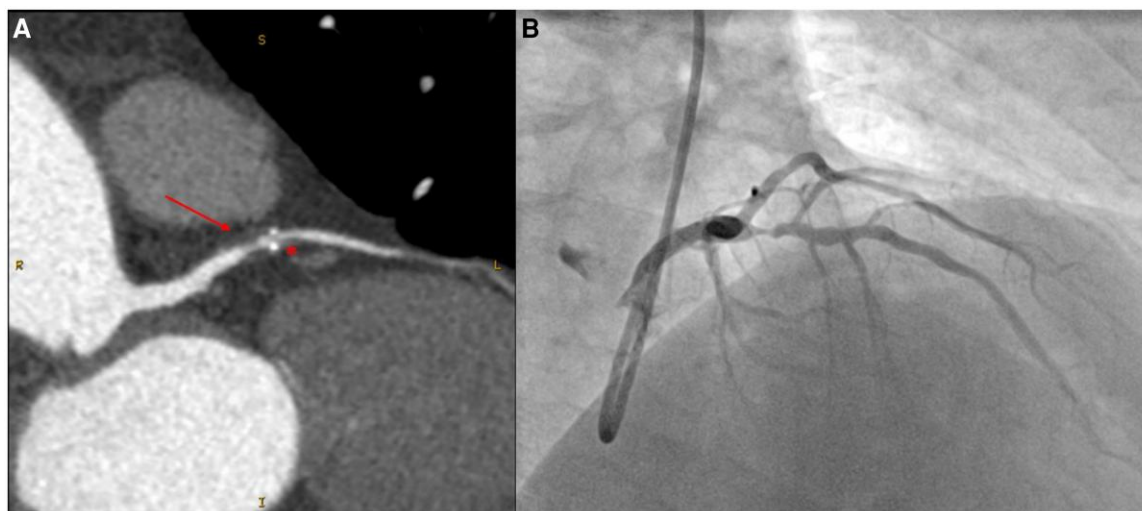


Figure 2 Significant stenosis of the proximal LAD at CCTA (panel A) and ICA (panel B) evaluation. At CCTA evaluation plaque analysis enables the recognition of two features of HRP: positive remodelling (light-grey area indicated by the arrow) and spotty calcifications (asterisk). CCTA, coronary computed tomography angiography; LAD, left anterior descending; ICA, invasive coronary angiography; HRP, high-risk plaque.

years to support the concept that, although acute cardiovascular events increase along with the percentage of luminal stenoses, most precursors of acute coronary syndrome (ACS) cases are related to non-obstructive CAD.¹⁵

Moving from this assumption, an important number of studies has verified the crucial prognostic role that a complete plaque characterization can portend both in an acute and chronic clinical setting. CCTA can, in fact, rapidly high-risk plaque (HRP) features such as the presence of spotty calcifications (little, focal calcifications with <3 mm of size, see Figure 2), positive remodelling (outer vessel diameter increased by at least 10% in correspondence of the plaque when compared with the reference segment of the same vessel, see Figure 2), low attenuation (low values of attenuation inside the plaque, namely with values of <30 HU), and the Napkin-Ring Sign (ring-like peripheral higher attenuation of the non-calcified portion of the atherosclerotic plaque).¹⁶

The presence of any of these high-risk characteristics has been associated to an impressive increase of the relative risk (RR 32) of experiencing an ACS in a substudy of the ROMICAT II trial that stratified 472 patients who underwent CCTA in the emergency department. Importantly, this result was maintained after adjustment for the presence of 50% or 70% coronary stenoses.¹⁶

Similar results were obtained in a substudy of the PROMISE trial, when analyzing the contribute of HRP features in the prognostication of symptomatic outpatients with stable CAD. The analysis, conducted on more than 4000 patients, revealed that the presence of HRP features were associated with a higher major cardiovascular event (MACE) rate (6.4% vs. 2.4%; hazard ratio, HR, 2.73).¹⁷ This association persisted after adjustment for clinical CV risk score and the presence of significant stenoses (adjusted HR, aHR: 1.72).

Finally, plaque characterization is useful also to guide a powered primary prevention therapy. In this context, in fact, the results from PARADIGM trial revealed that, at serial CCTA scan assessment, patients under statin therapy showed a slower progression of overall coronary

atherosclerosis volume compared to statin-naïve patients.¹⁸ Moreover, statin treatment showed high efficacy in mitigating the risk connected to the present atherosclerotic pathology by stabilizing the plaque. At CCTA follow-up, in fact, the authors reported an increased burden of calcified components at expenses of the non-calcified portions of the atheroma and a significant reduction in the number of plaques with high-risk features.¹⁸

Epicardial and pericoronary adipose tissue

Systemic and vascular inflammation are well-known stimuli for coronary atherosclerotic plaque formation and instabilization, leading to plaque rupture and ACS manifestations also in presence of non-obstructive CAD.

The detection of the inflammation of the vascular wall is, however, challenging since no blood or imaging tests are capable of directly detecting this important phenomenon. In the last years, interest has grown on the modifications that CCTA can identify in the adipose tissue surrounding the heart and, more specifically, the coronary arteries (namely the PCAT).

In 2017, Antonopoulos et al.,¹⁹ starting from the observation that vascular inflammation inhibits adipogenesis in the perivascular adipose tissue, identified a novel CT marker of vascular inflammation, called perivascular fat attenuation index (FAI), which consists in the detection of shifting in the attenuation values of the PCAT from values close to -200 HU, typical of lipid layers, to less negative values (e.g. -30 HU), typical of the aqueous phase compatible with inflammation.

The same group demonstrated, with a post-hoc analysis of prospective outcome data (CRISPR CT study), the prognostic role of FAI which has the power to enhance CV risk prediction over the established CV risk scores.²⁰ Oikonomou et al. also established a FAI cut-off (values equal or above -70.1 HU), above which identified patients at high-risk of all-cause mortality (aHR: 2.55, $P < 0.000$) and cardiac mortality (aHR: 9.04, $P < 0.0001$).²⁰

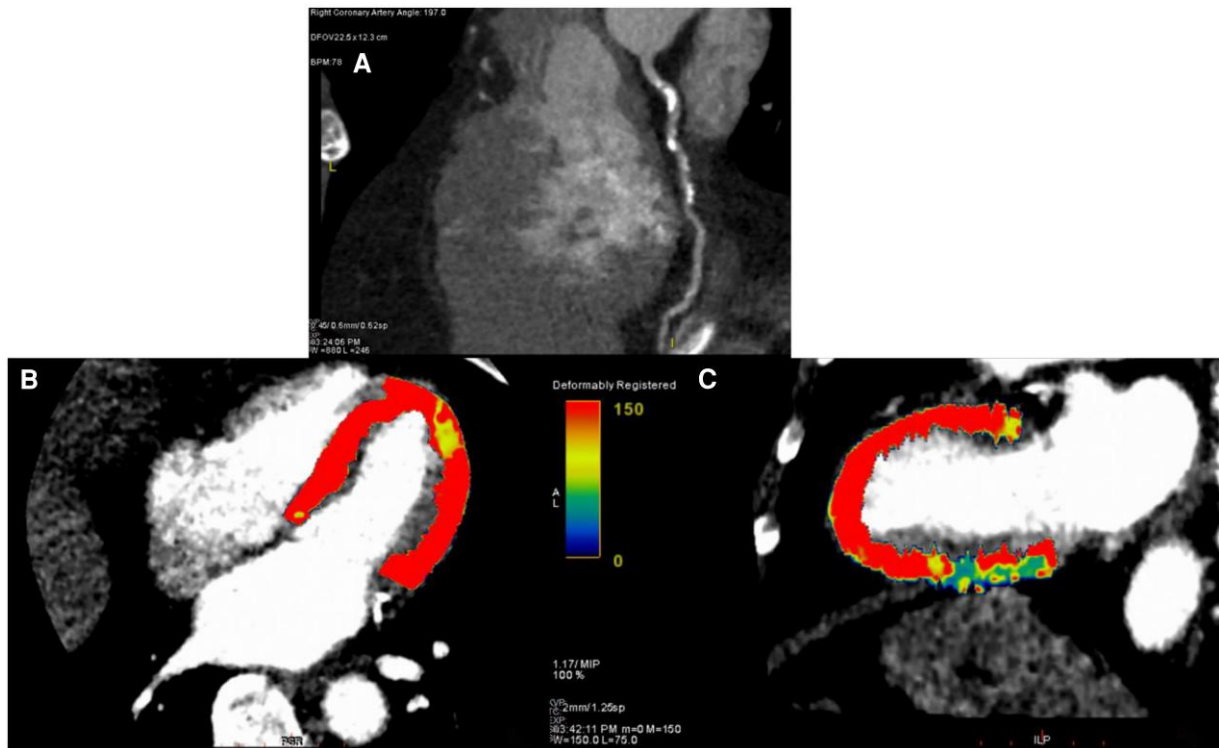


Figure 3 Heavy calcifications of the proximal and mid RCA do not allow a reliable luminal stenosis quantification (*panel A*). The study of myocardial perfusion enhances the diagnostic power of the CT scan, showing a pathologically reduced MPI in the corresponding territory of coronary distribution (mid and basal inferior wall, green and blue zones in *Panels B and C*) *CT*, computed tomography; *MPI*, myocardial perfusion imaging; *RCA*, right coronary artery.

This evidence paves the way to targeted therapy against inflammation, which have already shown the potential to decrease cardiovascular risk in the CANTOS trial, a randomized, double-blind study that proved the role of canakinumab, a powerful monoclonal antibody antagonist of interleukin-1 β .²¹ In the trial, canakinumab was used as a secondary prevention therapy in patients with a previous MI. The anti-inflammatory therapy decreased the risk of CV events and death compared with placebo (HR: 0.85; $P=0.02$) during a median follow-up of 3.7 years.²¹

Functional CT analysis

As highlighted from the Scot-Heart and other major trial abovementioned, a clinical strategy completely based on the anatomical assessment of CAD provided by CCTA provides the clinician with a large number of reliable prognostic information, helping also in tailoring pharmacological and invasive therapy on a single patient base.⁷ So comes the question, do we still need to assess ischaemia or the advent of CCTA has led us to a pure anatomical approach?

An important answer to this question has been provided by the results of the CREDENCE trial,²² that demonstrated on a cohort of 612 patients that a comprehensive anatomic interpretation with CCTA (namely the quantification of obstructive and non-obstructive atherosclerotic plaque, percentage of non-calcified atheroma volume, lumen volume, the number of lesions with HRP and the number of lesions with stenosis greater than 30%) was superior to functional imaging in the diagnosis of invasive FFR (AUC 0.81 for CCTA vs. 0.67 respectively, $P<0.001$).

However, the scenario of patients with known CAD or of those with a previous surgical or percutaneous revascularization is significantly more complex, challenging the ability of non-invasive anatomical coronary imaging in correctly assessing patients' prognosis. In this subset of patients, additional information regarding the functional significance of CAD would still be useful, even in presence of a complete anatomical assessment.

In this context, CCTA is the only non-invasive test that offers the possibility to integrate the anatomical and functional evaluation in a single exam. Two are the options nowadays available to investigate the presence of inducible ischaemia with cardiac CT: CT-derived fractional flow reserve (FFR_{CT}) and perfusion CT (CTP). In the next paragraph, we will summarize their applicability and prognostic implications.

CT-derived FFR

The invasive measure of fractional flow reserve actually represents the gold standard for the functional evaluation of coronary stenoses when performing ICA. After intra-arterial administration of adenosine, the invasive measurement is performed with a dedicated tool and values below 0.8 are considered indicative of functionally significant coronary stenoses.

FFR_{CT} has been introduced to derive the same measure of the invasive approach with the use of a non-invasive method. FFR_{CT} is based on fluid dynamics algorithms developed by HeartFlow (HeartFlow Inc., Redwood, CA, USA), that simulate the effect of arterial injection of adenosine and reproduce the invasive measure only on the base of

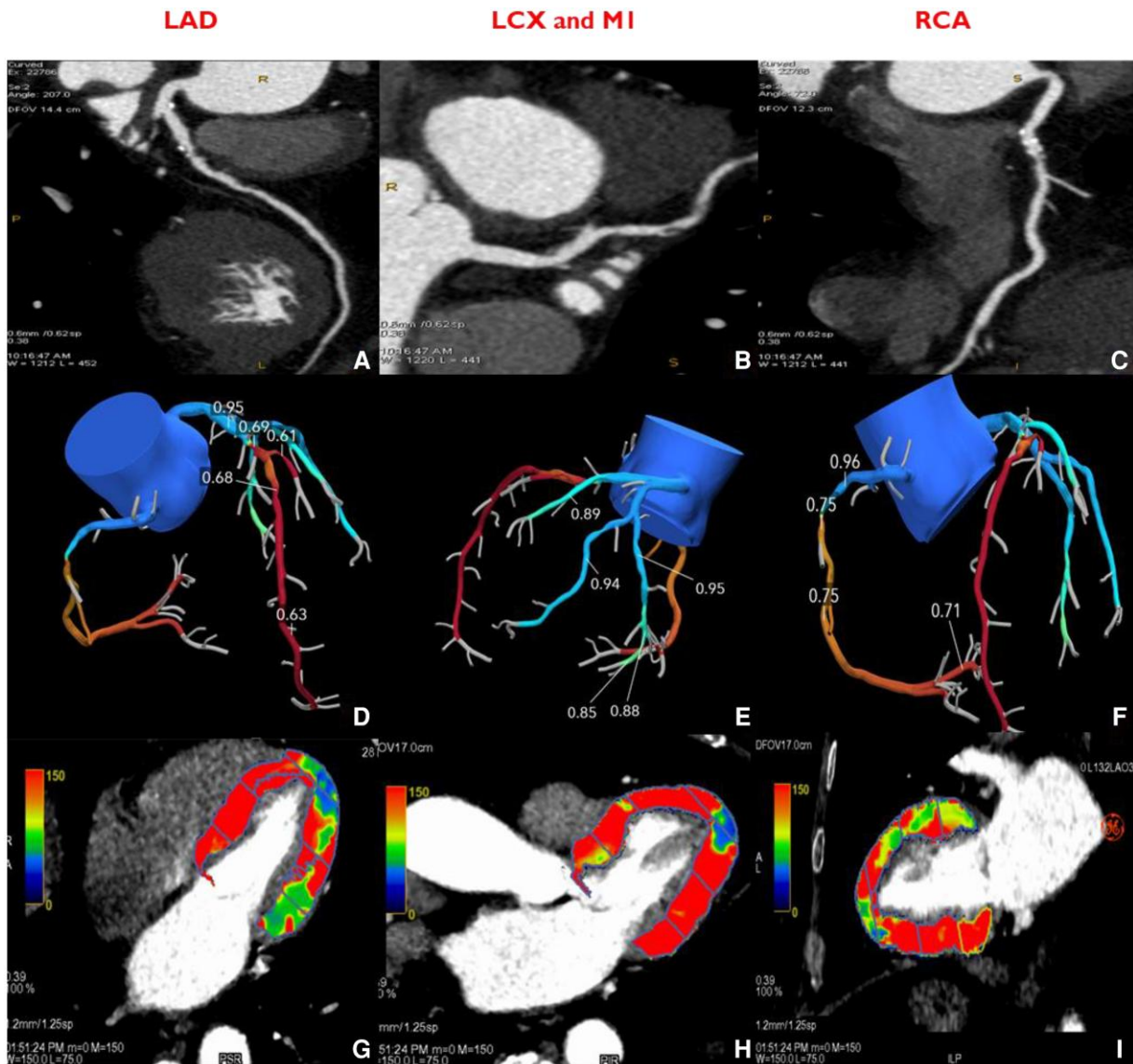


Figure 4A Clinical case of a 75-year-old man with stable chest pain. The figure depicts a complete anatomical and functional assessment with the use of CCTA, CT-derived FFR and CTP. *Panels A, D and G* depict severe pathology of LAD with corresponding values of pathological CT-derived FFR and lower MPI in the LAD and diagonal territory of distribution. *Panels B, E, and H* depict significant pathology of M1, without corresponding pathological values of CT-derived FFR and MPI. *Panels C, F, and I* show moderate pathology of proximal RCA, with borderline values of CT-derived FFR and normal MPI in the RCA territory of distribution. CCTA, cardiac computed tomography angiography; FFR, fractional flow reserve; CTP, computed tomography perfusion; MPI, myocardial perfusion index; LAD, left anterior descending; M1, first marginal branch; RCA, right coronary artery.

coronary anatomy, provided by traditional CCTA, performed without the need of special acquisition protocols. FFRct algorithm has been progressively improved to overcome initial limits, especially connected with high coronary calcium burden, and has subsequently proven its unquestionable reproducibility in respect to its invasive counterpart in the NXT trial (AUC for the detection of functionally significant CAD: CCTA vs. invasive FFR: 0.81; FFRct vs. invasive FFR: 0.90, $P=0.0008$).²³ Importantly, the NXT trial also showed that FFRct correctly reclassified 68% of patients with coronary CTA false-positive findings and 67% of those with coronary CTA false-positive vessels as true negative.²³ This observation paved the way for a larger clinical application of FFRct. In fact, it highlighted

that, despite being an expensive tool that needed to be added to an already efficient technique (i.e. CCTA), FFRct was able to reclassify 2/3 of false-positive results from CCTA, avoiding a great number of unnecessary and expensive invasive procedures. Moving from these bases, the PLATFORM trial confirmed the equivalent clinical outcomes of using CCTA plus FFRct vs. standard care (ICA) in patients with stable, new onset chest pain and highlighted a positive cost-effectiveness ratio in favour of the FFRct approach, obtained with a net reduction of inappropriate ICAs.²⁴

An interesting field of application of the combined approach with CCTA and FFRct is the evaluation of patients with left main disease or three-vessel CAD to guide the

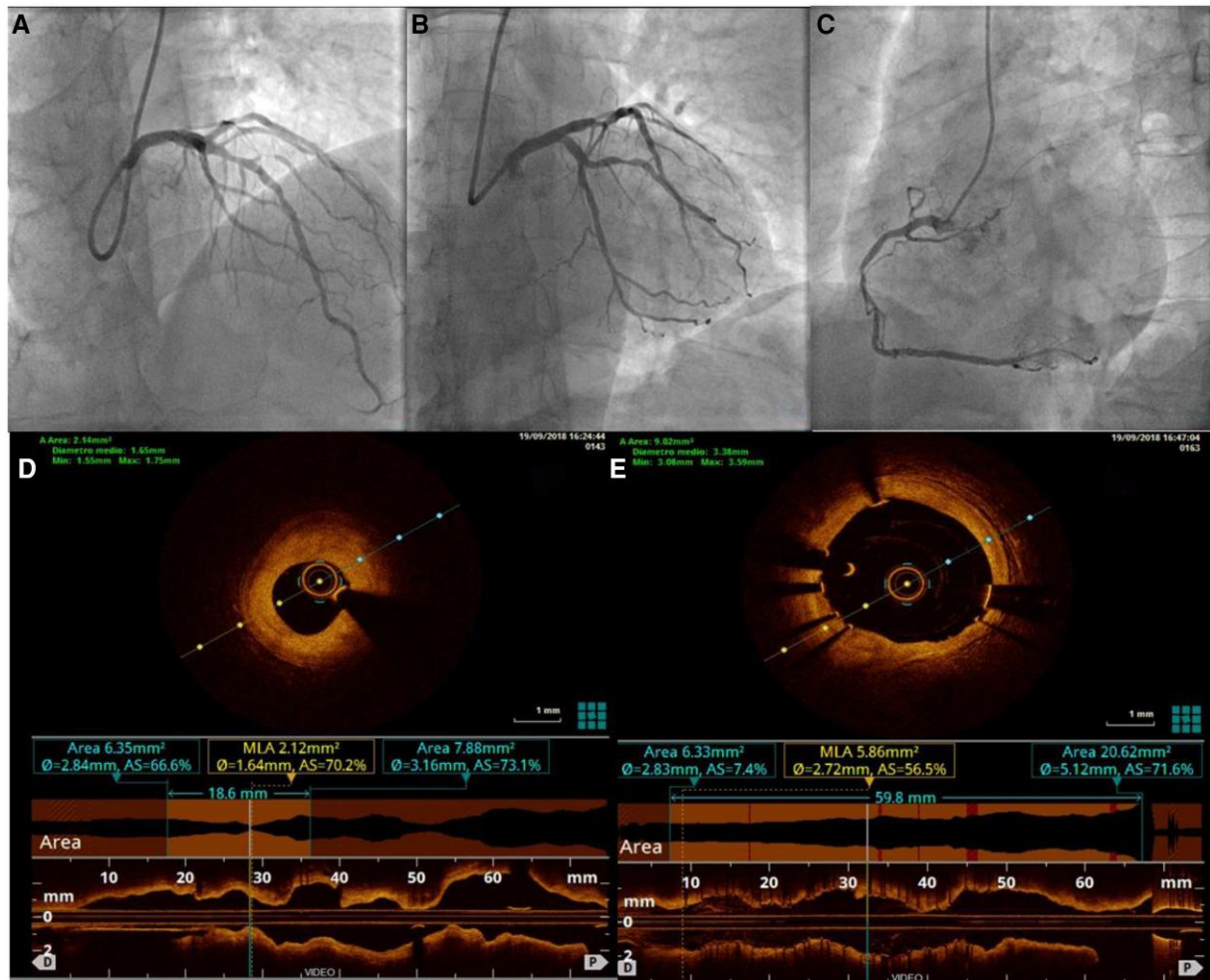


Figure 4B Invasive evaluation with ICA and OCT of the patient presented in Figure 4A. ICA confirmed the presence of significant pathology on LAD and M1 and of moderate pathology on RCA (Panels A, B and C respectively). Pre and post angioplasty OCT on LAD is depicted in Figure D and E. M1 was treated in a subsequent procedure. ICA, invasive coronary angiography; LAD, left anterior descending; M1, first marginal branch; RCA, right coronary artery; OCT, optical computed tomography.

decision of Heart Teams towards a percutaneous or surgical revascularization. In 2018, Collet et al. validated the feasibility of using the non-invasive integrated approach to calculate a ‘non-invasive’ Syntax Score, with good accuracy when compared to the calculation through invasive pressure-wire assessment. The accuracy was particularly increased thanks to integration of functional to anatomical assessment (AUC 0.85 in the detection of functionally significant stenoses).²⁵ A subsequent paper, moving from this evidence, showed good agreement between the decision of the revascularization strategy between two groups of blinded Heart Teams, each using the non-invasive or the invasive Syntax Score to evaluate real patients’ cases (agreement in 93% treatment recommendations, Cohen’s kappa 0.82).²⁶

CT-derived myocardial perfusion imaging

CTP imaging is a valid alternative to FFRct in adding a functional evaluation to the anatomical evaluation provided by CCTA. This technique, alike FFRct, needs the performance of dedicated acquisitions, thus increasing patients’

radiation exposure, and the use of stressors agents such as adenosin or regadenoson. These disadvantages of CTP in respect to FFRct are however balanced by important aspects. CTP does not rely on geometrical and fluidodynamic assumptions, but on a more physiological evaluation after a stressor stimulus and it is probably more reliable in evaluating microcycle dysfunctions; moreover, alike FFRct, CTP is not limited by the presence of previous revascularizations, either surgical or percutaneous. This consideration is not trivial, if we consider that the request for CT-based examinations in the context of chest pain recurrences in patients with previous revascularizations is steeply increasing.

Finally, CTP exams can be acquired either by the use of a static or dynamic protocol. The former is performed using a single acquisition phase after contrast medium first-pass and the detection of inducible ischaemia is based on the qualitative visual assessment of myocardial areas of lower blood flow, which are visualized as ‘black areas’. The latter is based on multiple and rapid CT scans acquisitions (from 20 to 25) during the wash-in and wash out phases of the contrast medium and needs a dedicated post-processing; however, it ensures quantitative data on

myocardial blood flow (MBF) levels, which are less prone to inter-observer variability and to less beam hardening artefacts.²⁷ An example of dynamic CT scan is provided in *Figure 3*.

A direct comparison between the two functional CT methods applied to CCTA (i.e. FFRct plus CCTA vs. CTP plus CCTA) has been performed in the PERFECTION trial, which demonstrated a comparable diagnostic performance of the two functional techniques in evaluating CAD in 147 symptomatic patients referred for ICA.²⁸ Interestingly, both static and dynamic perfusion techniques showed good and similar performances.²⁸

In the next future, a possible approach to study symptomatic patients with intermediate pre-test risk of CAD will be represented by the use of CCTA to rule-out obstructive CAD with the addition of FFRct alone or plus stress CTP in FFRct grey zones to better assess functionally relevant significant stenoses.²⁷ An interesting clinical case of an integrated non-invasive and invasive anatomical and functional evaluation is provided in *Figure 4A and B*.

Conclusions

Drawing the conclusions from what has been exposed so far, it is clear that CCTA portends the great potential to progressively become the cornerstone examination in the great majority of patients with a suspected or concealed CAD and the fundamental gatekeeper for invasive coronary angiography.

The limitations that nowadays impact more on a wider spread of CCTA are connected to the concerns for the exposure to radiations and to the cost of the technique if compared with simpler tests like effort stress test. Finally, CCTA reports are time-consuming and a steep increase in their number would for sure represent a concern.

Research is actually addressing each of these limitations, to favour the widespread of CCTA. First, new technologies as photon-counting CTs and artificial intelligence algorithms are progressively and dramatically lowering radiation exposure without affecting diagnostic quality; second, CCTA cost-effectiveness has been established in a solid body of Literature and its use represents an investment to avoid more expensive and futile invasive examinations. Moreover, the introduction of increasingly integrated functional and anatomical non-invasive approaches will even increase the efficacy of CCTA also in economic terms. Finally, the introduction of artificial intelligence has the potential to rapidly change reporting workflow, for example shorten the time needed for images reconstruction or by providing pre-reading chem

evaluation of normal exams, to let the reporting physician to focus only on pathological examinations.

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Data availability

Data included in the present article are stored in Centro Cardiologico Monzino clinical electronic database.

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