Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS II)

A Randomized Controlled Clinical Trial of 3 Therapeutic Strategies for Multivessel Coronary Artery Disease

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Background—Despite routine use of coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI), no conclusive evidence exists that either modality is superior to medical therapy (MT) alone for treating multivessel coronary artery disease with stable angina and preserved ventricular function.

Methods and Results—The primary end points were total mortality, Q-wave myocardial infarction, or refractory angina requiring revascularization. The study comprised 611 patients randomly assigned to undergo CABG (n = 203), PCI (n = 205), or MT (n = 203). At the 5-year follow-up, the primary end points occurred in 21.2% of patients who underwent CABG compared with 32.7% treated with PCI and 36% receiving MT alone (P = 0.0026). No statistical differences were observed in overall mortality among the 3 groups. In addition, 9.4% of MT and 11.2% of PCI patients underwent repeat revascularization procedures compared with 3.9% of CABG patients (P = 0.021). Moreover, 15.3%, 11.2%, and 8.3% of patients experienced nonfatal myocardial infarction in the MT, PCI, and CABG groups, respectively (P < 0.001). The pairwise treatment comparisons of the primary end points showed no difference between PCI and MT (relative risk, 0.93; 95% confidence interval, 0.67 to 1.30) and a significant protective effect of CABG compared with MT (relative risk, 0.53; 95% confidence interval, 0.36 to 0.77).

Conclusions—All 3 treatment regimens yielded comparable, relatively low rates of death. MT was associated with an incidence of long-term events and rate of additional revascularization similar to those for PCI. CABG was superior to MT in terms of the primary end points, reaching a significant 44% reduction in primary end points at the 5-year follow-up of patients with stable multivessel coronary artery disease. (Circulation. 2007;115:1082-1089.)

Key Words: angina ■ angiography ■ bypass ■ coronary disease ■ follow-up studies ■ prognosis ■ revascularization

Coronary heart disease is the leading cause of death among adults, and its management continues to be an issue of major clinical importance. Patients with symptoms from flow-limiting atherosclerotic coronary artery narrowing can be managed with medical therapy (MT), percutaneous coronary intervention (PCI), bypass surgery (CABG), or combinations of these strategies. The fact that patients with chronic ischemic heart disease benefit from these therapies is incontrovertible. What is arguable, however, is which treatment modality is best for specific patient groups and subgroups. Large-scale randomized clinical trials have been and will continue to be crucial to objectively discern which patients are most suitable for each therapeutic strategy.1

Editorial p 1064

Two major randomized trials in the prestatin and prestent era comparing medical treatment with surgical interventions2 and percutaneous procedures3 reported occurrences of myocardial infarction (MI) and cardiac death similar to the 1-year data from Medicine, Angioplasty, or Surgery Study (MASS II).4 However, these trials have produced some different results on the extent of revascularization, similarity to baseline characteristics between study groups, and clinical outcomes compared with those in our study. In the meantime, medical approaches for patients with multivessel coronary artery disease (CAD) have changed considerably in recent years.
Because of the lack of a combined comparative study of the 3 therapeutic strategies currently available and because very few studies with 5-year follow-up that includes MT have been reported, the present study was designed to address this deficiency and to compare the relative efficacy of CABG with that of PCI or MT in patients with symptomatic multivessel CAD requiring revascularization.

Methods
Details of the MASS II design, study protocol, patient selection, and inclusion criteria have been reported previously. Briefly, patients with angiographically documented proximal multivessel coronary stenosis of >70% by visual assessment and documented ischemia were considered for inclusion. Ischemia was documented by either stress testing or the typical stable angina assessment of the Canadian Cardiovascular Society (class II or III). Patients were enrolled and randomized if the surgeons, attending physicians, and interventional cardiologists agreed that revascularization could be attained by either strategy. Patients gave written, informed consent and were randomly assigned to a treatment group. The Ethics Committee of the Heart Institute of the University of São Paulo Medical School (São Paulo, Brazil) approved the trial, and all procedures were performed in accordance with the Helsinki Declaration.

Clinical criteria for exclusion included refractory angina or acute MI requiring emergency revascularization, ventricular aneurysm requiring surgical repair, left ventricular ejection fraction of <40%, a history of PCI or CABG, single-vessel disease, and normal or minimal CAD. Patients also were excluded if they had a history of congenital heart disease, valvular heart disease, or cardiomyopathy; if they were unable to understand or cooperate with the protocol requirements or to return for follow-up; or if they had left main coronary artery stenosis of ≥50%, suspected or known pregnancy, or another coexisting condition that was a contraindication to CABG or PCI.

Treatment Intervention
In MASS II, all patients were placed on an optimal medical regimen consisting of a stepped-care approach using nitrates, aspirin, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs unless contraindicated. Lipid-lowering agents, particularly statins, also were prescribed, along with a low-fat diet, on an individual basis. The medications were provided for free by the Heart Institute. Patients were then randomized to continue with aggressive MT alone or to undergo PCI or CABG concurrently with MT.

Requirements were to perform optimum coronary revascularization in accordance with current best practices. Equivalent anatomic revascularization was encouraged but not mandatory. For patients assigned to PCI, the procedures were performed within 3 weeks after randomization. Devices used for catheter-based therapeutic strategies, including stents, lasers, directional atherectomy, and balloon angioplasty, were available to the interventionist. Angioplasty was performed according to a standard protocol. Glycoprotein IIb/IIIa agents were not used. Successful revascularization in the PCI group was defined as a residual stenosis of <50% reduction in luminal diameter with Thrombolysis in Myocardial Infarction flow grade 3.

For patients assigned to CABG, the procedures were performed within 12 weeks after randomization. Complete revascularization was accomplished, if technically feasible, with saphenous vein grafts, internal mammary arteries, and other conduits such as radial or gastroepiploic arteries. Standard surgical techniques were used with patients under hypothermic arrest with blood cardioplegia. No off-pump CABG was performed.

Follow-Up
Adverse and other clinical events were tracked from randomization. Patients were assessed with follow-up visits every 6 months for 5 years at the Heart Institute. Patients underwent a symptom-limited treadmill exercise test, according to a modified Bruce protocol, at baseline and every year until the end of the study unless contraindicated. We considered exercise test results positive when exertional angina developed or when we observed an ST-segment with an abnormal depression (horizontal or downsloping of 1 mm for men and 2 mm for women) at 0.08 seconds after the J point. Routine examinations included ECG and routine blood tests every 6 months.

Coronary arteriography was performed with the Sones or Seldinger techniques. For assessment of ventricular function, patients underwent contrast left ventriculography at baseline in the right anterior oblique projection, and ejection fraction was calculated with the Dodge formula.

Symptoms of angina were graded according to severity, from 1 to 4 as previously defined. Angina was considered refractory only when patients had been treated with full anti-ischemic therapies to their level of tolerance. MI was defined as the presence of significant new Q waves in at least 2 ECG leads or symptoms compatible with MI associated with creatine kinase-MB concentrations that were >3 times the upper limit of the reference range.

The predefined primary end point was the incidence of overall mortality, Q-wave MI, or refractory angina requiring revascularization. The performance of a revascularization procedure was considered an end point for patients in any group. In such a manner, therapeutic PCI or CABG performed during an episode of unstable angina at any time during follow-up was considered an end point and was applied equally across all 3 arms of therapy. Secondary end points included angina status and stroke or a cerebrovascular accident.

Statistical Analyses
The sample size calculation was performed, assuming the largest difference among the treatment groups. With a significance level of α=0.05 and a power of 80%, we calculated the needed number of events to be 41 in each group, and using the formula of Makuch and Simon, we determined that a minimum of 191 patients in each group was necessary to conduct the present study. On the basis of the 5-year event rate of 21.4% of the Randomised Intervention Treatment of Angina trial, assumptions included 41 composite events for each group to be reached during follow-up. All data were analyzed according to the intention-to-treat principle rather than treatment received. The event rates were assumed to be the combined major events of death, acute MI, or unstable angina requiring revascularization.

Furthermore, the event-free survival time was defined as the interval between random assignment and the occurrence of 1 of the components of a primary end point or the latest follow-up. Event-free survival was estimated with the Kaplan-Meier method, and differences among groups were assessed by means of the log-rank test. Continuous variables were estimated as mean±SD and compared among the 3 groups by 1-way ANOVA, followed by the multiple-comparisons test. The χ² and Fisher exact tests were used to compare qualitative variables among the 3 groups. Multivariate analysis was performed to assess the relationship between pairwise treatment comparisons and primary end points by the Cox proportional-hazards survival model. Tests were 2-tailed, and values of P<0.05 were considered statistically significant. Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc, Chicago III).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Baseline Variables
A total of 20 769 patients who had a presumptive clinical diagnosis of CAD and who underwent coronary arteriography were screened at the Heart Institute of the University of São Paulo between May 1995 and May 2000. Of these, 18 692...
patients (90%) did not meet the clinical or angiographic requirements for study inclusion. The most frequent reasons for exclusion were single-vessel disease, refractory angina, stenosis ≤70%, previous PCI or CABG, and valvular disease. The remaining 2077 patients (10%) who had indications for revascularization were enrolled. Of these patients, 1466 (71%) could not be randomly assigned because they refused to participate in this trial or specifically refused the surgical procedure. The remaining eligible 611 patients (29%) who met all entry criteria were randomly assigned to 1 of the 3 therapeutics: PCI, MT, or CABG.

The vital status of all randomly assigned patients was ascertained in May 2005. The minimal duration of follow-up was 5 years. Randomization created balanced treatment groups with respect to important prognostic characteristics, as shown in Table 1. All patients received medical regimens according to a predefined approach.

### Treatment Outcomes

No significant differences were noted in major in-hospital complications among PCI and CABG groups. The hospital mortality rates were 2.4% and 2.5% for PCI and CABG, respectively. The Q-wave MI incidence was 1% in both PCI and CABG. No patient in the CABG group needed in-hospital PCI or emergency CABG, whereas 2% of patients who underwent PCI needed emergency PCI or CABG. The overall major adverse cardiac events at the 5-year follow-up by 1 of 3 therapeutic strategies are shown in Table 2.

### Medical Therapy

Of the 203 patients assigned to receive MT, 10 (5%) had an uncomplicated or nonfatal MI during the 1-year follow-up, and 31 (15.3%) did at the 5-year follow-up. Twelve (6%) underwent CABG at the 1-year follow-up, and 31 (15.3%) did at 5-year follow-up. Furthermore, 4 (1.97%) underwent angioplasty at the 1-year follow-up because of refractory angina, and 18 (8.9%) underwent PCI at the end of follow-up. During the first-year follow-up, 3 patients (1.5%) died of MI, and 3 (1.5%) other patients had a cerebrovascular accident, whereas 25 patients (12.3%) died of MI and 7 (3.5%) had a cerebrovascular accident at the 5-year follow-up. No patient in this group was lost to follow-up.

### Surgical Therapy

Of the 203 patients assigned to the CABG group, 198 (98%) received the assigned treatment. However, 4 (2%) received table: Characteristics of the 611 Patients Assigned to MT, PCI, or CABG in MASS II

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MT (n=203)</th>
<th>PCI (n=205)</th>
<th>CABG (n=203)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±9</td>
<td>60±9</td>
<td>60±9</td>
<td>0.959</td>
</tr>
<tr>
<td>Female, %</td>
<td>31</td>
<td>33</td>
<td>28</td>
<td>0.412</td>
</tr>
<tr>
<td>Employed, %</td>
<td>29</td>
<td>27</td>
<td>24</td>
<td>0.088</td>
</tr>
<tr>
<td>Current or past smoker, %</td>
<td>33</td>
<td>27</td>
<td>32</td>
<td>0.013</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>39</td>
<td>52</td>
<td>41</td>
<td>0.024</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55</td>
<td>61</td>
<td>63</td>
<td>0.215</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36</td>
<td>23</td>
<td>29</td>
<td>0.062</td>
</tr>
<tr>
<td>Angina CCS class II or III</td>
<td>78</td>
<td>78</td>
<td>86</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Laboratory values, mmol/L

- Total cholesterol: MT 5.74±1.01, PCI 5.69±1.06, CABG 5.53±1.09, P=0.063
- LDL cholesterol: MT 3.83±0.88, PCI 3.80±0.93, CABG 3.70±0.93, P=0.305
- HDL cholesterol: MT 0.96±0.26, PCI 0.98±0.26, CABG 0.96±0.26, P=0.870
- Triglycerides: MT 2.01±0.93, PCI 2.04±0.82, CABG 1.91±0.95, P=0.235

- Positive treadmill test, %: MT 47, PCI 33, CABG 56, P=0.705

- Mean ejection fraction: MT 68±7, PCI 67±8, CABG 67±9, P=0.984

- Double-vessel disease, %: MT 41, PCI 42, CABG 42, P=0.980

- Triple-vessel disease, %: MT 59, PCI 58, CABG 58, P=0.980

- LAD disease, %: MT 89, PCI 93, CABG 93, P=0.312

CCS indicates Canadian Cardiovascular Society; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and LAD, left anterior descending. Some patients had both angina and positive treadmill test or abnormal rest ECG. Unless otherwise indicated, data are mean±SD.

Medical Therapy

Of the 203 patients assigned to receive MT, 10 (5%) had an uncomplicated or nonfatal MI during the 1-year follow-up, and 31 (15.3%) did at the 5-year follow-up. Twelve (6%) underwent CABG at the 1-year follow-up, and 31 (15.3%) did at 5-year follow-up. Furthermore, 4 (1.97%) underwent angioplasty at the 1-year follow-up because of refractory angina, and 18 (8.9%) underwent PCI at the end of follow-up. During the first-year follow-up, 3 patients (1.5%) died of MI, and 3 (1.5%) other patients had a cerebrovascular accident, whereas 25 patients (12.3%) died of MI and 7 (3.5%) had a cerebrovascular accident at the 5-year follow-up. No patient in this group was lost to follow-up.

Surgical Therapy

Of the 203 patients assigned to the CABG group, 198 (98%) received the assigned treatment. However, 4 (2%) received

<table>
<thead>
<tr>
<th>Overall mortality, %</th>
<th>PCI</th>
<th>MT</th>
<th>CABG</th>
<th>P (Log-Rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death, %</td>
<td>11.6</td>
<td>12.3</td>
<td>7.9</td>
<td>0.631</td>
</tr>
<tr>
<td>Additional intervention, %</td>
<td>32.2</td>
<td>24.2</td>
<td>3.5</td>
<td>0.021</td>
</tr>
<tr>
<td>AMI, %</td>
<td>11.2</td>
<td>15.3</td>
<td>8.3</td>
<td>0.785</td>
</tr>
<tr>
<td>CVA, %</td>
<td>3.4</td>
<td>3.5</td>
<td>5.9</td>
<td>0.310</td>
</tr>
</tbody>
</table>

AMI indicates acute MI; CVA, cerebrovascular accident.
MT because they refused the surgical treatment. All these patients were alive at the end of the 5-year follow-up. Initial revascularization was performed within 3 weeks of assigned treatment in 47% of the patients. The remaining 53% received the assigned treatment within 7 weeks (mean, 4 weeks).

Each patient who underwent CABG had an average of 3.3/0.8 vessels bypassed. All intended vessels were grafted in 74% of patients. At least 1 internal thoracic artery was used for grafting in 92% of patients, and the internal thoracic artery and radial artery were used in 36% of patients. The epigastric artery was used in 10% of patients.

The median hospital stay after CABG was 10 days. During the first-year follow-up, only 1 patient in this group underwent PCI, whereas 5 patients (2.5%) were referred for PCI and 2 patients (1%) underwent further CABG at the 5-year follow-up. Four (2%) and 17 (8.3%) had an uncomplicated MI at the 1- and 5-year follow-ups, respectively. At the 1-year follow-up, 8 patients (4%) died of MI and 3 other patients (1.5%) had a cerebrovascular accident, whereas 16 (7.9%) died of MI and 12 (5.9%) had a cerebrovascular accident at the 5-year follow-up. No patient in this group was lost to follow-up.

Percutaneous Coronary Intervention

Of the 205 patients assigned to the PCI group, 194 (95%) received the assigned treatment, 6 (3%) underwent CABG as their initial treatment, and 2 (0.98%) died before treatment. The deaths were due to automobile and occupational accidents. In addition, 3 patients (1.5%) received MT because they refused the PCI procedure; 2 of these patients were alive at the end of the 5-year follow-up.

Angioplasty as the initial revascularization was performed within 3 weeks (mean, 2.7 weeks) of treatment assignment in 70% of patients. Each patient who underwent PCI had an average of 2.1±0.7 vessels dilated. Multivessel PCI was performed in 147 patients (73%). Immediate angiographic success was achieved in 92% of patients in whom it was attempted; 62% of them received 2 or 3 stents, and only 11% received 1 stent, reaching a total of 72% of patients who received stents.

Complete revascularization (defined by successful intervention in all major vessels with ≥70% stenosis) was achieved in 41% of patients. Two additional patients (1.03%) in whom PCI was uncomplicated but unsuccessful were referred for elective CABG during the initial hospitalization; 2 patients (1.03%) required repeat PCI before discharge.

During the 1-year follow-up, 18 patients (8.8%) underwent further PCI and 7 (3.4%) underwent CABG, whereas 47 patients (22.9%) were referred for further PCI and 19 (9.3%) underwent CABG at the 5-year follow-up. Furthermore, in the 1-year follow-up, 9 patients (4.5%) died of MI, 16 patients (8.3%) had an uncomplicated Q-wave MI, and 2 had a cerebrovascular accident. On the other hand, at the 5-year follow-up, 24 patients (11.6%) died of MI, 23 (11.2%) had an uncomplicated Q-wave MI, and 7 (3.4%) had a cerebrovascular accident.

Event-Free Survival

The rates of event-free survival, namely the combined incidence of overall mortality, MI, or refractory angina requiring revascularization, were significantly different among patients in the 3 therapeutic groups (P=0.0026). Patients assigned to the PCI group had more events (113, 55.12%) than did those
in the MT (89, 43.41%) or CABG (30, 14.63%) group (Figure 1). The pairwise treatment comparisons of the primary end points demonstrated no difference between PCI and MT (relative risk [RR] 0.93; 95% confidence interval, 0.67 to 1.30). By using a multivariate logistic regression model and Cox analysis for proportional-hazards risk, we can demonstrate a significant protective effect for CABG compared with MT (RR, 0.53; 95% confidence interval, 0.36 to 0.77) and PCI (RR, 0.24; 95% confidence interval, 0.16 to 0.38).

Table 3 depicts the model adjusted for age, sex, smoking status, hypertension, MI, total cholesterol, high-density lipoprotein cholesterol, triglycerides, ejection fraction, diabetes mellitus, angina status, number of diseased vessels, positive treadmill test, and treatment allocation in the MASS II Study.

### Overall Mortality

No significant differences existed among the cumulative overall mortality curves associated with the 3 therapeutic strategies (Figure 2). Twenty-four deaths occurred in the PCI group, 16 in the CABG group, and 25 in the MT group (P=0.631). The cumulative survival rates at 5 years for patients assigned to each group were 88.44% for PCI, 92.12% for CABG, and 87.69% for MT.

### Additional Revascularization Procedures

The greatest difference among the groups was the frequency of additional interventions (surgery or angioplasty) required during the 5-year follow-up. Only 7 additional interventions (3.5%) were required among patients in the CABG group in contrast to 49 additional interventions (24.2%) required for patients in the MT group. Furthermore, 66 patients (32.5%) in the PCI group required additional intervention as a result of unstable angina (P<0.0001).

After 5 years of follow-up, additional surgical revascularizations had been performed in only 2 patients (0.98%) in the CABG group, 31 (15.3%) in the MT group, and 19 (9.3%) in

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**Table 3. Cox Proportional-Hazards Model for the Association Between Each End Point and Treatment Allocation in the MASS II Patients**

<table>
<thead>
<tr>
<th>Variables and Treatment</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/MT</td>
<td>0.92</td>
<td>0.46–1.86</td>
<td>0.8359</td>
</tr>
<tr>
<td>CABG/MT</td>
<td>0.79</td>
<td>0.43–1.43</td>
<td>0.4399</td>
</tr>
<tr>
<td>CABG/PCI</td>
<td>1.08</td>
<td>0.64–1.83</td>
<td>0.8595</td>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/MT</td>
<td>1.22</td>
<td>0.66–2.25</td>
<td>0.5085</td>
</tr>
<tr>
<td>CABG/MT</td>
<td>0.41</td>
<td>0.18–0.94</td>
<td>0.0366</td>
</tr>
<tr>
<td>CABG/PCI</td>
<td>0.37</td>
<td>0.13–1.07</td>
<td>0.0844</td>
</tr>
<tr>
<td>Additional intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/MT</td>
<td>0.90</td>
<td>0.58–1.40</td>
<td>0.6506</td>
</tr>
<tr>
<td>CABG/MT</td>
<td>0.13</td>
<td>0.05–0.32</td>
<td>0.0001</td>
</tr>
<tr>
<td>CABG/PCI</td>
<td>0.24</td>
<td>0.16–0.38</td>
<td>0.0155</td>
</tr>
<tr>
<td>Primary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI/MT</td>
<td>0.93</td>
<td>0.67–1.30</td>
<td>0.6981</td>
</tr>
<tr>
<td>CABG/MT</td>
<td>0.53</td>
<td>0.36–0.77</td>
<td>0.0010</td>
</tr>
<tr>
<td>CABG/PCI</td>
<td>0.24</td>
<td>0.16–0.38</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

AMI indicates acute MI; CI, confidence interval. Models were adjusted for age, gender, smoking status, hypertension, MI, total cholesterol, high-density lipoprotein cholesterol, triglycerides, ejection fraction, diabetes mellitus, angina status, number of diseased vessels, positive treadmill test, and treatment allocation in the MASS II study.

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![Figure 2. Probability of survival free of overall mortality among patients in the MT, CABG, and PCI treatment groups.](http://circ.ahajournals.org/)

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1086 Circulation March 6, 2007

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the PCI group ($P<0.0001$). In addition, during this period, 5 patients (2.4%) in the CABG group and 18 (8.9%) in the MT group underwent subsequent angioplasty compared with 47 (22.92%) in the PCI group ($P<0.0001$).

Next, the pairwise treatment comparisons of the secondary end points showed no difference in PCI versus MT (RR, 0.90; 95% confidence interval, 0.58 to 1.40) and a significant protector effect in CABG compared with MT (RR, 0.13; 95% confidence interval, 0.05 to 0.32) using Cox analysis for proportional-hazards risk.

**Secondary End Points**

Patients treated with angioplasty were most likely to be free of anginal symptoms after 5 years of follow-up. In contrast, a marked presence of anginal symptoms was observed among patients randomly assigned to the MT group. More specifically, 92 patients (54.8%) in the MT group were free of anginal symptoms after the 5-year follow-up compared with 126 (74.2%) in the CABG group and 119 (77.3%) in the PCI group. A statistically significant benefit was found in the CABG group compared with the MT group ($P<0.001$) and in the PCI group compared with the MT group ($P<0.001$) but not for the CABG group compared with the PCI group ($P=0.165$). None of the study patients in any treatment group had refractory angina (Canadian Cardiovascular Society class III or IV) at the end of follow-up; moreover, we observed a significant reduction in rates of positive tests for CABG (26.11%; $P<0.001$), no difference in PCI group (35.56%; $P=0.122$), and a significant increase in positive tests in the MT group (51.14%; $P<0.001$) at the end of follow-up.

**Discussion**

MASS II is the first randomized controlled clinical trial at a single institution to report on 5-year outcomes of patients with stable multivessel CAD treated with 1 of the 3 current therapeutic strategies: bare metal stenting, CABG, or MT alone. The present study has demonstrated no significant clinically relevant differences among the 3 therapeutic strategies in relation to cardiac-related death or total mortality. However, refractory angina requiring further revascularization was higher in the PCI compared with the CABG group and was similar to the rates for MT. Furthermore, the MT patients had less relief from symptomatic angina than patients who underwent CABG or PCI. Although a placebo effect related to the invasive nature of former modalities could not be ruled out, we should emphasize that these difference in angina status were paralleled by a highly significant reduction in the rate of objective ischemia in both CABG and PCI compared with MT. This trial also found a strong association between CABG and the protective effect against primary end points. CABG reached a significant 47% reduction in MI, death, or additional revascularization compared with MT, regardless of sex, smoking, cholesterol, need for medications, previous MI, ventricular function, hypertension, diabetes mellitus, angina status, and number of diseased vessels.

These findings differ from the meta-analysis of previous randomized trials of balloon angioplasty versus CABG conducted in patients with multivessel disease, which showed a significantly higher mortality rate with percutaneous treatment at 5 years. However, in the Bypass Angioplasty Revascularization Investigation study, the 5-year difference in mortality rate was not significant (10.7% for CABG compared with 13.7% for angioplasty). In the present study, which includes the MT strategy in multivessel patients eligible for revascularization by either CABG or PCI, we showed mortality rates of 7.9% in the CABG group, 11.6% in the PCI group, and 12.3% in the MT group at 5 years. The same results were observed in the Arterial Revascularization Therapies Study (ARTS), which compared bare metal stenting with CABG, even though the mortality rates in the PCI group were smaller (8%) than those in the MASS II PCI group. This difference in the PCI group could be due to the more serious clinical characteristics of our population, with a higher incidence of risk factors and a higher incidence of triple-vessel disease, with 93% of proximal left anterior descending coronary artery involvement, compared with the ARTS population (58% and 30%, respectively). Furthermore, in ARTS, the major adverse cardiac events were higher in the stent group, driven by the increased need for additional revascularization; similar results were found in MASS II.

The role of CABG surgery versus MT was assessed prospectively in a meta-analysis of the 3 major trials, as well as in some smaller trials that showed a significant survival benefit for patients with triple- or double-vessel CAD with or without abnormal left ventricular function. Moreover, CABG surgery compared with MT improved quality of life during the first 5 years of follow-up, but it was quite similar in 10 years of follow-up. On the other hand, modern medical therapeutics has evolved to offer patients a survival rate that is much higher than the natural history of their disease. Regarding drug therapy, none of the drugs (eg, β-blockers) have been shown to prolong life in patients with stable angina. Moreover, no evidence exists that PCI prolongs life. Yet, very little information is currently available from randomized controlled trials that include the medical strategy alone. In MASS II, CABG was superior to MT for relief of angina and less objective ischemia. Moreover, CABG reached an independent significant reduction in 44% of major adverse cardiac events compared with MT. These results provide evidence that improved perioperative management and intraoperative techniques over time result in a reduction in mortality compared with previous results of CABG trials in the 1970s, as well as these better outcomes compared with MT and PCI found in our study.

Although MASS II is underpowered to look at separate components of the primary end point, the occurrence of MI and additional interventions was significantly higher in the PCI and MT groups than in the CABG group, which provided a 59% and 86% reduction in risk of MI and additional interventions compared with MT. However, these results could be attributed to lack of the use of stents.
(28%) in patients in the PCI group. No differences existed between PCI and MT in these end points. As to the secondary end points, the occurrence of stroke was not significantly different among the 3 groups. Finally, a meta-analysis of 6 randomized controlled trials comparing PCI with MT showed that PCI significantly improved angina relief and short-term exercise tolerance but did not significantly reduce death, MI, or need for further revascularization.

In our study, the CABG patients achieved higher complete anatomic revascularization compared with PCI patients; however, the number of angina-free patients was similar between the 2 groups. These results might be related because of the further revascularization procedures in the PCI group, a high occlusion rate of vein and radial grafts in the CABG group, or even the progression of atherosclerosis.

Regarding the lower rate of complete revascularization in the PCI group, the recent 7-year outcome data from the Randomized Intervention Treatment Angina-2 trial do not support the concept that prophylactic dilatation of significant coronary stenoses regardless of symptoms or compelling evidence of ischemia reduces the risk of progression to coronary occlusion, prevents MI, or improves prognosis. Moreover, several trials comparing CABG with PCI for multivessel CAD addressed this issue, and all showed equivalent rates of MI and death. However, rates of repeat revascularization were higher in the PCI-treated patients; this finding was similar across the studies, regardless of whether a complete or incomplete revascularization was achieved. Conversely, we considered incomplete but functionally adequate revascularization in our patients who underwent PCI.

Finally, ongoing effort toward clarifying the role of PCI in the contemporary treatment of stable CAD is being addressed by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial. It is comparing aggressive MT alone with aggressive MT plus PCI during 3 to 7 years of follow-up in patients with documented myocardial ischemia. This trial also will be an important landmark trial that may clarify the best therapeutic approach for managing mild to moderate angina in patients with multivessel CAD.

Clinical Implications and Conclusions

The findings of MASS II strongly suggest that a routine strategy of PCI for patients with stable multivessel CAD is not superior to CABG surgery or MT and may be associated with lower rates of event-free survival, driven by the need for repeat revascularization. Most patients with mild to moderate angina can be safely managed medically, whereas PCI or CABG is appropriate if symptoms are not adequately controlled by medication or if other high-risk features are apparent. Therefore, clinicians should be restrained in their recommendations for both PCI and CABG, reserving the interventions for patients whose symptoms of angina are not well controlled on medical treatment.

It should be emphasized, however, that important developments in PCI have taken place since this trial was started. The use of glycoprotein IIb/IIIa antiplatelet agents, the long-term use of the oral antiplatelet agent clopidogrel, and the development and more widespread application of drug-eluting stents have significantly reduced restenosis and revascularization rates. In addition, surgery without cardiopulmonary bypass could have a significant effect on surgical results. Similarly, aggressive medical treatment and lifestyle prescriptions with comprehensive risk factor modification will also enhance the MT strategy.

In summary, the MASS II trial found no differences in cardiac-related death or overall mortality in patients treated with CABG, PCI, or MT during a 5-year follow-up. In our PCI group, incomplete revascularization might in all probability contribute to a significantly greater need for additional revascularization procedures in patients undergoing angioplasty. Our results also suggest that CABG surgery is an independent predictor of lower rates of event-free survival.

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Disclosures

None.

References

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In the article by Hueb et al, “Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS II): A Randomized Controlled Clinical Trial of 3 Therapeutic Strategies for Multivessel Coronary Artery Disease,” which appeared in the March 6, 2007 issue of the journal (Circulation. 2007;115:1082–1089), an error in the author listing occurred:

The name of author Luiz A.C. Machado should have appeared as “Luiz A.M. Cesar.”

The authors regret the error.

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