



Review



Perspectives in noninvasive imaging for chronic coronary syndromes

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ARTICLE INFO

Keywords:

Myocardial ischemia

Imaging

Echocardiography

Cardiac magnetic resonance

Nuclear imaging

CCTA

ABSTRACT

Both the latest European guidelines on chronic coronary syndromes and the American guidelines on chest pain have underlined the importance of noninvasive imaging to select patients to be referred to invasive angiography. Nevertheless, although coronary stenosis has long been considered the main determinant of inducible ischemia and symptoms, growing evidence has demonstrated the importance of other underlying mechanisms (e.g., vasospasm, microvascular disease, energetic inefficiency). The search for a pathophysiology-driven treatment of these patients has therefore emerged as an important objective of multimodality imaging, integrating "anatomical" and "functional" information. We here provide an up-to-date guide for the choice and the interpretation of the currently available noninvasive anatomical and/or functional tests, focusing on imaging techniques (e.g., coronary flow velocity reserve, stress-cardiac magnetic resonance, hybrid imaging, functional-coronary computed tomography angiography, etc.), which could provide deeper pathophysiological insights to refine diagnostic and therapeutic pathways in the next future.

Abbreviations: CAD, coronary atherosclerotic disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CFVR, coronary flow velocity reserve; CMR, cardiac magnetic resonance; CTP, computed tomography perfusion imaging; ECG, electrocardiogram; FFR, fractional flow reserve; GLS, global longitudinal strain; ICA, invasive coronary angiography; LAD, left anterior descending coronary artery; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; MBF, myocardial blood flow; MCE, myocardial contrast echocardiography; MI, myocardial infarction; MPI, myocardial perfusion imaging; PAD, posterior descending coronary artery; PET, positron emission tomography; PSS, post-systolic shortening; PTP, pre-test probability; SE, stress echocardiography; SPECT, single photon emission computed tomography; STE, speckle tracking echocardiography.

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<https://doi.org/10.1016/j.ijcard.2022.07.038>

Received 10 May 2022; Received in revised form 5 July 2022; Accepted 21 July 2022

Available online 25 July 2022

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1. Introduction

A diagnostic algorithm for patients with suspected chronic coronary syndromes (CCS) has been proposed, articulated into 6 steps: 1) exclusion of acute conditions, 2) comprehensive clinical evaluation, 3) first-line examinations (e.g., transthoracic echocardiogram), 4) assessment of the pre-test probability (PTP), 5) choice of a diagnostic testing, 6) choice of the appropriate therapy. When the PTP is intermediate, either the assessment of vessel anatomy through coronary computed tomography angiography (CCTA) and/or of inducible myocardial ischemia, through a functional stress testing, is advised. In the latter case, preference should be given to imaging testing (stress echocardiography – SE, cardiac magnetic resonance – CMR, single photon emission computed tomography – SPECT, or positron emission tomography – PET) over stress electrocardiogram (ECG), because of its lower diagnostic accuracy. CCTA should be preferred when the PTP is low-to-intermediate, and functional testing when the PTP is intermediate-to-high. A functional imaging test is also recommended when CCTA results are non-diagnostic, and vice versa [1]. A different algorithm has been proposed in the American guidelines for the evaluation and diagnosis of chest pain [2]. Here patients with stable symptoms and classified to be at low risk may be discharged without any second-level test (considering the assessment of coronary calcium and/or stress-ECG), while either functional imaging or CCTA are recommended for patients at intermediate-to-high risk [2].

An ever-deeper knowledge of the strengths and limitations of functional and anatomical imaging is required to the clinicians when approaching the conundrum of CCS, especially after the results of ISCHEMIA trial in which an initial invasive strategy did not show any benefit in patients with CCS and moderate or severe ischemia [3].

The present review aims to provide an overview of imaging modalities for a comprehensive management of CCS patients, focusing on less commonly used techniques, and future perspectives.

2. Functional versus anatomical imaging

Both functional and anatomical aspects must be considered in patients with suspected CCS to tailor the best therapeutic approach. In particular, functional assessment may be crucial to identify the mechanisms behind myocardial ischemia, and, eventually, angina, thus guiding symptomatic treatment. On the other hand, the identification of CAD may prompt the implementation of preventive strategies, thus reducing the risk of major adverse events [4].

Although ischemia has been historically associated with poor outcomes, ever more evidence suggest that the atherosclerotic more than the ischemic burden is the major determinant of myocardial infarction (MI) or death in patients with CCS⁵. While the use of outdated and heterogeneous tests may have contributed to these findings, the possible operator-, structure-, and/or vendor-dependence is another limit of functional imaging [6,7], which could be overcome through novel evidence-based techniques. Since myocardial ischemia could be secondary to mechanisms other than atherosclerosis (e.g., vasospasm, microvascular dysfunction, energetic mismatch), advanced imaging may thus provide pathophysiological information to tailor therapeutic choices, aimed at alleviating symptoms, and improving quality of life [8].

CCTA represents the gold standard anatomical test for CCS. It allows the visualization of coronary anatomy (useful to rule out congenital anomalies) [9], the quantification of coronary calcium (a predictor of adverse events) [10], and the detection of coronary stenoses, graduating their severity and detailing plaques' composition [11]. Considering its high sensitivity, CCTA may be the optimal choice to rule-out obstructive CAD [11]. Moreover, by quantifying the atherosclerotic burden CCTA yields crucial prognostic information [5]. In this regard, the demonstration of CAD, also in absence of obstructive lesions, may significantly reduce the risk of major cardiovascular events by incentivizing the

adoption of a secondary prevention strategy (i.e., high-intensity statins and antiplatelet therapy) [11–13]. On the other hand, since traditional CCTA does not provide functional information, the symptoms of patients with nonobstructive-CAD may be downplayed, missing therapeutic opportunities. The implementation of functional analyses may overcome these limits [14].

3. Functional imaging

3.1. Stress-echocardiography

Among functional tests, SE is accurate for the assessment of extent of myocardial ischemia, accessible, cheap, and potentially performed bedside [15]. During SE, the transient change in regional function during stress is considered the diagnostic endpoint for the detection of myocardial ischemia, since in the presence of coronary obstruction the reduction in sub-endocardial blood flow results in a reduction in wall thickening and endocardial excursion in the ischemic regions [16].

Exercise stress, when practicable, should be preferred providing information related to physical tolerance. Otherwise, pharmacologic stressors such as dobutamine or arteriolar dilators (e.g., dipyridamole, adenosine, and ragadenoson) may be used. Whereas dobutamine holds adrenergic-like properties, vasodilators induce myocardial ischemia by inducing a diversion of coronary blood flow from regions supplied by critical stenosis toward those supplied by normal vessels (coronary steal) [16].

Response to stress stimuli can be divided in different patterns: normal, characterized by a reduction of left ventricle (LV) dimensions compared and an increase in endocardial motion and systolic wall thickening; ischemic, characterized by an increase in LV systolic dimension and wall motion abnormalities identified with ≥ 2 adjacent segments; viable, characterized by improvement of contractile function after the administration of an inotropic agent. In patients with resting regional wall motion abnormalities but viable myocardium, high dose of dobutamine may show a typical biphasic response, characterized by improved contractility in the dysfunctional segments at low doses and a new ischemic impairment of wall motion at higher doses. Low dose or combined low and high dose of dobutamine infusion protocols retain well-balanced sensitivity (75–80%) and specificity (80–85%) for identification of viable segments with functional recovery after revascularization [17].

Finally, SE could also be used in the suspect of vasospasm, by using either physiological (e.g., hyperventilation, cold pressor test) or pharmacological triggers (e.g., ergonovine) and providing important prognostic implication [18,19].

3.1.1. Coronary flow velocity reserve

CFVR is the ratio between maximal hyperemia (obtained with a vasodilator) and baseline coronary flow, which may be assessed through an ultrasound probe sampling the coronary Doppler velocity [20].

Although CFVR can be measured on all 3 coronary arteries, the distal portion of the left anterior descending (LAD) artery is most easily investigated, followed by the posterior descending artery (PDA), and by the circumflex artery. Technical feasibility to investigate LAD is high, reaching >90% in experienced hands and nearly 100% with the use of contrast agents, and both inter- and intra-observer variability remain low [20]. A CVFR >2 is considered a normal value, while a lower ratio has been shown to predict myocardial ischemia with >90% sensitivity and specificity, secondary to either epicardial CAD or microvascular dysfunction [21].

In patients with established CAD, CFVR is a useful tool to assess the functional significance of intermediate stenoses and when CFVR is >2 revascularization could be safely deferred [21,22], while a CFVR <2 in the LAD after a successful PCI predicted restenosis with a high sensitivity (78–89%) and specificity (90–93%) [23]. The diagnostic accuracy in detecting myocardial ischemia of CFVR has been compared with

fractional flow reserve (FFR) in a prospective study including 172 vessels of 140 patients with at ≥ 1 stenosis $\geq 50\%$ in a major epicardial artery, identifying an optimal cut-off of 2.2 [24].

CFVR represents a useful tool to assess microvascular dysfunction, which could contribute to chest pain in $\geq 20\%$ of patients referred to invasive coronary angiography (ICA) and can be identified in various cardiovascular conditions (e.g., diabetes, hypertension, cardiomyopathies) [25] (Fig. 1).

Reduced CVFR holds prognostic significance in several settings. In a study of 1660 patients with chest pain and no wall motion abnormalities at rest and during SE, decreased CFVR in the LAD was associated with a significantly higher 4-year event rate (death or MI) in both sexes [26]. In the setting of intermediate coronary stenosis, a CFVR >2 predicted good prognosis during a mean follow-up of 15 months [27], while a CFVR <2 was associated with a worse clinical outcome independently of LV systolic dysfunction, wall motion abnormalities, and significant CAD [28]. In a multicenter study, including patients with known or suspected CCS and/or heart failure ($n = 3410$), CFVR was assessed in 88% of patients and, when reduced, showed an independent predictive value over regional wall motion abnormalities [29]. Finally, CFVR holds prognostic significance also in the setting of microvascular angina, as firstly observed in nearly 400 patients during almost 5-year follow-up [30], and confirmed in 1853 women [31].

Standing this growing evidence, the assessment of CFVR has been for the first time included in the latest American guidelines when dealing with patients with ischemia and non-obstructive CAD [2].

3.1.2. Myocardial contrast echocardiography (MCE)

The image quality and reproducibility in the assessment of global and regional LV function during SE may be improved using MCE. The currently available tracers are composed of microbubbles (i.e., a gas core and a lipid or albumin shell), which remain in the vascular lumen and oscillate in resonance, producing the signals.

Detailed recommendations for MCE applications in clinical practice can be found in a consensus document by the European Association of Cardiovascular Imaging [32]. To assess LV function, MCE should be used when ≥ 2 contiguous segments are not clearly visualized on standard echocardiography and patient management depends on regional wall abnormalities. Stress-MCE may be considered in all patients undergoing dobutamine or vasodilator-SE and high-risk patients undergoing exercise-SE to refine diagnosis and risk stratification. When myocardial viability is evaluated, MCE may be performed to improve detection of viable myocardium in segments not responsive to dobutamine, where wall thickness is preserved [32].

3.1.3. Speckle tracking echocardiography (STE)

STE indicates an angle-independent semi-automatic method that allows to assess myocardial deformation, called “strain,” in longitudinal, circumferential, and radial directions, and the velocity of deformation, called “strain rate”. STE provides more sensitive and more objective data over visual assessment of myocardial wall motion and the measurements are not influenced by tethering movement in the adjacent segments [33].

In the context of CCS, STE could be applied to SE to overcome the qualitative interpretation and to improve diagnostic accuracy [34], although further validation in multicenter studies and standardization among vendors is needed [16]. Notably, global longitudinal strain (GLS) is considered an earlier marker of myocardial damage [35] and predicts mortality in patients with CCS independently of LV ejection fraction (LVEF) [36] (Fig. 1). It also proved helpful for the identification of microvascular angina, since the stress-increase in GLS may be an index of coronary flow reserve [37,38]. Moreover, the measurement of time dispersion to peak GLS (LV mechanical dispersion) could help to identify patients at risk of ventricular arrhythmias [39].

Another STE-derived parameter, named post-systolic shortening (PSS), is defined as myocardial shortening that occurs after end-systole,

during isovolumic relaxation; it could be assessed throughout pharmacological-SE, during which its amplitude increases [40]. Whereas it is still controversial whether PSS represents active but delayed contraction induced by ischaemia or passive recoil due from shortening of the surrounding non-ischaemic myocardium, its presence has been correlated with both ischaemia on myocardial scintigraphy and coronary lesion during angiography as well as with adverse outcomes. Nevertheless, PSS can occur in conditions other than ischaemia, such as LV hypertrophy or left bundle branch block, and in normal hearts, too.

The lack of definite cut-offs to quantify abnormal wall-motion response in CCS and inter-vendor variability remain the main limitations of the use of STE during SE [41]. Reliability on local expertise, image quality, software’s tracking, frame rate, and heart rate are other limits.

3.1.4. Stress echocardiography as a multiparametric test

Although its strengths and potentiality, SE has important weaknesses: the operator-dependence can be minimized, but not abolished, and regional wall motion abnormalities are not helpful to identify factors that are not linked to a coronary stenosis, while the introduction of medical therapy resulted in a reduction of positive tests in the last decades [42].

To overcome such limitations, a multiparametric SE strategy has been proposed and synthesized in the ABCDE protocol [43]. A corresponds to wall motion abnormalities; B to lung B lines; C to LV contractile reserve (the ratio between systolic pressure and end-systolic LV volume, from baseline to peak exercise); D to LAD-CFVR; and E to heart rate reserve. In a cohort of patients with known or suspected CCS ($n = 3574$) such score was effective in stratifying the risk of all-cause death [43].

3.2. Cardiovascular magnetic resonance

Resting CMR provides several useful information in the context of CCS. While biventricular morphology, volumes and systolic function are assessed with steady-state free-precession cine sequences, tissue characterization is performed using T1- and T2-weighted pre-contrast sequences [44]. After gadolinium-based contrast agent injection, first pass perfusion and late gadolinium enhancement sequences (LGE) complete a standard exam [44]. The acquisition of T1 maps before and after gadolinium administration allows to measure native T1 values and to calculate the myocardial extracellular volume [44].

Stress-CMR is currently recommended for the diagnosis and prognostic stratification of patients with known or suspected CCS [1,2]. Inducible ischemia can be studied by evaluating myocardial perfusion under maximal pharmacological vasodilation [45] since myocardial areas subtended by a stenotic coronary artery present a delayed gadolinium wash-in (enhancement) compared to normally perfused areas (Fig. 2). A large multicenter trial (MR-IMPACT) on 241 patients reported a greater diagnostic accuracy compared to myocardial SPECT [46]. Similar results were confirmed by the MR-IMPACT II (533 patients) [47] and the CE-MARC studies (752 patients) [48].

Besides qualitative analysis, a semiquantitative method to calculate myocardial perfusion reserve is based on the ratio between myocardial signal intensity maximal upslope at peak stress and at rest, normalized for blood pool signal intensity [45]. A quantitative estimation of myocardial perfusion is also feasible with very recent sequences, based either on the dual gadolinium bolus technique or the dual sequence (myocardial/arterial input function) technique [49]. An automated pixel-wise perfusion mapping technique based on adenosine stress-CMR has been shown to detect physiologically significant coronary lesions (defined by invasive FFR) and to discriminate microvascular dysfunction (defined by index of microcirculatory resistance –IMR) from multivessel epicardial disease [50].

Alternatively, myocardial ischemia can be assessed during dobutamine infusion, acquiring cine-images during each step; first-pass

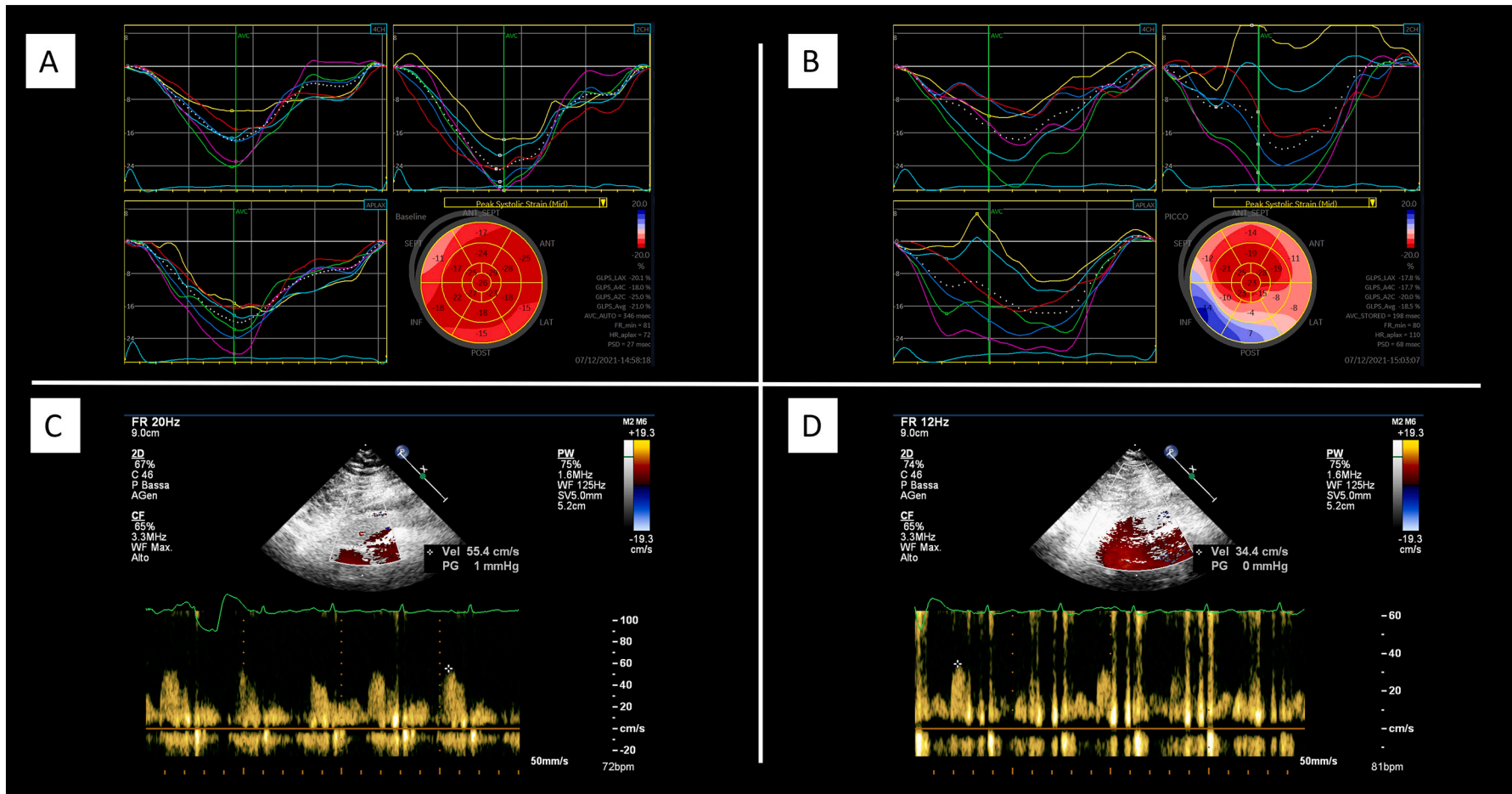


Fig. 1. Perspective in stress-echocardiography.

A 57-years-old diabetic man, with a stress-ECG positive for inducible ischemia, underwent a stress-echocardiography, which did not show any evident abnormality in wall motion at rest and during exercise. Speckle tracking analysis was then applied through a post-processing software and showed preserved left ventricular GLS (-21%) at baseline (A), but reduced GLS (-18.5%) at peak exercise, with regional reduction in inferior, posterior and lateral segments (B). The patient underwent ICA, which revealed a critical stenosis of the right coronary artery.

A 65-years-old woman, with a history of effort chest pain and breathlessness underwent a stress-echocardiography with dipyridamole which did not show any wall motion abnormality. However, a reduced CFVR in the mid-LAD was observed: hyperemic peak diastolic velocity (55.4 cm/s, C)/baseline peak diastolic velocity (34.4 cm/s, D) = 1.61 (normal value >2). At ICA, no obstructive lesions were observed. In the suspect of microvascular coronary disease, the patient was treated with anti-ischemic medications, with a complete remission of symptoms at 6-months follow-up. CFVR, coronary flow velocity reserve; GLS: global longitudinal strain; ECG: electrocardiogram; ICA: invasive coronary angiography; LAD: left anterior descending artery.

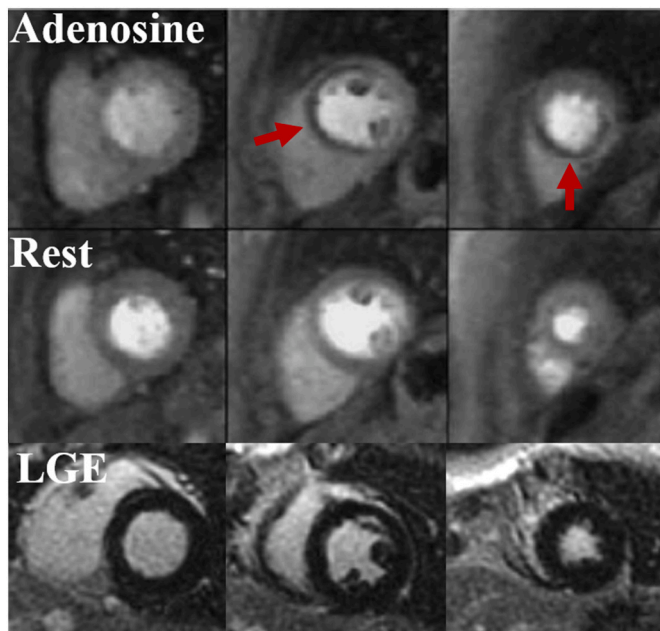


Fig. 2. Stress-CMR integrates functional imaging and tissue characterization. A 63-years-old hypertensive man underwent a stress-cardiac magnetic resonance for his story of stable angina. Adenosine stress (top row) unveiled a myocardial perfusion deficit in the midventricular and apical septum (red arrows), whose perfusion was normal during rest acquisition (middle row). Late enhancement images (LGE, bottom row) confirmed the absence of previous myocardial infarction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

perfusion can also be acquired at peak stress, and compared with rest perfusion. Dobutamine-CMR has been shown to be superior to dobutamine-SE, mainly due to better image quality and greater reproducibility [51]. Although technically challenging, CMR-compatible bicycle ergometers have also been devised for the study of myocardial kinetics and perfusion with CMR [45]; nevertheless, their clinical use is currently extremely limited.

Stress-CMR provides good risk stratification: in the CE-MARC 2 trial ($n = 1202$) the use of CMR (or of nuclear imaging) resulted in a lower probability of unnecessary ICA within 12 months compared with a standard approach [52], whereas in the MR-INFORM study ($n = 918$) the use of CMR was associated with a lower rate of revascularization than invasive FFR, being noninferior in the risk major adverse cardiac events [53]. Similarly, in the SPINS trial on 2349 patients with stable angina followed for a median of 5.4 years, patients without ischemia or LGE on stress-CMR experienced a low incidence of cardiac events, coronary revascularization, and subsequent ischemia testing [54].

In patients with post-infarction LV dysfunction, CMR allows the assessment of biventricular functions and tissue characterization, discriminating ischemic versus non-ischemic substrates. Moreover, LGE location, extent and transmuralities have been correlated to functional recovery after revascularization [55], response to cardiac resynchronization therapy, and arrhythmic risk [56].

3.3. Nuclear imaging

Myocardial perfusion imaging (MPI) by SPECT or PET is a consolidated approach as initial evaluation in patients with stable chest pain, and intermediate PTP of CCS [1,2] (Fig. 3).

SPECT uses i.v. injection of gamma-emitting radiotracers (marked with either ^{99m}Tc or ^{201}Tl), extracted by cardiomyocytes and accumulate proportionally to myocardial blood flow (MBF), at rest and during physical or pharmacological stress. Reduced regional tracer uptake

during stress expresses relative myocardial hypoperfusion. While reduced regional uptake both during stress and at rest expresses myocardial scar, microvascular disease and diffuse CAD may also be associated with abnormal perfusion scans, too [57].

PET uses i.v. injection of positron-emitting radiotracers at rest and during pharmacologic stress. Radiotracers are extracted by cardiomyocytes (e.g., ^{82}Rb , ^{13}N -ammonia) or diffuse in the myocardium (^{15}O -water) proportionally to MBF. PET-MPI has some advantages such as lower radiation dose, better image quality, interpretative certainty, and diagnostic accuracy. By measuring the absolute MBF and flow-reserve, PET allows the discrimination of functionally significant stenoses even in cases of a multivessel disease as well as the assessment of microvascular dysfunction [58]. However, PET scanners are more expensive and PET tracers are less available than SPECT tracers, limiting its use, even if the development of new PET tracers may overcome these limitations [59].

MPI is a powerful tool for non-invasive risk stratification, identifying patients at risk for death and MI: while a normal study is associated with a subsequent rate of cardiac death and MI of 1% per year, a large stress-induced perfusion defects, defects in multiple coronary artery territories, transient post-stress ischemic LV dilatation are all adverse prognostic indicators [60]. Patients with stress-induced reversible perfusion deficits >10% of the total LV myocardium represent a high-risk subset, beyond traditional risk factors [61]. Moreover, coronary vasodilator dysfunction quantified by PET is an independent correlate of cardiac mortality in different settings [62].

SPECT imaging with ^{201}Tl - or ^{99m}Tc -labeled radiotracers provides information on myocardial perfusion and viability. The uptake and retention of the tracers is dependent on regional blood flow and membranes integrity, thus areas with reversible defects from stress to rest indicate inducible ischemia. Stress-redistribution-reinjection or redistribution protocols for thallium [63] or modified stress-rest protocols (nitrate-enhanced rest imaging and combined assessment of perfusion/function with gated-SPECT) for ^{99m}Tc -labeled radiotracers [64] are used to optimize viability detection. As compared with thallium, the latter have shorter half-life, more favorable dosimetry, and improved quality of gated images. On the other hand, PET perfusion imaging – with the generator-produced [82]Rubidium, the cyclotron-produced ^{13}N -ammonia, ^{18}O -water or more recently ^{18}F -flurpiridaz – provides more accurate information on MBF in viable myocardium [63]. The higher spatial and temporal resolution, the accurate correction for photon attenuation, and the more favorable myocardial kinetics of the tracers allow absolute quantification of MBF, which holds prognostic significance [65].

Finally, PET myocardial ^{18}F fluorodeoxyglucose (FDG) metabolic imaging combined with MPI is the current nuclear approach of choice for the evaluation of myocardial viability [66]. Viable myocardium, in the presence of repetitive ischemia and after a glucose load, shows an increased uptake of FDG reflecting preferential glucose utilization over fatty acids. The typical viability study consists of FDG-PET images paired with resting perfusion images. In regions with resting hypoperfusion a concordant reduction in both flow and metabolism (“match”) represents myocardial scar while an increase in FDG uptake compared with flow (“mismatch”) represents hibernating but viable myocardium. PET-FDG has a high negative (90%) and a good positive predictive values (73%) for segmental recovery after revascularization [67].

4. Anatomical imaging

4.1. Coronary computed tomography angiography

CCTA is an accurate non-invasive method for direct visualization of coronary arteries, and CAD assessment [68]. From a technical standpoint, recent advances have made CCTA a safer technique, reducing radiation and contrast media exposure [69] and while high spatial resolution is essential to visualize small arteries and plaques and delineate

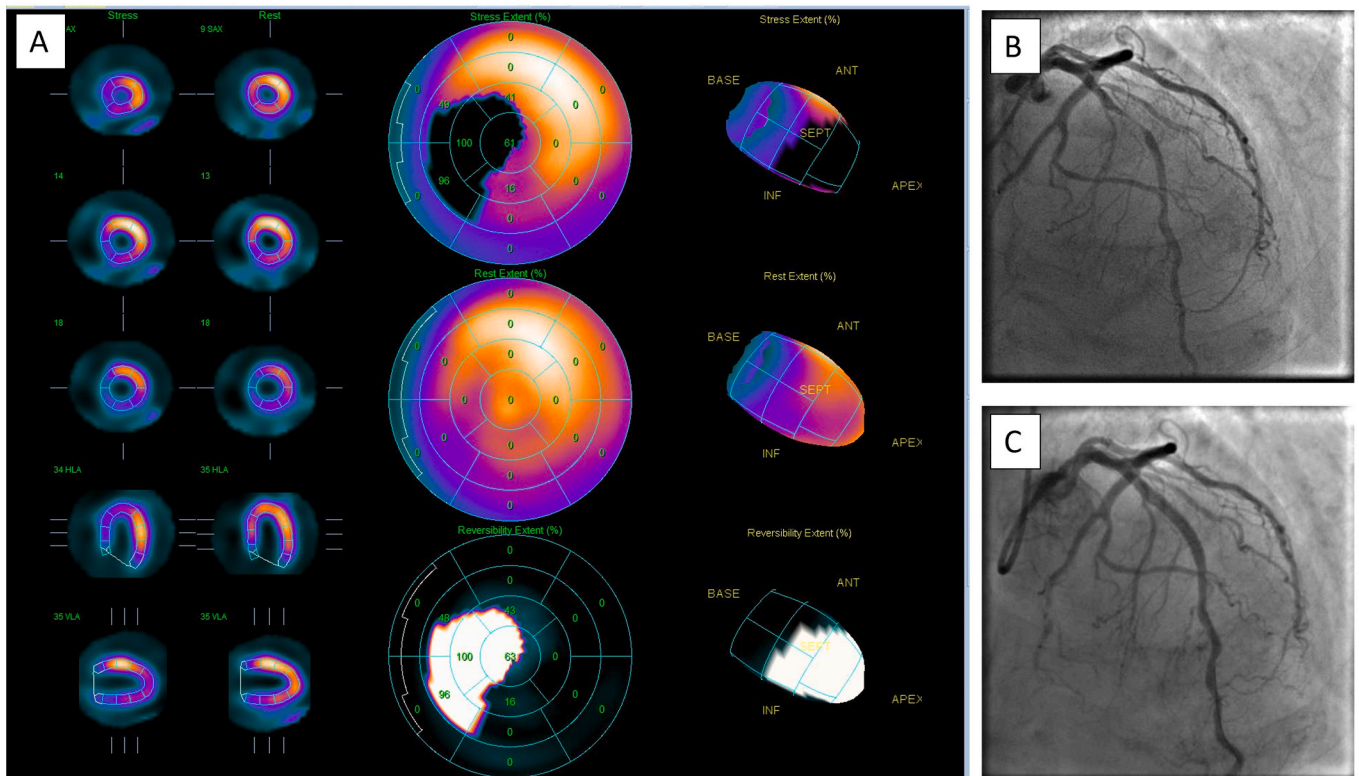


Fig. 3. Stress-SPECT is an established and reliable functional imaging test to assess inducible myocardial ischemia in patients with CAD.

A 79 years-old patient underwent a stress-SPECT for a recent onset of dyspnea on effort and multiple cardiovascular risk factors (yielding an intermediate-to-high pre-test probability of obstructive CAD). The perfusion tracer was injected during bicycle exercise at submaximal load in the presence of ST-segment depression in the inferior and lateral leads. The SPECT images (A) showed a reversible effort-induced perfusion defect mainly in the septal and apical walls (LAD territory) of moderate-severe extension. The patient was then referred to ICA (B) which showed a sub-occlusive lesion on the mid LAD, hence successfully revascularized (C). CAD: coronary atherosclerotic disease; ICA: invasive coronary angiography; LAD: left anterior descending artery; SPECT, single photon emission computed tomography.

complex anatomies, high temporal resolution is critical to reduce/eliminate motion artifact [9]. However, ECG gating remains mandatory and X-ray data are obtained during the phase of the cardiac cycle with minimal coronary motion (end-systole, 40–50% of the R-R interval, or mid-late diastole, 70–80% of the R-R interval), lowering heart rate with beta-blockers (or ivabradine), whereas nitroglycerin should be administered as vasodilator [70].

In the context of CCS, CCTA has emerged as a noninvasive technique to assess CAD severity stenosis in epicardial arteries [71,72], showing sensitivity and specificity up to 98% and 90%, respectively [73], and a negative predictive value of 95–100% to rule-out obstructive CAD. Nevertheless, heavily calcified arteries may overestimate CAD severity, because of blooming artifact, but the use of higher-spatial-resolution scanners has improved diagnostic accuracy also in this setting [73].

Various clinical studies support the diagnostic and prognostic roles of CCTA in the context of CCS. Of note, the PROMISE [6] and SCOT-HEART [11] studies suggested that a CCTA-based strategy improves diagnostic certainty. While in the SCOT-HEART the addition of CCTA to standard management was also associated with a lower risk of death or MI [11], in the PROMISE trial the use of CCTA also provided better prognostic information than functional testing by identifying patients with non-obstructive CAD, in which 54% of events occurred [12]. Moreover, the CONSERVE study found that a selective CCTA-based referring to ICA in patients with suspected CCS was associated to lower cost and a greater diagnostic yield [74]. In the outcome analysis of the EVINCI study, only patients undergoing early revascularization on the base of both CCTA and stress imaging results had a similar outcome to those without significant stenoses, whereas obstructive CAD at CCTA was the only

independent imaging predictor of adverse events [75]. Thus, the study results suggested that although a strategy using CCTA as the first test is reasonable in a population with low prevalence of significant stenoses, functional imaging before ICA is necessary to identify those patients with significant inducible ischemia. In a health-economics analysis of the same study [76] it was shown that combined non-invasive strategies with CCTA and stress imaging are cost effective as gatekeepers to ICA and to select candidates for early revascularization. On the contrary, in a recent sub-analysis of the ISCHEMIA trial, CCTA-assessed CAD severity but not ischemia severity was associated with increased risk of adverse events [5]. However, in this study ischemia severity was assessed with multiple modalities [5].

To date, despite the high-level of recommendation for the use of CCTA in the current guidelines [1,2,77], the availability of latest generation scanners in European country is limited and, in real world, the implementation of CCTA for the evaluation of suspect CCS depends on the new health strategy based on the reconfiguration of current finances and staffing levels [78].

4.1.1. Anatomical and functional assessment of coronary stenoses

CCTA may be limited by low positive predictive value, which could improve with the implementation of CCTA-derived FFR (FFR_{CT}) and CT stress myocardial perfusion imaging (CTP) (Fig. 4).

FFR, the ratio of maximal hyperemic blood flow of a stenosis divided by normal hyperemic blood flow in the absence of stenosis, determines the lesion-specific functional significance and its use may improve outcomes and reduce costs [79,80]. Noninvasive FFR (i.e., FFR_{CT}) has been extensively validated against the invasive technique [81–83]. In

particular, FFR_{CT} applies computational fluid-dynamics to calculate FFR values in all epicardial arteries without the need for additional medications and is based on 3 steps: (1) reconstruction of a 3D-model including the aortic root and coronaries, (2) identification of inflow and outflow boundary conditions that mimic hyperemic coronary physiology, and (3) performing a numerical solution of the laws governing fluid-dynamics [84].

Several studies have already tested the accuracy of FFR_{CT} in the setting of CCS. In the PLATFORM study, the use of FFR_{CT} safely canceled 61% of ICA, reducing those with no obstructive CAD by 83%, improving patient quality of life, and reducing costs [6,85]. In the ADVANCE registry, a real-world large prospective examination, FFR_{CT} modified treatment recommendation in two-thirds of subjects as compared to CCTA alone, was associated with less negative ICA, predicted revascularization, and identified subjects at low risk of adverse events over 90 days [86]. The SYNTAX III study showed that in patients with left main or three-vessel disease, a strategy based on coronary CCTA and FFR_{CT} demonstrated high agreement with the decision derived from conventional ICA [87]. Finally, in the randomized FORECAST trial ($n = 1400$) a strategy of CCTA with selective FFR_{CT} reduced the use of ICA, with no differences in term of costs and clinical outcomes compared with the standard care [88]. Of note, the use of FFR_{CT} has been introduced in the American guidelines as a second-level test in case of uncertain CAD severity (particularly in case of coronary stenosis of 40–90% and located in a proximal or mid-coronary segment) [2].

CTP is another tool to combine anatomical and functional coronary stenosis evaluations. Although technical limitations have restricted the clinical use of CTP so far, they could be overcome with more modern scanners. Two kinds of stress-CT can be performed: (1) static stress-CTP, obtained from a single data sample acquired in arterial phase timing; (2) dynamic stress-CTP, obtained from multiple samples of myocardial

attenuation at sequential time points after contrast injection. Both approaches imply adenosine as stressor [84] and significantly increase the diagnostic accuracy of CCTA (using invasive FFR as gold standard) [89–92]. In the PERFECTION study, the diagnostic accuracy of FFR_{CT} was compared with that of static stress-CTP finding no significant differences [93,94], while in patients with suspected CCS at intermediate-to-high risk, the addition of quantitative dynamic stress-CTP on top of CCTA and FFR_{CT} improved diagnostic accuracy [93].

Nuclear imaging may complement CCTA results [95]. Integration of functional information from MPI with anatomical description of CAD is now also obtainable in 3D-reconstructions by hybrid SPECT/CCTA and PET/CCTA imaging [96], with an overall radiation dose of 4–10 mSv. Hybrid imaging is potentially able to define different CCS phenotypes (Fig. 5) and, by directly assessing the functional significance of a coronary stenosis, holds much promise for future clinical application in better selecting patients for ICA. The clinical value of this approach has been explored in the population of the EVINCI trial [97]. In this multi-center population of 252 patients with intermediate PTP of CCS, hybrid images have been obtained by 3D-fusion and evaluated by independent observers. The presence of anatomical-functional “match” (inducible perfusion defect downstream an obstructive coronary lesion at CCTA) allowed to recognize a significant stenoses in 24% of patients, while a negative “match” excluded significant stenoses in 41% of patients with an optimal diagnostic accuracy as compared with ICA (positive and negative predictive values of 87% and 88%). It also allowed to reallocate perfusion defects to the appropriate coronary territory in 42% of patients and predicted subsequent revascularizations. Other studies have confirmed such a higher diagnostic accuracy, as compared with single techniques [98], and reported the prognostic value of hybrid imaging over CCTA alone [99,100].

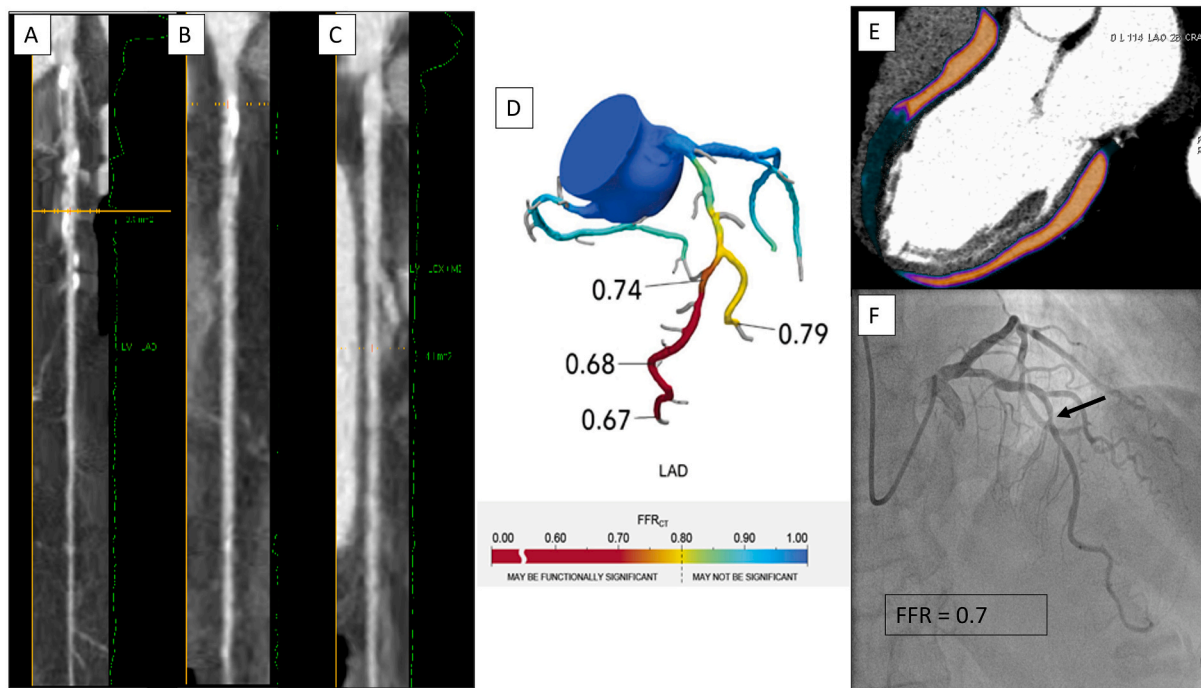


Fig. 4. Modern CCTA integrates anatomical and functional assessment of CAD.

A 64-years-old man underwent a CCTA for atypical chest pain. The exam highlighted the presence of mixed plaques on the proximal and mid segments of the LAD (A) and of the RCA (B), hardly quantifiable for the high amount of calcium, but of at least moderate degree (C). A functional assessment was then performed, showing a significant flow reserve reduction on the mid LAD (i.e., an $FFR_{CT} < 0.8$) (D), whereas the CTP (E) demonstrated a large perfusion defect of the mid and apical anterior interventricular septum. The patient was then referred to undergo ICA (F), which confirmed a severe stenosis on the mid LAD, with an invasive $FFR < 0.8$. CAD: coronary atherosclerotic disease; CCTA: coronary computed tomography angiography; CTP: computed tomography perfusion imaging; FFR : fractional flow reserve; ICA: invasive coronary angiography; LAD: left anterior descending artery; LCx: left circumflex; RCA: right coronary artery.

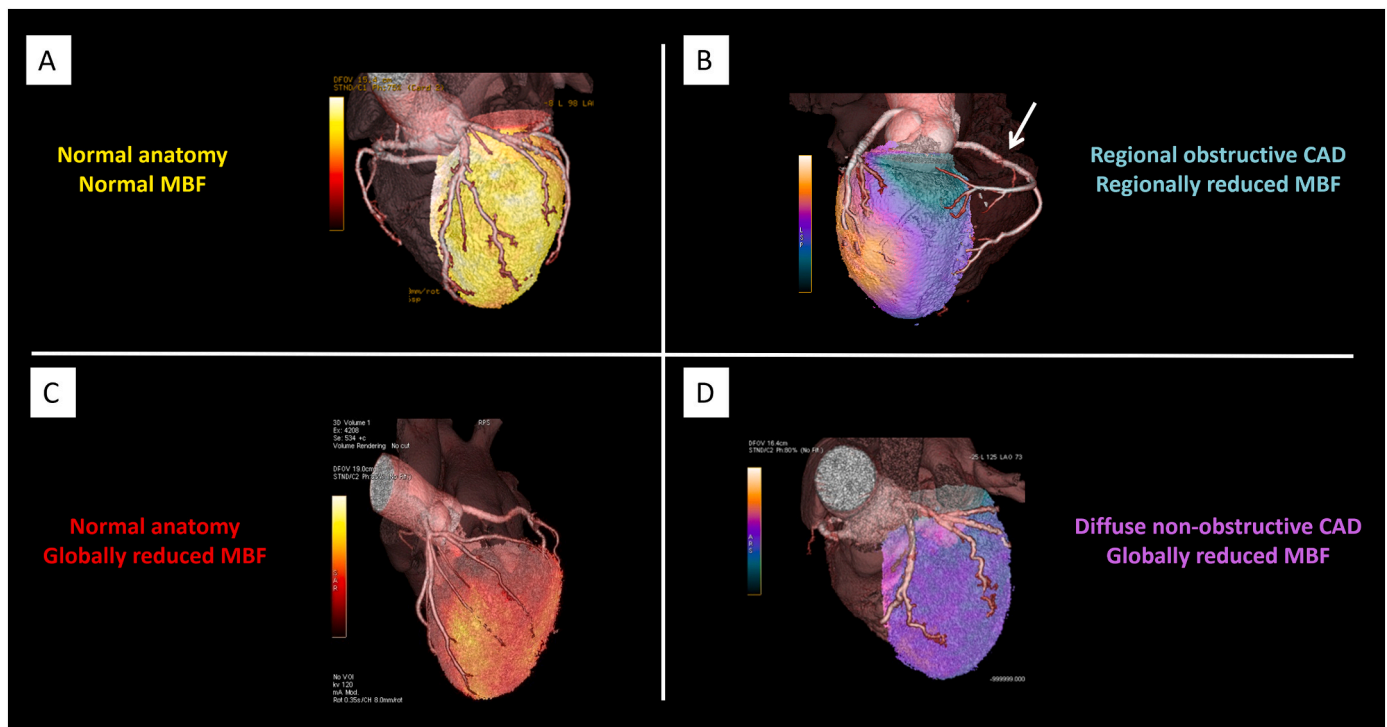


Fig. 5. Hybrid imaging to dissect CCS patients' phenotypes.

Beyond assessing the presence and severity of stress-induced regional perfusion defects, PET and, more recently, SPECT may also measure absolute MBF and MBF reserve. The combination of normal coronary anatomy at CCTA and normal MBF (A) is associated with an excellent prognosis, while the association of obstructive CAD with a large perfusion abnormality (B) warrants referral of the patient to invasive procedures. The combination of normal coronary anatomy with a globally reduced absolute MBF and MBF reserve indicates microvascular/endothelial dysfunction (C), whereas a diffuse MBF impairment may also be associated with diffuse CAD (D) requiring aggressive medical treatment. CAD: coronary atherosclerotic disease; CCS: chronic coronary syndrome; CCTA: coronary computed tomography angiography; MBF: myocardial blood flow; PET: positron-emission tomography; SPECT, single photon emission computed tomography.

4.1.2. Morphological assessment of coronary plaques

CCTA also allow a morphological evaluation of CAD, of potential importance since more than two-thirds of acute MI may be due to non-significant plaques. Indeed, CCTA may identify plaque features as positive remodeling, low attenuating plaque, and spotty calcification as well as noncalcified plaque volume that are associated to an increased risk of events even in patients with nonobstructive CAD [101,102]. However, in the PROSPECT study only 5% of high-risk plaques identified by intravascular ultrasounds caused coronary events [103]. Therefore, the presence of high-risk plaques is not the only substrate of acute MI, but also local rheological and hemodynamic phenomena could contribute [71]. Interestingly, high risk plaques may induce greater rates of ischemia and reduced FFR/FFR_{CT} compared with non-lipid-rich plaques independent of the degree of luminal narrowing [104], probably because of complex phenomena such as oxidative stress and local inflammation which could negatively influence endothelial function and lead to clinically relevant stenoses. Hence, FFR_{CT} may provide the best platform for defining the relationships among the determinants of CCS and future acute events. Furthermore, CCTA-derived information may enhance the options to optimize medical therapy based on a combination of anatomy, physiology, and plaque characteristics [105], and reduce adverse events, as suggested by the results of the SCOT-HEART trial [106].

5. Multimodality imaging in the clinical reality of chronic coronary syndromes

Although the integration of functional and anatomical tests is nowadays mandatory for a comprehensive management of patients with CCS, the clinical context should never be overlooked. Since the prevalence of coronary stenosis is lower than previously expected [6,107],

both the latest European and American guidelines proposed new algorithms to define PTP of CCS, integrating age, sex, and symptoms with other clinical parameters [1,2,108,109]. As anticipated, CCTA may be a first choice to “rule out” CAD, while stress imaging may be preferred as a “rule-in” strategy [6,48,107,109].

However, a multimodality and/or stepwise approach should be adopted in case of uncertainty. For example, in case of a patient complaining typical chest pain, the evidence of a significant stenosis at CCTA, in absence of “high risk” criteria (such as left main, three vessels and/or proximal LAD obstruction), should prompt the introduction of anti-ischemic drugs, reserving noninvasive or invasive functional tests to the cases with symptoms persistence. Conversely, a clinical presentation consistent with vasospasm, in absence of obstructive CAD, should prompt the introduction of a tailored medical therapy, reserving functional tests to refractory patients, avoiding unnecessary ICA in most cases [1,2,108].

Despite such recommendations, real World data suggest that ICA often remains a first diagnostic step in the context of CCS, resulting in higher costs, high rates of negative findings, or unnecessary revascularizations [110]. Furthermore, even when performed, the results of stress imaging may be overlooked [97,110,111] and, also in the context of randomized trials, an unjustified high proportion of patients' cross-over toward an invasive approach could have affected – at least partially – their findings [3,112,113]. A deeper knowledge of multimodality imaging seems hence crucial not to miss the growing opportunities available in this clinical scenario.

Finally, it should be noted that although CAD may be responsible of myocardial ischemia, other possible mechanisms (e.g., vasospasm, microvascular dysfunction, energetic mismatch) should not be neglected [114] and the use of novel testing opportunities (e.g., CFVR, full ABCDE approach, stress-CMR, FFR_{CT}, hybrid imaging) could be of help to

correlate a coronary stenosis – whether detected – to functional abnormalities or to identify other pathological substrates (Central Illustration). Indeed, CAD may involve ~18% of men and ~ 11% of women >65 years of age (up to 19% and 16%, respectively, at >75 years) [115]. Therefore, while negative anatomic findings should not rule-out myocardial ischemia as responsible of patient's symptoms in the absence of corroborative functional testing, positive anatomic findings should not imply a direct correlation of “atypical” symptoms to “incidental” lesions. The use of multimodality imaging should then be warranted to prompt mechanism-tailored therapeutic choices. This concept is explicitly recognized by the ACCF (American College of Cardiology Foundation) in its definition of an appropriate imaging study as “one in which the expected incremental information, combined with clinical judgment, exceeds the expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication” [116].

Moreover, we have sufficient evidence clarifying that an event rate reduction from an invasive approach in CCS should not be expected when compared with optimal medical therapy; therefore, imaging test should not be seen anymore as the gatekeeper for coronary revascularization, but may change outcome affecting care throughout the implementation of the medical therapy. In this regard, it is now clear that the documentation of CAD, even if in absence of obstructive lesions, could positively affect hard outcomes prompting a tighter control of risk factors, which should not be overlooked also in case of negative functional tests [4]. Finally, it should be acknowledged that waiting list, poor availability, or the necessity of local expertise may hamper the clinical application of the more advanced imaging techniques. Nevertheless, a further optimization of patients' referral and the implementation of a more personalized approach, mainly based on clinical presentation, may help overcoming such limits in the next feature.

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