Ten-year outcomes of patients randomized to surgery, angioplasty, or medical treatment for stable multivessel coronary disease: Effect of age in the Medicine, Angioplasty, or Surgery Study II trial

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Objective: With progressive aging, coronary artery disease has been diagnosed at more advanced ages. Although patients aged 65 years or more have been referred to surgical or percutaneous coronary interventions, the best option for coronary artery disease treatment remains uncertain. The current study compared the 3 treatment options for coronary artery disease in patients aged 65 years or more and analyzed the impact of age in treatment options.

Methods: Patients were separated according to age: 65 years or more ($n = 200$) and less than 65 years ($n = 411$). All patients were followed for 10 years. The rates of overall mortality, acute myocardial infarction, and new revascularizations were analyzed.

Results: Of 200 patients aged 65 years or more, 68 were randomized to medical therapy, 68 were randomized to percutaneous coronary intervention, and 64 were randomized to coronary artery bypass grafting. At 10 years, overall survival was 63% (medical therapy), 69% (percutaneous coronary intervention), and 66% (coronary artery bypass grafting) ($P = .93$). The survival free of combined events was 43% (medical therapy), 38% (percutaneous coronary intervention), and 66% (coronary artery bypass grafting) ($P = .007$). The survival free of myocardial infarction was 82% (medical therapy), 77% (percutaneous coronary intervention), and 90% (coronary artery bypass grafting) ($P = .17$), and survival free of new revascularizations was 59% (medical therapy), 58% (percutaneous coronary intervention), and 91% (coronary artery bypass grafting) ($P = .0003$). When the 2 age groups were compared, survival free of myocardial infarction for patients treated by percutaneous coronary intervention was 77% (older patients) and 92% (younger patients) ($P = .004$).

Conclusions: In this analysis, treatment options for patients aged 65 years or more who have coronary artery disease yield similar overall survival. However, coronary artery bypass grafting was associated with fewer coronary events, and percutaneous coronary intervention was associated with a higher incidence of myocardial infarction. (J Thorac Cardiovasc Surg 2013;146:1105-12)

In recent decades, the world population has become proportionally older. According to the United Nations, by 2050 the number of people aged 60 years or more in the world will exceed the number of children (0-14 years) for the first time in history.¹

With the aging of the population, coronary artery disease (CAD) has become more frequent at advanced ages. This

demographic change has led to an increase in the number of older patients referred for coronary revascularization. However, because of methodological questions, clinical trials of long-term follow-up have routinely decreased the number of older patients undergoing mechanical interventions.²

Older patients with CAD usually have more diffuse, systemic atherosclerosis.³ In addition, noncardiac comorbidities, such as peripheral vascular disease and impaired renal and pulmonary function, are more prevalent in older patients,⁴⁻⁶ providing a worse prognosis for interventional treatment.^{7,8} This higher-risk profile of older patients with CAD contributes to their increased complication rates after both percutaneous coronary intervention (PCI)⁹ and coronary artery bypass grafting (CABG).¹⁰ Consequently, several clinical trials have confirmed that a relation exists between clinical outcomes from either method of mechanical revascularization and the patient's age.¹¹ However, other studies suggest that older patients have greater benefits from mechanical intervention than from medical

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Abbreviations and Acronyms

BARI	= Bypass Angioplasty Revascularization Intervention
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
MASS II	= Medicine, Angioplasty, or Surgery Study II
MI	= myocardial infarction
MT	= medical treatment
PCI	= percutaneous coronary intervention

therapy.¹² Another study¹³ concluded that a greater absolute risk reduction is associated with revascularization in older compared with younger patients.

Thus, the most appropriate therapeutic strategy for older patients—PCI, medical treatment (MT), or CABG—remains controversial mainly because of the lack of clinical studies investigating a direct comparison of the 3 treatment strategies in these age groups.

This analysis from a 10-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II) aims to compare the 3 treatment options for CAD in patients aged 65 years or more and the effect of age on the results of each treatment strategy.

MATERIALS AND METHODS**Trial Design**

The details of the MASS II design, study protocol, patient selection, inclusion criteria, and general results have been published.¹⁴ Briefly, the MASS II study was a prospective, randomized, controlled clinical trial designed to compare MT, PCI, and CABG in patients with stable multivessel CAD and preserved left ventricular function. As previously reported,¹⁴ from a total of 20,769 patients with a presumptive diagnosis of CAD who underwent coronary arteriography at the Heart Institute of the University of São Paulo between May 1995 and May 2000, 2077 (10%) had an indication for coronary revascularization and met the study entry criteria. The most frequent reasons to exclude patients from the initial population were single-vessel disease, refractory angina, stenosis 70% or less, previous PCI or CABG, and valvular disease. Of these 2077 patients, 1466 (71%) could not be randomized because they refused to participate in this trial or specifically refused the surgical procedure. The remaining 611 patients (29%) were randomly assigned to 1 of the 3 therapeutics: PCI, MT, or CABG. The predefined primary end point was the combined incidence of overall mortality, myocardial infarction (MI), or persistent angina requiring additional mechanical revascularization. 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 randomized if the surgeons, attending physicians, and interventional cardiologists agreed that revascularization could be attained by one of the strategies. Clinical criteria of exclusion included unstable angina or acute MI requiring emergency revascularization, ventricular aneurysm requiring surgical repair, left ventricular ejection fraction less than 40%, a history of PCI or CABG, single-vessel disease, and left main coronary artery stenosis 50% or greater. Patients also were excluded if they had another coexisting condition associated with reduced life expectancy. In this trial, all patients were placed on optimal MT for CAD. This consisted of a stepped-care

approach using aspirin, nitrates, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and statins. All medications were provided for free by the Heart Institute.

Patients were randomized to continue with MT alone or to undergo PCI or CABG concurrently with MT. Complete revascularization by PCI or CABG in accordance with current best practices was encouraged but not mandatory. Patients assigned to PCI had their procedures performed within 3 weeks after randomization. Devices available to the interventionist included conventional stents, lasers, directional atherectomy, and balloon angioplasty, if necessary. Each PCI-treated patient had an average of 2.1 ± 0.7 vessels dilated. Patients assigned to CABG had their procedures performed within 12 weeks after randomization. Revascularization was performed with the use of saphenous vein grafts, internal thoracic 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. Each patient undergoing CABG had an average of 3.3 ± 0.8 vessels bypassed. At least 1 internal thoracic artery was used for grafting in 92% of patients.

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.

Older patients were considered those aged 65 years or more at the time of randomization. Patients ($n = 611$) were separated according to age into 2 groups: 65 years or more (group 1 = 200) and less than 65 years (group 2 = 411). All patients were followed up for 10 years. We analyzed the rates of overall mortality and the occurrence of MI, angina requiring new revascularizations, and combined major events (death, MI, and new revascularizations) in group 1. We also analyzed the differences between groups 1 and 2 in terms of major cardiovascular events and in each treatment strategy.

Data Collection and Long-Term Follow-up

Demographic and clinical data were obtained at baseline for all 611 patients. The collected demographic and laboratory data included sex, ethnicity, traditional risk factors (eg, previous coronary events), hypertension, diabetes, smoking status (current smokers, never smokers), chronic kidney disease (defined as creatinine level ≥ 1.5), number of diseased coronary vessels, cholesterol and triglyceride profiles, and renal function.

MI was defined as the presence of significant new Q waves in at least 2 electrocardiogram leads or symptoms compatible with MI associated with creatine kinase-MB concentrations that were more than 3 times the upper limit of the reference range.

Adverse and clinical events were tracked from randomization. All mortality events were confirmed by death certificates. Patients were assessed with follow-up visits every 6 months over 10 years at the Heart Institute. The minimum length of follow-up for patients alive was 9 years, and the maximum was 15 years (mean, 11.4 years).

Statistical Analysis

All data were analyzed according to the intention-to-treat principle. Primary end points were the overall mortality, occurrence of MI, occurrence of angina requiring additional mechanical revascularization (PCI or CABG), and occurrence of combined events (overall mortality, MI, and new revascularizations). The survival free of overall mortality and isolated major events was defined as the interval between the random assignment and the occurrence of death or the major event up to 10 years of follow-up. The survival free of combined events was defined as the interval between random assignment and the occurrence of the first major event up to 10 years of follow-up. Event-free survival was estimated by the Kaplan-Meier method, and differences among age groups and treatment groups were assessed by means of the log-rank test. Mean levels of continuous variables were compared by 1-way analysis of variance, followed by Tukey's multiple-comparisons test. The Pearson chi-square test was used to compare qualitative variables between

the 2 groups. Multivariate analysis by Cox regression also was performed for variables with a possible association ($P < .1$). Tests were 2-tailed. Statistical analyses were performed with the Statistical Package for the Social Sciences version 17.0 (SPSS Inc, Chicago, Ill).

RESULTS

Baseline Findings

Patients ($n = 611$) were separated according to age into 2 groups: 65 years or more (group 1 = 200 patients) and less than 65 years (group 2 = 411 patients). Baseline data of the 2 age groups are summarized in Table 1.

Compared with group 2, group 1 included more women (36.5% vs 28.0%, $P = .032$), had fewer current smokers (20.5% vs 37.0%, $P = .0001$), had higher high-density lipoprotein cholesterol levels (39.9 vs 36.0, $P < .001$), and had lower triglyceride levels (175.0 vs 204.9).

Older patients ($n = 200$) were stratified according to the randomized treatment into 3 groups: angioplasty, bypass surgery, or MT alone. The baseline characteristics of the 3 treatment groups were similar with respect to important prognostic characteristics, except for the higher percentage of white persons in the PCI-treated group (Table 2).

End Point Events in the Older Group

Of the 200 patients aged 65 years or more, 68 were randomized to MT, 68 were randomized to PCI, and 64 were randomized to CABG treatment. At the 10-year follow-up, overall survivals in each treatment strategy were 63% (MT, 40 patients), 69% (PCI, 41 patients), and 66% (CABG, 40 patients) ($P = .93$) (Figure 1, A). The survivals free of combined events were 43% (MT, 27 patients), 38% (PCI, 26 patients), and 66% (CABG, 41 patients) ($P = .007$) (Figure 1, B). The survivals free of MI were

TABLE 1. Baseline characteristics of 611 patients from the Medicine, Angioplasty, or Surgery Study II trial, according to age

Groups	≥65 y (n = 200)	<65 y (n = 411)	P value
Age, mean ± SD, y	70.0 ± 3.4	54.7 ± 6.5	
Female %	36.5	28.0	.03
White %	84.5	85.4	.76
Hypertension %	59.5	59.6	.97
Diabetes mellitus %	31.5	30.9	.88
Current smoker %	20.5	37.0	<.001
Never smoker %	58.0	43.1	<.001
Previous MI %	41.0	45.7	.26
3-vessel disease %	67.8	61.0	.10
CKD %	7.0	6.3	.75
Total-C, mean ± SD	224.3 ± 45.1	222.6 ± 48.9	.68
LDL-C, mean ± SD	147.9 ± 39.8	146.8 ± 44.6	.76
HDL-C, mean ± SD	39.9 ± 12.2	36.0 ± 9.0	<.001
TG, mean ± SD	175.0 ± 89.2	204.9 ± 132.9	.0043
Serum creatinine, mean ± SD	1.12 ± 0.6	1.09 ± 0.5	.52

SD, Standard deviation; MI, myocardial infarction; CKD, chronic kidney disease; C, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

TABLE 2. Baseline characteristics of older patients, according to treatment option

Groups	MT (n = 68)	PCI (n = 68)	CABG (n = 64)	P value
Age, mean ± SD, y	70.5 ± 3.5	69.9 ± 3.5	69.5 ± 3.2	.20
Female %	39.7	39.7	29.7	.038
White %	76.5	94.1	85.9	.01
Hypertension %	55.9	57.4	64.1	.59
Diabetes mellitus %	33.8	29.4	29.7	.82
Current smoker %	23.5	17.6	21.9	.32
Never smoker %	54.4	55.9	65.6	.32
Previous MI %	36.8	50.0	34.4	.13
3-vessel disease %	35.3	34.3	28.1	.63
CKD %	7.4	8.8	4.7	.64
Total C, mean ± SD	227.6 ± 41.9	224.6 ± 43.8	221.6 ± 50.0	.75
LDL-C, mean ± SD	151.4 ± 36.7	150.3 ± 36.6	142.8 ± 46.1	.42
HDL-C, mean ± SD	39.4 ± 12.7	39.7 ± 10.8	40.5 ± 13.1	.87
TG, mean ± SD	172.7 ± 76.1	176.0 ± 98.9	177.3 ± 92.0	.95
Serum creatinine, mean ± SD	1.05 ± 0.2	1.21 ± 0.8	1.09 ± 0.5	.20

MT, Medical therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; SD, standard deviation; MI, myocardial infarction; CKD, chronic kidney disease; C, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

82% (MT, 55 patients), 77% (PCI, 53 patients), and 90% (CABG, 58 patients) ($P = .17$) (Figure 1, C), and the survivals free of new revascularizations were 59% (MT, 43 patients), 58% (PCI, 41 patients), and 91% (CABG, 58 patients) ($P = .0003$) (Figure 1, D).

End Point Events in Older Versus Younger

When we compared the older group with the younger group, in a univariate analysis, the overall survivals were 57% versus 77%, respectively ($P < .001$; Figure 2, A). When we compared the older and younger groups in each treatment strategy, the overall survivals were 57% versus 67% for patients receiving MT ($P = .03$; Figure 2, B), 52% versus 81% for patients receiving PCI ($P = .0002$; Figure 2, C), and 62% versus 80% for patients receiving CABG ($P = .0029$; Figure 2, D), respectively. After multivariate analysis, overall survivals in these 2 age groups were still statistically different, 56% versus 78% ($P = .0001$), even when treatment groups were analyzed separately.

Older patients had similar survivals free of MI compared with younger patients, 83% versus 86% ($P = .09$; Figure 3, A). When treatments were analyzed separately for the older versus younger groups, survivals free of MI were 82% versus 79% for MT ($P = .98$; Figure 3, B), 77% versus 92% for PCI ($P = .004$; Figure 3, C), 90% versus 89% for CABG ($P = .93$; Figure 3, D), respectively. After multivariate analysis, survival results were similar, with higher rates of MI in PCI-treated elderly patients (survivals free of MI 76% vs 93%, $P = .0032$, in older vs younger patients, respectively).

The survivals free of new revascularizations were similar between the older and younger groups, 69% versus 72%

FIGURE 1. Survival without overall death (A) and freedom from major cardiovascular events (B-D) in 10-year follow-up of 200 elderly patients from the MASS II trial according to treatment strategy (MT, PCI, or CABG): combined events (B), acute MI (C), and angina requiring new interventions (D). CABG, Coronary artery bypass grafting; MT, medical treatment; PCI, percutaneous coronary intervention.

($P = .45$). When we compared the 2 age groups in each treatment strategy, the survivals free of revascularizations were 59% versus 60% for MT ($P = .94$), 58% versus 62% for PCI ($P = .77$), and 90% versus 93% for CABG ($P = .32$).

DISCUSSION

With progressive aging, CAD has become more frequent and its treatment more challenging. With successful aging and improvement in technical revascularization procedures, a higher proportion of older patients have been referred for invasive interventions to relieve angina symptoms and improve life expectancy, although it is still uncertain whether these interventions are superior to MT alone for the management of patients aged 65 years or more who have CAD. In addition, numerous studies demonstrate a higher

risk of periprocedural complications related to older age.^{2,15-17} Moreover, fewer studies compared the 3 treatment options for CAD in patients aged 65 years or more. Most of them compared only 2 treatment options.^{15,18-20}

The MASS II trial is one of the few studies that have compared the 3 therapeutic options for CAD. One third of MASS II trial patients were aged 65 years or more at the time of the randomization. The baseline characteristics of this specific population in the 3 treatment groups were similar in terms of the main prognostic parameters. When the older group was compared with the younger group, except for age, the other main parameters were similar in frequency, despite sex, smoking status, and triglyceride profile, which differed significantly between these age groups.

FIGURE 2. Ten-year overall survival in the 2 age groups from the MASS II trial (A) and in each treatment strategy comparing the age groups: MT (B), PCI (C), and CABG (D).

Our results reveal that the 3 options for treatment of CAD in patients aged 65 years or more demonstrated similar overall mortality. This is similar to the findings of other trials, such as the analysis of elderly patients from the Bypass Angioplasty Revascularization Intervention (BARI)¹⁵ and Stent or Surgery¹⁸ trials, although these studies only compared PCI with CABG.

Our mortality results also were in accordance with the results of BARI 2D age study.²¹ Although patients selected were all diabetic, this study demonstrated similar mortality rates with both strategies (MT vs intervention) in the subgroup of patients aged more than 70 years.

Moreover, in a prespecified analysis of clinical outcomes by age from the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation trial,¹⁹ PCI plus MT compared with MT alone resulted in similar survivals in older patients in a median 4.6 years of follow-up (88% survival in each strategy).

However, an analysis of older patients from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease study¹³ showed better survival outcomes for older patients who were referred to CABG and PCI treatments compared with MT. The largest risk reductions were noted in the oldest group of patients. Meanwhile, this was a cohort study, and it included patients with acute coronary syndromes and left ventricular dysfunction, clinical situations that favor revascularization strategies.

In accordance with the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease study,¹³ an analysis of elderly patients from the Coronary Artery Surgery Study showed better survival for CABG recipients compared with MT recipients at 6-year follow-up, although that was a nonrandomized study and even the authors concluded that the 2 treatment groups differed substantially with regard to important baseline characteristics.²⁰

FIGURE 3. Survival free of acute MI in the 2 age groups from the MASS II trial (A) and in each treatment strategy comparing the age groups: MT (B), PCI (C), and CABG (D).

In a recent database study²² that compared PCI with CABG in 189,793 patients aged 65 years or more with multiarterial CAD, mortality was similar between these 2 treatments at 1 year, but at 4 years there was a lower adjusted mortality with CABG treatment. However, this was a non-randomized study.

To date, on the basis of these trials and our data, none of the therapeutic options for chronic CAD treatment in patients aged 65 years or more seem to be superior to the others in terms of overall mortality. Our study highlights the importance of MT as a safe and possible treatment option to this specific population and brings results from long-term follow-up.

In our study, CABG recipients had a lower incidence of combined major cardiovascular events, especially related to fewer additional coronary interventions. Older patients in medical and angioplasty groups had rates of 41% and

42%, respectively, of new mechanical interventions in 10 years compared with only 9% in CABG recipients. These results are also similar to those of other trials, such as the BARI,¹⁵ Stent or Surgery,¹⁸ and Trial of Invasive versus Medical Therapy in the Elderly.²³ In the Trial of Invasive versus Medical Therapy in the Elderly, very old patients (mean age, 80 years) who were assigned to MT had similar overall mortality compared with the invasive group, but they had a greater than 50% chance of late nonfatal events, mainly hospitalizations for refractory symptoms with the need for late revascularization.

In our analysis, PCI-treated elderly patients had a higher incidence of MI compared with MT and CABG (23% PCI vs 18% MT vs 10% CABG), although this was not statistically significant ($P = .17$). In another study,¹⁸ the incidence of MI was similar between treatment groups in the elderly.

In this analysis, the incidence of angina requiring additional interventions was high in PCI-treated elderly patients, as high as in the medically treated group (58% vs 59%, respectively).

Thus, in elderly patients from the MASS II trial, PCI treatment did not confer any additional advantage over MT in terms of overall mortality, MI, and angina requiring additional interventions. These results are also similar to the findings of the Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation elderly analysis.¹⁹

When we analyzed the main cardiac events in the older group compared with the younger group, the event rates were higher in the elderly patients, and this also occurred independently of the treatment strategy. Even after multivariate analysis, age was still an independent factor related to a worse prognosis. This was confirmed by other treatment studies.^{15,20}

There was no difference between the 2 age groups in terms of additional coronary interventions, even when stratified by treatment options. However, when we analyzed the occurrence of MI, the older group of patients receiving PCI treatment had a higher incidence of MI compared with the younger group (23% vs 8.3%, $P = .004$), and even after adjustment for baseline differences, this finding did not change. This difference did not occur in the MT and CABG groups.

These results contrast with those reported by Kelsey and colleagues,²⁴ who found in a 2-year follow-up registry study similar rates of MI in elderly and younger patients treated with PCI. However, this was a nonrandomized study, and its short outcomes follow-up probably did not detect a late progression of CAD. In a retrospective study by Nasser and colleagues,²⁵ the occurrence of MI was similar regarding age groups, but this was a 6-month follow-up study, and there were fewer MI events.

Despite progressive declines in PCI complications in the last 2 decades,²⁶ long-term clinical outcomes related to PCI treatment have been understudied in the literature, especially in the older population. In a retrospective study by De Gregorio and colleagues,²⁷ older patients with CAD had a higher incidence of angiographic restenosis compared with the younger group (47% vs 28%, $P = .0007$) 6 months after PCI. However, in this study the older group had a higher proportion of unstable angina, angina Canadian Cardiovascular Society class III or IV, and severe coronary disease (higher proportion of 3-vessel disease, ostial, calcified, and complex lesions), which can explain these higher restenosis results.

In the current study, possible explanations for the higher MI frequency in older patients undergoing PCI can be the more diffuse atherosclerotic burden in this group. Although we found the same proportion of 3-vessel coronary disease in older and younger patients, we did not analyze other coronary characteristics, such as frequency of ostial, calcified, and complex lesions, generally more prevalent in older

population. The analysis of the SYNTAX score²⁸ from the coronary arteriographies of our population would have been helpful to evaluate more accurately possible anatomic differences between the 2 age groups, which could explain this finding of higher MI frequency in PCI-treated older patients. A lower frequency of complete revascularizations in these patients can be another possible cause of our results. Left ventricular dysfunction cannot explain these worse results, because all patients in the MASS II trial had preserved ventricular systolic function.

This study provides important insights. Initial MT is safe for older patients with multiarterial CAD with preserved left ventricular function, because it resulted in similar rates of death and MI when compared with PCI or CABG in a long-term follow-up. In addition, as the population ages and angioplasty extends its indication to patients with higher-risk profiles, including older persons, this treatment strategy has been increasingly indicated, but it should be carefully evaluated. The finding of a greater incidence of MI in PCI-treated older patients will need further studies, but it is important to cardiologists to consider it when they indicate percutaneous interventions based on only anatomic features. Finally, CABG does not prevent death or MI in older patients with CAD, but it protects, especially when there is the need for further coronary interventions.

Study Limitations

Our study has some limitations. In addition to the relatively small sample size, which may lead to an inability to detect treatment differences, it presents the problem of all long-term follow-up studies, that is, the evolution of standard care, especially related to improvements in interventions. In our study, angioplasty was performed with bare-metal stents and all CABGs were performed on-pump. The absence of information on stroke is another limitation of the present study, which may be relevant information in older patients.

CONCLUSIONS

In this MASS II trial analysis, the treatment options for patients with CAD who are aged 65 years or more yield a similar overall survival. However, CABG in older patients was associated with fewer subsequent coronary interventions, whereas PCI treatment was associated with a higher incidence of MI. Age was independently associated with overall mortality.

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