The Clinical Utility of 2-Deoxy-2-[^{18}F] Fluoro-D-Glucose Positron Emission Tomography in Guiding Myocardial Revascularisation

Author Information

Dineo Mpanya[1], Akinwale Ayeni[2], Stuart More[3], Bawinile Chonco[4], Mike Sathekge[5] & Nqoba Tsabedze[1]

[1]Division of Cardiology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[2]Divisions of Clinical Associates/Family Medicine, Department of Family Medicine & Primary Care, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3]Division of Nuclear Medicine, Department of Radiation Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

[4]Department of Nuclear Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

[5]Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South-Africa

Corresponding Author

Dr Dineo Mpanya

Division of Cardiology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand and the Charlotte Maxeke Johannesburg Academic Hospital, 17 Jubilee Road, Parktown, Gauteng, South Africa, 2193

Tel: 27 11 488 3611

Fax: 27 11 642 9041

Email: Dineo.Mpanya@wits.ac.za

ORCID ID

Dineo Mpanya: 0000-0003-3769-4686; Akinwale Ayeni: 0000-0001-6754-4553; Stuart More: 0000-0001-6957-916X; Bawinile Hadebe: 0000-0002-2322-9452; Mike Sathekge: 0000-0002-2806-0625; Nqoba Tsabedze: 0000-0002-7210-1447

Abstract

Introduction

Current myocardial revascularisation guidelines recommend that patients with acute coronary syndromes be timeously revascularised. Despite these class I recommendations, immediate access to timeous revascularisation is often not achievable in low and middle-income countries (LMIC) and remote regions in high-income countries (HIC). Many patients present late outside of the therapeutic window for guideline-recommended interventions. 2-Deoxy-2-[^{18}F] Fluoro-D-glucose (2-[^{18}F] FDG) is a radiopharmaceutical agent used to identify cardiac regions with viable or hibernating myocardium. Viable myocytes with impaired contraction may recover their contractility with successful myocardial revascularisation. However, there are conflicting hard outcomes data on patients with hibernating myocardium who are subsequently revascularised. Whether this management strategy results in improved major adverse cardiovascular events remains uncertain.

Methods

In this narrative review, we will critically appraise the existing body of evidence on whether using 2-[^{18}F] FDG Positron emission tomography (PET) in guiding myocardial revascularisation leads to compelling clinical outcomes or not. Furthermore, we will discuss possible reasons for the lack of differences in patient outcomes.

Results

A few randomised controlled trials have challenged the concept of viability testing with 2-[^{18}F] FDG PET. One trial demonstrated that a reduction in mortality could be observed if PET recommendations are followed.

Conclusion

The current evidence from a few randomised control trials is insufficient for many clinicians in LMIC or remote areas in HIC without timeous access to catheterisation laboratories to refrain from referring patients for viability imaging to triage those who ought to be revascularised.

Keywords

Positron emission tomography, Fluorodeoxyglucose, Myocardial revascularisation, Myocardial viability

Declarations

Funding

The authors did not receive support from any organization for the submitted work.

Conflict of interest/competing interests

NT has received consultation fees from Novartis Pharmaceuticals, Novo Nordisk, Boston Scientific, Pfizer, Servier, Phillips, Takeda, AstraZeneca, Acino Health Care Group and Merck. He has also received educational and travel grants from Medtronic, Biotronik, Boston Scientific and Vertice Health Care Group.

Availability of data and material

Not applicable

Code availability

Not applicable

Ethics approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

Consent to participate

Not applicable

Consent for publication

Not applicable

Introduction

Successful, timeous coronary revascularisation of patients with left ventricular systolic dysfunction secondary to obstructive coronary artery disease relieves angina, improves exercise capacity and leads to improved survival [1-4]. Before the advent of myocardial viability imaging, patients with ischaemic cardiomyopathy were subjected to either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery without objective evidence of salvageable myocardium.

Revascularisation techniques are not without risk, particularly emergency or urgent CABG surgery in acute coronary syndrome (ACS) late presenters with left ventricular systolic dysfunction [5-8]. Before performing PCI or CABG surgery, clinicians may opt for viability testing to select patients with left ventricular systolic dysfunction likely to improve after successfully restoring blood flow. Allman and colleagues identified 24 studies where 3 088 patients with a mean left ventricular ejection fraction (LVEF) of 33% were followed up for two years after viability testing with 2-Deoxy-2-[^{18}F] Fluoro-D-glucose (2-[^{18}F] FDG) positron emission tomography (PET), ^{201}Thallium and Dobutamine stress echocardiography. In their meta-analysis, patients with viability who were subsequently revascularised had a 79.6% reduction in annual mortality compared to patients treated with medical therapy [9]. In contrast, one of the largest multicentre randomised control trials evaluating the utility of PET compared to standard care in selecting ideal candidates for coronary revascularisation suggests that PET-guided management does not translate to improved clinical outcomes [10]. This review aims to discuss contemporary evidence for the clinical utility of 2-[^{18}F] FDG PET in evaluating myocardial viability and outline factors that may be responsible for the conflicting outcomes data.

Histological Basis of Myocardial Viability

Hibernating myocardium refers to the resting left ventricular systolic dysfunction due to reduced coronary blood flow that may be partially or entirely reversed by myocardial revascularisation or by reducing myocardial oxygen demand [11]. The reduction in contractile function occurs as an adaptive response to preserve energy. In essence, hibernating myocytes are "living sleeping cells." A study by Pagano et al. demonstrated that an ionotropic contractile response to dobutamine was absent in segments with a severe form of hibernation, in contrast to patients with mild hibernation [12]. Moreover, histological specimens of 22 systolic dysfunctional but viable segments obtained during CABG surgery showed cellular dedifferentiation with loss of myofibrillar content, depletion of the sarcoplasmic reticulum, small and abnormally shaped mitochondria as well as an abundance of glycogen in the cytosol [12]. In addition to these cellular changes, interstitial fibrosis has been found in patients with hibernating myocardium, and the contractile reserve and function after reperfusion are inversely correlated with the extent of fibrosis [12]. Nagueh et al. found that viable segments that recovered function after the restoration of blood flow with CABG surgery had less fibrosis than segments that did not recover [13]. The observed cellular dedifferentiation resembling the foetal phenotype seen in hibernating segments of the myocardium suggests that the contractile

response is influenced by the degree of myofibrillar content loss, such that if perfusion is not restored *timeously*, dysfunctional segments may not regain their full contractile function, despite complete revascularisation.

The Rationale for Imaging with 2-Deoxy-2-[^{18}F] Fluoro-D-glucose Positron Emission Tomography

The energy requirements for cardiac myocytes are supplied by fatty acids, glucose, lactate and ketones [14]. Under normal conditions, when there is sufficient blood flow to the myocardium, oxidative phosphorylation is the main pathway involved in energy production in myocytes. However, during episodes of ischaemia, when there is a sustained reduction in oxygen delivery to the myocardium, the heart preferentially uses glucose as a substrate. As a result, both exogenous glucose uptake and glycogen breakdown are increased. In addition, glycolysis is stimulated, and adenosine triphosphate is produced from the anaerobic metabolic breakdown of glucose associated with lactate formation [15]. This is the molecular basis for imaging the myocardium of patients with obstructive coronary artery disease (CAD) with a glucose analogue, 2-[^{18}F] FDG.

In preparation for the 2-[^{18}F] FDG PET study, both the referring doctor and the patient need to be informed about the importance of strict adherence to the guideline-recommended patient preparation protocol. Prior to the study, patients are requested to fast for 6-12 hours. Upon arrival at the nuclear medicine department, fasting blood glucose level is checked. If the fasting blood glucose level is less than 250 mg/dl (~13.9 mmol/l), 25-100 grams of oral glucose mixed with water is given to patients [16]. The transient elevation in blood glucose levels induces a pancreatic insulin response and subsequent reduction in plasma fatty acid levels. In some centres, intravenous glucose is used instead of an oral dose as a strategy to mitigate problems associated with delayed gastrointestinal absorption of glucose.

If the fasting blood glucose level exceeds 250 mg/dl, intravenous insulin titrated according to blood glucose levels is administered to patients. We refer the reader to the American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging nuclear cardiology procedure guidelines for a detailed patient preparation protocol [16]. The rationale for the cumbersome patient preparation protocol is to ensure that myocardial substrate concentrations during the 2-[^{18}F] FDG PET study favour glucose metabolism, hence improving entry and retention of 2-[^{18}F] FDG in the myocardium, resulting in superior image quality.

2-Deoxy-2-[^{18}F] Fluoro-D-glucose contains fluorine-18, a radioactive atom and a D-glucose analogue, fluorodeoxyglucose. Upon the intravenous administration of 185-555 Mbq of 2-[^{18}F] FDG, the radiopharmaceutical agent travels in the venous system and eventually enters the myocytes via the glucose transporters (**Figure 1**). Once inside the myocytes, FDG is phosphorylated by the enzyme hexokinase to form FDG-6-phosphate, which is not further metabolised along the glycolytic pathway as it is not a substrate for enzyme glucose-6-phosphate isomerase, but remains trapped in myocytes for sufficiently long periods, thus allowing imaging of the myocardium [15]. However, in in-vitro studies and animal models, the metabolism of FDG beyond FDG-6-phosphate has been observed [17, 18].

Image acquisition typically begins 45-60 minutes after the administration of 2-[^{18}F] FDG and may be delayed up to 90 minutes in patients with diabetes mellitus and/or higher blood glucose levels. The delay in image acquisition is a trade-off between improved blood pool clearance and a reduced count rate. Myocardial perfusion images should always be acquired before PET images since non-visualisation of perfusion defects precludes the assessment of myocardial viability. Abnormal wall motion should also be elicited in segments of the myocardium with reduced or absent tracer uptake on the perfusion images. The 2-[^{18}F] FDG PET images are interpreted in conjunction with the perfusion images obtained via single-photon emission computed tomography (SPECT) or PET methods.

The imaging criteria for hibernating myocardium on imaging is supported by reduced or absent perfusion, impaired wall motion and preserved or increased glucose metabolism (*perfusion-metabolism mismatch*). Whereas, if both perfusion and metabolism are reduced or absent (*perfusion-metabolism match*), a patient is deemed to have non-viable myocardium that is not amenable to revascularisation. A reverse mismatch pattern, depicted by normal perfusion and reduced metabolism, has been reported in patients with non-transmural myocardial infarction, multivessel disease and early reperfusion, often seen when the viability study is performed early after an acute infarct [19-21]. The reverse mismatch pattern is typical among heart failure patients and is inversely correlated to insulin sensitivity [22]. The clinical significance of the reverse mismatch pattern remains debatable, although some authors have demonstrated its lack of association with cardiac morbidity and mortality [22]. Nuclear physicians interpreting cardiac perfusion and metabolism images should also indicate the extent of viability, expressed as a percentage of the left ventricle, as this semi-quantitative index provides prognostic information [16].

Other Radiopharmaceuticals for Assessment of Myocyte Energy Metabolism

^{11}C-acetate is a unique PET tracer accumulated and washed out independently from myocytes' metabolic substrate usage [23]. The initial ^{11}C-acetate uptake indirectly reflects regional myocardial blood flow, permitting the assessment of myocardial perfusion. Once in the cytosol, ^{11}C-acetate is converted to acetyl coenzyme A by the enzyme acetyl-CoA synthase and oxidised through the tricarboxylic acid cycle with further oxidative phosphorylation to ^{11}C-carbon dioxide and water (**Figure 1**). The myocardial turnover and clearance of ^{11}C-acetate in the form of ^{11}C-carbon dioxide reflect oxidative metabolism [24]. Accordingly, viable myocytes show preserved oxidative metabolism. Some studies have demonstrated the superiority of ^{11}C-acetate over 2-[^{18}F] FDG when assessing myocardial viability [25]. Also, a single injection of ^{11}C-acetate is used to assess both perfusion and oxidative metabolism. Despite this, the widespread clinical use of ^{11}C-acetate is limited by the short half-life of ^{11}C of 20 minutes, requiring an onsite cyclotron.

Experimental metabolic radiopharmaceuticals include markers of glucose metabolism and utilisation such as ^{11}C-glucose. In addition, numerous long-chain fatty acid metabolic probes exist for evaluating fatty acid metabolism (**Figure 1**). These include metabolically cleared probes such as ^{11}C-palmitate and ^{18}F-fluoroheptadecanoic acid, as well as metabolically trapped probes such as ^{18}F-fluoro-4-thia-palmitate and 18-^{18}F-fluoro-4thia-oleic acid [26].

Clinical scenarios where 2-[^{18}F] FDG PET may play a role in the assessment of myocardial viability

Myocardial Viability in Coronary Syndromes

The clinical presentation of patients with coronary syndromes varies and is depicted in **Figure 2.** In the acute setting of coronary artery occlusion, patients complain of severe exertional chest pain and may have a typical electrocardiogram and biochemical profile of ST-segment elevation myocardial infarction. Therefore, such patients should be promptly referred to the catheterisation laboratory for immediate revascularisation without evaluating for ischaemia nor viability. Moreover, those without overt ST-segment elevation with ongoing chest pain and a positive high-sensitivity troponin enzyme leak should also be promptly managed as high-risk non-ST segment elevation myocardial infarction.

Cardiologists in low and middle-income countries (LMIC) often face a clinical conundrum when deciding on an appropriate management plan for a patient initially diagnosed with ACS but only transferred to a centre equipped with a catheterisation laboratory after the 48-hour window of opportunity. In such a scenario, the treating cardiologist may refer such patients for non-invasive imaging to confirm ischaemia or viability before deciding on the subsequent management plan.

According to recent guidelines, patients with chronic coronary syndromes presenting to healthcare facilities with stable angina, dyspnoea or clinical features of heart failure must be subjected to non-invasive imaging to confirm underlying obstructive coronary artery disease as the cause of left ventricular systolic dysfunction and to exclude stress-induced ischaemia. If ischaemia is not detected, such patients should only be treated with medical therapy [27-29].

Chronic Total Occlusion and Viability

Chronic total occlusion (CTO) refers to a long-standing complete or near-complete blockage of an epicardial coronary artery, typically for three months or longer [30]. The occluded artery visualised on coronary angiography may exhibit faint antegrade flow associated with an incomplete filling of the distal coronary bed or no evidence of blood flow [31].

Although most patients with CTO are treated actively with either CABG surgery or conservatively with medical therapy, in selected cases PCI may be considered [29]. For example, in a multicentre study involving 1 000 consecutive patients in the United States of America with CTO referred for PCI using a hybrid approach, among the 800 patients with documented dyspnoea before PCI, 70% reported less dyspnoea after one month post PCI [32]. Similarly, Werner and colleagues also observed an improved quality of life and a reduction in the frequency of angina symptoms in patients with CTO managed with PCI compared to medical therapy after one year of follow-up [33].

Non-invasive imaging modalities such as PET, SPECT, cardiac magnetic resonance imaging (MRI), and stress echocardiography play a crucial role in confirming ischaemia or viability in the myocardium supplied by an artery with a CTO. Imaging allows clinicians to carefully select patients in whom interventions will likely improve angina symptoms and reduce the unnecessary expenditure and complications associated with restoring perfusion in an artery supplying necrotic tissue.

Guideline Recommended Criteria for Selecting Patients Suitable for Revascularisation

The 2018 European Society of Cardiology/European Association of Cardiothoracic Surgeons (ESC/EACTS) guidelines on myocardial revascularisation recommends non-invasive *stress* imaging in patients with ischaemic cardiomyopathy using SPECT, PET, stress echocardiogram or cardiac MRI to assess for myocardial ischaemia and viability [29]. Current literature demonstrates that the detection of myocardial ischaemia has incremental benefits over testing for viability in patients with mild to moderate CAD [29]. Whereas in patients with extensive CAD, viability imaging may be considered. Moreover, revascularisation should be carried out within two weeks for high-risk patients and within six weeks in patients with stable CAD where therapeutic interventions are not carried out in the same sitting as the diagnostic coronary angiogram.

According to 2018 ESC/EACTS myocardial revascularisation guidelines, before evaluating patients for the suitability of CABG surgery, the risk of surgical mortality and the extent of CAD should be appraised. The risk of surgical mortality should be estimated using an online calculator, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, which predicts the risk of 30-day mortality after cardiac surgery [34, 35] or the Society of Thoracic Surgeons (STS) score. A Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score should be estimated for the anatomical complexity of coronary artery lesions. This angiographic grading tool is used to predict the post-procedural risk associated with PCI and CABG [36]. The rationale for the risk stratification is to ensure that revascularisation is both anatomical and functionally complete since anatomically incomplete revascularisation is associated with inferior long-term outcomes after both CABG surgery and PCI [29].

The more recent 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes do not discuss viability testing at great length, except as part of a diagnostic algorithm for *symptomatic* patients with suspected obstructive CAD [28]. Previous ESC guidelines on myocardial revascularisation listed testing for myocardial viability as a class IIb indication, suggesting that viability testing *may* be considered in some patients [29]. Also, the 2011 American guidelines for PCI and the 2012 guidelines for diagnosing patients with stable ischaemic heart disease only briefly mention non-invasive testing for myocardial viability without providing direction on when and in whom should viability imaging be considered [27, 37].

Contemporary Evidence from Randomized Control Trials on the Use of Positron Emission Tomography in the Assessment of Myocardial Viability

A few randomised controlled trials have challenged the concept of viability testing. Although still relevant, the Surgical Treatment for Ischemic Heart Failure (STICH) trial will not be discussed in this manuscript as PET was not used to evaluate myocardial viability in this trial. The PET and Recovery following revascularisation (PARR-2) trial randomised 218 patients to PET guided management and 212 to standard care. After removing three sites without long-term follow up data, 197 and 195 patients remained in the PET guided management and standard care arm, respectively [10]. After a year of follow up, the study did not demonstrate a significant reduction in cardiac events in both arms, but a trend towards reducing cardiac events was seen in the PET arm. Importantly, in up to 25% of patients, PET recommendations were not adhered to, and this led to investigators in one of the centres experienced in interpreting PET images (Ottawa-FIVE Sub-study of the PARR-2 Trial) to conduct a sub-study post hoc analysis.

In the Ottawa-FIVE Sub-study, 111 patients were studied. Fifty-six were randomised to the PET arm and 55 to the standard care arm. Among the patients referred for PET imaging, 19, 21 and 15 patients had large, medium and small amounts of viable myocardium, respectively [38]. Four (7.5%) patients in the PET arm experienced cardiac death compared to eight (14.8%) in the standard care arm. Although the study was not adequately powered to compare mortality between the two arms, there were two non-cardiac death, one in each arm of the study [38]. Overall, composite events were lower in the PET arm (19% vs 41%). Thus, despite the lack of post-intervention angiography or follow-up imaging assessing the completeness or adequacy of revascularisation, the Ottawa-FIVE Sub-study demonstrated that a reduction in mortality could be observed if PET recommendations are followed.

In the initial PARR-2 trial, outcomes were studied again after five years of follow-up, and 53% of patients in the PET arm and 111 (57%) patients in the standard care arm experienced composite events. Sixty-two patients in the PET arm died compared to 65 in the standard arm [39].

The second trial, the Heart Failure Revascularisation Trial, was designed to determine the effect of revascularisation on survival in ischaemic heart failure patients with left ventricular systolic dysfunction. In this trial, 138 patients with previous myocardial infarction, heart failure, a LVEF $\leq$ 35% and evidence of viable myocardium on PET or Dobutamine stress echocardiography were randomised to a conservative management strategy without angiography or invasive management with the performance of a diagnostic angiogram and revascularisation within 6-12 weeks [40]. After a median follow-up of 59 months, there were 51 (37%) deaths. Twenty-five of these deaths occurred among patients assigned to the conservative strategy arm [40]. The trial was non-blinded and underpowered. As such, the overall findings from this trial should be treated with caution.

Possible reasons for the lack of differences in outcomes in patients referred for viability assessment compared with standard care

Varying Clinical Populations Studied

The clinical presentation of patients referred for myocardial viability tends to differ significantly. Some patients may present with a chronic coronary syndrome phenotype manifesting with either angina, ischaemic cardiomyopathy or de novo heart failure. Some patients may also present late with acute coronary syndromes outside of the stipulated therapeutic window. Although all patients may have varying degrees of left ventricular systolic dysfunction, the prognosis differs significantly between these different clinical manifestations. Furthermore, the burden of obstructive CAD, comorbidities such as atrial fibrillation and diabetes mellitus, and the lack of optimisation of background guideline-mandated medical therapy may significantly influence outcomes.

Different Myocardial Revascularisation Strategies Used

In a systematic review evaluating evidence from trials where PCI was performed in patients with stable and unstable CAD, PCI did not reduce all-cause mortality, cardiac death or occurrence of myocardial infarction in patients with stable CAD [41]. As such, PCI should be reserved for symptomatic patients with positive angina symptoms while on optimal doses of guideline-recommended medical therapy [41]. Our literature review found a large body of studies where patients referred for viability imaging with PET were subjected to PCI [22, 38, 42-50].

The quality and integrity of the veins and arteries used as a conduit in CABG surgery may negatively influence outcomes. After one year of follow-up, 81-97.9% of saphenous vein grafts remain patent post CABG surgery [51]. Although the relationship between graft failure and adverse outcomes is not well established, some studies have demonstrated a close correlation between graft failure and the need for reoperation and decreased survival [52-54]. Similarly, in patients referred for PCI, acute and late stent thrombosis is associated with cardiac death and myocardial infarction [55, 56]. As previously discussed, the completeness and the timing of myocardial revascularisation may also influence adverse events in patients referred for revascularisation. To the best of our knowledge, there are no studies where serial biopsies were taken from patients to estimate the time duration of progression from viable to necrotic myocytes. Therefore, there are no data to guide the permissible period before revascularisation may be futile.

Differences in Measured Outcomes

Outcomes measured in patients referred for viability imaging with PET vary significantly, making it challenging to perform pooled analysis. Some of the outcomes studied include all-cause mortality, cardiac death, heart transplantation and hospitalisation [10, 22, 38, 57-62]. Likewise, an improvement in the LVEF has been studied in a significant number of patients referred for imaging with 2-[^{18}F] FDG PET [10, 63-66]. The LVEF is one of the parameters primarily influenced by the degree of ventricular remodelling [67]. However, most studies evaluating outcomes in patients referred for 2-[^{18}F] FDG PET tend to focus purely on patients with a severely reduced LVEF [9, 64]. Bax et al. showed that extensive left ventricular remodelling might not improve the LVEF after

revascularisation despite the presence of viability [64]. Therefore, the lack of standardisation in reporting outcomes and the absence of an evidence-based cut-off point defining prognostically significant improvement in the LVEF may lead to conflicting study results.

Differences in Study design

To the best of our knowledge, the PARR-2 trial is the only randomised control trial designed to measure outcomes in patients subjected to PET and standard care. For a scientifically sound measurement of outcomes, an ideal study design should have four arms of patient groups, with patients subjected to PET and those managed with standard care compared (**Figure 3)**. Furthermore, in the standard care arm, patients should be randomised to revascularisation and medical therapy. In the PET arm, patients with and without evidence of viability should also be randomised to revascularisation and medical therapy.

Pitfalls in 2-[^{18}F] FDG PET imaging

2-[^{18}F] FDG PET is a well-established imaging modality in patients with oncological conditions. However, for the evaluation of cardiac conditions, including distinguishing between viable and necrotic cells, the utility of PET is primarily affected by the physiological uptake in the myocardium. Patient preparation before imaging with PET may require prolonged fasting, oral glucose loading, an insulin-euglycemic clamp or intravenous heparin [68]. There is no consensus on the ideal method for optimum suppression of physiological glucose utilisation in the heart [68]. Also, the software used for reporting perfusion and metabolic images may be supplied by different vendors in some institutions, making it difficult to visually compare images or use polar maps that estimate hibernation scores.

Other Imaging modalities Used to Evaluate Myocardial Viability

The following section discusses other non-invasive imaging tools for evaluating myocardial viability, namely SPECT, echocardiography and cardiac MRI. Additional data on imaging modalities used for the assessment of myocardial viability is summarised in **Table 1**.

Single Photon Emission Computed Tomography with Technetium-labelled agents

The technetium-labelled agents used for assessing perfusion may also be used to assess viability, but their clinical role is limited. These agents have clinical utility when segments of the myocardium supplied by a stenotic artery demonstrate normal (*perfusion score: 0)*, equivocal or moderately reduced perfusion (*perfusion scores: 1 and 2)*. Once segments demonstrate ≥ 50% reduction in tracer uptake on SPECT imaging, corresponding to severely reduced or absent perfusion (*perfusion scores: 3 and 4)* along with dyskinesia or akinesia, further imaging is

required either with 2-[18F] FDG PET or any other imaging modality used to evaluate myocardial viability. Despite nitrate-augmentation, SPECT has a sensitivity of 81% and a specificity of 69% for detecting viable myocardium [69].

Single Photon Emission Computed Tomography with Thallium-201

^{201}Thallium is a potassium analogue that enters viable myocytes via the Na^+/K^+ ATPase channels (**Figure 2)**. This radiopharmaceutical agent is used to assess both myocardial perfusion and cellular membrane integrity. Various ^{201}Thallium imaging protocols for differentiation between scar and viable cells exist. A representative protocol involves injecting a dose of 92.5 to 129.5 megabecquerel (MBq) just before peak exercise stress or at peak pharmacological vasodilatation. Single-photon emission computed tomography images are then acquired 10-15 minutes later. After 2.5 to 4 hours, rest perfusion images, also known as redistribution images, are acquired. If there is evidence of fixed or reversible perfusion defects on these images, myocardial viability is assessed with a late redistribution image, acquired 18-24 hours after tracer injection or with reinjection of an additional 37 to 74 MBq of ^{201}thallium [70]. Another imaging protocol for viability entails administering 92.5 to 118.4 MBq of ^{201}thallium at rest, followed by 3 to 4 hour or 18-24 hour redistribution images.

Due to its long physical half of 73 hours, ^{201}thallium exposes patients to a higher radiation dose; therefore, smaller amounts of radioactivity are generally administered to patients. However, a reduced dose causes a clinical challenge when imaging obese patients since ^{201}thallium emits a high abundance of low energy photons of 76-82 kiloelectron volt absorbed by surrounding adipocytes, hence degrading imaging quality. Therefore, the detection of viable myocardium with PET is preferred over ^{201}thallium and technetium labelled agents since PET has a higher sensitivity [69].

Dobutamine Stress Echocardiography

Echocardiography is an easily accessible and inexpensive non-invasive imaging modality for assessing ventricular morphology and function. However, none of the parameters available on the resting echocardiogram can predict recovery of ventricular function after revascularisation. For example, a left ventricular end-diastolic wall thickness (EDWT) $\leq 0.5 - 0.6$ cm with increased echogenicity was initially thought to be a marker of non-viable myocytes [71, 72]. However, in a study by Shah and colleagues involving 1 055 patients with CAD, the EDWT in thinned regions with limited scar burden on cardiac MRI increased from 0.4 to 0.75 cm after revascularisation ($p < 0.001$), resulting in resolution of wall thinning [73].

Therefore, dobutamine *stress* echocardiography is a more reliable tool for differentiating between viable and non-viable myocytes. A low dose of dobutamine, usually between 5 to 10 µg/kg/min, is administered as an intravenous infusion. Continuous echocardiographic monitoring is required to monitor for subtle or transient increases in systolic function. The contractility in hibernating segments generally improves after the dobutamine infusion.

Deterioration in function is subsequently seen after a high dose of dobutamine (10 to 40 μg/kg/min) due to induced ischaemia. This is known as a biphasic response [74], a hallmark of functional recovery after revascularisation. The contractile reserve may also be assessed using low-level exercise, vasodilators and phosphodiesterase inhibitors [74]. The main limitation of stress echocardiography is the heavy reliance on the operator for interpretation. To overcome this limitation, newer techniques that are less operator-dependent, such as speckle-tracking echocardiography, have been used to assess regional myocardial deformation and its velocities, hence detecting subtle changes in wall motion. Longitudinal strain measurements can differentiate between viable and non-viable myocytes, while a reduction in circumferential strain is a stronger predictor of non-viable cells [75].

Cardiac Magnetic Resonance Imaging

Cardiac MRI uses various techniques to differentiate between infarcted and viable myocytes. The most commonly employed technique involves the intravenous administration of a gadolinium-based contrast agent (GBCA). Gadolinium is a heavy metal with a large molecular size that prevents it from entering the intracellular space. In the acute phase of myocardial infarction, GBCA enters the necrotic myocytes through a disrupted cellular membrane and subsequently accumulates intracellularly. Due to the expansion caused by collagen deposition in chronic myocardial infarction, GBCA accumulates in the extracellular environment [76-78]. As a result of these pathological changes, cardiac images acquired 10-20 minutes after the administration of GBCA will exhibit hyperenhancement in infarcted tissue caused by delayed washout of the GBCA. A cut-off value of less than 50% of transmural late gadolinium enhancement (LGE) is indicative of residual viable myocardium [79, 80].

Dobutamine may also be used to assess contractile reserve. Similar to the dobutamine stress echocardiography, segments that are viable on cardiac MRI will increase their contractility after the administration of dobutamine. One of the advantages of cardiac MRI over other non-invasive imaging modalities is its ability to detect microvascular obstruction, mural thrombus formation, and peri-infarct zones. All these factors have prognostic significance in patients with chronic coronary syndromes [81]. While more recently manufactured intra-cardiac devices are "MRI friendly", these devices may introduce image artefacts that degrade image quality. Furthermore, caution should be exercised in patients with end-stage renal disease, especially those undergoing dialysis, when administering GBCA [82].

Computed Tomography

Hyperenhancement was first introduced with computed tomography (CT) and later applied in cardiac MRI. Hyperenhancement on CT suggests the presence of infarcted myocytes. However, the poor contrast to noise ratio on CT compared to cardiac MRI has restricted the application of CT in evaluating myocardial viability. Some investigators are now taking advantage of the improved spatial and temporal resolution of multidetector CT and

studying its utility in assessing myocardial viability using animal models [83]. To date, this imaging modality dominates when evaluating patients suspected of CAD, but its role in evaluating myocardial viability is still limited.

PET/CT versus PET/MRI

During the acquisition of cardiac PET images with a camera equipped with a CT component, low dose CT is used for attenuation correction. Most cardiac PET software vendors allow users to display PET only images segmented in the same manner as the perfusion images acquired with a SPECT camera. As such, anatomical localisation using the CT component is not routinely performed. In contrast, hybrid PET/MRI images show PET, MRI and fused PET/MRI images. Regions of the myocardium with LGE are directly comparable to PET viability images.

Hybrid cardiac PET/MRI has added value over PET/CT. Firstly, the intrinsic resolution of ~ 1- 3 mm allows one to differentiate thinned myocardium from scarring on MR images in areas with decreased 2-[^{18}F] FDG uptake [84]. Secondly, small areas of scar tissue are possible to visualise on MR images [85]. Whether hybrid PET/MRI leads to improved outcomes when selecting patients for coronary revascularisation remains to be determined. A few studies have focused on establishing a correlation between parameters obtained during the simultaneous acquisitions of 2-[^{18}F] FDG PET and cardiac MRI and determining complementary and redundant parameters when evaluating myocardial viability [86-88]. A moderate to good agreement between 2-[^{18}F] FDG PET and cardiac MRI parameters was observed in these studies.

Hybrid PET/MRI is not without limitations. Magnetic resonance imaging-related pitfalls include truncation, attenuation, scatter and motion-related image artefacts [89]. Also, the ^{82}Rubidium generator for PET perfusion imaging cannot be kept in the same camera room as the hybrid PET/MRI machine since generators cannot be safely operated within a strong magnetic field [90]. This limitation has led to the anticipation of a novel PET perfusion tracer, ^{18}F-Flurpiridaz, which binds avidly to the mitochondrial complex-1 enzyme in myocytes. This enzyme oxidises nicotinamide adenine dinucleotide + hydrogen (NADH) transferring electrons to ubiquinone, a lipid-soluble electron carrier located in the lipid bilayer of the inner mitochondrial membrane [91]. Unlike most PET perfusion tracers with physical half-lives demanding an onsite cyclotron, ^{18}F-Flurpiridaz has a relatively longer half-life of 110 minutes, permitting bulk order of injections from centres equipped with cyclotrons. ^{18}F-Flurpiridaz is currently being investigated in phase III clinical trials and has shown promising results as a perfusion imaging agent [92].

Future Directions

The role of 2-[^{18}F] FDG PET could be well delineated by high-powered and appropriately designed randomised clinical trials. We also recommend a multidisciplinary approach involving nuclear physicians, cardiologists and cardiothoracic surgeons when discussing the appropriate revascularisation management of patients referred for imaging, thereby bringing this imaging modality to the forefront of clinical cardiology care.

Conclusion

Objective guidance is required for the management of patients with chronic coronary syndromes with left ventricular systolic dysfunction. Positron emission tomography imaging using 2-[^{18}F] FDG plays a crucial role in selecting patients with left ventricular systolic dysfunction likely to improve after revascularisation. The current evidence from a few randomised control trials is insufficient for many clinicians in LMIC or remote areas in high-income countries without timeous access to catheterisation laboratories to refrain from referring patients for viability imaging to triage those who ought to be revascularised.

Acknowledgements

All figures in this manuscript were created using Biorender.com.

Author contribution

NT contributed to the conception, design and pertinent insights to the controversies relating to the clinical applications of the subject matter. Furthermore, NT critically reviewed and approved the final manuscript. DM, SM, AA and BC reviewed the literature and participated in the critical revision of the article for important intellectual content. DM, NT, MS, SM, AA, and BC all read and approved the final version to be published.

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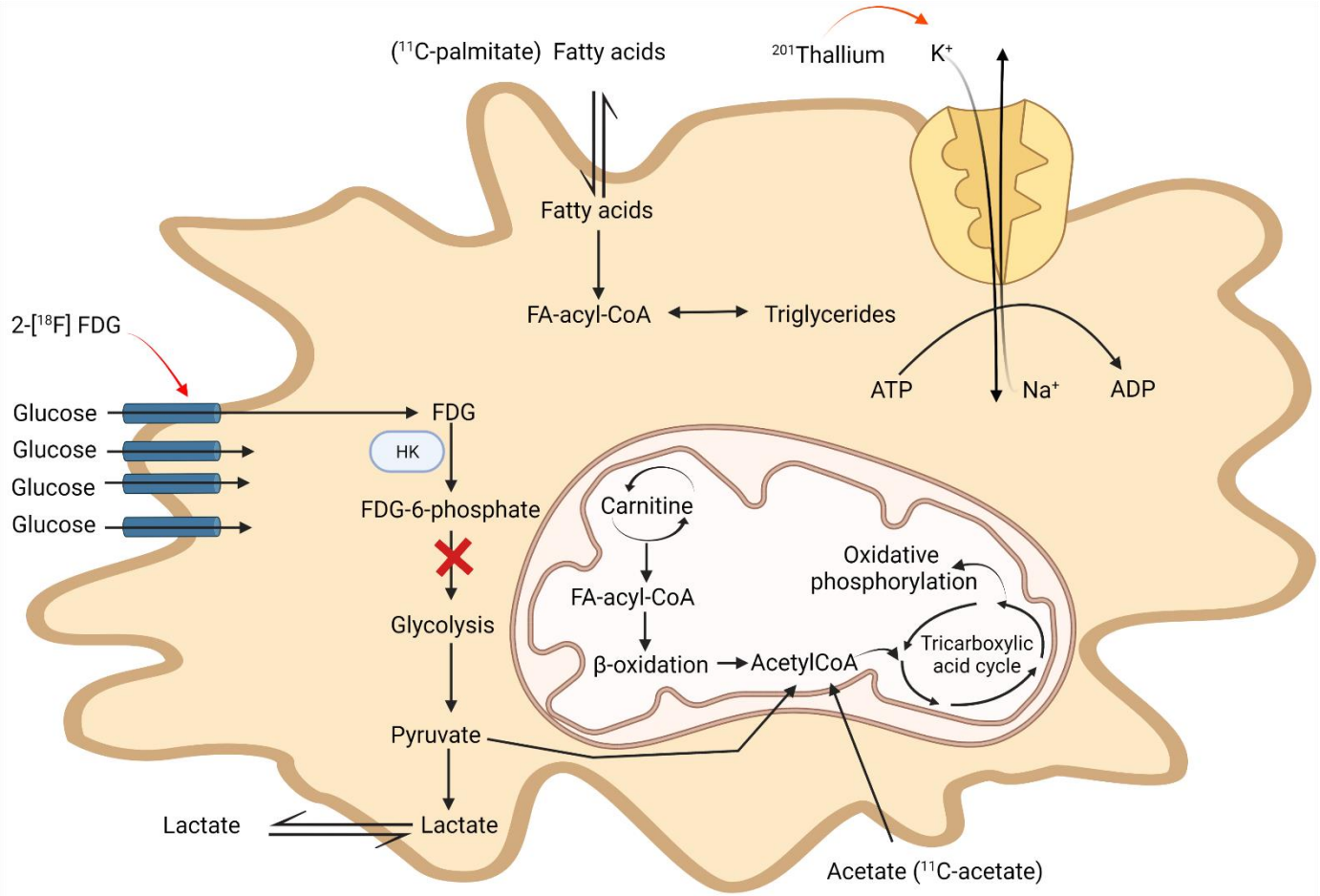

Figure 1 Metabolic pathways in a myocyte. The ischaemic myocyte shows overexpression of glucose transporters as well as entry and retention of 2-Deoxy-2-[18F] Fluoro-D-glucose, Thallium-201, ^{11}C-acetate and ^{11}C-palmitate into the cell. ADP = adenosine diphosphate; ATP= adenosine triphosphate; FDG= fluoro-d-glucose; HK= Hexokinase; K^+=Potassium; Na^+= Sodium. *Diagram modified from Dilsizian V, Narula J: Imaging Cardiac Metabolism. Atlas of Nuclear Cardiology. Fourth Edition. 2013*

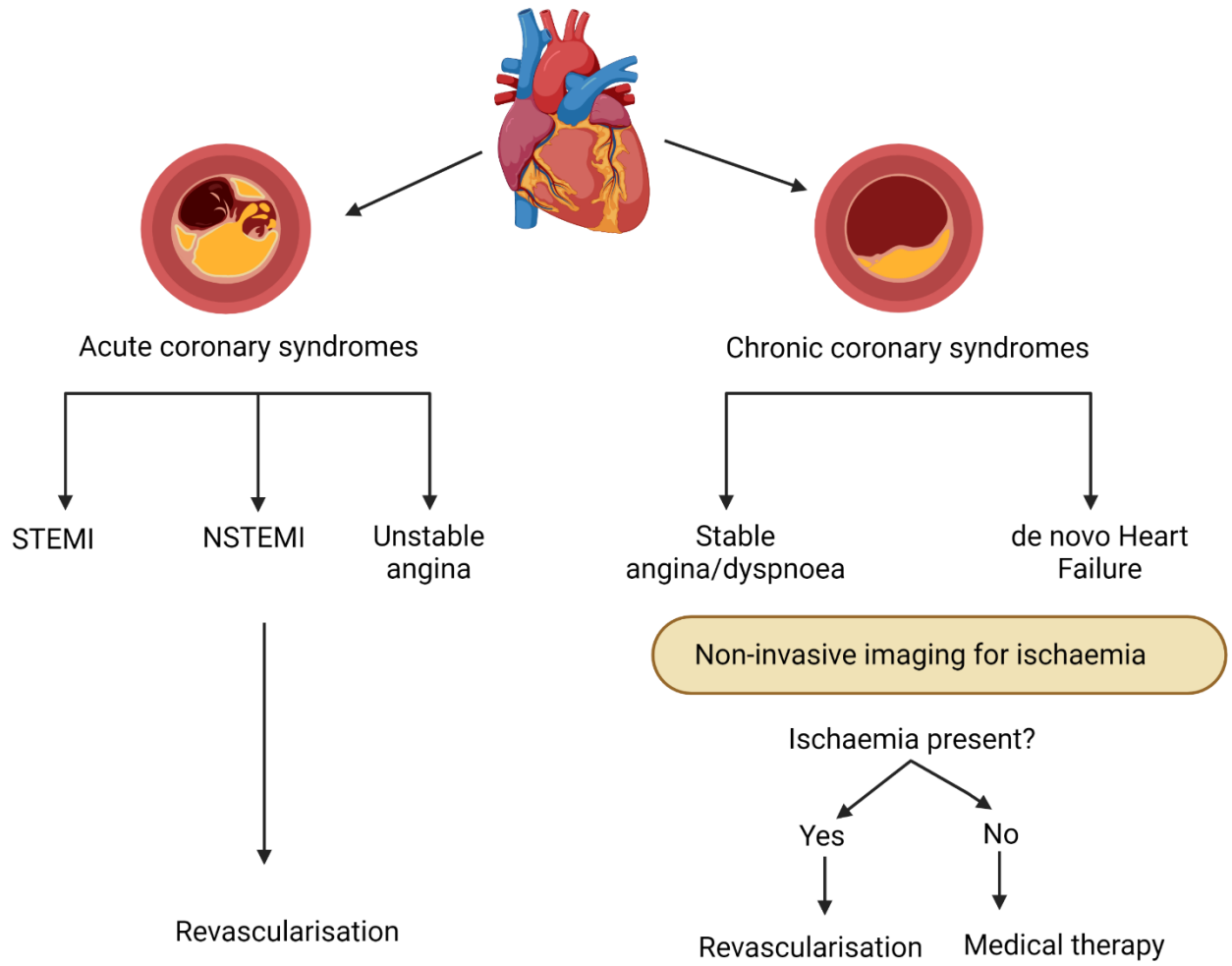

Figure 2 Clinical presentation of patients with acute and chronic coronary syndromes and a suggested management strategy by the 2018 European Society of Cardiology guidelines on myocardial revascularisation. NSTEMI= non-ST elevation myocardial infarction; STEMI= ST-elevation myocardial infarction.

Table

	Nuclear Techniques			
	Positron Emission Tomography	**Single Photon Emission Computed Tomography**	**Cardiac Magnetic Resonance Imaging**	**Dobutamine Stress Echocardiography**
Technique for detection of viable myocardium	Glucose utilisation in myocytes supplied by a stenotic artery	Active transportation of thallium-201 chloride across myocytes via the Na/K ATPase-dependent channels	Visualisation of a transmural scar occupying < 50% of the total myocardium. Measurement of End-diastolic wall thickness Ionotropic reserve of segmental contractile function	Augmentation of contractility or assessment of contractile reserve
Diagnostic criteria for viable myocardium	Presence of 2-[^{18}F] FDG uptake in segments with reduced perfusion and abnormal wall motion	Increased thallium-201 chloride uptake ≥ 10% in segments with a perfusion defect	Accumulation of gadolinium in the intracellular space or delayed washout in the extracellular space	Improvement in contractility after the administration of dobutamine
Sensitivity[69, 93]	92%	87%	LGE: 95% Db: 81%	80%
Specificity [69, 93]	63%	54%	51% 91%	78%
PPV[69, 93]	74%	67%	69% 93%	85%
NPV [69, 93]	87%	79%	90% 75%	83%

Contraindications	None	None	Claustrophobia and patients with certain metallic objects End-stage renal disease	Uncontrolled hypertension and tachyarrhythmia
Disadvantages	Exposure to ionising radiation Requires fasting and suppression of physiologic glucose uptake in the myocardium	Highest radiation burden	Image quality dependent on breath-holding	Operator dependent The image quality depends on the patient's body habitus Requires less scar and a greater percentage of viable myocytes to detect contractile reserve

Db=Dobutamine; FDG=Fluorodeoxyglucose; LGE=Late gadolinium enhancement; NPV= Negative predictive value; PPV= Positive predictive value

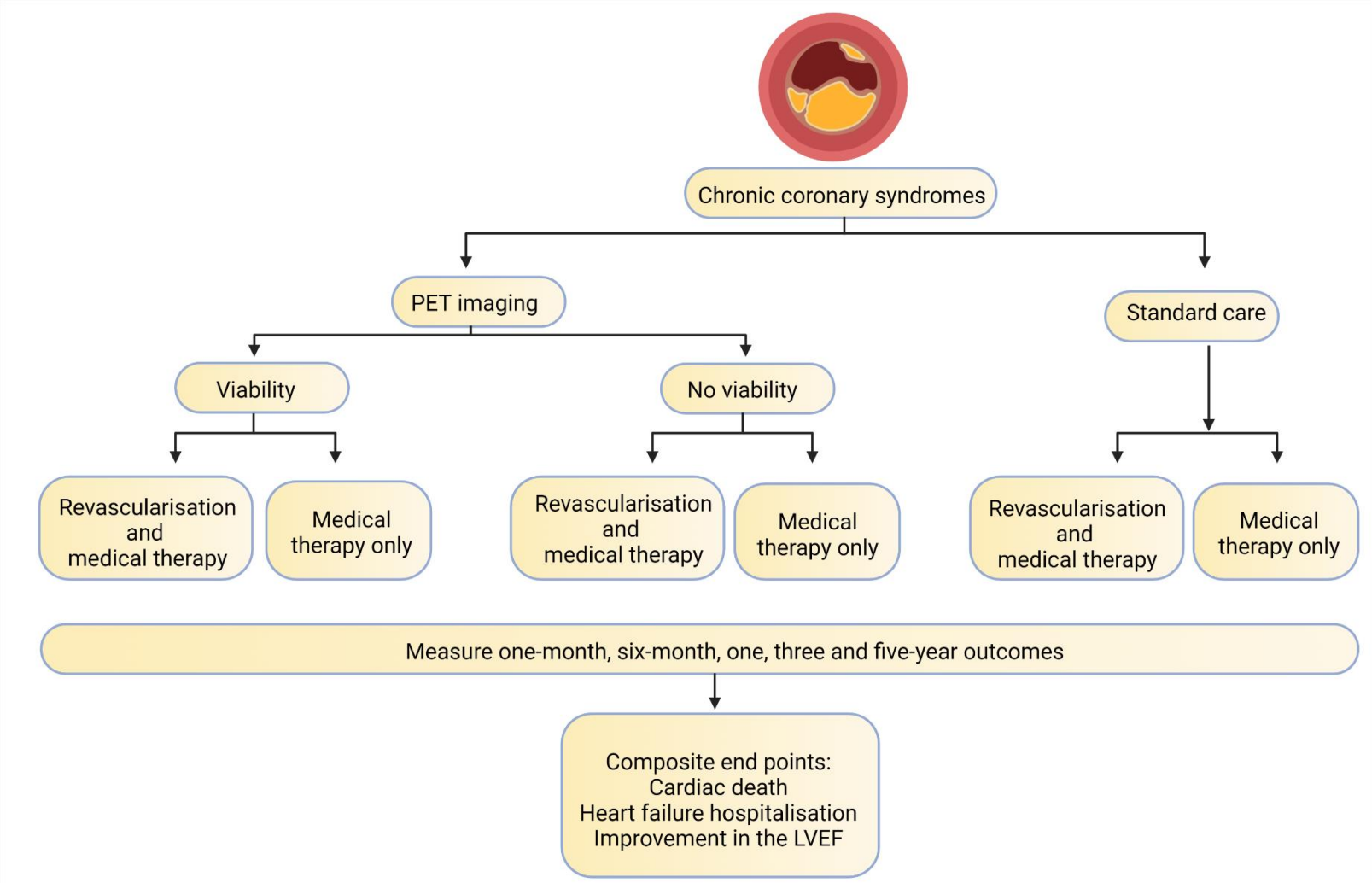

Figure 3 Proposed study design for randomisation of patients with chronic coronary syndromes into Positron emission tomography-guided management plan and standard care.