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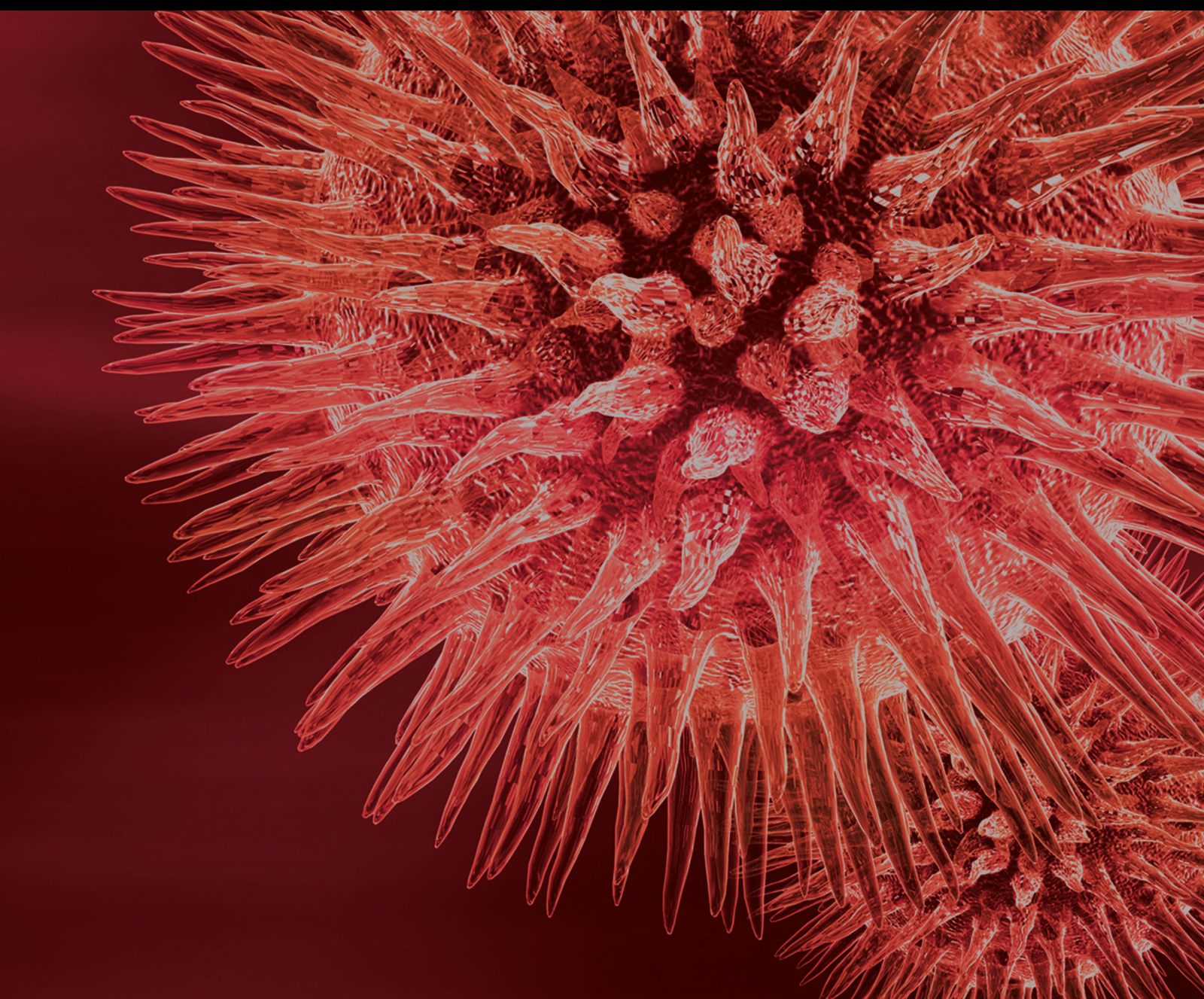
Ischemic Heart Disease: New Insights from Imaging Diagnostic Techniques

Special Issue Editor in Chief: Gianluca Pontone
Guest Editors: Andrea I. Guaricci, Maurizio Galderisi, Giovanni Aquaro, and Nazario Carrabba



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Editorial

Ischemic Heart Disease: New Insights from Imaging Diagnostic Techniques

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Coronary artery disease (CAD) is the first cause of mortality worldwide and the majority of individuals older than 60 years of age suffer from its consequences. It is ascertained that the epidemiology and social impact of ischemic heart disease (IHD) are huge and big efforts are mandatory in diagnostic and prognostic fields.

Modern and thrilling technology such as coronary computed tomography angiography (CCTA) and cardiac magnetic resonance (CMR) has been emerging and offering the possibility to characterize both the coronary arteries and the myocardium at a very high level of detail.

Our special issue, which had opened for 6 months in the first half of 2018, mainly focused on scientific evidences of advance in cardiac and coronary CT and CMR and included four narrative reviews and two original articles.

Carrabba et al. critically analyzed the National Institute for Health and Care Excellence (NICE) guidelines on chest pain published in 2016 and underscored the key changes provided in comparison to the 2010 version [1]. At first, the previously proposed pretest probability risk score was no longer recommended. Moreover, the guidelines changed approach for patients with low pretest probability and calcium score of zero who should not be considered by default "free from CAD". Importantly, the new guidelines recommended CCTA as a first-line investigation in all patients with new onset chest pain. The authors argued that few clinical and economic data existed in support of the use of CCTA over all other noninvasive imaging testing especially in patients at intermediate-to-high risk of CAD. Other issues in contrast with the new NICE guidelines recommendation consisted of the limited availability of latest generation scanners in European countries and the negative effects of high cumulative radiation dose exposure from multiple serial CCTA investigations.

Ball et al. described the fractional flow reserve (FFR) derived from CCTA datasets (FFR_{CT}) as major advance in cardiovascular imaging, able to provide critical information of coronary tree without exposing the patient to added risk. According to authors' report, invasive FFR measurements represent a guide to percutaneous coronary revascularization and have demonstrated to reduce contrast use, cost, or care and improve outcomes [2]. As being a noninvasive method, FFR_{CT} values are obtained using resting 3D CCTA images through computational fluid dynamics. Several multicenter clinical trials demonstrated the diagnostic superiority of FFR_{CT} over traditional CCTA for the diagnosis of functionally significant CAD and put it in competition with refined diagnostic tools as stress CMR and coronary CT perfusion [3]. Thanks to the high diagnostic accuracy, FFR_{CT} offers the possibility to distinguish between patients who can safely

avoid invasive coronary angiography and those patients who require revascularization.

Seitun et al. focused their paper on the new generation multidetector row (≥64 slices) CT systems which allow an accurate assessment of both coronary epicardial stenosis and myocardial CT perfusion imaging at rest and during pharmacologic stress as "one-stop-shop" method [4]. Indeed, this application leads to the comprehensive assessment of both anatomical coronary details and its physiological consequences and represents a valid alternative to FF_{CT}. The authors detailed the technical aspects of coronary CT perfusion and, at the same time, pinpointed its strength and limitation points and summarized the evidences about its clinical applications. Indeed, the recent literature suggests that this method is safe and powerful and able to improve the accuracy and the positive predictive value of CCTA alone adding functional information [5]. In their conclusions, Seitun et al. invited to perform large prognostic studies in order to assess if this combined approach might have substantial impact on patients management and costs.

Carità et al. considered in their review that primary prevention of major cardiac events needed a strong implementation for ethic and economic reasons. The authors took into consideration the prognostic value of CCTA in the first half of the manuscript and concluded with the description of the recent literature upon the therapeutic perspective. As well described by the authors, CCTA offers the possibility to study the coronary arteries beyond the assessment of coronary stenosis, evaluating the plaque composition and the presence of positive remodeling. This ability has opened a new scenario about the possibility of estimating the prognostic profile of the single patient [6]. Indeed, together with coronary stenosis severity, which represents a powerful predictor of prognosis in CAD, other elements identified by CCTA have been added as prognostic predictors, such as the spotty calcifications, the low attenuation plaque (<30 HU), and the high positive remodeling index [7]. Therefore, early identification of CAD, characterization of atherosclerotic progression, and assessment of "vulnerable plaque", sometimes in the context of "vulnerable patient", are considered by the authors as mandatory endpoints [8]. Afterwards, Carità et al. underscored that research in this field may also advance towards the definition of individualized medical therapy on the basis that statins may delay plaque progression and change some plaque features [9].

Catalano et al. sought to evaluate the added prognostic value of CMR as compared to conventional risk profiling, including clinical history, atherosclerosis risk factors, electrocardiography, and echocardiography, in 465 patients affected by stable CAD who underwent a comprehensive CMR evaluation which consisted of left ventricle dimensions and functioning, late gadolinium enhancement (LGE) and stress perfusion sequences. The authors concluded that LGE and stress perfusion assessment independently predicted MACE beyond conventional risk stratification in this subset of patients. Moreover, authors discussed some critical insight of CMR partially explored from existing literature, such as the prognostic value of LGE in the middle-long term [10] and the importance of a comprehensive CMR assessment, including the stress perfusion acquisition, which may be a useful facility to predict morbidity as well as mortality [11].

Lin et al. aimed to explore the role of the CHADS2 score in the evaluation of carotid atherosclerosis in 109 patients with nonvalvular atrial fibrillation undergoing carotid artery ultrasonography and velocity vector imaging (a parameter reflecting the long-axis longitudinal motion function of carotid arteries) [12, 13]. Interestingly, the authors revealed that carotid arterial structure and function were significantly altered, including increased arterial wall stiffness, decreased elasticity, and aggravated atherosclerosis, in patients with atrial fibrillation and that the burden of carotid atherosclerosis depended on the duration of atrial fibrillation. Finally, they postulated that the CHADS2 score might be useful as a predictor of the extent of carotid atherosclerosis in this subset of patients.

Conflicts of Interest

Dr. Pontone received institutional fee and/or institutional research grant from GE Healthcare, Bracco, Bayer, Medtronic, and Heartflow. The other guest editors have no conflicts of interest.

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Review Article

Old and New NICE Guidelines for the Evaluation of New Onset Stable Chest Pain: A Real World Perspective

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Stable chest pain is a common clinical presentation that often requires further investigation using noninvasive or invasive testing, resulting in a resource-consuming problem worldwide. At onset of 2016, the National Institute for Health and Care Excellence (NICE) published an update on its guideline on chest pain. Three key changes to the 2010 version were provided by the new NICE guideline. First, the new guideline recommends that the previously proposed pretest probability risk score should no longer be used. Second, they also recommend that a calcium score of zero should no longer be used to rule out coronary artery disease (CAD) in patients with low pretest probability. Third, the new guideline recommends that all patients with new onset chest pain should be investigated with a coronary computed tomographic angiography (CTA) as a first-line investigation. However, in real world the impact of implementation of CTA for the evaluation of new onset chest pain remains to be evaluated, especially regarding its cost effectiveness. The aim of the present report was to discuss the results of the studies supporting new NICE guideline and its comparison with European and US guidelines.

1. Introduction

In the last two years a great debate occurs about the value of anatomical information by coronary computed tomographic angiography (CTA) in comparison to functional imaging tests on the evaluation of patients with new onset chest pain and unknown coronary artery disease (CAD) [1–5]. Stable chest pain is a common clinical presentation that often requires further investigation using noninvasive or invasive testing [6–8]. Recently, PROMISE [9] and SCOT-HEART [10] studies suggest that an evaluation strategy based on CTA improves diagnostic certainty, as well as efficiency of triage to invasive catheterization; it also may reduce radiation exposure when compared with functional stress testing, with similar rates of cardiac events. Moreover, the EVINCI [11] trial supports the use of CTA for stable chest pain, highlighting a better performance in comparison to other imaging strategies. After the publication of these studies, the National Institute for Health and Care Excellence (NICE) [12] recommended CTA as the first-line investigation for all patients presenting with chest pain due to suspected CAD.

2. Functional and Anatomical Tests for Suspicion of CAD

In current era of modern cardiology, the diagnostic workup test for patients with suspicion of CAD remains matter of debate [6–8]. Whatever the use of functional or anatomical tests, their additional values should be implied on guide the decision-making process to improve outcome, reducing cardiac death and nonfatal myocardial infarction [13–21]. For this purpose, it is conceivable that the first-line diagnostic test should have a high level of diagnostic accuracy as well as the ability to better stratify individuals risk and, finally, the ability to establish proper treatment regimes. In

addition, taking into account a reduced economical resource of the health system around the world, in the practice the cost-effective clinical aspects may play a pivotal role in planning a diagnostic workup test for CAD. Several studies have compared different stress imaging modalities in order to detect obstructive CAD. However, there are no strict recommendations based on the evidence of one diagnostic test' superiority over another [9–21]. Specifically, diagnostic functional tests are encumbered by a high rate of false-positive results. The low prevalence of obstructive CAD following elective ICA has been clearly demonstrated in the registry data, raising more criticisms regarding the ability of functional test in detecting markers of significant myocardial ischemia [22, 23]. All this has generated a great debate as to which test is best placed to serve as a "gatekeeper" to invasive coronary angiography (ICA). The rationale for the use of noninvasive testing prior to ICA is established in the recent publication of Clinical Evaluation of Magnetic Resonance Imaging in Coronary Artery Disease 2 (CE-MARC-2), confirming that risk models may overestimate the presence of obstructive CAD [21]. Ideally, considering several noninvasive tests available, ICA is only rarely mandatory to confirm the diagnosis of obstructive CAD and should be reserved for those likely to have coronary intervention. In the last decade, the additional values of coronary CTA to improve diagnostic accuracy and risk stratification of coronary artery disease have been evaluated in depth from several studies. Recently, two 'test-and-treat' multicenter randomized control trials furnished evidences into whether coronary CTA could be incorporated into chest pain care pathways [9, 10]. In similar way, both trials were focused on the evaluation if the incorporation of noninvasive test into a care pathway may confer benefit to patients with suspicion of CAD. Namely, the Prospective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial enrolls a large cohort from USA and Canadian centers in order to settle whether an initial assessment of suspected stable CAD using CTA improves outcomes, reducing major adverse cardiovascular events [9]. This study demonstrated that coronary CTA was associated with more ICA within the first 90 days; however the use of coronary CTA reduced invasive angiograms without obstructive CAD. Moreover, at 2-year follow-up, the use of CTA was not associated with improvement in death, myocardial infarction, or major procedural complication in comparison to functional strategy. Differently, the Scottish Computed Tomography of the HEART (SCOT-HEART) trial recruited UK patients referred for recent onset chest pain to cardiology clinics with suspected angina [10], all of whom presented with chest pain and one-third reported typical angina symptoms. In comparison with a PROMISE trial, a higher rate of obstructive CAD was reported in CTA arm of SCOT-HEART. Moreover, there was a nonsignificant reduction in cardiac death and myocardial infarction (hazard ratio 0.62, 95% confidence interval 0.38–1.01, p=0.0527). In the SCOT-HEART study, differently from the PROMISE study, coronary CTA did not replace functional testing but was added to a standard care protocol with exercise ECG for most. In these two studies the low prevalence of CAD and the low occurrence of MACE in patients with stable chest pain were reported, raising questions concerning the use for new imaging test. Generally, it is well known that, in patients with low CAD prevalence, the probability of CAD may be overestimated by standard prediction rules [9, 10]. Indeed, the prevalence of CAD in PROMISE was low 8.8% in comparison to the 53% predicted probability by the Diamond and Forrester model. In the SCOT-HEART study, a higher rate of obstructive CAD was reported in the CTA arm compared with the PROMISE trial. Moreover, in the SCOT-HEART study, after 50 days clinicians reviewed the test result and started preventive medical therapy. From this time, post hoc landmark analysis was associated with an impressive reduction rate of cardiac death and myocardial infarction (hazard ratio 0.50, 95% confidence interval 0.28–0.88, p=0.020) [23]. Thus, not surprisingly, the findings of randomized SCOT-HEART study confirmed the results previously reported from the observational CONFIRM registry, where for the first time the beneficial effect of statin therapy in individuals with subclinical atherosclerosis was demonstrated [24]. Importantly, the longer-term impact of coronary CTA use in clinical practice remains unexplored. Until recently, the long-term clinical outcomes of the SCOT-HEART trial was published [25], showing that the use of CTA in comparison to than standard care alone is associated with a lower rate of death or nonfatal myocardial infarction (2.3% versus 3.9%; HR 0.59; 95% CI 0.41 to 0.84; P = 0.004). These results are mainly related to the change of treatment based on CTA findings. In addition, the use of CTA is associated with an increase rate of ICA in the short follow-up, but 5 years the use of ICA and coronary revascularization were not different. Moreover, according to design of study, the SCOT-HEART trial encouraged the secondary prevention strategy in patients with nonobstructive CAD. This strategy may be very important, considering that near the half of subsequent myocardial infarctions occurred among patients with nonobstructive CAD. The clinical, social, and financial implications of this consideration could be very relevant in the next future, considering the exponential increase of the subclinical and nonobstructive coronary atherosclerosis reported from CTA in patients with suspicion of CAD.

3. NICE Guidelines Update 2016

Specifically, the NICE guideline update (2016) makes three key changes to the 2010 version [12]. The first is the recommendation for a clinical assessment of the likelihood of CAD, based on the typicality of the chest pain into typical, atypical, or noncardiac, instead of the previous pretest probability (PTP) risk score (RS). The second change in the guideline is that a zero calcium score is no longer used to rule out CAD in patients with low PTP. Thirdly, and most radically, NICE now recommends that all patients with new onset chest pain with atypical or typical anginal features, as well as those with noncardiac chest pain and an abnormal resting ECG, should first be investigated with CTA using a 64-slice (or above) CT scanner. Functional imaging tests are now reserved for the assessment of patients with chest pain symptoms who are known to have CAD and for patients where the CTA has been nondiagnostic or has shown CAD of uncertain significance.

4. Comparison with European and American Recommendations

The 2013 European Society of Cardiology (ESC) guideline on stable chest pain recommends the use of a PTP RS that is calculated using age, gender, and typicality of chest pain, but not cardiovascular risk factors [26]. This RS is based on an updated Diamond-Forrester method, which adjusts the likelihood of CAD for a more contemporary population [26]. The ESC recommends that patients with an intermediate RS (15–85%) have a functional imaging test and, if there is limited availability, exercise ECG is recommended as an alternative in patients with RS 15–65% and CTA for patients with RS 15–50%. The 2012 guidelines from the American cardiology societies on stable chest pain recommend clinical evaluation of the PTP of CAD [27]. Patients able to exercise with interpretable resting ECGs and a low to intermediate likelihood of CAD are recommended to have an exercise ECG. Patients with uninterpretable ECG and patients with intermediate to high likelihood of CAD are recommended to have functional imaging tests. Patients with low to intermediate PTP, who are unable to exercise, may also undergo CTA as an alternative to exercise stress testing.

5. The 2016 Update to NICE CG95 Guideline

The PTP model was based on USA cohorts of patients undergoing invasive coronary angiography (ICA) in the 1970s who had a much higher prevalence of CAD than current rapid access chest pain clinic populations. Thus, in the latest guidance, NICE has parted from its PTP model; it may overestimate the risk in current rapid access chest pain clinic populations [28, 29]. Since the ESC RS was based on a contemporary population and has been externally validated and shown to be a good predictor of risk [29, 30], there was an expectation that NICE may adopt it. Not surprisingly, the most striking change in the new NICE guideline is the expansion of the use of CTA to all patients with new onset of chest pain. NICE no longer recommends coronary artery calcium scoring followed by CTA if the calcium score is above zero because of case reports of significant coronary stenoses in patients with a zero calcium score. Another reason is that the radiation dose from CTA on high-specification CT scanners is now as low as the radiation dose for the calcium score itself (less than 1 mSv). More controversially, NICE expanded the recommendation for CTA as first line to patients with intermediate and high likelihood of CAD based on their cost-effectiveness analysis suggesting that this would be a lower cost strategy. While recent clinical trials, such as PROMISE, demonstrated that patients investigated with CTA and functional tests had similar clinical outcomes [9], one has to remember that this trial was in a low-intermediate disease prevalence population with only approximately 11% having CAD. Although the SCOT-HEART trial had a higher prevalence of CAD and demonstrated that the use of CTA in patients with chest pain improves the diagnosis when added to standard of care, the standard of care was the exercise ECG and not functional imaging tests [10]. In fact, there are no published data demonstrating the diagnostic accuracy or cost effectiveness of CTA in patients with chest pain and higher likelihood of CAD, making the NICE recommendations for CTA in this population somewhat surprising. Interestingly, however, there are UK data demonstrating higher utilization rates of the costly ICA following a CTA strategy [31].

6. Disinvestment in Stress Imaging Services in Favor of CT Imaging: A New Question

The advance in management and the adoption of modern effective treatment have reduced the cardiovascular mortality for patients with acute coronary syndrome worldwide, but not for patients with stable CAD. Currently, healthcare system focused their efforts on delivering management of stable CAD that is both clinical and cost effective. Notably, the populations with stable CAD increase in age and consequently their access to the healthcare system may increase exponentially worldwide. This picture of stable CAD is true worldwide; thus the treatment for stable CAD should be not only efficacious but also sustainable for healthcare system. Moreover, differently to the previous two decade, now the rapid clinical assessment of patients with suspected angina is necessary for the community of cardiology to select out high-risk individuals [32]. In this way, the attending physician may avoid the risk of potential complications following the onset of chest pain symptoms, as well as may avoid unnecessary diagnostic tests. In current clinical practice, the ICA remains the more precise test to confirm or to exclude the presence of obstructive CAD against which all other noninvasive tests have been validated. Since the hospitalization is required to perform ICA, this examination remains the most expensive diagnostic investigation and, importantly, it exposes individuals to the highest risk of procedural complications, although the radial access may reduce the burden of complications and now should be the preferred approach [33]. After a number of publications, now coronary CTA is recognized as accurate diagnostic test to evaluate the presence of coronary atherosclerosis. The publication of the updated NICE guideline CG95 confirms and reinforces this message, but in the same time it rises some concerns about the impact of the use of coronary CTA as first-line investigation on the resource of healthcare system. In England the adoption of this strategy for CAD diagnosis has been estimated as favorable, since it will be associated with an annual savings of £16 million, by prompt exclusion of significant CAD and more effectively use of resources [34]. However, caution needs in interpretation these findings, since the availability of CT scan in other countries may be different in comparison to the UK, and the applicability of this model in other healthcare system remains to be explored. On this regard, the British Society of Cardiovascular Imaging/British Society of Cardiovascular CT (BSCI/BSCCT) estimated an impressive increase of near 700% in coronary CTA across the UK [35]. The situation is quite similar in most European countries as well as in USA, although the UK has a relatively low number of CTA scanners per head of population [35]. Thus, the potential adoption for most western countries of updated NICE recommendations for stable CAD may require a substantial investment in CTA technology and training.

Out of the setting of randomized and well conducted trial, in clinical practice the use of CTA will generate a number of equivocal CTA test, due to the nonoptimal expertise in exam execution and image interpretation. Consequently, in order to solve the doubt raise from the equivocal tests the attending physician may require in the diagnostic workup more additional functional imaging test. Thus, it is likely that the potential disinvestment in stress imaging services in favor of CTA imaging could not occur in the next years. Notably, the rapid development of new CT technologies may help us to reduce the burden of false-positive CTA for patients with stable CAD. In this setting, the routine use of fractional flow reserve CTA and CT perfusion (CTP) appears to be the most promising and valuable tool, even if the accuracy of both techniques remains to be demonstrated on revascularized patients with recurrent chest pain [36–38]. In addition the availability of both modern techniques is very restricted in some dedicated centers. Moreover, in case of wide dissemination of coronary CTA in western countries, the preservation of quality imaging is very important, since it is strongly related to the diagnostic accuracy of coronary CTA. In this regard, current recommendation should be followed in order to optimize image quality in cardiac CTA [39, 40], and, moreover, standardized informative reports of CTA studies should be provided by the physician as well as the radiation dose exposure should be reported on this report. Recently, CAD-RADS reporting and data system are also available for the structured reporting of cardiac CTA, which may facilitate and simplify the communication of results to clinicians and patients [41]. Especially, this program may optimize downstream investigations in order to avoid an increase in the use of ICA when cardiac CTA identifies nonobstructive CAD. Not surprisingly, in setting of chest pain patients with suspicion of CAD the nonobstructive CAD was the most common pattern of coronary atherosclerosis disease and its detection may increase with the increase availability and use of coronary CTA. Currently, the management of nonobstructive CAD represents in the community of cardiology one of the major challenge. The concept of stenosis severity alone for the classification of CAD appears old and it does not feet with the continuum of risk associated with nonobstructive atherosclerotic plaque. The identification of features of vulnerability in coronary plaques rather than the luminal narrowing in isolation may improve the risk stratification of future cardiac events [42–56]. This concept is very important, especially in women with suspicion of CAD showing frequently a nonobstructive CAD or minimal coronary lesion from CTA, associated with features of microvascular dysfunction [57].

7. The Radiation Dose

The practical implementation of the new guidelines will meet many challenges. The recommendations are in part based on the assumption that the radiation dose of CTA is in the order of 1–2 mSv, which is achievable in most patients with the latest generation CT scanners [58–62]. However, most UK hospitals do not have these and instead use 64-slice CT scanners that can perform a CTA with a radiation dose of 3–5 mSv, provided prospective gating is used, which requires a heart rate of 60 bpm; otherwise, CTA is performed with retrospective gating, which allows for a heart rate up to 70 bpm, but with radiation doses of 10–15 mSv, a similar radiation dose to MPS. In PROSPECT, a trial comparing CTA and MPS in patients with intermediate risk chest pain, the total radiation dose was high in both arms (24 versus 29 mSv) and no difference was found in the rates of ICA between the two strategies. To implement the NICE guidelines without increasing the radiation burden on the population, the National Health Service (NHS) will need to make a significant investment in high-specification CT scanners and/or carefully consider the choice of the follow on functional imaging test, based on the patient's age, sex, and their cumulative radiation dose, from other radiation-based investigations. This UK picture is similar to that observed in the majority of the European country, highlighting that the investment in the latest generation CT scanners should be planned as an appropriate and rationale strategy rather than occasional investment. A further major challenge, if the NICE recommendations are to be adopted on the next European guidelines, will be to identify and train the increased requirement for radiographers and consultants (both cardiologist and radiologist) to perform and report the additional CTA.

8. Conclusions

CTA is an excellent rule-out test for CAD when used in the appropriate disease prevalence population. Despite the good performance of CTA in recent PROMISE, SCOT-HEART, and EVINCI trials, there is little clinical or health economic data to support the use of CTA over other noninvasive imaging tests in patients at intermediate-high risk of CAD in real world. Furthermore, the availability of latest generation scanners in European country is limited. Thus the potential for high cumulative radiation dose exposure from multiple serial CTA investigations could be a big problem. Finally, in real world the implementation of CTA for the evaluation of new onset chest pain fundamentally depends on the new health strategy based on the reconfiguration of current finances and staffing levels.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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Review Article

CT Myocardial Perfusion Imaging: A New Frontier in Cardiac Imaging

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The past two decades have witnessed rapid and remarkable technical improvement of multidetector computed tomography (CT) in both image quality and diagnostic accuracy. These improvements include higher temporal resolution, high-definition and wider detectors, the introduction of dual-source and dual-energy scanners, and advanced postprocessing. Current new generation multidetector row (≥64 slices) CT systems allow an accurate and reliable assessment of both coronary epicardial stenosis and myocardial CT perfusion (CTP) imaging at rest and during pharmacologic stress in the same examination. This novel application makes CT the unique noninvasive "one-stop-shop" method for a comprehensive assessment of both anatomical coronary atherosclerosis and its physiological consequences. Myocardial CTP imaging can be performed with different approaches such as static arterial first-pass imaging, and dynamic CTP imaging, with their own advantages and disadvantages. Static CTP can be performed using single-energy or dual-energy CT, employing qualitative or semiquantitative analysis. In addition, dynamic CTP can obtain quantitative data of myocardial blood flow and coronary flow reserve. The purpose of this review was to summarize all available evidence about the emerging role of myocardial CTP to identify ischemia-associated lesions, focusing on technical considerations, clinical applications, strengths, limitations, and the more promising future fields of interest in the broad spectra of ischemic heart disease.

1. Introduction

Since the clinical introduction of multidetector computed tomography (CT) in the late 1990s [1, 2], coronary computed tomography angiography (CTA) has become the mainly used noninvasive imaging modality in the suspicion of coronary artery disease (CAD).

In consideration of its high sensitivity and negative predictive value (≥95%) for the detection of significant coronary stenosis [3], coronary CTA is currently recommended as the first diagnostic test in symptomatic, low-to-intermediate risk population [4–6].

The EVINCI (EValuation of INtegrated Cardiac Imaging for the Detection and Characterization of Ischaemic Heart Disease) study, a prospective multicenter European comparative effectiveness trial, has demonstrated that comprehensive assessment of anatomic CAD by CTA had a sensitivity of 91% and specificity of 92%, which were higher than functional test including myocardial perfusion imaging by either single photon emission computed tomography (SPECT) or positron emission tomography (PET) and ventricular wall motion imaging by either stress echocardiography or magnetic resonance imaging (MRI) [7]. However, this study has several limitations that may explain the lower accuracy of functional imaging, such as the lack of additional information (myocardial perfusion analysis and late-gadolinium enhancement for MRI and quantitative myocardial perfusion for PET), and the submaximal stress for echocardiography in 41% of cases [7].

The effects on clinical decision-making due to incorporation of CTA in the chest pain care pathway, jointly with its safety, are demonstrated in the SCOT-HEART [8] and in the PROMISE [9] prospective multicenter trials.

Coronary CTA has also a prognostic value providing information on the total plaque burden, with a better outcome when there is no evidence of CAD and a worse prognosis in case of detection of coronary atherosclerosis, depending on its severity and extension [10–15].

Moreover, it has the ability to detect nonobstructive non-flow-limiting CAD, helping to identify patients at risk of future cardiac events with more precision than functional testing [16].

The actual limit of coronary CTA is the impossibility to assess the functional significance of coronary stenosis related to its moderate positive predictive value (about 50%) in detecting inducible myocardial ischemia [17–19].

Physiological evaluation needs to be improved, because it influences the outcome of CAD more than its anatomical detection. In fact, studies using fractional flow reserve (FFR) have demonstrated that ischemia-guided coronary revascularization, especially percutaneous coronary intervention (PCI), is superior to angiography-guided strategy [20–23].

In absence of myocardial ischemia, revascularization is associated with no symptomatic or prognostic benefit for patients, while it is effective in patients with moderate to severe ischemia (total myocardial ischemia >10%) [20].

The evidence of coronary stenosis, especially for luminal narrowing of 30-70%, is not predictive of inducible ischemia. Further functional test, such as SPECT, stress echocardiography, or stress perfusion MRI are needed to guide revascularization indication [19].

Furthermore, a subanalysis of the EVINCI study has shown that, in patients at intermediate risk of CAD, hybrid imaging with CTA and SPECT allows noninvasive colocalization of myocardial perfusion defects and subtending coronary arteries, impacting clinical decision-making in almost one in every five subjects [24].

In the last decades, we observed a rapid technological improvement, which led to a notable reduction of the scan time, motion artifacts, use of contrast agent, and radiation dose exposure, while yielding, at the same time, higher spatial and temporal resolution [25–27] which widened the application of CT from anatomical detection of CAD to physiological assessment of myocardial ischemia leading to the first human report of stress myocardial CT perfusion (CTP) by Kurata et al. in 2005 [28]. Currently, feasibility of CTP imaging with modern multidetector row (≥64 slices) CT systems at rest and during pharmacologic stress [29–35] has been demonstrated by several clinical studies and recent multicenter trials.

The purpose of this review was to summarize all available evidence about the emerging role of myocardial CTP in the assessment of the hemodynamic impact of coronary lesions, focusing on technical considerations, clinical applications, strengths, limitations, and the more promising future field of interest in the broad spectra of ischemic heart disease.

2. The Physiologic Basis of Stress Myocardial Perfusion

In the classic ischemic cascade, perfusion abnormalities are the first to occur, before metabolic alterations, wall motion abnormalities, ECG changes, and symptoms.

Stress tests evaluating myocardial perfusion have a higher sensitivity in detecting flow-limiting stenosis compared with other imaging modalities based on the induction of stress-induced wall motion abnormalities or ECG changes [19].

Gould in 1974 was the first to investigate the relationship between luminal artery narrowing and the maximal hyperemic response [36].

Thanks to coronary autoregulation, involving myogenic and metabolic mechanism, myocardial perfusion at rest is normal until the luminal diameter narrowing of a coronary artery exceeds 85-90%.

However, in presence of coronary stenosis greater than 45% maximal coronary hyperemia induced by coronary arteriolar vasodilator leads to a progressive decrease in the hyperemic response [36].

In this situation, exercise or pharmacological vasodilation of subepicardial resistance vessels results in a reduction in distal coronary pressure that redistributes flow away from the subendocardium, leading to a "transmural steal" phenomenon [19].

Pharmacological stress agents are used to induce the hyperemic response in patients who cannot afford exercise test, that is, the preferred method to induce myocardial hyperemia.

For stress CTP, the most used substances are adenosine and dipyridamole that lead to arteriolar vasodilation by both direct and endothelium-mediated mechanisms through stimulation of A2A receptors in the microvasculature. In the absence of microcirculatory dysfunction, the vasodilatory response is associated with a 3.5- to 4-fold increase in myocardial blood flow [34].

Two intravenous (IV) lines are essential in CTP imaging for injection of the contrast media and of the vasodilator agent, respectively.

Adenosine is a powerful, endogenous molecule with a nonselective activation of four distinct subtypes (A1, A2A, A2B, and A3) receptors. Its infusion rate is 140 mcg/kg/min for 3 to 5 minutes with an infusion pump. Side effects could be AV block, peripheral vasodilation, and bronchospasm, but the most common are flushing, chest pain, dyspnea, dizziness, or nausea. Compared to dipyridamole, adenosine has a more rapid onset of action and a shorter half-life of 30 s; therefore most side effects resolve in a few seconds after discontinuation of the adenosine infusion.

Dipyridamole increase intracellular and interstitial concentration of adenosine, indirectly leading to coronary arteriolar vasodilatation, and it does not require an IV pump for infusion as it can be applied manually at a slow rate in a dose of 0.56 mg/kg to 0.84 mg/kg over a 4- to 6-minute period. Due to its longer half-life of approximately 30 minutes, dipyridamole-stress patients may require administration of aminophylline (slow intravenous injection of 50 mg to 250 mg) for reversal of persistent symptoms [19, 34, 37].

Recently, a new agent named regadenoson, an A2A selective agonist administered via a prefilled syringe in a single dose (400 mg) over 10 seconds, has been introduced as a pharmacologic stress vasodilator. It has a safer side effect profile in comparison to adenosine and dipyridamole, especially for patients with asthma or severe chronic obstructive pulmonary disease but it is limited by its cost and it is not widely available.

Regadenoson has been shown to be accurate for the detection of obstructive CAD in nuclear perfusion imaging, stress echocardiography, and, more recently, stress CTP studies [29, 38], even if a recent study by Johnson and Gould using quantitative Rb-82 PET imaging [38] showed a lower vasodilatory effect of regadenoson stress compared to dipyridamole stress, with an efficacy around 80%.

Of note, the myocardial perfusion can be evaluated by dobutamine as well [31]. The synthetic catecholamine dobutamine is primarily a β1-adrenergic receptors agonist, with mild effect on α1- and β2-receptors [39]. At low doses (≤ 10 μg/kg/min), dobutamine improves myocardial contractility and induces coronary vasodilation; at higher doses (20-40 μg/kg/min), it causes systematic vasodilation and serves as a positive chronotrope [39]. At these high doses, dobutamine mainly acts through increased of heart rate and myocardial oxygen consumption rather than "steal phenomenon" [31]. In the clinical practice, dobutamine stress is widely accepted as a noninvasive tool for stress echocardiography or stress MRI to detect myocardial ischemia by identifying regional wall motion abnormalities (RWMA), with similar accuracy and sensitivity of dipyridamole-stress imaging [39, 40]. Contrast-enhanced echocardiography and perfusion MRI may further improve diagnostic accuracy of dobutamine stress in detecting myocardial ischemia [39, 40].

Dobutamine is not the preferred pharmacological stressor in CTP imaging. However, as described by a recent case report, it may have a value to risk stratify patients with an anomalous coronary artery, since vasodilator stress imaging might not be sufficiently sensitive to identify dynamic coronary compression [41].

3. Protocol of CTP Imaging

The protocol of CTP imaging includes evaluation of myocardial perfusion during both rest (baseline) and stress (hyperemia) conditions and it is similar to other noninvasive imaging techniques such as stress cardiac MRI and nuclear imaging [19].

CTP analysis is performed after administration of iodinated contrast through an antecubital IV access by imaging the left ventricular (LV) myocardium during the first pass of the contrast bolus. Iodinated contrast attenuates X-rays directly proportionally to iodine content in tissue; thus myocardial perfusion defects can be directly visualized as hypoattenuated or nonenhancing regions.

Imaging during the early portion of first-pass circulation is critical, since after about 1 min a rapid wash-out of contrast agent due to diffusion to the extravascular space is expected [34].

Contrast injection needs, at high flow rate, at least 5 mL/s for optimizing the strength of enhancement in the first-pass arterial phase [34].

There are two protocols mostly used, named according to sequence of scan acquisitions: rest/stress or stress/rest. An interval of 10-15 minutes between the two sequences provides optimal contrast wash-out [19, 34].

The rest/stress protocol uses the ability of coronary CTA to rule out obstructive CAD. CTP is performed only in the presence of anatomically defined CAD of intermediate or obstructive degree, avoiding further radiation and iodinated contrast exposure in absence of coronary artery stenosis. This protocol is limited by the cross-contamination of contrast in the stress phase and beta-blocker administrated before the rest acquisition, leading to underestimation of myocardial ischemia.

The stress/rest protocol avoiding the risk of residual contrast media derived from the rest phase that may confound perfusion defects is optimized for the detection of myocardial ischemia.

The contrast media contamination of the rest phase may decrease sensitivity for infarction [19, 34].

Definitely, the best approach should be tailored on the patient's risk profile, reserving the rest/stress CTP for patients with low-to-intermediate pretest probability of CAD and stress/rest CTP for patients with high pretest probability of ischemia-associated lesions [34].

Myocardial CTP imaging can be performed with different approaches such as static arterial first-pass imaging and dynamic time-resolved CTP imaging, with their own advantages and disadvantages.

3.1. Static CTP Imaging: Monoenergetic CT Acquisition. The static CTP imaging is based on acquisition of one single phase during the first-pass of the contrast agent. Certain technical challenges involving scan timing relative to maximum contrast enhancement and optimal contrast material delivery must be met [19].

Generally, rest myocardial CTP imaging is derived from the coronary CTA examination.

ECG-gating of coronary CTA or CTP can be retrospective (with prospective tube current modulation) [42, 43] but also prospective, which is a new feature of latest multislice CT scanners (64 or more slices), allowing a significant reduction in radiation dose (less than 5 mSv), without causing any significant decrease in image quality [44, 45].

Prospectively ECG-triggered high-pitch spiral acquisition implemented with the second-generation 128-slice dual-source CT (DSCT) scanner allows the acquisition of the volumetric data of the heart in a single cardiac cycle with radiation exposure as low as 1 mSv [27, 46].

Visual qualitative assessment is the analyzing method of static CTP. Thick multiplanar reconstructions of approximately 5 mm to 8 mm are usually recommended for myocardial perfusion analysis to improve the contrast-to-noise ratio.

Myocardial contrast enhancement increases proportionally with iodine concentration, so perfusion defects appear as hypodense region with subendocardial or transmural distribution with respect to the normal myocardium.

An integrated review of stress and rest images is important to characterize not only ischemic from nonischemic myocardium, but also viable versus nonviable myocardium by differentiating between fixed and inducible perfusion abnormalities [19].

Hypoperfusion in stress with normal perfusion in rest underlines ischemia, whereas hypoperfusion in stress that persists with same extension in rest is indicative of necrosis [47]. Furthermore, hypoperfusion in stress that persists in rest with less extension than in stress is specific for peri-infarct ischemia [47]. A relative hyperenhancement to differing degrees of an infarct may be visualized on the second sequence of the acquisition protocol due to contrast distribution into the extravascular, extracellular interstitial space [19, 47].

The final step to the analysis of a CTA/CTP study is the match of perfusion defects with the anatomic localization of coronary epicardial stenosis, Figure 1. This is crucial for the interpretation of the hemodynamic significance of CAD [19, 34].

Automated software application provides analysis of semiquantitative metrics such as the transmural perfusion ratio (TPR), determined as the ratio of subendocardial to mean subepicardial contrast attenuation, which has been already initially validated for MRI perfusion. However, the accuracy of TPR may be significantly affected by motion and beam-hardening artifacts or by a thinning myocardial wall in the context of prior infarction [47].

In conclusion, the patient specific ischemic burden may be determined in terms of volume of CT perfusion defect or percentage of ischemic myocardium relative to global myocardial volume [48].

3.2. Static CTP Imaging: Dual-Energy CT Acquisition. Dual-energy CT (DECT) myocardial perfusion imaging technology provides additional information about myocardial tissue composition compared with conventional single-energy computed tomography (SECT). Moreover, DECT improves limitations that are commonly present in SECT such as beam-hardening artifacts and blooming artifacts by using monochromatic image reconstruction [49].

Based on the specific attenuation spectral characteristics of the different tissues when exposed to two different photon energy levels, DECT enables distinguishing the features of the tissue and evaluating the myocardial blood supply by mapping iodine distribution within the myocardium [50].

Iodine map provides a measure of per-voxel iodine myocardial concentration expressed in mg/mL, which improves accuracy when compared to standard visual analysis [34, 49, 51], Figure 2.

Different vendor-specific CT technologies have been developed to perform dual-energy acquisitions. Dual X-ray source system (Siemens Healthcare) is the most commonly used technology: there are two independent tubes paired with two detectors that simultaneously emit high (140-150 kV) and low (80-90-100 kV) energy levels [52].

A second modality is based on single-source CT with rapid (about 0.25 ms) switching of tube voltage between 80 and 140 kV either in a single gantry rotation (GSI Cardiac, GE Healthcare) or in sequential rotations (Acquilion One, Toshiba) [19].

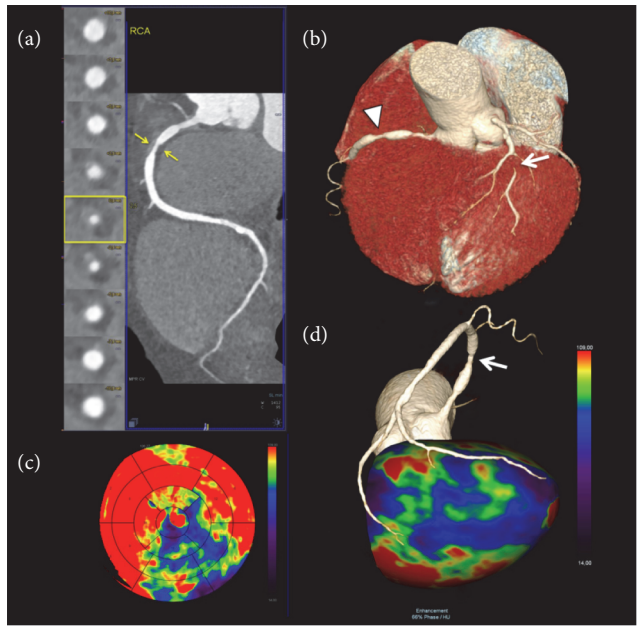

Figure 1: **Static single-energy CTP imaging**. 61-year-old male patient with multiple cardiovascular risk factors (smoke, hypercholesterolemia, and hypertension) presented with recurrent atypical chest pain. (a) Coronary CT angiography curved multiplanar reconstruction of the right coronary artery (RCA) with the corresponding orthogonal views showed a critical stenosis (>70% luminal narrowing) at the proximal segment sustained by a large noncalcified atherosclerotic plaque with positive remodeling (arrows). (b) Three-dimensional volume-rendering reconstruction demonstrating the critical stenosis of the proximal RCA (arrowhead) and showing also a tight stenosis (>90%, arrow) of the main diagonal branch (arrow). (c) 17-segment polar plot display of CT perfusion data acquired with a prospectively ECG-triggered high-pitch spiral technique at stress during the first pass, arterial phase, showed large, and severe perfusion defect color-coded in violet/blue/green at the inferior and inferolateral wall; note also a severe area of hypoperfusion in the apical lateral segment and in the apex. (d) Three-dimensional volume-rendering modeling of the left ventricular myocardial perfusion data with superimposed coronary tree (inferior view) showed the critical stenosis of the proximal segment of RCA (arrow) associated with an extensive perfusion defect at the inferior and inferolateral wall extending to apex (color-coded in violet/blue/green).

The dual-layer ("sandwich") detector (Philips Healthcare) is an alternative approach made of two different materials able to differentiate between low and high energy photons, with the source operating at constant tube voltage; however this system is not yet available in routine clinical practice [49].

Finally, the use of second- or third- generation DSCT scanners with high temporal resolution (75 ms or 66 ms, respectively) could help discriminate between motion artifacts due to irregular or high heart rates and true perfusion defects, avoiding false positive findings [19].

3.3. Dynamic CTP Imaging. The only CT based technology that permits absolute quantification of myocardial perfusion

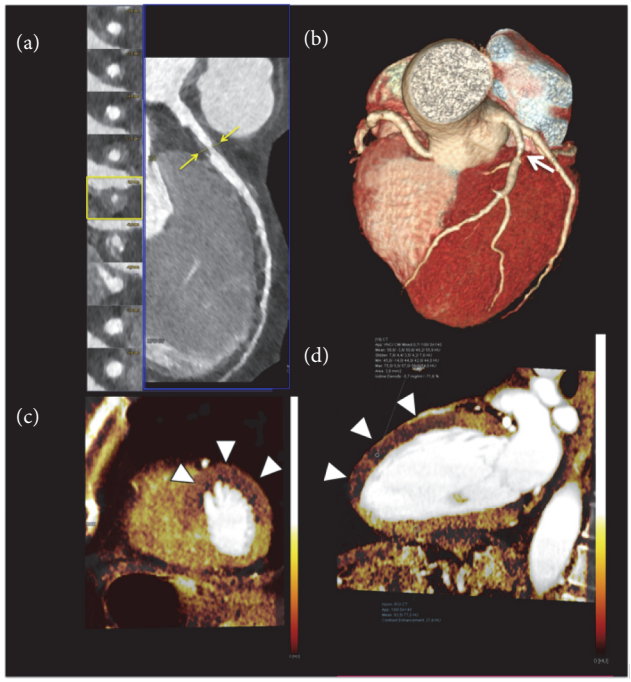

Figure 2: **Static retrospectively ECG gated dual-energy myocardial perfusion imaging**. 56-year-old man with multiple cardiovascular risk factors and stable angina. (a) Coronary CT angiography curved multiplanar reconstruction of the left anterior descending artery (LAD) with the corresponding perpendicular views showed a critical stenosis (>70% luminal narrowing) at the proximal segment (arrows) sustained by a large concentric predominately noncalcified plaque with positive remodeling (Remodeling Index= 2.1). (b) The corresponding three-dimensional volume-rendering reconstruction demonstrating the critical stenosis of the proximal LAD (arrow). (c-d) Myocardial short-axis (c) and 2-chamber long-axis (d) color-coded iodine distribution maps of dual-energy CTP imaging during stress showed perfusion defects at the antero-septal, anterior, and antero-lateral wall corresponding to the territory of the left anterior descending artery (arrowheads). Quantitative analysis of the dual-energy map at the level of the anterior wall shows a 71.6% reduction in iodine content (Iodine Density: −0.7 mg/ml) with respect to the remote myocardium at the inferior wall.

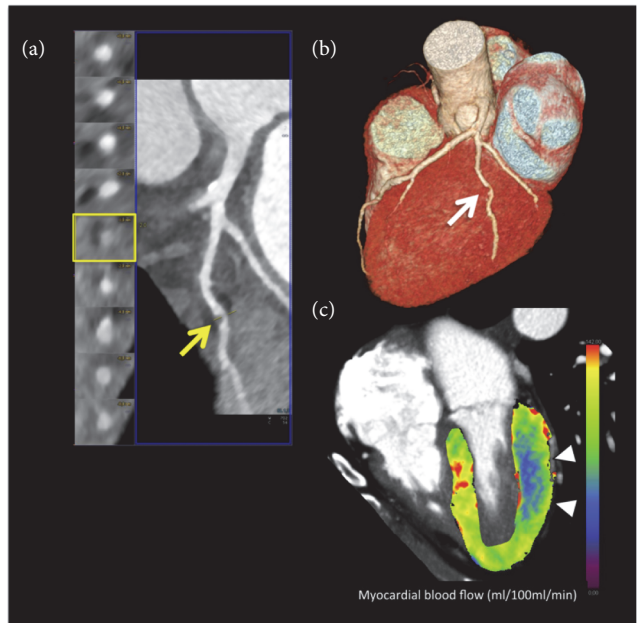

Figure 3: **Dynamic CTP imaging**. 67-year-old obese female patient with history of hyperlipidemia and smoking with suspected coronary artery disease. (a) Curved multiplanar reformation of coronary CT angiography data showed eccentric noncalcified plaque of the main obtuse marginal branch (OM) causing focal critical stenosis (>70% luminal narrowing), arrow. (b) Three-dimensional volume-rendering reconstruction confirmed the severe coronary artery stenosis of the OM (arrow). (c) Three-dimensional color-coded 4-chamber CT perfusion map image derived from the time-resolved dynamic acquisition during stress with the shuttle mode shows extensive perfusion defects in the territory of the OM (basal-middle lateral wall), color-coded in blue, arrowheads. The colors of the myocardium are coded according to the flow values with red, green, and yellow representing higher flow values than blue. The corresponding value of the hemodynamic parameters derived from the time-attenuation curves (TACs) demonstrates a significant reduction of myocardial blood flow in the territory of the OM, consistent with inducible ischemia. Absolute myocardial blood flow was 61.6 mL/100 mL/min and 118.2 mL/100 mL/min in the OM and remote myocardium (septal wall) territories, respectively.

is dynamic CTP imaging. It is based on repeated acquisition of the myocardial tissue during the first-pass contrast uptake to create time-attenuation curves (TACs) for the region of interest (ROI) [53], providing more objective and reproducible assessment of myocardial iodine distribution in a similar way of positron emission tomographic (PET) perfusion imaging [37].

Hemodynamic parameters, such as the myocardial blood flow (MBF), MBF ratio, and myocardial blood volume (MBV), and semiquantitative parameters such as the upslope, peak enhancement, time to peak (TTP), tissue transit time (TTT), and area under the curve (AUC) are derived by dedicated algorithms of these TACs (most of which are based on deconvolution methods already used in CMR studies) [54, 55].

Recently, the introduction of semiautomated three-dimensional software allowed a substantial reduction of the postprocessing phase, making the dynamic CTP more suited to routine clinical practice [34], Figure 3.

Whole-heart spatial coverage with appropriate temporal resolution is crucial to obtain multiple consecutive images at high heart rates [37].

Dynamic datasets acquisition is currently performed with two different approaches. The first one provides the use of single-tube multidetector CT scanners with 256 or 320 detector rows, which cover the whole cardiac volume while the table is stationary (detector Z-coverage is 78 or 160 mm, respectively). An alternative approach is second- and third-generation DSCT scanners, able to perform dynamic CTP imaging: by moving the scanner table back and forth ("shuttle mode") between two scanning positions; it is possible to

Table 1: Main differences between static and dynamic CTP imaging.

	STATIC CTP	DYNAMIC CTP
BREATH HOLD	Shorter	Longer (about 30 sec)
WALL MOTION EVALUATION	Yes	No
MYOCARDIAL PERFUSION QUANTIFICATION	No	Yes
RADIATION EXPOSURE	+/++	++/+++

achieve a coverage of 73 or 105 mm, respectively, for the second- and third-generation DSCT scanners [34].

In both cases, image acquisition is performed during the systolic phase of the cardiac cycle when apical-basal length is shorter and myocardial wall is at maximal thickness.

Systolic phase length is relatively constant (about 200 ms) even when heart rate is high and irregular, so, images acquired in systole are less vitiated to beam-hardening artifacts because the amount of contrast medium needed for this phase is lower (typically 50 mL of contrast medium followed by 50 mL of saline at 5-6 mL/s is required) [53].

The obstacles to the clinical routine application of dynamic CTP are high radiation exposure, the relatively long breath-hold (approximately 30 sec) necessary for whole cardiac volume scanning, and spatial misalignment from two separated table positions when shuttle mode is used [19].

The use of motion correction and beam-hardening correction algorithms could minimize artifacts, improving image quality and diagnostic accuracy [34].

Advantages and disadvantages of static and dynamic CTP imaging are summarized in Table 1.

4. Accuracy of CTP Imaging

Many clinical studies and the first prospective multicenter trials have established the clinical feasibility and the diagnostic accuracy of static and dynamic CTP compared to SPECT, stress MRI, and/or invasive coronary angiography with and without fractional flow reserve (FFR), Tables 2–4.

A recent meta-analysis including 1188 patients in 19 studies showed that static CTP imaging in case of suspicion of known CAD, had a good agreement with SPECT and stress MRI perfusion with a sensitivity and specificity of 85% and 81%, respectively. When ICA was used as reference standard alone or in combination with SPECT or FFR, combined coronary CTA and CTP compared to coronary CTA alone significantly increased the specificity from 62% to 84% without significant decrease in sensitivity [79].

Similar results were obtained in a meta-analysis of Takx et al. [80] evaluating the diagnostic accuracy of different stress myocardial perfusion imaging modalities for the diagnosis of hemodynamically significant CAD compared to ICA with FFR as a reference standard. Takx et al. showed that the performance of CTP imaging was comparable to that of PET and stress MRI and substantially higher than that of SPECT and echocardiography, with a pooled sensitivity of 88% and specificity of 80% [80]. This finding was noted at both the vessel and the patient level. Furthermore, CTP showed a higher sensitivity than SPECT (88% versus 74%, respectively), because of a small number of false negative results [80].

A prospective multicenter international trial, the CORE 320 study (n=381), has confirmed that static CTP imaging has a higher accuracy in comparison with SPECT in terms of significant CAD (≥ 50%) detection, using as reference ICA [61]. The better performance of CTP imaging was due in part to its higher sensitivity in the detection of left main and multivessel CAD and in part to its superior spatial resolution, which permits a better evaluation of small subendocardial defects [61].

The increased sensitivity of CTP also derives from the more favorable extraction characteristics of iodinated contrast material allowing for a linear relationship between CT-derived metrics and myocardial blood flow. Conversely, Technetium-based tracers show a nonlinear net-tracer uptake in particular in the higher coronary flow range, causing the well-known-roll-off phenomenon [61].

The CORE 320 studies have also proved that the specificity and overall accuracy of coronary CTA in detecting significant CAD (≥50%) defined by ICA and SPECT are significantly increased by the addition of CTP at both the patient and vessel levels [60, 63]. This finding has been shown in patients with as well as without known CAD [60, 63].

Another recent randomized, multicenter, multivendor CTP study with regadenoson (n=110) by Cury et al. has shown that regadenoson-CTP imaging improved the diagnostic accuracy of coronary CTA from 69% to 85%, in particular by reducing the rate of false positive CTA results [64].

Moreover, CTP showed a high sensitivity and specificity of 90% and 84%, respectively, for the detection of myocardial ischemia as defined by a reversible perfusion defect in ≥ 2 myocardial segments on SPECT, with an agreement rate of 87% [64].

A considerable increase in diagnostic performance has also been largely proved when dual-energy myocardial CTP was coupled to coronary CTA, especially in terms of specificity, Table 3.

According to Meinel et al. the rest-stress protocol should be the first choice for evaluation of the myocardial blood supply in dual-energy CTP, with a sensitivity of 99%, specificity of 97%, positive predictive value (PPV) of 92%, and NPV of 100% using SPECT as reference of standard [66].

The DECIDE-Gold, an ongoing prospective multicenter study, will define the diagnostic accuracy of dual-energy to detect hemodynamic significant CAD, comparing it to fractional flow reserve (FFR) as a reference standard [81].

The available published data seem to suggest that static dual-energy and quantitative dynamic CTP imaging have a higher sensitivity, with respect to standard static monoenergetic CTP [34, 53], Tables 3 and 4. This might be due to the easiest detection of small perfusion defects from the

Table 2: Static single-energy CTP imaging.

Author (Year)	Patients No.	CT Scanner	CTP Protocol	Stress Agent (dose)	Analysis	Reference Standard	SE (%)	SP (%)	PPV (%)	NPV (%)	Average CT Dose
Blankstein et al [42] (2009)	34	DS (1st)	STRESS (Retrosp) / REST (Prosp) / LE (Prosp)	Adenosine (0.14 mg/kg/min)	Visual	SPECT (for vessel)	84	80	71	90	9.1 mSv
Rocha-Filho et al [43] (2010)	35	DS (1st)	STRESS (Retrosp) / REST (Prosp)	Adenosine (0.14 mg/kg/min)	Visual	QCA (for vessel)	91	91	86	93	9.8 mSv
Feuchtner et al [46] (2011)	30	DS (2nd)	STRESS (Prosp) / REST (Prosp)	Adenosine (0.14 mg/kg/min)	Visual	MRI 1.5 T (for vessel)	96	88	93	94	0.93 mSv
Cury et al [56] (2011)	26	64-slice	STRESS (Retrosp) / REST (Retrosp)	Dypiridamole (0.56 mg/Kg)	Visual	SPECT (for patient)	94	78	89	87	14.4∗ mSv
Ko et al [57] (2012)	40	320-slice	REST (Prosp) / STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	TPR	FFR (for vessel)	74	66	56	81	4.5 mSv
					Visual§	FFR (for vessel)	87	95	89	94	
George et al [44] (2012)	50	320-slice	REST (Prosp) / STRESS (Prosp) / LE (Prosp)	Adenosine (0.14 mg/kg/min)	TPR	SPECT (for patient)	72	91	81	85	7.0 mSv
Nasis et al [45] (2013)	20	320-slice	REST (Prosp) / STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	Visual§	QCA + SPECT (for patient)	94	98	94	98	4.8 mSv
Bettencourt et al [58] (2013)	101	64-slice	STRESS (Retrosp) / REST (Prosp)	Adenosine (0.14 mg/kg/min)	Visual§	FFR (for patient)	89	83	80	90	5.0∗ mSv
						MRI 1.5 T (for patient)	67	95	91	78	
Wong et al [59] (2014)	75	320-slice	REST (Prosp) / STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	Visual + TAG§	FFR (for vessel)	97	84	76	98	4.8 mSv
Rochitte et al (CORE320 study) [60] (2014)	381	320-slice	REST (Prosp) / STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	Semiq	QCA + SPECT (for patient)	80	74	65	86	5.31 mSv
George et al (CORE320 study) [61] (2015)	381	320-slice	REST (Prosp) / STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	Semiq	QCA (for patient)	88	55	75	75	NA
Yang et al [62] (2015)	75	DS (2nd)	STRESS (Retrosp) / REST (Retrosp)	Adenosine (0.14 mg/kg/min)	Visual	FFR (for patient)	89	86	96	63	6.5 mSv
						FFR (for vessel)	80	95	92	87	

Table 2: Continued.

Author (Year)	Patients No.	CT Scanner	CTP Protocol	Stress Agent (dose)	Analysis	Reference Standard	SE (%)	SP (%)	PPV (%)	NPV (%)	Average CT Dose
Magalhaes et al (CORE320 study) [63] (2015)	381	320-slice	REST (Prosp) / STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	Visual§	QCA + SPECT (for patient)	78	73	64	85	NA
Cury et al (Regadenoson crossover study) [64] (2015)	110	Multivendor	STRESS (Retrosp or Prosp) / REST (Retrosp)	Regadenoson (0.4mg)	Semiq	SPECT	90	82	53	97	17.7∗ mSv

CTP, computed tomography perfusion; 1st and 2nd, first and second generation; CT, computed tomography; DS, Dual-Source scanner; FFR, fractional flow reserve; MRI, magnetic resonance imaging; PROSP, prospective ECG-gating acquisition; RETROSP, retrospective ECG-gating acquisition; NA, nonassessable; NPV, negative predictive value; PPV, positive predictive value; QCA, quantitative coronary angiography; SE, sensitivity; SP, specificity; Semiq, semiquantitative analysis using a stress score; SPECT, myocardial perfusion scan; TPR, transmural perfusion ratio; TAG, transluminal attenuation gradient; ∗, global radiation dose of the stress-rest protocol; §, accuracy of CT perfusion integrated with the coronary anatomic data.

Table 3: Static dual-energy CTP imaging.

Author (Year)	Patients No.	CT Scanner	CTP Protocol	Stress Agent (dose)	Analysis	Reference Standard	SE (%)	SP (%)	PPV (%)	NPV (%)	Dose
Ko et al [65] (2012)	45	DS (1st)	CCTA SECT (Retrosp) / STRESS DECT (Retrosp) / REST DECT (Retrosp)	Adenosine (0.14 mg/kg/min)	Iodine Map (for vessel)	QCA	89	74	80	85	5.7 mSv
Meinel et al [66] (2014)	55	DS (2nd)	STRESS DECT (Retrosp) / REST DECT (Retrosp) / LE DECT (Retrosp)	Adenosine (0.14 mg/kg/min) Regadenoson (0.4 mg)	Iodine Map (for segment)	SPECT	99	97	92	100	7.1 mSv
Delgado et al [67] (2013)	56	DS (2nd)	STRESS DECT (Retrosp)	Adenosine (0.14 mg/kg/min)	Iodine Map (for segment)	MRI 1.5T	76	99	89	98	5.2 mSv
Kido et al [68] (2014)	21	DS (1st-2nd)	CCTA SECT (NA) / STRESS DECT (Retrosp)	Adenosine (0.16 mg/kg/min)	Iodine Map (for vessel)[§]	QCA	67	92	84	82	7.7 mSv
Kim et al [69] (2014)	50	DS (2nd)	STRESS DECT (Retrosp) / CCTA SECT (Retrosp)	Adenosine (0.14 mg/kg/min)	Iodine Map (for segment)	MRI 1.5T	77	94	53	98	6.5 mSv
Ko et al [70] (2014)	40	DS (1st)	CCTA SECT (Retrosp) / STRESS DECT (Retrosp) / REST DECT (Retrosp)	Adenosine (0.14 mg/kg/min)	Iodine Map (for vessel)	QCA + MRI 3T[§]	87	79	71	91	4.6 mSv
Ko et al [71] (2014)	100	DS (1st)	STRESS DECT (Retrosp) / CCTA SECT (Retrosp)	Adenosine (0.14 mg/kg/min)	Iodine Map (for vessel)	QCA + MRI 1.5T and 3T[§]	88	79	73	91	4.2 mSv

CTP, computed tomography perfusion; 1st and 2nd, first and second generation; CT, computed tomography; DS, Dual-Source scanner; CCTA, coronary computed tomography angiography; DECT, dual-energy computed tomography; SECT, single-energy computed tomography; RETROSP, retrospective ECG-gating acquisition; NA, nonassessable; MRI, magnetic resonance imaging; No., patients' number; NPV, negative predictive value; PPV, positive predictive value; QCA, quantitative coronary angiography; SE, sensitivity; SP, specificity; SPECT, myocardial perfusion scan; [§], accuracy of CT perfusion integrated with the coronary anatomic data.

Table 4: Dynamic CTP imaging in human study.

Author (Year)	Patients No.	CT Scanner	CTP Protocol	Stress Agent (dose)	Analysis	Reference Standard	SE (%)	SP (%)	PPV (%)	NPV (%)	Average CT Dose
Bastarrika et al [72] (2010)	10	DS (2nd)	CCTA (Prosp) / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Visual Semiq Quantitative MBF	MRI (segment)	86	98	94	96	12.5 mSv
Ho et al [73] (2010)	35	DS (2nd)	STRESS (Shuttle mode) / CCTA (Prosp)	Dypiridamole (0.56 mg/Kg in 4′)	Quantitative MBF	SPECT (segment)	83	78	79	82	9.1 mSv
Bamberg et al [74] (2011)	33	DS (2nd)	CCTA (Prosp) / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Quantitative MBF	FFR[§] (vessel)	93	87	75	97	10 mSv
Wang et al [75] (2012)	30	DS (2nd)	CCTA (Prosp) / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Visual Quantitative MBF and MBV	QCA + SPECT (vessel)	100	76	54	100	9.5 mSv
Greif et al [55] (2013)	65	DS (2nd)	CCTA (Prosp) / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Quantitative MBF	FFR (vessel)	95	74	49	98	9.7 mSv
Huber et al [76] (2013)	32	256-slice	STRESS (Prosp)	Adenosine (0.14 mg/kg/min)	Quantitative MBF	FFR (vessel)	76	100	100	91	9.5 mSv
Bamberg et al [77] (2014)	31	DS (2nd)	CCTA (Prosp) / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Quantitative MBF and MBV	MRI 3T (vessel)	100	75	92	100	11.08 mSv
Rossi et al [78] (2014)	80	DS (2nd)	CCTA (Prosp) / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Quantitative MBF	FFR (vessel)	88	90	77	95	9.4 mSv

CTP, computed tomography perfusion; 2nd, second generation; CT, computed tomography; CCTA, coronary computed tomography angiography; PROSP, Prospective ECG-gating acquisition; DS, Dual-Source scanner; FFR, fractional flow reserve; MRI, magnetic resonance imaging; MBF, myocardial blood flow; MBV, myocardial blood volume; No., patients' number; NPV, negative predictive value; PPV, positive predictive value; QCA, quantitative coronary angiography; SE, sensitivity; Semiq, semiquantitative analysis; SP, specificity; SPECT, myocardial perfusion scan; [§], accuracy of CT perfusion integrated with the coronary anatomic data.

quantitative analysis that cannot be appreciated by visual qualitative perfusion analysis of static CTP [53].

Stress dynamic myocardial CTP has been initially studied in preclinical trials demonstrating a good correlation of CT-derived perfusion values with microsphere derived MBF data, histopathology, and invasive measurements of coronary blood flow and FFR, Table 5.

It is important to note that, as reported by a recent large animal study, dynamic CTP has a superior discriminatory power in detecting myocardial ischemia than static first-pass CTP, using fluorescent microspheres as a reference standard for MBF [34, 84]. A significant difference in accuracy was noted at lower degree of stenosis (50%), demonstrating a higher sensitivity of dynamic CTP for the detection of subtle differences of myocardial perfusion as compared to single phase CTP acquisition [84].

Clinical researches have demonstrated that dynamic stress CTP may improve the PPV and specificity of coronary CTA alone [77, 78], especially for interpretation of the hemodynamic impact of intermediate-grade stenosis (30-70%) by using invasive FFR as the reference standard [78].

This modality also enables the quantification of the absolute value of coronary flow reserve (CFR) calculated as the ratio of hyperemic to baseline MBF with a high degree of correlation to SPECT [33, 54].

Moreover, dynamic CTP is useful in the global quantitative evaluation of left ventricular myocardial perfusion, especially in case of balanced ischemia caused by multivessel CAD [86].

According to quantitative PET and CTP studies, the relative MBF (an absolute MBF-to-remote MBF ratio) leads to better detection of hemodynamically significant coronary stenosis than does the absolute MBF derived from dynamic CTP imaging, probably reducing the impact of microvascular resistance on myocardial perfusion [87–89].

Semiquantitative parameters such as the TPR and myocardial reserve index (defined as the ratio of hyperemic and resting blood flow) have been suggested for static and dynamic myocardial CTP; however, they have a lower diagnostic accuracy than qualitative analysis by standard visual assessment [19, 57, 90].

The CATCH-2 (CArdiac cT in the treatment of acute CHest pain 2), a prospective randomized controlled multicenter study published in 2017, has showed the usefulness of myocardial CTP assessment in addition to CTA, in patients with recent acute-onset chest pain when acute coronary syndrome had been excluded, and who had a clinical indication for outpatient noninvasive testing [91]. Coupling CTA with CTP, the amount of patients with suspected CAD requiring invasive examination and treatment decreases [91].

Finally, as proved by a CATCH-trial substudy, myocardial CTP parameters predict mid-term clinical outcome in patients with recent acute-onset chest pain independently of the pretest probability of obstructive CAD [92]. Interestingly, patients with an ischemic burden involving >10% of the LV myocardium demonstrated the poorest prognosis [92].

5. Radiation Exposure

During the last years, CT scanners with higher spatial resolution (approximately 1/3 of millimeter), temporal resolution (up to 66 ms), and wider detector array (up to 320-detector row) were developed, with a substantial improvement in CT performance and reduction of radiation exposure [19]. Furthermore, the introduction of ECG-driven tube current modulation, BMI-adapted tube voltage modulation, and prospective ECG-triggered sequential scanning combined with advanced iterative image reconstruction algorithms has achieved 30-90% reductions in patient radiation exposure while guaranteeing the image quality [19].

Consequently, the contemporary estimated effective dose of coronary CTA and myocardial static CTP imaging will typically range between approximately 1.5 and 5.0 mSv, with an effective dose even to sub-millisievert levels for some exams [19, 93].

However, numerous factors may influence the radiation dose, such as patient's characteristics (BMI, cardiac output, and heart rate), the type of CT equipment available, and the CT protocols used, which has to be tailored to the patient. Despite these promising innovations, the relatively high radiation exposure during dynamic CTP acquisitions remains a problem to be solved since it acquires a series of multiple low-dose acquisitions for the generation of TACs. Recent data have demonstrated that the average radiation exposure of dynamic CTP imaging is greatly depending on protocol optimization with an average value of 9.23 mSv (versus 5.93 mSv for static CTP) [34], which is favorably comparable with that of traditional nuclear imaging approaches [53].

However, Hubbard et al. validated a low-dose dynamic CTP technique based on a first-pass analysis model by using only 2 volume scans as compared with standard protocol based on multiple acquisitions in an animal model, showing good correlation with invasive FFR at different stenosis severity reaching overall effective radiation doses of 2.64 mSv [94].

So current efforts are directed towards further reducing radiation exposure while maintaining a high diagnostic performance. In this regard, the use of recent technical innovations, including the low voltages (70 kV to 80 kV) acquisition, automated tube current modulation, and iterative reconstruction, seems to be able to achieve this ambitious goal [19].

6. Comparison with Other Noninvasive Techniques for Myocardial Perfusion Imaging

Many noninvasive techniques can perform an evaluation of myocardial perfusion, including SPECT, stress MRI, stress echocardiography, and positron emission tomography (PET) [95]. Nuclear imaging techniques such as PET and SPECT are established modalities for myocardial perfusion evaluation. These techniques are able to evaluate also myocardial viability and function but provide limited information regarding anatomy [96].

Table 5: Dynamic CTP imaging in animal studies.

Author (Year)	No.	CT Scanner	CTP Protocol	Stress Agent (dose)	Reference Standard	Analysis	Dose
Bamberg et al [82] (2012)	7 pigs	DS (2nd)	REST / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Microsphere MBF	Quantitative MBF	10.6 (mSv)
Rossi et al [83] (2013)	7 pigs	DS (2nd)	STRESS (Shuttle mode)	Adenosine (0.50 mg/kg/min)	CBF and FFR	Quantitative MBF	17.1 (mSv)
Schwarz et al [84] (2013)	6 pigs	DS (2nd)	REST / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Microsphere MBF	Quantitative MBF + attenuation values (HU)	11.3 + 0.88 (mSv)
Bamberg et al [85] (2014)	12 pigs	DS (2nd)	REST / STRESS (Shuttle mode)	Adenosine (0.14 mg/kg/min)	Histopathology Microsphere MBF	Quantitative MBF, MBV, K_{trans}	NA

2nd, second generation; No., number of animals; CT, computed tomography; CBF, coronary blood flow; CTP, CT perfusion imaging; DS, Dual-Source scanner; FFR, fractional flow reserve; HU: Hounsfield Unit; Ktrans, permeability constant; MBF, myocardial blood flow; MBV, myocardial blood volume; NA, nonassessable.

PET is the gold standard for absolute quantification of myocardial perfusion particularly when 13N-ammonia is used and may be superior to SPECT in spatial resolution, image quality, and diagnostic accuracy [96]. However, SPECT is more widely available and cheaper than PET, and the radionuclides are easier to prepare and less expensive and have longer half-lives compared to PET; thus this approach is more suitable in daily clinical routine [97]. SPECT is an excellent noninvasive modality for the diagnosis of CAD with a sensitivity of 87-89% and specificity of 73-75%, depending on the radionuclide and stress protocol [19, 37]. Additionally, SPECT may provide a refinement of risk stratification and has an independent prognostic value in different clinical settings such as stable CAD, prior to non-cardiac surgery, after coronary revascularization, and in acute coronary syndromes [93]. Furthermore, recent advances in SPECT technology, including cadmium-zinc-telluride (CZT) semiconductor detector material, may allow absolute MBF measurements by SPECT but have yet to be implemented in clinical practice [98].

These observations have fueled the pursuit of hybrid imaging strategies in which radionuclide myocardial perfusion imaging is combined with coronary CTA. While promising, this approach has some important disadvantages including higher radiation doses and elevated costs [99].

Moreover, important SPECT limitations are the underestimation of the true extent of disease in patients with multivessel CAD and the photon attenuation artifacts typically due to breasts in women and diaphragm in men [99].

MRI is the most versatile imaging modality: it can be used for morphology, function, viability, and quantitative myocardial perfusion assessment [100]. Stress perfusion MRI performs better than SPECT for diagnosis of obstructive CAD, as reported in two large prospective randomized studies (MR-IMPACT and CE-MARC trials), and yields a similar diagnostic accuracy as PET, with a poll sensitivity of 89% and specificity of 76% [100]. Moreover spatial resolution of perfusion MRI (1-2 mm) is superior to that of SPECT, especially for the detection of subendocardial perfusion abnormalities [37]. Despite these excellent features, limitations to the clinical routine implementation of MRI perfusion assessment are the time-consuming image acquisition, the limited accessibility, and lack of widespread competence in cardiac MRI [37, 100].

Stress echocardiography is a well-established, real-time imaging modality with advantages including lack of radiation exposure, versatility, and affordability. Dobutamine stress echocardiography could provide information about ischemic abnormal ventricular wall motion but this modality is lower than dobutamine stress MRI in terms of specificity (87.5% versus 72.9%), negative predictive value (80.8% versus 67.3%), and overall diagnostic accuracy (80.4% versus 72%) [97].

The introduction of ultrasound contrast agents (microbubbles) has optimized the detection of RWMA and has enabled simultaneous assessment of left ventricular perfusion and viability, improving the sensitivity of the technique [100].

According to a large multicenter prospective trial, myocardial contrast echocardiography (MCE) has higher sensitivity but lower specificity compared to SPECT for CAD evaluation [101]. The superior sensitivity of MCE was independent of the severity of CAD and was especially evident in case of single vessel disease [101]. The major disadvantages of echocardiography are the well-known operator and reader dependence and the intrinsic technical limitations related to artifacts and poor thoracic imaging window, resulting in uninterpretable images in 10% of cases [100, 102].

Although functional information provided by any of these techniques is well-validated and extremely useful, none of them provide a comprehensive anatomical-functional evaluation within the same study. Currently, myocardial CTP imaging is the only noninvasive modality that allows quantifying coronary stenosis and determining its functional relevance, rendering it a potential "one-stop-shop" method for the diagnosis and global management of patients with ischemic heart disease [53].

Moreover, the imaging matrix of 512 × 512 pixels with an isotropic high spatial resolution (approximately 0.3 mm) of CTP is superior to nuclear imaging and enables evaluation of transmural differences in myocardial blood flow [100].

Moreover, CTP imaging using the iodinated contrast agent does not suffer of the nonlinear relationship between myocardial signal intensity and gadolinium contrast concentration, which might affect the accuracy of quantitative analysis of MBF in MRI perfusion imaging [103].

Finally, the wide availability of modern CT scanners makes CTP more accessible compared with other noninvasive tools, such as MRI or PET imaging [19].

Advantages and disadvantages of functional imaging with echo, SPECT, MRI, and CTP imaging are reported in Table 6.

7. CTP Imaging versus Noninvasive FFR (FFR_{CT})

Recently, a new technique to allow for noninvasive calculation of FFR based on conventional coronary CTA data (FFR_{CT}) using computational fluid dynamics has been clinically validated [104].

In a recent study by Yang et al. [105], the combinations of static CTP imaging with coronary CTA and FFR_{CT} with CTA improved diagnostic performance compared with CTA alone. However, in the highest tertile of calcium score, specificity and positive predictive value of FFR_{CT} were significantly lower than those of first-pass CTP.

Accordingly, a combined approach of dynamic CTP imaging and FFR_{CT} has been demonstrated to improve diagnostic performance in detecting functional relevance CAD in comparison with invasive FFR [106]. For various reasons, it is unlikely that in clinical practice both CTP and FFR_{CT} techniques will be routinely applied in each patient. The best strategy in the future could be a stepwise approach, reserving CTP for intermediate FFR_{CT} results. This approach has been demonstrated to improve diagnostic performance while omitting nearly one-half of the population from dynamic CTP examinations [106].

The PERFECTION study (comparison between stress cardiac computed tomography PERfusion versus Fractional flow rEserve measured by Computed Tomography angiography In the evaluation of suspected cOroNary artery disease)

Table 6: Major advantages and limitations of current noninvasive techniques for myocardial perfusion evaluation.

	Advantages	Limitations
PET	(i) Modality of choice for absolute myocardial perfusion quantification. (ii) Superior to SPECT in spatial and temporal resolution, image quality and diagnostic accuracy. (iii) Can be performed in patients with pacemakers or implantable cardioverter defibrillator.	(i) High cost. (ii) Radiation exposure. (iii) Not much available ⟶ more suitable in research setting then in clinical practice.
SPECT	(i) Radionuclides are easier to prepare, less expensive and have longer half-lives compared to PET ⟶ more suitable in daily clinical routine. (ii) High SE and high SP for detection of ischaemia. (iii) Allows evaluation of LV function. (iv) Very useful for risk stratification. (v) Provides important prognostic information in different clinical settings, especially in stable CAD.	(i) Radiation exposure. (ii) Relatively high cost and time consuming. (iii) Limited information regarding anatomy due to low spatial resolution. (iv) Photon attenuation artefacts (particularly in obese subjects) may produce FP. (v) In patients with multivessel disease, SPECT may underestimate the true extent of disease (balanced reduction in myocardial hyperaemic blood flow not detectable by semi-quantitative analysis) ⟶ prefer other modalities in patients with higher pre-test likelihood of multivessel CAD.
MRI	(i) Not require ionizing radiation. (ii) Higher SE and SP for detection of ischaemia than SPECT. (iii) High spatial resolution. (iv) Allows evaluation of LV function (v) Multiparametric imaging technique ⟶ strong role in differentiate ischaemic from non-ischaemic cardiac diseases. (vi) Provides important prognostic information.	(i) Time-consuming image acquisition (ii) Limited availability (iii) Lack of widespread expertise (iv) Common cardiac devices as pacemakers, implantable defibrillators, etc.. are still considered a contraindication to CMR. (v) Claustrophobia. (vi) Heart rate and respiratory motion artefacts.
ECHO	(i) Radiation-free. (ii) Rapid and safe ⟶suitable technique as a first-line approach. (iii) Can be performed at the bedside. (iv) Less expensive than other modalities. (v) Provides simultaneous evaluation of perfusion and function in real time. (vi) Allows assessment of many non-ischemic cardiac diseases. (vii) MCE with microbubbles has superior spatial/temporal resolution and SE compared to SPECT.	(i) Poor thoracic window in at least 10% of patients. (ii) Operator and reader dependence. (iii) Artifacts.
CTP	(i) Provides integrated anatomic and functional evaluation in a single examination. (ii) Very fast exam. (iii) Widely available. (iv) High sensitivity and high specificity. (v) Superior submillimetre spatial resolution with respect to SPECT⟶ detection of smaller, especially subendocardial, perfusion defects. (vi) Allows evaluation of important non-coronary cardiac findings. (vii) Provides important prognostic information.	(i) Radiation exposure, especially for dynamic CTPI (but still lower than nuclear imaging) (ii) Breath and beam hardening artifacts. (iii) High heart rate artifacts.

PET, positron emission tomography; SPECT, single photon-emission computed tomography; MRI, magnetic resonance imaging; ECHO, echocardiography; CTP, computed tomography perfusion imaging; SE, sensitivity; SP, specificity; CAD, coronary artery disease; LV, left ventricular; FP, false positive; MCE, myocardial contrast echocardiography.

will compare the diagnostic performance of an FFRCT-guided strategy to stress CTP for the detection of functionally significant CAD, using invasive FFR as the reference standard [107].

8. Discussion

8.1. Strengths, Limits, and Future Perspectives. The current evidence suggests that myocardial CTP imaging improves diagnostic accuracy of coronary CTA alone mainly by reducing the number of false positive findings, even when compared with invasive FFR.

With respect to this issue, an integration of both anatomical and physiological assessment of CAD may be a more robust "gatekeeper" to ICA by increasing the diagnostic accuracy while maintaining higher sensitivity compared to anatomical assessment alone. This may be particularly useful in difficult-to-interpret situations, such as in patients with coronary stents and heavily calcified coronary arteries in which blooming artifacts can hamper lumen visualization and correct stenosis measurements. Accordingly, recent studies have shown that stress CTP improves diagnostic performance in patients with a high Agatston calcium score [108] or coronary artery stents [109].

The utility of hemodynamic assessment by the integration of CTP and coronary CTA may have a potential role in stratifying cardiovascular risk and in the decision-making for the optimal medical intervention, although this potential role warrants further investigation.

Furthermore, in line with PET imaging, dynamic CTP imaging offers the ability to obtain quantitative data of hemodynamic parameters (such as MBF and MBV) and the assessment of absolute CFR. The combination of coronary CTA and dynamic myocardial CTP makes CT a very promising technique to evaluate patients with microvascular dysfunction because it not only reveals the absence of demonstrable obstructive CAD but also provides data about CFR, the current gold standard for clinically assessing microvascular function.

Quantification of hemodynamic parameters may be particularly useful for evaluation of specific patient population, such as patients with multivessel CAD, extensive nonobstructive CAD, hypertension, and diabetes mellitus [110].

When global myocardial ischemia exists due to multivessel CAD, it may be difficult to achieve an accurate diagnosis with the qualitative analysis method by static CTP. Conversely, MBF analysis may be able to identify multivessel disease and predict the extent of ischemia more accurately than static CTP imaging [34, 53].

The ability to quantify absolute MBF with dynamic stress CTP imaging permits identification of patients in whom the relative regional distribution of contrast agent may appear normal because of a balanced reduction of blood flow. Moreover, in patients with diffuse nonobstructive epicardial disease but no significant stenosis, the combination of plaque analysis by coronary CTA and CFR assessment derived by stress/rest dynamic CTP imaging may be helpful in identifying hemodynamic relevant coronary plaques, although not yet obstructive, and to avoid ascribing patient's symptoms to microvascular disease [111]. In fact, besides luminal area stenosis, other coronary plaque morphology and composition parameters may affect downstream myocardial perfusion. Accordingly, lesion-specific morphological features such as positive remodeling and noncalcified plaque volume have been associated with detrimental downstream hyperemic myocardial perfusion and FFR, independent of lesion severity, and are strong predictors of major cardiovascular events [112–114].

Furthermore, MBF analysis might also be advantageous in monitoring disease progression or perfusion changes in response to therapy such as for PET and MRI imaging [103, 115], although this potential application has still to be evaluated.

However, important considerations have to be highlighted when interpreting quantitative measurements of dynamic CTP. A substantial underestimation of absolute MBF from dynamic CTP has been reported, with a significant influence of CT-derived MBF by temporal sampling rate [33, 54, 94, 116, 117]. This may be related to the assumption of most modeling of dynamic CTP techniques that blood volume during the passage remains relatively constant. However, using iodinated contrast material blood volume actually increases [33]. In addition some contrast material may actually leave the intravascular space and enter the interstitium during the measurement time [33].

Finally, it is well-known that all iodinated contrast agents have an immediate and direct vasodilatory effect [36]. All these factors may explain the underestimation of maximal MBF by CTP imaging, although rest and hyperemic flow in the CTP studies are within the documented range of that in PET studies [34].

Moreover, the reported optimal MBF cutoff values for the differentiation of normal and ischemic myocardium varied considerably between dynamic CTP studies, ranging from 75 mL/100 mL/min to 103.1 mL/100 mL/min with a dual-source CT scanner and as high as 164 mL/100 mL/min using a 256-slices CT scanner [19, 34]. This broad range of cutoff values may be related to study design, pathophysiological and methodological factors, technical issues (different scanner technology, scanning protocols, and mathematical algorithms), patient risk profile, prevalence of CAD, sample sizes, and the used reference standard.

Moreover, numerous individual factors such as age, gender, race, BMI, presence and severity of CAD, the status of the microvasculature, individual adaptive vasodilator responsiveness, and/or the presence of collateral flow may affect MBF [19, 78, 87, 118].

Accordingly, considerable regional heterogeneity of the myocardial perfusion across coronary territories has been demonstrated in healthy and low-risk subjects [54, 119].

Large inter- and intraindividual differences in MBF distribution are already known from PET and MRI studies [19, 34]. Therefore large databases on normal perfusion values such as for nuclear imaging are needed to assure accurate clinical interpretation of quantitative perfusion values [53].

However, a major limit of dynamic CTP is the higher dose profile respect to static CTP due to the time-resolved acquisition of multiple phases.

Furthermore, CTP imaging may be affected by several artifacts, such as partial volume, beam hardening, breathing, and motion artifacts. In particular, the patient's breathing motion poses a major challenge for dynamic CTP, which requires a long acquisition time of approximately 30 s. Furthermore, the sequence "shuttle mode" implemented with the second-generation dual-source CT scanner to dynamically cover the entire left ventricle myocardium may be a source of motion artifact influencing the estimation of MBF derived from the TACs. Beam-hardening artifacts arise from the polychromatic nature of the X-rays in the CT acquisitions and the presence of high-density iodine contrast agent in the heart chambers, which results in a hypoattenuated shadowing artifact [47]. Areas affected by beam hardening can be misinterpreted as perfusion defects with a false positive finding artifact [47]. A potential strategy to overcome this limitation is to acquire dynamic images during the end-systolic phase when the volume of LV contrast agent is less [19].

Furthermore, some of these artifacts may be partially attenuated by well-validated beam hardening and motion correction algorithms implemented with latest CT scanner technology [19, 34].

Moreover, in most of the CTP studies, anti-ischemic drugs such as beta-blockers have not been withheld prior to stress testing; this may negatively affect the accuracy of CTP by decreasing the severity and the extent of myocardial perfusion defects. However, it is expected that the diagnostic performance of CTP imaging performed in patients without background medications could be even higher than reported.

Finally, other limits are the broad spectrum of clinical characteristics of the studied populations and the difficult to standardize the CTP imaging due to the heterogeneity of scanner manufacturers, acquisition protocols, stress protocols, image analysis algorithms, and postprocessing parameters.

In addition, no large-scale multicenter studies have demonstrated the clinical value of CTP imaging. Further researches with larger sample size and improved standardization of CTP imaging technique are warranted.

9. Conclusions

Current evidence suggests that adding CTP imaging is a safe and powerful tool to improve the accuracy and the positive predictive value of coronary CTA alone because it not only provides anatomic information concerning luminal stenosis, plaque morphology, and total plaque burden but also provides data on myocardial tissue hemodynamics.

Different acquisition protocols for CTP imaging are available, which can assess myocardial perfusion in a qualitative, semiquantitative, or quantitative manner, with their own advantages and disadvantages.

In conclusion, coronary CTA combined with myocardial CTP imaging hold immense potential to evaluate almost every aspect of the broad spectra of ischemic heart disease with the possibility of guiding treatment decisions for a patient on an individual basis. Further researches with larger sample size should be designed and implemented to decide whether to adopt this new diagnostic modality in a routine clinical setting.

Finally, prognostic studies are needed to assess if this combined approach will likely have substantial impact on treatment costs, patient management, and outcome. The time to challenge this hypothesis with randomized prospective trials has come.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Prognostic Value and Therapeutic Perspectives of Coronary CT Angiography: A Literature Review

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Coronary stenosis severity is both a powerful and a still debated predictor of prognosis in coronary artery disease. Coronary computed tomographic angiography (CCTA) has emerged as a noninvasive technique that enables anatomic visualization of coronary artery disease (CAD). CCTA with newer applications, plaque characterization and physiologic/functional evaluation, allows a comprehensive diagnostic and prognostic assessment of otherwise low-intermediate subjects for primary prevention. CCTA measures the overall plaque burden, differentiates plaque subtypes, and identifies high-risk plaque with good reproducibility. Research in this field may also advance towards an era of personalized risk prediction and individualized medical therapy. It has been demonstrated that statins may delay plaque progression and change some plaque features. The potential effects on plaque modifications induced by other medical therapies have also been investigated. Although it is not currently possible to recommend routinely serial scans to monitor the therapeutic efficacy of medical interventions, the plaque modulation, as a part of risk modification, appears a feasible strategy. In this review we summarize the current evidence regarding vulnerable plaque and effects of lipid lowering therapy on morphological features of CAD. We also discuss the potential ability of CCTA to characterize coronary atherosclerosis, stratify prognosis of asymptomatic subjects, and guide medical therapy.

1. Introduction

The diagnostic approach to cardiac and coronary diseases is rapidly changing with the advent and implementation of radiologic techniques [1–14]. Coronary computed tomographic angiography (CCTA) is increasingly emerging as a noninvasive technique that enables direct anatomic visualization of atherosclerotic stenosis in the epicardial coronary arteries, with low radiation exposure [15–18]. Although such factors (i.e., high heart rate, arrhythmia, obesity, and high coronary calcium burden) may limit overall evaluability [19–21], the significant improvement in technologies during the last past decades has opened new perspectives in cardiac imaging permitting the acquisition within few seconds and with a higher spatial resolution [22–24]. CCTA has proven to have a high diagnostic accuracy compared with the invasive coronary angiography (ICA), which represents until now the standard of reference for evaluating coronary artery disease [25–33]. Using at least a 64-slice multidetector row, a sensitivity and specificity of 98% and 90%, respectively, have been reported on a per patient level. The elevated sensitivity turns out into a negative predictive value (NPV) ranging from 95 to 100% to rule out obstructive coronary artery disease (CAD) [23]. This high negative predictive value for CAD translates into an excellent negative predictive value for future events. In a recent study analyzing more than six hundred patients, normal CCTA findings were associated with an event-free survival rate of 100% in both diabetic and nondiabetic patients with suspected CAD [34].

In 2013, the European Society of Cardiology proposed CCTA as an alternative to stress imaging techniques for the assessment of patients with suspected stable CAD and low-to-intermediate pretest probability of CAD [35]. Recently, the update of the NICE-UK guidelines on the management of patients with new onset chest pain proposed CCTA as first-line diagnostic tool for people in whom stable angina cannot be excluded by clinical assessment alone [36].

In this context, coronary stenosis severity is considered a powerful although debated prognostic index of CAD prognosis. Both invasive and noninvasive angiographic studies have demonstrated the correlation between stenosis degree and clinical events. However, in a recent study Min et al. evaluated a large consecutive cohort of patients without history of CAD and showed a similar incidence of all-cause mortality in nonobstructive and 1-vessel obstructive CAD as assessed by CCTA (HR: 1.62 vs. 1.75) [37]. Moreover, it has been reported that more than two-thirds of acute myocardial infarction (MI) may be due to nonobstructing lesions [38]. Beyond the degree of stenosis, other features are pivotal determinants of events. Numerous clinical biomarkers and imaging modalities have been investigated during the past few decades in order to identify patients harboring plaques at high risk of rupturing (vulnerable plaque), hoping to be able to prognosticate events. While ICA is focused only on the evaluation of the degree of coronary stenosis (luminography), CCTA looking at both the wall and the lumen of coronary artery reliably measures the overall plaque burden, differentiates plaque subtypes, and identifies adverse features of coronary high-risk plaques [39, 40]. In addition, CCTA may help us to avoid a PCI in case of obstructive CAD in a small vessel and may help us to start an early and aggressive optimal medical therapy in case of nonobstructive extensive CAD. Currently, there are increasing interest and continuing debate on the potential role of CCTA as a noninvasive method for mapping CAD, identifying nonobstructive lesions with features of vulnerability, defining prognosis of otherwise low-to-moderate risk subjects, and guiding therapeutic interventions. Research in this area may advance us towards an era of personalized risk prediction and individualized medical therapy. Indeed, since various medications—principally acting on lipid profile and inflammation—may prevent plaque progression or even induce regression, the search for simple techniques makes us able to assess these changes could provide physician a valuable tool for patients management. The present paper, moving beyond coronary stenosis, reviews the features of coronary vulnerable plaques and the ability of CCTA to noninvasive plaque characterization with practical prognostic implication in patient risk stratification. Moreover, current and future therapeutically perspectives are elucidated.

2. Definition of Vulnerable Plaque and Features by CCTA

Histologic studies suggest that plaque composition plays a central role in the pathogenesis and clinical consequences of epicardial lesions [41]. Expert consensus points that the morphology, composition, and degree of inflammation of coronary atherosclerotic plaques are more important than the degree of luminal stenosis [42].

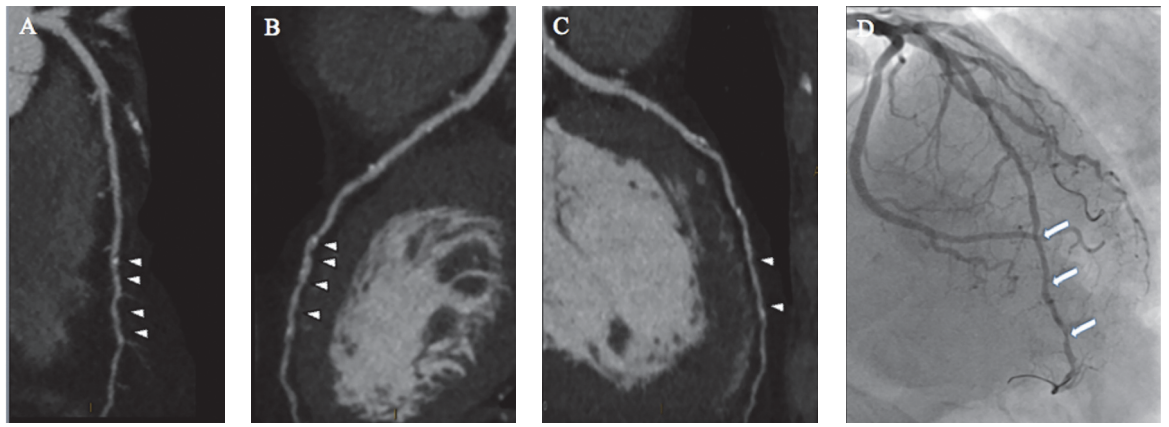
If advances in acute coronary syndromes (ACS) are to occur, it is important to recognize their precursor lesions [43]. Most of the ACS are thought to be the result of sudden luminal "thrombosis" that begins from three different pathologies. The most common cause of thrombosis is plaque rupture, followed by plaque erosion. Less commonly dense calcified nodules can penetrate the fibrous cap and cause thrombosis [44–46]. Plaque rupture is the most common cause of coronary thrombosis in both genders: approximately 76% of all fatal coronary thrombi are precipitated by plaque rupture [47, 48]. Consequently, although the term "vulnerable plaque" should be globally reserved for plaques that resemble all three causes of luminal thrombosis, it is usually strictly referred to a rupture-prone plaque. The nonthrombosed lesion that most nearly resembles the acute plaque rupture and then represents its precursor is the thin-cap-fibroatheroma (TCFA) [43].

It has been widely accepted that atherosclerosis is usually a generalized—rather than a focal— process, characterized by a dynamic nature with plaques undergoing biological remodeling and compositional alterations [49]. Autoptic findings from various stages of atherosclerosis have provided a putative sequence of events where lesion progression is not necessarily a process of slow, steady, and indolent accretion [50].

Intimal thickening is observed early in the disease process. The early lesion is composed of smooth muscle cells and is affected by increased macrophage and lipid influx. The next phase is represented by the formation of a necrotic core and the development of a fibrous cap atheroma. The necrotic core contains a certain lipid amount and apoptotic macrophages. Intraplaque hemorrhages are also frequently seen in this entity and lead to further enlargement of the lipid core. A stable fibrous cap may prevent rupture of the lesion. If the fibrous cap loses matrix proteins and smooth muscle cells, a thin cap atheroma can result [51, 52]. The positive remodeling is considered a compensatory outward enlargement of coronary artery accumulating atherosclerosis in its walls [53]. Fibrocalcific plaques might represent an end stage of the atherosclerosis process and can contain extensive calcifications. Because of a stable fibrous cap and lower lipid content, these lesions rarely cause thrombosis but can cause chronic ischemic symptoms because of lumen narrowing [51, 52].

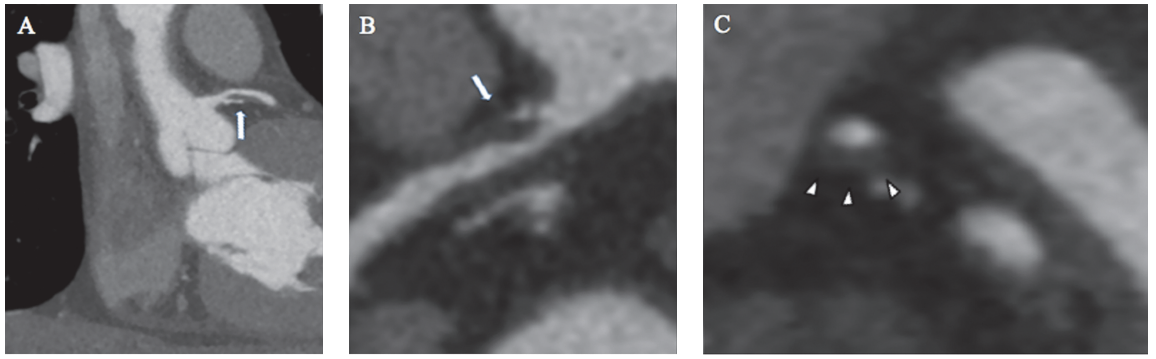
Differently, TCFA are characterized by a large necrotic core, with an overlying thin fibrous cap containing rare smooth muscle cells but numerous infiltrating macrophages [43, 54, 55]. Vessels demonstrating TCFA do not usually show severe lumen narrowing but a positive (expansive) remodeling. Understandably, clinicians aim to detect these plaques before they rupture in order to be able to undertake measures and obtain prevention goals. The search for "vulnerable plaque" is then subject of an intense scientific investigation. Identifying coronary artery lesions prone to future cardiac events and high-risk patients may direct more potent local and systemic approaches for preventive treatments.

Invasive coronary angiography evaluation delineates the vessel lumen with high quality. The additional step of



(a) (b) (c) (d)

Figure 1: A fifty-two-year-old male patient with familial history of coronary artery disease and inconclusive ECG stress test underwent cardiac computed tomography angiography. Multiplanar reconstruction shows in panels (a), (b), and (c) the presence of severe coronary artery disease at the level of distal left anterior descending artery (arrowhead). Invasive coronary angiography confirmed the diagnosis (panel (c), arrows) and the patient underwent successfully coronary revascularization.



(a) (b) (c)

Figure 2: A fifty-three-year old-male patient with history of arterial hypertension and dyslipidemia was admitted at the emergency department for atypical chest pain. Cardiac computed tomography acquired during hospitalization showed in multiplanar reconstruction a soft plaque determining stenosis of 70% in proximal left anterior descending artery ((a) (b) arrow). Cross sectional images showed positive remodeling of a soft plaque ((c) arrowhead).

intravascular ultrasound (IVUS), also known as virtual histology, constitutes the current gold standard for plaque evaluation and quantification [56]. Moreover, optical coherence tomography (OCT) provides a higher magnitude of resolution (10 μm) when compared with IVUS (permitting direct visualization of thin cap fibroatheroma) but lacks delineation of the outer vessel boundary due to weaker penetration [57]. Although providing high-resolution images, these techniques are highly expensive and invasive, being used only in conjunction with coronary artery catheterization.

Recently, CCTA has emerged as a promising tool that enables direct visualization of the vascular lumen (with assessment of presence and extent of angiographic stenosis) together with the arterial wall characterization (Figure 1). CCTA focalizes attention on validated measures of plaque vulnerability. There is increasing interest and continuing debate on its potential role as a "noninvasive" method for (1) mapping coronary atherosclerosis, (2) better understanding the adverse features of coronary plaques, and (3) achieving potential benefits in guiding therapeutic interventions [58].

CCTA imaging has been extensively compared with IVUS and became realty after the demonstration of the existence of a good correlation with virtual histology [59]. Identification of noncalcified plaques (NCP), particularly low-attenuation plaques (LAP) with spotty calcifications (SCPs), positive vessel remodeling (PR), and napkin-ring-like NRS has been considered as important landmarks of plaque vulnerability and instability [60]. Using CCTA, in comparison with grayscale IVUS, calcified versus noncalcified plaque can be quantified on the basis of density cutoff values [61]. Low attenuation suggests high lipid content and has defined for attenuations below 30 Hounsfield Units (HU) [58, 62] (Figure 2). Different HU cut-off limits used in different laboratories presumably have weakened the estimated risk

of ACS associated with LAP. Positive remodeling is usually assessed using vessel area (PRI = lesion plaque area/reference area). SCs are scattered calcified nodules within the context of a plaque with a diameter <3 mm. Usually, SCc are well represented on the shoulder of the plaque and are associated to enzyme activity. Finally, the NRS is a thin ring of high attenuation around the plaque along the outer contour of the vessel. This is typically due to the presence of a hypodense deposit of necrotic material in the center of the plaque itself [58, 62]. Importantly, despite ex vivo comparison to histology showed the ability of CCTA to differentiate no calcified, mixed, and calcified plaques [63]. A limitation of commonly used computed tomography (CT) scanners is the relatively poor soft tissue contrast which means difficulty in further subclassification (with possible misclassification) of noncalcified subcomponents (i.e., fibrous versus fatty components) on the only basis of HU attenuation [64, 65]. It has been indeed reported a tendency to overlapping the HU between lipid-rich and fibrous noncalcified plaques. CT technology is, however, rapidly evolving and several solutions are available. In the latest generations of CT devices, faster acquisition speeds have been achieved by faster rotation, larger detectors, and dual source systems. Dual-energy CT can reduce blooming effects that occur near to calcium and iodine and leads to more valid density measurements [66, 67]. The two sources of energy are particularly apt at achieving material decomposition (i.e., differentiation of different tissues), with improved plaque characterization [68, 69]. Moreover, complex image (iterative) reconstructions, recently introduced in commercial systems, seem to be able to improve image quality with regard to noise, resolution, artifacts, and finally diagnostic accuracy [29].

3. Prognosis Beyond Degree of Stenosis

Despite advances in preventive approaches and therapies, CAD is one of the main causes of morbidity and mortality in both industrialized and low income to middle-income countries. Sudden cardiac death has been reported to occur in 50% of men and 64% of women without previous cardiovascular symptoms [70]. Coronary stenosis severity is both a powerful but a still now debated predictor of prognosis. A large number of studies have confirmed the long-term prognostic power of CCTA in attributing excellent prognosis to patients (including diabetics) without coronary plaques and intermediate prognosis in patients with nonobstructive lesions. In a long term follow-up, event-free survival rates of symptomatic patients with CT diagnosed CAD decreased proportionally from normal coronary arteries (98.3%) to nonobstructive (95.2%) to obstructive CAD (87.5%) [71]. Similarly, in the very low risk cohort of patients of the CONFIRM registry, followed for a mean of 5 years, Cheruvu et al. reported that the incidence of major adverse cardiovascular events (MACE; all-cause death, nonfatal MI, unstable angina, or late coronary revascularization) increased from 5.6% in those without CAD to 13.24% in those with nonobstructive disease and to 36.28% in those with obstructive CAD ($p<0.001$) [72].

The novel Coronary Artery Disease-Reporting and Data System (CAD-RADS) scores used to standardize CCTA reporting ranked CAD stenosis severity as 0 (0%), 1 (1% to 24%), 2 (25% to 49%), 3 (50% to 69%), 4A (70% to 99% in 1 to 2 vessels), 4B (70% to 99% in 3 vessels or ≥50% left main), or 5 (100%). It is not surprising that CAD-RADS effectively identify patients at risk for adverse events. Cumulative 5-year event-free survival ranges from 95.2% to 69.3% for CAD-RADS 0 to 5 ($p< 0.0001$). Higher scores are associated with elevations in event risk (hazard ratio: 2.46 to 6.09; $p< 0.0001$). Its incorporation into coronary CTA reports may provide a novel opportunity to promote evidence-based care [73]; however, this system, as well as the segment involvement score (SIS), is flawed for several reasons, being probably the main that it oversimplifies prognosis of CAD strictly relating it to the degree of stenosis.

Notably, in a recent substudy of the above mentioned CONFIRM registry, even the presence of a single nonobstructive (1%-49% stenosis) left main plaque in elective CCTA for suspected CAD increased in a 5-year follow-up the risk for composite outcome in women (adjusted hazard ratio, 1.48; $p=0.005$) but not in men (adjusted hazard ratio, 0.98, $p=0.806$). This turns out into a nearly 80% higher risk for events than men. This sex-specific prognostic significance, not observed across other patterns (e.g., location or extent) of preclinical coronary plaque, had to be considered since may increase risk stratification efforts [74].

These and similar findings highlight the prognostic importance of both angiographically significant (potentially flow-limiting) and nonobstructive coronary stenosis, as well as the excellent prognosis for patients without evident plaque on CCTA. This means that absence of coronary atherosclerosis on high-resolution CCTA images identifies a patient with an exceptionally low risk of long-term cardiovascular events [75].

Of note, more than two-thirds of acute MI may be due to mild to moderate plaques that did not significantly compromise the coronary lumen before the event [36]. As a consequence, beyond the effective degree of stenosis, other lesion features—reflecting plaque composition—are pivotal determinants of untoward outcomes. The ability of CCTA to assess the entire coronary tree for the presence (present/absent), extent (proximal and/or distal), distribution (per vessel and per segment) of CAD, degree of vessel stenosis (<50% or >50%), and plaque morphology (i.e., calcified, mixed, and no calcified), with further subclassification of plaque subcomponents, makes it a unique non-invasive modality. Starting the first evidence reporting the role of CCTA in improving the prognostic stratification of patients with suspected CAD, there is a growing interest in testing the correlation between the coronary plaque features and the occurrence of MACE [76–78].

In a multicenter study, the presence of a large plaque burden, TCFA, and a small lumen area were independent predictors of future events [56]. Tian et al. demonstrated in 643 patients enrolled in an OCT, IVUS, and angiography study that severe coronary stenosis has a twofold probability to show the features of vulnerable lesions suggesting a potential overlapping between degree of stenosis and plaque characteristics to influence outcome of patients [79]. Undoubtedly, the prevalence of severe coronary stenosis is

however significantly lower than that of mild-to-moderate atherosclerotic lesions. Moreover, many of these lesions despite a clinical relevant high plaque burden may be not severely stenotic at ICA.

Ahmadi et al. have showed that survival rate of subjects with nonobstructive CAD decreases significantly with the number of diseased coronary arteries (from single to triple vessels disease, $p<0.001$) and is significantly affected from the plaque morphology. Death rate increases incrementally from calcified plaque (1.4%) to mixed plaque (3.3%) to no calcified plaque (9.6%). The risk-adjusted hazard ratios of all-cause mortality were 3.2 (95% confidence interval 1.3 to 8.0, $p=0.001$) for mixed plaques and 7.4 (95% confidence interval 2.7 to 20.1, $p=0.0001$) for noncalcified plaques compared with calcified plaques. In subjects with mixed or calcified plaques, the death rate also increased with the severity of coronary artery calcium from 1 to 9 to > 400 [30].

High-risk plaque (HRP) features have been also shown to be associated with an increased risk of events even in patients with nonobstructive CAD. In a recently published study it has been shown that the use of an integrated score easily obtained with CCTA (based on the presence of mixed and remodeled atherosclerotic plaques) may improve MACE prediction in symptomatic patients without previous cardiovascular history but at intermediate pretest likelihood of CAD, beyond standard clinical (Diamond & Forrester) and coronary (based on presence and degree of stenosis) scores used in clinical practice [78]. This finding underlines the importance of a comprehensive coronary evaluation even taking into consideration the low prevalence of some high-risk plaque characteristics.

The prognostic value of risk assessment determined on the basis of plaque anatomy alone, however, has been partially disappointing, because of a low positive predictive value [56]. It is indeed worth mentioning that, despite the ability to identify potentially vulnerable plaques with CCTA, there is no clear indication of which and how many plaques with high-risk features will actually rupture and cause events. In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study only 5% of TCFA plaques identified by IVUS caused coronary events [56]. Therefore, the presence of high-risk plaques is probably just a factor in the more complex framework of ACS pathophysiology [80]. The consequences of a plaque disruption depend not only on the composition of the atheroma itself but also on local rheological and hemodynamic phenomena [81]. How plaque composition and local phenomena interact is an important question and several investigators have tried to address it. Moreover, the morphology and underlying activity of individual coronary plaques are heterogeneous and dynamic**.** Probably, taking into consideration other important pathophysiological principles applied to CCTA imaging, such as plaque inflammation-induced ischemia and the CT-derived fractional flow reserve, it will be conceivable in the next future to further improve the prognostic power of noninvasive coronary evaluation [82].

4. CCTA in Asymptomatic Patient

Still evaluating with certainty the role of CCTA in asymptomatic subjects now is not possible and further data are needed to be collected on this topic. Notably, with the technological advance the accuracy of CCTA has constantly improving and, at the same time, possible adverse effects, costs, and radiation exposure reduction are enlarging the indication of the CCTA. Recent recommendations give a criterium of "uncertainty" to the indication of CCTA in asymptomatic patients [Andreini jcm 2016].

The evaluation of asymptomatic patients may sometimes imply a wider evaluation looking for different signs of atherosclerotic involvement of multiple vascular districts. In a cohort of nondiabetic ambulatory subjects, prevalently referred by their physicians for risk-stratification screening, it has been demonstrated that the number of coronary arteries with any amount of disease on CCTA was significantly correlated with increased intima media thickness (IMT) and carotid plaque on vascular ultrasound. CAD was present in most patients with carotid plaque or increased IMT and absent in most patients without carotid plaque or with lower IMT values [83]. Being IMT a well-established marker of subclinical systemic atherosclerotic process and increased global cardiovascular risk beyond traditional system for risk scoring, this relationship supports the concept that an integrated noninvasive approach should be needed [84–86].

Among asymptomatic patients, diabetics represent a particular category in which CCTA could be very useful for prognostic purpose. Two aspects need to be considered. At first, although diabetes mellitus is an important risk factor for future cardiovascular events, some studies suggest that it should not be considered a "coronary risk equivalent" [87]. This consideration is confirmed by studies employing CCTA. Indeed, the absence of coronary atherosclerosis was associated with 100% disease-free survival at follow-up [88]. Second, since the diabetic patient carries a condition of high coronary risk per se [89–91], it is conceivable to postulate that standard risk stratification does not add any additional prognostic information. A recent study supporting this concept has enrolled 517 consecutive asymptomatic patients (63% male, 17.6%diabetics) who underwent CCTA and were evaluated for the prediction of MACE. Over a median follow-up of 4.4 [3.4-5.1] years there were 53 MACE (10%). The authors found that the presence of obstructive CAD and plaque positive remodeling increased MACE prediction as compared to a model based on 10-year-FRS, carotid disease, and coronary calcium scoring in the subgroup of nondiabetic patients. Importantly, the percentage of segments with remodeled plaque was the only predictor of MACE in the subgroup of diabetic subjects [92]. Therefore, CCTA may represent a tool able to make a certain diagnosis of CAD with significant prognostic impact in diabetics. Anyway, since a wide stratification with the use of CCTA of all diabetic patients is not possible for economic reasons, screening patients whit more than 10-year-old diabetes mellitus could be a suitable strategy [93].

5. Future Perspectives for Prognosis Improvement

It has been demonstrated that an ischemia-guided revascularization yields improved clinical outcomes in a cost-effective fashion compared with anatomy-guided revascularization alone [38]. As a consequence, in patients with suspected or known disease, noninvasive functional testing should be used as gatekeeper to catheterization. At the time of ICA, the evaluation of fractional flow reserve (FFR) may be instead considered for assessment of the hemodynamic significance of coronary lesion with moderate stenosis (50%-90%). Indeed, the identification of obstructive coronary lesions is only one aspect of the complex relationship between stenosis and ischemia, since there is an increasing awareness on the unreliable relationship between stenosis severity and functional relevance [94].

Even if most CCTA-detected obstructive lesions are confirmed by ICA, lesser than half of those studied with invasive FFR effectively causes ischemia. On the other hand, nonobstructive lesions can be associated with inducible ischemia [95]. Also in this context plaque characterization may help for clinical purpose. Park et al. showed that plaque remodeling, when adjusted for stenosis severity, remained a predictor of ischemia for all degrees of stenosis [96]. Similarly, it has been reported that in moderately stenotic vessels perfusing ischemic territories the prevalence of PR, LAP, and SCs was three to fivefold higher than in vessels without ischemia [97].

The pathogenetic mechanism linking HRP features and inducible ischemia in moderate anatomic stenosis is still not completely clear. It has been postulated that the necrotic core could be responsible for oxidative stress. The resulting local inflammation may compromise the production and bioavailability of the vasodilator nitric oxide and increase the levels of vasoconstrictors such as isoprostanes. The latter along with local endothelial dysfunction could cause a focal "functional stenosis" with inability of the vessel segment containing high-risk plaques to vasodilate adequately during stress [98]. For example, the ongoing presence of endothelial shear stress, which is considered a potent proatherogenic and proinflammatory stimulus, has been associated with a more inflamed and unstable coronary plaque phenotype [56]. Revascularization procedures could be reserved for patients with lower FFR in the presence of obstructive disease on invasive angiography, while high-intensity statin therapy should be prescribed for patients with abnormal FFR in the setting of nonobstructive but high-risk plaques with the aim to obtain plaque stabilization [94].

In this new optic, CCTA with newer applications—due to combination of both plaques characterization and functional evaluation of flow-limiting stenosis in the same examination—seems to represent the Holy Grail for a comprehensive coronary disease assessment [99]. Recently, two methods for the evaluation of the functional relevance of stenosis by cardiac CT have been introduced in the clinical field, stress myocardial computed tomography perfusion (CTP), and fractional flow reserve computed tomography (FFRCT) [24, 82, 100]. Stress CTP demonstrated similar performance to nuclear imaging and additional diagnostic value to CCTA alone as compared to invasive FFR [22]. Software to determine FFR from CCT dataset (FFR-CT) using computational fluid dynamics laws has been recently developed. FFR-CT is derived from routinely anatomic images (acquired at rest only) and subsequent mathematically simulated hyperemia without the need of vasodilator administration.

Gaur et al. showed that plaque tissue characterization and FFR-CT improve the ability to predict inducibility of ischemia in a myocardial territory dependent on a specific coronary lesion compared to mere luminal stenosis assessment [98]. Specific studies have already been designed to investigate whether plaque characterization is a better approach to predict and detect myocardial ischemia compared to current standard of care. Preliminary results from CREDENCE trial are hopefully waited [101].

Moreover, to improve the prognostic power of CCTA, a better clarification of the relationship between plaque burden and cardiac inflammation biomarkers would be very useful [102, 103]. Molecular imaging of plaque activity is also gaining ground and is poised to provide prognostically significant information if the current exciting results are expanded.

6. Therapeutic Perspectives

Before CCTA wide spreading, patients without obstructive plaques were often overlooked and, in the absence of inducible ischemia, were included without distinctions in the same group of those without CAD. In fact, among patients with nonobstructive lesions, those with low-risk plaque morphology may be differentiated from those in whom plaque characteristics are associated with an increased risk of future events. Randomized trials have shown that patients undergoing CCTA have significantly reductions in the risk for mortality, revascularizations, and incident MI, probably related to the increased utilization of preventive therapies (i.e., aspirin and statin) among patients with stable chest pain and nonobstructive CAD, as compared to patients who underwent functional provocative test [104, 105].

It is well known that hypocholesterolemic and antiplatelet therapies are considered as some of the most important preventive strategies for coronary artery disease decreasing relative risk of MACE by 20-45% [106, 107].

Reduction in circulating levels of atherogenic lipoproteins has been postulated as one mechanism by which statins exert favorable benefits. However, other pathways beyond cholesterol contribute to CV risk through pleiotropic mechanisms. The statins also reduce intraplaque inflammation, neoangiogenesis, apoptosis, and metalloproteinase activity. These pleiotropic properties, acting together for the plaque stabilization, may contribute to the clinical outcome [108, 109].

Coronary angiography and IVUS techniques for serial examination have demonstrated that statins are able to slow the rate of plaque progression and even to induce a small amount of coronary atherosclerosis regression if target of low-density lipoprotein (LDL) cholesterol levels are achieved.

Reduction in LDL cholesterol level to 80 mg/dl by atorvastatin was associated with no increase in coronary plaque burden [110], and more intensive therapy with rosuvastatin to reduce LDL cholesterol to 60 mg/ml results in significant reduction of coronary atherosclerosis [111]. This means a strong relation between cholesterol reduction and changes in atheroma volume.

However, to date, limited data exists to relate the effect of statin use to specifically coronary plaque "features" and morphology beyond stenosis severity [112]. For example, it has been shown that statins increase plaque hyperechogenicity by grey-scale IVUS (independently by plaque volume) and significantly reduce the degree of the fibrofatty intraplaque constituents (conversely increasing intraplaque calcified composition) by virtual histology IVUS [113]. However, IVUS requires an invasive approach and is not suitable for nonischemic patients with nonobstructive plaques (only moderate cardiovascular risk).

Cardiac CT has historically had a role in risk stratification using the Coronary Artery Calcification Score (CAC). CAC is strongly associated with cardiovascular risk. Once coronary calcification is initiated, it follows a predictable pattern of progression, with no consistent evidence of the ability to regress in response to therapy. Although standard CAC score appears to have no role in evaluating therapeutic response or change in atherosclerotic disease over time [40, 114], new CAC scoring approaches discriminating calcium density from volume might provide significant assessment of therapeutic changes, supporting the often asserted (but as yet unvalidated) view that calcification may play a role in plaque stabilization [115].

CCTA is the most promising noninvasive method that has the potential to fully phenotype an individual's coronary artery plaque volume. It has been shown that noncalcified plaques as detected by CCTA represent the component of atherosclerotic plaque that is relevantly influenced by statin therapy and then account for the benefits of therapy [116, 117]. Compared to IVUS, CCTA has undoubtful advantages as noninvasiveness and lower cost. Various studies demonstrated the feasibility of using serial CCTA to assess plaque changes with high intra- and interobserver reproducibility, allowing this method to potentially track atherosclerosis noninvasively. [118]

Inoue et al. in a preliminary study on 32 patients, who underwent CCTA with suspected coronary artery disease, demonstrated that the use of statins—even at a low dosage—resulted in a reduction in plaque quantity and decrease in necrotic core volume. Interestingly, changes in plaque morphology may even occur with relatively less robust changes in the lipid profile and early after initiation of downstream statin treatment [119].

In a recently published multicenter prospective observational study, Li et al. divided patients with baseline mild noncalcified coronary plaque on CCTA according to the statin protocol undertaken [intensive statin therapy (n= 55), moderate statins (n = 85), and no statin (n = 66)]. Their results confirmed that statin can delay progression and even induce plaque regression of mild non-calcified coronary plaque. LAP volume, total plaque volume, and percent plaque volume showed significant regression among intensive statins compared to no statin group. On multivariable model both moderate and intensive statin therapy were independent predictors of plaque regression (although standardized coefficients of the intensive statin was greater than that of the moderate statin: -0.36P < 0.001 vs -0.21 P = 0.004, respectively). Moreover, patients with greater baseline plaque burden and higher basal hyperlipidemia are more likely to benefit from statin therapy. These results could have important implications for disease prevention strategy, suggesting the potential need of stronger statin approach for patients with noncalcified plaque, especially for patients with high risk vulnerable plaque features [117].

The greater benefit from statin therapy even among asymptomatic individuals with higher coronary plaque burden as assessed by CCTA has recently been confirmed also independently from scores for the prediction of 10-year cardiovascular risk [120]. However, despite reducing progression and promoting regression of coronary atherosclerosis, statin therapy just partly addresses residual cardiovascular risk. More than 20% of patients with LDL-C$\leq$70 mg/dL continue to have progression over time in pooled analysis of IVUS studies [40]. This residual risk could potentially be minimized by intensification of lipid-lowering therapy or initiation of non-statin medications, but these approaches are not without drawbacks.

Literature shows that omega-3 fatty acid eicosapentaenoic acid (EPA) has a broad range of beneficial effects on the atherosclerotic pathway, including those on lipids, lipoproteins, inflammation, oxidation, phospholipid membranes, and the atherosclerotic plaque itself [121]. The implications of eicosapent ethyl add-on to statin therapy (in subjects with well-controlled low-density lipoprotein cholesterol levels) for changes in atherosclerotic plaque morphology (plaque burden and/or plaque vulnerability as assessed by CCTA) are currently investigated from ongoing trials that will provide important imaging-derived data [122].

The activation of renin–angiotensin system (RAS) is another important risk factor in atherogenesis. Angiotensin II promotes atherogenesis by stimulating inflammation, oxidative stress, and endothelial dysfunction. In animal models ACE inhibitors and ARBs have been shown to reduce the progression of atherosclerosis [123], and in human study the perindopril has shown to prevent coronary remodeling [124]. Recent studies with CCTA indicate that combination of statins with ACE inhibitor or ARB would be more effective for antiatherosclerotic therapy than statin alone even in patients with CAD, suggesting an inhibitory effect of the combination therapy on vascular remodeling [125].

Also colchicine has been postulated to have beneficial effects on atherosclerosis. In a recently published paper on 80 patients with recent ACS (<1 month) followed for 1 year, colchicine therapy (0.5 mg/day colchicine plus OMT vs OMT alone) was significantly associated with greater reduction in low attenuation plaque volume (p= 0.039) on CCTA, independent of high-dose statin therapy. The improvements in plaque morphology were likely driven by the anti-inflammatory properties, as demonstrated by reductions in high-sensitivity C-reactive protein (hsCRP), rather than

changes in lipoproteins. Colchicine could be beneficial as an additional second-lines, add-on, and prevention therapy in patients post-ACS if validated in future studies [126].

Although currently it is not possible to recommend serial scans to monitor the therapeutic efficacy of a medical interventions, the plaque modulation, as a part of risk modification, is a feasible strategy. Direct visualization of the natural course of atherosclerosis, as well as identification of the clinical determinants of plaque progression or regression, holds the potential to shift the paradigm of CAD monitoring among low- to moderate-risk patients with suspected CAD, with aims of offering earlier therapeutic strategies [127]. It is reasonable to accept that a substantial reduction in plaque vulnerability by therapeutic intervention should contribute into plaque stability and in turn decrease cardiovascular event rates. Further studies should be warranted for elucidates this matter.

7. Conclusions

Nowadays, primary prevention of major cardiac events needs a strong implementation for ethic and economic reasons. Early identification of CAD, characterization of atherosclerotic process, evaluation of ischemia-related plaque features, and assessment of "vulnerable plaque," sometimes in the context of "vulnerable patient", are mandatory endpoints in order to reach this aim. To date, CCTA is the only technique able to approach comprehensively these topics. Moreover, according to the first encouraging literature reports, CCTA could be able to monitor and guide the therapeutic approach which is the ultimate goal of events prediction.

Conflicts of Interest

No relationship with industry and financial associations within the past 2 years posing conflicts of interest in connection with the submitted article exists.

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Research Article

Role of the $CHADS_2$ Score in the Evaluation of Carotid Atherosclerosis in Patients with Atrial Fibrillation Undergoing Carotid Artery Ultrasonography

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Objective. This study investigated the characteristics of carotid atherosclerosis in patients with atrial fibrillation (AF) and determined the feasibility and significance of the $CHADS_2$ score in predicting the degree of carotid atherosclerosis. *Methods*. Consecutive patients (n = 109) with nonvalvular AF were registered and classified into two groups, the paroxysmal AF group (n = 59) and persistent AF group (n = 50). Fifty healthy patients, matched by sex and age, were considered the control group. All patients were examined using carotid ultrasound and velocity vector imaging (VVI). *Results*. Compared with the control group, the mean intimal-medial thickness in the paroxysmal AF group (0.56 ± 0.11 versus 0.61 ± 0.10, respectively, $P < 0.05$) and the persistent AF group (0.56 ± 0.11 versus 0.64 ± 0.13, respectively, $P < 0.001$) was significantly increased. The plaque index (PI) in the persistent AF group was significantly higher than that observed in the paroxysmal AF group (1.05 ± 1.33 versus 1.42 ± 1.47, respectively, $P < 0.001$). Regarding the VVI indices, those reflecting the long-axis longitudinal motion function of carotid arteries were significantly decreased in both AF groups. Compared with the control group, a significantly lower total longitudinal displacement (tLoD) index was observed in the persistent AF group (0.73 ± 0.66 versus 0.31 ± 0.23, respectively, $P < 0{\cdot}0001$) and the paroxysmal AF group (0.73 ± 0.66 versus 0.34 ± 0.17, $P < 0{\cdot}0001$). The $CHADS_2$ score was related to indicators reflecting the structure and function of the carotid artery. *Conclusions*. Carotid arterial structure and function were significantly altered in patients with AF. The degree of carotid atherosclerosis depended on the duration of AF. The $CHADS_2$ score may be useful as a predictor of the extent of carotid atherosclerosis in patients with AF.

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias observed in clinical practice. Thromboembolic complications are the most serious consequences of AF [1]. Previous studies [2] documented that the main source of emboli in ischemic stroke with AF was left atrial thrombus. However, the major underlying causes of nonvalvular AF (hypertension, diabetes, coronary heart disease, and advanced age) have also been associated with a high risk for the development of atherosclerotic lesions. AF and atherosclerosis may mutually influence the development of each other [3, 4]. AF combined with carotid atherosclerotic stenosis may markedly increase the risk of recurrent ischemic stroke [5].

The $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke) score is used to evaluate the risk of stroke in patients with AF [6]. It has a strong predictive effect regarding the development of cardiac adverse events of left atrial origin in patients with AF [7, 8]. However, its role in predicting

embolism of carotid plaque origin has not been determined.

Doppler ultrasound is able to evaluate the structure and function of the carotid artery intuitively to reflect related indices of atherosclerosis. Velocity vector imaging (VVI) is a novel ultrasound method, based on multiple M-mode evaluations and speckle-tracking technique [9, 10]. VVI allows the simultaneous evaluation of longitudinal and radial velocity, strain, strain rate, and displacement of the common carotid artery (CCA) wall motion [10]. The combination of VVI technology and Doppler ultrasound may evaluate the elasticity of the carotid vascular wall more comprehensively.

In the present study, Doppler ultrasound and VVI were used to explore the characteristics of carotid atherosclerosis in patients with AF and determine the feasibility and significance of the $CHADS_2$ score in predicting the degree of carotid atherosclerosis.

2. Methods

2.1. Study Design. A total of 109 patients with nonvalvular AF fulfilling the inclusion criteria were enrolled in the study between September 2011 and May 2012. Of those, 59 patients had paroxysmal AF (22 males and 37 females, mean age: 58.32 ± 10.18 years [range: 30–75]) and the remaining 50 had persistent AF (18 males and 32 females, mean age: 59.30 ± 8.94 years [range: 25–78]). Nonvalvular AF was defined as AF in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair [11, 12]. AF which resolved spontaneously was designated as paroxysmal. Sustained AF which resolved through pharmacological intervention or electrical cardioversion was designated as persistent [12].

For the control group, 50 healthy patients (22 males and 28 females, mean age: 55.98 ± 7.19 years [range: 38–76]), matched by sex and age, were recruited from hospital staff and volunteers.

All patients were examined using electrocardiography (ECG) and 24-hour dynamic electrocardiography and echocardiography. Data including medical history, history of thromboembolism, history of drug use, and history of smoking/drinking were collected in detail.

2.2. Biochemical Assessments. All samples were collected following a 14-hour overnight fast and centrifuged within 30 minutes of collection. The levels of total serum cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and fasting blood glucose were analyzed from blood samples and measured using routine laboratory methods.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects. Written informed consent was provided by all patients, and the study protocol was approved by the institutional ethics committee.

2.3. Acquisition of Carotid Ultrasound Index. The carotid ultrasound index of the study population was acquired using a Siemens Sequoia™ 512 color Doppler ultrasonic diagnostic apparatus. The probe frequency was 8.0–14.0 MHz. B-mode real-time ultrasound was performed to evaluate the wall thickness of the carotid artery. An expert sonographer, blinded to the data of the patients, performed the sonographic evaluations. Patients were examined in the supine position, as previously reported [13–15].

The probe was deployed approximately 1.5 cm proximally to the bifurcation of the CCA, and the longitudinal plane was used to visualize the maximum diameter of the lumen. Five segments were identified and measured in the anterior and posterior planes. At each of these sites the intimal-medial thickness (IMT) was determined, defined as the distance between the echogenic line representing the intimal blood interface and the outer echogenic line representing the adventitial junction. The maximum IMT value was determined as the mean IMT of the left and right arteries and was used for analysis.

During ultrasound assessments, the blood flow velocity in the carotid artery, arterial compliance, carotid stiffness index, resistance index, and other related indicators were measured. All detected plaques were counted, and their characteristics (fibrous, calcified or soft, presence, or absence of stenosis) were determined. The degree of plaque was graded on a scale from 0 to 3 (0 = no observable plaque; 1 = one small plaque [<30% of vessel diameter]; 2 = one medium plaque [30%–50% of vessel diameter] or multiple small plaques; and 3 = one large plaque [50% of vessel diameter] or multiple plaques with at least one medium plaque) [16].

2.4. Velocity Vector Imaging Acquisition and Analysis. All VVI-measurements were performed offline at a workstation by two independent observers. The VVI software (syngo® US workplace) was used to determine vessel wall velocity, strain, strain rate, and displacement of both the near and far wall of the CCA. Using the VVI mode of the device, the frame rate was adjusted to >60 frames/s. The transverse distal CCA approximately 1-cm inferior to the carotid bulb and free of plaque was used for analysis. Five guiding points were equally distributed (0.25-cm apart) within a 1-cm segment on the near wall and far walls; i.e., a total of 10 measuring points were used [17]. Dynamic images of three consecutive cardiac cycles were acquired and stored. The segmental values of the VVI parameters from both sides of the CCA were measured independently and averaged [17–19]. The total longitudinal displacement (tLoD) during a cardiac cycle was calculated as the sum of absolute values of the maximal systolic and maximal diastolic displacements. Patients with paroxysmal atrial fibrillation undergo carotid ultrasound during the onset of atrial fibrillation.

2.5. Statistical Analysis. All analyses were performed using the SPSS software (version 18.0, IBM Crop., Armonk, USA). Descriptive statistics were used to summarize the data. Categorical variables were expressed as percentages, while continuous variables were expressed as mean ± standard deviation. Differences between groups distributed variables were evaluated using one-way analysis of variance. Student's t-test was used to compare parameters between two groups. Correlation coefficients and their significance were calculated using Spearman's test. Possible predictors, identified through

Table 1: Baseline clinical characteristics.

		Atrial fibrillation (n = 109)	
	Control group (n = 50)	Paroxysmal AF group (n = 59)	Persistent AF group (n = 50)
Age (years)	55.98 ± 7.19	58.32 ± 10.18	59.30 ± 8.94
SBP (mmHg)	122.74 ± 13.34	135.19 ± 19.41***	137.48 ± 18.37***
DBP (mmHg)	81.1 ± 611.29	79.51 ± 13.81	83.90 ± 12.44
Heart rate min^{-1}	66.60 ± 11.72	71.68 ± 24.20	88.58 ± 20.99***†††
Body mass index (kg/m^2)	24.76 ± 4.53	26.18 ± 3.52	26.12 ± 3.67
Waist-hip ration	0.87 ± 0.06	0.89 ± 0.06*	0.91 ± 0.05***
Fasting glucose (mmol/L)	5.42 ± 0.79	5.67 ± 2.04	5.48 ± 1.06
Cholesterol(mmol/L)	5.02 ± 0.99	4.77 ± 0.95	4.79 ± 1.40
HDL cholesterol (mmol/L)	1.35 ± 0.27	1.29 ± 0.30	1.23 ± 0.30
LDL cholesterol (mmol/L)	2.65 ± 0.62	2.74 ± 0.72	2.76 ± 1.02
Triglycerides (mmol/L)	1.50 ± 0.91	1.50 ± 0.74	1.73 ± 1.19
Male (%)	22 (44%)	37 (62%)	32 (64%)
Smoking history (%)	17 (33%)	23 (39%)	23 (46%)*
Drinking history (%)	15 (29%)	27 (46%)**	27 (53%)**
Hypertension (%)	8 (16%)	36 ($62^{\%}$)**	29 (57%)
Diabetes mellitus (%)	24 (4%)	12 (20%)*	8 (16%)
CAD (%)	0	21 (36%)**	21 (41%)**
Prior Stroke (%)	0	3 (5%)	13 (26%)**††
Statins (%)	0	13 (22%)*	13 (26%)**
Beta-blockers (%)	1 (2%)	36 (61%)**	32 (64%)**
ACEI (%)	0	22 (37%)**	12 (23%)**
ARB (%)	0	14 (24%)**	20 (39%)**
Anticoagulants (%)	1 (2%)	24 (41%)**	19 (37%)**
Aspirin (%)	2 (4%)	35 (60%)**	36 (71%)**
$CHADS_2$ score			
0 (%)	38 (76%)	20 (33.9%)	17 (34%)
1 (%)	12 (24%)	30 (50.8%)	12 (24%)
2 (%)	0	8 (13.6%)	14 (28%)
3 (%)	0	0	7 (14%)
≥4 (%)	0	1 (1.7%)	0

Note. Compared with the control group, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
Compared with the paroxysmal atrial fibrillation group, $^{\dagger}P < 0.05$;$^{\dagger\dagger}P < 0.01$; $^{\dagger\dagger\dagger}P < 0.001$.
SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary atherosclerotic heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

univariate analysis, were further analyzed using multiple logistic regression analyses to determine independent predictors. A p-value <0.05 denoted statistical significance in all analyses.

3. Results

3.1. Comparison of Clinical Characteristics between the AF and Control Groups. There were no statistically significant differences in sex and age among the three groups. In the paroxysmal AF and persistent AF groups, the proportion of patients with high systolic blood pressure, high waist-hip ratio, alcohol history, hypertension, diabetes, coronary heart disease, and hyperlipidemia was significantly increased compared with the control group (Table 1). In addition, the proportion of patients receiving concomitant treatment with antiplatelet therapy, anticoagulation therapy, angiotensin-converting enzyme inhibitors, β-receptor antagonists, and statins was significantly increased (Table 1). Of note, the proportion of patients suffering a stroke in the persistent

Table 2: Comparison of carotid ultrasound indices and VVI indices between the control group and the AF groups (grouped according to the type of AF).

		Atrial fibrillation (n = 109)	
	Control group (n = 50)	Paroxysmal AF group (n = 59)	Persistent AF group (n = 50)
Plaque index	0.16 ± 0.62	1.05 ± 1.33***	1.42 ± 1.47***†††
Mean IMT (mm)	0.56 ± 0.11	0.61 ± 0.10*	0.64 ± 0.13***
Max IMT (mm)	0.71 ± 0.13	0.77 ± 0.12	0.83 ± 0.15
Ds (mm)	6.71 ± 0.80	7.42 ± 1.14**	7.72 ± 1.63***
Dd (mm)	6.24 ± 0.82	6.95 ± 1.04**	7.22 ± 1.63***
Ep (kPa)	751.32 ± 682.21	876.08 ± 410.27	1091.29 ± 828.84*
Ep*	9.22 ± 7.68	11.42 ± 5.87	13.58 ± 12.76*
DC (mmHg-1×10^{-2})	0.15 ± 0.09	0.14 ± 0.06	0.14 ± 0.11
AC (mm^2/kPa)	1.21 ± 1.23	3.35 ± 2.57**	3.14 ± 2.76*
β	7.35 ± 5.95	8.42 ± 3.92	10.34 ± 9.32*
Vs (cm/s)	0.56 ± 0.12	0.49 ± 0.15*	0.45 ± 0.20**
Vd (cm/s)	0.29 ± 0.07	0.24 ± 0.07**	0.24 ± 0.10**
Vm (cm/s)	0.42 ± 0.09	0.35 ± 0.14**	0.37 ± 0.11*
Long Pv S (cm/s)	0.60 ± 0.71	0.31 ± 0.18*	0.24 ± 0.20**
Long Pv D (cm/s)	0.32 ± 0.19	0.21 ± 0.12**	0.19 ± 0.13**
Long Ps S (%)	5.04 ± 3.63	3.28 ± 2.13*	2.67 ± 2.78**
Long Ps D (%)	8.74 ± 8.48	4.86 ± 2.45**	4.10 ± 3.37**
Long Psr S (1/s)	1.21 ± 1.23	0.67 ± 0.39*	0.57 ± 0.49**
Long Psr D (1/s)	0.65 ± 0.41	0.51 ± 0.28*	0.43 ± 0.31**
Long Pd S (mm)	0.27 ± 0.24	0.13 ± 0.08**	0.13 ± 0.12**
Long Pd D (mm)	0.47 ± 0.53	0.21 ± 0.12**	0.17 ± 0.15**
tLoD (mm)	0.73 ± 0.66	0.34 ± 0.17***	0.31 ± 0.23***
Ra Pv S (cm/s)	0.22 ± 0.17	0.19 ± 0.18	0.14 ± 0.14*
Ra Pv D (cm/s)	0.15 ± 0.12	0.10 ± 0.05*	0.12 ± 0.11
Ra Pd S (mm)	0.10 ± 0.11	0.07 ± 0.06	0.06 ± 0.06*
Ra Pd D (mm	0.18 ± 0.20	0.12 ± 0.08	0.09 ± 0.08*

Note: compared with the control group, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Compared with the paroxysmal atrial fibrillation group, $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$; $^{\dagger\dagger\dagger}P < 0.001$.

IMT, intima media thickness; VVI, velocity vector imaging; AC, arterial compliance; Ds, systolic diameter; Dd, diastolic diameter; Ep, pressure strain elastic modulus; DC, distensibility coefficient; β, stiffness index; Vs, systolic peak velocity; Vd, diastolic peak velocity; Vm, mean velocity; Long Pv S, systolic longitudinal peak velocity; Long Pv D, diastolic longitudinal peak velocity; Long Ps S, systolic longitudinal peak strain; Long Ps D, diastolic longitudinal peak strain; Long Psr S, systolic longitudinal peak strain rate; Long Psr D, diastolic longitudinal peak strain rate; Long Pd S, systolic longitudinal peak displacement; Long Pd D, diastolic longitudinal peak displacement; Ra Pv S, systolic radial peak velocity; Ra Pv D, diastolic radial peak velocity; Ra Pd S, systolic radial peak displacement; Ra Pd D, diastolic radial peak displacement; tLoD, total longitudinal displacement.

AF group was significantly higher than that observed in the paroxysmal AF group (26% versus 5%, respectively, $P < 0.01$).

3.2. Comparison of Carotid Sonography Indices and VVI Indices between the AF and Control Groups (Grouped according to Type of AF). Compared with the control group, in the paroxysmal AF group the mean IMT (0.56 ± 0.11 versus 0.61 ± 0.10, respectively, $P < 0.05$) and arterial compliance (AC) index (1.21 ± 1.23 versus 3.35 ± 2.57, respectively, $P < 0.001$) were significantly increased. The index for blood flow velocity in the carotid was significantly decreased (Table 2).

Compared with the control group, in the persistent AF group the mean IMT (0.56 ± 0.11 versus 0.64 ± 0.13, respectively. $P < 0.001$), AC index (1.21 ± 1.23 versus 3.14 ± 2.76, respectively, $P < 0.05$), and carotid stiffness index (β) (7.35 ± 5.95 versus 10.34 ± 9.32, respectively, $P < 0.05$) were significantly increased, whereas the index for the blood flow velocity in the carotid was significantly decreased (Table 2).

The plaque index (PI) was significantly higher in the persistent AF group than the paroxysmal AF group (1.05 ± 1.33 versus 1.42 ± 1.47, respectively, $P < 0.001$).

For the VVI indices, those reflecting the long-axis longitudinal motion and the long-axis radial motion of the carotid artery were significantly decreased in both AF groups compared with the control group (Table 2). The persistent AF group showed significantly lower tLoD compared with the

Table 3: Comparison of carotid ultrasound indices and VVI indices between the AF groups (grouped according to the $CHADS_2$ score).

	score = 0 (n = 38)	Score = 1 (n = 42)	score ≥2 (n = 29)
Plaque index	0.78±1.03	1.46±1.57	1.52±1.48
Mean IMT (mm)	0.60±0.12	0.62±0.10	0.67±0.10*
Max IMT (mm)	0.75±0.14	0.80±0.12	0.86±0.14**
Ds (cm)	0.72±0.17	0.77±0.11	0.77±0.11
Dd (cm)	0.68±0.17	0.72±0.10	0.71±0.10
Ep (kPa)	887.81±854.52	1027.38±441.45	1017.86±574.22
Ep*	12.25±14.20	12.58±5.64	12.42±6.88
DC (mmHg-1×10^{-2}	0.14±0.06	0.12±0.06	0.16±0.14
AC (mm2/kPa)	2.19±0.95	3.84±3.02*	3.80±3.19*
β	9.26±10.21	9.39±4.14	9.25±4.93
Vs (cm/s)	0.51±0.16	0.48±0.19	0.42±0.15*
Vd (cm/s)	0.26±0.07	0.23±0.09	0.21±0.08*
Vm (cm/s)	0.39±0.11	0.35±0.13	0.32±0.11*
RI	0.48±0.07	0.51±0.11	0.48±0.12
PI	0.63±0.12	0.60±0.21	0.65±0.21
Long Pv S (cm/s)	0.25±0.17	0.31±0.21	0.25±0.19
Long Pv D (cm/s)	0.18±0.10	0.21±0.13	0.22±0.14
Long Ps S (%)	2.58±1.86	3.65±2.74	2.62±2.58
Long Ps D (%)	3.94±2.21	5.05±3.19	4.49±3.25
Long Psr S (1/s)	0.57±0.34	0.72±0.47	0.58±0.50
Long Psr D (1/s)	0.43±0.25	0.52±0.32	0.47±0.32
Long Pd S (mm)	0.10±0.09	0.14±0.09	0.16±0.13*
Long Pd D (mm)	0.17±0.12	0.23±0.16	0.16±0.10
tLoD (mm)	0.27±0.17	0.38±0.21	0.32±0.20
Ra Pv S (cm/s)	0.17±0.16	0.19±0.19	0.13±0.12
Ra Pv D (cm/s)	0.10±0.08	0.10±0.06	0.13±0.12
Ra Pd S (mm)	0.05±0.04	0.07±0.06	0.07±0.06
Ra Pd D (mm)	0.11±0.09	0.11±0.08	0.10±0.08

Note: compared with the low-risk group (score = 0), $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
IMT, intima media thickness; VVI, velocity vector imaging; AC, arterial compliance; Ds, systolic diameter; Dd, diastolic diameter; Ep, pressure strain elastic modulus; DC, distensibility coefficient; β, stiffness index; Vs, systolic peak velocity; Vd, diastolic peak velocity; Vm, mean velocity; Long Pv S, systolic longitudinal peak velocity; Long Pv D, diastolic longitudinal peak velocity; Long Ps S, systolic longitudinal peak strain; Long Ps D, diastolic longitudinal peak strain; Long Psr S, systolic longitudinal peak strain rate; Long Psr D, diastolic longitudinal peak strain rate; Long Pd S, systolic longitudinal peak displacement; Long Pd D, diastolic longitudinal peak displacement; Ra Pv S, systolic radial peak velocity; Ra Pv D, diastolic radial peak velocity; Ra Pd S, systolic radial peak displacement; Ra Pd D, diastolic radial peak displacement; tLoD, total longitudinal displacement.

control group (0.31 ± 0.23 versus 0.73 ± 0.66, respectively, $P < 0.0001$). This significant decrease in the tLoD index was also observed in the paroxysmal AF group (0.34 ± 0.17 versus 0.73 ± 0.66, respectively, $P < 0.0001$), suggesting that the long-axis motor function of the carotid artery was impaired in patients with AF.

Detailed examples of output derived from the VVI software are shown in Figures 1 and 2. The Figures display longitudinal displacement curves during heart cycles in control subjects and patients with AF.

3.3. Comparison of Carotid Ultrasound Indices and VVI Indices between Patients (Grouped according to the $CHADS_2$ Score). Compared with the low-risk group ($CHADS_2$ scores of 0), in the high-risk group ($CHADS_2$ scores >2) the mean IMT (0.60 ± 0.12 versus 0.67 ± 0.10, respectively, $P < 0.05$), maximum IMT (0.75 ± 0.14 versus 0.86 ± 0.14, respectively, $P < 0.01$), and AC index (2.19 ± 0.95 versus 3.80 ± 3.19, respectively, $P < 0.05$) were significantly increased (Table 3). However, the index for blood flow velocity was significantly decreased (Table 3). The PI showed a tendency to increase, without reaching statistical significance. There were no statistically significant differences in these indices between the moderate-risk and high-risk groups.

3.4. Correlation Analysis between the $CHADS_2$ Score, Carotid Sonography, and VVI Indices in the AF Groups. In patients with AF, the $CHADS_2$ score was linked to indicators reflecting

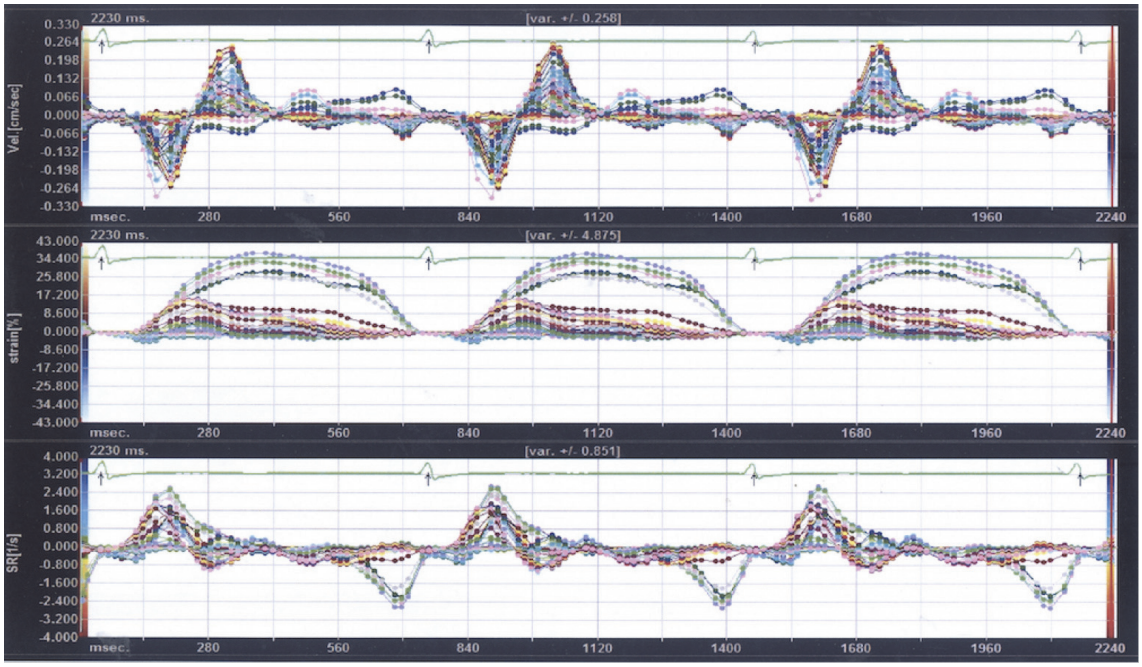

Figure 1: **Tracing curve of common carotid artery longitudinal motor function using velocity vector imaging in a patient with sinus rhythm.** The curves show regular synchronized motion of the common carotid artery intima during the cardiac cycle, with consistent velocity direction and magnitude.

the structure of the carotid artery, including PI (r = 0.297, P = 0.002), mean IMT (r = 0.272, $P < 0.001$), and maximum IMT (r = 0.337, $P < 0.001$). Moreover, it correlated with indices reflecting carotid function (Table 4). Correlation analysis using the VVI indices showed that the $CHADS_2$ score was correlated with indicators reflecting the long-axis longitudinal motion of the carotid artery (Table 4).

3.5. Logistic Regression to Identify Risk Factors for IMT Thickening (Table 5). The $CHADS_2$ score, total cholesterol, and LDL cholesterol were entered into the multivariate logistic regression analysis. The results showed that individuals with a high $CHADS_2$ score [odds ratio (OR): 1.676, 95% confidence interval (CI): 1.075–2.661, P = 0.023], increased total cholesterol (OR: 0.225, 95% CI: 0.085–0.596, P = 0.003), and increased LDL cholesterol (OR: 14.526, 95% CI: 3.329–63.385, $P < 0.001$) were susceptible to IMT thickening.

4. Discussion

Clinical evidence has suggested that atherosclerosis and AF may be correlated and mutually promoted [20–22]. Patients with concurrent AF and atherosclerosis have a higher mortality rate compared with those diagnosed with either AF or atherosclerosis [23]. Studies have shown that the risk of developing AF is higher in patients with carotid atherosclerosis [21–23]. Other studies have also shown that AF itself may accelerate the occurrence and development of coronary atherosclerosis and myocardial infarction [20, 22].

Atherosclerotic plaques develop mainly in sites of frequent hemodynamic changes such as arterial bifurcations, openings, or curving. This suggests that abnormalities in hemodynamics play a major role in the development of atherosclerosis. In 1997, Minamino et al. [24] proposed that the abnormality in hemodynamics caused by AF was in part responsible for endothelial dysfunction and that endothelial injury was the initiating factor for atherosclerosis. Pober and Cotran proposed the shear stress hypothesis [25], suggesting that laminar flow shear stress may selectively induce the blood vessel endothelium to express "protective factors of atherosclerosis." However, in cases of abnormal blood flow shear stress, this expression of protective factors in vascular endothelial cells is decreased or ceased. Therefore, the function of antiatherosclerosis would be inaccessible. Endothelium injury is the basis for the occurrence of atherosclerotic plaques.

Carotid arteries are useful for the observation of systemic atherosclerosis. Therefore, in the present study, high-resolution color Doppler ultrasound was used to evaluate the vascular structure and function of carotid arteries in patients with AF. The results indicated significant changes in carotid artery structure for patients with AF and a significant increase in the incidence and deterioration of atherosclerosis. At the same time, several indicators of carotid hemodynamics were altered, indicating decreased elasticity and increased stiffness in patients with AF. The PIs of carotid arteries in patients with persistent AF were significantly greater than those in patients with paroxysmal AF. This finding indicated that the development of atherosclerosis is dependent on the duration of AF [26, 27]. In our study, the data demonstrate that the systolic blood pressure was higher in both paroxysmal and persistent AF groups than in the control group. Hypertension

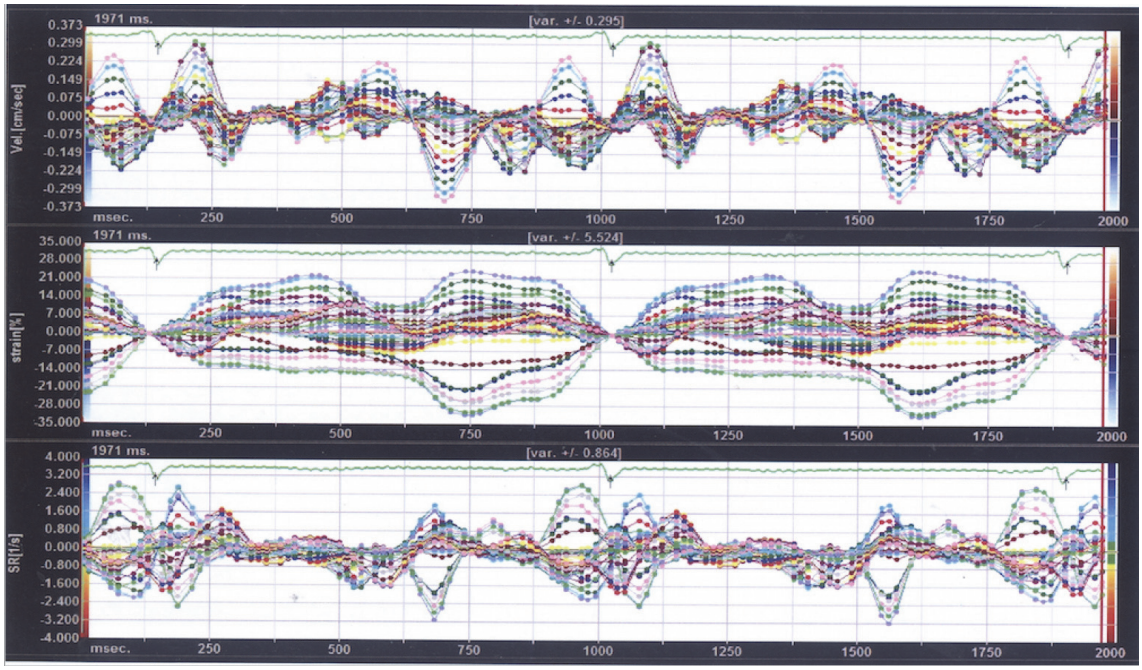

FIGURE 2: **Tracing curve of common carotid artery longitudinal motor function using velocity vector imaging in a patient with persistent atrial fibrillation.** The curves show that the motion of the common carotid artery intima at each point was desynchronized and the curves were disordered and irregular.

is an important risk factor for arterial stiffness [28] and also for atrial fibrillation [6]. Studies [29, 30] and animal models of genetic or experimental hypertension [31–33] suggest hypertension exerts a direct effect on the cardiovascular system, stimulates hyperplasia and hypertrophy of vascular smooth muscle cells and adventitial cell migration, and may therefore lead to notable pathophysiological consequences, such as interfering with vessel mechanical properties. Therefore, the increased carotid stiffness in patients with atrial fibrillation in our study was also influenced by hypertension. Hypertension aggravates the hemodynamic changes in patients with atrial fibrillation, thereby promoting the structural changes and further reducing the function of the carotid artery.

Furthermore, VVI was used to observe and compare motion characteristics of the long axis of the CCA in patients with AF and controls. The results demonstrated long-axis motor dysfunction of the CCA in patients with AF. During VVI, patients traced in the two-dimensional image are tracked automatically in real time. Changes and intervals of pixels on each successive frame of the image are tracked and compared, thus displaying the true motion speed and displacement of the tissue in a vector manner and showing the indicators in curves. In this way, quantitative analysis for structural mechanics of the patients is possible in multiple planes and at various phases [19, 34]. Svedlund et al. used VVI to evaluate the long-axis motion of the CCA and found that the anterior and posterior walls of CCA in controls showed similar motion tendency. In contrast, the motion of the long axis of the CCA in patients with coronary atherosclerotic heart disease was significantly weaker than that observed in controls [17]. Therefore, VVI may be used to visually observe characteristic variations in the structural mechanics of the vascular endothelium and evaluate the elasticity of vascular walls [18, 19, 34]. In this study, regular synchronous motion was observed in the cardiac cycle of tunica intima of the CCA in patients with sinus rhythm, and the direction and size of the velocity vector tended to be inhibited. Nonetheless, the movements of the common carotid intima in patients with AF were not synchronous, with disordered and irregular curves, along with significantly impaired longitudinal and radial motor functions. These findings reflect stiffness and poor elasticity of the CCA wall and deteriorated atherosclerosis in patients with AF. Regional hemodynamic disturbances caused by AF may be a driving factor for carotid atherosclerosis. The shear stress of such abnormal blood flow causes damage to the carotid endothelium, becoming the initiating factor for the formation of atheromatous plaques [24, 25, 27].

The correlation between the $CHADS_2$ score and carotid artery ultrasound indicators was investigated to estimate the degree and risk for the development of carotid atherosclerosis. The results showed that the $CHADS_2$ score was correlated with multiple ultrasound indicators reflecting the structure and function of the carotid artery. The degree of carotid atherosclerosis in patients with a high $CHADS_2$ score (≥ 2) was significantly higher than that observed in patients with a low-risk score (0). Therefore, the $CHADS_2$ score is able to also predict the degree of carotid atherosclerosis in patients with nonvalvular AF. The increase in the score is accompanied with impaired structure and dysfunction of the carotid artery. This assessment method is simple and feasible, prompting physicians to determine the need for administration of statins

Table 4: Correlation analysis of $CHADS_2$ score, carotid ultrasound, and VVI indices.

	$CHADS_2$ score	
	r	*P*
Plaque index	0.297	0.002
Mean IMT (mm)	0.272	<0.001
Max IMT (mm)	0.337	<0.001
Ds (cm)	0.345	<0.001
Dd (cm)	0.346	<0.001
Ep (kPa)	0.334	0.001
Ep*	0.278	0.001
DC ($mmH^{-1}\times10^{-2}$)	−0.157	0.047
AC (mm2/kPa)	0.252	0.001
β	0.259	0.001
Vs (cm/s)	−0.315	<0.001
Vd (cm/s)	−0.342	<0.001
Vm (cm/s)	−0.288	0.003
Long Pv S (cm/s)	−0.196	0.013
Long Pv D (cm/s)	−0.102	0.203
Long Ps S (%)	−0.134	0.092
Long Ps D (%)	−0.166	0.037
Long Psr S (1/s)	−0.191	0.016
Long Psr D (1/s)	−0.100	0.210
Long Pd S (mm)	−0.065	0.416
Long Pd D (mm)	−0.215	0.007
tLoD (mm)	−0.19	0.017
Ra Pv S (cm/s)	−0.127	0.112
Ra Pv D (cm/s)	0.012	0.884
Ra Pd S (mm)	0.023	0.77
Ra Pd D (mm)	−0.134	0.093

IMT, intima media thickness; VVI, velocity vector imaging; AC, arterial compliance; Ds, systolic diameter; Dd, diastolic diameter; Ep, pressure strain elastic modulus; DC, distensibility coefficient; Vs, systolic peak velocity; Vd, diastolic peak velocity; Vm, mean velocity; Long Pv S, systolic longitudinal peak velocity; Long Pv D, diastolic longitudinal peak velocity; Long Ps S, systolic longitudinal peak strain; Long Ps D, diastolic longitudinal peak strain; Long Psr S, systolic longitudinal peak strain rate; Long Psr D, diastolic longitudinal peak strain rate; Long Pd S, systolic longitudinal peak displacement; Long Pd D, diastolic longitudinal peak displacement; Ra Pv S, systolic radial peak velocity; Ra Pv D, diastolic radial peak velocity; Ra Pd S, systolic radial peak displacement; Ra Pd D, diastolic radial peak displacement; tLoD, total longitudinal displacement.

Table 5: Logistic regression to identify risk factors for IMT thickening.

	β	*P*	OR	95% CI
$CHADS_2$ score	0.516	0.023	1.676	1.075–2.661
Cholesterol (mmol/L)	−1.491	0.003	0.225	0.085–0.596
LDL cholesterol (mmol/L)	2.676	<0.001	14.526	3.329–63.385

in patients with a high $CHAD_2$ score. This approach may alleviate the progression of atherosclerosis and reduce the risk of stroke.

5. Conclusions

The carotid arterial structure and function in patients with AF were significantly changed, including increased arterial wall stiffness, decreased elasticity, and aggravated atherosclerosis. A positive correlation between the $CHADS_2$ score and carotid ultrasound indicators was found, indicating that risk stratification of AF stroke may also reflect the degree of structural and functional impairment of the carotid artery. Consequently, this may contribute to the assessment of the degree of carotid atherosclerosis.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Le-yu Lin and Lian-wei Yang contributed equally to this study.

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Review Article

Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography Datasets: The Next Frontier in Noninvasive Assessment of Coronary Artery Disease

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Fractional flow reserve (FFR) derived from coronary CTA datasets (FFR_{CT}) is a major advance in cardiovascular imaging that provides critical information to the Heart Team without exposing the patient to excessive risk. Previously, invasive FFR measurements obtained during a cardiac catheterization have been demonstrated to reduce contrast use, number of stents, and cost of care and improve outcomes. However, there are barriers to routine use of FFR in the cardiac catheterization suite. FFR_{CT} values are obtained using resting 3D coronary CTA images using computational fluid dynamics. Several multicenter clinical trials have demonstrated the diagnostic superiority of FFR_{CT} over traditional coronary CTA for the diagnosis of functionally significant coronary artery disease. This review provides a background of FFR, technical aspects of FFR_{CT}, clinical applications and interpretation of FFR_{CT} values, clinical trial data, and future directions of the technology.

1. Introduction

The last decade has brought rapid and exciting change to the field of cardiac imaging. In this context, coronary computed tomography angiography (CCTA) represents an excellent noninvasive tool for the evaluation of patients with coronary artery disease (CAD) [1–4]. The diagnostic accuracy of this technique has improved thanks to more effective strategies of premedication and implementation in image acquisition and postprocessing [5–10]. Likely, the most exciting technical advance is the ability to noninvasively measure the functional impact of coronary artery plaques. Advances in imaging techniques, mathematics, and computer science provide the ability to accurately measure fractional flow reserve (FFR) derived from coronary CTA datasets (FFR_{CT}) [11]. FFR_{CT} has the ability to provide critical information to the Heart Team without exposing the patient to unnecessary risk of an invasive procedure. What follows is a review of FFR_{CT}, including the theory and technology behind the imaging technique, accuracy data, clinical applications, and future directions.

2. Fractional Flow Reserve: Applications

Traditionally, coronary artery plaques were identified via invasive coronary angiography (ICA), using visual assessment of vessel stenosis to determine when a patient required revascularization, regardless of whether the visual assessment findings were supported by quantitative coronary angiographic techniques. However, oftentimes this results in revascularizing lesions that are not hemodynamically significant or lesions that are not the true etiology of the patient's symptoms, as well as failing to identify hemodynamically significant lesions [12]. Several techniques are now available in the cardiac catheterization lab to assess the hemodynamic significance of coronary lesions and therefore guide the interventional cardiologist to appropriate revascularization. At present, the most widely accepted measure of the hemodynamic significance of coronary stenoses is fractional flow reserve (FFR) which serves to identify specific vessels and lesions that are prone to induce ischemia during appropriate stress. FFR is a measure of the ratio of maximal blood flow through the coronary artery distal to a stenotic lesion to

the normal maximal blood flow. It is traditionally measured in the cardiac catheterization lab using a pressure wire and administering an intracoronary or intravenous vasodilator to produce maximal hyperemia [13]. For example, an FFR value of 0.75 means that a stenosis is causing a 25% drop in pressure across the lesion, which means that maximal hyperemic flow is equally reduced by 25%. Recent large trials have demonstrated the benefit of FFR as a tool to assess the appropriateness of revascularization, particularly for patients with stable coronary artery disease (CAD). The DEFER Trial demonstrated that it is safe to defer percutaneous coronary intervention (PCI) in patients with stable angina with lesions of >50% visual stenosis on ICA but an invasive FFR value ≥ 0.75 [14]. Further, the FAME I trial demonstrated that, in patients with stable multivessel CAD, using invasive FFR during PCI reduced a composite outcome of death, nonfatal myocardial infarction, and revascularization [15]. Moreover, the FAME investigators found a decreased use of contrast, fewer stents, and lower procedure-related costs in patients randomized to undergo FFR-guided revascularization. Among patients with stable CAD the FAME II trial found that PCI to lesions with an invasive FFR value ≤ 0.80 compared with optimal medical therapy reduced the composite outcome of death, nonfatal myocardial infarction, and urgent revascularization [16]. Five-year follow-up from the FAME II trial confirmed that an FFR-guided PCI strategy was associated with a significantly lower rate of a combined outcome of death, myocardial infarction, or urgent revascularization when compared to patients managed with medical therapy alone [17]. There is a continuous, inverse relationship between the numeric FFR value and adverse outcomes, which is true regardless of whether or not the lesion is revascularized [18]. Despite its demonstrated clinical benefit and recommendations by major societies such as the American College of Cardiology (class IIa recommendation) and the European Society of Cardiology (class IA recommendation), given the invasive nature of the FFR procedure, the added time, radiation, contrast administration and cost of adenosine which must be given to patients during FFR measurement, the high costs of the pressure-sensing wires, and limited reimbursement, FFR evaluation is infrequently performed in clinical practice [19–22]. Invasive FFR was performed in only 6.1% of patients using data from over 60,000 ICA cases in the American College of Cardiology registry [23]. A priori knowledge of the presence and functional significance of specific coronary artery lesions before angiography may aid the cardiologist in deciding whether or not to proceed with ICA and redefine the revascularization strategy (Figure 1).

3. Technical Aspects of FFR_{CT}

Advances in computational fluid dynamics (CFD) allow determination of coronary flow from static high quality coronary CTA images. CFD is based on the Navier-Stokes equations [24, 25]. While the Newtonian laws of motion and the understanding of viscous fluid dynamics that underpin the Navier-Stokes equations have been used in other disciplines for centuries, it was not until recent advances in supercomputing that these equations could be applied to the complex, three-dimensional, and time-sensitive flow patterns of the coronary arteries.

CFD requires defining the vessel shape anatomically, as well as adequate descriptions of the "boundary conditions" of the arterial system. To define vessel shape for CFD calculations one must first obtain coronary CTA images in accordance with the Society of Cardiovascular Computed Tomography (SCCT) guidelines to sufficiently define the vessel walls [26]. Currently, the only commercially available mechanism for computing FFR_{CT} is via HeartFlow (HeartFlow Inc., Redwood, CA). For FFR_{CT}, 3-dimensional (3D) geometric modelling and computationally intricate blood flow analysis require off-site supercomputing power, and boundary conditions are determined by allometric scaling laws and assumptions regarding microvascular resistance [25]. Computation of FFR_{CT} involves (a) construction of an accurate patient-specific 3D anatomic model of the epicardial coronaries, (b) specifying microcirculatory models for coronary blood flow during maximal hyperemia, and (c) performing a computational solution of the laws of physics governing fluid dynamics. The physiologic model is created using the patient's anatomical model and is based on 3 scientific principles: (1) resting coronary blood flow is quantified relative to the myocardial mass. Mass can be calculated from myocardial volume, which is easily extracted from volumetric CCTA data; (2) microcirculatory resistance at rest is inversely proportional to the size of the lumen; and (3) vasodilatory response of the coronary microvasculature to adenosine is predictable. The reproducibility of FFR_{CT} is high. In one study, the difference between the first and second FFR_{CT} analyses was 0.035 and for invasive FFR repeated measurements was 0.043 [27].

There is growing data evaluating the diagnostic performance of reduced order models and 1D processing of the image data without the use of supercomputers for coronary CTA-derived FFR [28–31]. These algorithms are not commercially available, will require more extensive testing prior to clinical use, and require approximately 1 hour of physician work effort to produce the anatomical models needed.

Advances in technology have reduced the total radiation exposure from CCTA, which results in lower radiation exposure in patients undergoing FFR_{CT}. Some centers report performing CCTA at doses < 0.1mSv. [32]

4. Clinical Applications and Interpretation of FFR_{CT} Values

HeartFlow FFR_{CT} has been approved by the United States Food and Drug Administration (FDA) for functional evaluation of CAD and is currently commercially available. Recently, the NICE (National Institute for Health and Care Excellence) updated their chest pain guidelines which recommend coronary CTA as the initial diagnostic test for patients with stable chest pain and suspected CAD and issued positive medical guidance on FFR_{CT} stating the technology is safe, has high accuracy, and may avoid the need for ICA and reduce cost to the healthcare system [33, 34]. In clinical practice, the application of FFR_{CT} is to safely eliminate unnecessary

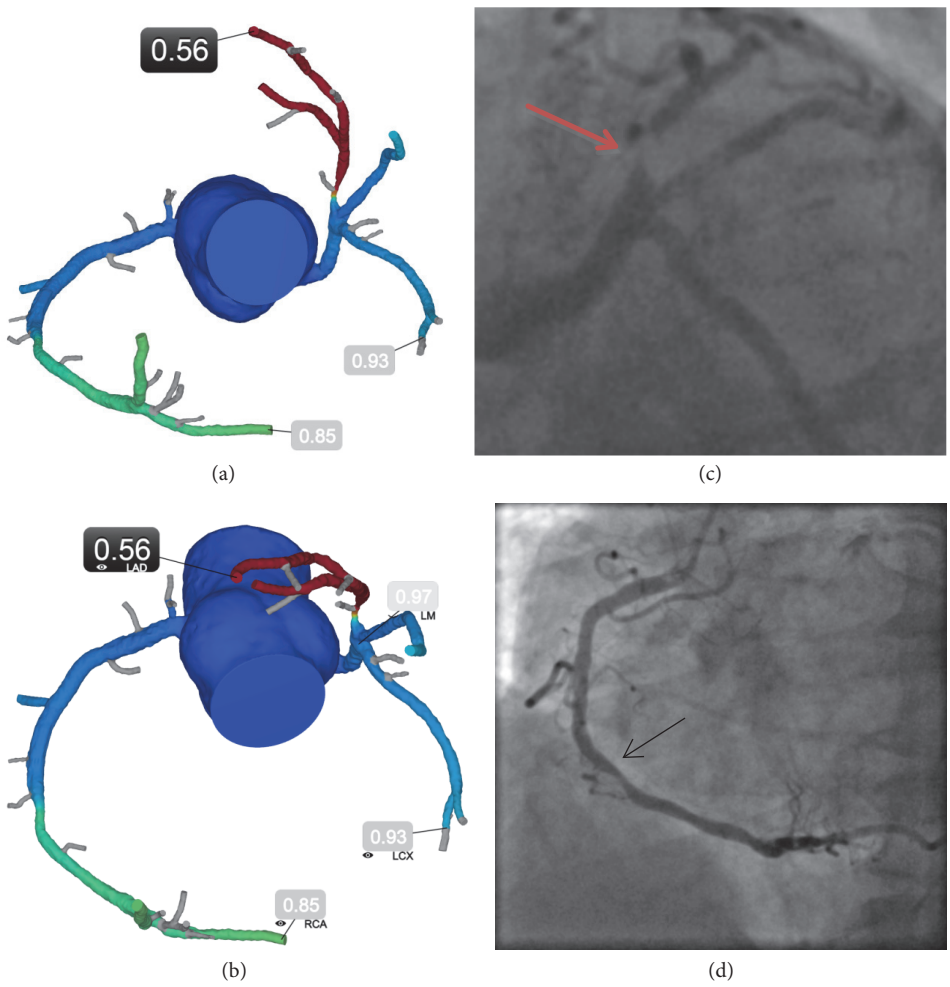

Figure 1: FFR_{CT} redefining revascularization strategy. A 68-year-old male with tobacco abuse, hypertension, hyperlipidemia, diabetes, and shortness of breath underwent coronary CTA demonstrating a 70%-90% stenosis of the proximal LAD and a 50%-70% stenosis of the mid-RCA. The initial decision based on the coronary anatomy alone was to refer the patient for coronary artery bypass graft surgery. However, FFR_{CT} was performed to help inform the invasive procedure. FFR_{CT} distal to the proximal LAD and mid-RCA stenoses were 0.56 and 0.85, respectively. The patient was rescheduled for PCI, received one stent in the proximal LAD, and is asymptomatic at three-year follow-up. Teaching points: with the functionally significant stenosis in the proximal LAD supplying a large territory of myocardium and his continued symptoms on optimal medical therapy, the patient was taken to the catheterization laboratory where a drug-eluting stent was placed. In addition, the cardiologist performed invasive FFR for the moderate stenosis in the RCA which was 0.86, corroborating the nonfunctionally significant lesion and no intervention was performed. This case highlights the unique opportunity to noninvasively provide physiological information on a per-lesion level. This enables a more informed decision around recommendations for ICA, specifically about which vessels to further interrogate and may redefine revascularization strategy. Even when the decision on referral to ICA is already taken because of symptoms and high-risk anatomy as determined by coronary CTA, FFR_{CT} may be of relevance by guiding decisions about other intermediate range lesions. FFR_{CT} (a,b) and ICA (c,d). LAD demonstrates a focal proximal severe stenosis (**red arrow**) that is hemodynamically significant. RCA demonstrates a focal mid moderate stenosis (**black arrow**) that is not hemodynamically significant. FFR_{CT} indicates fractional flow reserve derived from coronary computed tomography angiography (CTA) datasets; ICA, invasive coronary angiography; LAD, left anterior descending artery; and RCA, right coronary artery.

ICA and to better identify patients who may benefit from revascularization [35]. In the most recent Appropriate Use Criteria (AUC) for coronary revascularization, the American College of Cardiology recognized FFR_{CT} as a noninvasive "combination technique" with coronary CTA to help guide treatment [36].

Currently, clinicians using FFR_{CT} provided an interactive color-coded 3D model of the coronary tree with FFR values reported distal to stenoses [37]. The physician can manipulate the interactive model, examine each coronary segment and vessel, and determine the location and severity of lesions along the length of the coronary artery. The primary role of FFR_{CT} both clinically and as evaluated in clinical trials is to act as an alternative to invasive FFR by evaluating the FFR_{CT} distal to a focal stenosis. Diffuse coronary artery disease without a focal stenosis may lead to a progressive pressure drop along the length of the vessel and the treatment of these patients warrants further investigation. Nadir FFR_{CT}

Table 1: Summary of presented FFR_{CT} clinical trials.

Trial	Study Population	n	Intervention	Findings
NXT	Stable CAD scheduled to undergo invasive angiography	251	CCTA vs FFR_{CT}	FFR_{CT} had higher diagnostic accuracy than CCTA
PLATFORM	New stable CAD	584	Noninvasive stress testing vs FFR_{CT} and ICA vs FFR_{CT} prior to ICA	In patients randomized to an early invasive coronary angiogram for stable CAD, FFR_{CT} was associated with a lower rate of angiography showing no obstructive CAD and safe cancellation of ICA.
RIPCORD	Stable chest pain	200	CTA vs FFR_{CT}	FFR_{CT} data resulted in a change in management in 36% of cases.
ADVANCE	Stable CAD	1000	CCTA Findings Reviewed	CCTA stenosis severity, importantly, even for mild CCTA stenosis, in addition to diabetes and hypertension were predictive of abnormal FFR_{CT}.
Functional Syntax Score	Stable multivessel disease	77	Noninvasive vs invasive anatomic and functional SYNTAX score.	Functional SYNTAX score utilizing FFR_{CT} yielded similar results to those obtained invasively and reclassified 30% of patients from the high- and intermediate- SYNTAX score to the low-risk tertile. FFR_{CT} has good accuracy in detecting functionally significant lesions in patients with multivessel disease.

CAD = coronary artery disease. CCTA = coronary computed tomography angiography. FFR_{CT} = CTA-derived fractional flow reserve. ICA = invasive coronary angiography.

values should not be used alone when determining the need for ICA or revascularization [38]. Clinical decision-making should involve additional information such as patient history, medication use, anatomy, location of stenoses, vessel size, and suitability for revascularization. Ongoing prospective clinical registries such as ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) will shed light on the optimal treatment strategy for patients with diffuse CAD and progressive FFR_{CT} drop and which parameter (distal vessel tip value versus value distal to a lesion) is more appropriate to guide decision-making and yield superior prognostic information [39]. Of note, FFR_{CT} data were analyzed in 952 of the initial 1000 patients (95.2%) enrolled in the ADVANCE real-world registry [40].

5. FFR_{CT} Clinical Trials

To date, several multicenter clinical trials of FFR_{CT} have been completed and are summarized in Table 1 [41–44]. In the three large diagnostic accuracy studies comparing FFR_{CT} and coronary CTA to invasive FFR as the reference standard, FFR_{CT} had better diagnostic performance than coronary CTA alone [41–43]. The NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) [45] trial is the latest diagnostic performance trial of FFR_{CT}, which used the latest version 1.4 of the HeartFlow software. It was a 10-center prospective study and enrolled 254 patients and 484 vessels that were scheduled to undergo ICA for suspected stable CAD. Patients underwent coronary CTA and FFR_{CT} prior to the planned ICA. The investigators found an increased area under receiver-operating characteristic curve for FFR_{CT} (0.90, 95% CI 0.87-0.94) versus standard coronary CTA (0.81, 95% CI 0.76-0.87), which was statistically significant. Moreover, reported per-vessel sensitivities and specificities were 84% and 86%, respectively [43].

The PLATFORM (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts) study was a large multicenter prospective clinical utility trial of FFR_{CT} to assess clinical outcomes and sought to assess how FFR_{CT} affects the need for ICA [44]. The PLATFORM study assigned patients with new symptoms of stable ischemic heart disease to either "usual testing" or a coronary CTA/FFR_{CT}-driven strategy. For patients in the planned invasive cohort, they either went directly to ICA or were assigned to a coronary CTA/FFR_{CT} strategy, with possible cancellation of the planned ICA based on the results of the coronary CTA/FFR_{CT}. In the invasive arm of the PLATFORM study, a coronary CTA/FFR_{CT} strategy resulted in cancellation of 61% of previously planned ICA without any subjects with ICA cancelled experiencing an adverse event in 1-year follow-up. The use of a combined coronary CTA and FFR_{CT} strategy resulted in a reduction in the incidence of ICA showing nonobstructive disease by 83%. Importantly, follow-up at one year demonstrated lower health care costs for those patients in the planned invasive arm who underwent FFR_{CT} prior to ICA [44, 46, 47].

The FFR_{CT} RIPCORD study evaluated the impact of FFR_{CT} on clinical decision-making and demonstrated that the availability of FFR_{CT} results had a substantial effect on the labeling of significant CAD and management of patients compared to coronary CTA alone [48]. Data from 200 consecutive patients from the NXT trial were utilized. Three experienced cardiologists interpreted the coronary CTA data alone and reached a consensus on management strategy. FFR_{CT} data were then revealed to the same cardiologists and a second plan for each patient was again reached by consensus. FFR_{CT} resulted in a change in treatment decisions in 44% of patients. 30% of patients originally thought to require PCI based upon coronary CTA alone were reallocated to optimal medical therapy on the basis of a negative FFR_{CT}. In fact, FFR_{CT} was >0.80 in 13 of 44 vessels (29.5%) graded as having a stenosis >90%. In contrast, FFR_{CT} was ≤0.80 in 17 of 366 vessels (4.6%) graded as having stenosis ≤50% [48]. These data and others underscore the unreliable relationship between anatomic measures of stenosis and lesion-specific ischemia [49, 50].

Clinical experience from Aarhus University Hospital demonstrated that deferring ICA in patients with FFR_{CT} >0.80 had favorable short-term prognosis (median follow-up period of 12 months) and was associated with a high rate of cancellation of planned ICA [51, 52].

6. Future Directions

The scope of FFR_{CT} reaches far beyond the identification of FFR values [53]. New measures, such as percent myocardium at risk, are on the horizon which should further help clinicians make decisions, especially about the clinical significance of distal or branch vessel stenosis. It is conceivable that revascularization in patients with small areas of ischemic myocardium, as determined by FFR_{CT}, offers no advantage to optimal medical therapy alone. With the clinical adoption of FFR_{CT}, we are seeing individuals with diffuse atherosclerosis and/or small coronary arteries with low FFR_{CT} values. These findings are in line with prior reports on the continuous decline in pressure along the length of diffuse atherosclerosis without focal stenosis [54]. The ratio of vascular volume to myocardial mass (V/M) may shed light into the ischemic potential of these patients and better characterize the disease states in patients with vessel sizes that are insufficient to meet myocardial demand, with or without focal stenoses [55].

Akin to the invasive arena, we may soon be able to utilize the anatomic and functional information derived from FFR_{CT} to calculate SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) scores to aid clinicians to both decide between optimal medical therapy and revascularization and between PCI and coronary artery bypass graft surgery. Recently, the calculation of the noninvasive functional SYNTAX score utilizing FFR_{CT} was noted to be feasible, yielded similar results to those obtained invasively, and reclassified 30% of patients from the high- and intermediate-SYNTAX score to the low-risk tertile (REF). [56] Applications of coronary CTA-derived computational models may enable us to determine outcomes after revascularization. Virtual stenting by FFR_{CT} demonstrated diagnostic accuracy of 96% in the prediction of residual lesions prone to ischemia when placed under the appropriate stress [57]. Virtual stenting and bypass grafting have the potential to advance our knowledge and optimize coronary revascularization. Finally, data from the EMERALD (exploring the mechanism of the plaque rupture in acute coronary syndrome [ACS] using CCTA and CFD) study illustrated that CFD derived hemodynamic forces across lesions improved the prediction of acute coronary syndrome [58]. In fact, noninvasive hemodynamic parameters were better at identifying culprit lesions causal of acute coronary syndrome than either stenosis severity or high-risk plaque features. This data demonstrates the extraordinary potential bridging CFD to coronary CTA to provide not just an FFR value but valuable insight into identifying the *vulnerable patient*.

7. Conclusion

FFR_{CT} represents an exciting development in the evaluation of ischemic heart disease. Using advances in imaging and CFD, FFR_{CT} offers a noninvasive diagnostic strategy to identify functionally significant lesions in order to distinguish between patients who can safely avoid ICA and those patients who require revascularization.

Abbreviations

CCTA: Coronary computed tomography angiography
FFR: Fractional flow reserve
FFR_{CT}: Fractional flow reserve derived from coronary computed tomography angiography datasets
ICA: Invasive coronary angiography
PCI: Percutaneous coronary intervention
CFD: Computational fluid dynamics
FDA: Food and Drug Administration
CAD: Coronary artery disease.

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Cardiac Magnetic Resonance in Stable Coronary Artery Disease: Added Prognostic Value to Conventional Risk Profiling

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Aims. Cardiovascular magnetic resonance (CMR) permits a comprehensive evaluation of stable coronary artery disease (CAD). We sought to assess whether, in a large contemporaneous population receiving optimal medical therapy, CMR independently predicts prognosis beyond conventional cardiovascular risk factors (RF). *Methods*. We performed a single centre, observational prospective study that enrolled 465 CAD patients (80% males; 63±11 years), optimally treated with ACE-inhibitors/ARB, aspirin, and statins (76-85%). Assessments included conventional evaluation (clinical history, atherosclerosis RF, electrocardiography, and echocardiography) and a comprehensive CMR with LV dimensions/function, late gadolinium enhancement (LGE), and stress perfusion CMR (SPCMR). *Results*. During a median follow-up of 62 months (IQR 23-74) there were 50 deaths and 92 major adverse cardiovascular events (MACE). CMR variables improved multivariate model prediction power of mortality and MACE over traditional RF alone (F-test $p<0.05$ and $p<0.001$, respectively). LGE was an independent prognostic factor of mortality (hazard ratio [95% CI]: 3.4 [1.3–8.8]); moreover, LGE (3.3 [1.7–6.3]) and SPCMR (2.1 [1.4–3.2]) were the best predictors of MACE. *Conclusion*. LGE is an independent noninvasive marker of mortality in the long term in patients with stable CAD and optimized medical therapy. Furthermore, LGE and SPCMR independently predict MACE beyond conventional risk stratification.

1. Introduction

Coronary artery disease (CAD) is a leading cause of mortality worldwide [1]. In spite of improvements in medical therapy and revascularization procedures over the last few decades, many areas of uncertainty still exist. In patients with stable CAD, it is unclear why, despite prevalent use of stress imaging for inducible ischemia through techniques with recognized prognostic value, including stress echocardiography and single photon emission computerized tomography [2, 3], myocardial revascularization often fails to reduce hard endpoints, even in patients with extensive 3-vessel CAD, when compared to optimal medical therapy [4–8].

Cardiovascular magnetic resonance (CMR) is an established, robust, noninvasive, and radiation-free imaging technique for assessing CAD [9]. It allows in a single examination simultaneous evaluation of myocardial contractility, mass, wall motion, perfusion, tissue characteristics, and viability. In

particular, dobutamine stress CMR and stress perfusion CMR (SPCMR) can assess the hemodynamic significance of intermediate coronary stenoses and late gadolinium enhancement (LGE) CMR is useful for imaging focal myocardial scar determining viability [10]. However, it is unclear how a comprehensive CMR assessment strategy may impact long-term outcomes in a contemporaneous cohort of patients with stable CAD who are optimally treated. Specifically, there is lack of clarity as to whether such a CMR strategy may improve risk stratification beyond well-known conventional risk factors.

Therefore, the aim of our study was twofold: (1) to assess whether, in a large, well-characterized population with optimal medical therapy undergoing CMR for stable CAD, the presence of left ventricle (LV) dysfunction, SPCMR abnormalities, and/or fibrosis (assessed by LGE) was independent predictor of all-cause mortality in the long term, independently of traditional cardiovascular risk factors and (2) to assess the prognostic impact of CMR on major adverse cardiovascular events (MACE).

2. Methods

2.1. Study Population and Design. We performed a single centre, observational prospective study. Inclusion criteria: consecutive patients referred clinically for CMR with either definite diagnosis or a history suggesting stable CAD were enrolled. Exclusion criteria: we excluded patients with recent acute coronary syndrome (within 6 weeks), previous hospitalization for heart failure (NYHA class IV or need of infusive therapy) and signs of myocarditis, infiltrative or hypertrophic cardiomyopathy, and pericardial disease. Part of the study cohort participated in an earlier study on independent prognostic value of LGE [11] in which SPCMR assessment was not considered. Clinical history collection, electrocardiogram, and echocardiography evaluation criteria and CMR protocol (except for SPCMR) were the same as in the preceding study. In summary, patients underwent a conventional clinical and instrumental assessment as well as a comprehensive CMR evaluation. First pass SPCMR was evaluated 7.5 minutes after an intravenous infusion of dipyridamole stress (0.56 mg/kg for 4 minutes). Six contiguous short axis images, covering most of LV, were acquired. After stress perfusion images acquisition patients received an injection of aminophylline 240 mg i.v. in 10 minutes to antagonize dipyridamole effects. Perfusion images were semiquantitatively evaluated by two blinded operators with more than ten-year CMR experience and slice-to-slice compared with the corresponding LGE images. In each of the 17-segment standard segmentation, a perfusion defect was considered significant if it involved ≥75% of myocardium wall thickness, persisted at least 3 frames, and was detected in absence of LGE. A SPCMR study was considered positive if at least 2 segments (that equals to more than 10% of segments) showed significant perfusion defect. Figure 1 shows two studies with perfusion defects and, respectively, absence (positive SPCMR) or presence of LGE (negative SPCMR).

Informed consent to participate in the research study was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Review Board of the Fondazione Salvatore Maugeri (Pavia, Italy).

2.2. Follow-Up. Follow-up visits were conducted at our centre every 1–24 months, depending on clinical severity. Telephonic follow-up was performed for those patients whose last visit date was 6 months prior to the database closure. The primary outcome measure was all-cause mortality. The secondary outcome measure was a composite clinical endpoint of MACE, including all-cause mortality and hospitalization due to new onset New York Heart Association (NYHA) class IV or needing intravenous diuretics for heart failure, acute coronary syndrome (ACS), or myocardial revascularization procedures. Revascularization occurring within one month of CMR imaging was considered as CMR related and was not calculated as a separate MACE. Cases with more than one MACE were censored at the time of the first event.

2.3. Statistics. Categorical variables were expressed as counts and percentage, continuous variables as mean ± standard deviation or interquartile range (IQR). Two-sided $P<0.05$ was the significance level for hypothesis testing and SPSS Statistics 18.0 (IBM, USA) was the statistical package used. Differences at baseline between patients with and without events were tested with Pearson χ^2 or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables, where appropriate. Univariate hazard ratios were calculated by Cox proportional hazard analysis after converting continuous and ordinal variables into dichotomous variables. Threshold values were taken from the literature or were set equal to the 95th percentiles of the entire study population, when established threshold values were lacking (for example LGE cut-off was 40% of LV mass). Threshold values are indicated in brackets after each nondichotomous variable in Table 2. Proportional hazard assumption was graphically tested using plots of the log estimated cumulative baseline hazard against time. Conventional variables correlating with prognosis ($p<0.1$) at multivariate analysis (stepwise forward selection, forceful introduction of LVEF) were used to build the final model in which CMR assessment was introduced at the last step to test the hypothesis of its additional prognostic value over total mortality or MACE, on top of a conventional risk stratification approach. F-test for extra sum of square principle was applied to assess goodness of fit of the final model with respect to the conventional nested model.

3. Results

Five hundred eighty-nine patients were referred to our unit for CMR assessment during the period of interest. Forty-five (8%) were excluded as they presented exclusion criteria, and 54 (9%) because stress perfusion was not performed for clinical reason. Twenty-five (4%) patients were lost to follow-up. Thus, 465 patients entered the study, 397 (85%) with a definite diagnosis of CAD at enrollment and 68 (15%) with a history of likely CAD (Figure 2 summarizes the study flow chart). Patients were followed up for a median follow-up time

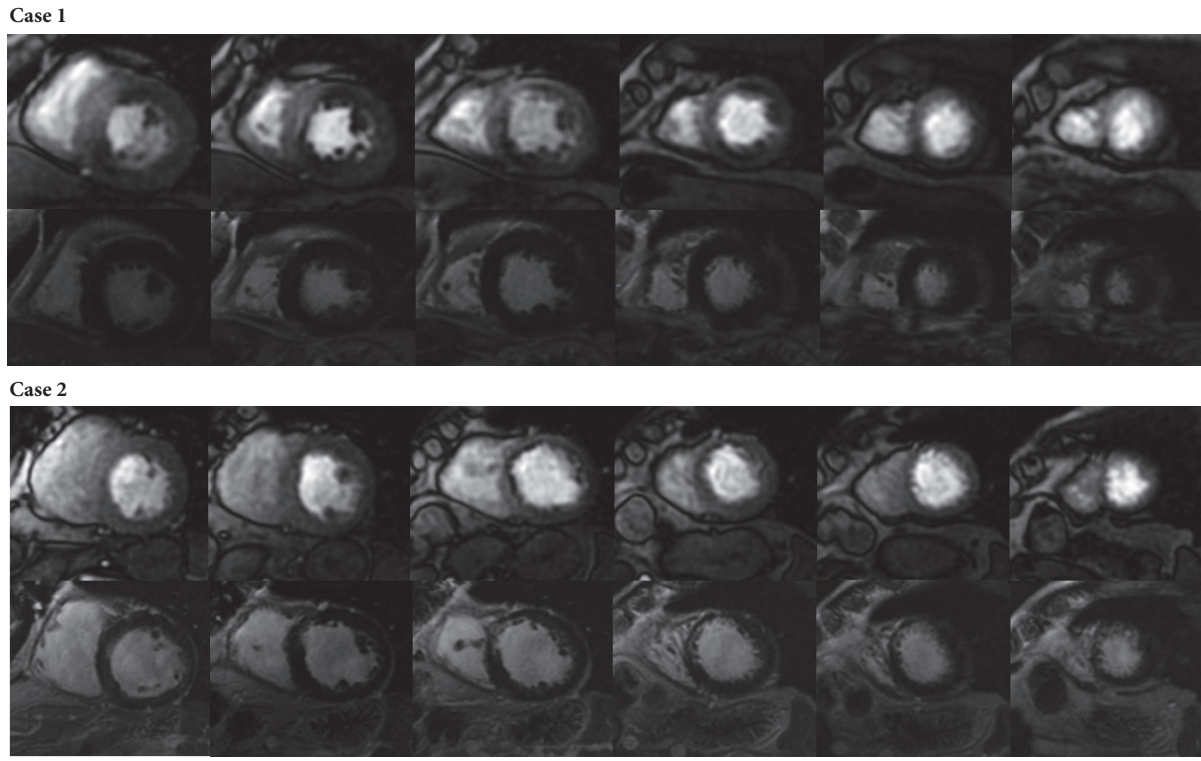

Figure 1: *First pass dipyridamole stress perfusion and late gadolinium enhancement CMR assessment*. Case 1 shows a positive stress perfusion study in two coronary territories by reason of a basal-mid anterior (partially) transmural as well as of a basal inferoseptal and mid inferior subendocardial stress perfusion defects (upper images) without late gadolinium enhancement (lower images). Case 2 depicts a negative stress perfusion study because of a mid anteroseptal and inferoseptal subendocardial stress perfusion defect (upper images) matching a similar late gadolinium enhancement area (lower images).

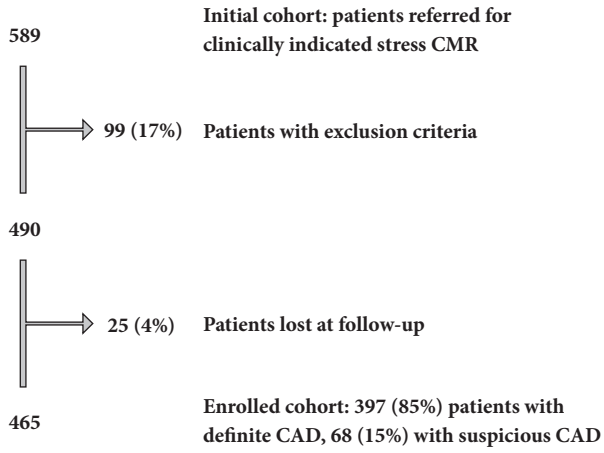

Figure 2: *Study enrollment flow chart*. Final cohort enrolled in the study after considering exclusion criteria and patients lost at follow-up.

of 62 months (interquartile range: 23-74), during which 142 events occurred (50 deaths, 20 new onset heart failure cases, 16 ACS, and 56 myocardial revascularization procedures). Twelve cases had more than one MACE.

Main baseline characteristics are reported in Table 1. Overall the study cohort was characterized by middle aged patients (63 years ± 11), with prevalence of male sex (80%) and preserved LV systolic function (LVEF at ECHO 53%± 13%). History of previous myocardial infarction was elicited in two-thirds, LM/3−vessel CAD in one-third, and diabetes in one-fifth of cases. Pharmacological treatment was characterized by optimal use of angiotensin converting enzyme- (ACE-) inhibitors/angiotensin receptor blockers (ARB), aspirin, and statins (76-85%). Accordingly, at the last follow-up contact, (1) mean LDL cholesterol value was 99 ± 32 mg/dl and LDL was < 100 mg/dl in 63% of cases, (2) mean systolic blood pressure (SBP) was 115 ± 16 mmHg and SBP was < 140 mmHg in 95% of cases and (3) mean diastolic blood pressure (DBP) was 70 ± 8 mmHg, and DBP was < 90 mmHg in 100% of cases. A fifth of patients had a positive dipyridamole SPCMR at baseline and a quarter of patients underwent at least one revascularization procedure during the follow-up.

3.1. Risk Stratification by Conventional Assessment

3.1.1. Prediction of All-Cause Mortality. Univariate analyses showed, in keeping with published literature, an association between all-cause mortality and LVEF and several other predefined factors. Among them, only a revascularization

Table 1: Baseline characteristics and differences between patients without and with primary outcome. (all-cause mortality).

	All patients (n=465)	Event free (n=415)	With events (n=50)	P Value*
ANTHROPOMETRY				
Age (years)	63 ± 11	63 ± 11	67 ± 10	0.006
Male sex	372 (80%)	334 (81%)	38 (76%)	0.454
Body mass index (kg/m2)	26 ± 4	26 ± 4	26 ± 5	0.088
CAD RISK FACTORS				
Family history of CAD	201 (43%)	183 (44%)	18 (38%)	0.454
Smoking	283 (61%)	245 (59%)	38 (76%)	0.018
Diabetes	88 (19%)	75 (18%)	13 (26%)	0.170
Hypertension	267 (57%)	238 (57%)	29 (57%)	0.417
Hypercholesterolemia	271 (58%)	241 (58%)	30 (60%)	0.763
No. of CV risk factors	2.4 ± 1.2	2.4 ± 1.2	2.6 ± 1.0	0.358
CLINIC HISTORY				
Previous CAD diagnosis	398 (86%)	350 (84%)	48 (96%)	0.027
Previous myocardial infarction	298 (64%)	257 (62%)	41 (82%)	0.005
LM or 3-vessel CAD	165 (35%)	144 (35%)	21 (42%)	0.292
NYHA classification (III class)	15 (3%)	11 (3%)	4 (8%)	0.111
Revascularization in the follow-up	112 (24%)	106 (26%)	6 (12%)	0.032
PHARMACOLOGICAL THERAPY				
β-blockers	361 (78%)	321 (78%)	40 (80%)	0.692
Ca^{++-} antagonist	97 (21%)	85 (21%)	12 (24%)	0.563
Nitrates	184 (40%)	161 (39%)	23 (46%)	0.325
Loop diuretics	146 (31%)	122 (29%)	24 (48%)	0.007
Aldosterone antagonist	54 (12%)	44 (11%)	10 (20%)	0.050
ACE-inhibitors/ARB	369 (79%)	330 (80%)	39 (78%)	0.802
ASA	396 (85%)	351 (85%)	45 (90%)	0.308
Statins	355 (76%)	317 (76%)	38 (76%)	0.952
Anticoagulant use	28 (6%)	22 (5%)	6 (12%)	0.117
ECG				
Heart rate (bpm)	64 ± 12	64 ± 11	70 ± 14	<0.001
Non sinus rhythm	14 (3%)	11 (3%)	3 (6%)	0.317
QRS duration (msec)	104 ± 19	103 ± 18	111 ± 24	0.021
QTc interval (msec)	423 ± 31	421 ± 31	436 ± 33	0.002
LV hypertrophy	66 (14%)	57 (14%)	9 (18%)	0.440
LBBB	55 (12%)	43 (10%)	12 (24%)	0.005
RBBB	59 (13%)	51 (12%)	8 (16%)	0.486
ST segment depression	28 (6%)	24 (6%)	4 (8%)	0.758
Negative T waves	217 (47%)	186 (45%)	31 (62%)	0.021
Q waves	178 (38%)	158 (38%)	20 (41%)	0.660
ECHOCARDIOGRAPHY				
LVEDV (ml/m^2)	60 ± 30	58 ± 29	72 ± 29	0.006
LVESV (ml/m^2)	29 ± 17	27 ± 15	44 ± 26	<0.001
LVEF (%)	53 ± 13	54 ± 12	43 ± 14	<0.001
LVWMSI	1.4 ± 0.4	1.3 ± 0.4	1.7 ± 0.5	<0.001
LV mass (g)	197 ± 64	195 ± 61	220 ± 86	0.053
LV diastolic dysfunction (≥pseudo-normal)	42 (9%)	34 (8%)	8 (16%)	0.119
Mitral regurgitation (≥ moderate)	65 (14%)	51 (12%)	14 (27%)	0.006
Pulmonary hypertension (sPAP>35 mmHg)	34 (7%)	27 (8%)	7 (14%)	0.102
RVIT dilatation (>40 mm)	30 (7%)	27 (7%)	3 (6%)	1.000
RV dysfunction (TAPSE<15 mm)	35 (8%)	28 (7%)	7 (14%)	0.122

Table 1: Continued.

	All patients (n=465)	Event free (n=415)	With events (n=50)	P Value∗
CARDIAC MAGNETIC RESONANCE				
CMR LVEF (%)	54 ± 15	56 ± 14	43 ± 18	<0.001
CMR LV mass (g)	153 ± 40	151 ± 37	174 ± 55	0.006
CMR LVEDV (ml/m^2)	70 ± 46	69 ± 47	85 ± 37	0.014
CMR LGE (% of LV mass)	11 ± 13	10 ± 12	19 ± 18	<0.001
CMR myocardial stress induced perfusion abnormality	82 (18%)	73 (18%)	9 (18%)	0.943

CAD = coronary artery disease; CV = cardiovascular; LM = left main; NYHA = New York heart association; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; QTc = corrected QT; LBBB = left bundle branch block; RBBB = right bundle branch block; LVEDV = left ventricle end diastolic volume, LVESV = left ventricle end systolic volume; LVEF = left ventricle ejection fraction; LVWMSI = left ventricle wall motion score index; TAPSE = tricuspid annular plane systolic excursion; RVIT = right ventricle inflow tract; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement.
∗Pearson χ^2 or Fisher's exact test for categorical data; Student's *t*-test or Mann–Whitney for continuous data.

procedure after the study enrollment was a protecting factor from mortality. Univariate hazard ratios are shown in Table 2.

Stepwise inclusion of variables reaching the predefined univariate significance value threshold (p<0.1) into a multivariate Cox model in which LVEF was included at the first step significantly improved the model predictability (extra sum of square χ^2 97 versus 69, F-test: p<0.001) with respect to considering LVEF alone. However, only ACS in the follow-up (Hazard Ratio [95% C.I]: 9.1 [3.8–21.8]; p<0.001), LV mass (2.6 [1.1–5.9]; p<0.05), QTc interval (2.6 [1.3–5.1]; p<0.01), and heart rate (2.4 [1.2–4.8]; p<0.05) were independently associated with an adverse prognosis after entering LVEF (3.9 [1.8–8.3]; p<0.001).

3.1.2. Prediction of MACE. Univariate analyses identified many conventional variables associated with MACE. Indeed, all variables associated with all-cause mortality, except mitral regurgitation, pulmonary hypertension, and previous MI, predicted MACE as well. Moreover, LM/3-vessel CAD, atherosclerotic risk factors burden (≥3 risk factors), and nonsinus rhythm emerged as relevant predictors of MACE too. Univariate hazard ratios with 95% confidence intervals of all conventional variables are shown in Table 2.

Multivariate analysis confirmed the prognostic relevance of LVEF (3.0 [1.7–5.2]; p<0.001) and identified only LM/3–vessel CAD (2.0 [1.4–2.8]; p<0.001) and smoking (1.7 [1.1–2.5]; p<0.01) as independent predictors of MACE. The inclusion of all conventional variables significant at univariate analysis improved the model predictability compared to the LVEF alone (χ^2 46 versus 21, F-test: p<0.001).

3.2. Prognostic Role of CMR

3.2.1. All-Cause Mortality. CMR metrics of LV volume, ejection fraction, and mass as well as total burden of LGE were strongly associated with all-cause mortality (LVEDV 6.7 [3.1–14.4]; LVEF 5.4 [3.0–9.6]; LV mass 3.5 [1.4–8.7]; LGE 7.6 [3.0–19.2]). However, an abnormal SPCMR result was not a predictor of death (1.1 [0.5–2.2]). Hazard ratios of CMR univariate analysis versus all-cause mortality are presented in Table 2.

Multivariate analysis, which introduced CMR at the last step, showed that CMR variables retain a prognostic value once LVEF at echocardiography and all other significant conventional variables have been taken into account. Indeed, CMR assessment slightly improved the model fit (χ^2 100 versus 95, F-test p<0.05) with respect to conventional variables alone. The presence of large amount of LGE, namely, replacement of more than 40 percent LV myocardium (equal to the 95th percentile of the entire population), was the sole independent prognostic indicator among CMR metrics (3.4 [1.3–8.8]; p<0.05). Independent prognostic factors were also a reduced LVEF at echocardiography (4.2 [2.0–9.0]; p<0.001), the occurrence of an ACS in the follow-up (6.7 [2.9–15.8]; p<0.001), and an increased LV mass (2.9 [1.3–6.6]; p<0.01). Hazard ratios of the final multivariate model versus all-cause mortality are summarized in Table 3(a).

3.2.2. Major Adverse Cardiovascular Events. CMR parameters were strongly associated with MACE in terms of LV dimensions (LVEDV 3.0 [1.6–5.8]), LV function (LVEF 2.6 [1.7–4.0]), fibrosis (LGE 5.1 [2.7–9.4]), and stress-induced perfusion abnormalities (2.3 [1.6–3.5]). Hazard ratios of CMR univariate analysis versus MACE are presented in Table 2.

After correction for the effect of conventional variables, introduction of CMR variables into the multivariate analysis significantly improved the model fit (χ^2 83 versus 62, F-test p<0.001). Furthermore, LGE and stress-induced perfusion abnormalities were the best predictors of the composite endpoint (3.3 [1.7–6.3] and 2.1 [1.4–3.2], respectively). The only others significant factors were LM/3-vessel CAD (1.9 [1.4–2.8]), LVEF (2.5 [1.4–4.4]), and smoking (1.5 [1.0–2.2]). Hazard ratios the final multivariate model versus MACE are shown in Table 3(b).

4. Discussion

Our study aimed at assessing prognostic power of CMR in a contemporary population with stable CAD and optimal medical treatment, in which CMR was used on top of standard conventional risk assessment. Main findings of the study were as follows: (1) new evidence in the long term of

Table 2: Univariate Cox analysis of conventional assessment and CMR metrics for all-cause mortality and MACE.

	All-Cause Mortality		MACE	
	Hazard Ratio (95%CI)	*P* Value	Hazard Ratio (95%CI)	*P* Value
ANTHROPOMETRIC				
Age (≥75 years)	2.6 (1.4–4.9)	0.003	1.6 (1.0–2.4)	0.036
Male sex	1.1 (0.8–1.5)	0.577	1.0 (0.8–1.2)	0.674
Body mass index (>30)	1.5 (0.8–3.0)	0.244	1.1 (0.7–1.8)	0.668
RISK FACTORS				
Family history of CAD	0.8 (0.4–1.4)	0.391	0.9 (0.6–1.3)	0.609
Smoking (previous or active)	2.2 (1.2–3.5)	0.017	1.7 (1.2–2.3)	0.005
Diabetes	1.4 (1.2–4.2)	0.206	1.5 (1.0–2.1)	0.056
Hypertension	0.8 (0.5–1.4)	0.488	1.1 (0.8–1.6)	0.448
Hypercholesterolemia	1.1 (0.6–2.2)	0.714	1.2 (0.9–1.8)	0.258
No. of CV risk factors (≥3)	1.5 (0.8–2.6)	0.168	1.6 (1.1–2.2)	0.013
CLINIC				
Previous CAD diagnosis	4,2 (1.0–17.3)	0.046	2.4 (1.3–4.6)	0.007
Previous myocardial infarction	2.7 (1.3–5.6)	0.006	1.2 (0.8–1.7)	0.392
LM or 3-vessel CAD	1.5 (0.8–2.6)	0.166	2.3 (1.6–3.2)	<0.001
NYHA classification (≥III)	3.3 (1.2–9.2)	0.022	2.5 (1.2–5.4)	0.018
Revascularization in the follow-up	0.4 (0.2–0.9)	0.037	-	
ACS in the follow-up	4.9 (2.2–10.8)	<0.001	-	
THERAPY				
β-blockers	1.2 (0.6–2.3)	0.536	1.0 (0.7–1.5)	0.941
Ca^{++-}antagonist	1.2 (0.6–2.3)	0.536	1.1 (0.7–1.7)	0.556
Nitrates	1.3 (0.7–2.2)	0.380	1.1 (0.8–1.6)	0.473
Loop diuretics	2.2 (1.3–3.9)	0.005	1.5 (1.1–2.2)	0.021
Aldosterone antagonist	2.4 (1.2–4.8)	0.013	1.4 (0.9–2.3)	0.158
ACE-inhibitors/ARB	0.9 (0.5–1.8)	0.841	1.3 (0.8–2.0)	0.297
ASA	1.7 (0.7–4.3)	0.262	1.3 (0.8–2.2)	0.253
Statins	1.0 (0.5–2.0)	0.943	1.0 (0.6–1.4)	0.831
Anticoagulant	2.3 (1.0–5.5)	0.053	1.9 (1.1–4.4)	0.027
ECG				
Heart rate (>75 bpm)	2.3 (1.2–4.3)	0.011	1.7 (1.1–2.6)	0.018
Non sinus rhythm	2.8 (0.9–9.1)	0.082	2.2 (1.0–4.8)	0.038
QRS duration (>120 msec)	3.4 (1.9–6.3)	<0.001	2.1 (1.4–3.3)	<0.001
QTc interval (≥460 msec)	3.3 (1.8–6.2)	<0.001	1.6 (1.0–2.6)	0.035
LV hypertrophy	1.4 (0.7–2.8)	0.380	1.2 (0.7–1.9)	0.483
LBBB	2.3 (1.2–4.4)	0.013	1.7 (1.0–2.7)	0.032
RBBB	1.4 (0.6–2.9)	0.431	1.4 (0.9–2.2)	0.161
ST segment depression	1.4 (0.5–3.8)	0.537	1.7 (0.9–3.2)	0.089
Negative T waves	1.9 (1.1–3.4)	0.028	1.4 (1.0–1.8)	0.048
Q waves	1.1 (0.6–1.9)	0.774	1.3 (1.0–2.0)	0.101
ECHOCARDIOGRAPHY				
LVEDV (≥105 ml/m^2)§	3.6 (1.7–7.7)	0.001	1.4 (0.7–2.7)	0.370
LVESV (≥75 ml/m^2)§	9.4 (4.4–20.2)	<0.001	2.4 (1.2–4.9)	0.016
LVEF (≤30%)	8.0 (4.0–16.0)	<0.001	3.2 (1.9–5.5)	<0.001
LVWMSI (≥2.32)§	5.5 (2.2–13.9)	<0.001	3.3 (1.7–6.5)	0.001
LV mass (≥310 g)§	4.4 (2.0–9.4)	<0.001	2.0 (1.1–3.6)	0.025
LV diastolic dysfunction (≥pseudo-normal)†	2.3 (1.1–4.8)	0.035	1.8 (1.1–3.0)	0.025
Mitral regurgitation (≥moderate)‡	2.5 (1.3–4.7)	0.005	1.5 (0.9–2.3)	0.098
Pulmonary hypertension (sPAP>35 mmHg)	2.3 (1.0–5.1)	0.040	1.7 (1.0–2.8)	0.065
RVIT dilatation (>40 mm)	1.0 (0.3–3.2)	0.989	1.1 (0.5 – 2.2)	0.892
RV dysfunction (TAPSE<15 mm)	2.2 (1.0–4.9)	0.053	1.1 (0.6–2.1)	0.706

Table 2: Continued.

	All-Cause Mortality		MACE	
	Hazard Ratio (95%CI)	*P* Value	Hazard Ratio (95%CI)	*P* Value
CMR				
CMR LVEDV (≥122 ml/m^2)§	6.7 (3.1–14.4)	<0.001	3.0 (1.6–5.8)	0.001
CMR LVEF (<35%)	5.4 (3.0–9.6)	<0.001	2.6 (1.7–4.0)	<0.001
CMR LV mass (≥236 g)§	3.5 (1.4–8.7)	0.008	1.4 (0.6–3.5)	0.443
CMR LGE (>40%)§	7.6 (3.0–19.2)	<0.001	5.1 (2.7–9.4)	<0.001
CMR myocardial stress induced perfusion abnormality	1.1 (0.5–2.2)	0.881	2.3 (1.6 – 3.5)	<0.001

CMR = cardiovascular magnetic resonance; MACE = major adverse cardiac events; CAD = coronary artery disease; CV = cardiovascular; LM= left main; NYHA =New York heart association; ACS = acute coronary syndrome; ACE =angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASA =acetylsalicylic acid; LBBB = left bundle branch block; RBBB = right bundle branch block; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; LVEF = left ventricular ejection fraction; LVWMSI = left ventricular wall motion score index; LV = left ventricle/ventricular; sPAP = systolic pulmonary artery pressure; RVIT = right ventricular inflow tract; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; LGE = late gadolinium enhancement.
† based on trans-mitral diastolic flow and pulmonary vein flow evaluation.
‡ based on effective regurgitant orifice area.
§ cut-off equal to the 95% percentile of the entire population.

Table 3

(a) Final model of Cox multivariate analysis for all-cause mortality

	Hazard Ratio	95% CI	*P* value
ACS in the follow-up	6.7	2.9–15.8	<0.001
LVEF on echocardiography (≤30%)	4.2	2.0–9.0	<0.001
QTc interval (≥460 msec)	2.8	1.5–5.4	0.002
LV mass (≥220 g)	2.9	1.3–6.6	0.009
TotalLGE burden (≥ 40% LV mass)	3.4	1.3–8.8	0.012
Heart rate (>75 bpm)	2.0	1.0–3.8	0.041

(b) Final model of Cox multivariate analysis for MACE

	Hazard Ratio	95% CI	*P* value
Total LGE burden (>40% LV mass)	3.3	1.7–6.3	<0.001
CMR myocardial stress induced perfusion abnormality	2.1	1.4–3.2	<0.001
LM or 3–vessel CAD	1.9	1.4–2.8	<0.001
LVEF on echocardiography (≤30%)	2.5	1.4–4.4	0.002
Smoking	1.5	1.0–2.2	0.038

ACS = acute coronary syndrome; LV = left ventricle; LVEF = left ventricle ejection fraction; QTc = corrected QT interval; LGE = late gadolinium enhancement; CMR = cardiovascular magnetic resonance; MACE = major adverse cardiac events; LM = left main coronary artery; CAD = coronary artery disease.

prognostic relevance of LGE as an independent predictor of all-cause mortality; (2) lack of independent prognostic value of SPCMR versus all-cause mortality; (3) confirmation of independent prognostic value of a comprehensive CMR exam, including stress perfusion assessment, for the prediction of a composite endpoint of morbidity and mortality.

At the time of enrollment closure the study had 465 patients that were followed up for a median time of 5.2 years. We primarily investigated the hard endpoint of all-cause mortality. Fifty deaths were observed in the follow-up period, corresponding to a global mortality rate of 10.8% and an annualized event rate of 2.1%. For comparison, all-cause mortality in clinical trials assessing different treatment strategies in stable CAD was in the range 1.3-2.7% [4–8].

4.1. Prediction of All-Cause Mortality: LGE. Quantification of fibrosis with LGE was confirmed to be independently associated with mortality. Replacement of large amount of myocardium with scar, namely, of more than 40 percent of LV mass, carried a mean 3.4-fold increase of risk of death after correction for all other factors, in particular LVEF. Given the length of the follow-up of our study, this finding is a confirmation in the long term of what has emerged in recent years from a series of studies showing a negative prognostic significance of myocardium replacement by fibrotic scar, beyond its effect on contractility [11–13].

4.2. Prediction of All-Cause Mortality: Stress-Induced Ischemia. Exploring predictors of all-cause mortality,

we unexpectedly found that stress-induced perfusion abnormalities at CMR are not independently correlated with prognosis. This finding was quite unpredicted if we consider (1) the good sensitivity and specificity shown by SPCMR for ischemia detection, also in comparison with established imaging techniques like single photon emission tomography [10]; (2) the results of a recent publication demonstrating the utility of SPCMR to reclassify patient risk beyond standard clinical variables (in particular those at moderate/high pretest risk) [14]; (3) numerous publications, summarized in recent meta-analyses [9, 15], showing a significant prognostic value of SPCMR.

In accordance with the literature, patients with a normal SPCMR study have a 1-year mortality of less than 1%, a level of risk significantly inferior to that of patients with positive stress testing. Consequently, the reason why stress perfusion data miss their prognostic significance when SPCMR is used on top of a conventional risk stratification process, as the present study seems to suggest, is not easily understandable. In detail, we found that a significant myocardial ischemia (involving>10% of LV, in accordance with recent guidelines) is not useful to predict mortality once all other well-known significant variables from the clinical history, electrocardiogram, and echocardiography, in particular LVEF, have been considered.

Over the last few decades, significant changes occurred in medical therapy of patients with CAD and atherosclerosis in general, due to the marketing of new drugs like statins, ACE-inhibitors/ARB or thienopyridine, and the wider use of old but efficacious drugs like aspirin. Consistent results of large randomized clinical trials showing reduction of hard events [16–18] have made the use of these drugs mandatory in patients with signs of atherosclerosis. This evidence together with factors like public health policies that reduce smoking has been advocated to explain changes recently observed in atherosclerosis biology and epidemiology: (i) significant decline over time of large atheromas and increase of plaques with more fibrous, noninflammatory characteristics in biobanked carotid plaques [19], (ii) shift in the presentation pattern of ACS with declining of ST segment elevation and rising non-ST segment elevation myocardial infarction incidence [20], and (iii) accumulating evidences that coronary artery bypass grafting and percutaneous coronary intervention may reduce composite endpoints but lack convincing data of an effect on global mortality in stable CAD [4–8], warranting new large international research studies like the ISCHEMIA study [21].

An optimized pharmacologic treatment is methodologically important to minimize the confounding effect of a suboptimal treatment. This goal was achieved in the population we studied thanks to a general policy of guidelines implementation adopted by our department. Compared to the aforementioned clinical trials, the population we investigated had similar levels of treatment with statins (76% versus 73-95%), ASA (85% versus 80-96%), and ACE-inhibitors/ARB (79% versus 30-92%).

Bearing in mind these considerations, the lack of independent prognostic relevance of stress-induced perfusion abnormalities versus mortality, shown by the present study, is not totally surprising. Indeed, optimal medical treatment of the cohort we studied might have hampered the prognostic impact of myocardial perfusion abnormalities, for example, by modifying atherosclerotic plaques stability. Conversely, lower levels of adherence to medical treatment in the study by Shah et al. (statins 50%, ASA 52% and ACE-inhibitors/ARB 44%) might have emphasized the relevance of stress-induced perfusion abnormalities, driving different conclusions about independent prognostic value of SPCMR. Moreover, differences in baseline characteristics between our study and previous studies, for example, higher prevalence of patients with known CAD or MI (86% and 64% in our cohort, respectively), might have influenced predictive value of ischemia versus mortality.

In the present study an indirect confirmation of the low relevance of inducible ischemia in predicting mortality may be considered the lack of independent prognostic value of incident revascularization procedures (49% of patients with positive SPCMR and 24% of the entire cohort underwent revascularization during the follow-up) despite a protective effect emerged at univariate tests. Moreover, none of ischemia related factors we examined, namely, CAD extension, presence of ST segment depression at electrocardiogram, and overall burden of atherosclerotic risk factors, emerged as relevant variables.

4.3. Prediction of MACE. The prognostic impact of CMR on a composite endpoint of mortality and relevant morbidities, such as hospitalization for new onset heart failure or ACS and myocardial revascularization procedures unrelated to CMR exam, was confirmed in the present study. CMR introduction into multivariate analysis significantly improved the model fit ($p<0.001$). Notably, in the final model, LGE and stress-induced perfusion abnormalities were the best predictors of MACE, performing better than LVEF. Large scar at LGE and significant perfusion abnormalities on SPCMR carried a mean 3.3- and 2.1-fold increase of risk of MACE after the correction for all other significant variables. These data confirm the results of previous studies showing that SPCMR is a powerful tool to predict future cardiovascular events [14, 22, 23]. Moreover, they highlight that CMR prognostic value is additional to a careful conventional assessment. Mortality-free and MACE-free survival curves of SPCMR and LGE adjusted for all other significant variables are depicted in Figure 3.

4.4. Limitations of the Study. We intentionally defined relatively loose, "real-world", entry criteria to enroll a population as representative as possible of referral of a standard outpatient CAD cardiology clinic, bearing in mind that the results of the randomized clinical trials are often difficult to translate into clinical practice due to the stringency of their enrollment criteria. However, loose selection criteria might have hampered the prognostic value of stress-induced ischemia at CMR in specific subsets of patients with stable CAD.

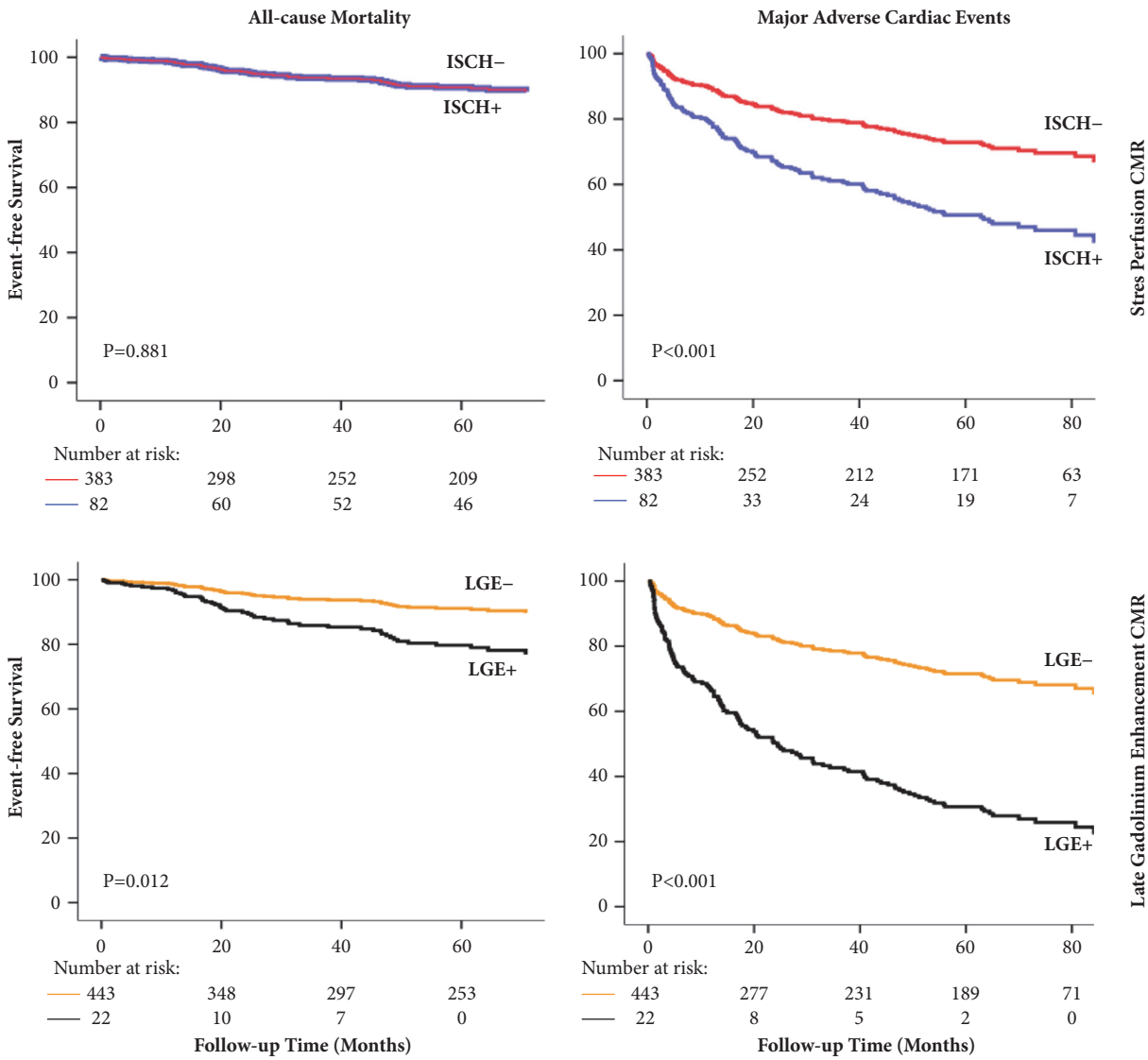

FIGURE 3: *Independent prognostic value of stress perfusion defects and late gadolinium enhancement at CMR*. Cox proportional model all-cause mortality-free (left panels) and MACE-free (right panels) survival curves, adjusted for all other significant variables. They show that the presence of ischemia in more than 10% of LV mass (ISCH+) is not independently associated with all-cause mortality whereas it predicts the occurrence of MACE (upper panels). Conversely, the presence of scar in more than 40% of LV mass (LGE+) is independently associated with both all-cause mortality and MACE (lower panel). Follow-up period is truncated to 100 months. P value is derived with the log-rank test. MACE = major adverse cardiac event; CMR = cardiovascular magnetic resonance.

This is a single centre observational study that needs to be confirmed by a randomized multicentre study before drawing definitive conclusions about SPCMR role as a stratifying tool in contemporary population with stable CAD.

Female sex was underrepresented in the study population. Accordingly, some caution must be kept in the inference of the results of the study to female patients.

Patients were enrolled in the study for a relatively long period of time. Although the study protocol, in particular CMR protocol, remained unchanged over time, this might be a source of bias.

5. Conclusions

Approaching contemporary populations with clinically stable CAD that already receives an optimal evidence based medical treatment: (i) myocardial viability investigation with LGE can be considered a useful tool to further stratify the risk of death in the long term beyond a careful standard clinical and echocardiography assessment; (ii) accurate investigation of myocardial ischemia through SPCMR evaluation does not seem to independently predict mortality; (iii) a comprehensive CMR assessment, including a SPCMR, may be a useful facility to predict morbidity as well as mortality and thus to

select subgroups of patients at high risk and high absorption of economical and medical resources.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declared no conflicts of interest.

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