Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circulation published online Aug 23, 2010;
DOI: 10.1161/CIRCULATIONAHA.109.911669
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Ten-Year Follow-Up Survival 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*—**This study compared the 10-year follow-up of percutaneous coronary intervention (PCI), coronary artery surgery (CABG), and medical treatment (MT) in patients with multivessel coronary artery disease, stable angina, and preserved ventricular function.

***Methods and Results*—**The primary end points were overall mortality, Q-wave myocardial infarction, or refractory angina that required revascularization. All data were analyzed according to the intention-to-treat principle. At a single institution, 611 patients were randomly assigned to CABG (n=203), PCI (n=205), or MT (n=203). The 10-year survival rates were 74.9% with CABG, 75.1% with PCI, and 69% with MT (P=0.089). The 10-year rates of myocardial infarction were 10.3% with CABG, 13.3% with PCI, and 20.7% with MT (P<0.010). The 10-year rates of additional revascularizations were 7.4% with CABG, 41.9% with PCI, and 39.4% with MT (P<0.001). Relative to the composite end point, Cox regression analysis showed a higher incidence of primary events in MT than in CABG (hazard ratio 2.35, 95% confidence interval 1.78 to 3.11) and in PCI than in CABG (hazard ratio 1.85, 95% confidence interval 1.39 to 2.47). Furthermore, 10-year rates of freedom from angina were 64% with CABG, 59% with PCI, and 43% with MT (P<0.001).

***Conclusions*—**Compared with CABG, MT was associated with a significantly higher incidence of subsequent myocardial infarction, a higher rate of additional revascularization, a higher incidence of cardiac death, and consequently a 2.29-fold increased risk of combined events. PCI was associated with an increased need for further revascularization, a higher incidence of myocardial infarction, and a 1.46-fold increased risk of combined events compared with CABG. Additionally, CABG was better than MT at eliminating anginal symptoms.

***Clinical Trial Registration Information*—**URL: http://www.controlled-trials.com. Registration number: ISRCTN66068876.

(*Circulation*. 2010;122:949-957.)

Key Words: angioplasty ■ bypass ■ drugs ■ heart diseases ■ surgery

Management of patients with stable multivessel coronary artery disease (CAD) and preserved ventricular function remains controversial. Treatments include medical therapy (MT), percutaneous coronary intervention (PCI), and coronary bypass grafting (CABG), all of which are used in conjunction with aggressive secondary prevention. Compared with treatment with CABG, several randomized trials have shown that treatment with PCI or MT is associated with higher rates of angina and subsequent revascularization, but no significant differences in mortality or rates of myocardial infarction (MI) have been found.[1–4] None of the cited studies, however, have evaluated end points for more than a 5-year follow-up period.

Editorial see p 943
Clinical Perspective on p 957

The second Medical, Angioplasty, or Surgery Study (MASS II)[5] is a single-center study designed to compare the long-term effects of MT, angioplasty, or surgical strategies among patients with stable angina symptoms of multivessel CAD and preserved ventricular function who are appropriate candidates for all 3 therapies. This study found that all 3

Received September 24, 2009; accepted June 1, 2010.

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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.109.911669

therapeutic regimens had similar rates of death at 5-year follow-up. No significant differences were found between MT and PCI in the combined end points of MI, additional revascularization, and overall mortality. CABG was superior to MT for the combined end points, although the difference in mortality was nonsignificant.

This superiority was reflected in a significant 47% risk reduction in the incidence of primary end points during 5 years of follow-up of patients with stable multivessel CAD ($P<0.001$, 95% confidence interval [CI] 0.36 to 0.77).[5] In the present report, we present the 10-year results of MT compared with surgical and percutaneous interventions with regard to survival, nonfatal MI, repeat revascularization, and anginal symptoms in patients from the MASS II trial.

Methods

Patient Selection

Briefly, patients with angiographically documented proximal multivessel coronary stenosis of more than 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.[6]

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 in 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 that required emergency revascularization, ventricular aneurysm that required surgical repair, left ventricular ejection fraction <40%, a history of PCI or CABG, single-vessel disease, and normal or minimal CAD. Patients were also 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% or more, 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 at baseline until the end of follow-up. This regimen consisted of a titrated approach with nitrates, aspirin, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs unless contraindicated. Lipid-lowering agents, particularly statins, were also prescribed, along with a low-fat diet, on an individual basis. The medications were provided without charge by the Heart Institute. Patients were then randomized to continue with aggressive MT alone or to undergo PCI or CABG concurrently with MT.

Researchers were required to perform optimum coronary revascularization in accordance with current best practice. Equivalent anatomic revascularization was encouraged but not mandatory.

For patients assigned to PCI, the procedures were available within 3 weeks after randomization. Devices used for catheter-based therapeutic strategies included stents, lasers, directional atherectomy, and balloon angioplasty. Angioplasty was performed according to a standard protocol.[7] 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 TIMI (Thrombolysis In Myocardial Infarction) flow grade 3.

For patients assigned to CABG, the procedures were available 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[8] 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 10 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 with documentation of 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 electrocardiography 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.[9]

Symptoms of angina were graded according to severity from 1 to 4 as defined previously.[10] Angina was considered refractory only when patients had been treated with full antiischemic 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 fraction concentrations that were more than 3 times the upper limit of the reference range.

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. The MASS II study ceased following up patients in May 2010.

The predefined primary end points were the incidence of total mortality, Q-wave MI, or refractory angina that required revascularization for patients in any of the 3 treatment groups. Secondary end points included angina status, death due to a cardiac cause, and a cerebrovascular accident. A priori subgroups specified by the MASS II protocol included sex, age, history of previous MI, hypertension, diabetes mellitus, and smoking status.

Statistical Analysis

All data were analyzed according to the intention-to-treat principle. Primary end-point event rates were assumed to be the events of overall death, acute MI, and angina that required mechanical revascularization (PCI or CABG). The event-free (combined end point) survival time was defined as the interval between random assignment and the first occurrence of 1 of the components of a primary end point or the latest follow-up.

Event-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 χ^2 test was used to compare qualitative variables among the 3 groups. Cox regression with model-robust standard errors (as implemented under the SAS PHREG routine) was used to compare survival time with combined primary end points and with each of the components of the primary end points between the different pairwise treatment groups. Multivariate analysis was also performed, adjusted for age, sex, diabetes mellitus, hypertension, treatment allocation, previous MI, smoking status, number of diseased vessels, and total cholesterol level (variables known to be related to poor outcomes). We performed subgroup analyses of assigned treatment with baseline characteristics using Cox regression. The percentage of positive tests between baseline and 10-year follow-up in each group was evaluated with the McNemar test. Tests were 2-tailed, and values of $P<0.05$ were considered statistically significant, except for the treatment comparisons within identified subgroups, in which $P<0.01$ was used to control for multiple comparisons. Statistical analysis was performed with SAS 9.1 software (SAS Institute Inc, Chicago, Ill).

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

Characteristics	MT (n=203)	PCI (n=205)	CABG (n=203)	P
Demographic variables				
Age, y	60±9	60±9	60±9	0.959
Female, %	31	33	28	0.412
Current or past smoker, %	33	27	32	0.013
Clinical history and status, %				
History of MI	39	52	41	0.024
History of hypertension	55	61	63	0.215
Treated diabetes mellitus	36	23	29	0.062
Stable angina class II or III	78	78	86	0.006
Laboratory values, mmol/L				
Total cholesterol	5.74±1.01	5.69±1.06	5.53±1.09	0.063
LDL cholesterol	3.83±0.88	3.80±0.93	3.70±0.93	0.305
HDL cholesterol	0.96±0.26	0.98±0.26	0.96±0.26	0.870
Triglycerides	2.01±0.93	2.04±0.82	1.91±0.95	0.235
Positive treadmill test, %	47	33	56	0.705
Angiographic profile				
Mean ejection fraction, %	68±7	67±8	67±9	0.984
Double-vessel disease, %	41	42	42	0.980
Triple-vessel disease, %	59	58	58	0.980
Proximal LAD disease, %	89	93	93	0.312

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and LAD, left anterior descending coronary artery.

Some patients had both angina and positive treadmill tests. Unless otherwise indicated, data are mean±SD.

Results

Characteristics of the Patients and Treatment Assignments

Between May 1995 and May 2000, 611 eligible patients who met all entry criteria were randomly assigned to 1 of 3 therapeutic strategies: PCI, MT, or CABG. The vital status of all randomly assigned patients was ascertained in December 2008. For patients still alive, the minimum length of follow-up was 9 years, and the maximum was 15 years (average 11.4 years). Randomization created balanced treatment groups with respect to important prognostic characteristics, except for angina status, previous MI, and smoking status, as shown in Table 1. All patients received medical regimens according to a predefined approach.

Table 2. Major Adverse Cardiac Events at 10-Year Follow-Up

	PCI	MT	CABG	P (Log-Rank)
Primary end points	42.4	59.1	33.0	<0.001
Overall mortality	24.1	31.0	25.1	0.089
Cardiac death	14.3	20.7	10.8	0.019
Additional intervention	41.9	39.4	7.4	0.001
AMI	13.3	20.7	10.3	0.010
CVA	5.4	6.9	8.4	0.550

AMI indicates acute MI; CVA, cerebrovascular accident.
Values are percentages.

Treatment Outcomes

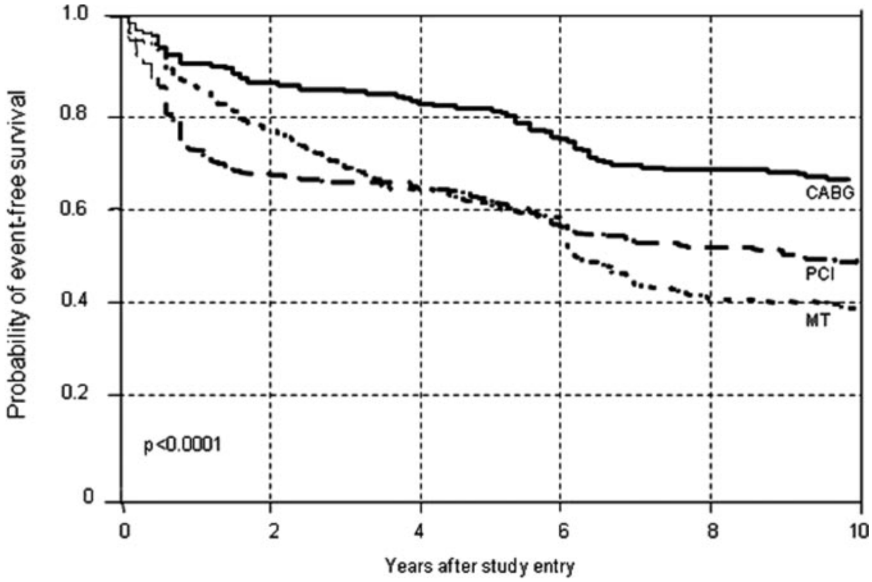
The overall major adverse cardiac and cerebrovascular events at the 10-year follow-up according to 1 of 3 therapeutic strategies are shown in Table 2. No patients were lost to follow-up in any of the 3 study groups.

Event-Free Survival

The rates of event-free survival, namely, the combined incidence of overall mortality, MI, or refractory angina that required revascularization, were significantly different among patients in the 3 therapeutic groups at 5-year ($P=0.0026$) and 10-year ($P<0.0001$) follow-up (Figure 1). Pairwise treatment comparisons of the primary end points at 5-year follow-up demonstrated no significant difference between PCI and MT (hazard ratio [HR] 0.93, 95% CI 0.67 to 1.30). At 10-year follow-up, this comparison also demonstrated a nonsignificant difference between the PCI and MT groups (HR 0.79, 95% CI 0.62 to 1.01). After multivariate Cox analysis at 10-year follow-up, a protective effect of CABG compared with MT (HR 0.43, 95% CI 0.32 to 0.58, $P<0.001$) and PCI (HR 0.53, 95% CI 0.39 to 0.72, $P<0.001$) was observed. The protective effect at 10-year follow-up is shown in Figure 2 for CABG compared with MT, in Figure 3 for CABG compared with PCI, and in Figure 4 for PCI compared with MT. Table 3 depicts the model adjusted for age, sex, smoking status, hypertension, previous MI, total cholesterol, diabetes mellitus, angina status, number of diseased vessels, and treatment allocation in the MASS II trial at 10-year follow-up.

Overall Mortality

No significant statistical differences existed among the cumulative overall mortality curves associated with the 3 therapeutic strategies by either 5- or 10-year follow-up. Twenty-four deaths occurred in the PCI group, 16 in the CABG group, and 25 in the MT group at 5-year follow-up ($P=0.824$). At 10-year follow-up, 49 deaths had occurred in the PCI group, 51 in the CABG group, and 63 in the MT group ($P=0.089$). The cumulative survival rates at 10 years for patients assigned to each group were 74.9% for PCI, 75.1% for CABG, and 69.0% for MT (Figure 5). No evidence was found of a treatment-time interaction, ie, the proportional hazards assumption was not violated. In addition, univariate and multivariate Cox regression models did not reveal a higher overall mortality at 10-year follow-up associated with randomization to MT (Table 3).



Patients at risk

Treatment Group	Initial	3 Year	6 Year	10 Year
CABG	203	175	155	150
PCI	205	147	130	108
MT	203	140	121	93

Figure 1. Probability of event-free survival (free of overall mortality, unstable angina that required revascularization, or Q-wave MI) among patients in the MT, CABG, and PCI treatment groups.

Nonfatal MI

CABG was significantly superior to PCI and MT at 10-year (P=0.016) but not 5-year (P=0.785) follow-up, with a lower incidence of nonfatal MI; 17 (8.3%) and 21 patients (10.3%) had an uncomplicated MI at 5- and 10-year follow-up, respectively, in the CABG group. In the PCI arm, 23 (11.2%) and 27 patients (13.2%) had an uncomplicated MI at 5 and 10 years, respectively. In the MT group, 31 (15.3%) and 42 (20.7%) had an uncomplicated or nonfatal MI during the 5- and 10-year follow-up, respectively.

Additional Revascularization Procedures

The greatest difference among the groups was the frequency of additional mechanical interventions (surgery or angioplasty) required during the 5- and 10-year follow-ups. At 5-year follow-up, 7 additional interventions (3.4%) were required in patients in the CABG group compared with 49 additional interventions (24.1%) required for patients in the MT group. Furthermore, 66 patients (32.2%) in the PCI group required additional interventions as a result of angina (P=0.021). At 10-year follow-up, 15 further interventions (7.4%) were required among patients in the CABG group compared with 85 additional interventions (41.5%) required for patients in the PCI group. In all, 80 patients (39.4%) in the MT group required an additional mechanical intervention due to the presence of uncontrolled angina (P<0.001).

After 10-year follow-up, additional surgical revascularizations had been performed in only 3 patients (1.5%) in the CABG group, 51 (25.1%) in the MT group, and 27 (13.2%) in the PCI group (P<0.001). Moreover, during this period, 12 patients (5.9%) in the CABG group and 29 (14.3%) in the MT group underwent subsequent angioplasty compared with 58 (28.3%) in the PCI group (P<0.001).

Subgroup Analyses

The effect of treatment on 10-year event-free survival was not changed by clinical characteristics of PCI versus CABG (Figure 3). We were not able to detect particular subgroups in which the overall effect of treatment allocation was not present when we compared MT versus CABG (Figure 2). On the other hand, we did disclose an effect of treatment (MT versus PCI) on specific subgroups. Younger patients suffering from the history of hypertension and females, had a higher risk of combined events in MT than patients who underwent PCI (Figure 4).

Secondary End Points

Patients treated with surgery were most likely to be free of angina symptoms after 10 years of follow-up. In contrast, a significant persistence of angina symptoms was observed among patients randomly assigned to the MT group. Specifically, 88 patients (43%) in the MT group were free of angina symptoms after the 10-year follow-up compared with 130 (64%) in the CABG group and 120 (59%) 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 there was no significant difference among the CABG and PCI groups. None of the study patients in any treatment group had refractory angina at the end of follow-up; on the other hand,

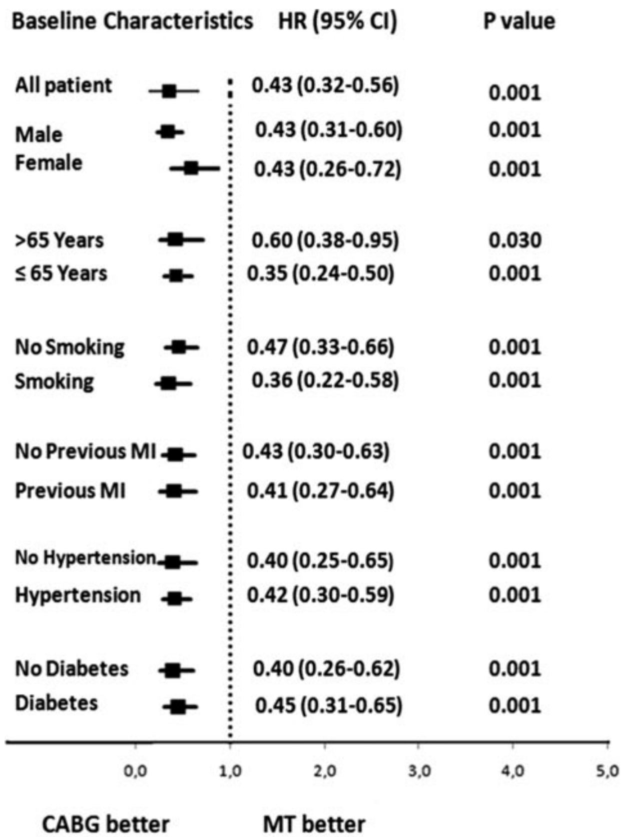


Figure 2. HRs measuring association between composite end point and treatment allocation: CABG vs MT.

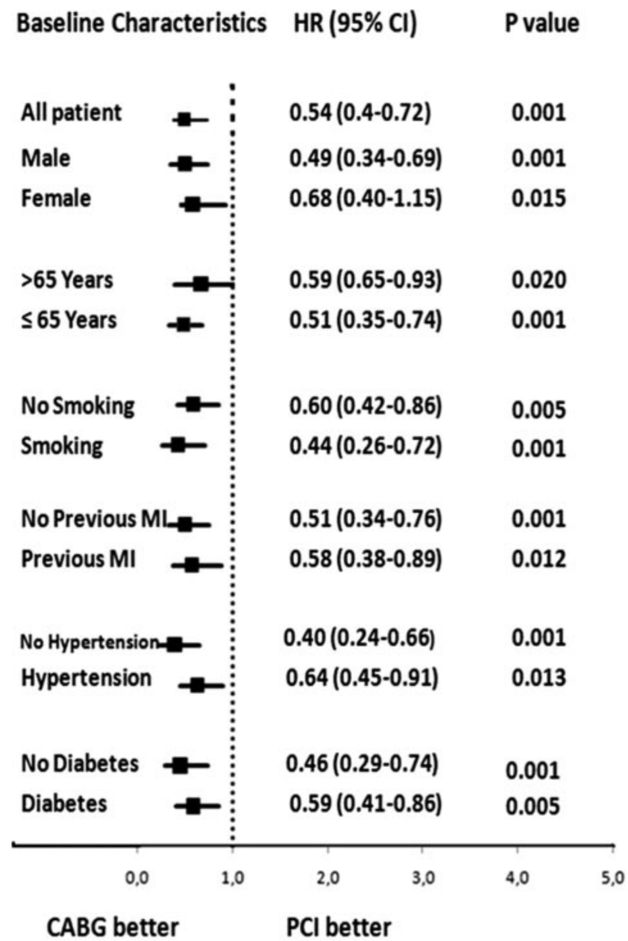


Figure 3. HRs measuring association between composite end point and treatment allocation: CABG vs PCI.

we observed a significant reduction in rates of positive stress tests for CABG (56% to 30%, $P<0.001$), no significant difference in the PCI group (33% to 36%, $P=0.912$), and a significant increase in positive tests in the MT group (47% to 51%, $P<0.001$) comparing baseline with the end of follow-up, respectively.

Relative to cardiac death, 42 (20.7%), 22 (10.8%), and 29 patients (14.1%) had died of MI in the MT, CABG, and PCI groups by 10-year follow-up, respectively ($P=0.019$). Finally, the incidence of stroke was similar for the 3 treatment strategies at the end of the study ($P=0.550$): 14 patients (6.9%) in the MT, 17 (8.4%) in the CABG, and 11 (5.4%) in the PCI group had had a cerebrovascular accident by 10-year follow-up.

Discussion

MASS II is the first randomized controlled clinical trial with unique long-term outcome data from a single institution to report on 10-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 data from the 10-year outcomes show that compared with CABG, MT was associated with a significantly higher incidence of combined events, cardiac death, and subsequent MI and a higher rate of additional revascularization. PCI was associated with an increased need for further revascularization, a higher incidence of MI, and a 1.85-fold increased risk of combined events compared with CABG. No statistically significant difference ($P=0.220$) was found in overall mortality with these 3 treatment options, although the present study was not specifically designed to detect a difference in 10-year mortality. Additionally, CABG was better than MT at eliminating anginal symptoms.

Thus, the 10-year follow-up data from MASS II do not confirm our prior observation from the 5-year follow-up relative to cardiac death and MI. A routine strategy of initial MT for patients with stable multivessel disease is associated with a significant reduction of event-free survival during the 10-year follow-up compared with revascularization procedures. This suggests the MT strategy may be considered as an initial strategy in this subset of patients; however, an interventional procedure may be necessary during follow-up.

Although there is some evidence from a meta-analysis that suggests a lower 5-year mortality rate with CABG in patients with multivessel disease compared with PCI,[11,12] this was not the case in the most complete meta-analysis of individual patient data from 10 randomized trials (except for patients with diabetes and those 65 years old or older)[13,14] or in the Bypass Angioplasty Revascularization Investigation (BARI; with the exception of diabetic patients)[15] or the MASS II trial, which included an MT arm, in which the cumulative survival rates were 88.44%, 92.12%, and 87.69% for the PCI, CABG, and MT groups, respectively ($P=0.631$), at 5-year follow-up.[5]

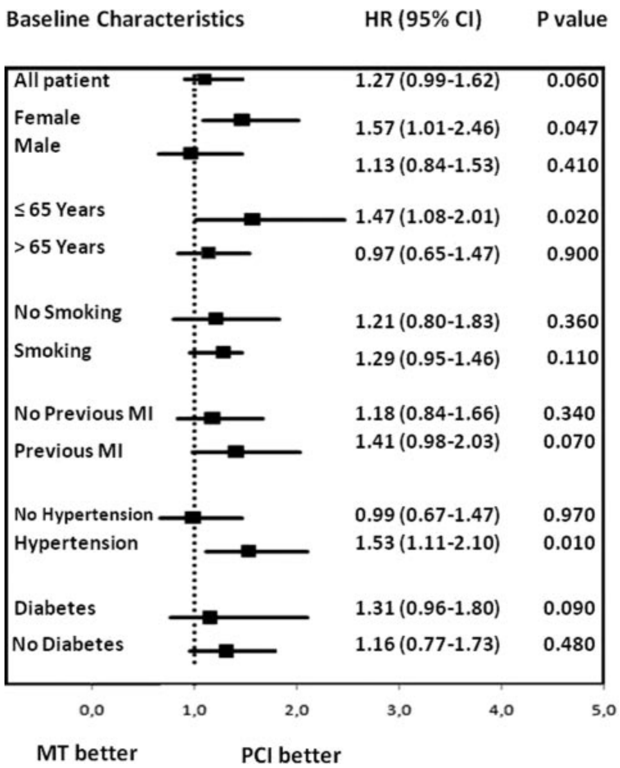


Figure 4. HRs measuring association between composite end point and treatment allocation: MT vs PCI.

We cannot rule out that the lack of power perhaps had an impact on this negative result; however, given the observed 10-year mortality rate in MASS II, more than 7200 patients would be required to participate in the study for it to have sufficient power to detect a 3% absolute difference in overall mortality, which reflects the challenge of conducting clinical trials.

The only other 10-year follow-up study comparing MT and CABG is the Coronary Artery Surgery Study (CASS), which also showed no difference in cumulative survival rates in patients with mild stable angina and normal left ventricular function (84% in MT versus 83% in CABG, $P=0.75$) and a longer event-free survival (MI and death; 75% versus 64%, $P=0.04$) with MT than with CABG.[16] The reason for the relatively higher survival rates in the CASS trial compared with the present results (69% in MT versus 75% in the CABG group) may be attributable to less severe CAD in this subset of the CASS study than in the MASS II trial or to the effect of newer revascularization techniques (the higher mortality and MI in the CASS CABG group was due to early postoperative MI and progressive graft occlusion after 4 to 5 years, which resulted from atherosclerosis in aortocoronary saphenous vein grafts; only 16% of conduits were mammary artery grafts compared with 92% in the present study) and MT that, as a whole, may have significantly changed the overall pattern of the incidence of events in this subset of patients.

The 10-year follow-up data of CABG versus PCI from MASS II were consistent with data from the BARI study in regard to overall mortality and subsequent mechanical revascularization, excluding cardiac-related death and MI.[15] In the BARI trial, the 10-year difference in survival rates was not statistically significant (73.5% for CABG compared with 71% for PCI, $P=0.18$).[2] The present study showed 10-year survival rates of 74.9% in the CABG group, 75.1% in the PCI group, and 69% in the MT group ($P=0.089$); however, the pairwise comparison analysis showed a significant 2.02- and 2.77-fold increased risk of cardiac death and subsequent MI with MT versus CABG, which demonstrates the better long-term prognosis of surgical patients, and it also showed that this treatment effect was not modified by other clinical characteristics that also had an impact on event rates. CABG patients also required fewer additional myocardial revascularizations than did patients in the PCI or MT groups, which confirms the superiority of CABG over PCI with regard to the need for subsequent mechanical revascularization. Yet, patients who underwent PCI had a higher incidence of MI in the long-term follow-up, a finding not observed at the 5-year follow-up or in the BARI 10-year results. Perhaps this discrepancy could be explained by the characteristics of the present study population, with a higher-risk prognosis. Finally, the MASS II trial found a strong protective association between CABG and the composite primary end point compared with MT and PCI.

Next, the subgroup analysis showed that treatment effect was not changed greatly by clinical characteristics at baseline. Nevertheless, this analysis suggests that the effect of treatment on risk of combined events may somehow be altered by some characteristics. In this sense, the effect of the lower risk of PCI versus MT was mainly observed in younger patients, patients with a history of hypertension, and female patients. These findings may point toward the effectiveness of coronary revascularization with regard to specific subgroups with clinical characteristics, especially in the PCI arm, which should be examined in further studies.

The lower rate of repeat mechanical revascularization procedures and MI in the CABG group is understandable on the basis of both clinical and anatomic arguments. Atherosclerosis is a progressive and diffuse disease, whereas PCI is directed against a target or "culprit" lesion or lesions. CABG bypasses most epicardial vessels and, as such, can provide protection at least in the intermediate term against disease progression involving "future" culprits.[17] Also, complete revascularization is more often accomplished by CABG than by PCI, as observed in the BARI trial (91% versus 51%)[17] and in the present study (74% versus 41%).[6] This could explain why CABG patients had fewer additional myocardial revascularizations than PCI or MT patients had.

Although complete revascularization is a desirable goal, the majority of the evidence would suggest that as long as the left anterior descending coronary artery is grafted, the impact of complete versus incomplete revascularization on the hard end points of death and/or MI or additional revascularization is small.[18,19] In the present study, even though the extent of the completeness of anatomic revascularization was initially greater in patients undergoing CABG, the frequency of angina at late follow-up was similar between the 2 groups. The reasons for the lack of any difference in symptoms may be multifactorial and could include "cross-overs" and the high rate of further revascularization in the PCI arm, a high occlusion rate of vein and radial grafts in the CABG group, and the impact of progressive diffuse coronary disease.[20] Yet,

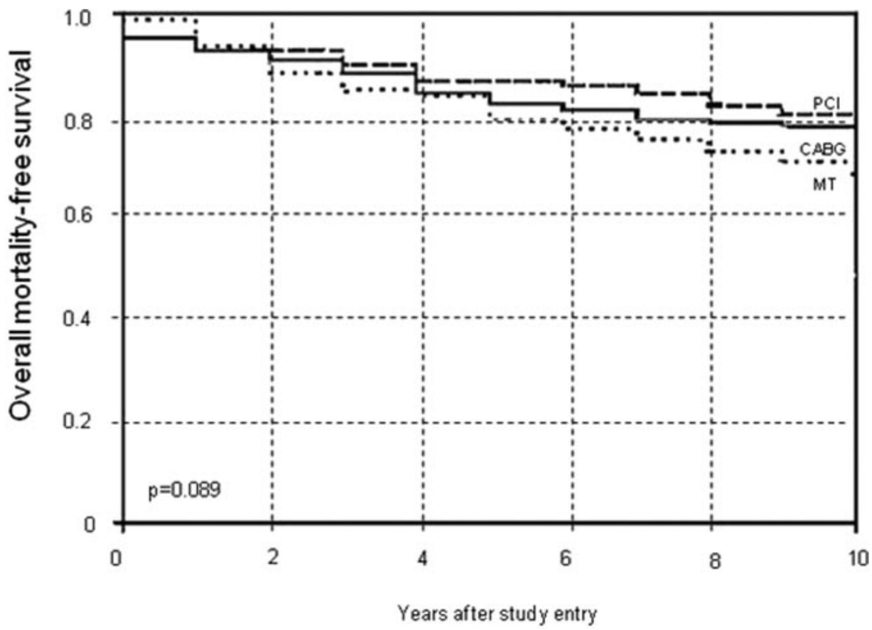
Table 3. Cox Regression for Association Between Each End Point and Treatment Allocation in the MASS II 10-Year Report

Variables and Treatment	Univariate HR	95% CI	*P*	Multivariate HR	95% CI	*P*
Primary end points						
Treatment			0.001*			<0.001*
PCI/CABG	1.85	1.39–2.47	0.001	1.46	1.06–2.02	0.021
MT/CABG	2.35	1.78–3.11	0.001	2.29	1.69–3.10	<0.001
Age (>65/<65 y)	1.40	1.10–1.79	0.007			
Diabetes mellitus	1.22	0.96–1.56	0.101			
Hypertension	1.36	1.06–1.74	0.015			
Previous MI	1.17	0.92–1.48	0.208			
Overall death						
Treatment			0.220*			0.241*
PCI/CABG	0.91	0.62–1.35	0.650	0.97	0.65–1.44	0.878
MT/CABG	1.25	0.87–1.81	0.230	1.29	0.89–1.87	0.175
Age (>65/<65 y)	2.20	1.62–2.99	0.001			
Diabetes mellitus	1.47	1.08–2.01	0.013			
Hypertension	1.41	1.02–1.95	0.039			
Previous MI	1.15	0.85–1.56	0.373			
Cardiac death						
Treatment			0.029*			0,026*
PCI/CABG	1.28	0.74–2.23	0.377	1.34	0.77–2.34	0.289
MT/CABG	1.94	1.16–3.26	0.011	1.99	1.19–3.35	0.009
Age (>65/<65 y)	2.16	1.44–3.25	<0.001			
Diabetes mellitus	1.61	1.07–2.41	0.022			
Hypertension	1.74	1.11–2.72	0.015			
Previous MI	1.13	0.75–1.70	0.563			
Acute MI						
Treatment			0.016*			0.012*
PCI/CABG	2.75	1.33–5.67	0.006	2.90	1.39–6.01	0.004
MT/CABG	2.66	1.28–5.51	0.009	2.69	1.30–5.60	0.008
Age (>65/<65 y)	1.39	0.83–2.31	0.204			
Diabetes mellitus	0.91	0.54–1.52	0.707			
Hypertension	1.15	0.69–1.91	0.600			
Previous MI	2.20	1.32–3.65	0.002			
Additional intervention						
Treatment			<0.001*			<0.001*
PCI/CABG	3.53	1.75–7.15	<0.001	3.71	1.82–7.52	<0.001
MT/CABG	7.14	3.66–13.94	<0.001	7.58	3.88–14.81	<0.001
Age (>65/<65 y)	0.85	0.55–1.30	0.453			
Diabetes mellitus	1.14	0.77–1.69	0.503			
Hypertension	1.41	0.94–2.11	0.096			
Previous MI	0.83	0.56–1.23	0.355			

Multivariate models were adjusted for age, sex, smoking status, hypertension, previous MI, total cholesterol, and diabetes mellitus.
*Summarizes 2 degrees of freedom tests comparing all 3 treatment groups.

the equivalent rates of death argue against complete versus incomplete revascularization having an effect on hard outcomes in this subset of patients considered at lower risk.

The MASS II trial found a strong, independent, protective association between CABG and the composite primary end point compared with MT and PCI after adjustment for sex, smoking, total cholesterol, previous MI, hypertension, diabetes, and the number of diseased vessels. Additionally, MT patients had less relief from symptomatic angina than did patients who underwent CABG or PCI. Although a placebo effect related to the invasive nature of both modalities could not be ruled out, these differences in angina status were



Treatment Group	Patients at risk Initial	3 Year	6 Year	10 Year
PCI	205	189	164	156
CABG	203	184	168	152
MT	203	179	159	140

Figure 5. Probability of survival free of overall mortality among patients in the MT, CABG, and PCI treatment groups.

paralleled by highly significant reductions in the rate of objective ischemia in both the CABG and PCI groups compared with the MT group. The lowest rate of repeat revascularization procedures (from the present study) has been noted after CABG, whereas a substantial proportion of patients undergoing MT alone (39%) cross over to revascularization, and 41.9% of PCI patients require repeat revascularization procedures.

The present findings should not be interpreted as an overwhelming endorsement of revascularization (PCI or CABG) in patients with multivessel disease. The COURAGE (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation) and BARI 2D (BARI 2 Diabetes) trials support this interpretation, without showing initial significant differences in death/MI in stable multivessel CAD patients treated with MT or intervention strategies, even for diabetic patients.[21–23] In the present study, 69% of patients randomized to MT were still alive at 10-year follow-up, with almost 40% of them free from infarction or additional revascularization procedures. Nevertheless, one should carefully consider the importance of continuous monitoring of patients allocated to MT, because in the long run, there appears to be a significant reduction in cardiac survival and a higher incidence of MI than with intervention procedures in this specific clinical scenario.

Clinical Implications and Conclusions

Despite the strength of the present study findings, significant developments in aggressive MT and lifestyle prescriptions with comprehensive risk factor modification have continued to occur since the MASS II trial was conducted, and this may impact the outcomes of an MT-based strategy, even for long-term follow-up. Further evidence in this long-running debate will be provided by the results of current trials of the initial MT strategy in patients with stable multivessel disease and preserved ventricular function. Moreover, the impact of drug-eluting stents on results demonstrating the superiority of CABG over PCI has been questionable, and some might argue that this procedural refinement makes the present results obsolete. However, data from randomized and nonrandomized trials show that this new type of stent has no advantageous effect on death and nonfatal MI relative to bare-metal stents despite yielding striking reductions in rates of restenosis and repeat revascularization procedures.[24] Thus, we believe that the observations reported herein with respect to death and MI remain applicable to contemporary practice.

In summary, the MASS II trial strongly showed the benefits of PCI and CABG over MT in regard to several primary end points at 10-year follow-up, although with similar rates of overall mortality. Additionally, CABG surgery was an independent predictor of higher rates of event-free survival.

Sources of Funding

Financial support for the present study was provided in part by a research grant from the Zerbini Foundation, São Paulo, Brazil. Medical writing support was provided by Ann Conti Morcos during the preparation of this paper, supported by the Zerbini Foundation.

Disclosures

None.

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CLINICAL PERSPECTIVE

Patients who are symptomatic because of coronary artery disease can be managed with medical therapy (MT), percutaneous coronary interventions (PCI), bypass surgery (CABG), or a combination of these strategies. It is unknown which treatment approach is best for specific patient subgroups. Here, we report 10-year follow-up of the second Medicine, Angioplasty, or Surgery Study (MASS II), a study that evaluated MT alone, PCI, or CABG among stable coronary patients with multivessel disease. No differences were observed in overall mortality in patients treated with CABG, PCI, or MT. Nevertheless, compared with CABG, MT was associated with a significantly higher incidence of cardiac death, subsequent myocardial infarction, and additional revascularization. Overall, compared with CABG, MT was associated with a 2.29-fold increased risk of combined events. Event rates for PCI patients were intermediate between MT and CABG. Indeed, by finding the lowest rate of further interventions in the CABG group, our results support a strategy of revascularization, and in particular CABG, in addition to MT for selected stable coronary patients with multivessel disease.