Long-term outcomes of high-risk elderly male patients with multivessel coronary disease: optimal medical therapy versus revascularization

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Abstract

Background Many studies have indicated that medical therapy and percutaneous coronary intervention have similar effects in terms of the long-term prognosis of patients with stable coronary artery disease. This study investigated the effects of optimal medical therapy (OMT) and revascularization-plus-OMT in elderly patients with high-risk angina. Methods In this prospective non-randomized study, 241 consecutive high-risk elderly male patients (65–92 years of age) with angiographically confirmed multivessel disease were enrolled in the registry from January 2004 to April 2005. Of these, 98 patients underwent OMT and 143 underwent revascularization therapy plus OMT. Results After 6.5 years of follow-up, we found that the rate of long-term cardiac mortality was significantly higher in patients who underwent OMT than in those who underwent revascularization (6.5-year unadjusted mortality rate, 14.3% for OMT vs. 7.0% for revascularization patients; log-rank P = 0.04). However, the overall risks of major adverse cardiac cerebrovascular events (MACCE) were similar among all patients (6.5-year unadjusted mortality rate, 29.6% for OMT vs. 27.3% for revascularization patients; log-rank P = 0.67). Conclusions OMT was associated with an increase in cardiac death but a similar 6.5-year risk of MACCE compared with revascularization in high-risk elderly male patients with coronary multivessel disease.

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1 Introduction

Coronary artery disease is a leading cause of death in many countries. In 2005, 7.6 million patients worldwide died from coronary disease.[1] In China, 3 million died from coronary disease in 2006 according to the 2007 Report on Cardiovascular Disease in China. In the United States, there are approximately 1.7 million hospital admissions annually for acute coronary syndromes (ACS).[2] An increasing number of patients with coronary artery disease undergo coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). Additionally, many drugs are now available for the treatment of coronary artery diseases. In earlier randomized trials including patients with chronic[1–5] stable coronary artery disease, PCI did not afford greater benefits in terms of death, myocardial infarction (MI), or the need for subsequent revascularization compared with conservative medical treatment. However, for patients with high-risk angina, no consensus has emerged on whether medical therapy or revascularization is optimal.[6–8]

In this prospective non-randomized study, we report the long-term (mean follow-up 6.5 years) outcomes of 241 consecutively enrolled high-risk elderly male patients with multivessel disease treated with either optimal medical therapy (OMT) or revascularization-plus-OMT.

2 Methods

2.1 Study population

From January 2004 to April 2005, 241 consecutive high-risk elderly male patients (65–92 years of age) with angiographically confirmed multivessel disease (including left main coronary artery disease) were enrolled in our hospital. Of these, 98 patients underwent OMT and 143 underwent revascularization-plus-OMT (110 patients underwent stent implantation, and 33 underwent CABG). A high-risk patient was defined as a patient with the following clinical characteristics: (1) Canadian Cardiovascular Society class III angina as the first symptom, developing within two months of enrolment; or (2) development of ACS or...
re-hospitalization to treat recurrent ACS within 2 weeks of enrolment; or (3) both (1) and (2) above.[8] Coronary multivessel disease was defined as stenosis \( \geq 70\% \) in at least two of the three main coronary arteries. Left main coronary artery disease was defined as stenosis \( \geq 50\% \) of the left main coronary artery. Patients who had previously undergone revascularization and those who presented with cardiogenic shock or a history of (a) cerebrovascular event (s) within the prior 6 months were excluded.

Before each patient was discharged, the following demographic data were recorded using a standard registry form: (1) name, nationality, birth date, occupation, home address, and contact telephone number; (2) time of onset of symptoms and nature of symptoms (chest pain, breathlessness on exertion, syncope, fatigue, other signs and symptoms); (3) medical history (hypertension, diabetes mellitus, hyperlipidemia, smoking, and cerebrovascular events); (4) personal and family history; (5) physical data [height, weight, blood pressure, heart rate, cardiac auscultation, New York Heart Association (NYHA) functional class]; (6) laboratory test results [total cholesterol, low-density-lipoprotein cholesterol (LDL-c), high-density-lipoprotein cholesterol (HDL-c), triglyceride, and fasting glucose levels]; (7) electrocardiographic data; (8) a chest X-ray; (9) an echocardiogram; (10) angiographic characteristics; (11) clinical diagnosis; and (12) medical treatment provided.

Our study was approved by the Ethics Committee of the Chinese PLA General Hospital and followed the principles of the Declaration of Helsinki (1997). Informed consent was obtained from all patients.

2.2 Treatment options

All patients were offered PCI or CABG. Every decision was made by consensus among the case cardiologists, cardiac surgeons, and the patient. OMT was considered for patients who refused revascularization because of advanced age, comorbidities, a refusal to tolerate the pain of surgery, or an inability to understand the revascularization technique.

For unstable patients, OMT was consistent with established practice guidelines for patients with unstable angina/non-ST-elevation MI and ST-elevation MI.[9–11] For stable patients, OMT was also consistent with established practice guidelines for patients with chronic stable angina and included antiplatelet therapy (aspirin at 100 mg per day or clopidogrel at 75 mg per day if the patient was aspirin-intolerant),[12,13] anti-ischemic therapy (long-acting metoprolol, amiodipine, and isosorbide mononitrate alone or in combination), lisinopril or losartan to treat (or secondarily prevent) hypertension, and aggressive therapy to lower LDL-c levels [simvastatin or atorvastatin alone, or in combination with ezetimibe; target 60–85 mg/dL (1.55 to 2.20 mmol/L)]. Lifestyle counselling with regard to diet, smoking cessation, glycemic control, and weight loss was provided to both groups.

Interventions for coronary artery disease were consistent with current practice guidelines. Upon insertion of drug-eluting stents, attempts were made to fully cover the diseased segment and to ensure complete stent apposition. The choice of drug-eluting stent (i.e., sirolimus-eluting or paclitaxel-eluting) was left to the discretion of the interventionist. PCI success was defined as angiographically normal coronary artery flow and residual stenosis < 20%, without major complications (i.e., acute MI, a need for CABG or repeat PCI, or death). Among patients who underwent PCI, antiplatelet therapy and periprocedural anticoagulation followed standard regimens. Before or during PCI, patients were given loading doses of aspirin (300 mg) and clopidogrel (300 mg) or ticlopidine (500 mg) unless they had previously received antiplatelet medications. After each procedure, patients were maintained on aspirin (100 mg once daily) and clopidogrel (75 mg once daily) or ticlopidine (250 mg twice daily) for at least six months after a drug-eluting stent was placed and for at least one month after a bare metal stent was placed. Prolongation of clopidogrel treatment was at the discretion of the surgeon. Patients with high-risk clinical profiles or who underwent complicated procedures were given cilostazol (100 mg twice daily) for at least one month (or longer, at the discretion of the surgeon). CABG surgery was performed using standard bypass techniques. Whenever possible, the internal thoracic artery was preferentially used for revascularization of the left anterior descending (LAD) artery. Complete revascularization was performed when possible, using atrial conduits or saphenous vein grafts. After the procedures, patients were given 100 mg aspirin per day indefinitely. The time between the index hospitalization and revascularization was 4.23 ± 4.46 h among the 110 patients who underwent stent implantation, and it was 17.42 ± 7.91 days among the 33 patients who underwent CABG.

2.3 Clinical follow-up

From February 1 to March 30, 2011, follow-up information was obtained during visits to the outpatient clinic, by review of medical records, or by telephone interview. Follow-up was complete for all patients (follow-up rate: 100%). The clinical parameters recorded during follow up included cardiac symptoms, survival status (survival or death), NYHA cardiac functional class, and electrocardiographic and echocardiographic data. In the revascularization-plus-OMT group, multislice computed tomography was performed six months
after PCI to assess restenosis status. If myocardial ischemia or bypass graft stenosis was evident on initial clinical assessment, follow-up coronary angiography was performed.

2.4 Clinical outcomes

Major adverse cardiac cerebrovascular events (MACCE) were defined as a composite of death from all causes, non-fatal MI, and cerebrovascular events. Death was defined as any post-procedural death. Cardiac death was restricted to death from MI, congestive heart failure, arrhythmia, or sudden death. Diagnosis of MI was based on the recommendations of the American College of Cardiology/American Heart Association (ACC/AHA). A cerebrovascular event was defined as a stroke, a transient ischemic attack, a reversible ischemic neurologic deficit, or a coma and was confirmed by a neurologist and on a computed tomography scan.

2.5 Statistical analysis

All Registry Forms were coded after collection. Data were input by two operators (separately) using Epidata 3.1 software. All data are expressed as means ± SD. An unpaired student’s t-test was used to compare data on continuous variables between the two groups. The chi-square test was used to compare non-continuous variables (expressed as proportions). Cumulative event rates were estimated using the Kaplan-Meier method, and differences were assessed with the aid of the log-rank test. Cox’s multivariable regression was used to adjust baseline differences including age, sex, blood pressure levels and serum lipid level that may influence clinical end points. P < 0.05 was considered to reflect significance in statistical interactions and subgroup comparisons. Calculations were performed with SPSS 18.0 software for Windows (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Baseline characteristics

The demographic and baseline clinical characteristics of the patients are summarized in Table 1. The average patient age was 75.0 ± 8.6 years (75.8 ± 8.7 years in the OMT group and 74.4 ± 8.5 years in the revascularization-plus-OMT group). Age at first medical examination did not differ between the groups (P = 0.18). Those aged ≥ 75 years constituted 62.2% of the OMT group and 60.8% of the revascularization-plus-OMT group (P = 0.82). In terms of clinical characteristics, the mean fasting glucose level was higher in the revascularization-plus-OMT group (5.5 ± 1.4 vs. 5.2 ± 1.0 mmol/L, P < 0.01). The two groups were similar with regard to other clinical characteristics. The prevalence of ST-elevation MI was higher in the revascularization-plus-OMT group than in the OMT group (26.6% vs. 26.6%, P = 0.001) and that of unstable angina was lower in the revascularization-plus-OMT group than in the OMT group (58.7% vs. 77.6%, P = 0.002). The frequency of non-ST-elevation MI was similar in the two groups (14.7% vs. 13.3%, P = 0.76) at enrolment.

The baseline angiographic characteristics of the two groups are presented in Table 2. The prevalence of two-vessel disease and three-vessel disease were similar in the

Table 1. Baseline clinical characteristics of patients in different groups.

| Characteristic | OMT (n = 98) | Revascularization-plus-OMT (n = 143) | P |
|---------------|-------------|-----------------------------------|---|
| Demographic characteristic | | | |
| Age, yrs | 75.8 ± 8.70 | 74.4 ± 8.5 | 0.18 |
| Age ≥ 75, yrs | 61 (62.2) | 87 (60.8) | 0.82 |
| Clinical characteristic | | | |
| Body mass index, kg/m² | 24.7 ± 2.70 | 24.5 ± 2.8 | 0.26 |
| Diabetes mellitus | 29 (29.6) | 47 (32.9) | 0.35 |
| Hypertension | 62 (63.3) | 95 (66.4) | 0.36 |
| Smoker | 33 (33.7) | 49 (34.3) | 0.52 |
| Stroke history | 13 (13.3) | 19 (13.3) | 0.99 |
| Family history | 27 (27.6) | 38 (26.6) | 0.87 |
| Peripheral vascular disease | 28 (29.0) | 40 (29.3) | 0.35 |
| Total cholesterol, mg/dL | 163.0 ± 33.90 | 162.2 ± 36.7 | 0.40 |
| LDL-c, mg/dL | 88.9 ± 27.1 | 89.0 ± 27.1 | 0.85 |
| HDL-c, mg/dL | 41.5 ± 11.8 | 40.2 ± 12.3 | 0.57 |
| Triglycerides, mg/dL | 140.7 ± 62.06 | 128.5 ± 56.02 | 0.49 |
| Fasting glucose, mmol/L | 5.2 ± 1.0 | 5.5 ± 1.4 | < 0.01 |
| Systolic blood pressure, mmHg | 136.1 ± 23.40 | 134.7 ± 22.7 | 0.21 |
| Diastolic blood pressure, mmHg | 71.4 ± 12.1 | 70.8 ± 12.2 | 0.16 |
| Clinical conditions at enrolment | | | |
| Unstable angina | 76 (77.6) | 84 (58.7) | 0.002 |
| Non-ST-elevation MI | 13 (13.3) | 21 (14.7) | 0.76 |
| ST-elevation MI | 9 (26.6) | 38 (26.6) | 0.001 |
| Angiographic characteristics | | | |
| Two-vessel disease | 55 (56.1) | 68 (47.6) | 0.19 |
| Three-vessel disease | 43 (43.9) | 75 (52.4) | 0.19 |
| Left main artery disease | 21 (21.4) | 28 (19.6) | 0.73 |
| Proximal LAD disease | 43 (43.9) | 68 (47.6) | 0.57 |
| Total occlusions ≥ 1 | 6 (6.1) | 13 (9.1) | 0.40 |
| Ejection fraction | 55.3% ± 15.6% | 55.3% ± 12.1% | 0.30 |
| Ejection fraction ≤ 50% | 6 (6.1) | 16 (11.2) | 0.18 |

Data are expressed as means ± SD or n (%) unless otherwise stated. HDL-c: high-density lipoprotein cholesterol; LAD: left anterior descending artery; LDL-c: low-density lipoprotein cholesterol; MI: myocardial infarction; OMT: optimal medical therapy.
two groups. The prevalence of left main disease, proximal LAD disease, and total occlusion of one or more vessels were also similar in the two groups. The ejection fraction was 55.3% ± 15.6% in the OMT group and 55.3% ± 12.1% in the revascularization-plus-OMT group (P = 0.30). Patients with an ejection fraction ≤ 50% were slightly more common in the revascularization-plus-OMT group (11.2% vs. 6.1), but statistical significance was not attained (P = 0.18).

Medical treatments given before and during observation are presented in Table 3. The level of angiotensin receptor blocker prescribed for patients in the OMT group was higher than that prescribed for those in the revascularization-plus-OMT group (11.2% vs. 7.0%, P = 0.04). The two groups did not differ significantly with regard to other medical treatments.

### 3.2 Survival analysis

The clinical endpoints of the two groups are shown in Table 3. The overall mean follow-up time was 78.4 ± 7.6 months. The mean follow-up time was 77.6 ± 6.9 months in the OMT group and 79.8 ± 8.1 months in the revascularization-plus-OMT group (P = 0.08). MACCE (a composite of death from any cause, non-fatal MI, and cerebrovascular events) occurred in 29 patients in the OMT group and 39 in the revascularization-plus-OMT group. The all-cause death rates were 21 (21.4%) in the OMT group and 21 (14%) in the revascularization-plus-OMT group (P = 0.13). The mean age at the time of all-cause death was 80.8 ± 6.9 years in the OMT group and 81.3 ± 4.7 years in the revascularization-plus-OMT group (P = 0.77). The mean age at the time of cardiac death was 82.5 ± 6.7 years in the OMT group and 80.1 ± 5.3 years in the revascularization-plus-OMT group (P = 0.37). Apart from cardiac death, other causes of death included cancer (lung and liver cancer, pancreatic cancer, gastric cancer, renal pelvic carcinoma), acute lymphoblastic leukemia, mesothelioma of the pleura, multiple organ failure, cerebrovascular events, pulmonary infection, acute respiratory failure, ischemic bowel disease, and infective complications of lower-limb venous thrombosis. The rate of re-hospitalization to treat unstable angina was 10.2% in the OMT group and 16.8% in the revascularization-plus-OMT group (P = 0.15).

Kaplan-Meier estimates showed that cardiac mortality was significantly higher in patients who underwent OMT compared with those who underwent revascularization-plus-OMT (log-rank test; 6.5-year unadjusted mortality rate 14.3% for OMT versus 7.0% for revascularization-plus-OMT; log-rank P = 0.04; Figure 1A). The frequencies of cardiac death/non-fatal MI did not significantly differ between the OMT and the revascularization-plus-OMT groups (log-rank test; 17.3% vs. 10.5%, P = 0.09, Figure 1B). The overall risks of all-cause death, non-fatal MI, and cerebrovascular events were similar among all patients (6.5-year unadjusted mortality rates 29.6% for OMT vs. 27.3% for revascularization-plus-OMT patients; log-rank P = 0.67, Figure 1C). After adjustment for baseline differences, these results did not change.

### 4 Discussion

Our study used a prospective, non-randomized design involving observations of clinical procedures to compare the long-term outcomes of high-risk elderly male patients with coronary multivessel disease treated with OMT and revascularization-plus-OMT. The 6.5-year clinical outcomes showed that the rate of long-term cardiac mortality was significantly higher in patients who underwent OMT than in those who underwent revascularization-plus-OMT. The

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Table 2. Medical treatments before and during observation.

| Medical treatment                  | OMT (n = 77) | Revascularization-plus-OMT (n = 123) | P     |
|-----------------------------------|-------------|-------------------------------------|-------|
| Patients evaluated, n             | 98          | 143                                 | 123   |
| Aspirin                           | 93 (94.9)   | 69 (89.6)                           | 136 (95.1) | 108 (87.8) | 0.94 |
| Clopidogrel                       | 86 (87.8)   | 11 (14.3)                           | 117 (81.8) | 23 (18.7)  | 0.21 |
| ACE inhibitor                      | 19 (19.4)   | 21 (27.3)                           | 32 (22.4) | 39 (31.7)  | 0.58 |
| Angiotensin receptor blocker      | 28 (28.6)   | 23 (29.9)                           | 23 (16.0) | 31 (25.2)  | 0.02 |
| β-blocker                         | 51 (58.0)   | 48 (62.3)                           | 87 (60.8) | 67 (54.5)  | 0.66 |
| Calcium-channel blocker           | 63 (64.3)   | 32 (41.6)                           | 91 (63.6) | 56 (45.5)  | 0.91 |
| Statins                           | 83 (84.7)   | 71 (92.2)                           | 121 (84.6) | 113 (91.9) | 0.99 |
| Nitroglycerin                     | 92 (93.9)   | 44 (57.1)                           | 138 (96.5) | 65 (52.8)  | 0.34 |

Data are expressed as n (%) unless otherwise stated. *P < 0.05 between OMT and revascularization-plus-OMT. ACE: angiotensin-converting enzyme; OMT: optimal medical therapy.

Table 3. Clinical endpoints at 6.5 years in different groups.

| 6.5-year cumulative MACCE         | OMT (n = 98) | Revascularization-plus-OMT (n = 143) | P     |
|-----------------------------------|-------------|-------------------------------------|-------|
| Mean follow-up time, months       | 47.6 ± 25.8 | 54.6 ± 26.5                          | 0.88  |
| Cardiac death, yrs                | 14 (14.3)   | 10 (7.0)                             | 0.06  |
| Age at cardiac death, yrs         | 82.5 ± 6.7  | 80.1 ± 5.3                           | 0.37  |
| All-cause deaths                  | 21 (21.4)   | 20 (14)                              | 0.13  |
| Age at all-cause death, yrs       | 80.8 ± 6.9  | 81.3 ± 4.7                           | 0.77  |
| Nonfatal myocardial infarction    | 3 (3.1)     | 5 (3.5)                              | 0.85  |
| Cerebrovascular events            | 5 (5.1)     | 14 (9.8)                             | 0.19  |
| Rehospitalization to treat UA     | 10 (10.2)   | 24 (16.8)                            | 0.15  |

Data are expressed as means ± SD or n (%) unless otherwise stated. MACCE: major adverse cardiac cerebrovascular events; OMT: optimal medical therapy; UA: unstable angina.
overall risks of all-cause death, non-fatal MI, and cerebrovascular events were similar in the two groups.

For patients with chronic stable angina, most prior studies have indicated that PCI did not afford any benefit in terms of any of death, MI, or the need for subsequent revascularization compared with conservative medical treatment. However, for patients with other clinical conditions, such a conclusion cannot yet be drawn. In the prospective study, 275 patients with medically refractory class IV angina and coronary disease were randomly assigned to receive transmyocardial revascularization or conventional medical therapy. Patients who underwent transmyocardial revascularization enjoyed significantly better outcomes in terms of improvement in angina, survival free of cardiac events, lack of treatment failure, and freedom from cardiac-related rehospitalization compared with similar patients who received medical therapy alone. In another study, conducted by Pfisterer et al., elderly patients with chronic angina who were similar in terms of symptoms, quality-of-life, and the frequencies of death and non-fatal infarction underwent either invasive or OMT. The invasive approach was associated with the risk of a need for early intervention, whereas medical management was associated with a near-50% probability of later hospitalization and revascularization. In a recent study, Maron, et al., analyzed 264 patients with high-risk coronary artery disease (the COURAGE trial) and found that OMT alone did not increase the risk of death or MI at 4.6 years of follow up or cause deterioration of angina at one year of follow up. However, such treatment was associated with a high rate of crossover to revascularization. To our knowledge, no study has yet compared the long-term effectiveness of OMT with revascularization-plus-OMT. Compared with other studies, all of our patients were high-risk, with angiographically confirmed multivessel disease, including left main coronary artery disease. Although the study was not a randomized trial, the choice of OMT or revascularization-plus-OMT was made collaboratively by cardiologists, cardiac surgeons, and patients, and the demographic and baseline clinical characteristics of all patients were similar at enrolment. Moreover, the mean patient age in our study was 75.0 ± 8.6 years, and those aged ≥ 75 years constituted > 60% of the OMT and revascularization-plus-OMT groups. The overall mean follow-up time was long (78.4 ± 7.6 months). Therefore, our conclusions are valid for elderly patients with multivessel disease who are in an unstable clinical condition.

The patients who participated in the present study had high mortality rates because of advanced age and their high-risk profiles. However, cancer and other diseases caused 41.5% of all deaths. Additionally, most cerebrovascular events were non-fatal. Therefore, cardiac mortality may be a more reliable measure to reflect the effectiveness of various therapies used to treat coronary multivessel disease.

Although the prevalence of ST-elevation MI was higher in the revascularization-plus-OMT group than in the OMT group (26.6% vs. 26.6%, P = 0.001), cardiac mortality remained significantly higher in patients who underwent OMT compared with those who underwent revascularization-plus-OMT (log-rank test), showing that revascularization-plus-OMT afforded more benefits for patients presenting with ST-elevation MI. This therapy reduced cardiac mortality regardless of age.

4.1 Limitations

Our study had several limitations. First, all patients were
recruited from our tertiary referral center rather than from the broader patient community, our results may reflect some selection bias. Second, our sample size was relatively small, and larger samples of patients enrolled in prospective cohort studies are needed to confirm our conclusions. Moreover, although previous studies have suggested that well-designed observational studies yield valid results and do not systematically overestimate the magnitude of treatment effects compared with randomized controlled trials, the inherent limitations of observational studies include non-randomization and the possible presence of unrecognized confounding factors.[14]

4.2 Conclusions

In high-risk elderly male patients with coronary multivessel disease, OMT was associated with an increase in cardiac death and similar 6.5-year risks of all-cause death, non-fatal MI, and cerebrovascular events compared with revascularization plus OMT.

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