Impact of number of vessels disease on outcome of patients with stable coronary artery disease: 5-year follow-up of the Medical, Angioplasty, and bypass Surgery Study (MASS)

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Abstract

Objective: To evaluate whether the number of vessels disease has an impact on clinical outcomes as well as on therapeutic results accordingly to medical, percutaneous, or surgery treatment in chronic coronary artery disease. Methods: We evaluated 825 individuals enrolled in MASS study, a randomized study to compare treatment options for single or multivessel coronary artery disease with preserved left ventricular function, prospectively followed during 5 years. The incidence of overall mortality and the composite end-point of death, myocardial infarction, and refractory angina were compared in three groups: single vessel disease (SVD n = 214), two-vessel disease (2VD n = 253) and three-vessel disease (3VD n = 358). The relationship between baseline variables and the composite end-point was assessed using a Cox proportional hazards survival model. Results: Most baseline characteristics were similar among groups, except age (younger in SVD and older in 3VD, p < 0.001), lower incidence of hypertension in SVD (p < 0.0001), and lower levels of total and LDL-cholesterol in 3VD (p = 0.004 and p = 0.005, respectively). There were no statistical differences in composite end-point in 5 years among groups independent of the kind of treatment; however, there was a higher mortality rate in 3VD (p < 0.001). When we stratified our analysis for each treatment option, bypass surgery was associated with a lower number of composite end-point in all groups (SVD p < 0.001, 2VD p = 0.002, 3VD p < 0.001). In multivariate analysis, we found higher mortality risk in 3VD comparing to SVD (p = 0.005, HR 3.14, 95%CI 1.4—7.0). Conclusion: Three-vessel disease was associated with worse prognosis compared to single- or two-vessel disease in patients with stable coronary disease and preserved ventricular function at 5-year follow-up. In addition, event-free survival rates were higher after bypass surgery, independent of the number of vessels diseased in these subsets of patients.

Keywords: Coronary disease; Surgery; Angioplasty; Prognosis; Number of vessels disease

1. Introduction

Prior studies have demonstrated that some anatomic subsets, such as the number of vessels disease, the involvement of proximal left anterior descending (LAD) or left ventricular dysfunction (LVD), define a prognostic high-risk angiographic subset of patients with chronic coronary artery disease (CAD) [1]. Additional prognostic information is provided by the severity of obstruction and the location, whether proximal or distal [1]. Studies of treated symptomatic patients have revealed that if only one of the three major coronary arteries has more than 50% stenosis, the annual mortality rate is approximately 2%. The importance of survival of the quantity of myocardial that is jeopardized is reflected in the observation that an obstructive lesion proximal to the first septal perforating branch of the LAD was associated with a 5-year survival rate of 90% in comparison with 98% for patients with more distal lesions [2].

Coronary artery bypass graft (CABG) surgery and later on, the percutaneous coronary intervention (PCI) were developed as alternatives to medical therapy for the treatment of patients with CAD. In several clinical trials, revascularization by coronary artery bypass graft surgery increased survival compared with medical therapy (MT) in patients with three-vessel disease and two-vessel disease (2VD) when the proximal LAD was involved, with or without LVD [3—5]. However, most of these data are derived from the classic observational studies designed in the late 1980s. Major technologic advances have been achieved in both PCI and CABG surgery and in recognition of the importance of risk factor reduction and new effective medical treatment for atherosclerosis.

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The last two decades witnessed major advances in coronary revascularization techniques for CAD, and several studies have examined the benefits of these two interventions relative to medical therapy and/or to one another. For the most part, the studies that have compared CABG and PCI have not found significant long-term mortality differences even when stratifying the analysis by number of diseased coronary arteries [6-9]. However, controversial results have also been published. A meta-analysis including nine trials of multivessel CAD treated by PCI or CABG showed a statistically significant benefit in terms of survival in favor of surgery at 5 and 8 years, but stents were not used in these studies [10]. Since then, both medical therapy and interventional techniques have markedly improved, so the impact of the classical angiographic predictor factors of worse prognosis in CAD need to be reanalyzed in the light of the current options treatment for chronic CAD.

Indeed, no data are currently available on the impact of the number of diseased vessels on clinical outcomes and on therapeutic results according to different treatment modalities of chronic stable CAD with preserved left ventricular function. The present study reports on the 5-year survival and event-free survival of patients enrolled in the Medical, Angioplasty and bypass Surgery Study (MASS) trial stratified by number of diseased vessels.

2. Methods

2.1. Study design and patient population

A total of 825 consecutive patients who had angiographically proximal single or multivessel coronary stenosis of more than 70% by visual assessment and documented ischemia and considered equally treatable with the three modalities were enrolled between May 1991 and May 2000 at the Heart Institute as part of the MASS trial. The MASS protocol, including details regarding aims, patient recruitment, inclusion and exclusion criteria, data collection, procedural guidelines and definitions has been published previously [11,12]. Briefly, the MASS study is a randomized, prospective, single-center study that compared three therapeutic strategies: medical, surgery and angioplasty in patients with single (MASS I) or multivessel disease (MASS II) and stable coronary artery disease. These clinically eligible patients who consented to enter the study were prospectively followed along 5 years. Ischemia was documented by either stress testing or the typical stable angina assessment of the Canadian Cardiovascular Society (CCS) (Class II or III). Patients were enrolled in this study if there was agreement on the part of the surgeon and interventionalist that revascularization could be attained by either strategy. In the present report, the overall MASS I and MASS II population was divided into three groups according to the number of vessels disease. So, the study population included 214 patients with single vessel disease (SVD), 253 patients with two-vessel disease (2VD) and 358 patients with three-vessel disease (3VD).

The ethics committee of the Heart Institute approved the protocol and all procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

2.2. Treatment protocol

The medication recommendations were not different for patients randomized to surgery, angioplasty, or medical therapy alone. All patients were treated with aspirin and an optimal medical regime consisting of a stepped-approach using nitrates, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs, unless contraindicated, were used to keep the patient free of angina. Statins were also prescribed along with a low-fat diet and carbohydrates on an individual basis. Insulin and oral hypoglycemic agents were also used in diabetic patients. The medications were provided for free by the Heart Institute. Patients were then assigned to continue with aggressive medical therapy alone or to undergo PCI or CABG concurrently with MT.

For patients assigned to PCI, the procedure was available within 3 weeks after the assignment. Devices used for catheter-based therapeutic strategies, including stents, lasers, directional atherectomy and balloon angioplasty were left at the discretion of the operator. Angioplasty was performed according to a standard protocol. The interventional cardiologist was encouraged to treat all arteries that were likely to contribute to ischemia and/or had lesion >70% diameter stenosis. Successful revascularization in the PCI group was defined as a residual stenosis of <50% reduction in luminal diameters with thrombolysis in myocardial infarction (TIMI) flow grade 3. Patients treated with coronary stents were maintained on ticlopidin 250 mg bid for 1 month in addition to lifelong aspirin.

Patients assigned to the CABG group underwent the operation 4 weeks after the assignment. Complete revascularization was accomplished, if technically feasible, with saphenous vein grafts, internal mammary arteries and other conduits such as radial or gastroepiploic arteries. Use of the left internal mammary artery to graft the left anterior descending coronary artery was strongly advised for all cases. Equivalent revascularization was encouraged but not mandatory. Standard surgical techniques were used under hypothermic arrest with blood cardioplegia. No off-pump CABG was performed.

2.3. Study endpoints

Patients were assessed with follow-up visits every 3 months during the first year and subsequently every other 6 months until 5-year clinical follow-up. The predefined combined endpoints were the incidence of overall mortality, myocardial infarction (MI) or refractory angina requiring revascularization. MI was defined as the presence of significant new Q-waves in at least two ECG leads or symptoms compatible with MI associated with creatine kinase, MB fraction concentrations that were more than three times the upper limit of the reference range.

The study’s primary end-point was to compare the impact of number of vessels disease in the mortality and event-free survival of patients with stable CAD and ventricular function preserved at 5 years. Also, we stratified our analysis according to the treatments allocated in each group of number of vessels disease in order to compare the medical, surgery or angioplasty by the number of vessels disease.
2.4. Statistical analysis

Statistical analysis was performed with the SPSS software. Differences in clinical and demographic baseline characteristics among groups were assessed by chi-square or Fisher’s test for dichotomous variables and t-tests or Wilcoxon tests for continuous variables. Event rates were estimated by the Kaplan–Meier method, and differences among groups were compared using the log-rank test. Cox proportional hazards method was used to develop a multivariate model of 5-year mortality rates, including variables such as age, hypertension, gender, hyperlipidemia, number of coronary disease and treatment allocation. All data were analyzed according to the intention to treat principle rather than treatment received. All tests were two-tailed, and \( p < 0.05 \) was considered statistically significant.

3. Results

3.1. Baseline and procedural characteristics

Most baseline characteristics were similar among groups, except by younger age in SVD and older age in 3VD (\( p < 0.001 \)), lower incidence of hypertension in SVD (\( p < 0.0001 \)) and lower levels of total and LDL-cholesterol in 3VD (\( p = 0.008 \) and \( p = 0.006 \), respectively). There were no differences in the distributions of treatment allocated among groups of number of vessels disease and the angiographic characteristics were similar among the groups (Tables 1 and 2).

The rates of revascularization of the coronary territories at the index procedure (right coronary artery, left circumflex, and left anterior descending) were similar among groups regarding the LAD coronary territory, either treated with PCI or CABG. However, they were significantly lower in the right and left circumflex territory of patients with 2VD compared to 3VD. Moreover, this index of procedure was lower in patients with 3VD treated with PCI than in surgical patients (data not shown). Overall, stents were used in >80% of patients randomized to PCI and LIMA or RIMA grafts were used in 95% of surgical patients. PCI was clinically successful in 96% of the 72 patients with single vessel disease, in 92% of the 86 patients with 2VD and in 92% of the 119 patients with 3VD assigned to PCI. Each multivessel patient who underwent PCI had an average of 2.1 ± 0.7 vessels dilated. All 70 patients with SVD assigned to CABG received LIMA and each patient with 2VD (\( n = 86 \)) or 3VD (\( n = 118 \)) who underwent to CABG had an average of 3.3 ± 0.8 vessels bypassed, and at least one internal thoracic artery was used to grafting in 92% of them, and two internal thoracic arteries and a radial artery were used in 36% of them. The epigastric artery was used in 10% of these patients. The rate of new intervention (PCI or CABG) along the follow-up was 29.1% and 19.5%, respectively. The hospital mortality rates were 2.4% and 2.5%, respectively, for PCI and CABG. The Q-wave MI incidence was 1% in both PCI and CABG. No patient in the CABG group needed inhospital PCI or emergency CABG, while 2% of patients who underwent PCI needed emergency PCI or CABG.

Of patients assigned to the CABG group, 0.4% received MT because they refused surgery; among the patients assigned to

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single vessel (( n = 214 ))</th>
<th>Two-vessels (( n = 253 ))</th>
<th>Three-vessels (( n = 358 ))</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 10</td>
<td>58 ± 9</td>
<td>60 ± 9</td>
<td>0.0000</td>
</tr>
<tr>
<td>Male</td>
<td>70.5</td>
<td>67.5</td>
<td>70.3</td>
<td>0.7109</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>37.3</td>
<td>35.9</td>
<td>32.4</td>
<td>0.4298</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.5</td>
<td>57.3</td>
<td>61.1</td>
<td>0.0000</td>
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<tr>
<td>Diabetes mellitus</td>
<td>31.3</td>
<td>37.9</td>
<td>38.8</td>
<td>0.1700</td>
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<tr>
<td>CCS class I or III angina</td>
<td>83</td>
<td>79</td>
<td>80</td>
<td>0.0307</td>
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<tr>
<td>Laboratory values (mmol/l)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>231 ± 48</td>
<td>227 ± 49</td>
<td>218 ± 44</td>
<td>0.0042</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>154 ± 38</td>
<td>153 ± 45</td>
<td>143 ± 41</td>
<td>0.0051</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>39 ± 8</td>
<td>38 ± 10</td>
<td>37 ± 10</td>
<td>0.176</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>191 ± 87</td>
<td>184 ± 97</td>
<td>178 ± 89</td>
<td>0.7851</td>
</tr>
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<td>Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>33.6</td>
<td>33.6</td>
<td>33.5</td>
<td>0.9995</td>
</tr>
<tr>
<td>MT</td>
<td>33.6</td>
<td>32.8</td>
<td>33.5</td>
<td>0.9995</td>
</tr>
<tr>
<td>CABG</td>
<td>32.7</td>
<td>33.6</td>
<td>32.9</td>
<td>0.766</td>
</tr>
<tr>
<td>Positive treadmill test</td>
<td>75</td>
<td>71</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data presented are the mean value ± SD; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; MT = medical therapy; CCS = Canadian Cardiovascular Society.
3.2. Clinical outcomes

Patients were followed up for an average period of 1702 ± 452 days (median 1840 days). Table 3 showed higher overall mortality in 3VD group compared to 2VD and SVD, but there were no statistical differences in the evidence of MI and new intervention among the three groups. Kaplan–Meier curves also showed there were no differences in the composite end-point at 5 years among groups by number

Table 3
Mortality and outcome of patients stratified by number of vessels

<table>
<thead>
<tr>
<th></th>
<th>SVD (n = 214)</th>
<th>2VD (n = 253)</th>
<th>3VD (n = 358)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality (%)</td>
<td>6.0</td>
<td>12.2</td>
<td>17.8</td>
<td>0.001</td>
</tr>
<tr>
<td>MI (%)</td>
<td>6.5</td>
<td>7.5</td>
<td>7.2</td>
<td>0.916</td>
</tr>
<tr>
<td>New intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (%)</td>
<td>10.7</td>
<td>14</td>
<td>9.5</td>
<td>0.183</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>8.8</td>
<td>7.5</td>
<td>8.9</td>
<td>0.800</td>
</tr>
</tbody>
</table>

MI = myocardial Infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; SVD = single vessel disease; VD = vessel disease.

Fig. 1. Kaplan-Meier mortality curves (A) and event-free curves (B) for patients with single vessel disease (SVD), two-vessels disease (2VD) and three-vessels disease (3VD). Note that patients with 3VD presented an increase in the risk of death at 5 years of follow-up (A). No difference in event-free curves was found among groups (B).

Fig. 2. Kaplan-Meier end-point cumulative rate of death, myocardial infarction or refractory angina needing revascularization for the three treatment strategies in SVD (A), 2VD (B) and 3VD (C). Significant differences were seen among CABG and PCI or MT treatment in all subgroups of number of vessels disease.
of vessels disease (Fig. 1B), however, there was a higher probability of 5-year mortality in 3VD compared to SVD and 2VD ($p = 0.004$ by log-rank, Fig. 1A). The cumulative survival rates at 5 years were 95.3%, 91.5% and 87.4% for patients with SVD, 2VD and 3VD, respectively.

When we stratified our analysis for each treatment option based on the number of vessels disease, bypass surgery was associated with a lower number of composite end-point in all subgroups of number of vessels disease, even though in SVD, the CABG superiority over PCI and MT in terms of lower risk of mortality was more prominent.

Finally, a multivariate analysis, including variables such as age, hypertension, gender, hyperlipidemia, number of coronary disease and treatment allocation, revealed a 3-fold increased risk of mortality in 3VD compared to SVD ($p = 0.005$, HR 3.14, 95% CI 1.4–97.0) (Table 4).

4. Discussion

The main findings of this present study are that 3VD was associated with a higher probability of mortality compared to single- or two-vessel disease than patients with stable chronic coronary disease and preserved ventricular function during 5-year follow-up, but the number of vessels disease did not influence the probability of combined event free. The presence of 3VD conferred a significant 3.1-fold increase in the mortality risk regardless of hypertension, total and LDL-cholesterol and type of treatment received. Also, bypass surgery was the best therapeutic option, independent of the number of vessels disease in this subset of patients.

The survival rate of patients with stable coronary disease and preserved left ventricular function is usually good, regardless of treatment option as we and others already have demonstrated [13—15]. However, the number of vessels disease might influence the prognosis even in this subset of patients. Our contemporary findings suggest that 3VD with proximal LAD involvement is still a predictor factor of higher mortality in the context of stable coronary disease and preserved ventricular function.

In several previous clinical trials, revascularization by CABG surgery increased survival compared with medical therapy in patients with three- and two-vessel disease when the proximal left anterior descending artery was involved, regardless of left ventricular dysfunction [4—8,16]. More recently, in the BARI study, there were no significant differences in 7-year survival between patients initially treated with PCI or CABG in both 2VD and 3VD with or without proximal LAD involved [17]. However, there was no report regarding the event-free survival in these studies. In the ARTS study, even though there were just 30% and 33% of patients of 3VD in the stent and CABG groups, respectively, they reported that there was no significant difference in event-free survival rate between patients with two or three vessels treated with stenting (57% vs 60%) or CABG (79% vs 76%), respectively [18].

To our knowledge this is the first post-hoc analysis of a randomized and prospective trial comparing medical, angioplasty with stent and CABG, stratified by number of vessels disease. We have not found any survival advantage at 5 years of follow-up to CABG compared to MT or PCI in all subgroups of number of vessels disease. This difference might be related to the use of stents, more homogeneity of patient characteristics, the improvement of medical therapy and interventional strategies observed in our study. Not surprisingly, however, the event-free survival rates were higher in CABG compared to PCI and MT, regardless of the number of vessels disease. The risk of event was 9.6 and 4.8 higher to PCI and MT compared to CABG, respectively in SVD patients.

In 2VD, we also found a 3.3 and 3.1-increased risk to PCI and MT compared to CABG, respectively in SVD patients. We have not found any survival advantage at 7 years of follow-up to CABG compared to MT or PCI in all subgroups of number of vessels disease. This difference might be related to the use of stents, more homogeneity of patient characteristics, the improvement of medical therapy and interventional strategies observed in our study. Not surprisingly, however, the event-free survival rates were higher in CABG compared to PCI and MT, regardless of the number of vessels disease. The risk of event was 9.6 and 4.8 higher to PCI and MT compared to CABG, respectively in SVD patients. In 2VD, we also found a 3.3 and 3.1-increased risk to PCI and MT compared to CABG, respectively. Conversely, in 3VD, a 2.9 and 2.5-fold increased to PCI and MT compared to CABG, respectively, were found. This benefit of CABG over the PCI and MT might be driven by the increased need for repeated revascularization, because the combined end-point of death, MI and angina refractory needing revascularization.

The present study has several limitations. The MASS trial was not specifically designed to compare the effects of the number of vessels disease on outcome after medical, angioplasty or CABG surgery. In the single vessel disease, the PCI group was treated with balloon angioplasty, which explained the higher risk of event compared to CABG. The higher incidence of new interventions in the patients

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>IC 95%</th>
<th>p-value</th>
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<tbody>
<tr>
<td>3VD versus SVD</td>
<td>3.14</td>
<td>1.40–7.03</td>
<td>0.0054</td>
</tr>
<tr>
<td>2VD versus SVD</td>
<td>1.89</td>
<td>0.75–4.56</td>
<td>0.1562</td>
</tr>
<tr>
<td>Age (&lt;65/&lt;65 years)</td>
<td>2.13</td>
<td>1.30–3.47</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

3VD = three-vessels disease; 2VD = two-vessels disease; SVD = single vessel disease.
submitted to PCI or MT might bias the CABG superiority results. Moreover, it was not powered to detect subtle differences on mortality. Nevertheless, a clear increase in the risk of death could be seen in 3VD after 5 years and in the multivariate analysis the 3VD was an independent predictor factor of mortality in our model.

5. Conclusions and clinical implication

Three-vessel disease was associated with worse prognosis compared to single- or two-vessel disease in patients with chronic coronary disease and preserved ventricular function at 5-year follow-up. In addition, event-free survival rates were higher for bypass surgery, independent of the number of vessel diseased in these subsets of patients.

Important developments in PCI have occurred since this trial was started. The use of glycoprotein IIb/IIIa receptor inhibitors, new antiplatelet agents and application of drug-eluting stents (DES) hold the promise of significant reduction in restenosis. In addition, surgery without cardiopulmonary bypass and other new surgery techniques could have an important effect on surgical results. The time of this analysis is also advantageous, because it provides baseline data for comparisons with the results of the new therapeutic strategies. Thus, future studies will be necessary to define the impact of the number of vessels disease on therapeutic results of stable CAD with the new current practice of CAD treatment.

References


