Effect of Complete Revascularization on 10-Year Survival of Patients With Stable Multivessel Coronary Artery Disease
MASS II Trial

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Background—The importance of complete revascularization remains unclear and contradictory. This current investigation compares the effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease (CAD) who were randomly assigned to percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

Methods and Results—This is a post hoc analysis of the Second Medicine, Angioplasty, or Surgery Study (MASS II), which is a randomized trial comparing treatments in patients with stable multivessel CAD, and preserved systolic ventricular function. We analyzed patients who underwent surgery (CABG) or stent angioplasty (PCI). The survival free of overall mortality of patients who underwent complete (CR) or incomplete revascularization (IR) was compared. Of the 408 patients randomly assigned to mechanical revascularization, 390 patients (95.6%) underwent the assigned treatment; complete revascularization was achieved in 224 patients (57.4%), 63.8% of those in the CABG group and 36.2% in the PCI group ($P=0.001$). The IR group had more prior myocardial infarction than the CR group (56.2% vs 39.2%, $P=0.01$). During a 10-year follow-up, the survival free of cardiovascular mortality was significantly different among patients in the 2 groups (CR, 90.6% versus IR, 84.4%; $P=0.04$). This was mainly driven by an increased cardiovascular specific mortality in individuals with incomplete revascularization submitted to PCI ($P=0.05$).

Conclusions—Our study suggests that in 10-year follow-up, CR compared with IR was associated with reduced cardiovascular mortality, especially due to a higher increase in cardiovascular-specific mortality in individuals submitted to PCI.


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Key Words: coronary revascularization ■ stable coronary artery disease ■ survival

The effect of complete revascularization in multivessel coronary artery disease (CAD) has been analyzed in multiple studies. The data suggest that more patients undergo complete revascularization in coronary artery bypass graft surgery (CABG) than in percutaneous coronary intervention (PCI). Theoretically, complete anatomic revascularization should promote greater protection of the myocardium. Although some studies have analyzed the outcomes of patients who have undergone complete or incomplete revascularization, the importance of complete revascularization remains unclear and contradictory.1–3

Data published come from registry studies or from randomized clinical trials. Registry studies suggest that incomplete revascularization is associated with an adverse impact on the long-term mortality of patients with multivessel disease who undergo PCI or CABG strategies.4–7 Nevertheless, randomized clinical trials indicate similar outcomes concerning myocardial infarction (MI) and mortality. Moreover, there is a lack of data from randomized clinical trials comparing the 2 therapeutic interventional strategies for long-term follow-up.8–10

This report is a post hoc analysis from 10 years of follow-up of the Second Medicine, Angioplasty, or Surgery Study (MASS II) trial. This current investigation compares the effect of complete revascularization in the long-term survival of patients with stable multivessel CAD who were randomly assigned to PCI or CABG.
Methods

Subjects
Details of the MASS II design, study protocol, patient selection, inclusion criteria, and general results have been previously published.11,12 Briefly, the MASS II study was a prospective, randomized, controlled clinical trial, designed to compare medical treatment (MT), angioplasty/stent placement (PCI), and surgical myocardial revascularization (CABG) with cardiopulmonary bypass in patients with stable multivessel CAD and preserved left ventricular function. The predefined primary end point was the combined incidence of overall mortality, MI, or persistent angina requiring revascularization. All data were analyzed according to the intention-to-treat principle. Patients with angiographically documented proximal multivessel coronary stenosis (>70% of stenosis) by visual assessment and documented ischemia were considered for inclusion. Patients were enrolled and randomly assigned if the surgeons, attending physicians, and interventional cardiologists agreed that revascularization could be attained by either strategy. Clinical criteria of exclusion included unstable angina or acute MI requiring emergency revascularization, ventricular aneurysm requiring surgical repair, left ventricular ejection fraction of <40%, a history of PCI or CABG, and single-vessel disease, and left main coronary artery stenosis of ≥50%. Patients also were excluded if they had another coexisting condition that was a contraindication to CABG or PCI. In this trial, all patients were placed on an optimal medical treatment for CAD.

Patients were randomly assigned to continue with MT alone or to undergo PCI or CABG concurrently with MT.

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.

Treatment Intervention
Complete revascularization was analyzed by anatomic revascularization definition. The coronary arteries were subdivided into 15 segments according to the American Heart Association/American College of Cardiology (AHA/ACC) criteria. All lesions occupying >50% diameter of a segment with a reference diameter of ≥1.50 mm were scored as potentially amenable to treatment. Trial operators were required to perform optimum coronary revascularization in accordance with current best practices. Equivalent and complete anatomic revascularization was encouraged but not mandatory.

For surgical patients, if all such defined segments had been treated according to the surgical report on the case-record form, the surgical procedure was scored as a complete revascularization. Complete anatomic revascularization was accomplished, if technically feasible, with internal mammary arteries, saphenous vein graft, and other conduits such as radial or gastroepiploic arteries. Standard surgical techniques and hypothermic arrest with blood cardioplegia were used. No off-pump CABG was performed.

For patients randomly assigned to stented angioplasty, both the diagnosis and procedural angiograms were reviewed. 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.

Follow-Up
Patients were assessed with follow-up visits every 6 months for 10 years at the Heart Institute. The vital status of each patient was ascertained on December 31, 2008; patients who had not completed 10 years of follow-up by that date were followed-up until they reached their 10-year visit.

Statistical Analysis
This post hoc analysis correlated overall death to the completeness of the revascularization after 10-year follow-up. An analysis was done on the patients who underwent the assigned treatment in the PCI or CABG group. Comparison was made on the overall death-free survival time of patients who underwent complete (CR) or incomplete revascularization (IR).

The overall death-free survival time was defined as the interval between random assignment and the occurrence of death or the latest follow-up. Overall death-free survival was estimated by the Kaplan-Meier method, and differences among groups were assessed by means of the log-rank test. Mean levels of continuous variables were compared by 1-way ANOVA, followed by the Tukey multiple-comparisons test. The Pearson χ² test was used to compare qualitative variables in the 2 groups. The Fisher exact test was used for categorical variables. The Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables were expressed as counts and percentages and composed in terms of relative risks with 95% confidence intervals. Tests were 2-tailed, and values of P<0.05 were considered statistically significant. Statistical analysis was performed with SAS 9.1 software (SAS Institute Inc, Chicago, IL).

Baseline Variables
A total of 611 eligible patients who had met all entry criteria were randomly assigned to 1 of 3 therapeutic strategies: CABG (n=203), PCI (n=205), or MT (n=203). The minimal duration of follow-up was 10 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.

Surgical Therapy
Each patient who underwent CABG had an average of 3.3±0.8 vessels bypassed. At least 1 internal thoracic artery

Table 1. Characteristics of the 611 Patients Assigned to MT, PCI, and CABG in the MASS II Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MT (n=203)</th>
<th>PCI (n=205)</th>
<th>CABG (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±9</td>
<td>60±9</td>
<td>60±9</td>
</tr>
<tr>
<td>Female, %</td>
<td>31</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>55</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Current or past smoker, %</td>
<td>33</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>MI, %</td>
<td>39</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td>Angina CCS class II or III, %</td>
<td>78</td>
<td>78</td>
<td>86</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.74±1.01</td>
<td>5.69±1.06</td>
<td>5.53±1.09</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.63±0.88</td>
<td>3.80±0.93</td>
<td>3.70±0.93</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.96±0.26</td>
<td>0.98±0.26</td>
<td>0.96±0.26</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.01±0.93</td>
<td>2.04±0.82</td>
<td>1.91±0.95</td>
</tr>
<tr>
<td>Positive treadmill test, %</td>
<td>47</td>
<td>33</td>
<td>56</td>
</tr>
<tr>
<td>Mean ejection fraction, %</td>
<td>68±7</td>
<td>67±8</td>
<td>67±9</td>
</tr>
<tr>
<td>Double-vessel disease, %</td>
<td>41</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Triple-vessel disease, %</td>
<td>59</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>LAD disease, %</td>
<td>89</td>
<td>93</td>
<td>93</td>
</tr>
</tbody>
</table>

MASS II indicates Second Medicine, Angioplasty, or Surgery Study; MT, medical treatment; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; CCS, 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 resting ECG. Unless otherwise indicated, data are mean±SD.
was used for grafting in 92% of the patients; the internal thoracic artery and radial artery were used in 36% of patients. The epigastric artery was used in 10% of patients. Of the 203 patients assigned to the CABG group, 198 (98%) received the assigned treatment. However, 4 received MT because they refused the surgical treatment, and 1 died before treatment. Of the 198 patients who underwent CABG, 143 (72.2%) received complete and 55 (27.8%) incomplete revascularization. During 10-year follow-up, of the 224 patients who received CR, 49 patients died (21.9%). Of the 166 patients who received IR, 44 patients died (26.5%). For cardiovascular specific mortality, from the 224 patients who received CR, 14 patients died (17.3%). Of the 111 patients who received IR, 29 patients died (26.1%). No patient in this group was lost to follow-up.

Percutaneous Coronary Therapy
Each patient who underwent PCI had an average of 2.1±0.7 vessels dilated; the mean value of vessels dilated was significantly different than the mean number of bypassed vessels (P<0.001). Multivessel PCI was performed in 147 patients (73%); 62% of them received 2 or 3 stents, and only 11% received 1 stent, reaching a total of 72% of patients who received stents.

Of the 205 patients assigned to the PCI group, 192 (93.7%) received the assigned treatment, 6 underwent CABG as their initial treatment, and 2 died before treatment. The deaths were due to automobile and occupational accidents. Furthermore, 3 patients received MT because they refused the PCI procedure. Besides these, in 2 additional patients, the PCI was uncomplicated but unsuccessful, and, because of this, they were referred for elective CABG during the initial hospitalization.

Of the 192 patients who underwent PCI, 81 (42.2%) received CR and 111 (57.8%) received IR. During 10-year follow-up, of the 81 patients who received CR, 14 patients died (17.3%). Of the 111 patients who received IR, 29 patients died (26.1%).

Complete Revascularization and Outcomes
For this study, we evaluated 390 patients; 198 patients underwent CABG and 192 underwent PCI. Complete revascularization was achieved in 224 patients (57.4%), 63.8% of those in the CABG group and 36.2% in the PCI group (P=0.001). Baseline demographic data and patient characteristics of subjects that underwent complete and incomplete revascularization are summarized in Table 2. The IR group had more previous MI than did the CR group (56.4%×41.4%, respectively; P=0.01). In addition, body mass index, left ventricular ejection fraction, and number of diseased vessels were also significantly different in a 4-group comparison. The other baseline data (age, sex, hypertension, smoking, and diabetes) were similar in both groups.

During 10-year follow-up, of the 224 patients who received CR, 49 patients died (21.9%). Of the 166 patients who received IR, 44 patients died (26.5%). For cardiovascular-specific mortality, from the 224 patients who received CR, 21 individuals died; of the 166 patients who received IR, 26 patients died (Figure 1, P=0.04). Interestingly, no difference was observed between complete and incomplete revascularization.
ization in the CABG group (CR, 15 individuals died \times IR, 6 individuals died), but a statistically significant difference was observed for the PCI group (CR, 6 individuals died \times IR 20 individuals died) (Figure 2, $P < 0.05$). In accordance to what was observed in the stratified analysis, in a multivariate Cox proportional hazards model adjusted for completeness of revascularization, randomization (CABG/PCI), age, smoking status, and body mass index, the interaction term randomization type \times completeness of revascularization was statistically significant (Table 3, $P = 0.03$).

**Discussion**

MASS II is the first randomized, controlled clinical trial to analyze the effect of complete revascularization on 10-year survival of patients with stable multivessel CAD treated with bare metal stents (BMS) or CABG. The present study demonstrates that complete revascularization promotes an improvement in survival free of cardiovascular mortality, and this benefit is independent of the therapeutic strategy used.

This finding differs from previous post hoc analyses of randomized clinical trials, which showed a similar outcome, or at most, a significantly higher subsequent revascularization. In fact, in the Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), completeness of revascularization was an independent predictor of combined end points (death and Q-wave MI). However, this analysis was selected in the minority of randomly assigned patients (21.2%) with a major vessel chronically occluded. The potential benefit of complete revascularization on long-term mortality in patients with multivessel CAD, undergoing PCI, or CABG was demonstrated in registry studies. Recently, Hannan et al analyzed, from the New York State’s Percutaneous Coronary Interventions Report System (PCIRS), the impact of complete revascularization in more than 33 000 patients who underwent PCI with BMS or drug-eluting stents (DES). In BMS, after adjustment for the baseline differences, IR patients were significantly more likely to die at 3-year follow-up than CR patients (adjusted hazard ratio, 1.15; 95% confidence interval, 1.01–1.30). In DES, IR was associated with higher 18-month mortality (adjusted hazard ratio, 1.23; 95% confidence interval, 1.04–1.45). Nevertheless, these published reports have suffered sharp criticism because the data come from a database created from the registry. This fact raises doubts about the real significance of the results, as was asked in an editorial titled “The Dueling Hazards of Incomplete Revascularization and Incomplete Data.”

**Table 3. Multivariate Cox Proportional Hazards Model for Cardiac Mortality**

<table>
<thead>
<tr>
<th></th>
<th>$P$ Value</th>
<th>RR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;0.01</td>
<td>1.08</td>
<td>1.04</td>
<td>1.13</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.13</td>
<td>1.89</td>
<td>0.84</td>
<td>4.25</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>0.25</td>
<td>1.53</td>
<td>0.75</td>
<td>3.13</td>
</tr>
<tr>
<td>Smoker, * %</td>
<td>0.04</td>
<td>2.10</td>
<td>1.03</td>
<td>4.26</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.85</td>
<td>0.99</td>
<td>0.90</td>
<td>1.09</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>0.41</td>
<td>1.33</td>
<td>0.67</td>
<td>2.65</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.17</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>MI</td>
<td>0.98</td>
<td>1.01</td>
<td>0.51</td>
<td>1.99</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.92</td>
<td>0.95</td>
<td>0.36</td>
<td>2.50</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>0.46</td>
<td>0.77</td>
<td>0.38</td>
<td>1.55</td>
</tr>
<tr>
<td>Received revascularization (CABG)</td>
<td>0.05</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Revascularization completeness (complete)</td>
<td>0.06</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>1.25</td>
</tr>
<tr>
<td>Received revascularization (CABG) times revascularization completeness (complete)</td>
<td>0.03</td>
<td>7.29</td>
<td>1.18</td>
<td>44.91</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval; BMI, body mass index; MI, myocardial infarction; CABG, coronary artery bypass graft surgery.

$P$ values are for 4-group comparison.

*Current or past smoker.
One of the limitations in interpreting the results of complete revascularization studies is that analyses are made after the unsuccessful attempt at complete revascularization. Usually, secondary to this, a bias in patient selection is present, with IR patients presenting more severe disease. In this study, the baseline demographic data and characteristics of the patients who underwent complete and incomplete revascularization were very similar. The main difference was related to previous MI. The IR group had more prior MI than did the CR group (56.2% versus 39.2%, respectively; \( P = 0.01 \)). The explanation for this baseline difference is based on the definition of complete revascularization. Different definitions have been adopted in the literature for complete revascularization. The comprehensive classification criteria of complete myocardial revascularization take into account 3 variables: the size of the vessel, the severity of the lesion, and the viability of the myocardial territory. Thus, the definitions are complete anatomic revascularization; incomplete anatomic but complete functional revascularization, that is, the revascularization of all coronary segments with >50% diameter stenosis that supply viable myocardium; and incomplete functional revascularization. Criteria for incomplete but functionally adequate anatomic revascularization explain the baseline difference, concerning prior MI, between the incomplete and complete revascularization groups.

Another topic of discussion is the successful rate for achieving complete revascularization in each therapeutic strategy. We demonstrated that more patients undergo complete revascularization in CABG than in PCI (63.8% versus 36.2%, respectively; \( P = 0.001 \)). Our data are similar to that in previous publications. The major cohort of surgery patients is from the Coronary Artery Surgery Study (CASS) registry. This retrospective analysis of 3372 non-randomly assigned patients demonstrated that complete revascularization, namely as grafts to 3 or more vessels, was achieved in 66.4%. An interesting finding is the lower rate of complete revascularization in the PCI group (36.2%). This finding is different from that of the Bypass Angioplasty Revascularization Investigation (BARI) and Arterial Revascularization Therapies Study (ARTS) trials, in which the rates were 64% and 76%, respectively.\(^{10,16}\) The explanation for this difference is patient baseline characteristics (severity of coronary artery disease). In the MASS II trial, 42% of patients had double-vessel disease, 58% had triple-vessel disease, and 92% had proximal left anterior descending involvement. On the other hand, in BARI and ARTS trials, respectively, 59% and 68% of patients had double-vessel disease and 41% and 32% had triple-vessel disease. The number of treated coronary segments was quite similar in these 3 trials: 2.1 in MASS; 2.4 in BARI; and 2.6 in the ARTS trial.

Final Considerations

The influence of incomplete revascularization on outcomes remains a controversial question. On the one hand, as several studies have reported, no differences in early morbidity and mortality were found among patients that underwent complete or incomplete revascularization. On the other hand, other experiences suggest a negative effect of incomplete revascularization on survival. In this scenario, our analysis showed that complete revascularization is associated with reduced long-term cardiovascular mortality compared with incomplete revascularization. This difference was dependent of the therapeutic revascularization strategy and was only observed in the PCI group.

There are many explanations for failure to achieve complete revascularization after PCI or CABG. In principle, complete revascularization is anticipated when patients undergo surgical revascularization. However, at the time of surgery, factors such as a lack of suitable conduits or the presence of small native vessels may become apparent and make it unsuccessful to achieve complete revascularization. On the other hand, incomplete percutaneous revascularization may not deliberately occur after a failed attempt to open a calcified or chronic occluded vessel. As a limitation of this study, we must consider that the patient cohort that was enrolled had stable symptoms and preserved left ventricular function and was thus a low-risk population.

This report complements the evidence of recent studies that have demonstrated that surgical revascularization, in patients with complex anatomy and high SYNTAX score, is a more appropriate revascularization method than PCI.

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Disclosures

None.

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