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Review

The Current Role of Viability Imaging to Guide Revascularization and Therapy Decisions in Patients With Heart Failure and Reduced Left Ventricular Function

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ABSTRACT

This review describes the current evidence and controversies for viability imaging to direct revascularization decisions and the impact on patient outcomes. Balancing procedural risks and possible benefit from revascularization is a key question in patients with heart failure of ischemic origin (IHF). Different stages of ischemia induce adaptive changes in myocardial metabolism and function. Viable but dysfunctional myocardium has the potential to recover after restoring blood flow. Modern imaging techniques demonstrate different aspects of viable myocardium; perfusion (single-photon emission computed tomography [SPECT], positron emission tomography [PET], cardiovascular magnetic resonance [CMR]), cell metabolism (PET), cell membrane integrity and mitochondrial function (201Tl and

RÉSUMÉ

Cet article décrit les données à l'appui de l'imagerie de viabilité en tant qu'outil pour orienter les décisions en matière de revascularisation, les controverses qu'elle suscite et ses répercussions sur les résultats pour les patients. Trouver l'équilibre entre les risques liés à l'intervention et le bienfait possible de la revascularisation est un enjeu fondamental chez les patients présentant une insuffisance cardiaque d'origine ischémique. Les différents stades de l'ischémie entraînent des changements adaptatifs dans le métabolisme et le fonctionnement du myocarde. Un myocarde dysfonctionnel mais viable est capable de se rétablir dès lors que le débit sanguin est rétabli. Les techniques d'imagerie moderne permettent d'observer les différents éléments d'un myocarde viable : perfusion (tomographie d'émission

Despite recent advances in the treatment of cardiovascular (CV) disease, heart failure (HF) continues to cause significant morbidity and mortality, driven by coronary artery disease (CAD) in two thirds of patients with HF.[1] The challenge is to define which patients with HF of ischemic origin (IHF) will benefit from a strategy of revascularization in addition to guideline directed medical therapy (GDMT), which is the mainstay of treatment in these patients.

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See page 1026 for disclosure information.

Fundamental Concepts Regarding Viability Imaging

In patients with IHF, left ventricle (LV) dysfunction can result from scar, stress-induced ischemia, resting ischemia, remodelling, stunning, hibernation, or a combination of these processes. To understand the potential benefits of revascularization, knowledge of the different myocardial states in IHF is essential.[2-7]

Myocardial ischemia refers to a state of inadequate oxygen delivery that cannot meet the myocardium's metabolic demand.[8] The severity of inadequate flow will determine the intrinsic molecular adaptations of the myocardium and accounts for both the time course and the extent of reversibility after a successful revascularization.[8]

Dysfunctional but viable myocardium develops as an adaptation to ischemia of varying degrees of severity and duration (after acute, subacute, or persistent perfusion deficits) not

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99mTc-based SPECT), contractile reserve (stress echocardiography, CMR) and scar (CMR). Observational studies suggest that patients with IHF and significant viable myocardium may benefit from revascularization compared with medical treatment alone but that in patients without significant viability, revascularization appears to offer no survival benefit or could even worsen the outcome. This was not supported by 2 randomized trials (Surgical Treatment for Ischemic Heart Failure [STICH] and PET and Recovery Following Revascularization [PARR] -2) although *post-hoc* analyses suggest that benefit can be achieved if decisions had been strictly based on viability imaging recommendations. Based on current evidence, viability testing should not be the routine for all patients with IHF considered for revascularization but rather integrated with clinical data to guide decisions on revascularization of high-risk patients with comorbidities.

monophotonique [TEM], tomographie par émission de positons [TEP], résonance magnétique cardiovasculaire [RMC]), métabolisme cellulaire (TEP), intégrité des membranes cellulaires et fonction mitochondriale (TEM après injection de 201Tl et de 99mTc), réserve contractile (échocardiographie à l'effort, RMC) et tissu cicatriciel (RMC). Les études observationnelles indiquent que les patients atteints d'une insuffisance cardiaque d'origine ischémique dont la viabilité myocardique est importante pourraient tirer des bienfaits de la revascularisation, au lieu de recevoir seulement un traitement pharmacologique, mais que chez les patients dont la viabilité myocardique est moindre, la revascularisation ne semble offrir aucun bienfait sur le plan de la survie et pourrait même aggraver le pronostic. Ce constat n'a pas été confirmé dans deux études à répartition aléatoire (études STICH [*Surgical Treatment for Ischemic Heart Failure*] et PARR [*PET and Recovery Following Revascularization*] -2), bien que les analyses *post-hoc* indiquent qu'un bienfait peut être obtenu si les décisions reposent uniquement sur les recommandations relatives à l'imagerie de viabilité. D'après les données probantes actuelles, les épreuves de viabilité ne doivent pas être systématiques chez tous les patients atteints d'une insuffisance cardiaque d'origine ischémique chez qui la revascularisation est envisagée. Leurs résultats doivent plutôt être intégrés aux données cliniques pour orienter les décisions concernant la revascularisation chez les patients à risque élevé présentant des comorbidités.

severe enough to cause cell death.[3] The resting contractile function is altered, but the myocytes are still alive, and cell dysfunction can be reversed after coronary flow is restored. Three types of response can occur and present a partially overlapping continuum: remodelling, stunning, and hibernation (Fig. 1[9-15]).

Myocardium in jeopardy refers to ischemic and/or viable tissue.

In *nonviable myocardium*, scar occurs when cell death is irreversible and noncontracting (fibrotic) tissue replaces the normal myocardium. Scar can be transmural or involve only part of the wall thickness. Viability testing aims to prospectively differentiate scar from jeopardized myocardium that has the potential to recover after revascularization.

Clinical Evidence for Viability Testing

Although there exists an abundance of nonrandomized data that suggest the presence of viability can define patients likely to benefit from revascularization,[3,16-20] randomized studies to date have not demonstrated statistically significant differences.[4,16,21-23] There are some observational data to suggest that the extent of hibernating myocardium can predict the likelihood of outcome benefit or recovery [5,24-27] and *post-hoc* randomized controlled trial (RCT) data observed that if there is adherence to imaging-based recommendations, there may be outcome benefit.[4,16,28]

Revascularization carries inherent upfront risks of mortality and morbidity, which are more pronounced in patients with HF. When revascularization is considered in patients with IHF, 2 important questions arise: first, does revascularization benefit patients with severe HF and, second, is viability testing of additional value in decision making?

The **S**urgical **T**reatment for **I**schemi**c** **H**eart Failure (STICH) extension study showed a long-term (10-year) survival benefit from coronary artery bypass grafting (CABG) compared with optimal medical therapy (OMT) in patients with LV dysfunction and target vessels suitable for revascularization.[29] However, given the conflicting and scarce evidence,[21,30] revascularization is not necessarily the treatment of choice for all. Viability testing might be beneficial in these cases. A multitude of observational studies suggest the presence of viable myocardium results in better recovery in LV function[3,17,25,31] and survival after revascularization.[3,16,17,24,26] Further, studies have shown that the extent of viability correlates with the magnitude of improvement in HF symptoms post-surgery[25,27] and that positron emission tomography (PET)-guided management results in improved quality of life.[32] However, these results are not consistent across studies.[22,33,34]

Many previous studies are limited by retrospective design with possible selection bias, and many predate the use of current evidence-based medications. Six meta-analyses of this topic have been published since 2002.[3,18,19] Their findings were that the beneficial effect of revascularization is largely dependent on the presence of myocardial viability. From Orlandini et al., 32 nonrandomized studies with 4328 patients and 4 randomized studies with 1079 patients were combined.[19] The results from nonrandomized studies suggested significant mortality benefit from revascularization only in patients with viability. However, no mortality benefit from revascularization was evident in the 4 randomized studies, leaving the overall interpretation of these results inconclusive.

There are 2 large randomized studies to address the question of viability testing in revascularization. The **P**ET **a**nd **R**ecovery Following **R**evascularization (PARR)-2 was the first study designed to answer to this question;[4] 430 patients with left-ventricular ejection fraction (LVEF) $\leq$ 35% from 9 centres were randomized to either viability assessment with 18fluordeoxyglucose (FDG)-PET or standard care without

PET. There was a trend toward benefit for the primary outcome (cardiac death, myocardial infarction, and cardiac hospitalization) at 1 year in the PET arm. However, not all the patients were treated according to what the imaging findings recommended. In a *post-hoc* analysis, a significant reduction in outcomes was observed in the PET arm (hazard ratio [HR] 0.62; $P = 0.019$) in the cohort in whom management decisions adhered to the imaging recommendations (75% of cases). Long-term (5-year) follow-up showed similar findings (HR 0.73; $P = 0.042$).[16]

The importance of expert image interpretation and subsequent clinical decision making was highlighted in the Ottawa-5 substudy that had 111 patients from an experienced centre with interpretation expertise and easy access to FDG-PET.[28] In this scenario, patients in the PET arm had a clear benefit when compared with standard care (19% vs 41%) at 1 year (HR 0.34; $P = 0.005$). In addition, the amount of hibernating myocardium plays an important role in patient outcome (Supplemental Fig. S1). Ling et al. showed that with increased extent of mismatch (hibernating myocardium), the likelihood of benefit with revascularization also increased.[24] In a PARR-2 substudy, a cutoff of 7% distinguished patients who would or would not benefit from revascularization.[5] Similar cutoffs of 5% to 10% have been found in other studies.[24,25]

In the STICH trial,[22] 1212 patients with ischemic LV dysfunction (EF $\leq$ 35%) and severe CAD eligible for CABG were randomized to CABG + OMT or OMT alone. Patients with $\geq$ 50% left main disease or class III to IV angina were excluded. There was no significant reduction in mortality at 5 years but a significant reduction in mortality in the extension study after 10 years (all-cause mortality 58.9% vs 66.1%, $P = 0.02$, CV mortality 40.5% vs 49.3%, $P = 0.006$).[29] There are some important limitations to this trial: namely, the crossover among groups and enrollment of patients without significant clinical HF (39% New York Heart Association [NYHA] class I-II).

The viability substudy of STICH looked at the outcome of 601 patients who, in a nonrandomized fashion, underwent viability testing with single-photon emission computed tomography (SPECT), dobutamine stress echo, or both.[34] Viability was defined in a binary manner; 487 (81%) had viable myocardium. At a median follow-up of 5.1 years, there was no outcome difference in patients with viability according to the randomized treatment strategy (CABG + OMT vs OMT alone). The STICH viability study was limited by the nonrandomized selection for viability testing, not using more advanced methods (cardiovascular magnetic resonance [CMR] or PET), LV remodelling (mean LV end-diastolic volume index was severely dilated 123 mL/m^2), and the observation that very few patients (19%) did not have viable myocardium.

The distinctions from PARR-2 and the STICH viability substudy may be explained by differences in patient selection, imaging modalities, and study methodology (Supplemental Table S1).

There are 2 other small RCTs. The **H**ealing and **E**arly **A**fterload **R**educing **T**herapy (HEART) trial used stress echocardiography and randomized 138 patients with CAD and LVEF $\leq$ 35% to conservative therapy or angiography with the intention to revascularization and showed no outcome difference but was acknowledged to be underpowered.[21] Siebelink randomized 103 patients to FDG PET vs 99mTc-MIBI SPECT and showed no outcome difference.[23] Only 36 (35%) of the 103 patients had reduced EF $\leq$ 30%.[23] The small sample sizes of these studies precluded any definitive conclusions.

Imaging Modalities to Assess Myocardial Viability

The techniques for assessing myocardial viability are based on detecting one or more of the markers of dysfunctional myocardium: perfusion, cell metabolism, mitochondrial function, cell membrane integrity, contractile reserve, and scar (Table 1). All these modalities have advantages and disadvantages (Table 1). Respectively, all these methods can be used with good accuracy (Supplemental Fig. S2) when interpreted by acknowledged experts.

Dobutamine stress echocardiography

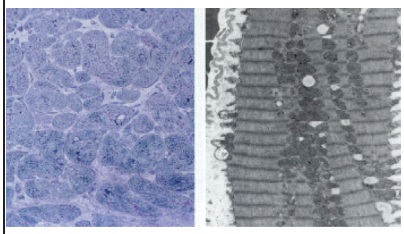
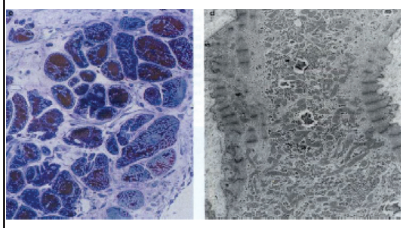
Dobutamine stress echocardiography (DSE) is used to assess regional myocardial contractile reserve.[35] Low-dose dobutamine can lead to increased contractility in dysfunctional segments that are viable. At higher doses, viable segments may further improve or show reductions in contraction, reflecting inducible ischemia, but will not show incremental contractility if they are scarred.[26,36,37] The reported sensitivity and specificity of DSE are 80% and 78%, respectively, in predicting regional LV function improvement following revascularization, considered the most specific of the methods in experienced hands[3] (Supplemental Fig. S2). Intravenous contrast agents can be used to improve the accuracy of DSE. Further, speckle tracking imaging represents a novel additional echo method to assess viability that can be used both at rest or with stress.[38,39]

SPECT

SPECT is a widely available modality with well-established clinical and prognostic validation.[40] Radionuclide-labelled tracers sequester within myocytes with intact cell membranes and the regional concentration is compared with the peak uptake to assess viability. The most widely used tracers for viability imaging are the potassium analog thallium-201 (201Tl) and lipophilic intramitochondrial molecule technetium-99m (99mTc)-labelled compounds, whereby their cardiac uptake reflects sarcolemma membrane integrity and mitochondrial function, respectively.[3,41] Compared with techniques based on the assessment of residual contractile recovery, SPECT has higher sensitivity and lower specificity.[3]

PET

PET imaging using perfusion tracers such as 13N-labelled ammonia (13NH3) or Rubidium-82 (82Rb) combined with images using the glucose analog 18F-FDG is an effective technique to provide information on both myocardial perfusion and metabolism.[42-44] Concordant reduction in both perfusion and FDG uptake ("flow-metabolism match") indicates irreversibly injured scarred myocardium, whereas regions in which FDG uptake is increased relative to a perfusion defect ("flow-metabolism mismatch") represent myocardial hibernation (Table 2). Healthy myocardium also uses glucose in the nonfasting state. The preparation for FDG PET viability imaging is straightforward and involves a 12-hour fast, then an oral glucose load, and then monitoring of glucose levels. Patients with abnormal glucose response will receive insulin. In patients with

Definition and picture	Structural / Phenotype	Metabolism	Cellular Membrane	Ca^{2+} handling proteins	Others
Normal myocardium  Preserved myocyte metabolism, cell membrane integrity, presence of blood perfusion, presence of contractile reserve, and preserved wall thickness	Myofibrillar phosphorylation Sarcomere in the perinuclear area	Use of free fatty acids during fasting Normal sarcoplasmic reticulum and O_2 consumption	Adhesion molecules (β_1 integrin, N-cadherin, desmoplatin, vinculin) in the intercalated disc area at the distal area of cardiomyocytes	Normal Ca^{2+} uptake Normal levels of SERCA/2a	
Viable dysfunctional myocardium 	↓ Myofibrillar volume density ↓ Protein (Actin, Myosin, Desmin, Titin) Myocyte apoptosis	Suppression of O2 consumption Suppression of mitochondrial function ↓Glucose uptake (↓ GLUT1) Glycogen deposit	Redistribution of adhesion molecules to the lateral membrane increasing tensile force between cells	↓Ca^{2+} influx ↓SERCA ↓SERCA2a	↑Pro-inflammatory cytokines (TNF-α etc)[9] Upregulation of inducible nitric oxide synthase (iNOS)[9] Sympathetic denervation Changes in the expression of α- and β- adrenergic receptors

Remodelling
Compensatory myocyte changes taking place in viable dysfunctional myocardium but also in remote normally perfused regions to maintain cardiac output. The changes in ventricular geometry, local wall strain, filling pressures, and neurohormonal factors initially induce compensatory hypertrophy, but, in the long term, deleterious adverse remodelling and ventricular dilatation occurs.[10,11]

Stunning
Reversible contractile dysfunction after abrupt, transient ischemia.[6] This situation normally occurs after a single brief episode of ischemia in which, after prompt restoration of blood flow, the contractile dysfunction persists temporarily followed by recovery (which may be minutes, hours, days, or weeks).

Hibernation
Result from repetitive stunning, repeated episodes of ischemia, persistent perfusion defects at rest, or reductions in the coronary flow reserve.[8,12,13] The contractile function at rest is reduced, what is thought to be a protective mechanism to downregulate oxygen consumption (and downregulation of perfusion) to ensure myocyte survival.[6,8,12] By definition, hibernating myocardium has the potential to recover with restoration of normal blood flow, and therefore it can only be defined with certainty after revascularization. Serial histologic and proteomic studies post-revascularization have shown that, for the most part, the cellular changes are recoverable.[7]

Figure 1. Definitions and cellular differences between normal and different types of viable dysfunctional myocardium. Adapted from Bayeva et al.[8] and Frangogiannis et al.[14] Pictures from Vanoverschelde et al.:[15] light microscopy pictures (**on the left**) and electron microscopy pictures (**on the right**); with permission from Wolters Kluwer Health.

known diabetes, the insulin clamp is the preferred approach, as it yields the best quality images.[45] An example of a PET viability study is shown in Figure 2.[46]

CMR

CMR, combined with the use of gadolinium-chelated contrast agents, can provide information on perfusion and viability concomitantly. Gadolinium does not penetrate myocytes with intact membranes. The contrast agent has a greater volume of distribution into regions of altered cell permeability, as occurs in scarred or acutely infarcted tissue, enabling the assessment of the transmurality of necrosis and the presence of viable tissue. In conjunction with dobutamine stress, CMR can also provide information on global LV function, regional wall motion, and thickening.[47] Romero et al. pooled 24 CMR

Table 1. Imaging modalities to assess myocardial viability

Modality	Mechanism	Findings indicative of viability	Advantages/disadvantages
Dobutamine echocardiography/ CMR	Contractile reserve*	Improvement by visual or strain rate imaging (echo)	A: Specific, widely available, without radiation, *can detect ischemia, assesses valvular disease* D: Interobserver variability, risk of dobutamine†
SPECT Thallium -201	Perfusion: Sarcolemma membrane integrity (K^+ analogue)	Tracer uptake: > 50% of maximum	A: Widely available, moderate cost D: Radiation dose, moderate sensitivity with low specificity
Technetium -99m-labelled tracers	Mitochondrial membrane integrity	> 50% to 65% of maximum	A: Widely available, moderate cost D: Moderate accuracy
PET Perfusion /metabolism	Perfusion: 13NH3, 82Rb, 15O-water Myocyte glucose utilization: FDG	Flow-metabolism mismatch = hibernation, (Match = non-viable)	A: Highly sensitive D: Limited availability, high cost, need for glucose load or insulin clamp in patients with diabetes
CMR	LGE Wall thickness	Scarring (LGE) < 50% wall thickness Systolic thickening of a dyskinetic segment	A: Highly sensitive, without radiation, assesses valvular disease D: Limited availability, high cost, risks in renal failure, cannot use with certain devices

CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; PET, positron emission tomography SPECT, single-photon emission computed tomography.

* Biphasic response. Dobutamine low dose 5 to 10 μg/kg/min leads to improved contractility in hibernating myocardium. Dobutamine high dose up to 40 μg/kg/min (+atropine) leads to increased oxygen consumption, induced ischemia, and decreased contractility.

† Risk of potentially life-threatening complications 0.2%.[37]

viability studies with 698 patients looking for functional improvement after revascularization. They found that delayed gadolinium enhancement < 50% of wall thickness, > 2 mm wall motion change in low-dose dobutamine infusion, and > 5.5-mm to 6-mm end-diastolic wall thickness predicted function myocardial recovery measured by serial CMR.[20] There are data supporting that even when the end-diastolic wall thickness is ≤ 5.5 mm, there is potential for recovery as long as the scar is not transmural.[48] Dobutamine CMR can detect ischemia and viabity by contractive reserve. Adenosine CMR can detect perfusion and define regions at risk of ischemia. Native T1 tissue mapping is an emerging method to assess transmurality of infarction without contrast material.[49] Figure 3 illustrates an example of a CMR study.

Data regarding cost effectiveness of viability testing and the different modalities are limited. One study applied a "decision analysis model" that evaluated patients undergoing revascularization or not and PET imaging or not; an algorithm was developed. They demonstrated that viability PET imaging "may be cost effective in the selection of patients with poor LV function referred for CABG."[50]

The optimal choice of which modality to use is determined, in part, by patient characteristics and local factors (expertise, availability, and practice patterns). In the absence of direct comparative outcome evidence, the authors suggest the following approach:[51,52]

1. Moderate LV dysfunction: any modality with local expertise.
2. Severe LV dysfunction: nuclear methods (SPECT, PET) or CMR late gadolinium enhancement (LGE), which are more sensitive than contractile reserve.[3,20]
3. Renal failure (GFR < 30) or CMR incompatible devices; avoid CMR.
4. Critical left main or proximal 3-vessel disease; avoid dobutamine.
5. Equivocal or negative results on another viability test, in which certainty is needed to completely rule (in or) out viability; consider PET or CMR as highly sensitive methods.[3,20]

Clinical Perspective

The decision whether to revascularize a patient with significant LV dysfunction can be one of the most difficult decisions in medical practice, notably in patients without significant ischemia or angina. As RCT data have not supported routine use of viability imaging in IHF, its use should be limited to situations in which decisions are most difficult. Based on *post-hoc* analyses and observational data, viability imaging may contribute to risk stratification and selection of patients considered eligible for myocardial revascularization.[3,4,16,18-20,28,53]

GDMT includes optimal pharmacological and non-pharmacological therapy for all patients and implantable-device therapy for appropriately selected patients as key therapies for patients with IHF. The selection for percutaneous mitral valve procedures is still in evolution.[54,55] In addition, LV-assist devices and cardiac transplantation are advanced treatment options for a minority of patients. Revascularization offers the potential for improved survival and quality of life for certain patients with IHF.[25,27,29,32,56] *Post-hoc* RCT and observational data suggest that this may be particularly true for patients with high ischemic burden and viable myocardium and/or low scar burden.[3,4,16,18-20,28,53,56] Other potentially useful parameters to guide therapeutic strategies include remodelling, LVEF, right

Table 2. Characteristics of viable and nonviable dysfunctional myocardium and their clinical relevance

Myocardium	Flow/ perfusion	Glucose metabolism (FDG)	Function/ contractile reserve	Structural changes	Potential to recover/ clinical relevance
Viable					
Stunning	Preserved at rest (following transient ischemic insult)	Variable (normal, increased or reduced)	Reduced	No	Likely to recover if ischemic injury does not persist or become repetitive; revascularization can prevent recurrent stunning
Hibernation	Reduced	Preserved or increased (= perfusion-metabolism mismatch)	Reduced	Yes some*	May have partial /delayed or full recovery if adequate revascularization can be achieved
Ischemia	Preserved at rest, impaired at stress	Normal at rest, increased at stress	Preserved at rest, impaired at stress	No	May benefit from revascularization to prevent recurrent ischemia
Nonviable					
Scar	Reduced	Reduced	Absent	Fibrosis	Unlikely to recover with or without revascularization

Data from multiple sources.[3-6,10,16,24,28,46,51,52,69]
FDG, 18F-fluorodeoxyglucose.
*See Figure 1.

ventricular failure, pulmonary hypertension, mitral or tricuspid regurgitation, as well as duration of cardiac dysfunction as suggested by Bax et al. and others.[53,57] However, the intersection and application of these complex parameters into a clinical decision remains a challenge.

Guideline-driven management supports revascularization for patients with IHF if they have reversible ischemia or a significant amount of viable myocardium above the method-specific cutoffs (Table 3).[58] Assessment should include scar burden (defined as the total amount of scar in the LV expressed as a percentage of the total LV), as it is an independent prognostic factor as well as an important variable for treatment choice.[20,31] The degree of LV remodelling also plays an important role. It is known that advanced remodelling in IHF is associated with poor outcomes, regardless of presence of viability/ischemia.[59-61] In at least 1 study, even viable myocardium did not improve with revascularization in the context of extensive remodelling.[62] On the other hand, others suggest that a larger LV end-systolic volume index (LVESVI) $>$ 79 mL/m^2) actually favours revascularization.[63] Therefore, the data on the interaction of remodelling and viability extent are contradictory and, at present, there are no validated remodelling cutoffs for revascularization benefit.[61-63]

Viability testing should be limited to patients with IHF for whom revascularization decisions are ambiguous and most difficult, such as patients without angina or demonstrated reversible ischemia with moderate-to-large regions of fixed perfusion defects and/or with multiple comorbidities (Table 4). In some patients, the decision to revascularize is less controversial, and, in this cohort, viability testing is unlikely to be of benefit.[51,63] These characteristics are angina Canadian Cardiovascular Society (CCS) $>$ II, patients with normal or mild LV dysfunction, critical left main CAD, patients with good revascularization targets, those with already demonstrated moderate-to-severe ischemia, and those with minimal or no comorbidities.[52,63]

The assessment of myocardial viability with noninvasive imaging modalities may be of importance in certain cohorts, such as patients with chronic total occlusions (CTOs) before the decision for revascularization is made.[64,65] Table 4 lists important clinical and imaging variables that can aid in the decision for requesting viability testing for patients with HF with reduced EF (HFrEF). This is based on the best current knowledge and evidence that, unfortunately, does not include high-quality data achieved through very large well-powered randomized controlled outcome trials.[51,63-65]

Several recently proposed algorithms could be adopted for viability testing in clinical practice.[52,66,67] The presence of ischemic symptoms may define patients who will derive *symptomatic* benefit from revascularization.[68,69]

Patients who have predominantly HF symptoms may benefit from viability testing if they have low-to-intermediate procedural risks without high-risk coronary anatomy features (Fig. 4).

Contributing Factors to Clinical Decision Making

The total amount of myocardium in jeopardy (viable and/or ischemic myocardium) is intuitively pivotal regarding the benefit from revascularization, although most studies have addressed them separately, and some have shown contradictory results. In the analysis of Ling et al., for 648 patients with mean LVEF of 31% undergoing PET, the percentage of viability was prognostic for benefit from revascularization, but ischemia and scar were not.[24] Further, in STICH, inducible ischemia with stress SPECT or dobutamine echocardiography did not correlate with survival prognosis, which was similar to the findings from STICH viability assessment discussed previously.[70] In a trial of 719 patients mostly without HF (only 15% with HFrEF), the patients with moderate-to-high ischemia burden on stress SPECT had better long-term outcomes after undergoing timely revascularization compared with pharmacological therapy only.[71] Complementary

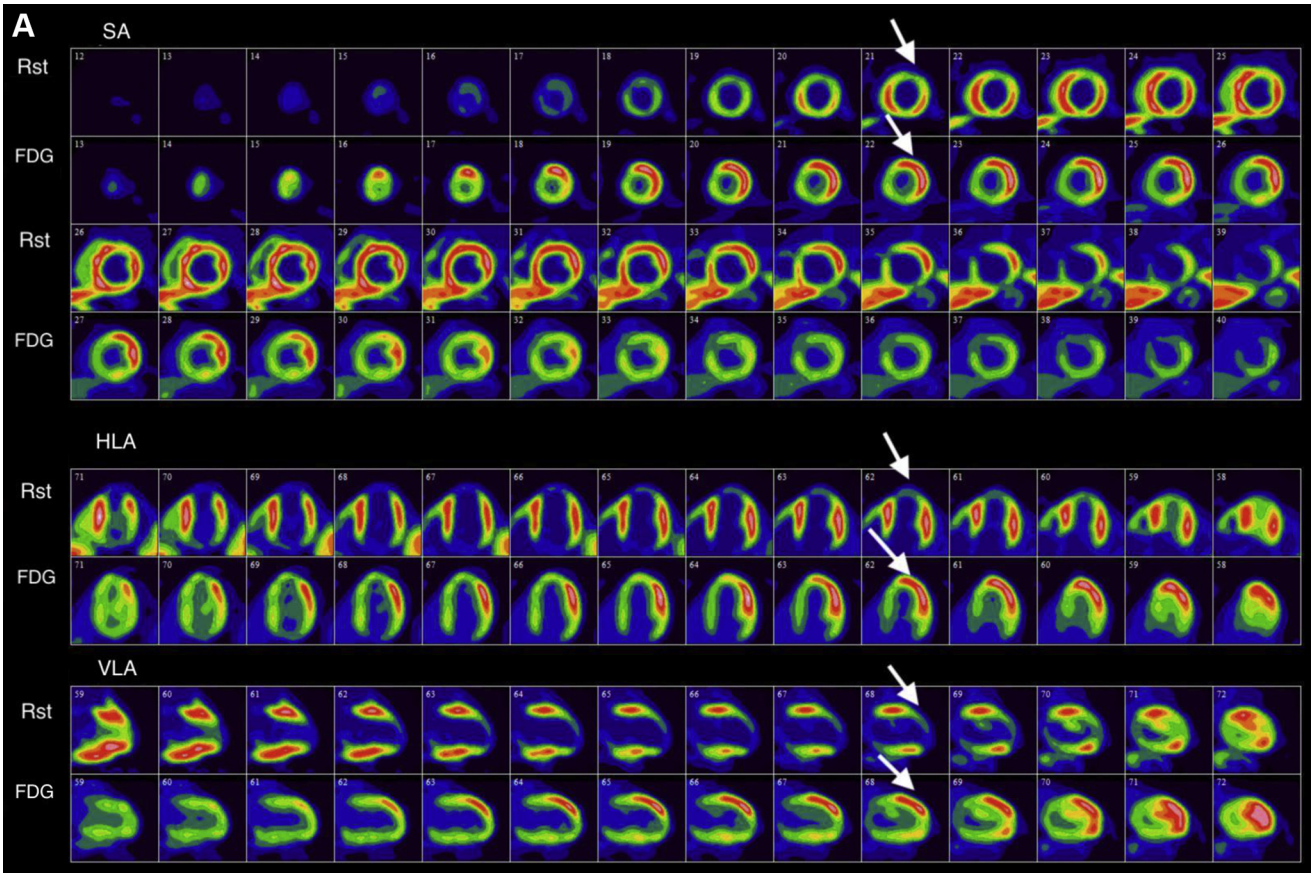


Figure 2. (**A**) Rest N-13-ammonia perfusion (Rst, **top row**) and 18FDG metabolism (FDG, **bottom row)** PET viability study in a patient with documented multivessel disease to aid in revascularization decision making. Perfusion images demonstrate moderate to severe reduction in tracer uptake in the left anterior descending (LAD) territory and moderate reduction in uptake in the basal to mid inferolateral wall (RCA/LCX territory). The FDG images demonstrate an extensive area of mismatch in the mid to distal anterior wall and apex (**white arrows**). (**B**) Polar map with quantitative analysis of the scar amount (7%, match defect) on the **bottom left** and hibernating myocardium (22%, mismatch defect) on the **bottom right**. Given the significant amount of hibernating myocardium, coronary artery bypass grafting was recommended. Reproduced from Wiefels et al.[46] with permission form Springer Nature.

findings were observed in a previous large cohort of 13,555 mainly patients who did not have HF, optimal medical therapy was superior to revascularization in patients with minimal ischemia.[72] The **I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness With **M**edical and **I**nvasive **A**pproaches (ISCHEMIA) trial, which recently completed enrollment, will shed further light on this concept, although not in patients with more severe LV dysfunction (https://clinicaltrials.gov, NCT01471522).

The upfront risk of operative mortality is greater in patients with severe LV dysfunction and needs to be balanced with the possible long-term benefit. The utility of viability testing seems to be greatest in patients for whom both the risks and benefits of revascularization are the highest. A meta-analysis of 26 observational studies with 4119 patients (mean age 64 years, LVEF $\leq$ 35%) undergoing CABG showed an operative mortality of 5.4%.[73] Surgical mortality risk calculators, such as **Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation (EuroSCORE II), (http://www.euroscore.org/calc.html) and the Society of Thoracic Surgeons (STS) score (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx) should be used for guidance. In the STICH trial, the early increased risk with CABG and long-term benefit curves crossed at 2 years, and thereafter mortality was lower in the CABG subgroup.[22]

The arrhythmogenic potential of viable myocardium might play an important role. Studies have shown that the prognostic benefit of revascularization in patients with viability is not tied to improved LV function alone.[74,75] One mechanism for the mortality reduction is related to revascularization of myocardial regions with potential to cause lethal arrhythmias.[76,77] Sympathetic nerves are more sensitive to ischemia compared with the myocytes. The **P**rediction of **Ar**rhythmic **E**vents With **PET** (PAREPET) study demonstrated that a greater amount of sympathetic denervation measured by 11C-HED-PET correlated with greater risk of sudden cardiac arrest.[78] In another study using voltage mapping, it was demonstrated that hibernating myocardium displays abnormal and heterogeneous properties, creating arrhythmogenic potential.[79]

Guidelines for Viability Imaging in Heart Failure

The current task force guidelines from CCS, American College of Cardiology Foundation/American Heart

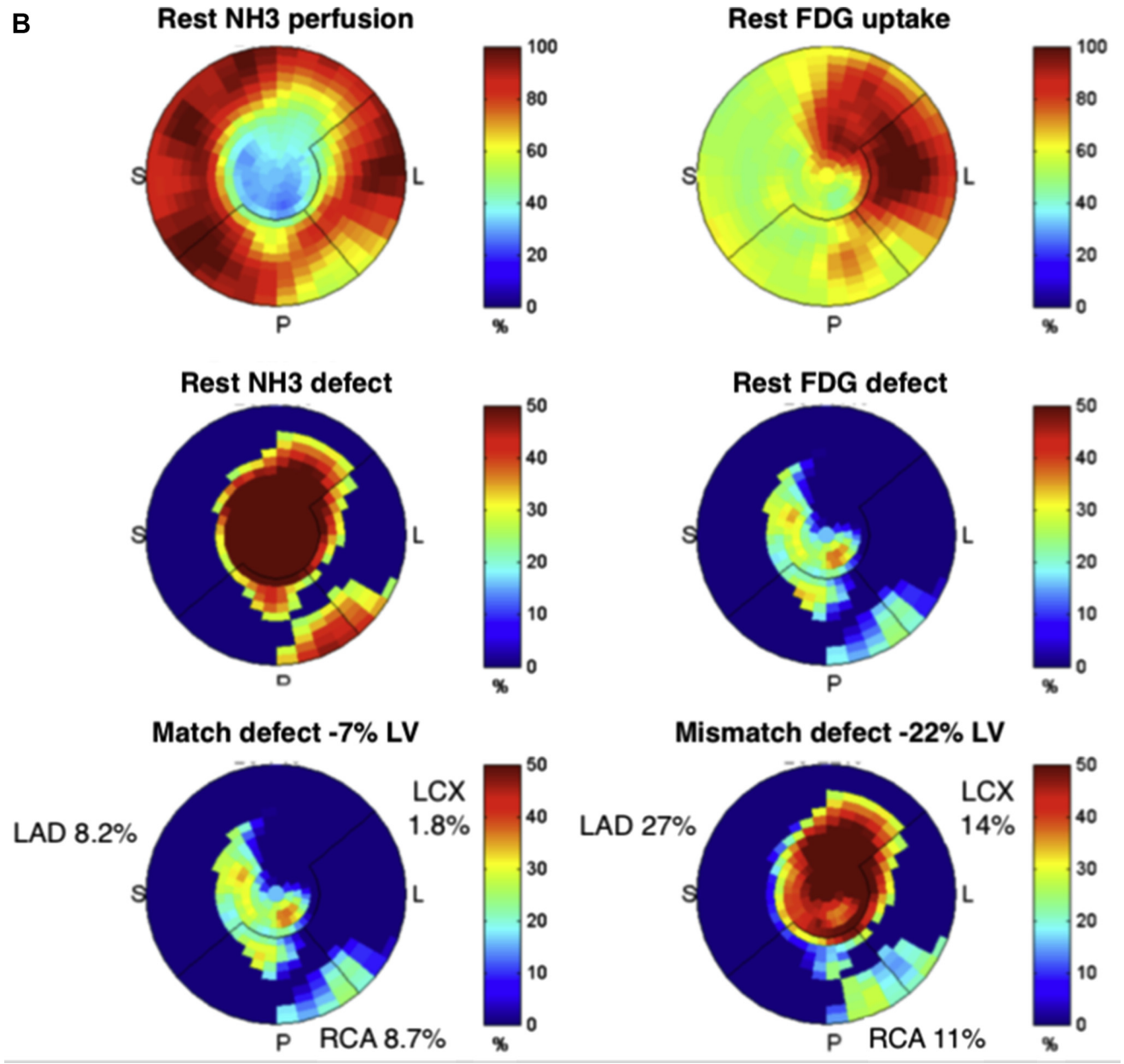


Figure 2. Continued.

Association (ACCF/AHA) and European Society of Cardiology (ESC) offer only general recommendations regarding viability imaging. They state that imaging for myocardial viability (and ischemia) is reasonable in select situations in patients with HF who are considered suitable for revascularization[80] and that noninvasive imaging modalities might provide critical information needed,[81] although the limited experience from RCTs has not been able to demonstrate the routine benefit from viability testing.[58,68,80,81] For recent heart failure guidelines, the class of recommendations for viability imaging is graded IIA (should be considered, level of evidence B-C)[80] or IIB (may be considered, level of evidence B),[68,81] largely because of the lack of support from large RCTs.

Ongoing Trials and Future Directions

The results of the STICH viability study questioned the value of viability testing and likely led to decreased use of viability imaging (or perhaps less inappropriate testing). The journey of viability testing is a fine example of constantly evolving knowledge translation and best practices of seemingly well-established concepts. It has become apparent that conducting a randomized study on the benefit of viability testing in guiding revascularization is challenging, as therapeutic decision making is difficult to control. Without supporting data from the existing RCTs, it is clear that not all patients with HF and CAD require viability testing before revascularization decisions.[4,16,21-23,34] Specifically, viability imaging is not likely to add value in patients with already documented

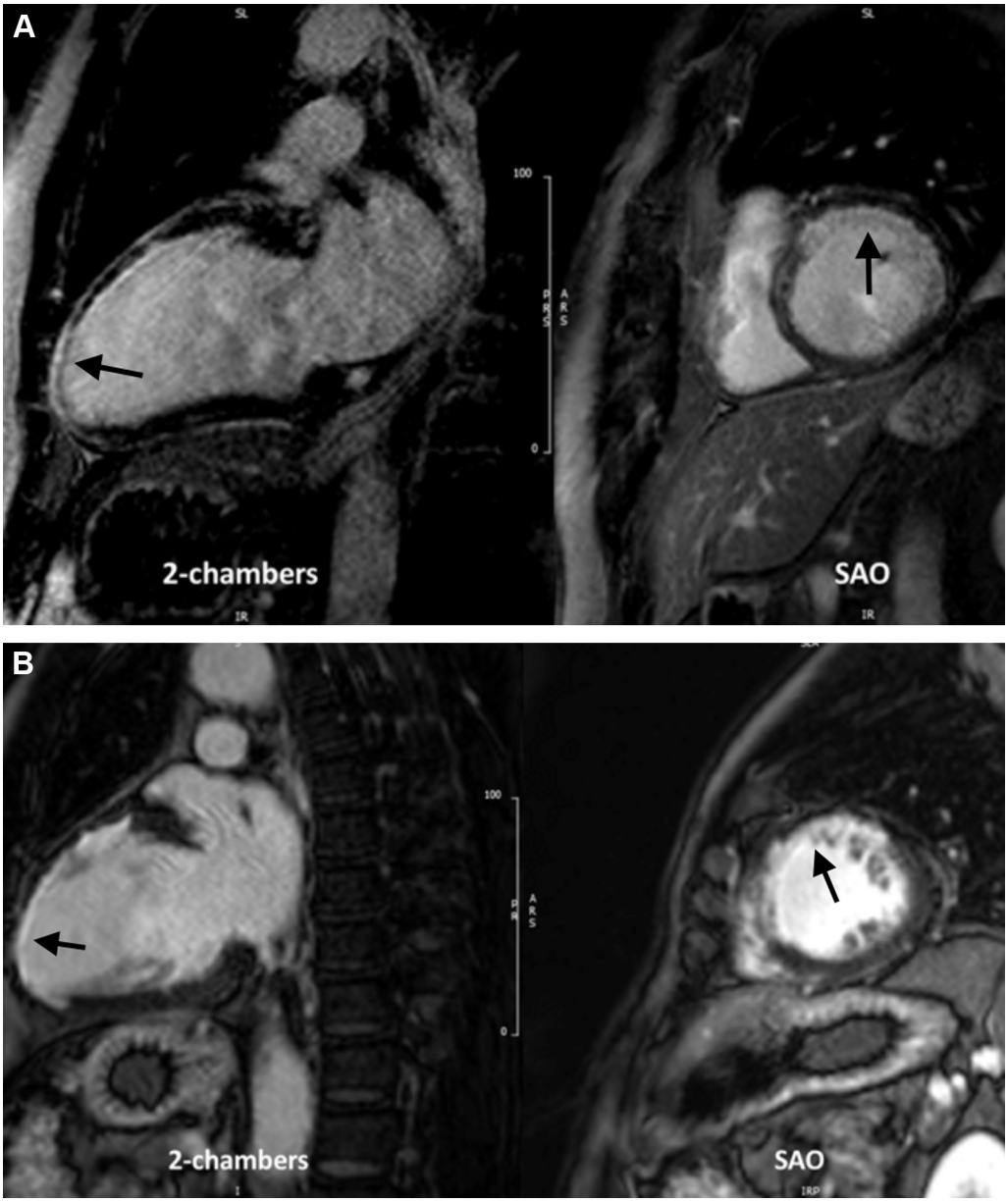


Figure 3. (**A**) Cardiac magnetic resonance (CMR) images of a patient with a history of previous anterior myocardial infarction and occluded mid-left anterior descending (LAD) artery on coronary angiogram showing subendocardial scar involving > 75% of the myocardium from the basal to apical anteroseptal wall, mid-to-apical anterior wall and apex, suggesting no viability in the LAD territory. (**B**) CMR images 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 underwent coronary artery bypass graft. Reproduced from Erthal et al.,[52] with permission from the International Journal of Cardiovascular Sciences, used under CC BY 4.0.

moderate-to-severe ischemia, angina, or severe left main/proximal left anterior descending (LAD) artery disease, as these parameters are generally enough for clinicians to make revascularization management decisions.[22,29,34,67,68,72,82] On the other hand, there is a growing number of patients with diffuse epicardial CAD, microvascular disease, and/or significant comorbidities such as advanced age or diabetes. Based on *post-hoc* RCT data and observational data, viability imaging may have value in patients with IHF,[3-5,16,18-20,28,53,56,57] but—as with any diagnostic test—it should only be applied when it may have impact on management decisions. This may be the case in such higher-risk cohorts, but further research is needed in these populations to prove the potential benefit.

This field has evolved significantly over the past 20 years, and future directions will explore personalized approaches to revascularization in HF including the role of CTO/complex anatomy, the method of revascularization, novel imaging techniques, and serum biomarkers. The likelihood for improvement in symptoms and prognosis is multifactorial. It has been suggested recently that a comprehensive approach that consideres clinical and imaging parameters—sometimes

Table 3. Findings on different imaging modalities for patients with ischemic LV dysfunction that indicate potential to improve LVEF after successful coronary revascularization[58,31]

Imaging modality	Findings
Dobutamine stress echo/stress CMR	Reversible ischemia or > 20% of the LV shown as viable
Single-photon emission computed tomography	Reversible ischemia or a large segment of viable myocardium (> 30% of the LV)
Positron emission tomography	Reversible ischemia or > 7% to 10% hibernating myocardium (or ≤ 27% scar, assuming LV dysfunction due to IHD)
CMR/LGE imaging	Less than 50% wall-thickness scarring shown by LGE in ≥ 4 dysfunctional segments

CMR, cardiac magnetic resonance; IHD, ischemic heart disease; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction.

using multiple imaging modalities—provides complementary information that might improve prediction.[57]

The ongoing **I**maging **M**odalities to **A**ssist With **G**uiding and **E**valuation of Patients With **H**eart **F**ailure (IMAGE-HF) trial, AIMI-HF is an RCT and registry of patients with IHF that compares standard care, which includes SPECT imaging to define ischemia or viability to advanced imaging modalities using PET or CMR. This study may shed light on the impact of advanced-viability imaging on clinical outcomes (composite of cardiac death, arrest, infarction and cardiac hospitalization) (http://clinicaltrials.gov NCT01288560).

Further, beyond revascularization decisions, assessment of contractile reserve,[83] defining regional scarring,[84-86] and septal glucose metabolism[87] have shown potential in resynchronizing therapy (CRT) decision making. Likewise contractile reserve, extent of scar, metabolism in the myocardium—including the papillary muscles—could, in theory, play a role in predicting response and aiding decision making for expanding catheter-based valvular interventions (eg, mitral clip procedures, although studies to date have not reported data on viability imaging).[54,55] Prospective studies are required to test these hypotheses.

Table 4. Parameters for consideration when deciding which patients may benefit from viability assessment[52,63-65]

Viability testing is usually not needed and unlikely to add useful information	Viability testing may add useful information
Younger patients	Older patients
HFrEF with > class II angina	HFrEF without angina
Proven moderate-to-severe ischemia on other testing	No evidence of ischemia; moderate to large persistent perfusion defects suggesting scar (but may be hibernating)
Higher LVEF (> 40 %)	Lower LVEF (< 40 %)
Left main coronary artery disease	Chronic total occlusion
No or limited comorbidities	Severe/multiple comorbidities (renal insufficiency, COPD, previous CABG)

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic index.

Patients with CTO

Although numerous registry studies have shown that successful revascularization of CTOs can be associated with favourable outcomes including improvement in LV function and mortality,[88,89] more recent RCTs have been more sobering.[90-92] The use of viability or ischemia imaging in CTO trials has been limited. The Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusion (EuroCTO) had a requirement of a noninvasive imaging test to assess myocardial viability in the territory of the CTO if there were myocardial dysfunction.[90] Patients with angina or angina equivalent symptoms (n = 396) without acute coronary syndrome were randomized for PCI + OMT vs OMT. The study demonstrated an improvement in symptoms and quality of life. In EXPLORE, patients with ST-elevation myocardial infarction (STEMI) and concurrent CTOs were randomized to percutaneous coronary intervention (PCI) of the CTO lesion early after primary PCI, or no PCI of the CTO lesion. PCI to the CTO lesion did not result in higher LVEF. However, a subgroup analysis showed that if the CTO lesion was in the LAD artery, PCI to the CTO lesion was associated with significantly higher LVEF after 4 months. Baseline CMR was performed in 49% of patients. In dysfunctional segments with transmural extent of infarction < 50% in the CTO territory, the CTO PCI resulted in significantly better recovery of wall thickening compared with no PCI.[91] However, the Recovery of Left Ventricular Function After Stent Implantation in Chronic Total Occlusion of Coronary Arteries (REVASC) showed that PCI of CTO lesions did not improve either CMR-assessed segmental or global LV function at 6 months, but there was little room for improvement, as baseline LVEF was > 43% and one third had no segmental wall-motion abnormalities.[92]

Although these trials used viability imaging as part of enrollment criteria, none of the trials was performed specifically in patients with significantly impaired LVEF with large territories subtended by a CTO and proven viability, whereby successful PCI may be expected to lead to a meaningful increase in LVEF. Indeed, the mean LVEF in EXPLORE was 41% in the PCI arm before randomization, and that of REVASC was > 55%.

One potential utility of viability testing in the presence of a CTO is to enable appropriate clinical decisions on revascularization strategy for concurrent multivessel CAD. Collateral circulation assessed by angiogram is not an effective way to assess viability in CTOs,[64,65,93] but viability imaging using thallium-201 SPECT, FDG-PET, or CMR can predict functional recovery accurately after revascularization.[65,94,95] Prospective studies underway will assess whether viability/ischemia testing can detect which patients benefit from CTO PCI.[96]

Serum Biomarkers

High-sensitivity troponins and N-terminal pro-type natriuretic peptide (NT-pro-BNP) have emerged as powerful prognostic markers in heart failure,[97] with elevated levels seen in situations with myocardial supply—demand mismatch, increased myocyte turnover, myocardial apoptosis, wall stress, and oxidative stress: processes similar to hibernation. In a pilot study of 49 patients with IHF, LVEF ≤ 45%, the presence

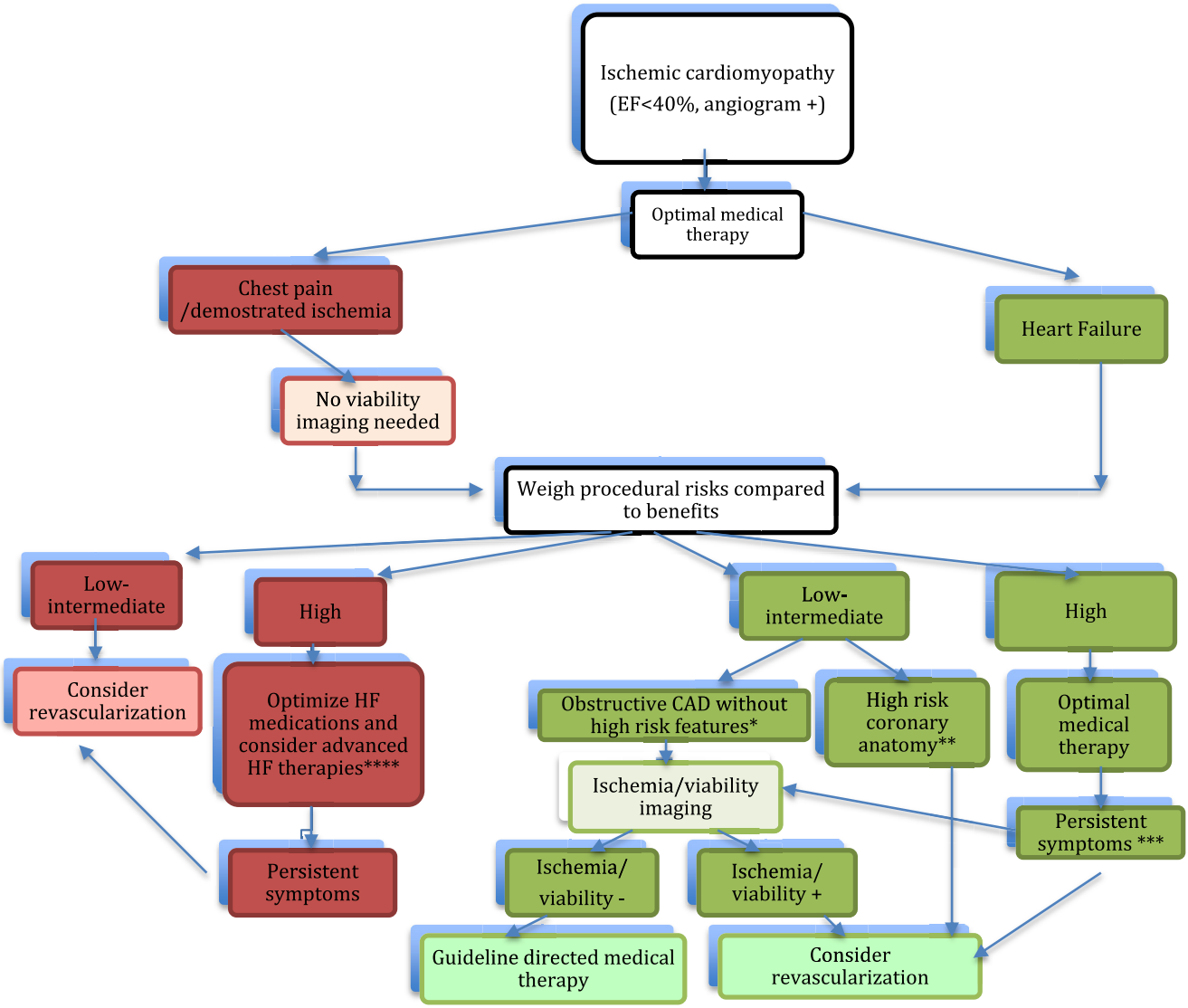


Figure 4. Proposed algorithm for the integration of ischemia/viability testing in guiding revascularization decisions in ischemic cardiomyopathy. *Including chronic total occlusions. ** > 50% Left main/proximal left anterior descending (LAD) coronary artery stenosis. ***Ischemia/viability testing may be considered depending on patient, anatomy, targets, and revascularization risk. **** For eligible candidates. EF, ejection fraction; CAD, coronary artery disease; (+) presence of, (−) absence of. Modified from Wiefels et al.[46] with permission form Springer Nature. Based on Neumann et al.[68] and the clinical evidence from observational data and guidelines discussed in this article.

and extent of viability assessed by FDG-PET correlated with high-sensitivity troponin T (hsTnT) and NT-pro-BNP levels independent of EF, age, and estimated glomerular filtration rate (eGFR), as well as the presence of scar[98] raising the theoretical possibility to combine image-guided approach with biomarker-guided approach to assist decision making.[99] At present, the evidence is limited.[100,101] The ongoing Role of **Bio**markers in **A**lternative **I**maging **M**odalities in **I**schemic **H**eart **F**ailure (Bio-AIMI-HF) substudy of the IMAGE-HF trial noted above will help to answer whether these and other biomarkers—with or without imaging—can better predict which patients will benefit from revascularization.

Method of Revascularization

According to the current guidelines, CABG is recommended as the first revascularization strategy in patients with "LVEF $\leq$ 35%, multivessel disease and acceptable surgical risk."[68] However, CABG vs PCI randomized trials have excluded patients with severe HF. The ongoing Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2) will be the first randomized study on the impact of revascularisation with PCI on the outcome of patients with severe IHF and will also investigate viability specifically in segments amenable to revascularization.[102]

Novel Imaging Techniques

Novel hybrid/fusion imaging techniques; PET/CMR, PET/CT, and stress-CMR will enable simultaneous assessment of different aspects of viability: metabolism, perfusion, and anatomy. Sympathetic denervation imaging might also serve as a novel method of risk stratification and therapeutic

target in patients with IHF, particularly around the prediction of risk for sudden cardiac death.[78]

Heart Team and Artificial Intelligence Approaches for Complex Decisions

The importance of a heart team combining expertise of HF, imaging, both surgical and interventional revascularization, as well as anaesthesiologists and gerontologists, cannot be overemphasized in making best decisions for these patients.[67,103,104] Ottawa-5 exemplified how the combined role of these experts with accessibility of technology could lead to outcome benefit.[28] In the future, machine learning/artificial intelligence may increase the diagnostic performance of any mode of (viability) imaging,[105] which may be further integrated for complex clinical decision making and a personalized approach to revascularization.

Conclusions

Definitive proof of whether viability imaging offers outcome benefit in patients with HF has been elusive. It is likely that, in the past, there was an over-reliance on viability information that was not needed to guide decisions in many patients. At present, decisions are made balancing patient-related factors, risks of the intervention, anatomic data, functional data, and patients' perspectives. Viability imaging should be limited to situations in which revascularization decisions are most difficult. Physicians should consider viability imaging when imaging findings will have impact on decision making. The results from ongoing trials and future evidence regarding the role in certain patient populations or clinical scenarios—as well as the roles of biomarkers, neurohormonal imaging, and artificial intelligence—will provide much-needed evidence to optimize revascularization decision algorithms in this difficult patient population.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.04.029.