The Medicine, Angioplasty or Surgery Study (MASS): A Prospective, Randomized Trial of Medical Therapy, Balloon Angioplasty or Bypass Surgery for Single Proximal Left Anterior Descending Artery Stenoses

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Objectives. This study sought to evaluate, in a prospective and randomized trial, the relative efficacies of three possible therapeutic strategies for patients with a single severe proximal stenosis of the left anterior descending coronary artery and stable angina.

Background. Although percutaneous transluminal coronary angioplasty and coronary artery bypass surgery are often performed in patients with a single proximal stenosis of the left anterior descending coronary artery, it is unclear whether revascularization offers greater clinical benefit than medical therapy alone.

Methods. At a single center, 214 patients with stable angina, normal ventricular function and a proximal stenosis of the left anterior descending coronary artery >80% were randomly assigned to undergo mammary bypass surgery (n = 70), balloon angioplasty (n = 72) or medical therapy alone (n = 72). Angioplasty had to be considered technically feasible in every case. The predefined primary study end point was the combined incidence of cardiac death, myocardial infarction or refractory angina requiring revascularization.

Results. At an average follow-up period of 3 years, a primary end point had occurred in only 2 patients (3%) assigned to bypass surgery compared with 17 assigned to angioplasty (24%) and 12 assigned to medical therapy (17%) (p = 0.0002, angioplasty vs. bypass surgery; p = 0.006, bypass surgery vs. medical treatment; p = 0.28, angioplasty vs. medical treatment, all by log-rank test). There was no difference in mortality or infarction rates among the groups. However, no patient allocated to bypass surgery needed revascularization, compared with eight and seven patients assigned, respectively, to coronary angioplasty and medical treatment (p = 0.019). Both revascularization techniques resulted in greater symptomatic relief and a lower incidence of ischemia on the treadmill test; however, all three strategies eventually resulted in the abolition of limiting angina.

Conclusions. The more aggressive therapeutic approach with initial bypass surgery for patients with a single severe proximal stenosis of the left anterior descending coronary artery is associated with a lower incidence of medium-term adverse events than coronary angioplasty or medical treatment. However, all three strategies resulted in a similar incidence of death and infarction during an average follow-up period of 3 years. This information should be taken into consideration when physicians and patients make therapeutic choices in this setting.

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Indeed, patients with proximal lesions before the first septal perforator have a significantly worse prognosis than those with distal disease in the same vessel (4).

Most of the information concerning the comparative usefulness of medical and surgical therapy in patients with stable angina is derived from the classic randomized studies performed in the 1970s. However, both medical therapy and surgical techniques have evolved significantly since then. One such example in the surgical field is the increasing use of the internal mammary artery grafts, now recognized for their association with improved long-term survival and freedom from cardiac events compared with that for saphenous vein grafts (5). Medical therapy has also evolved, with increased recognition of the benefits of antiplatelet, thrombolytic and beta-adrenergic blocking agents and angiotensin-converting enzyme inhibitors (6-8). Another factor is the frequent use of percutaneous transluminal coronary angioplasty. Coronary an-
surgery. Patients initially allocated to angioplasty usually un-

assigned to medical therapy underwent angioplasty or bypass
different treatment. If refractory angina occurred, patients
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study protocol were approved by our

institute’s committee on ethics and human research.

heart surgery were exchlded. Patients from other states or
dysfunction, a previous coronary inte~'ention or prior open
cardiovascular disease. Patients with unstable angina, prior infarction,
severe ventricular function and a single severe proximal stenosis of

To increase the homogeneity of the three
treatment groups, only patients screened and treated at a
single institution, the Heart Institute of the University of São
Paulo, were included in the study. In addition, the surgeon and
the interventional cardiologist who participated in the trial had
considerable experience, defined as the performance of
>10,000 procedures each. These two investigators were the
sole operators of revascularization procedures in the present
trial. Medical care and follow-up was provided by a senior staff
cardiologist with >15 years of experience in treating coronary
disease. Patients with unstable angina, prior infarction,
significant valvular disease, cardiomyopathy, left ventricular
dysfunction, a previous coronary intervention or prior open
heart surgery were excluded. Patients from other states or
those unable to make regular hospital visits were also excluded.
Written informed consent was obtained from all patients. Both
the consent form and the study protocol were approved by our
institute’s committee on ethics and human research.

From 1988 to 1991, we enrolled 214 patients with stable
angina and single-vessel disease with at least 80% diameter
stenosis in the left anterior descending coronary artery before
the first diagonal branch. Angiographic exclusion criteria were
total occlusion, lesion length >12 mm, involvement of the
ostium, heavy calcification, severe tortuosity and stenosis of the
left main coronary artery. The left anterior descending coronary
artery lesion was above the first septal perforator in 89% of
the patients on average, and the three treatment groups
were similar with respect to lesion location. All cine films were
reviewed by a cardiac surgeon, an interventional cardiologist
and the attending physician. Either revascularization strategy
had to be considered technically feasible by the consensus of
the three investigators before randomization.

If the treatment failed, patients could be withdrawn from
the protocol by their attending physician and assigned to a
different treatment. If refractory angina occurred, patients
assigned to medical therapy underwent angioplasty or bypass
surgery. Patients initially allocated to angioplasty usually un-
derwent surgical revascularization, and those who underwent
initial surgical revascularization also underwent angioplasty.
Repeat angioplasty in the event of restenosis was permitted as
an integral part of the angioplasty strategy, and the procedure
was repeated as many times as deemed necessary by the
attending physician and interventional cardiologist. The max-
imal number of repeat procedures was four, and the average
number of angioplasty procedures/patient was 1.6.

Twenty percent of the patients screened refused to partici-


ded if symptoms of angina recurred. Angioplasty was re-

procedure. Coronary angiograms were repeated at 6 months or
sooner if symptoms of angina occurred. Angioplasty was re-
peated if significant restenosis occurred. In the event of abrupt
closure of the dilated artery, the interventional cardiologist
and attending physician were allowed to decide whether to
ref er the patient for emergency bypass surgery.

Surgical revascularization. All patients assigned to surgical
revascularization underwent bypass grafting using the left
internal mammary artery. Extracorporeal circulation was used
for all patients, and the perfusion rate was maintained at 2.0 to
2.4 liters/m² per min under mild hypothermia (34 to 35°C). The
anastomoses were performed during a short period of cardiac
arrest after aortic cross-clamping. Distal anastomoses were
performed under optical magnification.

Follow-up. After discharge, all patients were seen and
examined every 3 mo at the Heart Institute. Unless contrain-
dicated, all patients received aspirin, nitrates and beta- and
calcium channel blockers. Patients underwent a symptom-
limited treadmill exercise test at baseline and after 2 years of
randomization according to a modified Bruce protocol, unless
contraindicated. Coronary angiography was repeated in all
patients after 2 years. Patients assigned to coronary angioplasty
underwent routine coronary angiography also at 6 months.

Study end points. The predefined primary study end point
was the combined incidence of cardiac death, myocardial
infarction or refractory angina requiring revascularization.
Surgical revascularization, but not repeat coronary angioplasty,
was considered an end point for patients assigned to coronary
angioplasty. Secondary outcomes were angina functional class
at the last follow-up visit, employment status and positive exercise test results 2 years after enrollment and degree of atherosclerotic involvement of the coronary arteries at the 2-year angiographic study.

Symptoms of angina were graded according to severity, from 1 to 4, as previously defined (16). Refractory angina was considered only when patients had been treated with anti-ischemic therapies (usually triple-drug therapy) to their tolerance level. Myocardial infarction was defined by the development of significant new Q waves in at least two electrocardiographic leads or when symptoms were compatible with a myocardial infarction associated with elevation of the creatine kinase, MB fraction to greater than three times the upper limit of normal.

Ventricular function. Patients underwent contrast left ventriculography during the baseline and follow-up cardiac catheterizations in the right anterior oblique projection. The endocardial contours were traced during systole and diastole of a normal sinus beat, and the global left ventricular ejection fraction was obtained using the area-length method, as previously described (17).

Statistical analysis. Data are reported as mean value ± SD. Discrete variables in the groups were compared by the Fisher exact and chi-square tests, and continuous variables were compared using analysis of variance. The event-free probabilities in the groups were estimated by the Kaplan-Meier method and compared by the log-rank test. All analyses were performed according to intention to treat, and the reported statistics are two-tailed; p < 0.05 was considered significant.

Results

Patients. Two hundred fourteen patients met all entry criteria and were randomized to undergo bypass surgery (70 patients), balloon angioplasty (72 patients) and medical treatment alone (72 patients). The three groups did not differ with respect to baseline clinical, angiographic and laboratory characteristics, as shown in Table 1. The average follow-up period was 3.5 ± 1.5 years.

Primary end points. Medical therapy. In the medical therapy group, two patients sustained an uncomplicated myocardial infarction, four were referred for bypass surgery, and three were referred for angioplasty because of refractory angina. There were no deaths or strokes.

Bypass surgery. Of the 70 patients assigned to left internal mammary artery bypass surgery, one patient had a perioperative infarction, and one died on the way to the hospital after the onset of chest pain 48 mo after bypass surgery. No patient required angioplasty and there were no strokes.

Coronary angioplasty. Angioplasty was clinically successful in 96% of the 72 patients initially assigned to coronary angioplasty. It was not possible to dilate the stenosis in three patients, two of whom had a periprocedural myocardial infarction and were referred for emergent bypass surgery. During the follow-up period, 27 patients assigned to this group (37.5%) had repeat angiography because of refractory angina, and 21 underwent one or more additional angioplasty procedures. Eight patients had refractory angina requiring elective bypass surgery. No patient was referred to bypass surgery solely as a result of 6-month follow-up angiography. One patient assigned to angioplasty died suddenly at home 8 months after the procedure. There were no strokes.

The event-free probability at an average follow-up period of 3 years in the patients initially allocated to bypass surgery was 97%, significantly greater than that for those assigned to the other two groups and did not differ between those randomized to coronary angioplasty (76%) and those randomized to medical therapy (83%) (p = 0.0002 for coronary angioplasty vs. bypass surgery; p = 0.006 for coronary angioplasty vs. medical treatment, log-rank test) (Fig. 1).

Angina. There was a marked suppression of angina in patients randomized to both revascularization strategies: 68 patients assigned to bypass surgery (98%) and 58 randomized to coronary angioplasty (82%) were totally asymptomatic at the last follow-up visit an average of 3 years after enrollment. In contrast, only 23 patients randomized to medical treatment (32%) were asymptomatic at the 3-year follow-up visit (p < 0.01 for bypass surgery vs. coronary angioplasty; p < 0.01 for coronary angioplasty vs. medical treatment). No patient in any randomized group had limiting angina (functional class III or IV) at the last follow-up visit.

Treadmill test. One hundred sixty-five patients underwent exercise treadmill tests after 2 years of follow-up. Ninety-four percent of those randomized to bypass surgery, 79% of those assigned coronary angioplasty and 34% of those assigned to medical therapy were ischemia free on this stress test (p < 0.01 for medical therapy vs. both revascularization strategies).

Table 1. Baseline Characteristics of 214 Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical Therapy</th>
<th>PTCA</th>
<th>Mammary Bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 72)</td>
<td>(n = 72)</td>
<td>(n = 70)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (yr)</td>
<td>58 ± 7</td>
<td>54 ± 9</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>Male gender (no.)</td>
<td>59</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>38</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20</td>
<td>15</td>
<td>18</td>
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<tr>
<td>Current smoker (%)</td>
<td>36</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>89</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Laboratory values (mg/dl)</td>
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<td></td>
<td></td>
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<tr>
<td>Total cholesterol</td>
<td>240 ± 40</td>
<td>213 ± 49</td>
<td>230 ± 45</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>162 ± 36</td>
<td>141 ± 42</td>
<td>155 ± 36</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>41 ± 9</td>
<td>38 ± 9</td>
<td>37 ± 8</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>199 ± 111</td>
<td>192 ± 126</td>
<td>220 ± 110</td>
</tr>
<tr>
<td>Positive TI-201 stress</td>
<td>86</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>74 ± 4</td>
<td>77 ± 6</td>
<td>74 ± 4</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data presented are mean value ± SD. HDL = high density lipoprotein; LDL = low density lipoprotein; PTCA = percutaneous transluminal coronary angioplasty; Thall = thallium.
Figure 1. Event-free probability for the three treatment groups during the follow-up period. Note that the patients assigned to bypass surgery had a lower incidence of events during follow-up (Kaplan-Meier analysis; see Methods for definition of events). Numbers below the graph are number of patients reaching each time point in each group.

Employment status. There was no difference among the groups with respect to the proportion of patients regularly working 2 years after randomization. Fifty-six of the patients assigned to medical treatment (78%), 46 of those randomized to coronary angioplasty (64%) and 56 of those who initially underwent bypass surgery (80%) were employed (p = NS).

Angiography. All patients agreed to undergo repeat angiography after 2 years of randomization. Fifty-four of these patients (35%) had evidence of progression to >50% diameter stenosis in a vessel that did not have significant disease previously. This progression occurred in 16 of the 54 patients assigned to bypass surgery, 19 of the 52 allocated to angioplasty and 19 of the 53 assigned to medical therapy (p = NS). There was no relation between baseline or follow-up total or fractionated cholesterol levels and angiographic progression of disease. Baseline and follow-up total cholesterol levels were, respectively, 225 ± 42 and 231 ± 44 mg/dl for those with new lesions and 236 ± 51 and 224 ± 42 mg/dl for those without new lesions (p = NS).

At 2-year follow-up angiography, 47 patients assigned to medical therapy (89%) had a lesion 70% to 99% diameter stenosis, and 6 had an occluded artery (11%). Thirty-three patients allocated to coronary angioplasty (63%) had a lesion <70% diameter stenosis; 15 (29%) had 70% to 99% diameter stenosis; and 4 (8%) had total occlusion of the left anterior descending coronary artery. Two patients assigned to bypass surgery (4%) had <70% diameter stenosis; 12 (22%) had 70% to 99% narrowing; and 40 (74%) had total occlusion of the left anterior descending coronary artery. Left internal mammary angiography disclosed no atherosclerosis and a patent anastomosis in all but one patient 2 years after bypass surgery.

Baseline and follow-up global left ventricular ejection fraction was 74 ± 4% and 71 ± 7% for those assigned to medical treatment, 77 ± 6% and 73 ± 7% for those assigned to coronary angioplasty and 73 ± 4% and 71 ± 5% for those undergoing bypass surgery (p = NS among the groups and for baseline vs. follow-up studies).

Discussion

Autopsy and nonrandomized studies (3,4,17-19) emphasize the prognostic importance of severe proximal lesions of the left anterior descending coronary artery. More aggressive therapy is also recommended for patients with severe proximal left anterior descending coronary artery disease because of the widespread assumption that prognosis is ultimately related to the amount of myocardium at risk (20,21).

Balloon angioplasty was introduced in the late 1970s as a less invasive form of limited coronary revascularization (22) and has since grown explosively. There were >300,000 angioplasty procedures performed in the United States in 1991, most of them single-vessel disease procedures, and, surprisingly, many were not performed in accordance with the established indications as outlined in some guidelines for the procedure (23). More recently, newer coronary angioplasty techniques have been compared with traditional balloon coronary angioplasty in patients with proximal left anterior descending coronary artery stenoses (24). Despite a slight increase in the procedural success rate with atherectomy devices, there was still a significant proportion of in-hospital complications, and the restenosis rate during follow-up remained high. There are also few data assessing the relative efficacies of coronary angioplasty and surgical revascularizations, and this issue has been the focus of ongoing trials comparing these treatments in different subsets of patients with coronary artery disease (10-12,14,15).

Nevertheless, despite the more guarded prognosis associated with left anterior descending coronary artery involvement versus that for other coronary arteries, the outlook for all patients with single-vessel disease and preserved ventricular function is generally good, and it is not clear whether revascularization strategies result in better medium- or long-term outcomes than medical therapy alone.

Study findings versus previous trials. We studied 214 carefully selected patients with stable angina randomized to the three available therapies for single proximal left anterior descending coronary artery stenosis. All three interventions resulted in significant symptomatic relief, although the proportion of patients totally asymptomatic in the medical arm (32%) was significantly less than those in the coronary angioplasty (82%) and surgical (98%) groups. These results are in agreement with data published recently from the Angioplasty Compared to Medicine (ACME) trial (13), indicating that patients with single-vessel disease assigned to coronary angioplasty have more complete angina relief than do those assigned to medical therapy. However, all three therapies in this study resulted in the elimination of limiting angina, and the symptomatic benefit in the revascularization groups may not be clinically important. Mammary bypass surgery was associated with a greater event-free probability at an average follow-up of 3 years than either coronary angioplasty or medical treatment. This benefit resulted from a very low surgical periprocedure complication rate, as well as the successful medium-term abolition of symptoms, which completely eliminated the need
for a repeat revascularization procedure. These results are comparable to other published series of patients with isolated 
left anterior descending coronary artery disease treated with 
bypass surgery (25). Death and infarction rates were also low in 
patients assigned to medical therapy and angioplasty. However, 
these treatments were associated with higher crossover 
rates to the other treatment arms because of the development 
of refractory angina during the follow-up period.

The relatively benign course in the nonsurgical patients 
with proximal left anterior descending coronary artery narrowing 
observed in the present study may be related in part to the 
normal ventricular function in our patients. Klein et al. (4) 
evaluated a group of patients with left anterior descending 
coronary artery disease and normal ventricular function and 
reported a survival rate of 97% over an average follow-up 
period of 17 months. However, the presence of proximal left 
artery descending coronary artery stenosis was a better 
predictor of worse outcome than was altered anterior wall motion. 
In patients medically managed with normal left ventricular function, Califf et al. (3) reported a survival rate of 
98% in those with isolated left anterior descending coronary 
artery disease located after, and 90% with disease located 
before, the first septal perforator at 5 years of follow-up.

The only other randomized comparison of coronary angioplasty and bypass surgery for the treatment of patients with isolated proximal left anterior descending coronary artery stenosis was recently reported by Goy et al. (12). In a similar 
group of 134 patients with stable angina, they observed that 
86% of surgically revascularized patients and 43% of coronary 
angioplasty–treated patients were free of adverse events after 
a median follow-up period of 2.5 years. These results parallel 
the significantly higher event-free probability of the patients who underwent bypass surgery in the present study (97% for 
bypass surgery vs. 76% for coronary angioplasty, p < 0.01). 
The lower proportion of events occurring during follow-up in the 
present report probably reflects a stricter definition of events and end points. However, in neither study was there a 
difference in cardiac death or myocardial infarction rates 
between coronary angioplasty and surgical revascularization. 
Also, Goy et al. (12) did not randomize a comparable group of 
patients to medical therapy alone.

A comparison between balloon-expandable stent implantation 
and balloon angioplasty in patients with single-artery 
disease has been recently reported (26). During a 7-month 
follow-up period, there was an improvement in clinical and angiographic outcomes in patients receiving stents compared with those who underwent balloon angioplasty only, who were at a significantly higher risk of vascular complications and a longer hospital stay. All patients in the present study who were 
treated by angioplasty underwent standard balloon angioplasty. Thus, it is unclear whether the use of newer intervention 
techniques such as stent implantation would alter the 
results presented here.

We also observed significant progression of coronary atherosclerosis during the study. At 2-year follow-up angiography, 
35% of the patients had developed >50% stenosis in vessels 
previously free of significant narrowing at the baseline exami-
nation. The atherosclerotic involvement of coronary arteries other than the left anterior descending coronary artery transforms the status of these patients from single-vessel to multivessel disease, which could significantly influence the clinical 
course and treatment strategies adopted.

Conclusions and clinical implications. The use of marmary bypass surgery for the treatment of patients with stable 
angina and isolated, severe proximal stenosis of the left anterior descending coronary artery with normal ventricular 
function was associated with a higher event-free survival rate due to a lower reintervention rate than coronary angioplasty or 
medical treatment alone during an average follow-up period of 3 years. However, there was significant progression of coronary 
atherosclerosis in nontreated vessels in all groups, and the three therapeutic strategies resulted in a similar success rate in 
terms of abolishing limiting angina and an equally low incidence 
of death or myocardial infarction during the 3-year follow-up period. Future cost-benefit analyses as well as longer 
follow-up studies are warranted. Ongoing efforts toward a 
meta-analysis of all available randomized data may result in 
greater insight into the effects of these interventions on hard 
end points, such as mortality and infarction rates.

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