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Myocardial Viability Testing and Impact of Revascularization on Prognosis in Patients With Coronary Artery Disease and Left Ventricular Dysfunction: A Meta-Analysis

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Concord, Australia; Atlanta, Georgia; and Boston, Massachusetts

OBJECTIVES
This study pools data from published series examining late survival with revascularization versus medical therapy after myocardial viability testing in patients with severe coronary artery disease (CAD) and left ventricular (LV) dysfunction.

BACKGROUND
Previous observational studies have suggested survival benefit in such patients if they are revascularized when myocardial viability is detected on imaging tests.

METHODS
A MEDLINE database search returned 24 viability studies reporting patient survival using thallium perfusion imaging, F-18 fluorodeoxyglucose metabolic imaging or dobutamine echocardiography. Annual death rates were extracted, pooled and analyzed with a random effects model. The risk-adjusted relationship between severity of LV dysfunction, presence of viability and survival benefit associated with revascularization was assessed by meta-regression.

RESULTS
There were 3,088 patients (2,228 men), ejection fraction 32 ± 8%, followed for 25 ± 10 months. In patients with viability, revascularization was associated with 79.6% reduction in annual mortality (16% vs. 3.2%, chi-square = 147, p < 0.0001) compared with medical treatment. Patients without viability had intermediate mortality, trending to higher rates with revascularization versus medical therapy (7.7% vs. 6.2%, p = NS). Patients with viability showed a direct relationship between severity of LV dysfunction and magnitude of benefit with revascularization (p < 0.001). There was no measurable performance difference for predicting revascularization benefit between the three testing techniques.

CONCLUSIONS
This meta-analysis demonstrates a strong association between myocardial viability on noninvasive testing and improved survival after revascularization in patients with chronic CAD and LV dysfunction. Absence of viability was associated with no significant difference in outcomes, irrespective of treatment strategy. (J Am Coll Cardiol 2002;39:1151–8)

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Left ventricular (LV) function is a powerful prognostic predictor in patients with coronary artery disease (CAD). The increasing number of patients with CAD and ischemic LV dysfunction is a major clinical problem (1). Potential reversibility of chronic LV dysfunction is an important clinical consideration in such patients when being considered for revascularization.

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Since this potential for reversibility was first identified (2,3), myocardial viability testing has been extensively evaluated for predicting clinical benefit. Studies documenting improvement in LV regional and global function after revascularization in this context have been recently summarized (4). Benefits in quality of life and diminished heart failure symptoms for patients with myocardial viability after revascularization have also been demonstrated (5,6).

In addition, patients revascularized with viable myocardium may have improved survival. Although this has been shown in some studies (7), these have been in limited patient populations reported predominantly from single centers. The goal of this analysis was to pool these individual studies to increase statistical power in an effort to examine the prognostic value of viability testing in order to aid clinical decision making in patients with severe CAD and associated LV dysfunction.

METHODS
This analysis summarizes the available studies reporting late clinical outcomes in patients with CAD and LV dysfunction who were tested for myocardial viability with cardiac imaging procedures. Late clinical outcomes in these studies were reported with respect to the presence or absence of an
investigator-defined threshold of preserved myocardial viability and also with respect to subsequent treatment strategy, either revascularization or medical therapy.

**Literature search.** A MEDLINE database search for literature published in English since 1966 was performed in August 1999, using PubMed, (National Library of Medicine, National Institutes of Health, Bethesda, Maryland 20894) and BioMedNet (Evaluated Medline). The search algorithm was: "viability, heart, outcome."

**Exclusions.** Twenty-eight citations were returned: (5,6,8–33) and the manuscripts scrutinized. Those not reporting either revascularization or medical therapy.

A meta-analysis was performed using a random effects model (34) to compare mortality rates in patients with/without viability treated by either revascularization/medical therapy. This model calculates a weighted-average percent decrease in mortality rates with 95% confidence intervals. A

### Table 1. Individual Studies

<table>
<thead>
<tr>
<th>Technique</th>
<th>Author</th>
<th>Year</th>
<th>Imaging Technique</th>
<th>Viability Criterion</th>
<th>Patients Entered</th>
<th>Age (yrs)</th>
<th>Follow-up (months)</th>
<th>LVEF (%)</th>
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<td>Dreyfus (12)</td>
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<td>FDG PET</td>
<td>FDG uptake</td>
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<td>Vom Dahl (20)</td>
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<tr>
<td></td>
<td>Beanlands (23)</td>
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<td>mibi SPECT/FDG PET</td>
<td>viability score</td>
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<td>62</td>
<td>18</td>
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<tr>
<td></td>
<td>Huitink (26)</td>
<td>1998</td>
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<td>flow/FDG mismatch</td>
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<td>47</td>
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<td>Williams (16)</td>
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<td>DASE</td>
<td>regional wall motion</td>
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<td>30</td>
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<tr>
<td></td>
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<td>DASE</td>
<td>“</td>
<td>353</td>
<td>64</td>
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<td>27</td>
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<td>LDDE</td>
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<td>16</td>
<td>33</td>
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<td>1998</td>
<td>LDDE</td>
<td>“</td>
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<td>Smart (33)</td>
<td>1999</td>
<td>DASE</td>
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<td>18</td>
<td>30</td>
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<td>LDDE</td>
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<td>“</td>
<td>76</td>
<td>61</td>
<td>19</td>
<td>28</td>
</tr>
</tbody>
</table>

DASE = dobutamine/atropine stress echocardiography; FDG = F-18 fluorodeoxyglucose; LDDE = low-dose dobutamine echocardiography; mibi = Tc-99m sestamibi; PET = positron emission tomography; SPECT = single photon emission computed tomography; TI = thallium.

Dataset entered into the analysis. The remaining 24 papers are summarized in Table 1. In two studies reporting results using multiple imaging techniques, data from only one technique are included to avoid duplicate entering of events: Pasquet et al. (31) (scintigraphy/echocardiography where scintigraphic data are included) and Tamaki et al. (9) (thallium/F-18 fluorodeoxyglucose [FDG] with positron emission tomography [PET] where PET data are included). However, all data were used for comparison between testing modalities.

**Meta-analysis.** Pooled, averaged rates of cardiac death plus patient age, gender and left ventricular ejection fraction (LVEF) were extracted from each report. Numbers of patients with and without demonstrated viability (according to individual studies’ author-defined criteria) were extracted (Table 1). These two groups were subdivided into patients subsequently revascularized and those treated medically. Annual mortality rates for each of the resulting four subgroups were calculated as well as average follow-up time (months) and follow-up completeness.

A meta-analysis was performed using a random effects model (34) to compare mortality rates in patients with/without viability treated by either revascularization/medical therapy. This model calculates a weighted-average percent decrease in mortality rates with 95% confidence intervals. A
Table 2. Pooled Data Patient Characteristics

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Gender</th>
<th>LVEF 32.9% (25%–51%)</th>
<th>Treatment</th>
<th>Results</th>
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<tbody>
<tr>
<td>61.4 (55–69)</td>
<td>Male</td>
<td>70.1% (38%–91%)</td>
<td>Revascularization 34.9% (32.56%–100%)</td>
<td>Viability demonstrated 42.3% (10.58%–100%)</td>
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<tr>
<td></td>
<td>Female</td>
<td>29.9% (9%–62%)</td>
<td>Medical therapy 65.1% (0%–67.44%)</td>
<td>Viability not demonstrated 57.7% (0%–89.42%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Test results</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration (months) 24.7 (12–47)</td>
<td>Completeness of ascertainment 87.4% (53%–100%)</td>
</tr>
</tbody>
</table>

Data are given as mean (range).

DISCUSSION

This analysis demonstrates a strong association between revascularization and improved survival among patients with CAD and significant LV dysfunction who have evidence of myocardial viability on imaging tests. The likelihood of improved survival was greatest in patients with demonstrated viability and the most severe LV dysfunction.
### Table 3. Individual Study Data

<table>
<thead>
<tr>
<th>Author</th>
<th>Viable Revascularized Deaths</th>
<th>Viable Revascularized Pts</th>
<th>Nonviable Revascularized Deaths</th>
<th>Nonviable Revascularized Pts</th>
<th>Viable Medical Therapy Survival</th>
<th>Nonviable Medical Therapy Survival</th>
<th>Viable Medical Therapy Survival</th>
<th>Nonviable Medical Therapy Survival</th>
<th>Viable Medical Therapy Survival</th>
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</thead>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Yoshida (10)</td>
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<td>0.8</td>
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<td>0.6</td>
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<td>0.92</td>
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<td>Lee (13)</td>
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<td>Gioia (14)</td>
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</table>

NI = not included; NS = not stated; Pts = patients.
Myocardial Viability: Meta-Analysis

Contemporary studies. Contemporary studies employing viability testing suggest that patients with ischemic LV dysfunction may undergo revascularization with acceptable periprocedural risk and subsequent improvement in regional and global cardiac function, as well as improved symptoms (5,17,30). However, individual studies examining long-term outcomes have shown variable results, related at least in part to differences in patient populations and the limited patient numbers studied.

The current analysis. This meta-analysis yields results supporting the prognostic value of demonstrating myocardial viability in patients with CAD and severe LV dysfunction. The patients in this analysis have relatively severe LV dysfunction: mean EF 32%, mean NYHA functional class 2.8.

The strong association demonstrated between decreased mortality and revascularization is seen only in patients with myocardial viability. There is no apparent outcome benefit of revascularization in the absence of demonstrated viability, and there is a trend toward higher mortality with revascularization. This could reflect higher procedural risk for patients with severe LV impairment associated with revascularization in the absence of a balancing clinical benefit.

Relationship to severity of LV dysfunction. Multivariate modeling and meta-regression demonstrate an inverse relationship between EF and prognostic benefit associated with revascularization in patients with viability. As severity of LV dysfunction increased, the potential survival benefit associated with revascularization of patients with viability also increased. This implies that, despite an increasing procedural risk of revascularization with worsening LV dysfunction, evidence of preserved viability may provide information on potential clinical benefit to balance against that risk.

Medical therapy. The annual mortality rate observed for patients with viability treated medically is similar to that seen in contemporary clinical trials in advanced heart failure. The 16% annual mortality rate in the current analysis is comparable with the placebo group annual mortality rate of 18% in the Randomized Spironolactone Evaluation Study (RALES) (41). The 16% mortality rate is comparable with the 18% seen in contemporary clinical trials in advanced heart failure. The 16% annual mortality rate in the current analysis is similar to that seen in contemporary clinical trials in advanced heart failure.

Prior studies. Before the advent of imaging techniques for myocardial viability testing, there were reports of the prognostic benefit of revascularization for some subgroups of patients with CAD, such as those with multivessel CAD and mild LV dysfunction (35–37). However, patients with ischemic LV dysfunction have higher periprocedural risk with revascularization compared with similar patients with normal LV function (38). This risk increases as LV dysfunction worsens. The presence of angina in the setting of significant LV dysfunction has been reported as a marker of potential survival benefit with revascularization (39). However, angina is an insensitive marker for ischemic, but viable, myocardium (40), and the benefit of revascularization may extend beyond patients with angina.

Figure 1. (a) Death rates for patients with and without myocardial viability treated by revascularization or medical therapy. There is 79.6% reduction in mortality for patients with viability treated by revascularization (p < 0.0001). In patients without myocardial viability, there was no significant difference in mortality with revascularization versus medical therapy. (b) Same data as (a) with comparisons based on treatment strategy in patients with and without viability. Annual mortality was lower in revascularized patients when viability was present versus absent (3.2% vs. 7.7%, p < 0.0001). Annual mortality was significantly higher in medically treated patients when viability was present versus absent (16% vs. 6.2%, p = 0.001). Revasc. = revascularization.
Imaging techniques. The three noninvasive testing techniques reported here interrogate distinct features of viable myocardial cells. Thallium-201 reflects cell membrane integrity; FDG reflects myocyte glucose utilization, and dobutamine echocardiography tests contractile reserve. However, there was no measurable difference between techniques in predicting prognostic benefit with revascularization. Differences between techniques have been reported in some studies regarding prediction of recovery of regional contractile function after revascularization (4), but these differences generally involve relatively small regions of myocardium. This analysis suggests that such small differences impact little on late survival. This is supported by a recent prospective randomized trial in which patients with ischemic cardiomyopathy and questions of viability were randomized to clinical decisions for revascularization based on FDG PET or Tc-99m sestamibi SPECT (43). There was no difference between groups in the proportion of patients sent for revascularization nor in two-year event-free survival, suggesting that clinical decisions and outcomes driven by these two techniques to assess viability were equivalent.

Study limitations. The data reported here are subject to limitations. The individual studies are observational, nonrandomized, unblinded and subject to publication and other biases, including patient selection bias to enter the studies and then proceed to either medical or revascularization.

![Figure 2](image1.png)

**Figure 2.** Relation between left ventricular ejection fraction (EF) and predicted change in mortality for patients with viable (circles) versus nonviable (triangles) myocardium based on the results of meta-regression. This demonstrates increasing potential for improved survival with lower left ventricular EF in patients with viable myocardium, $p < 0.0001$ (broken plot line), but not in those without viability, $p = 0.11$ (continuous line).

![Figure 3](image2.png)

**Figure 3.** Decrease in mortality with revascularization of viable myocardium for each testing technique shown as mean value with 95% confidence limits. Note wide confidence limits, especially for thallium and echocardiography. No measurable differences in test performance were observed. EF = ejection fraction; FDG = F-18 fluorodeoxyglucose.
therapy. Furthermore, the technical aspects and completeness of revascularization and individual patients’ medical therapy regimens may have varied widely. There was little information in the reports on background medical therapy, and whether these results would hold under the conditions of contemporary medical therapy with aggressive use of statins and beta-adrenergic blocking agents is not certain. For each imaging technique, there are substantial differences in methodology, protocols and criteria for definition of clinically significant viability (Table 1). In this meta-analysis, viability could only be interpreted as “present” or “absent” based on individual studies’ definitions. Therefore, the potential significance of the extent of demonstrated viability or the presence of inducible ischemia in relationship to the degree of subsequent prognostic benefit could not be examined. The individual studies did not report late EF, so the relationship between any improvement in LV function and potential prognostic benefit could not be explored. This may have been instructive because it has recently been reported that patients with CAD and LV dysfunction who are revascularized may have similar survival regardless of improvement/no improvement in late EF.

Recent technical innovations including gated SPECT, nitrate-enhanced SPECT and second harmonic echocardiography were not routine at the time these studies were published. Thus, the imaging techniques may not fully reflect current practice.

Ascertainment of events was not fully complete. Finally, despite the fact that the random effects model is conservative (allowing for factors operating beyond the reported data), this allowance may not necessarily be sufficient. Thus, these findings may not necessarily be applicable to all CAD patients with severe LV dysfunction being assessed for prognostic coronary revascularization. A limitation of the literature on viability in general (and, thus, any pooled analysis of the literature) is the question of applicability to patients with very advanced degrees of heart failure symptoms and more severe LV dysfunction. In this analysis, mean NYHA class was 2.8 when reported, reflecting a mild-to-moderate degree of symptoms.

Implications. The results of this meta-analysis suggest that a search for preserved myocardial viability in patients with CAD and significant LV dysfunction using noninvasive imaging techniques identifies patients at substantial risk of death, a risk which may be reduced by successful revascularization. The magnitude of the potential reduction in mortality increases as the severity of LV dysfunction increases. Hence, noninvasive imaging of myocardial viability can be used to inform the often difficult clinical decision regarding revascularization in such patients, providing data on the potential benefit to balance against the known risks.

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Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis

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