

An Initial Strategy of Intensive Medical Therapy Is Comparable to That of Coronary Revascularization for Suppression of Scintigraphic Ischemia in High-Risk But Stable Survivors of Acute Myocardial Infarction

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OBJECTIVES	The purpose of this study was to determine the relative benefit of intensive medical therapy compared with coronary revascularization for suppressing scintigraphic ischemia.
BACKGROUND	Although medical therapies can reduce myocardial ischemia and improve patient survival after acute myocardial infarction, the relative benefit of medical therapy versus coronary revascularization for reducing ischemia is unknown.
METHODS	A prospective randomized trial in 205 stable survivors of acute myocardial infarction was made to define the relative efficacy of an intensive medical therapy strategy versus coronary revascularization for suppressing scintigraphic ischemia as assessed by serial gated adenosine Tc-99m sestamibi myocardial perfusion tomography. All patients at baseline had large total ($\geq 20\%$) and ischemic ($\geq 10\%$) adenosine-induced left ventricular perfusion defects and an ejection fraction $\geq 35\%$. Imaging was performed during 1 to 10 days of hospital admission and repeated in an identical fashion after optimization of therapy. Patients randomized to either strategy had similar baseline demographic and scintigraphic characteristics.
RESULTS	Both intensive medical therapy and coronary revascularization induced significant but comparable reductions in total ($-16.2 \pm 10\%$ vs. $-17.8 \pm 12\%$; $p = \text{NS}$) and ischemic ($-15 \pm 9\%$ vs. $-16.2 \pm 9\%$; $p = \text{NS}$) perfusion defect sizes. Likewise, a similar percentage of patients randomized to medical therapy versus coronary revascularization had suppression of adenosine-induced ischemia (80% vs. 81%; $p = \text{NS}$).
CONCLUSIONS	Sequential adenosine sestamibi myocardial perfusion tomography can effectively monitor changes in scintigraphic ischemia after anti-ischemic medical or coronary revascularization therapy. A strategy of intensive medical therapy is comparable to coronary revascularization for suppressing ischemia in stable patients after acute infarction who have preserved LV function. (J Am Coll Cardiol 2006;48:2458-67) © 2006 by the American College of Cardiology Foundation



Advances in medical management have greatly improved patient outcome after acute myocardial infarction (AMI). Beta-blockers (BB) (1), angiotensin-converting enzyme (ACE) inhibitors (2), antiplatelet agents (3), statins (4), and certain rate-lowering calcium-channel blockers (CCB) (5) benefit patients through their targeted effects on thrombus formation (6,7), plaque progression (8), myocar-

dial ischemia (9), and left ventricular (LV) dysfunction and remodeling (10). However, despite this extensive trial-based evidence, coronary revascularization is generally considered the preferred treatment for patients after AMI, particularly when there is extensive coronary artery disease (CAD) on angiography or substantial myocardial ischemia detected by noninvasive testing. Prospective randomized trials directly comparing an optimal medical with a coronary revascularization strategy in patients with objective evidence of ischemia are limited (9,11-13).

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The INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation) is a prospective multicenter trial designed to define the role of adenosine Tc-99m sestamibi single-photon emission computed tomography (ADSPECT) for stratifying patient risk based on scintigraphic variables and LV ejection fraction (EF) (14,15). Its other main objective is to compare the relative efficacy of an initial intensive medical therapy strategy to one of coronary revascularization

Abbreviations and Acronyms

- ADSPECT = adenosine technetium-99m sestamibi single-photon emission computed tomography
- AMI = acute myocardial infarction
- BB = beta-blockers
- CABG = coronary artery bypass grafting
- CAD = coronary artery disease
- CCB = calcium-channel blocker
- EF = ejection fraction
- LAD = left anterior descending
- LV = left ventricular
- PCI = percutaneous coronary intervention
- PDS = perfusion defect size

for suppressing scintigraphic ischemia, specifically in the stable but high-risk cohort of the INSPIRE trial (14,15). Adenosine SPECT was chosen as the imaging method because it is a safe and reliable (15) technique for detecting scintigraphic ischemia early after AMI. The INSPIRE study was designed based on a previous exploratory pilot study in AMI patients which suggested that intensive medical therapy equaled percutaneous coronary intervention (PCI) for suppressing ischemia as assessed by sequential adenosine SPECT performed before and after therapy (9).

METHODS

Study population. Of the 728 patients enrolled in the INSPIRE trial, 205 had a large total ($\geq 20\%$) and ischemic ($\geq 10\%$) LV perfusion defect size (PDS) and an LV EF $\geq 35\%$ by adenosine SPECT and form the basis of this

Table 1. INSPIRE Inclusion and Exclusion Criteria (14)

Inclusion criteria	
1. Chest pain ≥ 30 min duration with	
a. ST-segment elevation or depression (≥ 0.1 mV) in ≥ 2 consecutive ECG leads and a rise in cardiac enzymes \geq twice the upper limit of normal	
OR	
b. ST-segment elevation (≥ 0.1 mV) in ≥ 2 consecutive ECG leads with development of diagnostic Q waves	
2. Age ≥ 18 yrs	
3. Total perfusion defect size $\geq 20\%$, ischemic defect size $\geq 10\%$, and left ventricular ejection fraction $\geq 35\%$ *	
Exclusion criteria	
1. Cardiogenic shock	
2. Recurrent chest pain unresponsive to anti-ischemic medications requiring emergency revascularization	
3. Uncompensated congestive heart failure	
4. Sustained ventricular tachycardia or fibrillation after the first 24 h	
5. Acute coronary angiography with primary percutaneous coronary intervention	
6. Left bundle branch block on initial 12-lead ECG	
7. Contraindication to adenosine	
8. Concomitant noncardiac illness that would limit 1-yr follow-up	
9. Premenopausal women unless documented not to be pregnant	
10. Inability to give informed consent	

*For randomization.
ECG = electrocardiogram/electrocardiographic.

Table 2. Medication Ranking for Determining the Intensity of Medical Therapy

	Total Daily Dose (mg)		
	Low	Medium	High
Long-acting nitrates			
Nitrodur (mg/h)	≤ 0.2	$> 0.2-0.4$	≥ 0.5
Isosorbide mononitrate	≤ 30	31-60	≥ 61
Isosorbide dinitrate	≤ 30	31-60	≥ 61
Beta-blockers			
Atenolol	25	$\geq 50-75$	≥ 76
Metoprolol	50-75	$\geq 76-125$	≥ 126
Propranolol	≤ 80	81-159	≥ 160
Sotalol	≤ 80	81-239	≥ 240
Carvedilol	≤ 12.5	12.6-37.5	> 37.5
Bisoprolol	≤ 5	6-14	≥ 15
ACE inhibitors/ARBs			
Accupril	≤ 10	11-20	≥ 21
Enalapril	≤ 10	11-20	≥ 21
Lisinopril	≤ 10	11-20	≥ 21
Monopril	≤ 10	11-20	≥ 21
Ramapril	≤ 2.5	2.6-5	> 5
Irbesartan	< 150	$\geq 150-300$	> 300
Captopril	≤ 20	20-75	≥ 76
Losartan	≤ 50	51-99	≥ 100
Calcium-channel blockers			
Diltiazem	≤ 120	121-240	≥ 241
Amlodipine	≤ 2.5	2.6-7.5	≥ 7.6
Lipid-lowering drugs			
Lipitor	≤ 20	21-40	> 40
Fluvastatin	≤ 40	40-60	> 60
Pravastatin	≤ 40	40-60	> 60
Simvastatin	≤ 30	31-60	> 60
Fenofibrate	≤ 54	55-160	> 160
Gemfibrozil	≤ 600	601-1,200	$> 1,200$

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor antagonist.

report (14,15). Although clinically stable, these patients were considered to be at high risk for subsequent cardiac events based on their scintigraphic profile (15). Inclusion and exclusion criteria for entry into the INSPIRE trial are shown in Table 1.

Study design. The research protocol was approved at each site by their respective institutional review boards, and all patients gave written informed consent. The INSPIRE study design is published (14). Patients underwent standard gated rest-stress adenosine SPECT within 10 days of hospital admission with quantification of total and ischemic LV PDS and LV EF (14,15). Those meeting entry criteria were randomized to either an initial strategy of intensive anti-ischemic medical therapy (strategy 1) or coronary angiography with the intent to revascularize (strategy 2). A second scan (SPECT 2) was performed a median of 62 days after optimizing therapy. Images were quantified by the core laboratory blinded to treatment allocation. Patients were followed 1 year, and all cardiac events were adjudicated by an end point committee (14,15).

Medical therapy group (strategy 1). Patients randomized to strategy 1 were not to have coronary angiography unless they developed clinical instability (14). Medical therapy was

Table 3. Therapeutic Considerations for Patients Randomized to Strategy 2 (14)

1. Coronary artery bypass surgery was recommended over percutaneous coronary intervention in patients with
 - a. >50% left main stenosis
 - b. 3-vessel coronary artery disease
 - c. Diabetes and multivessel disease
2. Patients undergoing coronary artery bypass surgery were encouraged to have grafting of all arteries with significant ($\geq 50\%$) stenosis as deemed technically feasible
3. Patients undergoing percutaneous coronary intervention were encouraged to have dilation and stenting of the infarct-related artery and any other artery with significant ($\geq 50\%$) stenosis
4. Anti-ischemic medical therapy as proposed in strategy 1 was recommended for patients who
 - a. Were not revascularized,
 - b. Had residual angina following revascularization, or
 - c. Had incomplete revascularization

titrated to maximally tolerated doses over 4 to 8 weeks using predefined recommended algorithms (14).

Intensity of medical therapy was based on a relative ranking of medications by drug class (Table 2). Total daily drug dosages were classified as: none = 0, low = 1, medium = 2, or high = 3. The intensity of medical therapy was calculated by adding the dose classification (0 to 3) of each anti-ischemic medication (i.e., BB, CCB, long-acting nitrates) and defined as low (0 to 3), medium (4 to 6), or high (7 to 9). A crossover occurred when a patient randomized to medical therapy had revascularization before SPECT 2.

Revascularization group (strategy 2). Patients randomized to strategy 2 were encouraged to have coronary angiography followed by PCI or coronary artery bypass graft surgery (CABG). Specific treatment recommendations are shown in Table 3. A crossover in this strategy was defined as any patient who did not undergo revascularization before SPECT 2.

Statistical analysis. The statistical analysis plan is published (14). The primary end point of the INSPIRE trial was to determine the relative efficacy of an initial intensive medical therapy strategy (strategy 1) compared with one of coronary revascularization (strategy 2) for reducing total and ischemic LV PDS. The sample size for detecting a therapeutic difference in scintigraphic parameters between the 2 randomized groups was based on a previous reproducibility study (16). With 169 patients, there was 80% power ($\alpha = 0.05$) to detect a 4% absolute difference between treatment groups (14).

Chi-square or *t* test statistics were used to compare baseline characteristics between randomized groups and detect differences in patients who did or did not have 2 SPECT studies. All comparisons were reported by frequency (%) or mean \pm standard deviation. Chi-square analysis compared the type and intensity of medical therapy used and the percentage of patients who had a >9% change in total and ischemic PDS in each strategy. The percentage change in total, ischemic, and scar PDS and LV EF were compared by strategy using analysis of variance techniques.

Paired *t* tests compared total, ischemic, and scar PDS and LV EF at SPECT 1 and 2.

A secondary observational end point was to compare time to first cardiac event in the 2 strategies using Kaplan-Meier estimates and Cox proportional hazards regression (14). The power of this analysis was $\sim 30\%$. All analyses are based on intention-to-treat.

RESULTS

Baseline characteristics. The baseline characteristics of the 2 randomized groups were well matched (Table 4). Of the 205 randomized patients, 36 (18 patients/group) were excluded from primary end point analysis for the following reasons: terminated study participation before SPECT 2 ($n = 12$); refused repeat imaging ($n = 8$); lost to follow-up ($n = 7$); expired after the first study ($n = 5$) with 1 cardiac death within strategy 1 and 2 within strategy 2; side effects to adenosine ($n = 2$); and poor-quality images ($n = 2$). Baseline clinical characteristics were not significantly different between those who did or did not have SPECT 2. Their initial scintigraphic profile, overall subsequent treatment, and clinical outcome were also similar (Table 5).

Crossover between strategies. The crossover rates between treatment strategies were comparable: 26 out of 101 strategy 1 patients (25.7%) were revascularized, and 24 out of 104 strategy 2 patients (23.1%) defaulted to medical therapy. Nine out of 26 (35%) patients who crossed from strategy 1 to strategy 2 did so outside of protocol owing to physician and/or patient preference rather than a clinically indicated reason. Although most patients had minimal or no angina during the therapy titration phase before SPECT 2 (74%), those who crossed over in either strategy more frequently had anginal episodes (37%) than those who did not (22%; $p = 0.52$).

Anti-ischemic medical therapy. Patients in both randomized limbs received medical therapy, although those in strategy 1 more frequently received a CCB, long-acting nitrate, and ACE inhibitor than those in strategy 2 (Table 6). Most patients (70%) in strategy 1 were on ≥ 2 anti-ischemic medications at the time of SPECT 2 versus 36% in strategy 2 ($p < 0.05$) (Table 6). Likewise, 60% of patients in strategy 1 were taking a medium (49%) or high (11%) intensity of medications versus 21% and 6% of patients, respectively, in strategy 2 ($p < 0.05$).

Coronary revascularization. Within strategy 2, 83 out of 86 patients who had serial SPECT underwent coronary angiography (97%), of whom 25 had single-vessel, 25 had double-vessel, and 33 had triple-vessel CAD. Twelve patients had concomitant left main stenosis.

Seventy out of 86 patients randomized to strategy 2 (81%) were revascularized (Table 7). Coronary artery bypass grafting (CABG) was performed in 27 patients: 21 with triple-vessel, 5 with double-vessel, and 1 with single-vessel CAD. The internal mammary artery was used to graft 23 out of 25 left anterior descending (LAD) coronary arteries. Saph-

Table 4. Baseline Characteristics for the Total Study Population

	Strategy 1 (Medical Therapy) (n = 101)	Strategy 2 (Revascularization Therapy) (n = 104)	p Value
Age (yrs)*	64 ± 11	63 ± 12	0.49
Women (%)	22	27	0.39
Hypertension (%; BP ≥140/90 mm Hg)	64	49	0.03
Diabetes (%)	26	31	0.42
Family history of CAD (%)	30	25	0.45
Hyperlipidemia (%)	69	62	0.24
Smoking history (%)	54	57	0.64
Prior CAD (%)	33	23	0.13
Prior AMI (%)	21	14	0.23
Killip class (%)			0.69
I	64	69	
II	12	9	
III-IV	24	22	
ST-segment elevation AMI (%)	54	48	0.39
Q-wave AMI (%)	47	38	0.19
AMI location (%)			0.08
Anterior	26	18	
Inferior	49	38	
Lateral	9	18	
Posterior	1	3	
Other	15	23	
Thrombolytic therapy (%)	34	27	0.29
TIMI risk score			0.12
Low (0-2)	51	50	
Intermediate (3-5)	33	42	
High (≥6)	16	8	
Total PDS (% LV)*	32.7 ± 11	32.6 ± 10	0.99
Scar PDS (% LV)*	10.7 ± 8	12 ± 8	0.21
Ischemia PDS (% LV)*	22.0 ± 10	20.6 ± 8	0.62
LVEF (%)*	49 ± 9	47 ± 9	0.11

*Mean ± standard deviation.

AMI = acute myocardial infarction; BP = blood pressure; CAD = coronary artery disease; LV = left ventricle; LVEF = left ventricular ejection fraction; PDS = perfusion defect size; TIMI = Thrombolysis In Myocardial Infarction.

nous vein grafts were placed in 2 LAD, 22 right, 19 circumflex, 2 ramus, and 7 diagonal arteries. A PCI was performed in 43 patients with dilation of the LAD in 9, right in 22, circumflex in 19, and ramus arteries in 2 patients. Most (85%) revascularized patients with single- (n = 20) or double-vessel (n = 21) CAD had PCI (95% and 76%, respectively) rather than CABG (15%). Stents were placed in 49 of 52 dilated arteries (94%) and 44% of patients also received a glycoprotein IIb/IIIa antagonist. In total, 69% of arteries with ≥50% and 71% with ≥70% stenosis had successful revascularization. In the 70 revascularized patients, this increased to 80% and 83%, respectively.

Twenty of 21 patients (95%) in strategy 1 who had serial SPECT and underwent revascularization had multivessel CAD. A CABG was performed in 2 patients with double-vessel and 8 patients with triple-vessel CAD. Eleven patients had PCI with stents placed in 11 out of 12 (92%) dilated arteries. Sixty-eight percent of arteries with ≥50% stenosis and 78% of those with ≥70% stenosis were revascularized (Table 7).

Primary end point: group adenosine SPECT results. In the 169 patients who had serial SPECT imaging, the overall total LV PDS decreased from 33.1 ± 8.9% to 16.1 ± 11% (p <

0.0001) (Fig. 1). The reduction in total PDS was almost entirely attributable to the reduction in ischemic PDS from 22 ± 7.1% to 6.4 ± 6.2% (p < 0.0001).

The serial SPECT comparison between the 2 randomized groups is the primary study end point (Table 8). Patients in strategy 1 and strategy 2 showed highly significant (p < 0.001) but comparable (p = NS) reductions in total (-16.2 ± 10% vs. -17.8 ± 12%) and ischemic (-15 ± 9% vs. -16.2 ± 9%) LV PDS with minimal absolute scintigraphic treatment differences between strategies (1.6 ± 11% for total PDS; 1.2 ± 9% for ischemic PDS).

Individual adenosine SPECT results. A ≥9% serial change in PDS represents a true individual patient change beyond technique variability (16). Consistent with mean group results, a comparable percentage of strategy 1 and strategy 2 patients had a significant reduction in total (75% vs. 79%) and ischemic (80% vs. 81%) PDS and achieved a low-risk (<20%) total PDS on SPECT 2 (64% vs. 69%; p = 0.51) (16) (Table 8, Fig. 2). Figure 3 is a representative example.

Cardiac events. Cardiac events occurred in 15 out of 101 patients randomized to strategy 1 (14.8%) and in 13 out of 104 randomized to strategy 2 (12.5%) (Δ2.4%, 95% CI

Table 5. Comparison Between Patients Who Did or Did Not Have Repeat SPECT

	2nd SPECT (n = 169)	No 2nd SPECT (n = 36)	p Value
Scintigraphic profile			
Total PDS (% LV)	33.1 ± 11%	30.8 ± 9%	0.24
Ischemic PDS (% LV)	22.0 ± 9%	18.1 ± 8%	0.02
LVEF (%)	48.1 ± 9%	48.8 ± 8%	0.67
Medical therapy received			
Aspirin/clopidogrel	165 (98%)	34 (94%)	0.30
Beta-blocker	151 (89%)	27 (75%)	0.02
Lipid therapy	136 (80%)	26 (72%)	0.27
Calcium-channel blocker	52 (31%)	11 (31%)	0.98
Long-acting nitrate	74 (44%)	18 (50%)	0.50
ACE inhibitor	113 (67%)	23 (64%)	0.73
Total number of anti-ischemic medications*			
0	13 (8%)	5 (14%)	0.18
1	67 (39%)	10 (28%)	
2	57 (34%)	17 (47%)	
3	32 (19%)	4 (11%)	
Crossover between strategies	37 (22%)	13 (36%)	0.07
% revascularized	91 (54%)	15 (42%)	0.18
Overall events	22 (13%)	6 (17%)	0.56
Death/AMI	10 (6%)	5 (14%)	0.10

*Beta-blocker, long-acting nitrate, calcium-channel blocker.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; LV = left ventricle; LVEF = left ventricular ejection fraction; PDS = perfusion defect size; SPECT = single-photon emission computed tomography.

-7.1 to 11.8%; p = NS), with a comparable incidence of death/nonfatal reinfarction (8 out of 101 or 7.9% vs. 7 out of 104 or 6.7%; Δ1.2%, 95% CI -5.9 to 8.3%; p = NS) (Fig. 4). By multivariate analysis, diabetes mellitus (p = 0.02), total PDS (p = 0.04), and scar PDS (p = 0.04) predicted subsequent outcome.

DISCUSSION

The INSPIRE study is the first large prospective randomized trial to describe the relative effects of intensive medical therapy versus coronary revascularization on scintigraphic ischemia

using serial adenosine SPECT imaging and specifically within clinically stable but high-risk patients after AMI. Our results demonstrate that an initial strategy of intensive medical therapy suppresses ischemia to a degree comparable to that achieved with revascularization in addition to standard medical therapy. Furthermore, ischemia suppression was achieved in ~80% of patients randomized to either strategy. Consistent with the similarity in scintigraphic treatment effects, 1-year cardiac event rates were comparable between strategies. The results from INSPIRE are similar to those reported in our original small pilot study (9) and indicate that serial SPECT

Table 6. Medical Therapy Administered to Patients in Both Strategies Who Had Two SPECT Studies

	Total Randomized Patients			Per Protocol*		
	Strategy 1 (Medical Therapy) (n = 83)	Strategy 2 (Revascularization Therapy) (n = 86)	p Value	Strategy 1 (Medical Therapy) (n = 62)	Strategy 2 (Revascularization Therapy) (n = 70)	p Value
Aspirin/clopidogrel	83/83 (100%)	82/86 (95%)	0.12	62/62 (100%)	68/70 (97%)	0.5
Beta-blocker	77/83 (93%)	74/86 (86%)	0.21	57/62 (92%)	59/70 (84%)	0.2
Lipid therapy	70/83 (84%)	66/86 (77%)	0.25	51/62 (82%)	54/70 (77%)	0.52
Calcium-channel blocker	35/83 (42%)	17/86 (20%)	<0.01	30/62 (48%)	11/70 (16%)	<0.001
Long-acting nitrate	47/83 (57%)	27/86 (31%)	<0.001	41/62 (66%)	14/70 (20%)	<0.001
ACE inhibitor	64/83 (77%)	49/86 (57%)	0.01	46/62 (74%)	41/70 (59%)	0.07
Total anti-ischemic drugs, †			<0.001			<0.001
0	3/83 (3%)	10/86 (12%)		2/62 (3%)	9/70 (13%)	
1	22/83 (27%)	45/86 (52%)		10/62 (16%)	43/70 (61%)	
2	37/83 (45%)	20/86 (23%)		32/62 (52%)	13/70 (19%)	
3	21/83 (25%)	11/86 (13%)		18/62 (29%)	5/70 (7%)	
Intensity of medical therapy †			<0.001			<0.001
Low (0-3)	33/83 (40%)	63/86 (73%)		19/62 (31%)	57/70 (82%)	
Medium (4-6)	41/83 (49%)	18/86 (21%)		35/62 (56%)	10/70 (14%)	
High (7-9)	9/83 (11%)	5/86 (6%)		8/62 (13%)	3/70 (4%)	

*Minus crossovers. †Long-acting nitrate, beta-blocker, calcium-channel blocker.

ACE = angiotensin-converting enzyme; SPECT = single-photon emission computed tomography.

Table 7. Coronary Revascularization Results Based on Stenosis Severity in Patients Randomized to Strategy 2 Who Had Two SPECT Studies

	Total Strategy 2 Patients (n = 86)		Patients Revascularized (n = 70)	
	≥50% Stenosis	≥70% Stenosis	≥50% Stenosis	≥70% Stenosis
Artery				
Left main	10/12 (83%)	7/8 (88%)	10/11 (91%)	7/7 (100%)
LAD	34/47 (72%)	33/43 (77%)	34/40 (85%)	33/38 (87%)
RCA	44/61 (72%)	42/57 (74%)	44/54 (81%)	42/51 (82%)
Cx	38/54 (70%)	38/51 (75%)	37/45 (82%)	37/42 (88%)
Ramus	4/9 (44%)	4/8 (50%)	4/7 (57%)	4/6 (67%)
Diagonal	7/17 (40%)	6/15 (50%)	7/14 (50%)	6/12 (50%)
Total	137/200 (69%)	130/182 (71%)	136/171 (80%)	129/156 (83%)
Major arteries*	126/174 (72%)	120/159 (75%)	125/150 (83%)	119/138 (86%)

*Left main, LAD, RCA, Cx.
 Cx = circumflex; LAD = left anterior descending; RCA = right coronary artery; SPECT = single-photon emission computed tomography.

can effectively track the effects of medical and revascularization therapies on scintigraphic ischemia. In this regard, intensive medical therapy alone may be a reasonable treatment alternative in stable patients after AMI who have ischemia but are not optimal revascularization candidates.

Treatment strategies in the INSPIRE trial. The intention of the INSPIRE trial was to randomize patients to receive either protocol-directed optimal medical therapy titrated to maximally tolerated doses, or state-of-the-art interventional approaches with additional medical therapy as clinically indicated. Patients randomized to strategy 1 entered a dose titration phase to ensure they would receive maximally tolerated medical therapy before SPECT 2. Accordingly, most patients in strategy 1 were on BB (93%), ACE inhibitors (77%), and lipid-lowering medications (84%), with approximately half also receiving a long-acting nitrate and CCB. The type and intensity of medical therapy prescribed in the INSPIRE trial is consistent with contemporary guidelines for patients recovering from AMI (14).

In patients randomized to strategy 2, 81% were revascularized before SPECT 2, a rate similar to that reported in other AMI (17) and acute coronary syndrome (18) trials. In accordance with accepted guidelines, most patients with left main or 3-vessel CAD underwent CABG, with PCI and

concomitant arterial stenting reserved for patients with less extensive involvement. The goal of INSPIRE to achieve high revascularization rates among patients assigned to this strategy was met in that most arteries (83%) with ≥70% stenosis were revascularized with stents placed in over 90% of dilated arteries.

Ischemia suppression with medical therapy. The substantial suppression of stress-induced scintigraphic ischemia with medical therapy alone may seem surprising, but is consistent with findings from earlier small reports in patients with chronic CAD (19). This beneficial effect on myocardial perfusion may be explained by a selective increase in coronary flow reserve within vascular territories supplied by stenosed coronary arteries, which results in more homogeneous myocardial perfusion during stress and therefore a smaller PDS. Resting myocardial blood flow is preferentially increased within initially ischemic areas by BB (19,20) and long-acting nitrates (21), thereby limiting the need for further arteriolar vasodilation to support resting flow and allowing an enhanced increase in flow during stress. Beta-blockers also improve myocardial efficiency by reducing oxygen demands and metabolic oxidative metabolism (22). Nitrates exert their beneficial effects through preload reduction, enhanced recruitment of collaterals (23), and/or epicardial arterial vasodilation (24). Statins improve endothelial dysfunction as their probable mechanism for scintigraphic benefit (25). The substantial reductions in scintigraphic ischemia we report with medical therapy may help explain the known beneficial effects of BB (1), statins (4), and certain CCB (5) for reducing cardiac events in patients recovering from AMI.

Previous studies. Few randomized prospective trials have addressed the relative clinical benefit of medical therapy versus coronary revascularization (9,11-13,26-29), and of these most have not focused on patients with AMI (11,12,27-29), none achieved the uniformly intensive medical therapy regimen reported in INSPIRE, and only 1 showed an advantage of revascularization over medical therapy for improving infarct-free survival (13). The INSPIRE trial results are similar to those reported in our initial

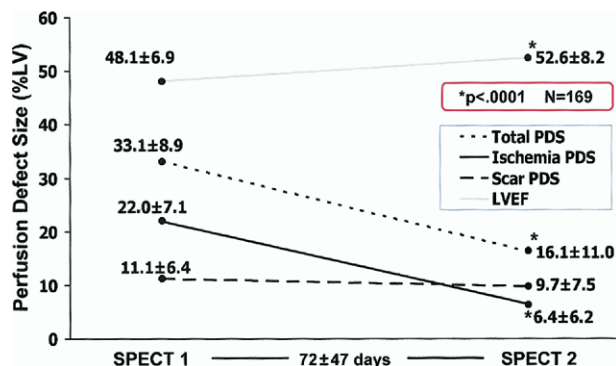


Figure 1. Absolute mean (± SD) change in scintigraphic variables in 169 randomized patients who had 2 adenosine single-photon tomographic (SPECT) studies. LV = left ventricle; LVEF = left ventricular ejection fraction; PDS = perfusion defect size.

Table 8. Primary End Point: Gated SPECT Results: Strategy 1 Versus Strategy 2 Patients

	Strategy 1 (Medical Therapy) (n = 83)	Strategy 2 (Revascularization Therapy) (n = 86)	p Value	Difference in Treatment Effect Strategy 1 vs. Strategy 2
Total LV PDS (absolute % change)	-16.2 ± 10 (-35.8 to 3.4)	-17.8 ± 12 (-41.3 to 5.7)	0.36	1.6 ± 11 (-20.0 to 23.3)
Ischemic LV PDS (absolute % change)	-15.0 ± 9 (-32.6 to 2.6)	-16.2 ± 9 (-33.8 to 1.4)	0.44	1.2 ± 9 (-16.4 to 18.8)
Scar LV PDS (absolute % change)	-1.2 ± 8 (-16.9 to 14.5)	-1.6 ± 7 (-15.3 to 12.1)	0.73	0.4 ± 7 (-14.3 to 15.1)
% patients ≥9% decrease				
Total LV PDS	75%	79%	0.50	
Ischemic LV PDS	80%	81%	0.76	
LV EF (absolute % change)	4.7 ± 7	4.6 ± 8	0.93	

95% confidence intervals in parentheses.

EF = ejection fraction; LV = left ventricular; PDS = perfusion defect size; SPECT = single-photon emission computed tomography.

pilot study where total (-12 ± 11% vs. -15 ± 14%) and ischemic (-12 ± 10% vs. -12 ± 9%) PDS were comparably reduced with medical therapy and PCI (9). Of note, despite a 4-fold increase in sample size, medical and interventional treatment effects remained as variable in INSPIRE as in the pilot study, with only 67% of patients decreasing their total PDS to a low-risk value of <20% (15). Thus, although each therapy comparably reduces the extent of scintigraphic ischemia within populations, there is significant individual patient heterogeneity in these treatment effects.

Clinical relevance of the INSPIRE trial. What conclusions should we reach from this randomized trial? The INSPIRE study was novel in randomizing AMI patients with a high-risk scintigraphic profile to medical therapy and then optimizing treatment as mandated by study design. Both randomized groups had similar reductions in scintigraphic ischemia and comparable cardiac event rates, thus challenging the conventional assumption that

an invasive strategy is superior to one of intensive medical therapy. The clinical lesson from the INSPIRE trial is not that this trial was unable to statistically detect the observed 1.2% difference in ischemia suppression between treatment strategies, but rather that this difference is so small and well within the variability reported with sequential SPECT imaging (16). An adequately powered cardiac event trial emulating the INSPIRE study design would best clarify whether such small relative scintigraphic improvements translate into clinical benefit (14,15). Although our reported event rates between strategies are not conclusive, they do provide ample preliminary data to design such a study. Strong support for the clinical relevance of INSPIRE comes from a recent large cohort study of 158,831 Medicare patients followed 7 years after AMI (30), where a routine invasive approach did not improve survival beyond that seen with standard medical management. Like the INSPIRE trial,

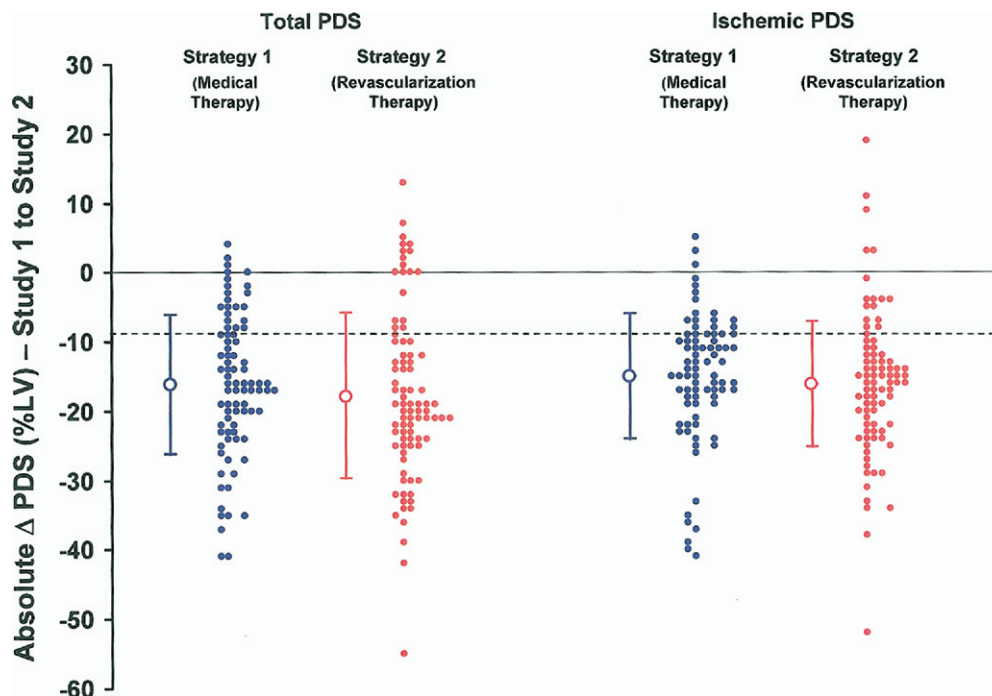


Figure 2. Primary end point: absolute mean (± SD) and individual changes in total and ischemic left ventricular (LV) perfusion defect size (PDS) from SPECT-1 to SPECT-2 study in the 2 randomized groups. The dashed line represents a 9% reduction in PDS (i.e., 95% confidence interval for a real patient change). Other abbreviations as in Figure 1.

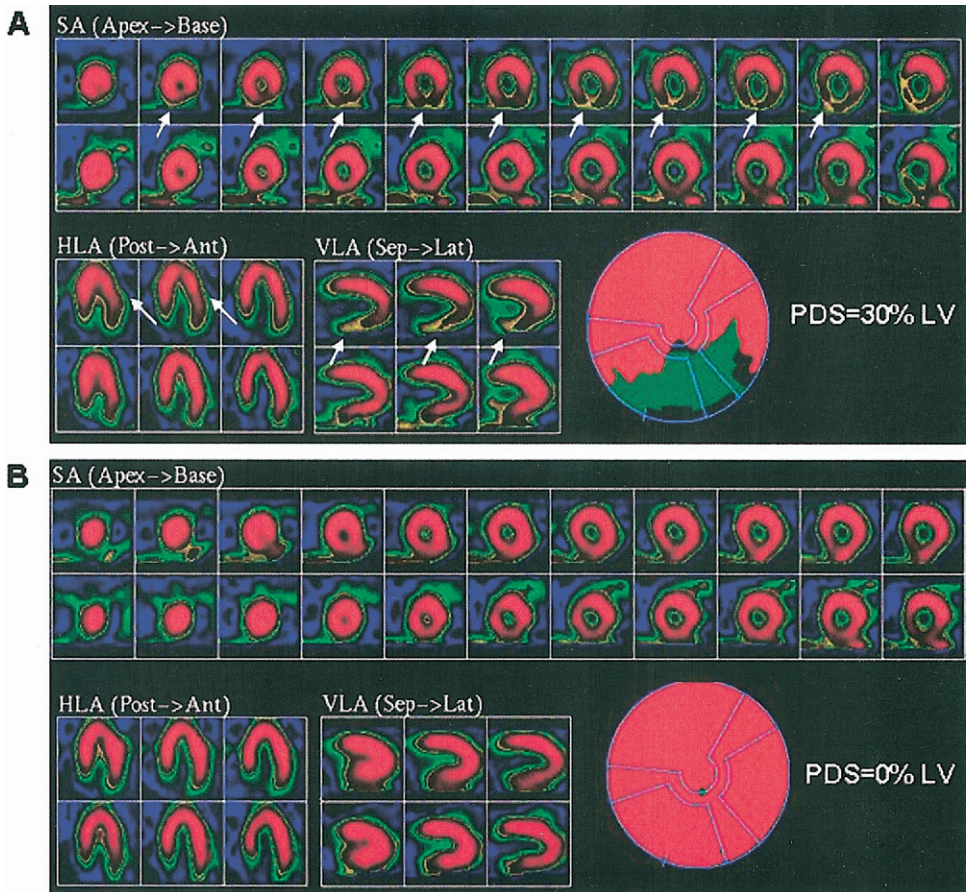


Figure 3. Serial SPECT images and polar plot of a patient randomized to medical therapy. Baseline SPECT (A) shows a large perfusion defect (arrows) in the short (SA), horizontal long (HLA), and vertical long (VLA) axis slices after stress (upper panels) which improves with rest imaging (lower panels). Ischemia is present in the right and circumflex vascular territories. Total LV PDS is 30% with 25% ischemia (green) and 5% scar (black). The patient was treated with a beta-blocker, calcium-channel blocker, and statin. Repeat SPECT (B) is entirely normal. This patient had no subsequent cardiac event. Other abbreviations as in Figure 1.

those results suggest that intensive medical management of ischemia is an acceptable alternative to coronary revascularization.

Study limitations. The INSPIRE study was designed before the use of drug-eluting stents which reduce the incidence of coronary restenosis (31). However, it is unlikely that newer-

generation stents would have changed our scintigraphic results, because serial imaging was performed before the typical time course of restenosis (32). We studied a stable cohort of patients after AMI who had significant scintigraphic ischemia but preserved LV function. Our results may not be applicable to patients who are clinically unstable or have poor LV function.

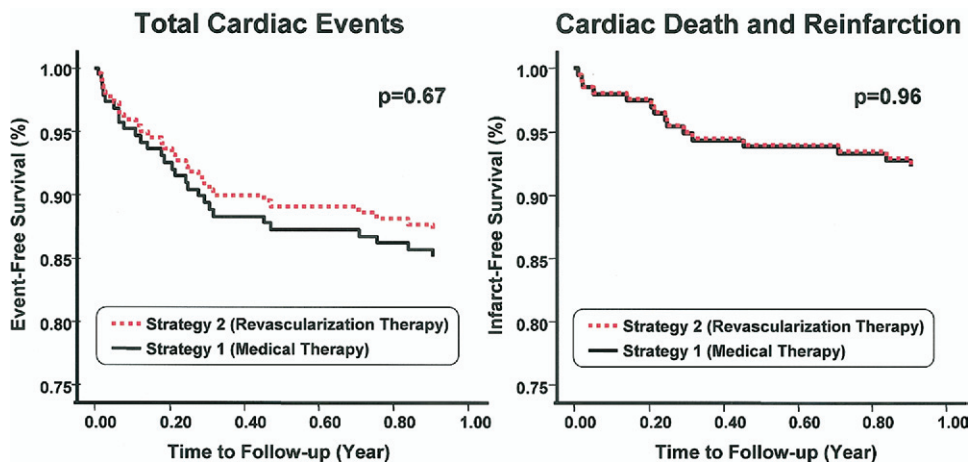


Figure 4. Patient outcome based on randomized treatment strategy.

Such patients generally undergo coronary angiography with the intent to revascularize and therefore were not considered appropriate for randomization. In the main INSPIRE trial, patients with ischemia and an LV EF <35% were routinely referred for an invasive evaluation (14,15). Serial SPECT was not performed in 36 patients, but generally for noncardiac reasons. It is unlikely that these patients would have altered our primary end point results, because they were evenly distributed across both treatment strategies, had similar baseline characteristics, and received comparable therapy. Finally, the crossover rate was approximately 25% in both randomized groups. As in all clinical trials assessing a treatment strategy, the INSPIRE trial explored the relative benefit of each strategy on the primary end point based on initial randomized treatment allocation. The crossover rates in the INSPIRE trial are generally lower than reported in other clinical event trials studying similar patients (18,33).

Conclusions. Sequential ADSPECT can effectively monitor changes in scintigraphic ischemia following either medical or interventional therapies. An initial strategy of intensive medical therapy suppresses ischemia to an extent comparable to coronary revascularization when combined with standard medical therapy and may therefore be a reasonable treatment alternative in stable patients after AMI who have preserved LV function but are not optimal revascularization candidates. This therapeutic approach is best further explored in an adequately powered outcome trial studying patients similar to those randomized in the INSPIRE trial.

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