Intensive Medical Therapy Versus Coronary Angioplasty for Suppression of Myocardial Ischemia in Survivors of Acute Myocardial Infarction
A Prospective, Randomized Pilot Study
Habib A. Dakik, MD; Neal S. Kleiman, MD; John A. Farmer, MD; Zuo-Xiang He, MD; Juliet A. Wendt, MD; Craig M. Pratt, MD; Mario S. Verani, MD; John J. Mahmarian, MD

Background—Patients who have inducible ischemia after acute myocardial infarction (AMI) generally undergo coronary angiography with the intent to revascularize. Whether this approach is superior to intensive treatment with anti-ischemic medications is unknown.

Methods and Results—We performed a prospective, randomized pilot study comparing intensive medical therapy with coronary angioplasty (PTCA) for suppression of myocardial ischemia in 44 stable survivors of AMI. Myocardial ischemia was quantified with adenosine 201Tl tomography (SPECT) performed 4.5 ± 2.9 days after AMI. All patients at baseline had a large total (≥ 20%) and ischemic (≥ 10%) left ventricular perfusion defect size (PDS). SPECT was repeated at 43 ± 26 days after therapy was optimized. The total stress-induced PDS was comparably reduced with medical therapy (from 38 ± 13% to 26 ± 16%; P < 0.0001) and PTCA (from 35 ± 12% to 20 ± 16%; P < 0.0001). The reduction in ischemic PDS was also similar (P = NS) in both groups. Cardiac events occurred in 7 of 44 patients over 12 ± 5 months. Patients who remained clinically stable had a greater reduction in ischemic PDS (−13 ± 9%) than those who had a recurrent cardiac event (−5 ± 7%; P < 0.02). Event-free survival was superior in the 24 patients who had a significant (≥ 9%) reduction in PDS (96%) compared with those who did not (65%; P = 0.009).

Conclusions—In this small pilot study, intensive medical therapy and PTCA were comparable at suppressing ischemia in stable patients after AMI. Sequential imaging with adenosine SPECT can track changes in PDS after anti-ischemic therapies and thereby predict subsequent outcome. Corroboration of these preliminary findings in a larger cardiac-event trial is warranted. (Circulation. 1998;98:2017-2023.)

Key Words: myocardial infarction ■ tomography ■ ischemia

Patients recovering from acute myocardial infarction (AMI) who have residual ischemia are at high risk for subsequent cardiac events.1,2 Although aspirin,3 lipid-lowering agents,4 β-blockers,5 and heart rate–lowering calcium antagonists6,7 improve event-free survival after AMI, patients with residual ischemia generally undergo coronary revascularization as the preferred approach. This therapeutic strategy is assumed to be optimal and is used in most large clinical trials,8,9 as well as in clinical practice.10,11

See p 1985

The purpose of this pilot study was to determine the relative efficacy of intensive anti-ischemic medical therapy versus coronary angioplasty (PTCA) for suppression of ischemia in high-risk but stable survivors of AMI. This study was not designed to determine differences in cardiac event rates between the 2 treatment strategies. Ischemia suppression was assessed with sequential adenosine 201Tl single-photon emission computed tomography (SPECT).

Methods

Study Population

Between February 1995 and June 1996, 167 consecutive patients (aged ≥ 18 years) were admitted to our coronary care unit with the diagnosis of AMI based on standard criteria.7,12 Thirty-four patients with initial clinical instability (ie, cardiogenic shock [n = 5], need for emergent coronary revascularization [n = 10], or concomitant serious noncardiac illnesses [n = 9]), death of ventricular fibrillation (n = 2), or a contraindication to adenosine (n = 8) were excluded. The remaining 133 patients (80%) had adenosine SPECT performed 4.5 ± 2.9 days after AMI.

Sixty-three (47%) of 133 patients had a large total (≥ 20%) and ischemic (≥ 10%) left ventricular (LV) perfusion defect size (PDS)
and were considered for study entry pending coronary angiography. This scintigraphic profile defines a population at high risk for recurrent cardiac events after AMI. Patients with significant (≥50%) left main stenosis, 3-vessel coronary artery disease (CAD) and an LV ejection fraction (EF) <35%[13,14] and CAD not amenable to PTCA were excluded. Forty-five of 63 patients met all entry criteria; 1 patient randomized to PTCA had CABG and was excluded. Thus, 44 patients constituted the study population.

Study Design
This was a prospective, randomized pilot study of a larger trial evaluating the clinical utility of adenosine SPECT early after AMI. The protocol was approved by the Baylor Institutional Review Board, and all patients signed informed consent forms.

Patients meeting entry criteria were randomized to either PTCA (n=21) or intensive anti-ischemic medical therapy (n=23); the latter combined isosorbide dinitrate (ISDN) with metoprolol (Lopressor) and diltiazem (Cardizem CD). After therapy was optimized, 22 of 23 patients randomized to medical therapy and 19 of 21 randomized to PTCA had repeat adenosine SPECT 43±26 days after their baseline study. All 44 patients were prospectively followed up for ≥6 months (mean, 12±5 months).

Medical Therapy Group
Anti-ischemic medications were titrated to maximally tolerated doses over 4 to 8 weeks. In patients with asymptomatic bradycardia and/or a systolic blood pressure <110 mm Hg, medications were not titrated to higher doses. All patients were to receive ISDN up to the target dose of 120 mg/d. In patients with an LVEF ≤40%, metoprolol was administered (maximal dose, 200 mg/d), whereas in those with an LVEF >40%, both diltiazem (maximal dose, 300 mg/d) and metoprolol were given as clinically tolerated. Metoprolol was initially chosen for patients with an LVEF ≤40% because of the known survival advantage with β-blockers in this population.[13,14] Diltiazem was chosen for patients with an LVEF >40% on the basis of trials demonstrating a significant reduction in early reinfarction[7] and late cardiac events[8] with this medication and no excess risk of heart failure.[9] All patients received aspirin, and lipid-lowering agents were given to treat hypercholesterolemia. Patients continued the same anti-ischemic dosing regimen throughout the study.

Coronary Angioplasty Group
All patients had PTCA of the infarct-related artery and any other artery with significant (≥50%) stenosis that was supplying an ischemic zone as determined by adenosine SPECT. Anti-ischemic medications were given to treat residual angina, and β-blocker use was empirically encouraged. Aspirin and lipid-lowering agents were administered as in the medical treatment group.

Adenosine 201Tl SPECT
Adenosine SPECT was performed as previously reported by our laboratory.[2] Adenosine was administered intravenously with a standard 6-minute protocol, with injection of 201Tl at minute 3. Initial and 4-hour-delayed images were acquired.

SPECT quantification was performed by 1 experienced investigator (J.J.M.) who was blinded to patient randomization. The initial and 4-hour-delay polar maps were independently computer generated and normalized with circumferential profile analysis.[2] Raw data polar maps for each patient were compared statistically with a corresponding normal data bank to determine total LV PDS and the extent of scarring and ischemia. Anti-ischemic medications were withheld ≥12 hours before SPECT 1 was performed but were given on the morning of SPECT 2.

Cardiac Events
All patients were closely monitored after hospital discharge in the outpatient clinic: weekly for the first 2 months, monthly for 3 months, and once every 3 months thereafter. Cardiac events were prospectively defined as (1) cardiac death, (2) nonfatal reinfarction (ie, rise in creatine kinase-MB in a patient with new ST changes and/or chest pain), and (3) unstable angina (ie, rest or worsening exertional chest pain requiring hospital admission, with transient ST changes but no rise in cardiac enzymes).[2]

Statistical Analysis
The primary study goal was to determine the extent to which each treatment strategy reduced the mean total LV PDS. Secondary goals were to compare reductions in mean ischemic PDS with each strategy and determine the relationship between changes in PDS and patient outcome. A ≥9% reduction in PDS with SPECT defines the 95% CI for a significant change beyond technique variability.[19] With a sample size of 40 patients, at an α of .05, this study had 80% power to detect a >4% absolute difference in total and ischemic PDS between strategies. Baseline characteristics and changes in SPECT variables between groups were compared with unpaired t tests. Differences in medication doses and SPECT variables over time were assessed by paired t tests. χ² analysis compared discrete data variables. Kaplan-Meier analysis compared event rates based on a change in PDS dichotomized at 9%. Data are presented as mean±SD. A P value <.05 was considered significant.

Results
Baseline Characteristics
The majority of patients had multivessel disease, and 51% had anterior infarction. No significant difference in any baseline variable was observed between the 2 groups (Table 1).

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<th>TABLE 1. Baseline Characteristics</th>
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<td>Age, y</td>
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<td>Male gender, n (%)</td>
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<td>Prior myocardial infarction, n (%)</td>
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<td>Myocardial infarction, n (%)</td>
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<tr>
<td>Q-wave</td>
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<td>Peak creatine kinase-MB</td>
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<td>LVEF ≥40%, n (%)</td>
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<td>Angiographic variables</td>
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<td>CAD extent (no. of vessels)</td>
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<td>IRA stenosis, %</td>
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<td>Scintigraphic variables, % LV</td>
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<td>Ischemia PDS</td>
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<td>Scar PDS</td>
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IRA indicates infarct-related artery.

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Anti-Ischemic Medical Therapy

Patients randomized to medical therapy had a marked increase in the number and doses of medications administered during the titration phase of the study (Figure 1). The dose of ISDN increased from 58±14 mg/d in 14 patients to 113±23 mg/d in 21 patients, whereas the dose of metoprolol doubled and that of diltiazem tripled. After therapy was optimized, all patients in the medical limb were taking either 2 (73%) or 3 (27%) drugs (Table 2). Furthermore, 95% and 59% of patients were taking maximal doses of at least 1 or 2 medications, respectively.

In the PTCA group, the number and doses of anti-ischemic medications did not significantly differ between SPECT 1 and 2 (Figure 1). These patients were ultimately taking 1 (42%) or at most 2 (58%) medications (Table 2). Only 3 patients (16%) were taking maximal doses of any medication, and in 2 this was for treatment of hypertension. Thus, at the time of SPECT 2, patients assigned to medical therapy were (1) taking significantly higher doses of metoprolol and ISDN and (2) taking a greater number of anti-ischemic medications (2.3±0.5 versus 1.5±0.6; P<0.0001) at maximal dosages (95% versus 16%; P<0.0001) than those assigned to PTCA. Ten patients in each treatment strategy were taking lipid-lowering medications (P=NS).

Coronary Angioplasty

No patient randomized to medical therapy had coronary revascularization before SPECT 2. Patients randomized to PTCA had revascularization performed in either 1 (n=17) or 2 (n=2) arteries: 12 left anterior descending, 4 circumflex, and 5 right coronary arteries. Stents were deployed in 6 patients. PTCA was successfully performed in 19 (79%) of 24 coronary arteries with >50% stenosis and scintigraphic ischemia within their vascular territory.

Side Effects With Medical Therapy

In patients randomized to medical therapy, ISDN was discontinued (n=1) or titrated downward (n=2) in 3 patients owing to headaches, but 19 of 22 were maintained on maximal doses (Table 3). Metoprolol was discontinued or titrated downward in 4 of 22 patients because of intolerable side effects. Nine additional patients did not achieve maximal doses because of asymptomatic bradycardia or hypotension or because of fatigue; 6 of these 9 patients were already taking high-dose diltiazem. Metoprolol was not added in 4 others who were taking maximal doses of ISDN and diltiazem. Diltiazem was discontinued in only 1 patient owing to tremor but was not started in 8 patients who had either an LVEF ≤40% (n=6) or asymptomatic bradycardia while taking high-dose metoprolol (n=2). Ten patients were taking maximal doses of diltiazem. Overall, 8 (36%) of 22 patients had 1 of their medications discontinued or titrated downward owing to side effects (Table 3).

In patients randomized to PTCA, ISDN was discontinued in 1 because of headaches, and metoprolol was titrated downward in another owing to fatigue.

SPECT Results

In the 41 patients studied with sequential SPECT, the total LV PDS significantly decreased from 37±13% at baseline to 23±16% after anti-ischemic therapy (P<0.0001). The reduction in ischemic PDS from 20±10% to 8±9% (P<0.0001) accounted entirely for the decrease observed in total PDS. The scar size did not significantly change with therapy.

Total and ischemic PDS were significantly reduced in patients randomized to either medical therapy or PTCA (Figure 2). The magnitude of the absolute reduction in total (−12±11% versus −15±14%) and ischemic (−12±10% versus −12±9%) PDS was similar (P=NS) in both groups. A significant (≥9%) reduction in total PDS was observed in an equal number of patients randomized to either strategy (n=12) (Figure 3).

<table>
<thead>
<tr>
<th>TABLE 2. Number and Doses of Anti-Ischemic Medical Therapy (SPECT 2)</th>
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<td>Anti-Ischemic Medications, n</td>
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Number in parentheses is number of patients taking medication.
Cardiac Events
Cardiac events occurred in 7 of 44 patients. In the medical therapy group, 1 patient died, and 3 developed unstable angina; 2 had CABG, but this occurred after SPECT 2. In the PTCA group, 1 patient died, and 2 had nonfatal reinfarction. One patient in each group continued to have intermittent exertional angina. Cardiac event rates were similar between patients treated medically (17%) and those who underwent PTCA (14%; P<NS).

Cardiac Events Based on Changes in Ischemia
Sequential adenosine SPECT assessed the relationship between ischemia suppression and patient outcome. Baseline total PDS (35±11% versus 37±13%) and ischemic PDS (18±12% versus 20±9%) were similar (P<NS) in patients who did (n=7) or did not (n=34) have a recurrent event. Patients who were clinically stable at follow-up had a greater reduction in their total PDS (−15±13% versus −6±7%; P<0.02) and ischemic PDS (−13±9% versus −5±7%; P<0.02) than those who had an event, respectively. Only 1 (4%) of 24 patients who had a significant (≥9%) reduction in PDS with anti-ischemic therapy returned to the hospital with a subsequent event versus 6 (35%) of 17 patients who had persistent defects (P=0.009) (Figure 4). The sequential SPECT images of a patient randomized to medical therapy are shown in Figure 5.

Discussion
The treatment of ischemia in stable survivors of AMI has been the subject of multiple large clinical trials. Patients without residual ischemia have a comparably low subsequent cardiac event rate whether they are treated medically or with PTCA.19 However, in patients with ischemia, coronary revascularization is frequently the preferred therapeutic approach. The widespread acceptance of an invasive strategy as the “community standard” has occurred despite the lack of definitive clinical trials supporting this strategy over medical therapy. In fact, subgroup analysis from the SAVE20 and GUSTO I trials report a comparable infarct-free survival among patients treated in the United States and Canada despite a 2- to 3-fold higher rate of coronary revascularization in the United States.

The present study is the first randomized, prospective trial to directly compare the anti-ischemic effects of intensive medical therapy and PTCA in clinically stable patients who had “high-risk” scintigraphic ischemia demonstrated early after AMI. By study design, patients with an LVEF <35% were excluded because CABG is preferable in this group of patients who also have ischemia.13 To avoid potential treatment bias, patients were only randomized after they were deemed amenable to PTCA. Our results indicate that intensive medical therapy suppresses myocardial ischemia to a degree comparable to that achieved by a combination of PTCA and low-dose background medical therapy. The sequential SPECT results suggest that ischemia suppression with either strategy results in a favorable event-free survival at 1 year.

Ischemia Suppression With Medical Therapy
Our results with medical therapy in patients surviving AMI are directionally similar to those reported in trials evaluating patients with stable CAD.21–26 Various nitrate prepara-


The present study titrated medical therapy over 4 to 8 weeks until protocol-directed dosing end points were achieved. Accordingly, all of our patients randomized to medical therapy were ultimately taking maximally tolerated doses of 2 (73%) or 3 (27%) drugs. These differences in study design may help explain the apparent disparity between our results and those reported by the ACIP and DANAMI investigators.

Tracking Ischemia Suppression With Adenosine SPECT

Exercise SPECT is an accurate and reproducible technique for the evaluation of ischemia suppression. The present study and others demonstrate that SPECT, when combined with pharmacological stressors, can also track changes in myocardial ischemia after medical therapy. The mechanisms underlying these changes may relate to the effects of medications on resting coronary flow reserve. Nitrates improve resting myocardial blood flow in patients with CAD through direct vasodilation of epicardial or collateral vessels. The improved detection of tissue viability in underperfused myocardium after nitroglycerin-augmented 201 Tl re-injection imaging further supports this finding. Anti-ischemic medications, by improving resting coronary flow demands in normal subjects and thereby increase coronary blood flow during pharmacologically induced hyperemia, may allow a more homogeneous increase in myocardial blood flow during pharmacologically induced hyperemia, thereby reducing perfusion defects.

Ischemia Suppression and Subsequent Outcome

The presence and extent of residual myocardial ischemia after AMI predict subsequent risk for cardiac events. Mounting...
evidence supports the concept that ischemia suppression in patients with CAD may reduce risk and improve long-term outcome. 36–38 In both the ACIP and Atenolol Silent Ischemia Study, suppression of ambulatory ECG ischemia predicted an improved event-free survival. 36,37 In the Angioplasty Compared to Medicine study, survival was improved if medical therapy or PTCA suppressed exercise-induced scintigraphic ischemia. 39 Our results are in agreement with these findings. Patients who remained clinically stable had a significantly greater reduction in ischemic PDS after therapy than those who had a subsequent event. In fact, event-free survival was 96% in patients who had a significant (≥9%) reduction in PDS compared with only 65% in those who did not. These preliminary data all indicate that ischemia suppression, by whatever means, may improve patient outcome. Our results support the role of adenosine SPECT for tracking patient risk on the basis of changes in the extent of inducible myocardial ischemia.

Study Limitations
The small sample size of this single-center pilot study precludes direct comparison of cardiac event rates between treatment groups. This is precisely why SPECT parameters were chosen as a surrogate end point for events. The high reproducibility of SPECT 9 affords evaluation of anti-ischemic therapies with relatively small sample sizes. 23,24,30 Although anti-ischemic medications and PTCA were comparable at suppressing ischemia, neither therapy accomplished this in all patients. It is possible that more complete coronary revascularization, as achieved with CABG, might have more effectively reduced ischemia than either medical therapy or PTCA. 30

Conclusions
This prospective, randomized study demonstrates that medical therapy and PTCA are comparable at suppressing myocardial ischemia in stable but high-risk survivors of AMI. The sequential imaging results further strengthen the concept that future outcome is closely linked to the degree of ischemia suppression. Adequately powered clinical event trials are needed to better define the independent and combined roles of medical and revascularization strategies in suppressing ischemia. Such trials will ultimately have profound implications for both the management of patients after AMI and the proper allocation of healthcare resources.

Acknowledgment
The authors wish to acknowledge the assistance of Maria E. Frias.

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