Five-Year Follow-Up of 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 Coronary Artery Stenosis

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Background—Although coronary angioplasty and myocardial bypass surgery are routinely used, there is no conclusive evidence that these interventional methods offer greater benefit than medical therapy alone. This study is intended to evaluate, in a prospective, randomized, and comparative analysis, the benefit of the 3 current therapeutic strategies for patients with stable angina and single proximal left anterior descending coronary artery stenosis.

Methods and Results—In a single institution, 214 patients with stable angina, normal ventricular function, and severe proximal stenosis (>80%) on the left anterior descending artery were selected for the study. After random assignment, 70 patients were referred to surgical treatment, 72 to angioplasty, and 72 to medical treatment. The primary end points were the occurrence of acute myocardial infarction or death and presence of refractory angina. After a 5-year follow-up, these combined events were reported in only 6 patients referred to surgery as compared with 29 patients treated with angioplasty and 17 patients who only received medical treatment (P<0.001). However, no differences were noted in relation to the occurrence of cardiac-related death in the 3 treatment groups (P=0.622). No patient assigned to surgery needed repeat operation, whereas 8 patients assigned to angioplasty and 8 patients assigned to medical treatment required surgical bypass after the initial random assignment. Surgery and angioplasty reduced anginal symptoms and stress-induced ischemia considerably. However, all 3 treatments effectively improved limiting angina.

Conclusions—Bypass surgery for single-vessel coronary artery disease is associated with a lower incidence of medium-term and long-term events as well as fewer anginal symptoms than that found in the patients who underwent angioplasty or medical therapy. In this study, coronary angioplasty was only superior to medical strategies in relation to the anginal status. However, the 3 treatment regimens yielded a similar incidence of acute myocardial infarction and death. Such information should be useful when choosing the best therapeutic option for similar patients.

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Key Words: coronary disease • angioplasty • bypass

Patients with obstructive single proximal left anterior descending coronary artery (LAD) stenosis accompanied by symptomatic ischemic syndromes, who have reduced tolerance to stress and who require maximum pharmacological therapy, are often candidates for revascularization,1,2 either by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting. However, in patients with both stable angina and preserved ventricular function, these 2 treatment modalities are no more efficacious than medical therapy alone in reducing the incidence of acute myocardial infarction or death.3,4 Despite its frequent use, PTCA carries a high risk of restenosis, frequently necessitating multiple interventions and thus limiting its usefulness.5,6 Furthermore, long-term studies comparing outcomes related to these 3 therapeutic strategies are not available.

The aim of the current study, therefore, was to evaluate, in a randomized, prospective manner, the 3 therapeutic options in patients with single proximal left anterior descending lesions and to compare1 anginal status and angiographically documented coronary atherosclerosis status at the end of the study,2 the occurrence of myocardial infarction and congestive heart failure at any time during follow-up, and1 survival in each group after 5 years of follow-up.
Methods

The Medicine, Angioplasty, or Surgery Study (MASS-I) is part of a larger project, which, through comparative analysis, aims at verifying the therapeutic effects on patients with coronary artery disease from a single institution. The present study refers to single proximal LAD stenosis patients, and MASS-II is an ongoing study in patients with multivessel disease. The study model, patient selection criteria, and randomization procedure were previously published.8 The study has been approved by the hospital’s scientific and ethics committee, and all patients gave written informed consent.

For this prospective study, 313 consecutive patients were selected between 1988 and 1991. Of these, 99 (31.6%) patients were excluded for the causes listed in Table 1. The 214 (68.4%) remaining patients were randomly assigned to 1 of the 3 available treatment modalities, of which 70 (32.7%) patients were referred to coronary artery bypass surgery, 72 (33.6%) to angioplasty, and the remaining 72 (33.6%) to medical treatment. Patients’ clinical, laboratory, and angiographic characteristics were similar among the 3 studied treatment groups (Table 2). The follow-up time for all patients was 5 years.

Patient Selection

Patients with stable angina whose angiograms showed a single stenotic lesion in the proximal third of the LAD, before the diagonal branch, were selected. Eligible patients had no prior intervention by coronary bypass or PTCA. The artery had to have ≥80% luminal stenosis by visual evaluation, and the lesion length had to measure ≤12 mm to be adequate to receive the 3.0-mm or larger catheter balloon. The specific angiographic criteria for exclusion from the study were (1) lesions >12.0 mm in length, (2) a ≥2.5-mm involvement in the artery ostium or artery diameter, or (3) an occluded, tortuous, or calcified artery. Patients with a ≥50% stenosis of the left main coronary artery were also excluded.

The clinical criteria for inclusion were (1) the presence of stable angina, (2) absence of previous infarction, and (3) normal left ventricular ejection fraction (LVEF). The endocardial contours were traced during systole and diastole of a normal sinus beat, and a global left ventricular ejection fraction was obtained by use of the area-length method. The LVEF calculation was obtained by the area-measurement method.8 Patients with associated valve disease, cardiomyopathy, ventricular dysfunction, or previous cardiac interventions were not included. The study also excluded patients who could not undergo periodic examinations or repeated angiography or who refused any one of the indicated treatments.

Once the inclusion criteria were defined, all angiograms were submitted for approval of an interventional cardiologist team, which assessed the patient’s suitability for treatment intervention. After approval, patients were randomly assigned to 1 of the 3 proposed treatment groups: bypass surgery, angioplasty, or medical therapy.

<table>
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<td>Lesion involving diagonal branch</td>
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</table>

Some patients had >1 reason for exclusion.

Table 1. Principal Reasons for Exclusion of Potential Subjects

Table 2. Baseline Characteristics of Study Patients According to Treatment Group

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The study design allowed for patients to cross over from one treatment to another, based on occurrence of symptoms, at any time during the study. Patients with unstable angina who were randomly assigned to the medical therapy group would be referred to angioplasty or surgery, if necessary. Those patients with unstable angina or acute myocardial infarction who were randomly assigned to the angioplasty group would receive surgical intervention or medical therapy. Patients who underwent surgery could be considered for medical treatment after the occurrence of acute myocardial infarction or unstable angina; they would be referred to angioplasty in the presence of stenosis at the site of anastomosis or on the appearance of a new lesion requiring a catheterization procedure.

Treatment Strategy

Medical Therapy

Patients assigned to medical therapy received agents indicated for the prevention and relief of angina symptoms including β-blockers, nitrates, calcium antagonists, and antiplatelet agents.

Surgical Revascularization

The left internal mammary artery was used for anastomosis with the LAD in all patients. Extracorporeal circulation was used in accordance with the conventional technique and with a 2.0- to 2.4-L·min⁻¹·m² perfusion and mild systemic hypothermia of 34°C to 35°C.

Balloon Angioplasty

The PTCA procedure was carried out under a standard technique.9 All patients received 100 mg aspirin and calcium channel blockers. During the preprocedure period, 10 000 U of intravenous heparin was given and intra-arterial or intravenous nitroglycerin or both were given, if necessary.

Follow-Up

After the revascularization procedure, all patients were referred to outpatient follow-up. Examinations were performed every 3 months by physicians participating in the research study. All 3 groups uniformly received the following drugs: calcium channel antago-
nists, β-blockers, nitrates, and antiplatelet agents. Crossover to other treatment groups was made in accordance with the previously proposed conditions. Repeat angiograms in the angioplasty group were planned for 6 months, 2 years, and 5 years after the procedure; the occurrence of an ischemic event at any time dictated a new angiogram and, in cases of restenosis, repeat angioplasty. After 5 years of follow-up, the patients in the 3 treatment groups underwent a final angiographic examination. All living patients complied with follow-up.

**Definition of Terms**

**Stable Angina**
Symptoms of angina were graded according to severity from 1 to 4 as defined by Canadian Cardiovascular Society.10

**Angina Class**
Class I indicates thoracic pain caused by high stress or prolonged physical activity; class II, thoracic pain caused by medium stress or striding; class III, thoracic pain caused by minimum walking or sometimes at rest; and class IV, thoracic pain at any stress level or even at rest.

**Unstable Angina**
Unstable angina was defined as pain at rest followed by reversible changes on ECG and mild creatine kinase-MB enzyme increases.

**Acute Myocardial Infarction**
Acute myocardial infarction was defined as the presence of a Q wave in ≥2 leads on the ECG, with creatine kinase-MB enzyme rise to at least 3 times its normal value.

**Initial Success of Angioplasty**
Initial success of angioplasty was defined as the reduction to <50% of the residual stenosis, with clinical improvement, and without myocardial infarction during hospitalization. Currently, this definition for success is established for procedures in our institution.

**Restenosis**
Restenosis was defined as the presence of ≥50% stenosis at the site where initial dilatation success was obtained.

**Surgical Success**
Surgical success was defined as survival to hospital discharge without myocardial infarction in patients originally randomly assigned to surgical treatment.

**Study End Points**
The primary end point was the combination of cardiac death, myocardial infarction, and refractory angina requiring revascularization. We also analyzed the angina status and the progression of coronary atherosclerosis at the end of the study.

**Statistical Analysis**
The primary end point was defined as one of the following events: cardiac-related death, acute myocardial infarction, and refractory angina requiring revascularization. The event-free survival time was defined as the interval between randomization and the occurrence of a primary end point or the last follow-up. The interval between randomization and the occurrence of cardiac-related death or last follow-up was used to estimate the survival probability. The likelihood of occurrence of events in each group was estimated by the Kaplan-Meier method and compared through the log-rank test.

Continuous variables were compared among the 3 groups by use of 1-factor ANOVA followed by multiple comparisons. Fisher’s exact and χ² tests were used to compare the 3 groups concerning qualitative variables.

All analyses were made according to the intention-to-treat principle. A probability value of <0.05 was considered significant. Statistical analyses were performed with the SAS (Statistical Analysis System) system.

**Results**

**Event-Free Survival**
The rates of event-free survival were significantly different among the 3 groups (P=0.001 by the log-rank test). Patients assigned to PTCA had more events (defined as additional revascularization, myocardial infarction, or death) than did patients treated with medical and surgical therapies. In the PTCA group, 29 patients had events. Seventeen events occurred in the group treated with medical therapy, and only 6 patients had events in the surgical group. The cumulative event-free survival rates at 5 years were 98.6% for patients assigned to PTCA, 63.9% for patients who underwent surgery, and 97.1% for patients assigned to medical therapy (Figure 1).

**Cardiac-Related Deaths**
There was no significant difference in the cumulative cardiac-related death curves for the 3 treatment groups (Figure 2). There were 4 deaths in the PTCA group; 2 deaths in the group submitted to surgery and 2 deaths in the medically treated group (P=0.622 by the log-rank test). The cumulative survival rates at 5 years were 94.3%, 97.1%, and 97.1% for patients assigned to PTCA, surgery, and medical treatment, respectively.
Medical Therapy
In this group, 3 of 72 patients had uncomplicated acute myocardial infarctions; 8 were referred to surgery and 4 to angioplasty because they showed signs of unstable angina. Two cardiac and 4 noncardiac deaths were recorded. The cardiac deaths were related to acute myocardial infarction and the noncardiac deaths to cancer (3 patients) and stroke (1 patient).

Bypass Surgery
In the 70 patients referred to surgery, 1 patient had a perioperative acute myocardial infarction. There were no in-hospital deaths in this group of patients; however, 1 patient died on his way to the hospital as a result of unstable angina after 43 months of outpatient follow-up, and 1 patient had cardiogenic shock and died during evolution of an acute myocardial infarction. Nonfatal myocardial infarction was observed in 3 patients and stroke in 1 patient. None of these patients required angioplasty during the follow-up period. Nonneoplasias were diagnosed in this group by the end of the study.

Coronary Angioplasty
A successful outcome was reported in 95.8% of the 72 patients randomly assigned to the angioplasty group. It was not possible to dilate the stenotic artery in 3 patients, and 1 patient required emergency surgery because of an acute myocardial infarction during the procedure. During the follow-up period, 27 (39.1%) of the 69 patients in this group underwent repeat catheterization for unstable angina and 21 (30.3%) required 1 or 2 additional angioplasty procedures for treatment of restenosis. Eight patients had unstable angina and were electively referred to cardiac surgery; none of these 8 patients required surgery during the first 6 months of follow-up. Four patients died during follow-up; 1 died suddenly at home and the other 3 died during acute myocardial infarctions. Noncardiac deaths occurred in 2 patients: 1 died of a stroke and the other of AIDS. Nonfatal myocardial infarction occurred in 4 patients during the follow-up period.

Anginal Symptoms
Patients treated by surgical bypass were the most likely to be free of anginal symptoms at the conclusion of the study, whereas a marked increase was observed in anginal symptoms among patients randomly assigned to medical therapy. Only 17 (25.8%) patients in the medically treated group were free of such symptoms at the end of the study, compared with 48 (72.7%) and 44 (64.7%) of the surgery and angioplasty groups, respectively. A statistically significant benefit was found for angioplasty as compared with medical therapy (P < 0.001). None of the study patients of all the groups had refractory angina (functional class III or IV) at final follow-up.

Treadmill ECG testing was performed in 161 patients (80%) at the end of the study period. The examination revealed that 72% of the patients randomly assigned to surgery, 66% of those assigned to angioplasty, and 46% of those in the medical therapy group were free from ischemia in the final stress test (P = 0.008).

Progression of Atherosclerosis
At the end of the study, 191 (89.2%) patients underwent coronary angiography; 96 (50.3%) patients had evidence of stenosis (>50% vessel diameter stenosis, which were normal at the beginning of the study). The progression of atherosclerosis occurred in 27 (42.9%) of 63 patients assigned to surgery who had completed follow-up, 30 (47.6%) of 63 patients referred to angioplasty, and 38 (58.5%) of 65 patients who received medical treatment (P = 0.193). No relation was observed between the baseline and follow-up levels of total serum cholesterol or its fractions, in patients who had coronary atherosclerosis; nor was there a difference in cholesterol level between patients with and those without atherosclerosis. Baseline and final cholesterol levels were, respectively, 239 ± 49 and 236 ± 52 mg/dL for patients who had new stenoses and 224 ± 15 and 228 ± 46 mg/dL for those who did not have new stenoses (P = 0.077).

At the end of the study, 49 (75.4%) patients assigned to medical treatment had vessel diameter stenosis between 70% and 99%, and 10 (15.4%) patients showed occlusion of LAD. Thirty-six (58.1%) angioplasty-referred patients had <70% diameter stenosis, and 11 (17.7%) had stenosis between 70% and 99%. Twelve (19.4%) patients had total occlusion of LAD. Two (3.2%) patients assigned to surgery had lesions <70% diameter stenosis, 17 (27.4%) patients had stenosis between 70% and 99%, and 41 (66.1%) had LAD occlusion. The left internal mammary artery was free from significant atherosclerosis in all
patients, except for 1 patient who demonstrated occlusion at the end of the study.

Ventricular Function
The LVEFs calculated at admission and at the end of the study were 75±6% and 71±7%, respectively, for patients assigned to medical treatment; 75±6% and 68±10%, for patients assigned to angioplasty; and 75±6% and 72±6% for patients assigned to surgical treatment (P=0.136 among the groups).

Employment Status
No difference was observed among the groups in terms of ability to return to regular employment after randomization. Fifty-six (84.8%) patients randomly assigned to medical treatment, 46 (69.7%) patients referred to angioplasty, and 56 (82.3%) patients in the surgical group were employed at the end of the study (P=0.072).

Discussion
Nonrandomized and necropsy studies\textsuperscript{11–15} have emphasized an unfavorable prognosis in patients with proximal LAD stenosis. Therefore more aggressive therapy, such as surgical revascularization, has been recommended because this artery supplies an important myocardial area.\textsuperscript{16,17} Coronary angioplasty was introduced in the late 1970s and became a less invasive alternative compared with surgery for revascularizing the ischemic myocardium.\textsuperscript{17} By the early 1990s, more than 300 000 procedures had been carried out in the United States, mostly in patients with single-vessel coronary disease. Surprisingly, so far there is no uniform therapeutic strategy defined for this procedure.\textsuperscript{18} Efforts have been made to develop alternatives to angioplasty. A recent study comparing balloon angioplasty with directional atherectomy in patients with proximal LAD lesions\textsuperscript{5} revealed a slight increase in the initial success rates for atherectomy. However, this new procedure could not reduce the frequency of complications in the hospital phase nor the restenosis rate during the outpatient follow-up, which remained significantly high. A recent comparative study observed the effects of treatment with implantation of expandable balloon stents and balloon-catheter angioplasty in patients with single-vessel coronary disease.\textsuperscript{19} During the 7-month follow-up, the authors did not find any significant clinical or angiographic benefits in patients who received the stents versus those treated with the balloon catheter alone. Moreover, the stent-treated patients had a higher risk for in-hospital complications and a longer hospitalization. All patients referred to angioplasty in our study were treated with the balloon catheter. Therefore it is not clear that the use of interventional techniques, by catheter, have proven to be of any benefit thus far.

Moreover, few studies have compared coronary angioplasty and surgical bypass in different subgroups of coronary disease.\textsuperscript{20–25} In addition, it is not clear whether or not coronary bypass results in a better short-term or long-term prognosis than medical treatment alone; hence the need for comparisons among these different therapeutic strategies is evident.

The MASS study enrolled 214 carefully selected patients with stable angina and preserved ventricular function who were randomly assigned to 1 of the 3 available therapeutic strategies for patients with single LAD stenosis. All 3 interventions led to a significant relief of anginal symptoms during follow-up. It was observed at the end of the study that the number of asymptomatic patients who received medical treatment (26%) was significantly lower than the number of patients who underwent angioplasty (65%), and, in turn, angioplasty patients were less symptomatic than the surgical group (73%). These results are in accordance with the data recently published from the Angioplasty Compared with Medical (ACME) Trial,\textsuperscript{23} which indicated that patients with single-vessel coronary disease, including the LAD, and who were treated with angioplasty, had better symptomatic relief than patients treated pharmacologically.

However, all 3 therapeutic strategies in our study led to the elimination of limiting angina, and the additional symptomatic benefit in the surgical bypass or catheter groups may not be clinically significant.

Surgical treatment, when compared with the other treatments, was significantly superior in terms of the estimated probability of event-free survival. This superiority probably resulted from the low perioperative complication rate, the improvement of symptoms, and the effectiveness of revascularization, which eliminated the need of repeat operations.

Our results are similar to those of other studies in patients with single LAD stenosis who received surgical treatment.\textsuperscript{26} A randomized, comparative study between coronary angioplasty and surgical bypass for treatment of patients with proximal LAD stenosis was recently published by Goy et al.\textsuperscript{22} In this study, which included a homogenous group of 134 patients with stable angina, the authors observed that 86% of the patients who received surgical bypass and 43% of those treated with angioplasty were free from adverse events after an average follow-up period of 2.5 years. Note, however, that the study by Goy et al did not include a medically treated group. Comparatively, our results demonstrate a higher estimated probability of absence of events among patients referred to surgery (97%) in relation to patients treated with angioplasty (64%) (P=0.001). The lower occurrence of events observed during the long-term follow-up probably reflects the strict study objectives and definition of events in our study. However, we found no significant differences between the occurrences of myocardial infarction or death between the surgery and angioplasty groups.

The relatively good prognosis evolution of patients with a nonrevascularized critical LAD stenosis observed in the current study may be partially attributed to the preserved ventricular function and also to the remission of anginal symptoms. Studies by Klein et al\textsuperscript{12} in clinically treated patients with LAD stenosis revealed an estimated survival of 97% in an average follow-up period of 17 months. However, even though the proximal stenosis in this artery is considered to be of unfavorable prognosis, it was the impaired ventricular function that determined the poor outcome. Another study by Califf et al\textsuperscript{11} in patients with preserved ventricular function and single LAD stenosis revealed an estimated
survival of 98% at 5 years when the stenosis was after the first septal branch and 90% when it was before this branch. Although prognosis is less optimistic in patients with LAD involvement, when compared with the involvement of other arteries, there is, however, a consensus of opinion that patients with single-vessel disease and preserved ventricular function have a fairly favorable long-term prognosis.

Progression of Atherosclerosis

At the end of the study, we angiographically evaluated the presence of coronary atherosclerosis. This final angiographic examination revealed that 96 (50%) patients who were free of apparent obstructive disease at baseline had developed stenosis in vessels other than the LAD >50% of the vessel diameter. Interestingly, the stenosis of the LAD in the medically treated patients remained stable, without progression, in 75% of the patients.

Even when coronary atherosclerosis progression can be identified in patients with previous arterial stenosis who develop clinical syndromes, thus warranting a repeat angiogram,22 there are few prospective and randomized studies aimed at determining the atherosclerotic disease progression, irrespective of the treatment received.23 Additionally, recognition of the development of stenosis in the apparently normal vessels and the plaque “stabilization” in previously diseased vessels in the same patient offers new perspectives for consideration and fuels debate about the pathophysiological role of established coronary atherosclerosis. Discussion of possible mechanisms involved in atherosclerosis progression, although most interesting, is beyond the scope of this study.

Therefore the atherosclerotic involvement of coronary arteries other than the LAD 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 mammary artery bypass surgery for the treatment of patients with stable angina and isolated, severe proximal stenosis of the LAD with normal ventricular function was associated with a higher event-free survival rate than coronary angioplasty or medical strategies alone during 5 years of follow-up. However, there was significant progression of coronary atherosclerosis in nontreated vessels in all groups, and the 3 therapeutic strategies resulted in a similar success rate in terms of abolishing limiting angina and on equally low incidence of death or myocardial infarction during 5 years of follow-up. Future cost-benefit analyses as well as longer follow-up studies are warranted. Ongoing efforts based on a meta-analysis of available randomized data may result in a greater insight into the effects of these interventions on hard end points such as mortality and infarction rates.29

Acknowledgment

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