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REVIEW

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Debates over NICE Guideline Update: What Are the Roles of Nuclear Cardiology in the Initial Evaluation of Stable Chest Pain?

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Abstract

Recent clinical trials have demonstrated the values of cardiac computed tomography (CT) in the initial evaluation of stable chest pain which led to drastic changes in the National Institute for Health and Care Excellence (NICE) guidelines in 2016. According to the updated NICE guidelines, cardiac CT should be performed as the initial cardiac testing in stable chest pain regardless of pre-test probability (PTP) of coronary artery disease (CAD). As a result, cardiac CT is now considered as a validated gatekeeper for assessing stable chest pain, which precedes all the functional studies including nuclear myocardial perfusion imaging (MPI). Nuclear MPI, in contrast, has been assigned as one of the second-line studies, which is inevitably dependent on the results of cardiac CT. However, nuclear MPI has genuine values in the diagnosis, treatment decision, and prognostic stratification of stable chest pain, which cannot be replaced by cardiac CT. In this review, the updated NICE guidelines and related cardiac CT trials will be critically reviewed from the view of nuclear physicians and the exceptional values of nuclear MPI will be described along with the future perspectives.

Keywords Stable chest pain · Cardiac computed tomography · Nuclear myocardial perfusion imaging

Introduction

A huge, revolutionary change has been made for the National Institute for Health and Care Excellence (NICE) guidelines of the UK in 2016 [1], regarding the initial approaches to patients with stable chest pain. Its previous version [2] recommended calculation of pre-test probability (PTP) of coronary artery disease (CAD), and downstream studies were to be assigned in accordance with the PTP. Similarly, the multimodality appropriate use criteria published and endorsed by cardiology-related societies of the USA [3] also suggested PTP calculation prior to assigning the most appropriate imaging modality. However, the modified NICE guidelines 2016 [1] discarded the calculation of PTP and suggested cardiac computed tomography (CT) as the first-line diagnostic study. Nuclear myocardial perfusion imaging (MPI) is now one of the second-line studies, which are to be referred for depending on the results of cardiac CT.

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Such a drastic change was based on the notable superiority of cardiac CT demonstrated in the recent clinical trials: representatively, EValuation of INtegrated Cardiac Imaging in Ischemic Heart Disease (EVINCI) [4], Scottish COmputed Tomography of the HEART (SCOT-HEART) [5], PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) [6], and Prospective LongitudinAl Trial of FFRct: Outcome and Resource IMpacts (PLATFORM) [7]. Those trials have shown increased accuracy, diagnostic certainty, and less unnecessary invasive coronary angiography (ICA) for cardiac CT in comparison with functional studies. Long-term follow-up data [8] also showed a significantly better prognosis for cardiac CT. Some investigators even suggest complete cardiac CT-based approaches to patients with stable chest pain [9]. Its merits not only are not limited to a high negative predictive value for excluding CAD but also include abilities to rule out obstructive lesion and detect non-obstructive but high-risk plaques and hemodynamic assessment of anatomical stenosis using fractional flow reserve measured by cardiac CT (FFRct). It seems that cardiac CT is a rising game changer and the roles of nuclear MPI, along with the other "functional" studies, may become less appreciated in the clinical arena.

Debates are, however, actively going on over the changes in the NICE guidelines [10–12]. Is it appropriate to discard

nuclear MPI in the initial evaluation of patients with stable chest pain? Can coronary anatomical and physiological data derived from cardiac CT be perfect substitutes for functional studies? Despite the innovative changes in the NICE guidelines 2016 and promising results from the related clinical trials, there remain many points to be argued, indicating genuine, non-replaceable strengths of nuclear MPI. In this review, the most notable changes and debates in the NICE guidelines 2016 and perspectives from nuclear physicians' viewpoint will be discussed.

Major Changes in NICE Guidelines 2016

There are two most notable changes in the updated NICE guidelines. First, the calculation of PTP is no longer recommended for the initial evaluation of patients with stable chest pain. The semiology of chest pain—typical, atypical, or non-anginal chest pain—is still included in the initial evaluation of patients, which is based on three factors: (1) location of chest pain (central chest), (2) provocation by exertion or emotional stress, and (3) relief by rest or nitrates. Typical angina requires the presence of all the 3 factors, while atypical angina requires 2, and the symptom is considered non-anginal when 0 or only 1 factor is present. Second, cardiac CT should be performed as the first-line diagnostic study. Cardiac CT is recommended for those having typical or atypical angina, and those with non-anginal chest pain but electrocardiogram (ECG) are consistent with coronary artery disease (CAD). Otherwise, *no cardiac testing is indicated*. Now nuclear MPI has no initiatives in the NICE guidelines 2016 and is only indicated when cardiac CT findings are nondiagnostic or uncertain [13].

The decision to discard PTP calculation was based on the judgment that PTP was not reliable and diagnostic testing did not depend on its estimates [13]. The traditional PTP calculation formulas have generally based on the patients undergoing ICA [14–18]. Therefore, following traditional PTP calculation would inevitably lead to significant overdiagnosis and consequent unnecessary ICA in many low-risk patients. At the same time, the under-recognition of patients with high risk was also problematic. A previous report described that about one-third of patients are misdiagnosed as non-anginal chest pain [13]. Cardiac CT fulfilled the needs of the NICE guidelines committee for reducing both over- and misdiagnosis of CAD in the clinical presentation of stable chest pain. It has an outstanding negative predictive value preventing patients without obstructive CAD from being referred for ICA. Also, FFRct enhances its diagnostic specificity and prognostic relevance [12, 19]. Some even suggest that the combination of cardiac CT and its derivative FFRct can substitute functional studies in the diagnostic workup and follow-up management of stable chest pain [9]. Eventually, further approval on FFRct was made by the NICE guideline, expecting that the use of FFRct would lead to cost savings of £214 per patient. Accordingly, FFRct should be considered as an option for patients with stable chest pain of recent onset, who are offered cardiac CT for the management [20].

Critical Reviews on Cardiac CT Trials Related to NICE Guideline Update

Despite all the promising aspects of cardiac CT mentioned above, it should be questioned whether the recent cardiac CT trials have clearly proved the superiority of cardiac CT to functional studies including nuclear MPI. From the nuclear physicians' point of view, it is still unclear if cardiac CT would actually bring better clinical management and future cardiovascular outcomes to patients with stable chest pain.

Functional Studies as the Opponent to Cardiac CT in the Recent Trials

The recent cardiac CT trials and their follow-up data [4–8, 21] have a common scheme of two opposite study arms, cardiac CT vs. functional studies. The functional studies consisted of several imaging modalities (e.g., stress echocardiography, magnetic resonance, and nuclear MPI), along with exercise ECG. As a result, those trials raise concerns regarding the heterogeneity of the diagnostic accuracy of each modality for detecting obstructive CAD. In particular, exercise ECG has suboptimal diagnostic performances in comparison with other functional studies [12, 22, 23], sensitivity and specificity of which range only 40–70%. Therefore, the proportions of exercise ECG must have critically affected the selection of downstream testing and eventually the prognosis of the study population. Notably, the proportion of exercise ECG is 85% in the SCOT-HEART trial [5, 8] and the primary functional test was exercise ECG in the Comprehensive Cardiac CT Versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) trial [24] (Table 1). They were the only trials that showed significantly better cardiovascular outcome for cardiac CT than functional studies. The other trials (the proportion of exercise ECG 10–30%) have failed to prove better prognosis for cardiac CT as compared to functional studies. It is assumable that the major cause of the worse prognosis for functional studies in the SCOT-HEART and CRESCENT trials might have resulted from the suboptimal diagnostic performances of exercise ECG. To be accurate, therefore, cardiac CT would be associated with better prognosis than would exercise ECG, but it does not guarantee the same result applies between cardiac CT and the other functional *imaging* studies.

Table 1 Comparison of recent major cardiac CT trials

Trials	Number of patients	Pretest probability of significant CAD*	Composition of functional studies**	Study endpoints	Revascularization rate	Incident primary cardiac event	Main results
EVINCI [4]	Cardiac CT 475 + at least one functional studies	65% (33–75%)	SE 261 (36%) Nuclear MPI 389 (53%) Stress CMR 85 (12%)	Diagnostic accuracy for obstructive CAD	Cardiac CT 54%† Nuclear MPI 37%† SE 48%† Stress CMR 56%†	N/A	Superior diagnostic accuracy for cardiac CT
SCOT-HEART [5, 8]	Cardiac CT 2073 Functional studies 2073	N/A	ExECG 1753 (85%) Nuclear MPI 213 (10%) Others 14 (1%)	1′: diagnostic certainty/frequency 2′: cardiac events	Cardiac CT 11.2% Functional studies 9.7% $p = 0.0611$	129(3.1%) at 4.8 years	Increased diagnostic certainty and better prognosis for cardiac CT at 5-year follow-up
PROMISE [6]	Cardiac CT 4996 Functional studies 5007	53.3%	ExECG 491 (10%) SE 1083 (22%) Nuclear MPI 3263 (68%)	Cardiac events	Cardiac CT 6.2% Functional studies 3.2% $p < 0.001$	312 (3.1%) at 2 years	No prognostic difference
PLATFORM [7, 21]	FFRct 297 Functional studies 287	49 ± 17%	ExECG 28 (30%) SE 34 (36%) Nuclear MPI 23 (24%) Stress CMR 9 (10%)	1′/2′: negative ICA Major safety endpoints: cardiac events, radiation exposure	FFRct 28% Functional studies 32% p = NS	5 (0.9%) at 1 year	Less negative ICA by FFRct No prognostic difference
CRESCENT [24]	Cardiac CT 239 Functional studies 108 (2:1 randomization)	45 ± 29%	ExECG as primary test Other testing if ExECG not available or abnormal	1′: absence of chest pain at 1 year 2′: diagnostic yield, time to diagnosis, diagnostic costs, cardiac events, radiation exposure	Cardiac CT 8.8% Functional studies 6.5% p = NS	19 (5.5%) at 1.2 years	Better symptom relief, sooner diagnosis, lower costs, less radiation exposure for cardiac CT Better prognosis for cardiac CT

CAD coronary artery disease, *ExECG* exercise electrocardiogram, *SE* stress echocardiography, *MPI* myocardial perfusion imaging, *CMR* cardiac magnetic resonance, *N/A* not available, *NS* not significant

*Data are mean, mean ± SD, or median followed by range in parenthesis

**The numbers in the parenthesis indicate proportions among the functional studies

† Proportions among positive study results are presented. No data are available for the revascularization rate for each modality as a whole in the EVINCI trial

Data Interpretation

As shown in Table 1, the revascularization rate tended to be higher for cardiac CT with or without statistical significance. It is rather striking when looking into the data from the PROMISE trial [6], where cardiac CT led to revascularizations in twice as many patients with functional studies (6.2% vs. 3.1% for cardiac CT and functional studies, respectively; this correlates to 155 more patients revascularized) without prognostic gain. Those results implicate that cardiac CT may not be able to classify patients with stable chest pain who will actually benefit from revascularization. Although several advantages of cardiac CT (e.g., diagnostic certainty, radiation exposure, cost-effectiveness) have been described, those trials are insufficient to establish cardiac CT in the first-line diagnostic study.

Moreover, the risk reduction by preventive medication is also in question. Additional commencement of preventive medication was observed in 402 vs. 305 patients in cardiac CT and standard care arms, respectively, in the SCOT-HEART trial [8]. As previously criticized [25], it is unlikely that additional detection of non-obstructive plaque in only 97 cases led to such dramatic differences in cardiovascular outcomes (41% risk reduction by cardiac CT). They might have resulted from selecting exercise ECG as the first diagnostic approach in a majority of patients for the opposite arm and inappropriate downstream testing in the group of functional studies, as pointed above.

Lack of Subgroup Analysis

The cardiac CT trials mentioned above have not differentially addressed the value of cardiac CT according to the PTP of the study participants. Hence, it is not appropriate to consider the data from those trials as that obtained from a homogeneous group of patients with similar characteristics. Although the average PTP lies within intermediate range (Table 1), the actual event rates vary from < 1% in PLATFORM [21] up to 8% in CRESCENT [24] at the same follow-up interval of 1 year. Therefore, it is questionable whether cardiac CT would bring better cardiovascular outcomes to every patient with different PTP, global CAD risk, and even more various clinical situations (e.g., variability in medical costs, doctors' expertise, study availability).

Can Cardiac CT Substitute Nuclear MPI?

The value of cardiac CT seems to be most prominent as a gatekeeper for preventing ICA with no obstructive CAD [26]. Based on its high negative predictive value for detecting coronary plaques (including non-obstructive plaques), cardiac CT can be an excellent choice when negative ICA is a major concern (e.g., low PTP). However, when CAD is highly probable, the initial diagnostic study should contribute not only to the diagnosis of CAD but also to the decision of treatment strategy at the same time.

Unfortunately, the image quality of cardiac CT is highly compromised in the presence of heavy calcification, which is associated with a higher prevalence of significant coronary stenosis [27] and higher global CAD risk [28, 29]. Studies have shown decreasing diagnostic accuracy (especially specificity) of cardiac CT with heavier calcification [30–32]. Can FFRct overcome the effects from coronary calcification? FFRct was initially introduced to add functional information to the anatomical assessment of coronary stenosis on cardiac CT [33]. Still, it should be noted that FFRct is not actually *measured* but *calculated* from coronary anatomy. Its derivation is based on numerous physical assumptions and virtual calculation of hemodynamics across the coronary trees. So, a high-resolution, patient-specific anatomic modeling is essential for FFRct calculation. Patient motion during image acquisition and heavy coronary calcification can significantly decrease the image quality of cardiac CT. The actual data in the recent studies show that FFRct was not available in ~ 12% of patients, mainly due to patient motion and vascular calcification [9, 21, 34]. Although a statistical significance was not reached, there was a stepwise decreasing pattern of area under the curve of FFRct for predicting FFR-positive stenosis as coronary calcification increased [35]. Even more, as FFRct is derived from coronary anatomy, microvascular resistance is purely assumed to be related to epicardial coronary diameter [36]. However, epicardial CAD and microvascular dysfunction can independently develop and there can be myocardial ischemia without epicardial CAD. It is referred as to "microvascular angina" and is gaining more clinical relevance in patients with stable chest pain [37–40]. Moreover, the volume-to-mass ratio, which is critical for calculating FFRct, is significantly lower in patients with acute ST segment elevation myocardial infarction [41]. So, the basic assumption for calculating FFRct cannot be identically applied to patients with prior myocardial infarction. Another important issue is the heteroscedasticity of FFRct against invasively measured FFR. A recent meta-analysis [42] showed that the scatter between FFRct and FFR was significantly greater for values below 0.8. Moreover, the diagnostic accuracy of FFRct for predicting FFR-positive lesions was only 46.1% in the interval of FFRct 0.7–0.8, which is critical for the decision of revascularization. Lastly, FFR is not the whole picture of CAD, not only for noninvasively measured FFRct, but also for invasively measured FFR. In patients whose revascularization had been deferred, low coronary flow reserve (CFR) values were associated with strikingly high cardiac event rate within the first year, despite preserved FFR (> 0.75). Such a trend sustained up to 10 years, showing higher cardiac event rate

than those with low FFR but preserved CFR [43]. Therefore, using merely FFRct for treatment decision (e.g., to revascularize or not) may be misleading in predicting a patient's prognosis.

Regarding all these aspects together, it is not appropriate to conclude that cardiac CT can be a perfect substitute for functional imaging, including nuclear MPI.

Non-replaceable Strengths of Nuclear MPI

Treatment Decision

The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) [44] and FAME 2 [45] trials showed prognostic benefits from ischemia-driven coronary revascularization, which was based on invasive FFR measurement. As a result, it is now generally accepted that a "significant" degree of myocardial ischemia is prerequisite for coronary revascularization in the setting of stable chest pain. Treatment decision based on nuclear MPI had already been established much earlier via a large-scale retrospective study [46]. Accordingly, cardiac death rate for medical treatment began to exceed that for revascularization in patients with 11%–20% of total myocardium ischemic (4.8% vs. 3.3% for medical treatment and revascularization, respectively), and the difference reached a statistical significance in those with > 20% of total myocardium ischemic (6.7% vs. 2.0%). By the virtue of this result, the decision of revascularization based on nuclear MPI is quite straightforward: the European Society of Cardiology suggests > 10% of ischemic left ventricular myocardium as the cutoff (Class I, Level of evidence B) for revascularization while the American College of Cardiology/American Heart Association suggests > 20% perfusion defect on stress nuclear MPI (Class IIa, Level of Evidence B) [47]. By performing nuclear MPI, the clinicians could be provided with information regarding not only the presence of significant obstructive CAD inducing myocardial ischemia but also the need for revascularization at the same time. It is especially helpful in the management of patients with intermediate-to-high PTP, for whom the CAD is more probable and treatment strategy should be instantly determined [48].

Assessment of Coronary Microvascular Dysfunction

The coronary microvasculature is the main determinant of total vascular resistance in normal subjects. It has a much wider net cross-sectional area as compared to that of the epicardial coronary arteries [49]. Hence, the changes in the caliber of the coronary microvasculature affect coronary resistance, which is critical for myocardial perfusion. Coronary microvascular dysfunction has been demonstrated in patients with various cardiovascular risk factors including hyperlipidemia [50], diabetes [51], obesity [52], and hypertension [53]. Microvascular angina—angina without evidence of epicardial obstructive CAD—tends to affect preferentially women and less responds to nitrates compared with angina due to epicardial CAD [54].

As the myocardial uptake of radiotracers is the final result of epicardial and microvascular conductance, nuclear MPI findings are affected by both the vascular systems. Myocardial perfusion PET can measure the global value of myocardial flow reserve (MFR), which can reflect the total burden of coronary microvascular dysfunction. Low MFR has been found to be associated with an increased cardiac event risk [55]. It was also predictive of cardiac events regardless of the presence of epicardial obstructive CAD [56–61].

The value of PET for evaluating coronary microvascular dysfunction is getting more relevant in the clinical fields. The Coronary Vasomotion Disorders International Study Group (COVADIS) suggested clinical criteria for suspecting microvascular angina [62], where nuclear MPI can serve as either objective evidence of myocardial ischemia (single photon emission computed tomography (SPECT) or PET) or evidence of impaired coronary microvascular function (PET-measured MFR). Therefore, nuclear MPI should be regarded as an essential tool for the evaluation of coronary microvascular dysfunction in patients with stable chest pain with risk factors, but without evidence of epicardial stenosis (Fig. 1).

Evaluating Effects from Collateral Circulation

Collateral circulation develops within days to weeks following acute coronary obstruction, with the aid of native collateral channels. They are enlarged by up to 12 times its original caliber to decrease vascular resistance and enhance blood flow to jeopardized myocardium. When the obstruction occurs slowly, the prevalence of collateral circulation reaches 95% [63]. Chronic total occlusion (CTO) of the coronary arteries indeed presents as stable chest pain in more than half of the cases [64]. The assessment of the extent of myocardial ischemia should be performed for patients with CTO, but collateral circulation and underlying complex hemodynamics beneath it cannot be fully understood by anatomical images only. There can be variable degrees of collateral channels feeding CTO artery, inducing substantial degrees of ischemia in its collateral donor. Unexpectedly, low FFR values of the donor arteries despite mild stenosis were described in patients with CTO, which was recovered by successful revascularization of CTO only [65, 66]. Therefore, the cause of chest pain can be due to

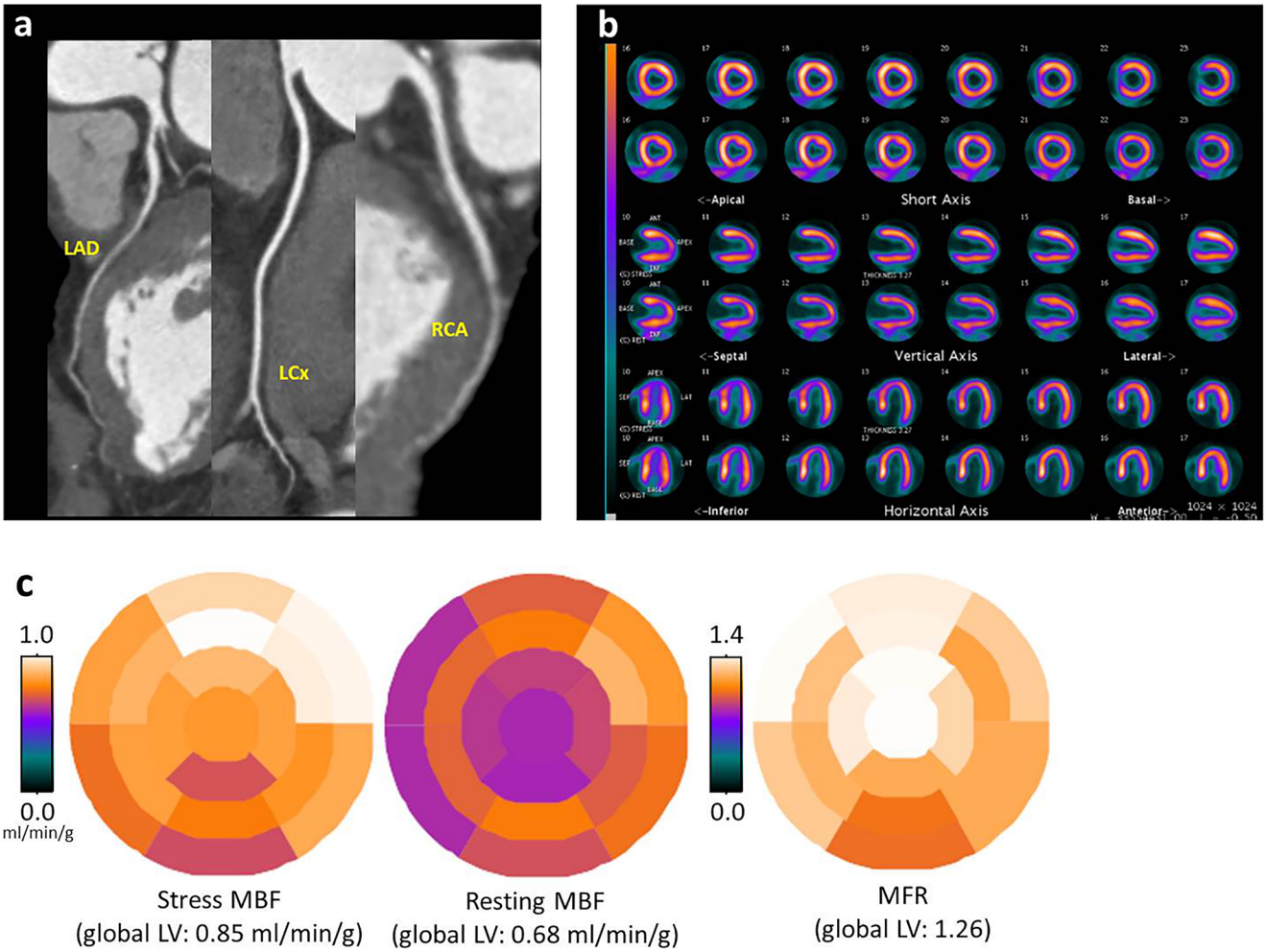

Fig. 1 A case of microvascular disease demonstrated by N-13 ammonia PET and absolute quantification of MBF and MFR. A 75-year-old female complained of stable chest pain, but cardiac CT scan did not reveal any notable stenosis or vascular calcification, except for a mild stenotic lesion in proximal LAD (**a**). N-13 ammonia PET was performed for further evaluation. On visual assessment, it did not show significant reversible or fixed perfusion defect (**b**). However, stress MBF and MFR were diffusely and homogeneously diminished throughout the left ventricle, indicating severe microvascular disease as the cause of the chest pain (**c**). PET positron emission tomography, MBF myocardial blood flow, MFR myocardial flow reserve, CT computed tomography, LAD left anterior descending artery, LCx left circumflex artery, RCA right coronary artery

ischemia of either CTO artery or its collateral donor. Nuclear MPI can evaluate myocardial perfusion of the collateral donor artery, as well as that beyond the CTO artery (Fig. 2). It was found that the alteration of hemodynamics across the collateral circulation before and after adenosine stress cannot be predicted and myocardial perfusion SPECT show variable patterns of perfusion defects in the donor territory. However, the severity of perfusion defects closely correlated with the amount of collateral circulation, as expressed by Rentrop's collateral grades [67]. Although it is still unclear whether treating ischemia of collateral donor arteries is associated with a better prognosis, the evaluation of myocardial perfusion beyond anatomical CAD is crucial for patients with CTO to evaluate the cause of chest pain as well as the volume and ischemic burden of jeopardized myocardium.

Prognostic Values

The association between ischemic burden on nuclear MPI and prognosis has been well established in stable chest pain, showing worse cardiovascular outcome for abnormal perfusion findings [68–70], which was consistently proved for the recently developed cadmium-zinc-telluride (CZT) cardiac dedicated SPECT camera [71]. In addition, normal nuclear MPI is associated with a $< 1\%$ annual cardiac death rate [71]. Normal findings on nuclear MPI warrant an event-free period of up to 60 months (5 years) in patients without cardiovascular risk factors. Moreover, it was found that 18 months of warranty period was derived for even those with decreased systolic function (left ventricular ejection fraction $< 50\%$) [72]. Notably, within those having normal perfusion on the visual or semiquantitative

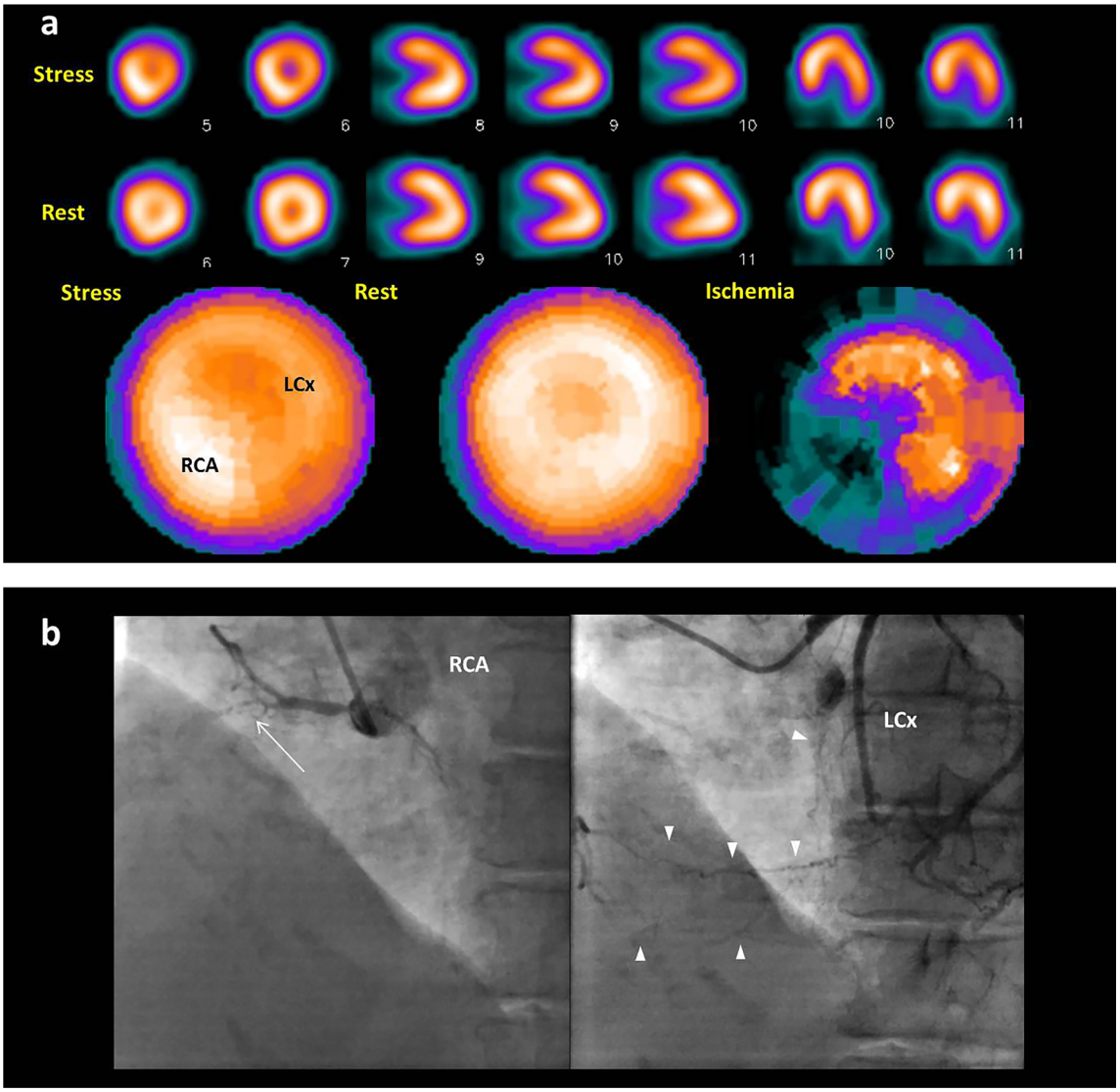

Fig. 2 Myocardial ischemia in collateral donor territory in a patient with CTO. Myocardial perfusion SPECT images (**a**) show a significant reversible perfusion defect in the LCx territory, where no stenosis was found, while the RCA territory has well-preserved perfusion without ischemia or infarction. On invasive coronary angiography (**b**), a CTO was found in the proximal RCA (arrow, left). There were collateral channels (Rentrop grade II) from LCx feeding RCA (arrowheads, right). Collateral circulation can induce myocardial ischemia in the donor artery's territory. CTO chronic total occlusion, SPECT single photon emission computed tomography, LCx left circumflex artery, RCA right coronary artery

assessment of nuclear MPI images, quantitative MFR could further stratify cardiovascular risk [73, 74].

MBF Quantification

The decision of revascularization may be difficult in the presence of multivessel disease or left main stenosis, where the relative assessment of perfusion defects frequently underestimates the severity of myocardial ischemia. In a previous study, only 10% of the patients with 3-vessel CAD showed perfusion defects [75]. Moreover, high-risk SPECT findings (> 10% of left ventricular myocardium ischemic) were present only in 56% of patients with left main stem CAD [76]. To overcome these limitations, absolute quantification of myocardial blood flow (MBF) can be performed using myocardial perfusion PET or CZT SPECT. The current guidelines on the use of MBF [77] recommend MBF and MFR quantification for excluding high-risk CAD (the advantage of MBF quantification will be discussed later in this review).

Several MBF parameters are available for diagnosing CAD: stress MBF, MFR, and relative flow reserve (RFR). They have different diagnostic characteristics, stress MBF being most sensitive, RFR most specific [78]. They in combination can derive additive information regarding the phenotypic

differences of CAD such as focal stenosis vs. diffuse atherosclerosis [79, 80]. A significant decrease in MFR may indicate the presence of diffuse atherosclerosis which would not be normalized by localized stent insertion but by complete revascularization such as bypass surgery [81]. Therefore, a combined assessment of various MBF parameters may enable comprehensive evaluation and treatment guidance for patients with stable chest pain.

Recent Technical Advances

The most notable recent technical advance in nuclear MPI is the introduction of the CZT cardiac dedicated SPECT camera. Two representative cameras are clinically available: D-SPECT (Spectrum Dynamics, Palo Alto, USA) and Discovery NM 530c or Discovery NM/CT 570c (GE Healthcare, Haifa, Israel). Although some details are not identical, photon detectors are commonly arrayed to cover emission lines from the heart, enabling simultaneous acquisition of the MPI without moving the gantry. It has 5–10 times higher sensitivity, 2–3 times better spatial resolution with only one-half–one-third of administered radioactivity [82]. A recent study describes that a full 1-day rest-stress MPI study could be accomplished with only one-fourth of Tc-99m tetrofosmin, with an excellent agreement in the differential diagnosis of normal perfusion vs. scar [83].

The quantitative MBF parameters measured using CZT SPECT are now being vigorously investigated for their integration into clinical practice. In a recent study, lower global myocardial perfusion reserve (MPR) measured by CZT SPECT was associated with the presence of multivessel CAD while regional MPR demonstrated significant correlations with anatomical stenosis severity, visual perfusion scores, and FFR (correlation coefficient −0.52 to −0.57, all $p < 0.001$) [84]. However, some technical hurdles exist. Despite excellent linear correlations (correlation coefficient 0.83 to 0.92) for both rest and stress measurements, the MBF values may not be identical. In comparison with N-13 ammonia PET, CZT SPECT tended to underestimate MBF values, especially for high-flow ranges (> 1.0 ml/min/g). It was considered that the MBF values need specific correction

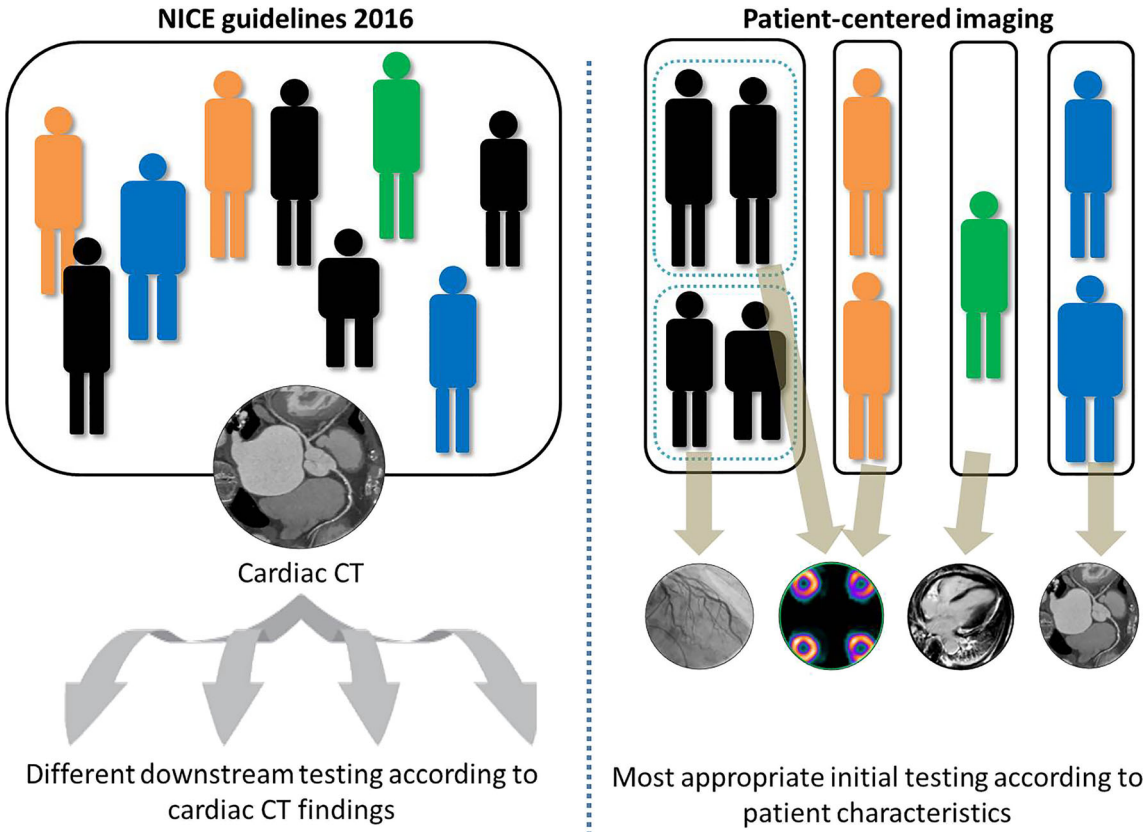

Fig. 3 Perspectives of patient-centered imaging for stable chest pain. The 2016 updated NICE guidelines recommend cardiac CT as the first-line diagnostic study in patients with stable chest pain regardless of the appropriateness of each imaging modality (left). However, the selection of imaging modality should be prudent based on the patients' characteristics (e.g., pre-test probability), availability of imaging modality, cost-effectiveness, medical history (e.g., prior PCI, contrast allergy), and the expertise of the managing doctors. The blueprint of the management of stable chest pain requires personalized, patient-centered imaging, considering personal factors to select the most appropriate imaging modality at the initial diagnostic step (right). NICE National Institute for Health and Care Excellence, PCI percutaneous coronary intervention

for the lower extraction fraction of Tc-99m-labelled myocardial perfusion agents relative to those of PET tracers [85]. In contrast, CZT SPECT overestimated stress and rest MBF compared to O-15 water PET, particularly for high-flow ranges (> 2.0 ml/min/g). It was possibly due to the positioning error of regions of interest and the lack of attenuation correction [86]. Simple modification by multiplying correction factor for extraction fraction may lead to a significant increase in image noise [87].

Future Perspectives

The initial evaluation of stable chest pain should still be accompanied by PTP calculation, although the NICE guideline committee has decided to discard it. Cardiac CT would effectively rule out patients without epicardial stenosis and prevent unnecessary ICA, which will be highly important for those with low-to-intermediate PTP. Several studies have shown that the value of nuclear MPI might be limited in those with low PTP [88, 89]. On the other hand, cardiac CT may not guide appropriate downstream testing or revascularization in those with intermediate-to-high PTP. The values of nuclear MPI can be maximized in the evaluation of those with intermediate-to-high PTP, diagnosing flow-limiting CAD and guiding revascularization simultaneously. To optimize the selection of imaging modalities, modifications of currently available PTP calculation should also be accompanied. Recent efforts to refine PTP calculation for the contemporary CAD population seem to be effective in identifying low-risk patients who do not need ICA [90].

The clinical management of stable chest pain should provide personalized care for individuals according to their distinctive features, rather than recommend the same study for all patients [91]. The future blueprint of "patient-centered imaging" is described in Fig. 3: patient characteristics are categorized and appropriate imaging modalities are appointed, where the characteristics may include clinical scenarios, the cost-effectiveness of specific imaging modalities, doctors' expertise, reimbursement, and other relevant demographic factors, as well as PTP. This workflow will help patients with stable chest pain get their best benefit from diagnostic studies and consequent treatment decision.

Some issues remain to be answered, including the level of evidence for deciding revascularization based on inducible ischemia on nuclear MPI. It is widely accepted as a standard treatment strategy for stable chest pain but never has been proved in randomized clinical trials. A worldwide prospective randomized trial, namely International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) [92], is now going on. Although the functional studies in the ISCHEMIA trial again include heterogeneous imaging studies and exercise ECG, the individual values of inducible ischemia on PET and SPECT for deciding revascularization will hopefully be proved with rich statistical power.

Conclusion

Despite the impressive changes in the NICE guidelines, cardiac CT cannot substitute the unique values of nuclear MPI in the initial evaluation of stable chest pain. Appropriate imaging modality should be appointed to patients regarding various factors for providing personalized care.

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Compliance with Ethical Standards

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Authors Sang-Geon Cho and Jahae Kim declare that they have no conflict of interest.

Ethical Approval This work does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

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