Myocardial viability testing: all STICHeed up, or about to be REVIVED?

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Patients with ischaemic left ventricular dysfunction frequently undergo myocardial viability testing. The historical model presumes that those who have extensive areas of dysfunctional-yet-viable myocardium derive particular benefit from revascularization, whilst those without extensive viability do not. These suppositions rely on the theory of hibernation and are based on data of low quality: taking a dogmatic approach may therefore lead to patients being refused appropriate, prognostically important treatment. Recent data from a sub-study of the randomized STICH trial challenges these historical concepts, as the volume of viable myocardium failed to predict the effectiveness of coronary artery bypass grafting. Should the Heart Team now abandon viability testing, or are new paradigms needed in the way we interpret viability? This state-of-the-art review critically examines the evidence base for viability testing, focusing in particular on the presumed interactions between viability, functional recovery, revascularization and prognosis which underly the traditional model. We consider whether viability should relate solely to dysfunctional myocardium or be considered more broadly and explore wider uses of viability testing outside of revascularization decision-making. Finally, we look forward to ongoing and future randomized trials, which will shape evidence-based clinical practice in the future.

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Evidence for the relationship between viability testing and clinical outcomes. Viability and prognosis: the STICH viability sub-study showed viability had no impact on prognosis after adjustment for baseline variables. Viability and prognostic benefit of revascularization: no association shown in the STICH viability sub-study, however, has been shown in PARR-2 substudy and observational data. Viability to functional recovery: a relationship has been demonstrated for medical therapy. Viability to functional recovery via revascularization—no association shown in randomised controlled trials (RCTs), but extensive observational data. A link between functional recovery and prognosis is suggested from long-term STICH follow-up data. A link between revascularization and prognosis was shown for CABG in the STICH trial (long-term follow-up, not seen in HEART trial).

**Keywords**
- Ischaemic left ventricular dysfunction
- Ischaemic cardiomyopathy
- Myocardial hibernation
- Myocardial viability

**Introduction**

Regions of extensively infarcted myocardium are unlikely to benefit from revascularization. Revascularization of myocardium that is both viable and dysfunctional might improve its contractile function, whilst revascularization of viable myocardium jeopardized by a coronary stenosis might reduce the risk of future injury, whether or not the myocardium exhibits contractile dysfunction at rest. Anecdotally, these concepts appear correct. There is remarkably little evidence, however, that revascularization improves left ventricular function or clinical outcomes over and above pharmacological treatment alone. The viability sub-studies of the Surgical Treatment for Ischaemic Heart Failure (STICH) and Heart Failure Revascularisation (HEART) trials failed to show that viability testing could identify patients with ischaemic left ventricular dysfunction (ILVD) who were more likely to benefit from revascularization. This has left clinicians and guideline committees pondering the role that viability should play in selecting patients for revascularization. In this article, we will address several pressing questions about the current use and interpretation of viability tests, including (i) should we refrain from viability testing in its current form? (ii) is a change in left ventricular function a valid surrogate endpoint for clinical outcomes?; and (iii) how should we now apply viability testing in clinical practice?

**Viability**

At the level of the myocyte, viability simply refers to a cell that is not irreversibly damaged. In clinical practice and research studies, however, the term is usually applied to areas of the myocardium which show...
contractile dysfunction at rest and in which contractility is expected to improve after revascularization. This definition relies heavily on the concept of myocardial hibernation: the adaptive down-regulation of myocardial function in favour of myocyte survival, triggered by recurrent ischaemia (Figure 1).7 Hibernation exists on a clinical spectrum of ischaemic dysfunction, which includes acute ischaemia (impaired contractility during a period of relative hypoperfusion, with maintained perfusion–contraction matching), stunning (impaired contractility following resolution of an episode of non-lethal acute ischaemia, with uncoupling of perfusion–contraction matching, where impairment persists for several hours to days but recovers spontaneously), hibernation (prolonged impairment of contractility due to recurrent episodes of non-lethal ischaemia, which persists unless an intervention is made to favourably alter supply/demand balance) and infarction (loss of myocyte viability and replacement with collagenous scar following a prolonged episode of ischaemia). Hibernation, therefore, represents a substrate of reversible contractile dysfunction; the following assumption is that an improvement in function leads to improved health outcomes.8 This assumption was supported by a range of retrospective observational studies.2 More recent data suggest, however, that this is an oversimplification.

**Does viability predict improvement in LV function?**

Viability tests are currently validated on their ability to predict the reversal of contractile dysfunction after revascularization. Improvement in contraction may occur within hours to days if the myocardium is stunned but may take many months for advanced hibernation. Each method of viability testing uses a different aspect of the pathophysiology of hibernation (Figure 2)5 and produces quantitative and/or qualitative measures of viability intended to predict the likelihood of functional recovery.1,9

There is a wealth of observational literature confirming that viability tests predict improvement in global LV function after revascularization.2,10 A meta-analysis of 158 studies demonstrated that all imaging modalities had similar utility, positron emission tomography having the highest sensitivity and negative predictive values and dobutamine stress echocardiography the highest specificity and positive predictive values at a segmental level.9 Further observational data support associations between the extent of viability and improved regional systolic function. It should be noted, however, that the effect of revascularization cannot be distinguished from other treatment effects in observational studies: the presence of extensive viability has been shown to predict the response to pharmacological1,11 and cardiac resynchronization therapy,12 and viability may indicate a myocardial substrate that can improve in response to a range of interventions, not just revascularization. Randomized studies of chronic total occlusion PCI suggested no improvement in regional function, even in the presence of viability, though these were not specific to patients with severe left ventricular systolic dysfunction.13,14

**Does improvement in LV function predict prognosis in ischaemic left ventricular dysfunction?**

Left ventricular ejection fraction (LVEF) is used to risk-stratify patients with heart failure and acts as a gatekeeper for access to...
prognosis-modifying pharmacological, device and revascularization therapy in all major international guidelines. In patients with a reduced ejection fraction, improvements in LVEF in response to therapy are often taken as a surrogate for a reduction in the risk of future adverse events, whilst a decline is assumed to reflect disease progression or lack of response with an associated poor prognosis. There is evidence to support this notion in patients with non-ischaemic cardiomyopathy, where an increase in LVEF has been consistently linked to favourable outcomes, including mortality. The association between increases in LVEF and mortality is more challenging to define in patients with ILVD, especially in relation to revascularization. As with non-ischaemic cardiomyopathy, the risk of death from pump failure in patients with ILVD appears dynamically related to LVEF, whereas sudden deaths of either arrhythmic or vascular aetiologies do not. An analysis of the association between ventricular function and mode of death in 7788 patients in the Digitalis Intervention Group trial, 69% of whom had an ischaemic aetiology, demonstrated a near-linear association between LVEF and death from worsening pump failure, whereas the risk of death due to arrhythmia was relatively constant across the spectrum of reduced LVEF. Populations with ILVD exhibit relatively small changes in LVEF, at least in the early stages following revascularization: in STICH, the mean improvement in LVEF was 2% at 4 months in a group determined to have ‘extensive’ viability. The reasons for this are likely to be multifactorial but include the definition of viability (which did not necessarily require contractile dysfunction of the affected segment and therefore could not improve), the regional nature of left ventricular (LV) dysfunction (which in turn may be due to a varying combination of scarred and hibernating myocardium), procedural factors such as the quality, completeness and durability of revascularization as well as the degree of perioperative myocardial injury. Another factor that complicates interpretation of data on LV remodelling after revascularization is the variable and sometimes prolonged time scale over which recovery may occur: a recent analysis of 24-month follow-up from the STICH trial demonstrated a clear association between (infrequently occurring) substantial improvements in LVEF (>10%) and improved mortality outcomes, though such analyses are at risk of survivor bias.

Are the STICH viability results definitive?

The main STICH trial demonstrated that a routine strategy of coronary artery bypass grafting (CABG) did not reduce mortality in patients with ILVD, compared to medical therapy alone, but on extended follow-up a survival benefit became apparent. Subsequent sub-analyses suggest a selective approach might be appropriate, as most of this benefit occurred in patients aged <60 years, those with three-vessel coronary disease and very severely impaired LV function, as well as those with a good exercise capacity at baseline.
As outlined above, the presence of viability has long been held as a key criterion for selecting patients with ILVD for revascularization. The results of the recent STICH viability study were, therefore, disruptive in two ways: first, because they demonstrated no link between the presence of viability and the benefit of CABG and second, because they demonstrated no relationship between improvement in LV function and clinical outcomes. Before abandoning viability testing, however, the results merit critical scrutiny.

Viability testing was only mandated in the early phase of the STICH trial and, thereafter, the use of viability testing was at the discretion of clinicians managing these patients at the enrolling centers.3,26 Both SPECT and DSE were permitted, with fundamentally different definitions used for each: DSE required the presence of both viability and resting dysfunction, whereas SPECT required the presence of only viability, regardless of resting function. Neither the decision to perform a viability test nor the use of the result to guide management was by randomized allocation and as such, when assessing the interaction between viability and outcome, caution should be applied. Most importantly, the results suggest that patients with extensive viability were strongly favoured for inclusion in the trial, with 81% of patients having ‘extensive’ viable myocardium, defined as >5 dysfunctional-but-viable segments on DSE or >11 viable segments on SPECT. Of the 601 patients included, 19% did not meet these criteria and were defined as having ‘no viable myocardium’. Of these 19%, 54 patients underwent CABG and 60 had medical therapy alone. Despite the high mortality rate (30 events in each arm at 10 years), there was therefore insufficient statistical power to reliably exclude a difference in this population or to test for an interaction between viability status and outcome. Conversely, for the 81% of patients with a large amount of viable myocardium (mean age 61 years), there appeared to be a substantial benefit from CABG over 10 years (Figure 3).

The historical perspective on the links between revascularization, viability testing and survival was summarized in a 2002 meta-analysis by Allman et al.2 This analysis had many limitations, most important of which were that the included studies were not randomized and were retrospective, with a risk of substantial confounding: the decision not to operate on a patient with insufficient viability may often be based on an adverse risk profile, which is either not measured or cannot be adequately adjusted for, which in turn could create the erroneous impression of a significant treatment benefit amongst those who are accepted for revascularization. In this scenario, the outcome may reflect the patient’s intrinsic risk rather than the treatment they received.

The only randomized trial to directly address the role of viability testing on clinical outcomes in ILVD was PARR-2, an imaging
strategy trial that investigated the use of PET-guided treatment in 430 patients with severe left ventricular dysfunction and coronary disease, compared to standard care. If substantial viable myocardium was identified in the PET arm, revascularization was recommended, though the application of the viability results was left to the discretion of the clinicians. Overall, 45% of patients underwent revascularization, predominantly with CABG, though the absolute difference in the revascularization rate between arms was only 13%. After 5 years follow-up, no significant differences were seen in mortality or major adverse cardiac events. In 25% of participants in the PET arm, management was discordant with the PET-recommended strategy, perhaps reflecting the prevailing uncertainty about the use of viability results and the influence of other factors on decision-making. A post hoc analysis of the PET-guided arm alone demonstrated a greater benefit of revascularization in patients with extensive hibernation, but this was also limited by confounding and lacks statistical power.

On balance, the available data suggest that revascularization reduces mortality for patients with ischaemic LVSD and a substantial volume of viable myocardium. The benefits of revascularization in the absence of a substantial amount of viable myocardium remain unclear, due in part at least, to the paucity of data.

Beyond contractile recovery

Current knowledge does not explain whether a lack of recovery in dysfunctional but viable segments should necessarily be considered a failure of treatment given that the treatment effect of CABG in STICH, independent of viability status, was driven by similar reductions in sudden cardiac death and pump failure.

Besides pump failure, many other causes of cardiovascular death are observed in people with ILVD, including ventricular arrhythmias and myocardial infarction, both of which may present as sudden death. These mechanisms may both be modified by revascularization independent of any effect on contractile function. Myocardial scar is a recognized arrhythmic substrate but the relationship between the amount of scar and risk is non-linear. The reduction in sudden death seen in the STICH trial may have been due to a reduction in fatal ventricular arrhythmias, but other mechanisms have been proposed, including the prevention of acute myocardial infarction.

The prior occurrence of non-fatal arrhythmias may provide insight into the mechanisms of sudden death however capturing such events is challenging without widespread cardiac device implantation.

The ‘border zone’ between infarcted and viable myocardium has been identified as the most arrhythmogenic location, characterized by areas of non-uniform conduction and varying refractoriness. However, the addition of ischaemia to this heterogeneous penumbra may further increase arrhythmogenesis, via intracellular acidosis and membrane depolarization. Incomplete revascularization (and hence varying residual ischaemic burden) and peri-procedural myocardial infarction (which could increase scar volume and alter heterogeneity) are well-documented predictors of adverse events, and therefore, it cannot be assumed that revascularization reduces arrhythmic risk in a predictable or reliable fashion. Whether such ‘electrical hibernation’ can exist in isolation or is intrinsically linked to mechanical dysfunction, as well as how such arrhythmic substrates are altered by revascularization of stable coronary disease, remains poorly understood. Prior studies showed alterations in the electrophysiological properties of the myocardium after revascularization occurred earlier than, and independent of, LV function recovery. The PARAPET study of 204 patients with ILVD meeting criteria for a primary prevention ICD investigated whether the extent of myocardial denervation measured with 11C-meta-hydroxyephedrine (11C-HED) PET predicted sudden cardiac arrest. After a median follow-up of 4.1 years and 33 events, the extent of denervated myocardium, rather than the presence of scar or hibernation, was the most effective PET predictor of sudden cardiac arrest. Participants were enrolled after revascularization, however, and the burden of hibernation was, therefore, small (3 ± 2% of total myocardial volume), leaving the role of hibernation in arrhythmogenesis in unrevascularized patients unclear.

Revascularization has also been associated with improvements in LV mechanics beyond regional systolic function, including reductions in LV volume, sphericity and diastology, important prognostic factors that are not reflected in regional wall thickening or LV ejection fraction.

This area merits further prospective study in a stable ILVD population, particularly focusing on anatomic, functional, sympathetic and electrophysiological characterization both before and after revascularization.

Ischaemia

Myocardial hibernation is triggered by recurrent episodes of inducible ischaemia, and the reversal of hibernation depends on two factors; the ability to remove the stimulus (inducible hyperperfusion/ischaemia) and a myocardial substrate that has the capacity to recover (viability). It follows that functional recovery is most likely to occur in territories with both inducible ischaemia and viability. This hypothesis is supported by some observational data, such as the greater diagnostic accuracy of both elements via a biphasic response on DSE, compared to the demonstration of contractile reserve alone, and was also shown in the CHRISTMAS trial. However, much remains unknown about the interaction between ischaemia and viability in predicting both clinical outcomes and treatment effects.

As patients with ILVD typically have extensive and severe coronary disease, they might be expected to exhibit a large ischaemic burden on functional testing. However, as hibernation itself is an adaptive response to mitigate the effects of ischaemia, the ability to demonstrate the latter stages of the ischaemic cascade (such as inducible contractile dysfunction) may be limited, depending on the method of testing used. Another practical limitation is the difficulty of assessing ischaemia in thinned and/or partially scarred myocardial segments. By way of example, despite the requirement for significant coronary disease to meet inclusion criteria, 36% of patients who underwent ischaemia testing in STICH exhibited no inducible ischaemia.

As for patients with stable CAD and normal left ventricular function, an increasing burden of inducible ischaemia is associated with poorer outcomes in ILVD. In observational series, the benefits of revascularization appeared greater in those with more extensive ischaemia. However, as with viability, treatment effect cannot be...
separated from clinician bias in the treatment assignment. Clinicians may hesitate to offer revascularization to frailest patients with other medical conditions that increase the procedural risk or reduce the chance of benefit, despite the presence of extensive ischaemia. Observational studies will often fail to capture important details that allow appropriate risk adjustments to be made in outcome analyses. The COURAGE\textsuperscript{45} and ISCHEMIA\textsuperscript{46} trials have, using more robust methods, excluded a prognostically important treatment benefit of revascularization in patients with extensive ischaemia and normal left ventricular function, though the follow-up of ISCHEMIA remains short when considered against STICH\textsuperscript{47}

Evidence on the role of ischaemia in selecting patients with ILVD for revascularization is conflicting. Early observational studies assessing ischaemia testing in ILVD suggested that low-dose DSE allowed the risk stratification of outcome after revascularization.\textsuperscript{42} Whilst some studies have identified an association between the presence of inducible ischaemia and better outcomes in patients selected for revascularization,\textsuperscript{47,48} others have shown that this becomes irrelevant when other clinical factors, such as scar burden, are considered.\textsuperscript{49,50} Rizzello et al\textsuperscript{11} identified that in patients already scheduled to undergo revascularization, viability was a strong predictor of long-term prognosis but the extent of ischaemia on DSE did not improve the prediction of cardiac death. An analysis from the STICH trial demonstrated no difference in the benefit of CABG in those with- or without-inducible ischaemia or angina,\textsuperscript{24} although the study may not have been adequately powered to explore interactions. Whilst there was no overall interaction, the risk of mortality was lower in patients without angina who underwent CABG than in those who received medical therapy: whether this was a statistical quirk in a small sample size or a genuine signal merits further investigation.

A sub-study of the ISCHEMIA trial has also explored the relationship between inducible ischaemia and the effect of revascularization on clinical outcomes in patients with heart failure and a mid-range ejection fraction (an LVEF \(\leq 35\%) \) was an exclusion criterion),\textsuperscript{51} suggesting improved outcomes following revascularization compared to pharmacological therapy for patients with inducible ischaemia, an LVEF of 35–45% and a history of heart failure. The analysis was limited by small sample size (\(n = 28\)) and lacked data to explore interactions between ischaemia and viability.\textsuperscript{52} Angina might also be considered an expression of myocardial ischaemia, although this may often not be associated with chest pain in patients with heart failure. Furthermore, angina does not localize the viable territories in patients with multivessel disease. However, revascularization relieves angina symptoms and this, rather than a prognostic benefit, might justify revascularization when symptoms are not readily relieved by pharmacological treatment.

### Pharmacological therapy
Pharmacological treatment can favourably alter the balance between myocardial oxygen consumption and demand, thereby preventing myocardial ischaemia and restoring contractile function and may also reduce the risk of recurrent vascular events and arrhythmias. Reducing heart rate through beta-blockade will reduce myocardial oxygen consumption and prolong the duration of diastole, an important factor in the efficiency of coronary perfusion;\textsuperscript{11} beta-blockers are also known to reduce the risk of recurrent myocardial infarction, arrhythmias and sudden death.\textsuperscript{55} Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers and mineralocorticoid receptor antagonists reduce LV end-diastolic volume,\textsuperscript{56} pressure and wall stress, improving subendocardial blood flow,\textsuperscript{57} with important clinical reductions in mortality and progression to symptomatic heart failure, though the degree to which this is dependent on the extent of hibernation is unknown. With regard to pathophysiology-specific effects, ACEI effectively prevented or reversed myocardial stunning in several randomized, placebo-controlled studies,\textsuperscript{58} whilst the effectiveness of beta-blockers in improving left ventricular function was linearly related to the extent of hibernation in the randomized CHRISTMAS trial.\textsuperscript{11} The implications of these observations are two-fold: first, the provision of goal-directed pharmacological therapy is a critical aspect of the treatment of ILVD that should not be overlooked in planning revascularization and second, the interactions between pharmacological therapy, revascularization and viability are so significant that controlling for their effects, either in mechanistic studies or clinical trials, can only be achieved through formal randomization. Several other pharmacological agents have demonstrated pathophysiology-specific effects in pre-clinical or early clinical models. Pre-treatment with glucagon-like peptide-1 prevents LV stunning following a 1-min balloon occlusion of the left anterior descending coronary artery.\textsuperscript{59} The administration of pravastatin has been shown to

### Applying trial data to clinical practice
Randomized trials are the only way to meaningfully inform the evidence base in conditions such as ILVD, where the influence of multiple interacting and confounding factors must be controlled to separate intrinsic risk from the effect of a testing strategy or treatment. Despite this, applying the lessons developed in such trials can be challenging where the results are not widely generalizable. The median age at enrollment in STICH was under 60 years, compared to an average age of 77 years at the time of diagnosis in a general heart failure population,\textsuperscript{53} whilst <15% of patients were female. Recruitment to both the STICH and ISCHEMIA trials was extremely challenging, requiring the participation of 99 hospitals in 22 countries for STICH and 320 hospitals in 37 countries for ISCHEMIA, over around 5 years in both cases. As a consequence, it is clear that only a tiny fraction of eligible patients were enrolled, and most patients with ILVD who are considered for revascularization will have been poorly represented in even the major randomized trials.

In addition, in clinical practice, a significant proportion of patients undergo coronary angiography as their initial investigation, preceding any functional assessment of viability. They may then either proceed directly to angioplasty or be referred for CABG,\textsuperscript{54} and the clinical momentum behind such decisions often creates a barrier to such assessments. Should evolving evidence show an important role for viability testing, the application of either appropriate use criteria or the development of viability tests, which can be performed as adjuncts to invasive angiography (similar to the development of Fractional Flow Reserve, which improved the use of ischaemia assessment in patients with stable coronary disease and normal LV function), may help to standardize application.\textsuperscript{7}
improve the regional myocardial function independent of myocardial perfusion in a swine model of hibernation,\(^\text{60}\) whilst endothelial nitric oxide synthase improved regional function in a perfusion-dependent manner through neovascularization via endothelial cell proliferation and collateral growth in a similar model.\(^\text{61}\) The clinical applicability of these findings has yet to be investigated.

**Avenues for future research**

Clarity on the role of viability testing, and more widely of advanced imaging in ILVD, will only be achieved through studies directly relating viability and treatment effects to hard clinical outcomes in randomized trials that provide control to ensure that it is the intervention rather than the natural history of the underlying disease that determines the outcome. To achieve this, robust randomized trials are needed, which consider the scope of viability testing more broadly: not simply for their value when viewed in a binary manner to decide whether to treat a patient or not but in their ability to provide detailed phenotyping to tailor a range of treatment options. The clinical reality of ILVD is not whether there is ‘myocardial viability’ or not but what volume or percentage of the myocardium is viable and how much of this suffers from contractile dysfunction. Ideally, a dose–response trial (with the amount of viable but dysfunctional myocardium being the ‘dose’) of revascularization should be done. The use of artificial intelligence and machine learning to examine interactions between multiple clinical factors in predicting benefit may also provide better understanding.

Future work must overcome the difficulties of integrating the interrelated but unknown questions (Graphical abstract). Does revascularization truly reverse hibernation, and is each modality of treatment equal? Does hibernation reversal only confer benefit through contractile recovery or are there other mechanisms? Can different methods of viability testing, with differing sensitivity and specificity, be tailored to the individual and the planned revascularization strategy, and what is the threshold of cellular injury at which each imaging modality predicts a positive effect on the different modes of death?

In the interim, there are two trials ongoing that will help to inform the debate on viability. REVIVED-BCIS2 is a prospective, multi-centre, open-label randomized controlled trial investigating the role of PCI in ILVD. A total of 700 patients with extensive CAD, an LVEF <35% and viability in >4 dysfunctional segments, which can be revascularized by PCI, will be randomized 1:1 to receive optimal medical therapy (OMT) or OMT + PCI.\(^\text{62}\) Viability testing is mandated in the trial protocol; data will, therefore, be available to compare outcomes and treatment effects across the spectrum of viability. The trial will test the hypothesis that for patients with heart failure with reduced ejection fraction (HFrEF) receiving guideline-recommended medical therapy, revascularization of viable myocardial segments with contractile dysfunction will improve event-free survival. The relationship between the completeness of revascularization of viable myocardium and subsequent clinical and remodelling outcomes will also be assessed. There will be an opportunity to confirm or refute the STICH observations, particularly whether change in LV systolic function (whether due to revascularization or medical therapy) correlates with outcomes in ischaemic LV dysfunction and with the presence of viability. Furthermore, the prespecified segmental remodelling analysis will provide insight into the accuracy of prospective viability tests at predicting the recovery of contractile function. The trial will not provide insights into the effects of revascularization in the absence of a substantial volume of viable but dysfunctional myocardium, as the protocol excludes such patients. Depending on the results of REVIVED-BCIS2 and the similarity of the populations recruited, a further trial comparing PCI to CABG may be warranted.

AIMI-HF is an ongoing multi-centre randomized trial and registry comparing the outcomes of patients with ILVD (EF <45%) whose management is based on ‘advanced’ imaging methods (PET/CT or CMR) compared to standard cardiac imaging with SPECT.\(^\text{63}\) The aim is to enrol 1511 patients and follow them for at least 2 years. The composite primary outcome is cardiac death, MI, resuscitated cardiac arrest, or cardiac hospitalization. Demonstration of viability is not mandatory for inclusion, but its detection will influence management strategies, similar to the design of the PARR-2 trial, and will therefore be an important secondary analysis.

**Conclusions**

The importance of myocardial viability testing in determining outcomes in ILVD remains controversial, especially since the publication of the 10-year follow-up of the STICH viability study. The failure of RCTs of revascularization to demonstrate clear benefits may reflect our current inability to select patients appropriately. The data hint at the possibility that the amount of viable myocardium in jeopardy, with or without contractile dysfunction, might identify those most likely to benefit from revascularization, assuming that they are at low peri-procedural risk and have few comorbidities that render them at the high risk of dying from causes other than heart failure. Chronological age is a powerful marker of biological age; those aged <60 years may have most to gain. However, we cannot currently exclude the possibility that revascularization is beneficial in those who lack a substantial volume of viable myocardium because these patients were underrepresented in the trials conducted thus far. It is likely, however, that the classical definition of viability does not adequately capture the importance of modifying the myocardial substrate beyond changes in contractile function. Whilst ongoing trial results are eagerly anticipated and may provide some answers, it is likely that gaps in our knowledge will remain, whilst trialists must endeavour to enrol participant cohorts who are truly representative of the population of patients with ILVD and avoid selective sampling. Future research into viability tests should consider their application and results more broadly, as is being investigated in the AIMI-HF trial.

1. Viable myocardium should not be considered as a single entity but as a spectrum, including jeopardized, stunned, early hibernation and advanced hibernation, the revascularization of which may each yield different pathophysiological benefits.
2. For patients with ILVD, the question is not whether they have viable myocardium, but how much they have of each type, where it is, whether it is likely to recover and how long this may take.

Central to this is the need for multidisciplinary collaboration to integrate clinical information with the myocardial and coronary substrate and in particular, that Heart Teams must carefully consider wider
patient factors and optimization of medical therapy (for which there is strong evidence), rather than debating the need for and mode of revascularization in isolation.

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