

## Myocardial Viability: From PARR-2 to IMAGE HF - Current Evidence and Future Directions

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### Abstract

Ischemic heart failure is a growing disease with high morbidity and mortality. Several studies suggest the benefit of viability imaging to assist revascularization decision, but there is controversy. Multiple imaging modalities can be used to accurately define hibernating myocardium; however, the best approach remains uncertain. This review will highlight current evidence and future directions of viability imaging assessment.

### Introduction

Ischemic heart failure (HF) is the leading cause of HF and an epidemic disease worldwide with growing prevalence and high mortality rate.<sup>1,2</sup> In 2011, 1 in 9 death certificates in the United States listed HF.<sup>1</sup> In 2015 in Brazil, 27,434 deaths occurred due to HF.<sup>3</sup> Medical treatment, cardiac rehabilitation, revascularization and the increased understanding of its pathophysiology have improved the overall prognosis and survival of patients with HF over the last years, but, despite that, around 50% of the patients diagnosed with HF will die 5 years after the initial diagnosis.<sup>2</sup>

Accumulated evidence of the past years has suggested that individualized-target therapy with viability imaging assessment may improve outcome.<sup>4,14,15</sup> This review will focus on the understanding of the viability concept and current evidence.

### Keywords

Heart Failure; Myocardial Stunning; Positron Emission Tomography Computed Tomography; Hibernating.

### What is viable myocardium?

A simplistic way to describe viable myocardium is all tissue that is not scar/fibrosis (non-viable myocardium). Naturally, normal myocardium is viable. Dysfunctional myocardium that is viable has the potential to recover from an injury.<sup>4,14,15</sup> Meanwhile, two concepts under the umbrella of “viable myocardium” can be often misunderstood. “Stunned” and “hibernating” myocardium are conditions in which function is impaired but is potentially reversible. Stunned myocardium is characterized by the persistent dysfunction that follows an episode of ischemia. Hence, there is normal rest flow and impaired function. The severity and duration of the stunning (post-ischemic dysfunction) depend on duration, extent and severity of the preceding ischemic insult. So long as there is no infarction during such ischemia, full recovery is expected, the timing of which also depends on the duration, extent and severity of the preceding ischemia. If stunning occurs repeatedly, the myocardium must adapt to the repetitive injury. It does so by reducing contractile function and flow in response to these events.<sup>15</sup> Repetitive stunning is believed to be the precursor to hibernating myocardium, where both measured perfusion and function are reduced but restorable in whole or in part if blood flow can be adequately restored before irreversible injury occurs. This is the area of focus for viability imaging (Table 1).<sup>4,14,15</sup>

### Imaging modalities for viability assessment

Several imaging modalities can be used to assess hibernating myocardium, and each has different metabolic/cellular targets and findings to detect viable and hibernating myocardium. Cardiac positron emission tomography (PET) with <sup>18</sup>Fluorodeoxyglucose (<sup>18</sup>FDG) uses a glucose analogue to measure myocardial

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**Table 1 - Viable and non-viable myocardium**

Myocardium	Flow	Glucose metabolism/ FDG	Function	Potential to recover
Non-Viable				
Scar/Fibrosis	Reduced	Reduced	Reduced	Unlikely
Viable				
Stunned	Preserved (has suffered an intermittent ischemic insult) <sup>65,66</sup>	Variable [can be normal, increased or reduced (reverse mismatch)] <sup>65-69,67-71,67-71</sup>	Reduced	Likely to recover if ischemic injury does not persist or become repetitive; <sup>4,14</sup> may benefit from revascularization
Hibernation	Reduced	Preserved (flow-metabolism mismatch)	Reduced	Likely to have part or full recovery if adequate revascularization can be achieved <sup>5,72</sup>
Ischemia	Preserved at rest (impaired at stress)	Normal at rest, increased at stress <sup>67</sup>	Preserved	May benefit from revascularization

glucose uptake. Single-photon emission computed tomography (SPECT) with thallium-201 (<sup>201</sup>Tl), a potassium analogue, has the sarcolemma membrane integrity as its target (sodium/potassium ATPase pump activity).<sup>16</sup> SPECT with technetium-99m (<sup>99m</sup>Tc)-based tracers test the mitochondrial membrane integrity.<sup>17,18</sup> Dobutamine echocardiogram (ECHO) and dobutamine magnetic resonance imaging (MRI) measure myocardial contractile reserve. Delayed enhancement MRI and computed tomography target the amount of fibrotic tissue, and myocardial contrast ECHO targets the microvascular integrity.<sup>19,20</sup>

In a meta-analysis by Schinkel et al.<sup>5</sup> reviewing 24 studies (756 patients) comparing all available imaging modalities, <sup>18</sup>FDG PET was shown to be the most sensitive to predict regional function recovery, and dobutamine ECHO was the most specific (92%, 63%, 74% and 87% and 80%, 78%, 75% and 83% of sensitivity, specificity, positive and negative predictive value for PET and ECHO, respectively).<sup>5</sup> Cardiac MRI, which was underrepresented in this meta-analysis, had sensitivity, specificity, positive and negative predictive values of 74%, 82%, 78% and 78% for dobutamine stress MRI and 84%, 63%, 72% and 78% for delayed enhancement MRI.<sup>5</sup>

In this same meta-analysis, a total of 721 patients underwent <sup>99m</sup>Tc-tracer-based SPECT and 1,119 had <sup>201</sup>Tl SPECT to assess viability. <sup>201</sup>Tl was more sensitive and <sup>99m</sup>Tc-tracer-based SPECT more specific to predict recovery, with sensitivity, specificity, positive and negative predictive values of 87%, 54%, 67% and 79% and

83%, 65%, 74% and 76% for <sup>201</sup>Tl and <sup>99m</sup>Tc, respectively.<sup>5</sup> Comparisons between nuclear techniques suggest <sup>18</sup>FDG PET is the superior technique to detect the amount of hibernating myocardium,<sup>21-25</sup> except for one study directly comparing <sup>201</sup>Tl and <sup>18</sup>FDG PET, which suggested similar viability detection for both methods.<sup>26</sup>

More recent data analyzing MRI performance in detecting viable myocardium have supported its high sensitivity.<sup>27-30</sup> Romero et al.<sup>27</sup> have conducted a meta-analysis of MRI prospective trials including 24 studies (698 patients) and found a sensitivity of 95% for predicting functional recovery for MRI with delayed enhancement. Dobutamine MRI was the most specific (91%) when compared to delayed enhancement and end-diastolic wall thickness techniques.<sup>27</sup> Kühl et al.<sup>29</sup> have studied 29 patients with chronic ischemic HF and mean ejection fraction of 32% who had both MRI and PET/SPECT (<sup>18</sup>FDG for metabolism and <sup>99m</sup>Tc SPECT for perfusion) performed at baseline and at 6-month follow-up after revascularization.<sup>29</sup> The group found MRI to have higher sensitivity and PET/SPECT to be more specific (97% versus 87% sensitivity and 68% versus 76% specificity for MRI and PET/SPECT, respectively).<sup>29</sup> A more recent study has analyzed the feasibility of PET/MRI scanners in evaluating segment functional recovery in 28 patients post-acute myocardial infarction (MI) and percutaneous revascularization.<sup>30</sup> All patients underwent PET/MRI with contrast for delayed enhancement and <sup>18</sup>FDG injection for uptake assessment 5-7 days after the acute event and had a follow-up MRI for contractility

assessment at 6 months.<sup>30</sup> The study has concluded that simultaneous assessment of glucose metabolism and scar assessment using a hybrid PET/MRI scanner is feasible. Moreover, the agreement between the techniques was high (82% of the segments were either non-viable or viable for both PET and MRI,  $k = 0.65$ ). In only 18% of the segments was there disagreement, and, in all of them, PET suggested non-viability while MRI suggested viability.<sup>30</sup> The recovery was higher in the segments in which there was agreement between the techniques (78% versus 41% for PET viable/MRI viable and PET non-viable/MRI viable, respectively). Recovery was similar between PET non-viable/MRI viable and PET non-viable/MRI non-viable segments, suggesting PET better dichotomized the degree of recovery between viable and non-viable

myocardium. In the PET non-viable/MRI viable segments, there was some recovery (41%), suggesting a lower threshold for % FDG uptake cutoff (40-45% instead of 50%) may have detected some viable segments identified by MRI. Overall the techniques appear complementary. Their combined use as PET/MR may offer comprehensive tissue characterization of metabolism, scar and function and may refine our ability to define viable myocardium. Further studies are warranted (Figures 1 and 2).<sup>30</sup>

### Clinical relevance of viability assessment: PARR-2 and STICH

Several non-randomized studies have reported data that suggest a benefit of viability imaging in patients

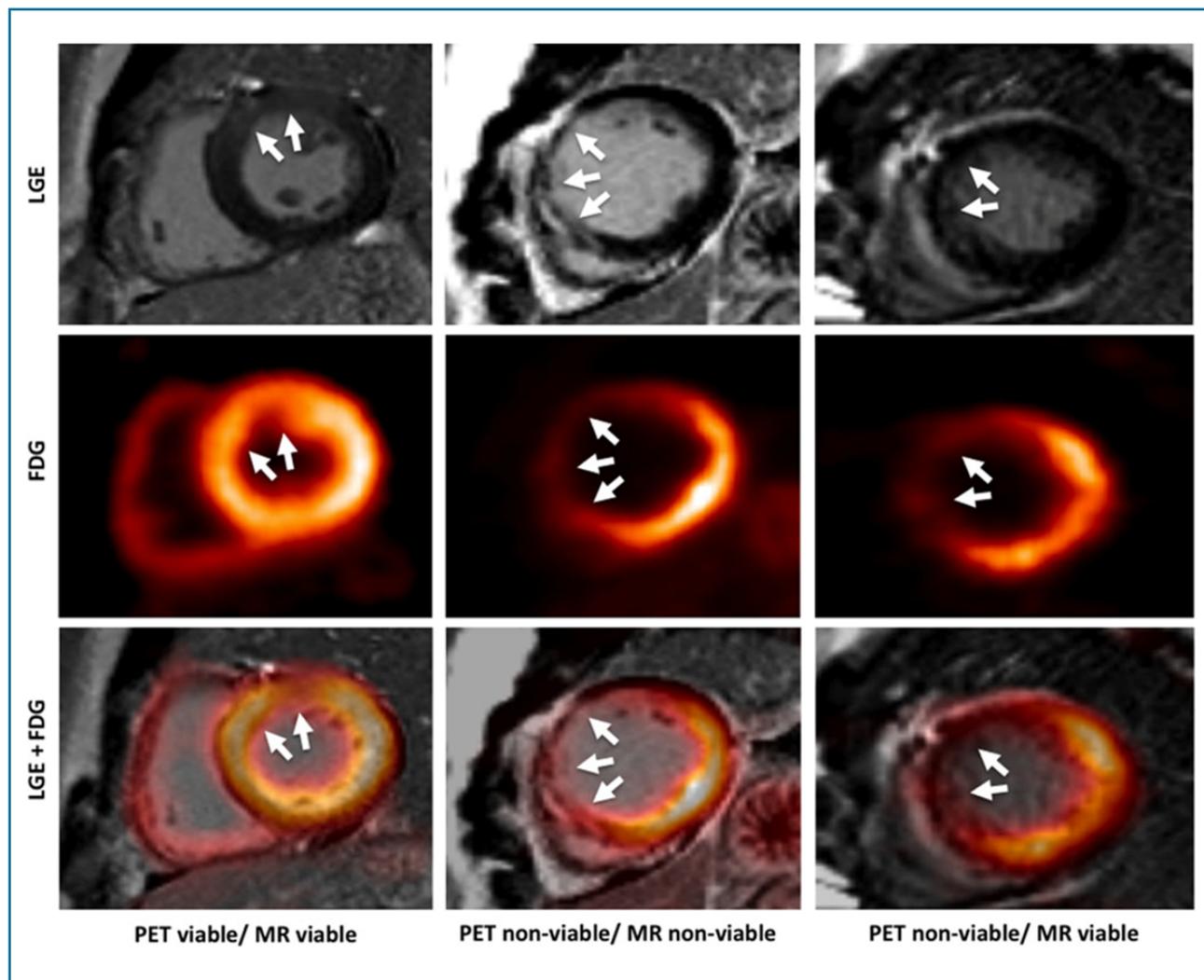
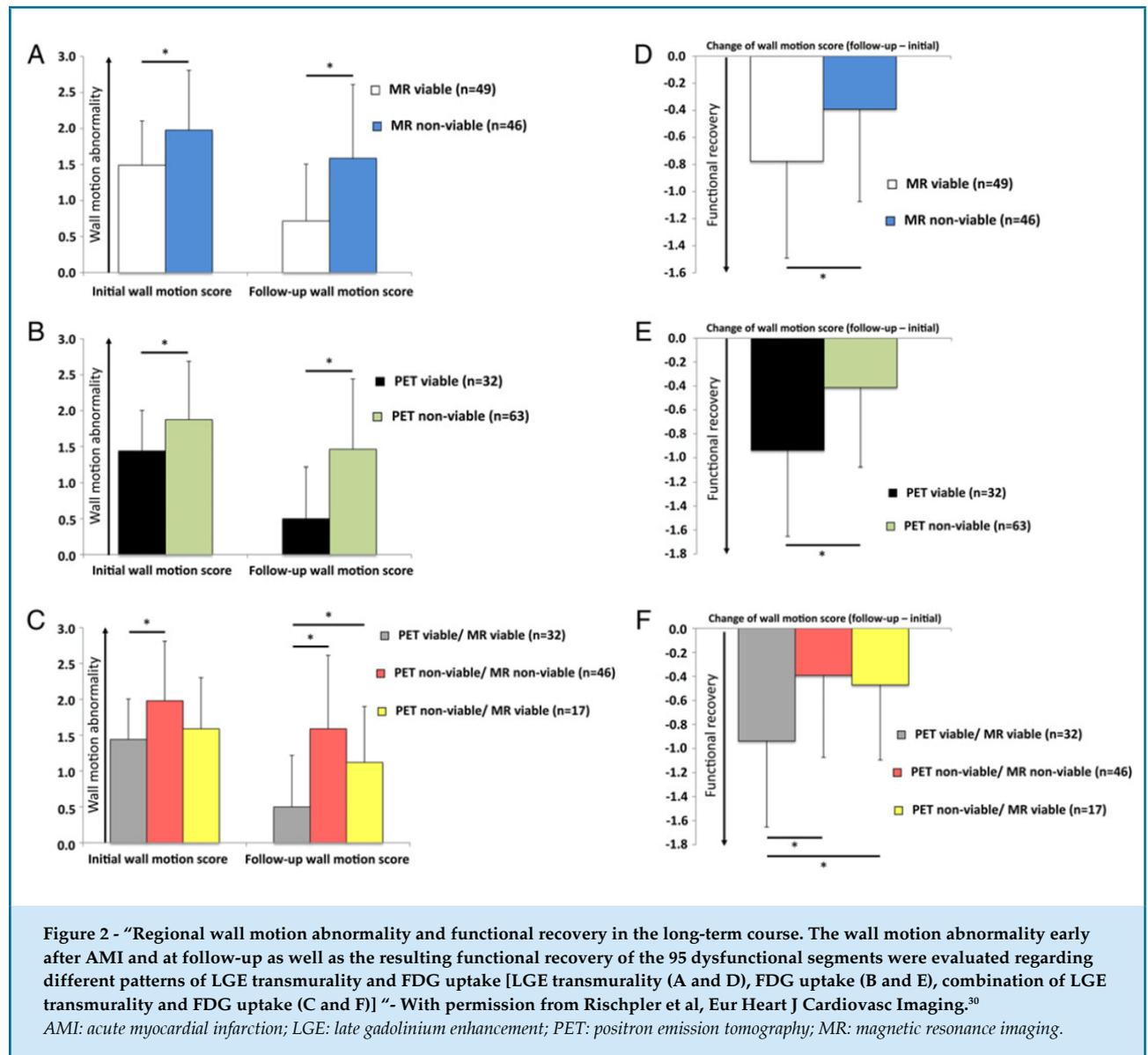


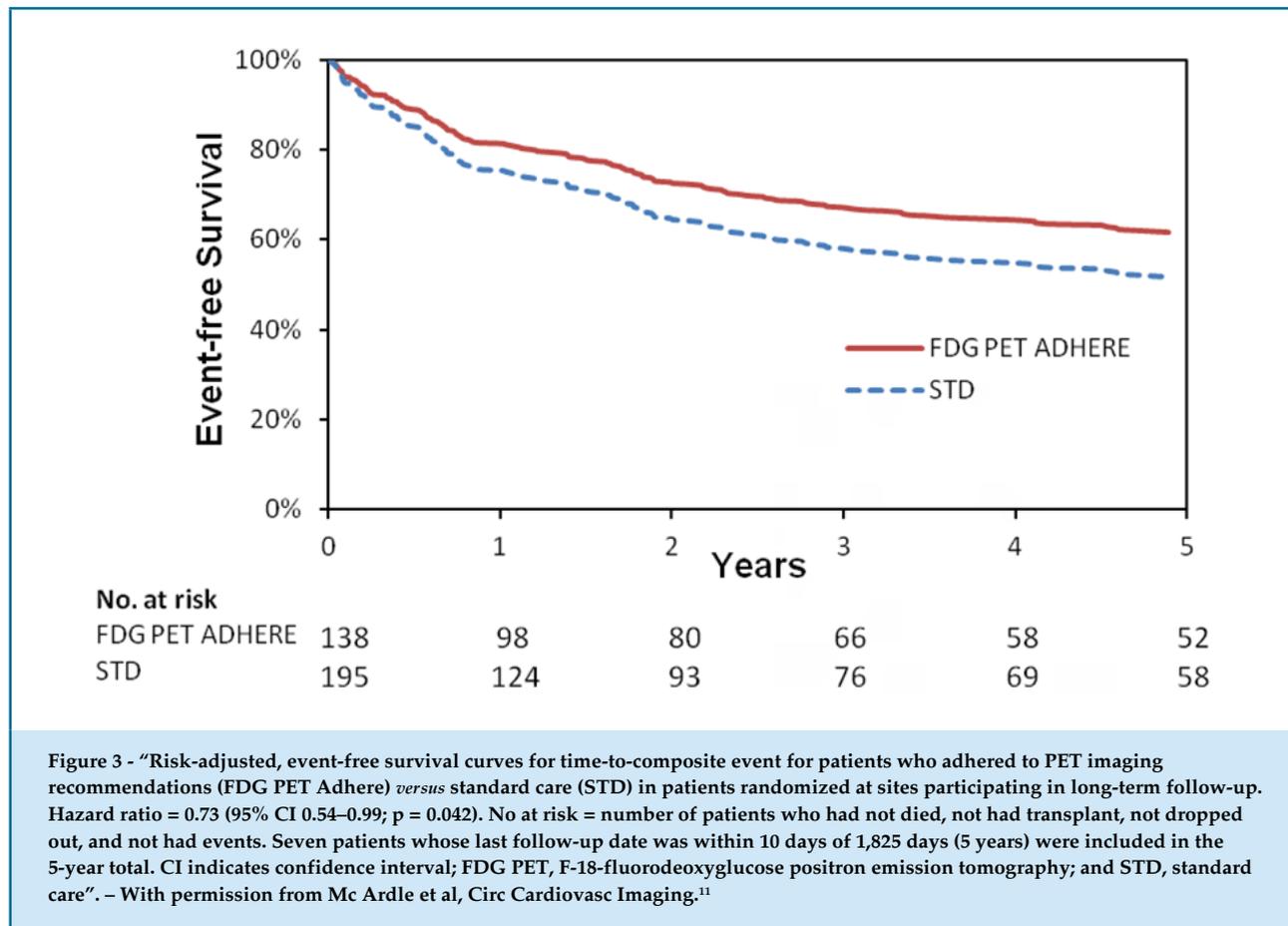
Figure 1 – “Images illustrating different combinations of FDG uptake and LGE transmural. First column:  $FDG \geq 50\%$ /LGE non-transmural (‘PET viable/MRI viable’); second column:  $FDG < 50\%$ /LGE transmural (‘PET non-viable/MRI non-viable’); third column:  $FDG < 50\%$ /LGE non-transmural (‘PET non-viable/MRI viable’). White arrows indicate the respective area of ischaemically affected myocardium.” – With permission from Rischpler et al, Eur Heart J Cardiovasc Imaging.<sup>30</sup>



with ischemic HF.<sup>9,31-34</sup> Allman et al.<sup>9</sup> have conducted a meta-analysis with 24 studies, and their analysis has shown the benefit of revascularization only in patients with viable myocardium as opposed to scar.<sup>9</sup> More recently, a meta-analysis including 29 studies by Inaba et al. has documented the benefit of revascularization over medical therapy in patients with dysfunctional viable myocardium.<sup>31</sup>

To date, there have been two major prospective randomized trials comparing outcome in patients with ischemic HF who underwent viability assessment: PARR-2 (Positron emission tomography And Recovery following Revascularization phase 2)<sup>6</sup> and STICH (Surgical Treatment for Ischemic Heart Failure) viability substudy<sup>35</sup> trials.

PARR-2 has randomized 430 patients from 9 centers, to have either viability assessment with <sup>18</sup>FDG PET or standard care without <sup>18</sup>FDG PET, before decisions regarding revascularization.<sup>6</sup> A trend toward benefit for the primary outcome (cardiac death, MI and cardiac hospitalization at 1 year) has been observed in the arm that underwent FDG PET to assist with clinical decision-making [36% of events in the standard care arm and 30% in the PET arm, relative risk 0.82; p = 0.16 and hazard ratio (HR) 0.78; p = 0.15].<sup>6</sup> However, not all patients in the study followed the imaging recommendation. When analyzing only the patients who adhered to the recommendations from the imaging report, a significant reduction in outcome was observed in the PET arm versus standard care (HR 0.62; p = 0.019), indicating that



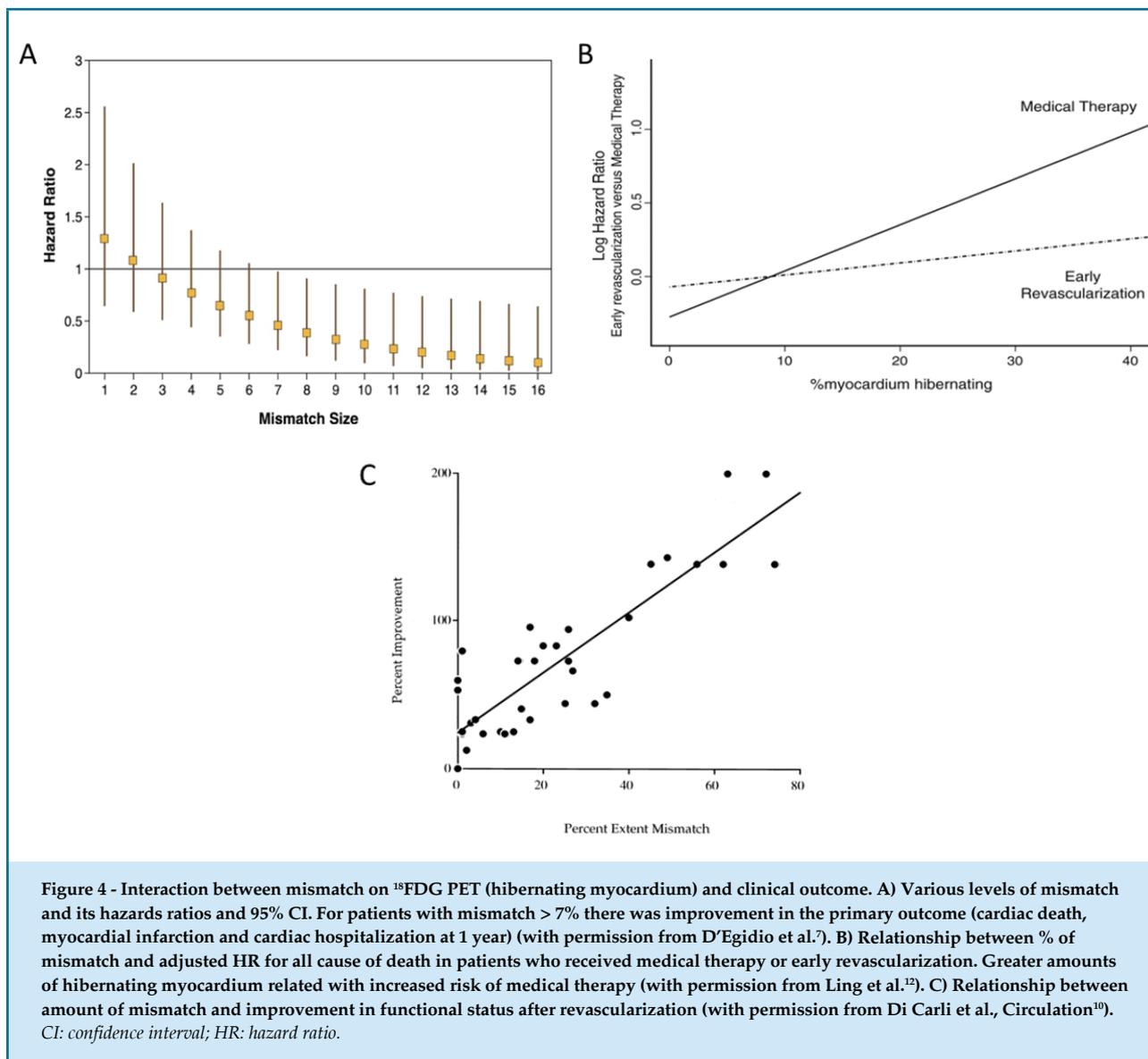
management adhered to the imaging recommendations may have an impact on patient outcome.<sup>6</sup>

A PARR-2 substudy has supported the importance of adherence to PET findings and that of teamwork of: i) revascularization (surgeons, interventional cardiology); ii) HF; and iii) imaging specialists.<sup>8</sup> This along with iv) access to FDG and v) the cardiac PET imaging experience of a centre has the potential to impact outcome. The Ottawa-FIVE (i.e. i-v above) study has had 111 patients from an experienced center in which PET was easily available and physicians were comfortable with the technology and its interpretation. In this scenario, patients in the FDG PET arm had clear benefit when compared to standard care (19% of cumulative proportion of events in the PET arm versus 41% in the standard care group) and multivariable analysis showed benefit (HR 0.34; 95% confidence interval 0.16–0.72; p = 0.005).<sup>8</sup>

In long-term (5 years) follow-up, the PARR-2 population in which PET recommendations were followed had improved primary outcome (HR 0.73, 95% confidence interval 0.54–0.99, p = 0.042) (Figure 3).<sup>11</sup>

In addition, PARR-2 has shown that the amount of hibernating myocardium also plays an important role in patient outcome.<sup>7</sup> With increasing extent of mismatch (hibernating myocardium), the likelihood of benefit with revascularization also increases. In this substudy of the PARR-2 trial involving 182 patients in the PET arm, a cutoff of 7% was able to distinguish between patients who would or would not benefit from revascularization, which is in accordance with previous values reported by Di Carli et al.<sup>10</sup> (5%), Lee et al.<sup>12</sup> (7.6%) and Ling et al.<sup>36</sup> (10%) (Figure 4).

The STICH trial has observed conflicting results compared to previous studies regarding the benefit of revascularization for patients with viable myocardium.<sup>35</sup> A total of 1,212 patients were randomized to receive optimal medical therapy alone or medical therapy plus revascularization.<sup>35,37</sup> Of these, 601 patients underwent viability assessment independently of the randomization. The primary outcome was defined as all-cause mortality and there was no significant difference in the endpoint between the groups after



adjustment for baseline characteristics.<sup>35</sup> More recently, the 10-year follow-up of the original trial, STICHES (STICH Extension Study)<sup>37</sup> has shown the benefit of revascularization for all-cause death, cardiovascular death and cardiovascular hospitalization over optimal medical therapy alone.<sup>37</sup>

In the STICH viability substudy, while viability did predict outcome, it was not independent of other parameters and did not predict outcome benefit from revascularization, leaving questions yet to be answered. The greater long-term benefit in the revascularization arm in the main trial indeed highlights the need for a careful assessment of patients with ischemic HF, balancing the risks and benefits in short and long term.

Although the ISCHEMIA trial (NCT01288560) does not specifically evaluate viability, its results may assist in understanding the role of ischemia imaging in guiding revascularization. Currently, more than 5,000 patients have been randomized worldwide to an invasive strategy +/- revascularization *versus* optimal medical management.

There was also a small randomized blinded study (total of 103 patients) comparing FDG PET to MIBI perfusion imaging to detect viability. While FDG PET appeared to have better outcomes, this did not reach statistical significance. The small sample size and the fact that < 1/3 of patients had significant left ventricular dysfunction limit conclusions from this study.<sup>38,39</sup>

Beyond clinical events, there is evidence that patients undergoing FDG PET have improved quality of life *versus* standard care (not undergoing FDG PET) at least in the short term.<sup>40</sup> Other studies have also reported revascularization directed by FDG PET improves HF symptoms and quality of life.<sup>10,41</sup> There is also evidence to support that viability imaging with PET is cost-effective when hibernation data are used to guide revascularization.<sup>42</sup>

### Comparing PARR2 and STICH

It is important to understand the differences between PARR-2 and STICH in order to appreciate their respective significance.<sup>6,35,40,43</sup> First, in STICH, patients had to be acceptable for revascularization. While patients were randomized to coronary artery bypass graft surgery *versus* optimal medical therapy, imaging was not randomized nor did it direct the therapy decision. Conversely, in PARR-2, patients in whom decisions regarding revascularization was uncertain were randomized to FDG PET viability imaging *versus* standard care with no FDG PET imaging. The tests for viability assessment were also different: <sup>18</sup>FDG PET in PARR-2 and SPECT or dobutamine ECHO in STICH. Compared to the STICH population, PARR-2 patients had more renal dysfunction (7.5% *versus* 34%), had more prior coronary artery bypass graft surgery (3% *versus* 19%), more multivessel coronary artery disease (75% *versus* 90%) and less viable myocardium (81% *versus* 22%), suggesting these patient cohorts were not the same (Table 2).<sup>40,43</sup> From those studies, it is safe to conclude that viability imaging is not needed in all patients with ischemic heart disease and left ventricular dysfunction who are being considered for revascularization. However, there may be high-risk patients whose decisions are particularly difficult where viability imaging has a role.<sup>40,43</sup>

### Viability tests: when should we use it?

Current evidence and guidelines support the use of viability imaging to assist decision-making in patients with ischemic HF (Table 3).<sup>44-50</sup> The imaging modality of choice for viability assessment needs to be individualized according to each clinical scenario, technology availability and institution expertise.<sup>14,40,41,49-52</sup>

In our experience, viability imaging is appropriate in patients with known or strongly suspected ischemic HF, New York Heart Association (NYHA)  $\geq$  II, moderate to severe left ventricular dysfunction (left ventricular ejection fraction  $<$  40%), moderate to large perfusion defects and no

**Table 2 - Comparison of the STICH Viability Substudy with PARR-2 - Adapted with permission from Mielniczuk et al., JACC Cardiovasc Imaging<sup>43</sup>**

	STICH substudy	PARR-2
Patient population		
Randomized?	Not the substudy	Yes
Mean age, years	60.7	63
Male sex	85	84
Previous CABG	3	19
Diabetes mellitus	39	39
Estimated GFR $<$ 60 mL/min/1.73m <sup>2</sup>	7.5	34
Mean serum creatinine		108 $\mu$ mol/L
Viability testing	SPECT or dobutamine echocardiography	PET
Prevalence of viability	81	22

*Values are % unless otherwise indicated. CABG: coronary artery bypass grafting; GFR: glomerular filtration rate; SPECT: single-photon emission computed tomography.*

significant ischemia, significant comorbidities and/or poor vessel targets (Figure 5).<sup>49,51,52</sup> On the other hand, viability is not (or less) useful in patients with predominantly angina CCS  $>$  II, those with normal or mild left ventricular dysfunction, critical left main coronary artery disease, patients with good revascularization targets, those with already-demonstrated moderate to severe ischemia and those with minimal or no comorbidities.<sup>51,52</sup> Figure 6 illustrates two examples of viability imaging.

When viability imaging is needed, the choice of which test depends on specific advantages of the different modalities, availability and local expertise. Until comparative evidence is available (see "Future Directions"), the following is an approach to select which test for viability in which circumstance as suggested by the authors:<sup>51,52</sup>

1. Normal or mild left ventricular dysfunction – viability imaging is rarely needed.
2. Moderate left ventricular dysfunction – any method can be considered depending on availability and local expertise.
3. Very severe left ventricular dysfunction - consider nuclear methods (SPECT, FDG PET) or late

**Table 3 - Guidelines, Appropriate Use Criteria and Position Statements for the use of viability imaging in patients with ischemic heart failure. With permission from Wiefels et al., Curr Cardiovasc Imaging Rep.<sup>73</sup>**

Recommendation	Grade	Level	Organization
Nuclear imaging for assessment of myocardial viability for consideration of revascularization in patients with CAD and LV dysfunction who do not have angina	I	B	ACC/AHA/ASNC Radionuclide Imaging 2003 <sup>44</sup>
Cardiac PET and CMR should be used in the evaluation and prognostication of patients with ICM and LV dysfunction	I	B	CCS/CAR/CANM/CNCS/Can SCMR 2007 <sup>47</sup>
Noninvasive imaging to detect myocardial ischemia /viability in HF and CAD	IIa	C	ACCF/AHA CHF 2013 <sup>48</sup>
Viability assessment is reasonable before revascularization in HF patients with CAD	IIa	B	ACCF/AHA CHF 2013 <sup>48</sup>
Non-invasive stress imaging (CMR, echo, SPECT, PET) may be considered for the assessment of myocardial ischemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization.	IIb	B	ESC CHF 2016 <sup>44</sup>
Myocardial viability testing should be considered in patients with ischemic CM and reduced LV EF eligible for revascularization	Appropriate use score: 9		AACF/ASNC/ACR/ASE/SCCT/SCMR/ SNM 2009 <sup>45</sup>

gadolinium enhanced MRI which are more sensitive than contractile reserve.<sup>5,27,53</sup>

4. Renal failure (GFR < 30) or implanted devices – avoid MRI.

5. Left main coronary artery disease or severe proximal 3-vessel disease – avoid dobutamine.

6. Equivocal results on another viability test or negative results on another viability test, where certainty is needed to completely rule [in or] out viability – consider FDG PET or MRI as highly sensitive methods.<sup>5,27,51,53</sup>

### Future directions

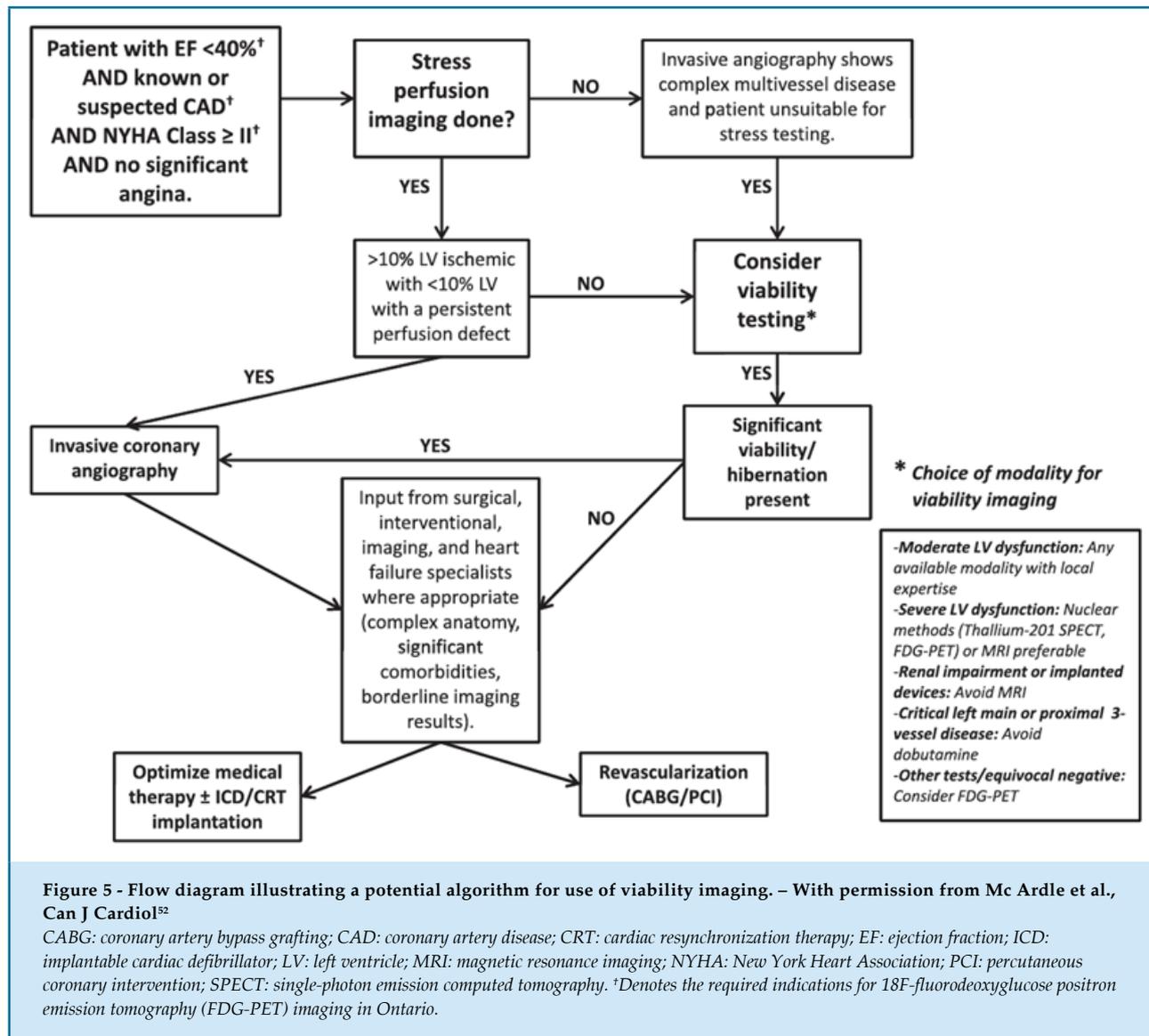
The IMAGE HF (Imaging Modalities to Assist with Guiding therapy in the Evaluation of patients with Heart Failure) project includes a group of clinical trials, one of which is the AIMI-HF trial (Alternative Imaging Modalities in Ischemic Heart Failure) (NCT01288560)<sup>54</sup> (Figure 7). AIMI-HF is a multicenter randomized trial and registry study involving centers from Canada, United States, Finland, Brazil and Argentina. It compares the impact of standard of care investigation (SPECT) *versus* advanced imaging (PET and MRI) for viability and ischemia assessment. Composite outcomes are cardiac death, resuscitated cardiac arrest, MI and cardiac hospitalization. In cases where the patient is not randomized to one or the other arm, they are included in a clinical registry.<sup>54</sup> This

study will help us understand the impact of the advanced cardiac imaging modalities for the viability assessment and their impact on patient outcome.

PET and MRI viability targets are different and may be complementary. The availability of PET/MRI scanners is growing, and an initial study suggests the feasibility of simultaneous assessment of FDG uptake and delayed enhancement.<sup>30</sup> Indeed, analysis per segment showed increased accuracy for predicting wall motion recovery in segments of accordance between the modalities.<sup>30</sup> Further trials are needed to show its reproducibility.

Cardiac biomarkers (troponin T and brain natriuretic peptide) are used for patient assessment and as prognostic tools.<sup>54-58</sup> A recent study has demonstrated their correlation with hibernating myocardium independently of ejection fraction, age and kidney function (Figure 8).<sup>58</sup> Future paradigm shifts in the work-up of patients with ischemic HF could involve the use of biomarkers to optimize image-guided therapy or in some cases be independent of imaging to decide revascularization therapy, but this theoretical approach requires specific study.

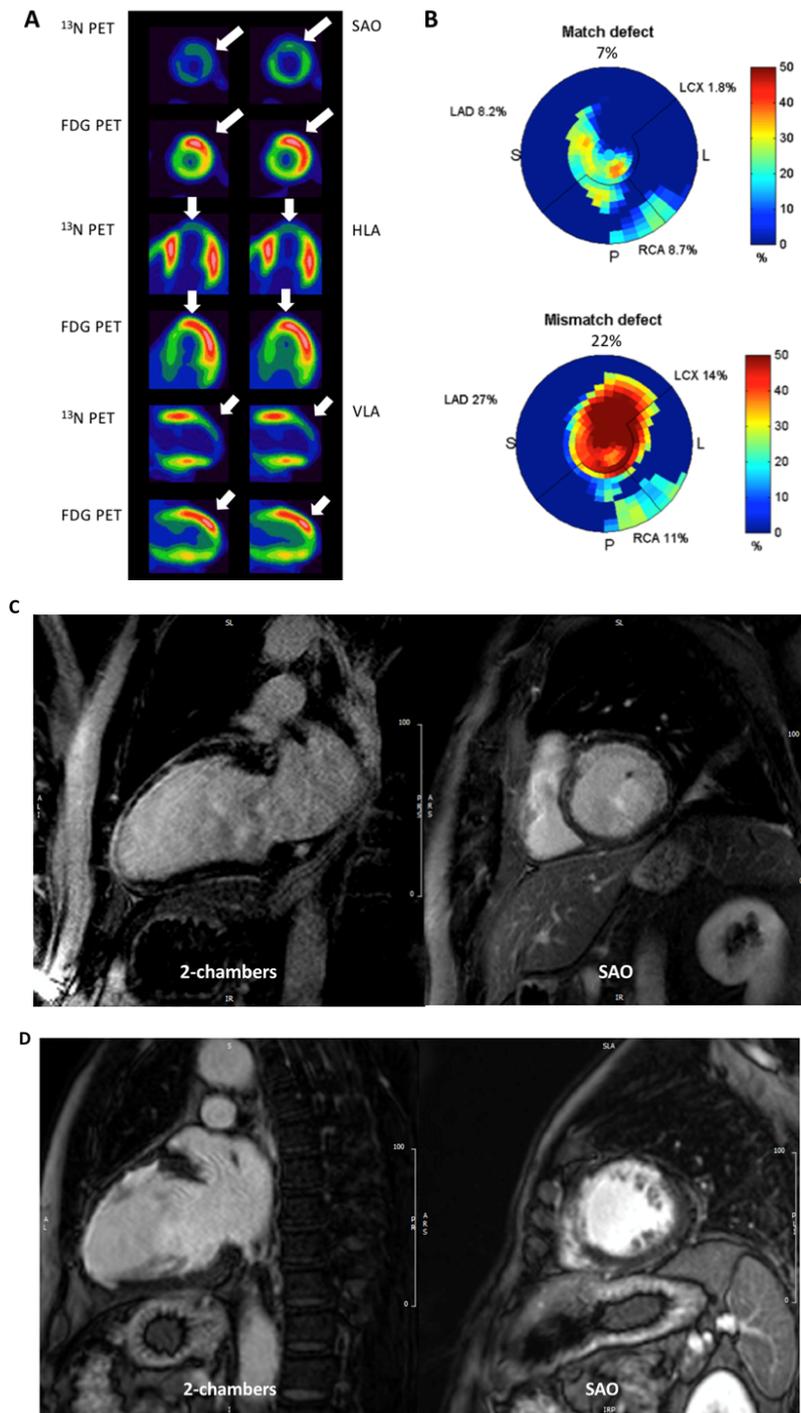
Hibernating myocardium is a substrate for arrhythmia and increases the risk of sudden cardiac death, possibly due to the sympathetic innervation inhomogeneity.<sup>58-62</sup> The ADMIRE trial has used MIBG SPECT to define altered sympathetic neuronal (SN) function in patients with HF, demonstrating higher risk in patients with



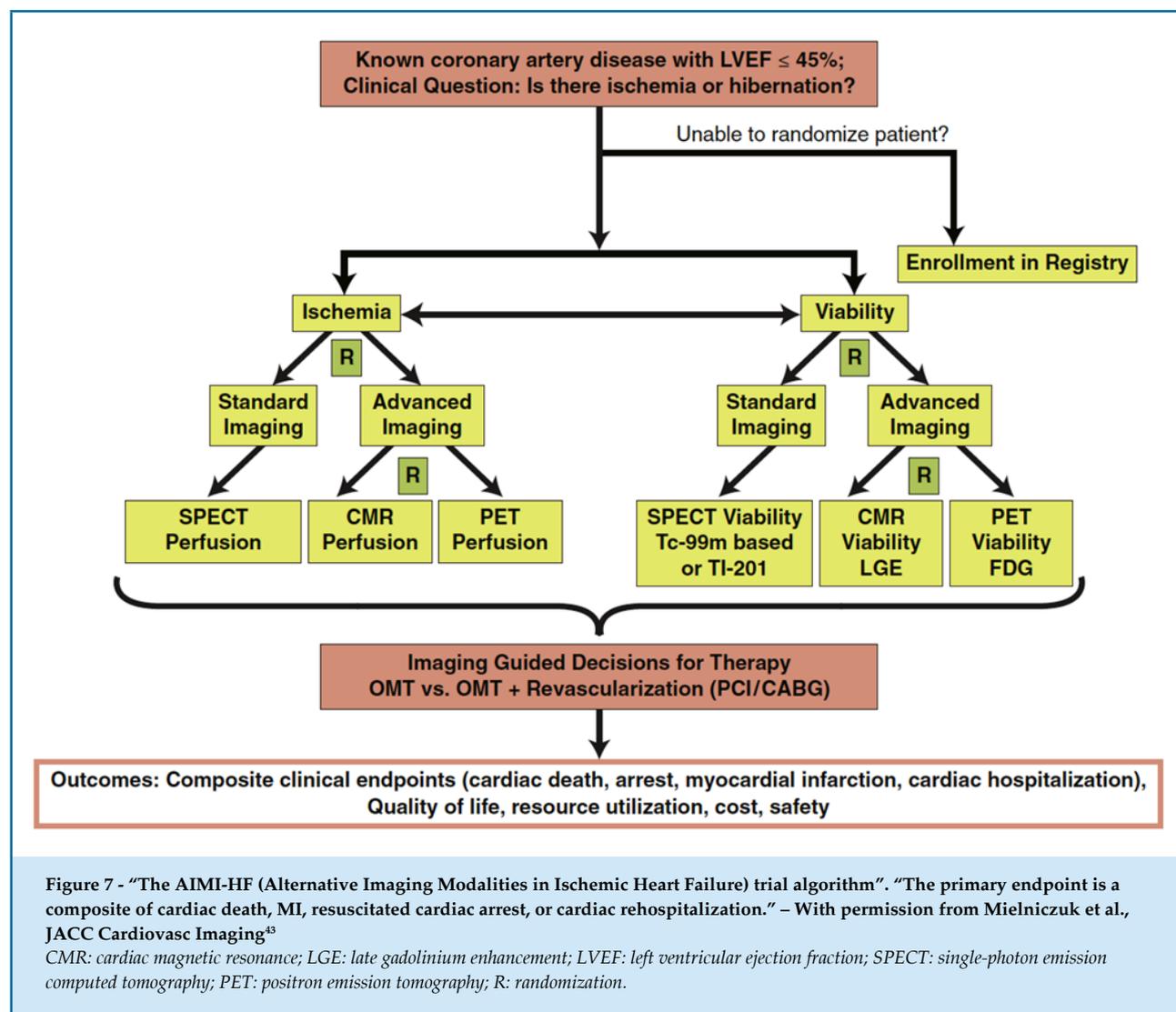
evidence of reduced MIBG uptake reflecting the high SN signal. The PARAPET study (Prediction of Arrhythmic Events with Positron Emission Tomography) has shown that sympathetic denervation measured by <sup>11</sup>C-meta-hydroxyephedrine (HED), a PET tracer able to quantify sympathetic denervation, could predict sudden cardiac death independently of ejection fraction and infarct size.<sup>61</sup> A novel F-18 PET tracer (LMI1195) is under initial evaluation and may be able to also measure myocardial innervation.<sup>62-64</sup> Its main advantage over HED is its longer half-life, which could enable wide distribution and hence potential for wider use of SN function imaging in the future.

## Conclusion

Although the value of viability imaging may have been called into question by the STICH trial, several studies have reinforced the relationship between the extent of hibernating myocardium and improvement in patient outcome, left ventricular ejection fraction and quality of life if nutrient flow can be restored with revascularization. In general, there is accepted utility in using viability imaging in patient populations where decisions for revascularization are most difficult. Ongoing trials will further enable the identification of which patients most benefit from viability imaging and by which methods. Can biomarkers be used to guide



**Figure 6 - (A)** <sup>13</sup>N perfusion PET and <sup>18</sup>FDG metabolism PET in short axis (SAO), horizontal long axis (HLA) and vertical long axis (VLA) showing extensive area of mismatch in the mid to distal anterior wall and apex (white arrow). **(B)** Polar map with quantitative analysis of the scar amount (7%) on the top (match defect) and hibernating myocardium (22%) on the bottom (mismatch). "Given the significant amount of hibernating myocardium, it was recommended that the patient proceed with coronary artery bypass grafting." (adapted from Weifels et al., with permission).<sup>73</sup> **(C)** Cardiac MRI showing subendocardial scar involving > 75% of the myocardium from the basal to apical anteroseptal wall, mid to apical anterior wall and apex, suggesting no viability in the LAD territory in a patient with a history of previous anterior myocardial infarction and coronary angiogram showing occluded mid LAD. **(D)** Cardiac MRI of a patient with occluded proximal LAD with collaterals, 95% stenosis ostial LCx and occluded OM1 showing subendocardial scar from the basal to apical anterior wall, mid to apical anteroseptal wall, and basal to mid lateral wall involving < 50% myocardium, suggesting viability in the LAD and LCx territories. Given these findings, the patient went on to have CABG (LITA->LAD, left radial->OM1, SVG->right PIV). He is clinically doing well one year post-CABG.  
 LAD: left anterior descending artery; LCx: left circumflex artery; OM1: first marginal artery; SAO: short axis.



revascularization or at least to guide imaging to guide revascularization? Further research is needed here. In the meantime, clinicians, surgeons, interventional cardiologists and imaging specialists must work together as a team to enable the best decisions for each individualized patient in order to optimize the patient's desired outcomes.

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### Author contributions

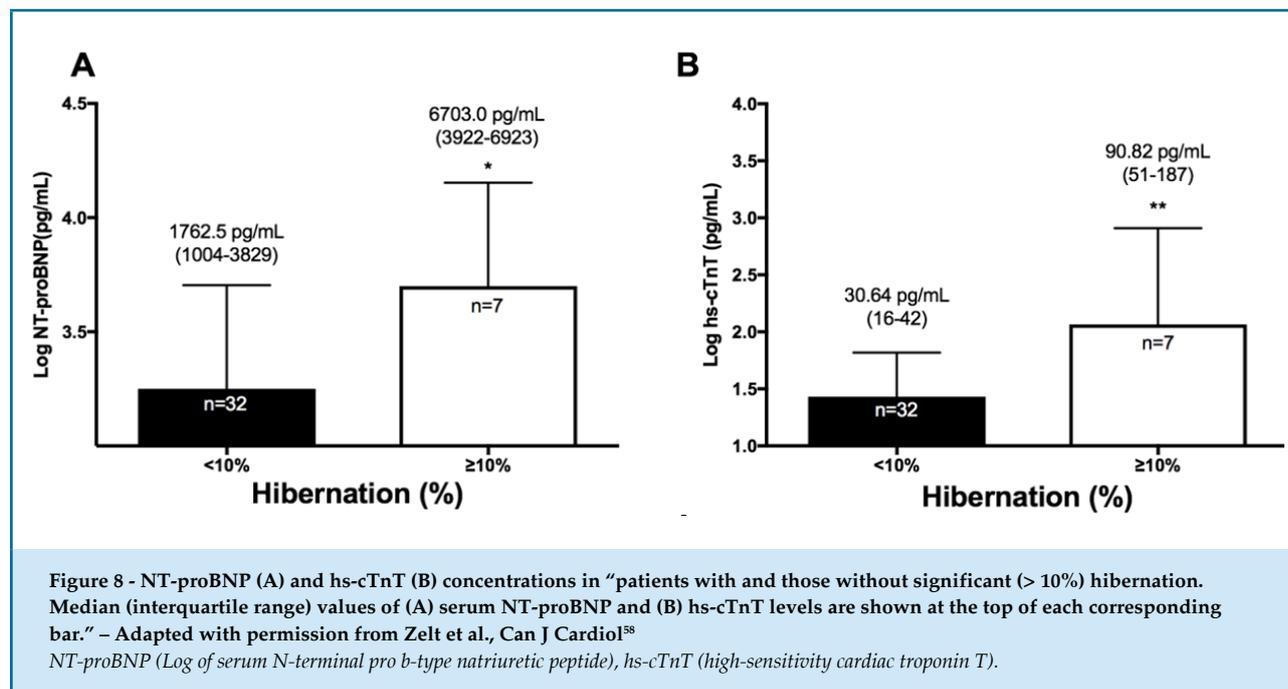
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### Potential Conflict of Interest

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### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

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

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