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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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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

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Abbreviations and Acronyms

CAD = coronary artery disease
DASE = dobutamine/atropine stress echocardiography
EF = ejection fraction
FDG = F-18 fluorodeoxyglucose
LDDE = low-dose dobutamine echocardiography
LV = left ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
PET = positron emission tomography
RALES = Randomized Spironolactone Evaluation study
SPECT = single photon emission computed tomography

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 deaths or where deaths could not be apportioned to patients with versus without viability were excluded (6,28,29). In cases of apparent serial reporting of a patient cohort only the most recent was included (5).

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 1. Individual Studies

Technique	Author	Year	Imaging Technique	Viability Criterion	Patients Entered	Age (yrs)	Follow-up (months)	LVEF (%)
Thallium	Gioia (14)	1995	rest/redistribution TI SPECT	TI uptake score	85	65	31	30
	Gioia (15)	1996	rest/redistribution TI SPECT	rest redistribution	89	69	31	27
	Pagley (18)	1997	rest/redistribution planar TI	Viability index 0.67	70	66	37	28
	Petretta (19)	1997	rest/reinjection TI SPECT	TI uptake score	104	57	22	40
	Cuocolo (24)	1998	rest/redistribution TI SPECT	rest redistribution	84	55	17	37
	Pasquet (31)	1999	stress/rest/reinjection TI SPECT	TI reversibility	141	62	33	35
FDG	Eitzman (8)	1992	FDG PET	flow/FDG mismatch	110	59	12	34
	Tamaki (9)	1993	stress redistribution TI SPECT/ FDG PET	FDG uptake	158	60	23	46
	Yoshida (10)	1993	rubidium/FDG PET	Rubidium/FDG uptake	35	54	36	44
	Dreyfus (12)	1994	rest redistribution TI SPECT/ FDG PET	rest redistribution/FDG uptake	50	58	18	23
	Di Carli (11)	1994	FDG PET	flow/FDG mismatch	107	65	14	25
	Lee (13)	1994	FDG PET	flow/FDG mismatch	137	62	17	38
	Haas (17)	1997	FDG PET	FDG uptake	34	62	15	28
	Vom Dahl (20)	1997	mibi SPECT/FDG PET	flow/FDG mismatch	161	57	29	45
	Di Carli (25)	1998	FDG PET	flow/FDG mismatch	93	68	46	25
	Beanlands (23)	1998	mibi SPECT/FDG PET	viability score	85	62	18	26
	Huitink (26)	1998	rest planar TI and FDG	flow/FDG mismatch	59	61	47	51
Echocardiography	Williams (16)	1996	DASE	regional wall motion	136	67	16	30
	Afridi (21)	1998	DASE	"	353	64	18	27
	Anselmi (22)	1998	LDDE	"	210	59	16	33
	Meluzin (27)	1998	LDDE	"	274	58	20	35
	Smart (33)	1999	DASE	"	350	61	18	30
	Senior (32)	1999	LDDE	"	87	62	40	25
	Bax (30)	1999	DASE	"	76	61	19	28
					3,088	61	25	33

DASE = dobutamine/atrophine 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.

Table 2. Pooled Data Patient Characteristics

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

Data are given as mean (range).
LVEF = left ventricular ejection fraction.

chi-square test for homogeneity was calculated, and Fisher exact test was used for comparing event rates ($p < 0.05$ considered significant). For the overall meta-analysis, three papers were considered outliers (31–33) and rendered the primary chi-square test with a $p < 0.05$. When these were removed, the chi-square test had a $p > 0.05$.

Meta-regression. The impact of revascularization on survival after risk adjustment for confounding variables was determined by multiple linear regression (meta-regression) using the event rate as the end point. This was used to examine the relationship between the severity of LV dysfunction and the prognostic benefit of revascularization as a function of the presence of viability (STATA software, version 6.0, Stata Corporation, College Station, Texas). This model included risk adjustment for all variables listed in Table 2 including year of publication and study sample size. A final multiple linear regression model was identified with variable inclusion at $p < 0.05$. Finally, to compare relative diagnostic performance of the imaging modalities, three individual meta-analyses (thallium, FDG, echocardiography) were performed.

RESULTS

Of the 24 studies, there were six using thallium-201 perfusion imaging (one planar, five single photon emission computed tomography [SPECT]), 573 patients, mean LVEF 33%, range 27% to 46%. These reports used various imaging protocols including rest/redistribution (14,15,18, 24) and stress/rest/reinjection (19,31).

Eleven studies employed FDG imaging with PET (8–13,17,20,23,25) or planar imaging (26): 1,029 patients, mean LVEF 35%, range 23% to 45%.

Eight studies utilized dobutamine echocardiography with low (LDDE) (22,27,32) or high dose protocol including atropine augmentation (DASE) (16,21,30,33): 1,486 patients, mean LVEF 28%, range 25% to 35%.

Patient characteristics. There were 3,088 patients (2,228 men), mean age 61 years and LVEF 32 ± 8%. Mean New York Heart Association (NYHA) functional class (where specified) was 2.8. Follow-up was 87.7% complete over 25 ± 10 months. Overall, 35% of the group underwent revascularization, and 65% received medical therapy. A total of 42% of patients had imaging-based evidence for myocardial viability (as defined by individual study authors). During follow-up 375 patients died (12%). Patient outcome data from the individual studies is summarized in Table 3.

Influence of myocardial viability and revascularization on death. Mortality rates from the pooled data are depicted in Figure 1a. For patients with defined myocardial viability, annual mortality rate was 16% in medically treated patients but only 3.2% in revascularized patients (chi-square = 147, $p < 0.0001$). This represents a 79.6% relative reduction in risk of death for revascularized patients (Fig. 1). For patients without viability, annual mortality was not significantly different by treatment method: 7.7% with revascularization versus 6.2% for medical therapy (p = NS).

Examining these data grouped by treatment strategy (Fig. 1b), annual mortality was lower in revascularized patients when viability was present versus those without viability (3.2% vs. 7.7%, $p < 0.0001$). When patients were treated medically, those with viability had a 158% higher mortality than those without viability (16% vs. 6.2%, $p = 0.001$).

The multiple linear regression model most predictive of death included LVEF, presence of viability and use of revascularization (chi-square = 15, $p = 0.004$, pseudo $r^2 = 0.71$). This indicates that, even after adjusting to the extent possible for differences between individual patient populations, revascularization was associated with an enhanced survival rate ($\beta = 2.79$, $z = 22.3$, $p < 0.001$). This model also indicated that survival benefit with revascularization was limited to patients with viability.

Influence of severity of LV dysfunction on the effect of revascularization. This is depicted in Figure 2. The meta-regression demonstrated an inverse relationship between EF and reduction in risk of death with revascularization for patients with viability, that is, as EF decreased, the prognostic benefit with revascularization increased. No benefit was associated with revascularization in patients without viability at any level of EF.

Influence of viability testing technique. The individual prognostic benefit (prediction of reduced mortality with revascularization of viable myocardium) for individual imaging techniques is plotted in Figure 3. Confidence limits for thallium-201, FDG imaging and dobutamine echocardiography are wide and overlapping. No statistically significant difference in prediction of survival benefit with revascularization was detected between testing methods.

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

	Viable Revascularized		Viable Medical Therapy		Nonviable Revascularized		Nonviable Medical Therapy		Viable Revascularized	Viable Medical Therapy	Nonviable Revascularized	Nonviable Medical Therapy	Viable	Nonviable
Author	Deaths	Pts	Deaths	Pts	Deaths	Pts	Deaths	Pts	Survival	Survival	Survival	Survival	Survival	Survival
Eitzman (8)	1	26	6	18	0	14	2	24						
Tamaki (9)	NS	NS	NS	NS	NS	NS	NS	NS					0.78 0.68 0.40	0.98 0.95 0.91
Yoshida (10)	2	20	0	5	3	6	2	4						
Di Carli (11)	3	26	4	17	1	17	6	33	0.88 0.88 0.88	0.5 0.5 0.5	0.94 0.94 0.94	0.92 0.92 0.82		
Lee (13)	4	49	3	21	1	19	5	40						
Dreyfus (12)	3	46	NI		NI		NI		0.8 0.8 0.8					
Gioia (14)	6	38	16	47	NI		NI		0.92 0.85 0.85 0.85	0.84 0.73 0.68 0.60	NI	NI		
Gioia (15)	NI		22	38	NI		11	43	NI	0.76 0.70 0.53 0.38		0.82 0.73 0.73 0.73		
Williams (16)	NS		NS		NS		NS						0.80 0.56	0.88 0.82
Haas (17)	1	34	NI		NS		NI		0.97 0.97 0.97					
Pagley (18)	6	33	NI		15	37	NI		0.91 0.87 0.87	NI	0.77 0.73 0.65	NI		
Vom Dahl (20)	2	57	2	14	2	27	7	63	NS	NS	NS	NS		
Petretta (19)	NI		NS		NI		NI			0.83 0.67		0.94 0.90		
Di Carli (25)	NS		NS		NS		NS		0.85 0.78 0.78	0.58 0.38 0.38	1.0 0.97 0.82	0.98 0.86 0.65		
									0.75 0.73	0.34 0.28	0.78 0.78	0.54 0.54		
Beanlands (23)	1	31	4	14	NI		NI							
Afridi (21)	5	85	24	119	5	30	17	84	0.96 0.93 0.93	0.86 0.82 0.60	0.92 0.80 0.80	0.94 0.78 0.61		
Cuocolo (24)	NS		NS		NI		NI		0.97 0.97 0.97	0.84 0.78 0.66				
Huitink (26)	NS		NS		NS		NS			0.81 0.63 0.63		0.93 0.93 0.93		
Anselmi (22)	4	64	4	52	4	25	6	61	0.85 0.77 0.77	0.83 0.76 0.76	0.63 0.56 0.56	0.88 0.70 0.56		
Meluzin (27)	2	29	NI		13	104	NI						0.86 0.84 0.84	0.93 0.93 0.93
Smart (33)	7	78	44	90	0	0	15	182					0.73	0.97
Senior (32)	1	31	10	32	3	6	8	18	0.97 0.97 0.97 0.97	0.93 0.73 0.70 0.62	0.72 0.50 0.50 0.50	0.88 0.61 0.54 0.54		
Bax (30)	1	23	NI		5	45	NI		0.87 0.82		0.71 0.53			
Pasquet (31)	5	58	4	16	9	36	7	27	0.97 0.93 0.91	0.81 0.75 0.74	0.88 0.81 0.76	0.86 0.78 0.75		

NI = not included; NS = not stated; Pts = patients.

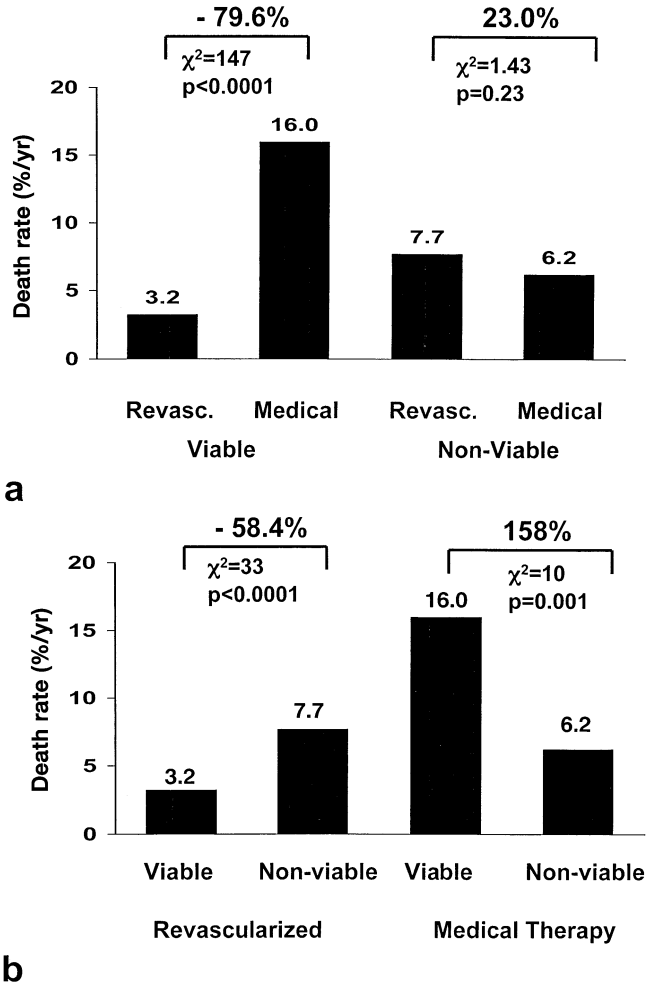

Figure 1. **(a)** Death rates for patients with and without myocardial viability treated by revascularization or medical therapy. There is 79.6% reduction in mortality for patients with viability treated by revascularization ($p < 0.0001$). In patients without myocardial viability, there was no significant 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.

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.

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) (patients with advanced heart failure on angiotensin-converting enzyme inhibitor therapy). The 80% reduction in death rate associated with revascularization in the current analysis exceeds the benefit generally observed in clinical trials of new therapeutics in heart failure (e.g., 30% mortality reduction in the RALES trial with spironolactone). This comparison must be tempered by the nonrandomized nature of the present analysis, as well as inevitable selection biases in making decisions for revascularization in the observational studies. However, a substantial reduction in mortality associated with revascularization in the setting of LV dysfunction is in keeping with recent autopsy data from a large heart failure clinical trial (42), suggesting that a considerable proportion of fatal events in patients with severe heart failure are associated with evidence of acute ischemia or infarction, even when death has been considered primarily arrhythmic or from progressive heart failure.

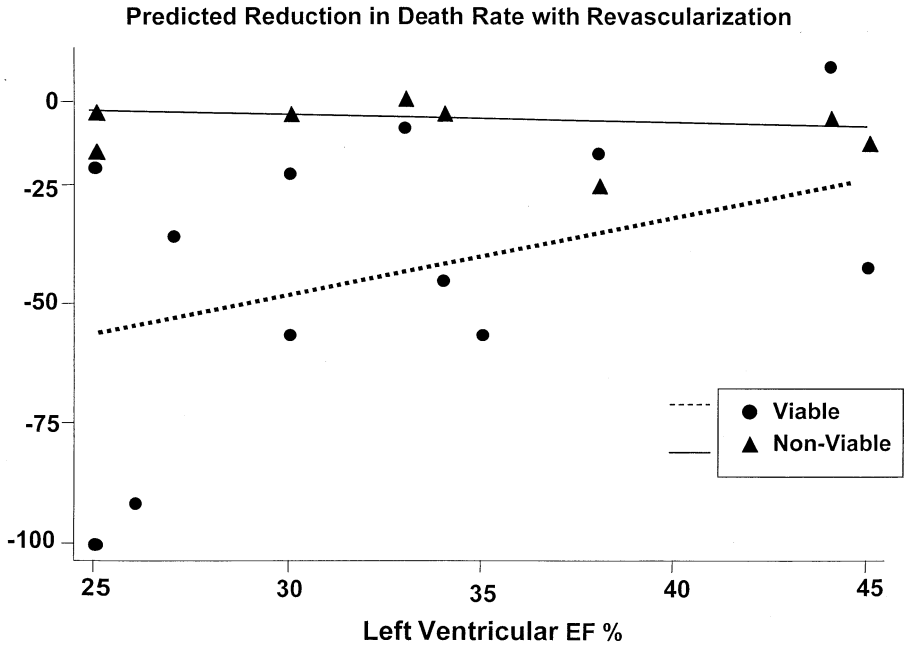

Figure 2. Relation between left ventricular ejection fraction (EF) and predicted change in mortality for patients with viable **(circles)** versus nonviable **(triangles)** myocardium based on the results of meta-regression. This demonstrates increasing potential for improved survival with lower left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

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 to then proceed to either medical or revascularization

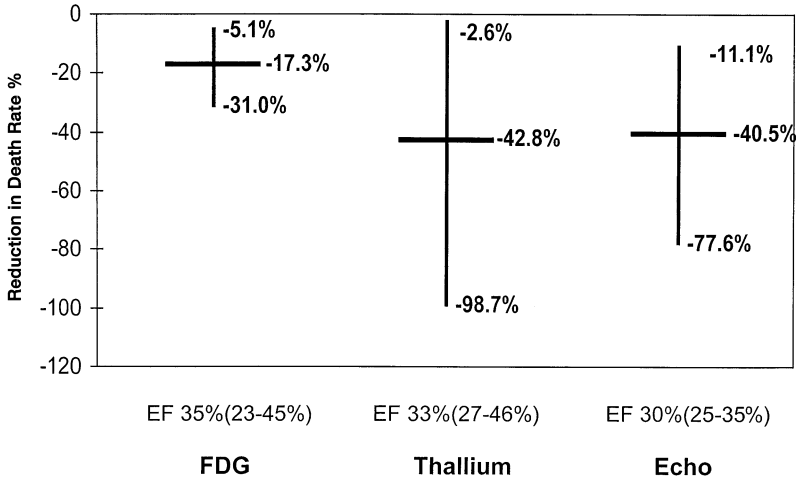

Figure 3. Decrease in mortality with revascularization of viable myocardium for each testing technique shown as mean value with 95% confidence limits. Note wide confidence limits, especially for thallium and echocardiography. No measurable differences in test performance were observed. EF = ejection 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 (44).

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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