Hibernating Myocardium: Diagnosis and Patient Outcomes

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Abstract: Approximately 50% of the patients with chronic obstructive coronary artery disease resulting in chronic contractile dysfunction have hibernating myocardium and may benefit from revascularization. This pooled analysis describes the relative merits of dobutamine echocardiography, thallium-201 and technetium-99m scintigraphy, positron emission tomography, and magentic resonance imaging, for the diagnosis of hibernating myocardium and prediction of patient outcomes. (Curr Probl Cardiol 2007;32:375-410.)

Assessment of hibernating, viable myocardium is important in the evaluation and management of patients with ischemic left ventricular (LV) dysfunction. Patients with viable myocardium may improve in function after revascularization, whereas patients without viable myocardium do not improve in function. Various noninvasive imaging techniques are available for assessment of viable myocardium, and their relative merits for prediction of improvement in regional LV function after revascularization have been reported in 2001 in a pooled analysis of the available literature studies.[1] The current report is an update of this pooled analysis with inclusion of all published studies between 2001 and 2007.

However, improvement of regional function is a very important but not the ideal endpoint after revascularization. Accordingly, the value of noninvasive assessment of viability and additional endpoints, including

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improvement of global LV function, exercise capacity, and heart failure symptoms, and long-term prognosis, are also addressed in the current pooled analysis.

Methods

The purpose of this pooled analysis of the available studies in literature is to determine and compare the relative merits of the most frequently used techniques for the evaluation of viable myocardium and assessment of patient outcomes. These patient outcomes included the following:

1. Recovery of segmental contractile function,
2. Recovery of global LV contractile function,
3. Improvement of heart failure symptoms and exercise capacity,
4. Long-term prognosis.

The available studies (1980 through January 2007) were identified by MEDLINE searches using the terms "myocardial viability" in combination with a set of terms for the techniques: "thallium-201 rest-redistribution," "thallium-201 reinjection," "technetium-99m sestamibi," "technetium-99m tetrofosmin," "dobutamine echocardiography," "F18-fluorodeoxyglucose," "magnetic resonance imaging" to update and extend the information that was collected previously in the extensive pooled analysis published in 2001.[1] In addition, referenced studies used by the selected articles were evaluated, and a manual search of cardiology and nuclear medicine journals (*American Heart Journal, American Journal of Cardiology, Circulation, European Heart Journal, European Journal of Nuclear Medicine, Heart, Journal of the American College of Cardiology, Journal of Nuclear Medicine,* and *the Journal of Nuclear Cardiology*) was carried out. All articles were reviewed and considered for inclusion in the pooled data set, if they provided data on myocardial viability assessment using previously defined criteria.[1] Studies that did not comply with these criteria were excluded.

Relative Merits for Prediction of Improvement of Regional and Global LV Function

From the pooled data, weighted sensitivities (test-viable segments/segments with recovery after revascularization), specificities (test-nonviable segments/segments without recovery after revascularization), positive-predictive value (PPV, segments with recovery after revascularization/test-viable segments), and negative-predictive value (NPV, segments without recovery after revascularization/test-nonviable segments) were calculated. Similarly, these values were determined for improvement of global LV function after revascularization. The 95% confidence intervals (CI) were

calculated ($p \pm 1.96 \times \sqrt{\{p \times (1 - p)/n\}}$, with p representing the fraction and n representing the total population). The 95% CIs for the different techniques were compared and differences between techniques were considered significant ($P < 0.05$) when the 95% CIs did not overlap.

Improvement of Exercise Capacity and Heart Failure Symptoms

The pooled results of the studies on improvement of exercise capacity and symptoms in relation to viability are presented; exercise capacity is expressed in metabolic equivalent (MET) and heart failure symptoms are graded according to the New York Heart Association (NYHA) classification. Data are presented as follows:

Viability present and METS and NYHA class before and after revascularization,
Viability absent and METS and NYHA class before and after revascularization.

Long-Term Prognosis

From the available studies on prognosis in patients who underwent viability testing, death rates were derived. Death rates from the different studies were pooled and annualized mortality rates were calculated. The mortality rates in relation to viability and therapy are presented in four groups:

Patients with viability who underwent revascularization,
Patients with viability who received medical treatment,
Patients without viability who underwent revascularization,
Patients without viability who received medical treatment.

Results

In addition to the 77 studies that were included and evaluated in the previously published pooled analysis, 81 recent studies meeting the inclusion criteria were selected for this new analysis. The results of the pooled analysis of these 158 studies are presented in four areas of clinical interest:

1. Prediction of recovery of regional function,
2. Prediction of global LV function,
3. Improvement of heart failure symptoms and exercise capacity, and
4. Prognosis.

TABLE 1. Studies using dobutamine echocardiography to predict improvement of regional function after revascularization

Reference	No. of patients	% Male	Age (y)	LVEF (%)	(%) Patients with MVD
Dellegrottaglie[2] LDDE	26	96	56 ± 10	42 ± 9	77
Leoncini[3] LDDE	25	92	58 ± 7	NA	68
Piscione[4] LDDE	33	94	56 ± 10	42 ± 10	57
Piscione[5] LDDE	53	94	59 ± 7	43 ± 9	77
Pace[6] LDDE	69	96	59 ± 8	40 ± 11	59
Cwajg[7] HDDE	45	84	61 ± 10	39 ± 13	69
Ling[8] HDDE	32	84	70 ± 7	30 ± 9	NA
Hanekom[9] HDDE	55	84	64 ± 10	36 ± 8	NA
Zaglavara[10] HDDE	24	92	63 ± 8	29 ± 8	100

CABG, coronary artery bypass grafting; *HDDE*, high-dose dobutamine echocardiography; *LDDE*, low-dose dobutamine echocardiography; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MVD*, multivessel disease; *NA*, not available; *PTCA*, percutaneous transluminal coronary angioplasty.

TABLE 2. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of dobutamine echocardiography to predict improvement of regional function after revascularization (1421 patients, 41 studies)

Reference	Sensitivity (%) (segments)	Specificity (%) (segments)	PPV (%) (segments)	NPV (%) (segments)
Data up to 2001 (1059 patients, 32 studies)[1]	82 (2382/2901)	80 (2929/3641)	77 (2362/3072)	85 (2929/3466)
Dellegrottaglie[2]	74 (50/68)	44 (22/50)	68 (50/74)	55 (22/40)
Leoncini[3]	57 (43/75)	85 (111/130)	69 (43/62)	78 (111/143)
Piscione[4]	64 (43/67)	62 (30/48)	70 (42/60)	75 (51/68)
Piscione[5]	69 (91/132)	71 (117/164)	66 (91/138)	74 (117/158)
Pace[6]	71 (117/165)	64 (111/174)	65 (117/180)	70 (111/159)
Cwajg[7]	91 (52/57)	69 (77/112)	60 (52/87)	94 (77/82)
Ling[8]	96 (197/223)	72 (66/92)	88 (197/223)	72 (66/92)
Hanekom[9]	73 (106/146)	77 (156/204)	69 (106/154)	80 (156/196)
Zaglavara[10]	77 (82/107)	68 (89/131)	66 (82/124)	78 (89/114)
Weighted mean	80 (3163/3941)	78 (3708/4746)	75 (3142/4174)	83 (3729/4518)

Prediction of Recovery of Regional Function

Dobutamine echocardiography. In 2001, 32 studies using dobutamine echocardiography (DE) involving 1059 patients were selected.[1] Over the last 6 years, nine additional studies[2-10] (362 patients) have been published (Tables 1 and 2). Inclusion of these nine additional studies yielded a total of 41 studies (1421 patients) with a weighted mean sensitivity and specificity of 80 and 78%, and a PPV and NPV of 75 and 83%.

TABLE 1. Continued

PTCA/CABG	Patients with MI (%)	Segments with recovery (%)	Technique and timing to assess function after revascularization
15/11	100	57	2D echo, 12 ± 5 mo
15/10	100	37	2D echo, 84 days
18/15	67	58	2D echo, 90 ± 48 days
27/26	74	44	2D echo, 90 ± 48 days
34/35	88	49	2D echo, 40 ± 20 days
31/14	58	38	2D echo, >2 mo
3/21	38	71	2D echo, 3 mo
NA	100	42	2D echo, 9 mo
0/100	71	45	2D echo, 6 mo

Subanalysis of the pooled data showed that low-dose dobutamine echocardiography (33 studies, 1121 patients) had a sensitivity and specificity of 79 and 78%, with a PPV and NPV of 76 and 82%. High-dose dobutamine echocardiography allows assessment of both contractile reserve and stress-induced ischemia. At present, eight studies (290 patients) have used high-dose DE, resulting in a weighted mean sensitivity and specificity of 83 and 79%, with a PPV and NPV of 73 and 85%. High-dose dobutamine echocardiography had a significantly higher sensitivity and NPV than low-dose dose dobutamine echocardiography (both $P < 0.05$), whereas specificity and PPV were comparable.

Thallium-201 imaging. In 2001, 33 studies (858 patients) were available that used Tl-201 imaging.[1] Over the last 6 years, seven additional studies (261 patients)[2,4,5,11-14] have been reported (Tables 3 and 4). Inclusion of these seven additional studies yielded a total of 40 studies (1119 patients) with a weighted mean sensitivity and specificity of 87 and 54%, with a PPV and NPV of 67 and 79%. Subanalysis of the pooled data revealed that 28 studies (776 patients) have used Tl-201 rest-redistribution imaging, with a weighted mean sensitivity and specificity of 87 and 56%, and a PPV and NPV of 71 and 78%. A total of 12 studies (343 patients) have used a Tl-201 reinjection protocol, yielding a sensitivity and specificity of 87 and 50%, with a PPV and NPV of 58 and 81%. Tl-201 rest-redistribution imaging had a significantly higher specificity and PPV than Tl-201 reinjection (both $P < 0.05$), whereas sensitivity and NPV were comparable.

TABLE 3. Studies using thallium-201 imaging to predict improvement of regional function after revascularization

Reference	No. of patients	% Male	Age (y)	LVEF (%)	Patients with MVD (%)
Cwajg[11]	45	84	61 ± 10	39 ± 13	69
Dellegrottaglie[2]	26	96	56 ± 10	42 ± 9	77
Duncan[12]	30	87	64 ± 9	29 ± 8	NA
Ling[13]	32	84	70 ± 7	30 ± 9	NA
Piscione[4]	33	94	56 ± 10	42 ± 10	57
Piscione[5]	53	94	59 ± 7	43 ± 9	77
Wu[14]	42	93	61 ± 13	38 ± 16	NA

CABG, coronary artery bypass grafting; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MVD*, multivessel disease; *NA*, not available; *PTCA*, percutaneous transluminal coronary angioplasty; *SPECT*, single-photon emission computed tomography.

TABLE 4. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of thallium-201 imaging to predict improvement of regional function after revascularization (1119 patients, 40 studies)

Reference	Sensitivity (%) (segments)	Specificity (%) (segments)	PPV (%) (segments)	NPV (%) (segments)
Data up to 2001 (858 patients, 33 studies)[1]	87 (1783/2059)	55 (1194/2155)	64 (1783/2773)	81 (1194/1480)
Cwajg[11]	91 (64/69)	50 (56/112)	53 (63/119)	90 (56/62)
Dellegrottaglie[2]	82 (56/68)	40 (20/50)	65 (56/86)	63 (20/32)
Duncan[12]	95 (255/269)	59 (51/86)	88 (255/290)	78 (51/65)
Ling[13]	96 (215/223)	25 (32/92)	78 (215/275)	80 (32/40)
Piscione[4]	77 (52/67)	65 (31/48)	75 (51/68)	67 (31/46)
Piscione[5]	76 (87/114)	43 (30/69)	69 (87/126)	53 (30/57)
Wu[14]	76 (47/62)	40 (17/43)	64 (47/73)	53 (17/32)
Weighted mean	87 (2559/2931)	54 (1431/2655)	67 (2557/3810)	79 (1431/1814)

Technetium-99m labeled agents. In 2001, 20 studies (488 patients) were available that used technetium-99m-labeled agents to predict improvement of regional contractile function after revascularization.[1] Over the last 6 years, five additional studies (233 patients)[3,12,15-17] were published (Tables 5 and 6). Inclusion of these five additional studies resulted in a total of 25 studies (721 patients) with a weighted mean sensitivity and specificity of 83 and 65%, and a PPV and NPV of 74 and 76%. Twenty of these studies (350 patients) used technetium-99m sestamibi, whereas the remaining five studies (166 patients) used technetium-99m tetrofosmin. Subanalysis of 17 studies (516 patients) using technetium-99m-labeled agents without the addition of nitrates yielded a weighted mean sensitivity and specificity of 83 and 57%, whereas PPV and NPV were 72 and 71%. The present analysis included eight studies

TABLE 3. Continued

PTCA/CABG	Patients with MI (%)	Segments with recovery (%)	Technique and timing to assess function after revascularization
31/14	58	38	2D echo, >2 mo
15/11	100	57	2D echo, 12 ± 5 mo
2/28	87	53	Gated SPECT, 6 wks
3/21	38	71	2D echo, 3 mo
18/15	67	58	2D echo, 90 ± 48 days
27/26	74	44	2D echo, 90 ± 48 days
11/5	68	59	2D echo, 9 ± 3 mo

(205 patients) using technetium-99m-labeled agents with nitrates, demonstrating a weighted mean sensitivity and specificity of 81 and 69%, with a PPV and NPV of 72 and 78%. Nuclear imaging with technetium-99m-labeled agents with the addition of nitrates had a significantly higher specificity and NPV than without nitrates (both $P < 0.05$), whereas sensitivity and PPV were comparable.

Robert O. Bonow: This updated analysis confirms previous studies and meta-analyses demonstrating that SPECT imaging with thallium-99m or technetium-99m perfusion tracers is more sensitive for detecting viable myocardium than dobutamine echocardiography, but that low-dose dobutamine echocardiography is more specific for predicting recovery of function after revascularization. Thus, markers of contractile reserve predict functional recovery with greater specificity than do markers of preserved cell membrane function.

FDG PET. In 2001, 20 studies (598 patients) were reported that used FDG PET to predict recovery of segmental contractile function.[1] Over the last 6 years, four new studies (158 patients)[18-21] have become available (Tables 7 and 8). Pooled analysis of all 24 studies (756 patients) showed a weighted mean sensitivity and specificity of 92 and 63%, with a PPV and NPV of 74 and 87%.

Magnetic resonance imaging. Currently, three magnetic resonance imaging (MRI) techniques are being used to assess myocardial viability. Resting MRI can be used to assess end-diastolic wall thickness and contractile function at rest. Segments with an end-diastolic wall thickness <6 mm most likely represent transmural scar formation and contractile function will not improve after myocardial revascularization. Dobutamine

TABLE 5. Studies using technetium-99m sestamibi to predict improvement of regional function after revascularization

Reference	No. of patients	% Male	Age (y)	LVEF (%)	(%) Patients with MVD
Duncan[12]	30	87	64 ± 9	29 ± 8	NA
Gonzalez[15]	82	85	59 ± 9	41 ± 14	78
Mabuchi[16]*	56	68	65 ± NA	55 ± 8	82
Murashita[17]*	40	73	66 ± 6	52 ± 8	95
Leoncini[3]	25	92	58 ± 7	NA	68

CABG, coronary artery bypass grafting; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MVD*, multivessel disease; *NA*, not available; *PTCA*, percutaneous transluminal coronary angioplasty; *SPECT*, single-photon emission computed tomography.
*Tetrofosmin was used.

TABLE 6. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) for technetium-99m sestamibi to predict improvement of regional function after revascularization (721 patients, 25 studies)

Reference	Sensitivity (%) (segments)	Specificity (%) (segments)	PPV (%) (segments)	NPV (%) (segments)
Data up to 2001 (488 patients, 20 studies)	81 (667/824)	66 (512/779)	71 (667/934)	77 (512/669)
Duncan[12]	96 (257/269)	55 (47/86)	87 (257/296)	80 (47/59)
Gonzalez[15]	72 (112/155)	53 (87/163)	60 (112/188)	67 (87/130)
Mabuchi[16]*	86 (48/56)	67 (14/21)	87 (48/55)	64 (14/22)
Murashita[17]*	80 (28/35)	50 (6/12)	82 (28/34)	46 (6/13)
Leoncini[3]	77 (58/75)	88 (112/128)	78 (58/74)	87 (112/129)
Weighted mean	83 (1170/1414)	65 (778/1189)	74 (1170/1581)	76 (778/1022)

*Tetrofosmin was used.

MRI can be used to evaluate contractile reserve in a similar manner to dobutamine echocardiography. Contrast-enhanced MRI, using gadolinium-based contrast agents, permits precise detection of the extent and transmurality of scar tissue.

Three studies (100 patients)[20,22,23] that used end-diastolic wall thickness assessed by MRI were selected (Tables 9 and 10). Pooled analysis resulted in a weighted mean sensitivity and specificity of 95 and 41%, whereas the PPV and NPV were 56 and 92%. Nine studies (272 patients)[20,22,24-30] using dobutamine stress MRI were selected. The mean sensitivity and specificity were 74 and 82%; PPV and NPV were both 78%. Five studies (178 patients)[21,29-32] employed contrast-enhanced MRI, with a weighted mean sensitivity and specificity of 84 and 63%, and PPV and NPV of 72 and 78%.

Comparison of the techniques. The sensitivities, specificities, PPV, and NPV of these noninvasive modalities for the prediction of segmental

TABLE 5. Continued

PTCA/CABG	Patients with MI (%)	Segments with recovery (%)	Technique and timing to assess function after revascularization
2/28	87	53	Gated SPECT, 6 wks
18/64	85	49	Gated blood pool, 6 mo
0/56	66	73	Gated SPECT, 3 mo
0/40	63	74	Gated SPECT, 3 mo
15/10	100	37	2D echo, 84 days

recovery after revascularization are summarized in Figs 1 and 2. FDG PET had the highest sensitivity ($P < 0.05$ versus other techniques), followed by nuclear imaging using Tl-201, and technetium-99m-labeled agents. In general, the nuclear imaging techniques had a higher sensitivity ($P < 0.05$) than dobutamine echocardiography. On the other hand, specificity was highest for dobutamine echocardiography ($P < 0.05$ vs other techniques). The highest PPV was observed for dobutamine echocardiography and FDG PET. Conversely, FDG PET had the highest NPV ($P < 0.05$ vs the other techniques). Nuclear imaging with technetium-99m-labeled agents had the lowest NPV ($P < 0.05$ vs the other techniques).

Robert O. Bonow: The authors make important points regarding the relative accuracies of the various imaging modalities. One difficulty in fully interpreting this analysis, however, is that each of the studies made a simple determination of myocardium being "viable" or "nonviable" using arbitrary thresholds. That is, viability is determined as if it were a binary variable, whereas numerous studies have shown that the likelihood of recovery of regional function is a continuous function related to the severity of the perfusion defect (Perrone-Filardi et al. Circulation 1996;94:2712-9), magnitude of contractile reserve,[34] or transmurality of MRI contrast hyperenhancement.[31]

Prediction of Recovery of Global Contractile Function

The accuracy of the various noninvasive imaging modalities for the prediction of recovery of global LV function following revascularization will be discussed per technique. The available studies are summarized in Tables 11 to 14. Comparison of the techniques is presented in Figs 3 and

TABLE 7. Studies using positron emission tomography and F18-fluorodeoxyglucose to predict improvement of regional function after revascularization

Reference	No. of patients	% Male	Age (y)	LVEF (%)	(%) Patients with MVD
Slart[18]	47	87	65 ± 9	33 ± 12	100
Nowak[19]	42	54	63 ± 11	38 ± 13	76
Schmidt[20]	40	84	57 ± 9	42 ± 10	73
Kuhl[21]	29	72	66 ± 9	32 ± 10	NA

CABG, coronary artery bypass grafting; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MRI*, magnetic resonance imaging; *MVD*, multivessel disease; *NA*, not available; *PTCA*, percutaneous transluminal coronary angioplasty.

TABLE 8. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of positron emission tomography using F18-fluorodeoxyglucose to predict improvement of regional function after revascularization (756 patients, 24 studies)

Reference	Sensitivity (%) (segments)	Specificity (%) (segments)	PPV (%) (segments)	NPV (%) (segments)
Data up to 2001 (598 patients, 20 studies)[1]	93 (751/807)	58 (417/725)	51 (751/1059)	86 (417/483)
Slart[18]	91 (130/143)	87 (105/121)	89 (130/146)	89 (105/118)
Nowak[19]	90 (36/40)	63 (20/32)	75 (36/48)	83 (20/24)
Schmidt[20]	100 (25/25)	73 (11/15)	86 (25/29)	100 (11/11)
Kuhl[21]	86 (83/96)	74 (67/91)	78 (83/107)	84 (67/80)
Weighted mean	92 (1025/1111)	63 (620/984)	74 (1025/1389)	87 (620/716)

4. Currently no studies have used MRI for the prediction of recovery of global LV function after revascularization.

Dobutamine echocardiography. Six studies (287 patients) used dobutamine echocardiography to predict improvement of global LV function following revascularization (one study used high-dose dobutamine,[9] the remaining five[4-6,33,34] used low-dose dobutamine infusion). Pooled analysis (Table 11) shows a weighted mean sensitivity and specificity of 57 and 73%, with a PPV and NPV of 63 and 68%.

Robert O. Bonow: There is one MRI study by Kim et al[31] that reported the predictive value of contrast-enhanced MRI relative to improved ejection fraction after revascularization. The greater the amount of dysfunctional but viable myocardium, the greater the improvement in ejection fraction.

Tl-201 imaging. Five Tl-201 studies (three rest-redistribution, two reinjection, total 235 patients) evaluated improvement of global func-

TABLE 7. Continued

PTCA/CABG	Patients with MI (%)	Segments with recovery (%)	Technique and timing to assess function after revascularization
20/27	72	54	MRI, 6 mo
8/7	79	50	2D echo, 17 ± 5mo
19/21	100	63	MRI, 4-6 mo
15/14	83	51	MRI, 6 mo

tion.[4,5,35-37] The weighted mean sensitivity and specificity were 84 and 53%, and the PPV and NPV were 76 and 64% (Table 12).

Technetium-99m-labeled agents. Two studies on prediction of improvement of global function are available; both used technetium-99m sestamibi with the addition of nitrates.[38,39] The weighted mean sensitivity and specificity were 84 and 68%, and the PPV and NPV were 74 and 80% (Table 13).

FDG PET. Sixteen studies (747 patients) using FDG PET were available.[18,33,40-53] Three of these studies provided sufficient information on the diagnostic accuracy.[18,33,40] Pooling of these three studies (Table 14) yielded a sensitivity and specificity of 83 and 64%, with a PPV and NPV of 68 and 80%.

Comparison of the techniques. For the prediction of recovery of global LV function, the diagnostic accuracy of the various techniques is summarized in Figs 3 and 4. Pooling of the available selected studies from four techniques showed a comparable sensitivity for the nuclear techniques. A lower sensitivity was observed for dobutamine echocardiography ($P < 0.05$ vs nuclear techniques). On the other hand, no significant changes were observed in the specificity of these four techniques. The PPV and NPV were not statistically different for the four techniques.

Robert O. Bonow: The importance of viability determinations to assess reversibly dysfunctional myocardium is not limited to predicting recovery of function after revascularization. Myocardial viability also predicts improvement in left ventricular function after initiation of beta-blocker therapy (Bello et al. Circulation 2003;108:1945-53; Cleland et al. Lancet 2003;362:14-21).

TABLE 9. Studies using magnetic resonance imaging (MRI) to predict improvement of regional function after revascularization

Reference	No. of patients	% Male	Age (y)	LVEF (%)	(%) Patients with MVD
EWDT					
Schmidt[20]	40	93	57 ± 9	42 ± 10	73
Baer[22]	43	93	58 ± 9	42 ± 10	70
Klow[23]	17	88	63	40	NA
Dobutamine MRI					
Schmidt[20]	40	84	57 ± 9	42 ± 10	73
Baer[22]	43	93	58 ± 9	42 ± 10	70
Baer[24]	52	92	58 ± 9	41 ± 10	75
Gunning[25]	30	90	61 ± NA	24 ± 8	100
Sayad[26]	10	70	NA	NA	NA
Sandstede[27]	25	88	58 ± 10	NA	NA
Trent[28]	25	100	64 ± 9	53 ± 16	NA
Wellnhofer[29]	29	93	68 ± 7	32 ± 8	NA
Van Hoe[30]	18	56	62 ± 8	52 ± 16	83
Contrast-enhanced MRI					
Wellnhofer[29]	29	93	68 ± 7	32 ± 8	NA
Kuhl[21]	29	72	66 ± 9	32 ± 10	NA
Kim[31]	50	88	63 ± 11	43 ± 13	NA
Selvanayagam[32]	52	NA	60	62 ± 12	NA
Van Hoe[30]	18	56	62 ± 8	52 ± 16	83

CABG, coronary artery bypass grafting; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MRI*, magnetic resonance imaging; *MVD*, multivessel disease; NA, not available; *PTCA*, percutaneous transluminal coronary angioplasty.

Prediction of Improvement in Heart Failure Symptoms and Exercise Capacity

Because only a limited number of studies focused on these issues, the 11 available studies are pooled (1 study used dobutamine echocardiography, 3 used Tl-201 imaging, 6 used FDG PET, and 1 study used both and FDG PET); the results are presented in Tables 15 and 16. Eight studies (423 patients) have focused on improvement of heart failure symptoms[45,48,50,51,54-57] (Table 15). In patients with viable myocardium, NYHA functional class improved from 2.9 to 1.6 after revascularization. Conversely, in patients without viable myocardium, NYHA class did not change significantly.

Three studies (122 patients, all using FDG PET) focused on improvement of exercise capacity[43,58,59] (Table 16). Overall, the mean exercise capacity (expressed in METS) was 4.4 before and 5.7 after revascularization in patients with viable myocardium, and 5.1 before and 5.9 after revascularization in patients without viable myocardium.

TABLE 9. Continued

PTCA/CABG	Patients with MI (%)	Segments with recovery (%)	Technique and timing to assess function after revascularization
19/21	100	63	MRI, 4-6 mo
22/21	100	46	MRI, 4-6 mo
0/17	100	35	MRI, 22 mo
19/21	100	63	MRI, 4-6 mo
22/21	100	46	MRI, 4-6 mo
29/23	100	56	MRI, 5 ± 1 mo
0/30	100	57	MRI, 3-6 mo
NA	NA	65	MRI, 4-8 wks
17/8	84	51	MRI, 6 mo
0/25	100	33	MRI, 3-6 mo
25/4	93	50	MRI, 3 mo
13/5	67	62	MRI, 9 ± 2 mo
25/4	93	50	MRI, 3 mo
15/14	83	51	MRI, 6 mo
14/27	42	53	MRI, 79 ± 36 days
0/52	NA	56	MRI, 6 mo
13/5	67	62	MRI, 9 ± 2 mo

Prognosis

The annualized mortality rates in relation to therapy (revascularization/medical therapy) will be discussed per technique. The available studies are summarized in Tables 17 to 23 and the results are displayed in Figs 5 to 7. Currently no prognostic studies using MRI are available.

Dobutamine echocardiography. Eleven studies (1753 patients) evaluated the prognostic role of dobutamine echocardiography (5 studies used high-dose dobutamine, 5 low-dose dobutamine, 1 both).[54,60-68] Details of the studies are presented in Table 17. The annualized event and mortality rates are summarized in Table 18 and Fig 5. Patients with viable myocardium undergoing revascularization had the best survival, whereas the highest annualized mortality rates were noted in patients receiving medical therapy, either with or without viable myocardium. An intermediate mortality rate was observed in patients without viable myocardium who underwent revascularization.

Tl-201 imaging. Nine studies (975 patients) assessed the prognostic value of Tl-201 imaging (six studies used rest-redistribution imaging, and

TABLE 10. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of magnetic resonance imaging (MRI) to predict improvement of regional function revascularization (420 patients, 13 studies)

Reference	Sensitivity (%) (segments)	Specificity (%) (segments)	PPV (%) (segments)	NPV (%) (segments)
EDWT				
Schmidt[20]	96 (24/25)	53 (8/15)	78 (25/32)	100 (8/8)
Baer[22]	94 (176/188)	52 (113/219)	62 (176/282)	90 (113/125)
Klow[23]	98 (63/64)	19 (23/120)	39 (63/160)	96 (23/24)
Weighted mean	95 (263/277)	41 (144/354)	56 (264/474)	92 (144/157)
Dobutamine MRI				
Schmidt[20]	96 (24/25)	87 (13/15)	92 (24/26)	93 (13/14)
Baer[22]	82 (155/188)	81 (177/219)	79 (155/197)	84 (177/210)
Baer[24]	86 (24/28)	92 (22/24)	92 (24/26)	85 (22/26)
Gunning[25]	50 (41/81)	81 (51/63)	77 (41/53)	55 (51/92)
Sayad[26]	89 (25/28)	93 (14/15)	96 (25/26)	82 (14/17)
Sandstede[27]	61 (65/106)	90 (91/101)	87 (65/75)	69 (91/132)
Trent[28]	71 (81/114)	70 (163/232)	54 (81/150)	83 (163/196)
Wellnhofer[29]	75 (93/124)	93 (152/164)	89 (93/105)	83 (152/183)
Van Hoe[30]	78 (56/72)	82 (37/45)	88 (56/64)	70 (37/53)
Weighted mean	74 (564/766)	82 (720/878)	78 (564/722)	78 (720/923)
Contrast-enhanced MRI				
Wellnhofer[29]	90 (111/124)	52 (85/164)	58 (111/190)	87 (85/98)
Kuhl[21]	98 (94/96)	70 (64/91)	78 (94/121)	97 (64/66)
Kim[31]	86 (365/425)	61 (232/379)	71 (365/512)	79 (232/292)
Selvanayagam[32]	78 (266/343)	64 (173/269)	73 (266/363)	69 (173/250)
Van Hoe[30]	78 (56/72)	92 (56/61)	92 (56/61)	78 (56/72)
Weighted mean	84 (891/1060)	63 (610/964)	72 (892/1247)	78 (610/778)

three used a reinjection protocol).[35,37,69-74] Details of these studies are presented in Table 19. The annualized event and mortality rates are summarized in Table 20 and Fig 6. Patients with viable myocardium who underwent revascularization had the best survival, whereas the highest annualized mortality rate was noted in nonviable patients undergoing revascularization. Intermediate mortality rates were noted in patients who were treated medically, with or without viable myocardium.

Technetium-99m-labeled agents. Limited data are available on the prognostic value of viability assessment with technetium-99m-labeled tracers. Only one study[74] evaluated 56 patients with a follow-up period of 40 months; the annualized mortality rate in viable patients who underwent revascularization was 3% as compared to 9% in patients who received medical therapy; nonviable patients were not studied.

FDG PET. Ten studies (1046 patients) have evaluated the prognostic role of FDG PET.[48,52,75-82] Details of these studies are presented in Table 21. The annualized mortality rates obtained from pooled analysis are summarized in

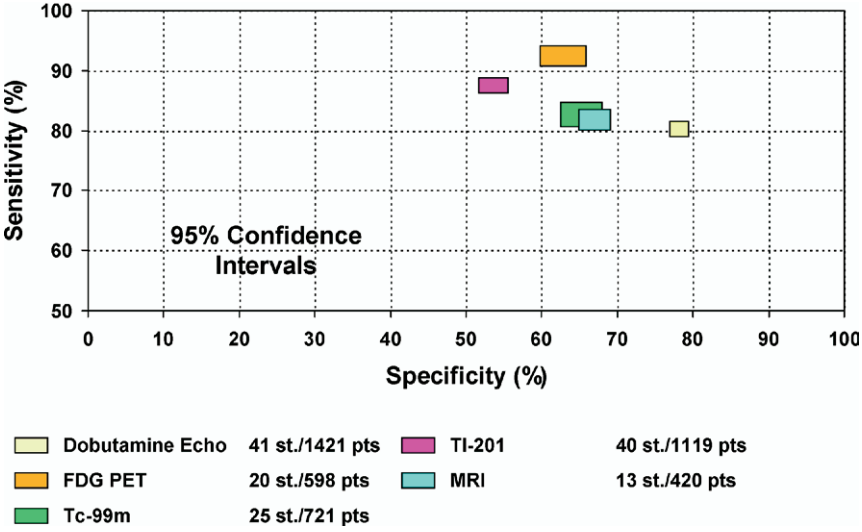

FIG 1. Comparison of sensitivities and specificities with 95% confidence intervals of the various techniques for the prediction of recovery of regional function after revascularization. (Color version of figure is available online.)

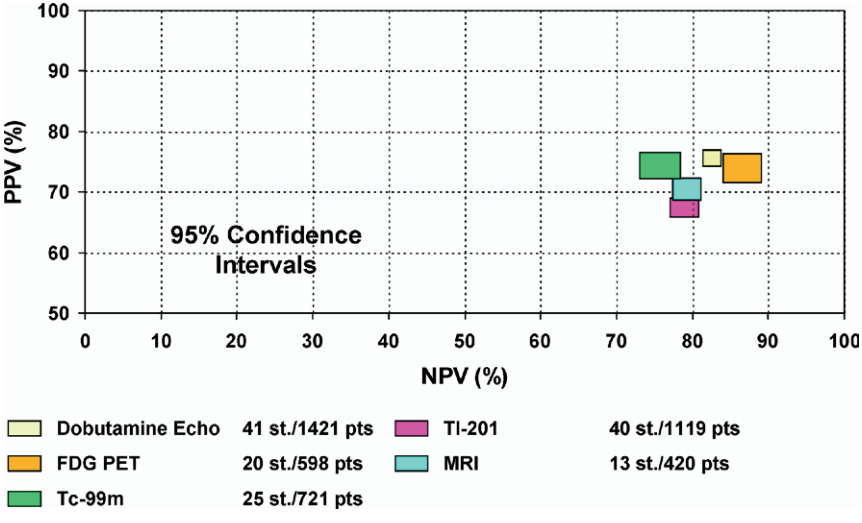

FIG 2. Comparison of positive-predictive values and negative-predictive values with 95% confidence intervals of the various techniques for the prediction of recovery of regional function after revascularization. (Color version of figure is available online.)

TABLE 11. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of dobutamine echocardiography to predict improvement of global function after revascularization

Reference	Criterium for viability	Criterium for improvement	Sensitivity (%) (patients)	Specificity (%) (patients)	PPV (%) (patients)	NPV (%) (patients)
Hanekom[9]	≥25% of LV	LVEF >5%	71 (15/21)	85 (22/26)	79 (15/19)	79 (22/28)
Piscione[4]	≥19% of LV	LVEF >6%	33 (3/9)	78 (7/9)	60 (3/5)	54 (7/13)
Piscione[5]	≥13% of LV	LVEF >6%	62 (8/13)	46 (6/13)	53 (8/15)	55 (6/11)
Pace[6]	≥17% of LV	LVEF ≥5%	47 (14/30)	69 (27/39)	54 (14/26)	63 (27/43)
Wiggers[33]	≥13% of LV	Wall motion score ≥2 of 16 segments (13% of LV)	71 (10/14)	81 (17/21)	71 (10/14)	81 (17/21)
Weighted mean			57 (50/87)	73 (79/108)	63 (50/79)	68 (79/116)

LV, left ventricular; *LVEF*, left ventricular ejection fraction.

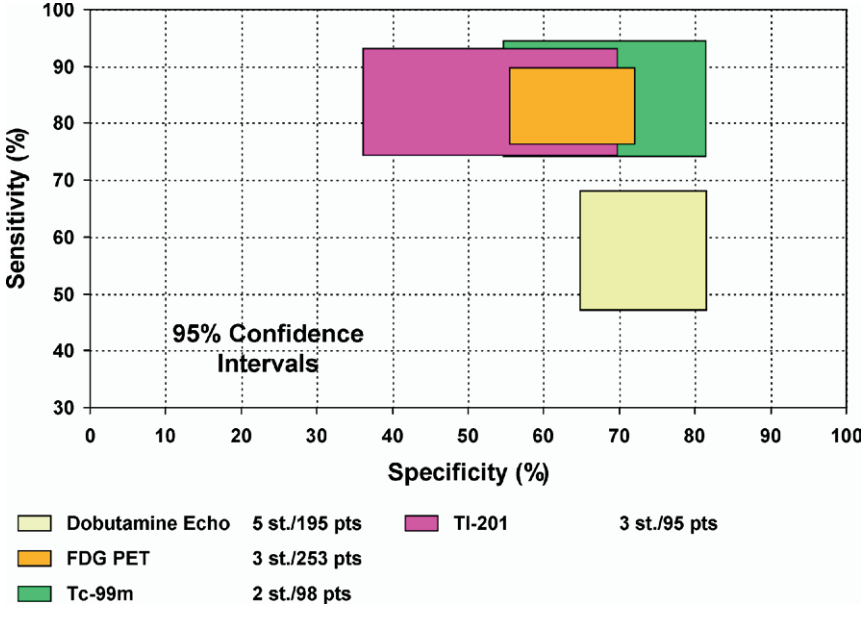

FIG 3. Comparison of sensitivities and specificities with 95% confidence intervals of the various techniques for the prediction of recovery of global left ventricular function after revascularization. (Color version of figure is available online.)

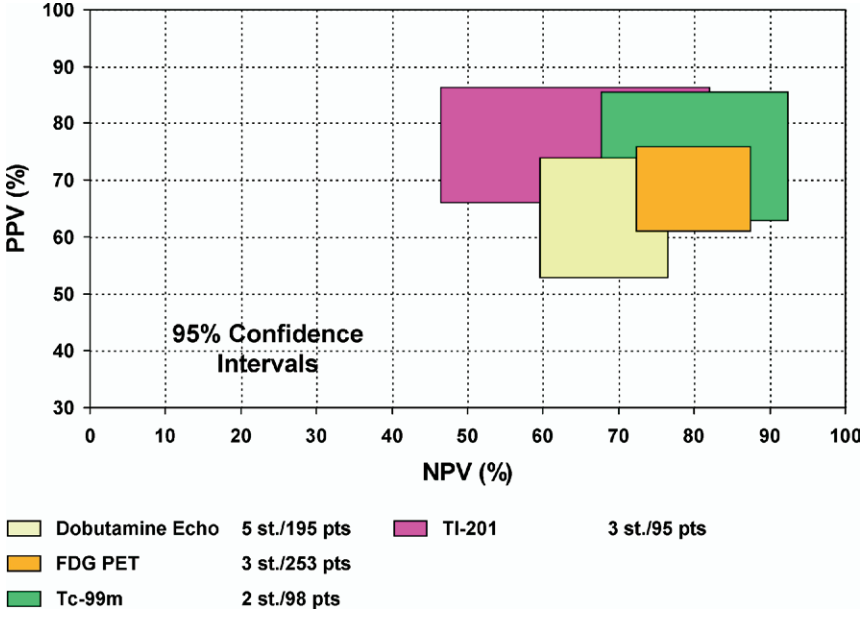

FIG 4. Comparison of positive-predictive values and negative-predictive values with 95% confidence intervals of the various techniques for the prediction of recovery of global left ventricular function after revascularization. (Color version of figure is available online.)

TABLE 12. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of thallium-201 imaging to predict improvement of global function after revascularization

Reference	Criterium for viability	Criterium for improvement	Sensitivity (%) (patients)	Specificity (%) (patients)	PPV (%) (patients)	NPV (%) (patients)
Piscione[4]	≥25% of LV	LVEF >6%	66 (6/9)	78 (7/9)	75 (6/8)	70 (7/10)
Piscione[5]	≥17% of LV	LVEF >6%	92 (12/13)	15 (2/13)	52 (12/23)	67 (2/3)
Petrasinovic[35]	NA	>1 of 12 segments improved (8% of LV)	85 (33/39)	75 (9/12)	92 (33/36)	60 (9/15)
Weighted mean			84 (51/61)	53 (18/34)	76 (51/67)	64 (18/28)

LV, left ventricular; *LVEF*, left ventricular ejection fraction.

TABLE 13. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of technetium-99m sestamibi to predict improvement of global function after revascularization

Reference	Criterium for viability	Criterium for improvement	Sensitivity (%) (patients)	Specificity (%) (patients)	PPV (%) (patients)	NPV (%) (patients)
Leoncini[38]	>25% of LV	LVEF >5%	89 (17/19)	67 (12/18)	74 (17/23)	86 (12/14)
Sciagra[39]	>23% of LV	LVEF ≥5%	81 (26/32)	69 (20/29)	74 (26/35)	77 (20/26)
Weighted mean			84 (43/51)	68 (32/47)	74 (43/58)	80 (32/40)

LVEF, left ventricular ejection fraction.

Table 22 and compared in Fig 7. Patients with viable myocardium who underwent revascularization had the best survival, whereas the highest annualized mortality rate was noted in viable patients receiving medical therapy. Intermediate mortality rates were noted in nonviable patients who were treated medically or underwent revascularization.

Comparison of the techniques. The mortality rates after coronary revascularization versus medical treatment, after viability assessment using the different imaging techniques, are summarized in Table 23. The different techniques all indicate the best survival of patients with viable myocardium who underwent revascularization (all <5%), whereas all other groups have mortality rates >5%. Generally, the highest mortality rates are observed in the viable patients who were treated medically.

Robert O. Bonow: The consistency of the data across these many studies and across all imaging modalities strongly supports the authors' conclusions. It should be noted, however, that all of the studies cited here represent retrospective analysis of patients in which treatment decisions were not standardized, and there was often no adjustment for comorbidities. Patients with viable myocardium who were not revascularized may have been poorer candidates for high-risk revascularization and hence inherently at greater risk of dying. It also cannot be determined if the medical therapies in the patients who did not undergo revascularization were consistent with current aggressive evidence-based guidelines for secondary prevention and medical therapy for left ventricular dysfunction.

Discussion

Prediction of Improvement of Regional Function

The present pooled analysis confirms and extends the findings of the previous pooled analysis from 2001.[1] For the prediction of recovery of regional function after revascularization, FDG PET has the highest

sensitivity followed by the other nuclear imaging techniques. A relatively low sensitivity was observed for dobutamine echocardiography. Conversely, specificity was highest for dobutamine echocardiography and lower for the nuclear imaging techniques.

Still, specificities were in general lower than sensitivities, indicating that a substantial percentage of segments that are classified as viable by the imaging techniques do not improve in function after revascularization. Does this mean that the techniques overestimate recovery of function?

Probably not, since various explanations as to why viable segments do not improve in function after revascularization have been published recently. These can be divided into issues before, during, and after revascularization.

Factors before revascularization may include the following:

1. The severity of cellular damage in the hibernating myocardium: too severely damaged myocardium may no longer improve in function after revascularization.[83]
2. The extent of LV remodeling: severely dilated left ventricles may no longer improve in function despite the presence of extensive viability.[84,85]
3. Subendocardial scar formation: a segment may be partially viable (with scar limited to the subendocardium); the already viable myocardium remains viable, and the subendocardial scar does not improve in function after revascularization. Techniques with higher spatial resolution are needed to make this differentiation between epi- and endocardial tissue within one segment. Currently contrast-enhanced MRI is the only technique that permits this distinction.
4. Large scar adjacent to viable myocardium may prohibit functional recovery.[86]
5. The duration of hibernation before revascularization; long waiting time before revascularization resulted in absence of recovery, probably due to transition of hibernating myocardium into scar tissue.[87,88]

Factors during revascularization may include the following:

1. Incomplete revascularization.
2. Ischemic damage during revascularization may result in transition of viable myocardium into scar tissue.

Factors after revascularization may include the following:

1. Graft-occlusion or restenosis may result in lack of recovery.
2. Timing of assessment of function after revascularization; severely damaged myocardium may take up to 1 year to improve in function

TABLE 14. Sensitivity, specificity, positive- and negative-predictive values (PPV, NPV) of positron emission tomography with F18-fluorodeoxyglucose to predict improvement of global function after revascularization

Reference	Criterium for viability	Criterium for improvement
Slart[18]	≥12% of LV	LVEF=5%
Gerber[40]	>38% of LV	LVEF ≥5%
Wiggers[33]	≥13% of LV	Wall motion score in ≥2 of 16 segments (6% of LV)
Weighted mean		

LV,left ventricular; *LVEF*, left ventricular ejection fraction.

TABLE 15. Viability versus improvement of symptoms (NYHA class)

Reference	Technique, criterium for viability	Viable NYHA pre	Viable NYHA post	Nonviable NYHA pre	Nonviable NYHA post
Bax[54]	DE, ≥25% of LV	3.2 ± 0.7	1.6 ± 0.5	3.1 ± 0.5	2.8 ± 0.7
Gunning[55]	TI-201, ≥22% of LV	2.7 ± 0.6	1.3 ± 0.7	—	—
Dreyfuss[45]	FDG PET, ≥50% of LV	3.1 ± 0.3	2.0 ± 0.3	—	—
Haas[48]	FDG PET, ≥2 of 3 vascular territories and <40% scar of LV	3.0	1.6	—	—
Schwarz[50]	FDG PET, NA	1.4 ± 1.2	1.1 ± 0.3	—	—
Beanlands[51]	FDG PET, ≥11% of LV	3.0 ± 0.8	1.6 ± 0.7	—	—
Mulle[56]	TI-201, ≥20% of LV	2.9 ± 0.7	2.1 ± 0.6	2.7 ± 0.5	2.7 ± 0.7
Chikamori[57]	TI-201, NA	3.1 ± 0.7	1.6 ± 0.7	—	—
Weighted mean		2.9	1.6	2.9	2.8

DE, dobutamine echocardiography; *LV*, left ventricle; *NA*, not available; *NYHA*, New York Heart Association; *PET*, positron emission tomography.

TABLE 16. Viability versus improvement of exercise capacity (expressed in METS)

Reference	Technique and criterium for viability	Viable METS pre	Viable METS post	Nonviable METS pre	Nonviable METS post
Marwick[43]	FDG PET, ≥29% of LV	5.6 ± 2.7	7.5 ± 1.7	6.5 ± 2.8	8.2 ± 2.2
Marwick[58]	FDG PET, ≥25% of LV	4.6 ± 1.5	5.6 ± 1.4	5.9 ± 2.8	6.3 ± 2.8
Marwick[58]	DE, ≥25% of LV	4.7 ± 1.3	5.1 ± 1.3	4.6 ± 1.5	5.1 ± 1.5
Di Carli[59]	FDG PET, ≥18% of LV	2.8 ± 0.7	5.7 ± 0.8	3.7 ± 0.6	4.9 ± 0.7
Weighted mean		4.4	5.7	5.1	5.9

DE, dobutamine echocardiography; *LV*, left ventricle; *MET*, metabolic equivalent; *PET*, positron emission tomography.

TABLE 14. Continued

Sensitivity (%) (patients)	Specificity (%) (patients)	PPV (%) (patients)	NPV (%) (patients)
85 (23/27)	100 (20/20)	100 (23/23)	83 (20/24)
79 (65/82)	55 (49/89)	62 (65/105)	74 (49/66)
100 (14/14)	67 (14/21)	67 (14/21)	100 (14/14)
83 (102/123)	64 (83/130)	68 (102/149)	80 (83/104)

after revascularization,[89] and nearly all studies have performed the functional follow-up study with 6 months after revascularization.

Recently, MRI has emerged as a new technique for assessment of viability. This technique can be used to assess different aspects of the myocardium related to viability (Tables 9 and 10). Assessment of end-diastolic wall thickness appears very sensitive but not specific for prediction of functional recovery, indicating that thinned myocardium (<6 mm) has a low likelihood to improve in function after revascularization and accurately reflects scar tissue. On the other hand, a substantial percentage of segments with preserved wall thickness do not improve in function after revascularization. This is most likely related to the presence of subendocardial infarction: these segments still have preserved wall thickness but do not improve in function after revascularization. Of interest, two studies that included patients in whom high-quality 2D echocardiography could be obtained also showed that segments of <5 to 6 mm had a 5% likelihood of improving in function.[7,90] Segments with 5 to 6 mm had a 50% likelihood of improving in function.

Dobutamine MRI detects, similar to dobutamine echocardiography, the presence of contractile reserve as a marker of viability. The sensitivity of this technique was relatively low, similarly to dobutamine echocardiography.

Contrast-enhanced MRI detects scar tissue (and not viability) and has a high sensitivity, but again a low specificity, most likely related to subendocardial infarction.

Robert O. Bonow: Contrast-enhanced MRI is exquisitely sensitive in differentiating viable from nonviable myocardium. However, in and of itself, it is limited in predicting improvement in function after revascularization. Viable but dysfunctional myocardium may represent the effects of left ventricular

TABLE 17. Studies using dobutamine echocardiography to assess myocardial viability in relation to prognosis

Reference	No. of patients	Technique	Viability criteria	Age (y)
Meluzin[60]	133	LDDE	NA	58 ± 8
Afridi[61]	318	HDDE/LDDE	≥25% of LV	64 ± 11
Anselmi[62]	202	LDDE	NA	59 ± 9
Senior[63]	87	LDDE	≥42% of LV	62 ± NA
Bax[54]	68	HDDE	≥25% of LV	61 ± 8
Chaudhry[64]	80	HDDE	≥31% of LV	64 ± 12
Meluzin[65]	124	LDDE	≥13% of LV	57 ± 9
Sicari[66]	425	LDDE	≥38% of LV	61 ± 10
Rambaldi[67]	80	HDDE	≥17% of LV	63 ± 9
Rizzello[68]	128	HDDE	≥25% of LV	61 ± 9

HDDE, high-dose dobutamine echocardiography; *LDDE*, low-dose dobutamine echocardiography; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *Med*, medical therapy; *MI*, myocardial infarction; *MVD*, multivessel disease; *NA*, not available; *Rev*, revascularization; *VD*, vessel disease.

TABLE 18. Mortality rates in relation to viability and treatment using dobutamine echocardiography (10 studies, 1645 patients)

		Mortality rate % (patients)			
Reference	Follow-up (mo)	V/Rev	V/Med	NV/Rev	NV/Med
Meluzin[60]	20 ± 12	3 (1/29)	—	13 (13/104)	—
Afridi[61]	18 ± 10	6 (5/85)	20 (24/119)	17 (5/30)	20 (17/84)
Anselmi[62]	16 ± 11	6 (4/64)	8 (4/52)	16 (4/25)	10 (6/61)
Senior[63]	40 ± 17	3 (1/31)	31 (10/32)	50 (3/6)	44 (8/18)
Bax[54]	19 ± 8	9 (2/23)	—	11 (5/45)	—
Chaudhry[64]	26	8 (2/24)	29 (10/34)	100 (4/4)	56 (10/18)
Meluzin[65]	27	10 (4/39)	34 (10/29)	26 (6/23)	32 (7/22)
Sicari[66]	37	8 (4/52)	36 (13/36)	27 (37/136)	36 (72/201)
Rambaldi[67]	108	8 (2/24)	—	29 (11/38)	—
Rizzello[68]	60	9 (6/64)	—	33 (21/64)	—
Death rate		31/435	71/302	109/475	120/404
Annualized mortality rate		3%	12%	7%	12%

NV, patients without viability; *V*, patients with viability; *Med*, medical therapy; *Rev*, revascularization.

remodeling, even in segments supplied by normal coronary arteries that would not be expected to improve with revascularization. This is where dobutamine echocardiography and stress nuclear imaging have the advantage of eliciting revascularization. Hence, Wellnhofer et al have shown that dobutamine MRI in addition to contrast enhancement may be superior to contrast enhancement alone in predicting functional recovery after revascularization.[29]

TABLE 17. Continued

% Male	LVEF (%)	VD	MI (%)	Rev/Med
97	34 ± 5	96% MVD	92	133/0
74	27 ± 7	17% 3-VD	59	115/203
86	33 ± 10	53% MVD	100	89/113
91	25 ± 9	2.3 ± 0.8	91	37/50
84	28 ± 6	2.5 ± 0.7	96	68/0
80	27 ± 7	NA	85	28/52
96	25 ± 4	NA	94	62/62
85	28	83% MVD	100	188/237
73	34 ± 11	NA	61	62/18
82	31 ± 8	2.5 ± 0.7	92	128/0

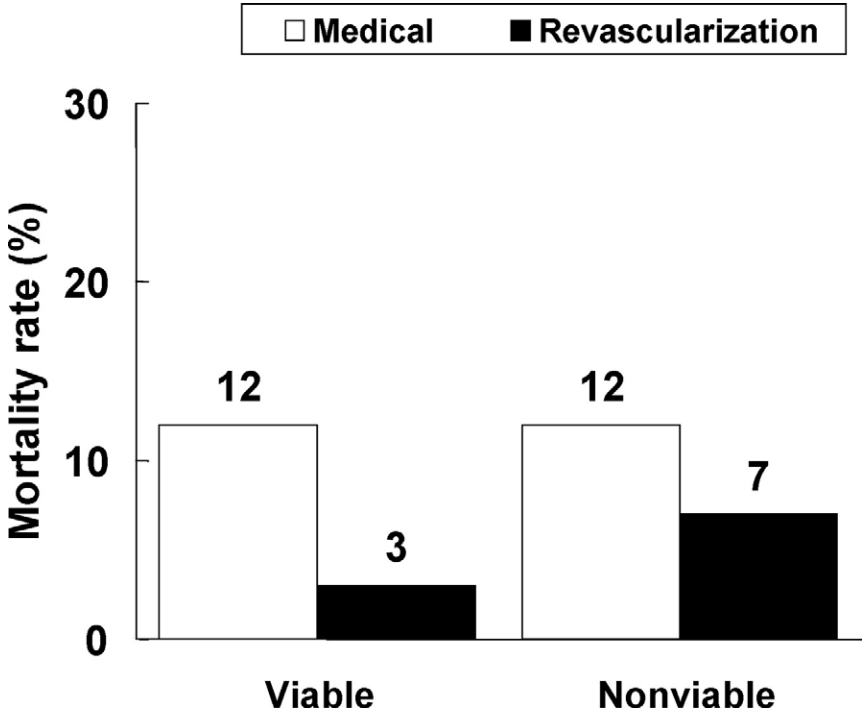

FIG 5. Annualized mortality rates in patients with viable and nonviable myocardium (assessed by dobutamine echocardiography) in relation to treatment (revascularization or medical therapy).

TABLE 19. Studies using thallium-201 imaging to assess myocardial viability in relation to prognosis

Reference	No. of patients	Technique	Viability criteria
Gioia[69]	81	RR	NA
Pagley[70]	70	RR	≥67% of LV
Cuocolo[71]	76	RR	≥54% of LV
Zafrir[72]	366	RI	NA
Pasquet[73]	137	RI	>50% of dysfunctional segments
Senior[74]	56	Rest Tl-201 with nitrates	≥42% of LV
Petrasinovic[35]	55	RR	≥8% of LV
Gursurer[37]	52	RI	≥47% of LV

LV, left ventricle; *LVEF,* left ventricular ejection fraction; *Med,* medical therapy; *M,*: myocardial infarction; *MVD,* multivessel disease; *NA,* not available; *Rev,* revascularization; *RR,* Tl-201 rest-redistribution; *RI,* Tl-201 reinjection; *VD,* vessel disease.

TABLE 20. Mortality rates in relation to viability and treatment using thallium-201 imaging (8 studies, 893 patients)

Reference	Follow-up (mo)	Mortality rate % (patients)			
		V/Rev	V/Med	NV/Rev	NV/Med
Gioia[69]	31 ± 24	—	51 (22/43)	—	29 (11/38)
Pagley[70]	1177 days	18 (6/33)	—	41 (15/37)	—
Cuocolo[71]	17 ± 8	—	75 (6/8)	—	3 (1/29)
Zafrir[72]	33 ± 12	—	11 (28/266)	—	12 (12/100)
Pasquet[73]	33 ± 10	9 (5/58)	25 (4/16)	22 (8/36)	26 (7/27)
Senior[74]	40 ± 17	10 (2/21)	29 (9/31)	—	—
Petrasinovic[35]	12	0 (0/25)	9 (1/11)	20 (2/10)	44 (4/9)
Gursurer[37]	49 ± 12	21 (6/29)	—	83 (19/23)	—
Death rate		19/185	70/375	44/106	35/203
Annualized mortality rate		4%	7%	14%	7%

NV, patients without viability; *V,* patients with viability; *Med,* medical therapy; *Rev,*: revascularization.

Prediction of Improvement of Global Function

The number of studies addressing improvement of global function is limited. Pooled analysis of the available data revealed that the nuclear imaging techniques have a relatively high sensitivity, whereas dobutamine echocardiography has the lowest sensitivity, in line with prediction of improvement of regional function. Dobutamine echocardiography appeared to have the higher specificity for prediction of improvement of global function, but the differences between techniques were not statistically significant.

TABLE 19. Continued

Age (y)	% Male	LVEF	VD	MI (%)	Rev/Med
69 ± 12	73	NA	NA	NA	0/81
66 ± NA	77	28 ± 6	100% MVD	57	70/0
55 ± 10	97	38 ± 9	97% MVD	100	39/37
NA	70	NA	NA	NA	0/366
62 ± 10	85	35 ± 12	77% MVD	85	94/43
64 ± 9	89	25 ± 9	87% MVD	88	21/31
58 ± 9	91	43 ± 10	36% MVD	100	35/20
57 ± 8	96	32 ± 3	96% MVD	94	52/0

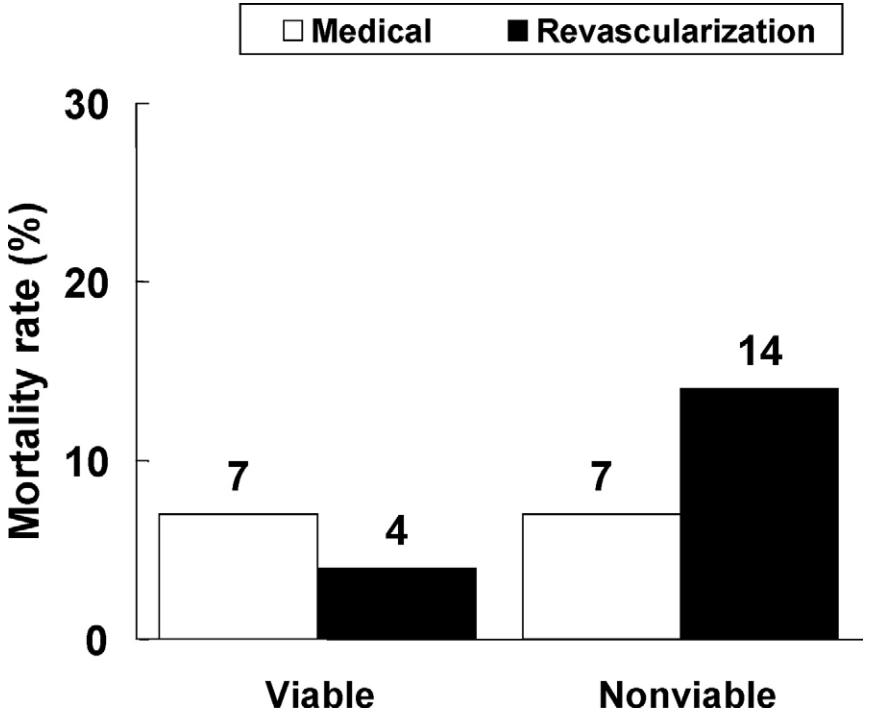

FIG 6. Annualized mortality rates in patients with viable and nonviable myocardium (assessed by thallium-201 imaging) in relation to treatment (revascularization or medical therapy).

TABLE 21. Studies using PET imaging to assess myocardial viability in relation to prognosis

Reference	No. of patients	Technique	Viability criteria
Eitzman[75]	82	FDG/NH3	≥11% of LV
Yoshida[76]	35	FDG/Rb	NA
Di Carli[77]	93	FDG/NH3	≥5% of LV
Lee[78]	129	FDG/Rb	≥8% of LV
Haas[48]	34	FDG/N13	≥2 of 3 VT and <40% scar of LV
vom Dahl[79]	161	FDG/MIBI	≥8% of LV
Di Carli[80]	93	FDG/NH3	≥5% of LV
Zhang[52]	123	FDG alone	≥ 22% of LV
Pagano[81]	35	FDG alone	≥50% of LV
Desideri[82]	261	FDG alone	≥6% of LV

LV, left ventricle; *LVEF,* left ventricular ejection fraction; *Med,* medical therapy; *MI,* myocardial infarction; *MVD,* multivessel disease; *NA,* not available; *PET,* positron emission tomography; *Rev,* revascularization; *VD,* vessel disease; *VT*, vascular territory.

TABLE 22. Mortality rates in relation to viability and treatment, using PET (10 studies, 1046 patients)

Reference	Follow-up (mo)	Mortality rate % (patients)			
		V/Rev	V/Med	NV/Rev	NV/Med
Eitzman[75]	12	4 (1/26)	33 (6/18)	0 (0/14)	8 (2/24)
Yoshida[76]	0.3 ± 3.0 y	0 (0/20)	40 (2/5)	50 (2/4)	50 (3/6)
Di Carli[77]	13.6	12 (3/26)	41 (7/17)	6 (1/17)	9 (3/33)
Lee[78]	17 ± 9	8 (4/49)	14 (3/21)	5 (1/19)	13 (5/40)
Haas[48]	14.6	3 (1/34)	NA	NA	NA
vom Dahl[79]	29 ± 6	0 (0/36)	22 (2/9)	8 (4/48)	10 (7/68)
Di Carli[80]	3.8 y	27 (7/26)	65 (11/17)	29 (5/17)	42 (14/33)
Zhang[52]	26 ± 10	0 (0/42)	27 (8/30)	8 (2/25)	4 (1/26)
Pagano[81]	33 ± 14	10 (2/21)	—	43 (6/14)	—
Desideri[82]	2.1 y	15 (8/55)	28 (17/60)	10 (4/39)	21 (23/107)
Death rate		26/335	56/177	25/197	58/337
Annualized mortality rate		4%	17%	6%	8%

NV, patients without viability; *V*, patients with viability; *Med*, medical therapy; *Rev*, revascularization.

The definition of improved global LV function was homogenous and most studies used considered an improvement of 5% or more in LV ejection fraction as significant.

However, the definition of a patient with viability varied significantly among the studies; as can be derived from Tables 11-149, the extent of viability to classify a patient as with viability ranged from 12 to 38% of the left ventricle. As a consequence, it is currently unclear how much viable myocardium is needed to predict improvement of LV ejection fraction after revascularization.

TABLE 21. Continued

Age (y)	% Male	LVEF	VD	MI (%)	Rev/Med
59 ± 10	88	34 ± 13	2.1 ± 0.8	NA	40/42
54 ± NA	63	NA	77% MVD	100	25/10
57 ± 9	84	56 ± 9	2.5 ± 7	68	43/50
62 ± 11	79	38 ± 16	74% MVD	NA	68/61
63 ± 9	91	28 ± 5	100% MVD	68	34/0
57 ± 9	89	45 ± 12	69% MVD	88	84/77
69	84	25	82% MVD	68	43/50
56 ± 9	93	35 ± 6	89% MVD	77	67/56
58 ± 7	89	24 ± 7	100% MVD	100	35/0
66	89	29	NA	81	167/94

Heart Failure Symptoms and Exercise Capacity

From a clinical point of view it is relevant to predict improvement of heart failure symptoms or exercise capacity following revascularization. Few studies suggest that patients with viable myocardium improve in symptoms and exercise capacity, although the precise extent of viability needed to result in improvement is unclear. It is also unclear whether the improvement of symptoms and exercise capacity is secondary to an improvement in LV function or not. More studies are needed to obtain a better understanding of the relationship between viability and improvement in symptoms and exercise capacity.

Long-Term Prognosis

Multiple studies have focused on the prognostic value of viability assessment in relation to therapy (medical or revascularization). Pooling of these studies clearly revealed that patients with viability who undergo revascularization have the best prognosis and extends results from a previous meta-analysis.[91] In addition, the majority of studies indicated that patients with viable myocardium who were treated medically had a high mortality rate. Considering the individual studies (Tables 17-22), however, the heterogeneity of the study populations becomes evident. Moreover, all previous studies were based on retrospective analyses. It is obvious that randomized, prospective trials are needed before definitive conclusions can be drawn.

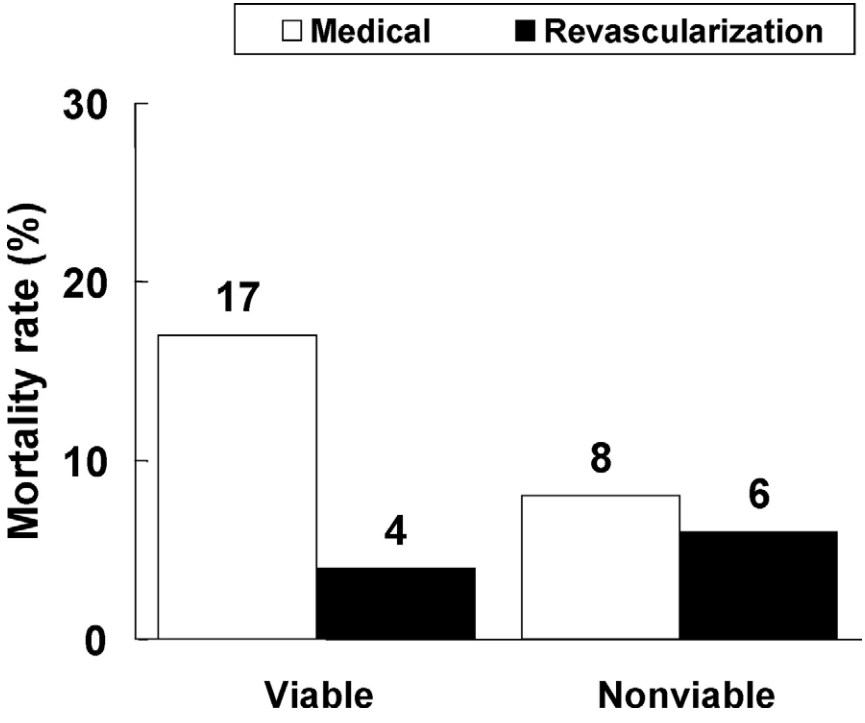

FIG 7. Annualized mortality rates in patients with viable and nonviable myocardium (assessed by positron emission tomography and F18-fluorodeoxyglucose) in relation to treatment (revascularization or medical therapy).

TABLE 23. Annualized mortality rates for the different techniques based on the pooled analysis

Technique	No. of studies	No. of patients	V/Rev (%)	V/Med (%)	NV/Rev (%)	NV/Med (%)
DE	10	1645	3	12	7	12
Tl-201	8	893	4	7	14	7
Tc-99m	1	56	3	9	—	—
FDG PET	10	1046	4	17	6	8

DE, dobutamine echocardiography; *FDG*, F18-fluorodeoxyglucose; *Med*, medical therapy; *NV*, patients without viability; *Rev*, revascularization; *Tc-99m*, technetium-99m labeled tracers; *Tl-201*, thallium-201 imaging; *V*, patients with viability.

Robert O. Bonow: The authors have identified an important void in our evidence base. It is hoped that the ongoing NHLBI-sponsored Surgical Treatment of Ischemic Heart Failure (STICH) Trial will provide the needed evidence from a multicenter randomized prospective clinical trial.

Conclusions

The results of this extensive pooled analysis emphasize the clinical value of viability assessment. Viable myocardium may improve in function after revascularization, whereas nonviable myocardium will not. In the presence of extensive viable tissue, LV ejection fraction may also improve after revascularization. The relation between viability and heart failure symptoms is not entirely clear, but patients with viable myocardium appear to improve in symptoms and exercise capacity. The prognostic value of viability assessment has been demonstrated in retrospective studies but needs confirmation in prospective, randomized trials.

Robert O. Bonow: This updated analysis by Schinkel et al is a comprehensive and authoritative review of an important but often overlooked component of the management of patients with left ventricular dysfunction. It is clear that two-thirds of patients with heart failure in the developed world have underlying coronary artery disease and that these patients have a significantly worse prognosis than patients with nonischemic heart failure (Gheorghiade et al. Circulation 2006;114:1202-13). However, coronary artery disease as the etiology of heart failure is often not considered in many centers, and testing to determine the reversibility of left ventricular dysfunction is not performed.

The consistency of the data concisely compiled in this review make a cogent argument for the role of diagnostic testing in virtually all patients with left ventricular dysfunction, especially those of appropriate age, gender, and risk factor profile, to establish the presence of coronary artery disease and to identify candidates for revascularization based on the extent of myocardial ischemia and/or viability. Establishing the diagnosis of coronary artery disease is important even in patients who are not candidates for revascularization, as they may benefit from aggressive secondary prevention measures in addition to medical therapy for heart failure.

As noted by the authors, the retrospective nature of virtually all available studies represents a major weakness in our collective evidence base, and this creates uncertainties in patient management recommendations. This uncertainty is reflected in the disparate recommendations for diagnostic testing and revascularization in patients for coronary artery bypass surgery, heart failure, and use of nuclear cardiology testing. Ongoing prospective randomized such as the STICH Trial are needed to solidify such recommendations. Until such prospective data are available, however, clinicians need to make difficult but important decisions in their high-risk patients with ischemic left ventricular dysfunction, and this extensive review will aid greatly in guiding patient management.

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