J-SAP Study 1-2: Outcomes of Patients With Stable High-Risk Coronary Artery Disease Receiving Medical-Preceding Therapy in Japan

A Comparison With CABG-Preceding Therapy

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Background
Stable coronary artery disease (CAD) is classified into 2 types: high-risk (ie, 3-vessel disease, left main trunk lesions, or ostial lesions of the left anterior descending (LAD)) and low-risk (1- or 2-vessel disease other than ostial lesions of the LAD). Generally, the former is treated with coronary artery bypass grafting-preceding therapy (CABG), but not medical-preceding therapy (Medical); however, this is based on evidence from 30 years ago or more and does not reflect the recent progression of Medical and CABG. In addition, a randomized study has not been performed in Japan.

Methods and Results
In high-risk CAD, the long-term outcomes of 77 Medical patients and age-, sex-, coronary-lesion-, symptom- and risk-factor-matched 99 CABG patients were surveyed over 3 years (mean: 3.4 years) starting in 2000 at 37 nationwide hospitals. The incidences of cardiac death and cardiac death + non-fatal acute coronary syndrome (9.1% and 11.7% in Medical, and 2.0% and 3.0% in CABG, respectively) were significantly higher and the improvement in clinical symptoms was significantly lower in Medical than CABG.

Conclusions
CABG is recommended in patients with high-risk CAD from the view of long-term prognosis; however, it should be remembered that the long-term outcome in Medical has considerably improved. (Circ J 2006; 70: 1012–1016)

Key Words: Coronary artery bypass grafting; High-risk coronary artery disease; Medical-preceding therapy

Coronary artery disease (CAD) is a serious and common disease that seriously influences the prognosis and quality of life of patients. Stable CAD is classified into 2 types according to the lesion site and number of affected vessels: high-risk CAD comprises 3-vessel disease, ostial lesions of the left anterior descending (LAD), or left main trunk (LMT) lesions, and carries a high risk of death; low-risk CAD is 1- or 2-vessel disease other than ostial lesions of LAD, and carries a low risk of death. Medical-preceding therapy is initial anti-anginal agents to control the angina attacks, and coronary intervention is only considered if medical therapy is not effective. Coronary artery bypass grafting (CABG)-preceding therapy is defined as initial CABG combined with medical therapy.

The strategy of CABG-preceding therapy for stable high-risk CAD is based on the evidence of many trials performed in Western countries; however, these trials were performed 30 years ago or more and do not completely reflect the recent progression of both medical and CABG therapies, which has been dramatic during the past 30 years and the recent long-term prognosis of patients with low-risk CAD has also improved. We hypothesized that the prognosis of patients with stable high-risk CAD treated with medical-preceding therapy has also improved dramatically and to our knowledge no comparison of long-term prognosis and cost between medical- and CABG-preceding therapies has been done in Japan.

Methods

Subjects and Data Collection
In 2001, 77 consecutive stable high-risk CAD patients who had received medical-preceding therapy (Medical group) during 2000 were retrospectively registered from 34 nationwide hospitals (Appendix 1). Ninety-nine high-risk CAD patients from the same 34 nationwide hospitals who had received CABG-preceding therapy during 2000 and were matched for age, gender, severity of angina, and number of lesion vessels were registered in 2001 as controls (CABG group). The reasons for selecting a particular therapy for each patient depended on the consensus between the doctor and patient at each hospital at the time of treatment. Each patient with high-risk CAD had significant coronary stenosis (≥75% stenosis according to the American Heart Association classification) of 3-vessel disease or ostial lesions of LAD, or LMT lesions (≥50% stenosis), on coronary cine-angiography. Patients with acute coronary syndrome (ACS) were excluded. Between 2002 and 2003, follow-up data from each patient were collected by the Second Department of Internal Medicine, Gifu University Graduate School of Medicine. The mean follow-up period

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was 1,236±182 days in the Medical group and 1,244±185 days in the CABG group. This study was approved by the local ethics committee on human research (Gifu University, Japan).

**Definition of ACS in This Study**

ACS was defined as a case of acute myocardial infarction or unstable angina requiring emergency cardiac catheterization; that is, patients who underwent elective percutaneous coronary intervention (PCI) for uncontrollable angina in the Medical group or the CABG group were not designated as ACS patients.

**Definition of the Severity of Angina Symptoms**

We classified the severity of angina symptoms into 5 grades using the modified Canadian Cardiovascular Society classification (Table 1). We investigated the severity of angina symptoms at initial entry and 1 year later in both groups.

**Statistical Analysis**

The percentages of patients progressing to the primary endpoints of cardiac death or ACS in each treatment group were compared using Kaplan-Meier estimates. Time courses to cardiac death and to cardiac death/ACS are presented using Kaplan-Meier curves. Averaged age and changes in the severity score of angina were compared between the Medical and CABG groups using 1-way analysis of variance (Bonferroni/Dunn), and if the difference was significant, a modified unpaired t-test was used to assess if it was significantly different. All values are expressed as the mean±SD. A p-value less than 0.05 was regarded as significant. Other outcomes were compared using the chi-square test.

**Results**

**Background of Patients**

The age, gender, mean value of initial symptom grade and number of patients with culprit lesions in the LMT were similar between the 2 groups (Table 2). The distribution of underlying diseases was similar, particularly for old myocardial infarction (approx. 40% in both groups; Table 3). There was no significant difference in medication (Table 4).

**Treatment Course**

During follow-up of 3.4 years, only 22 of the 77 patients (28.6%) in the Medical group had repeated coronary angiography (CAG) (average: 1.7±1.1 times, range 1–5 times), whereas 53 of the 99 patients (53.5%) in the CABG group had repeat CAG (2.3±2.5, range 1–14 times).

Only 10 patients (13.0%) in the Medical group had additional PCI (average: 1.5±0.8, range 1–3 times), whereas 11 (11.1%) in the CABG group had additional PCI and/or CABG (1.9±1.3, 1–6 times).

One year later, the severity of angina symptoms was well improved in both groups; in particular, CABG-preceding therapy was significantly more effective than medical-preceding therapy (p<0.05, Table 5).

**Long-Term Prognosis**

During the 3.4-year follow-up, the rate of cardiac death...
in the Medical group (9.1%) was significantly higher than in the CABG group (2.0%) (Fig 1A). The causes were ACS (3.9%) or other cardiac disease (5.2%) in the Medical group and only ACS (2.0%) in the CABG group. The rates of non-fatal ACS were similar between the 2 groups. However, the overall rates of cardiac death and non-fatal ACS were significantly lower in the CABG-preceding group than in the medical-preceding group. (B) In patients with disease of the LMT during the 3.4-year follow-up, the rates of cardiac death and non-fatal ACS were similar between the 2 groups. However, the overall rates of cardiac death and non-fatal ACS were significantly lower in the CABG-preceding group than in the medical-preceding group. CAD, coronary artery disease; ACS, acute coronary syndrome; LMT, left main trunk; CABG, coronary artery bypass grafting (CABG-preceding group); Medical, medical-preceding group. *p<0.05 vs Medical.

Fig 1. Kaplan-Meier curves showing the primary endpoints during the 3.4-years of follow-up. (A) In patients with high-risk CAD (LMT disease and 3-vessel disease), the rate of cardiac death in the medical-preceding group was significantly higher than in the CABG-preceding group. The rates of non-fatal ACS were similar between the 2 groups. Thus, the overall rates of cardiac death and non-fatal ACS were significantly lower in the CABG-preceding group than in the medical-preceding group. CAD, coronary artery disease; ACS, acute coronary syndrome; LMT, left main trunk; CABG, coronary artery bypass grafting (CABG-preceding group); Medical, medical-preceding group. *p<0.05 vs Medical.

Fig 2. Total cost during the 1st and the 2nd years. Averaged annual medical cost per patient was markedly cheaper in the medical-preceding group (Medical) than in the coronary artery bypass grafting-preceding group (CABG), 2.3-fold cheaper during first year. However, the cost during the second year was similar between the 2 groups.

Total Cost During the First and Second Years
The total cost per patient in the Medical and CABG groups during the first year was 1,908,230±1,606,810 yen and 4,474,450±2,491,600 yen, respectively, and 685,700±
1,223,730 yen and 715,650±1,054,500 yen during the following year, respectively. Thus, the total cost per patient was markedly lower in the Medical group, 2.3-fold cheaper during the first year; however, the cost during the second year was similar between the 2 groups (Fig 2).

Discussion

Long-Term Prognosis

This study demonstrated that for Japanese patients with high-risk stable angina, the incidence of cardiac death, as well as the overall rates of cardiac death and non-fatal ACS, are lower for those receiving CABG-preceding therapy than medical-preceding therapy. CABG-preceding therapy was also superior to medical-preceding therapy for angina relief. These are similar findings to data from Western countries previously reported 30 or more years ago; although a randomized trial has not been performed subsequently. Between the 2 groups in the present study, there was no significant difference in background (ie, age, gender, grade of initial symptoms, coronary lesion, risk factors and medical treatment). Thus, CABG-preceding therapy is still clearly superior, as it was 30 years ago, although there is no evidence from a recent meta-analysis or our data showing the favorability of intervention on long-term prognosis in patients with low-risk CAD (PCI-preceding therapy compared with medical-preceding therapy).

Long-Term Prognosis in Patients Recently Undergoing Medical- or CABG-Preceding Therapies

In the present study the incidence of cardiac death for high-risk CAD patients with medical-preceding therapy was 9.1% over 3.4 years, although we do not know previous or other recent data for Japan. In a trial performed in the USA in the 1970s in which the characteristics of the patients were similar to those of the present study, it was approximately 23% over 3 years, and to our knowledge there has not been a more recent study in Western countries. Our finding suggests that the long-term prognosis for medical-preceding therapy has improved, which can be explained by the recent progression of drugs such as statins, angiotensin receptor blockers, long-acting calcium antagonists etc.

In CABG-preceding therapy group of the USA study, the incidence of cardiac death over 3 years in patients with high-risk CAD was approximately 13% in the 1970s. Our study showed an incidence of cardiac death of 2.0% over 3.5 years in patients with high-risk CAD and CABG-preceding therapy. These data are similar to recent reports in Japan and Western countries; therefore, it is clear that the long-term prognosis for high-risk CAD patients with CABG-preceding therapy has improved recently, associated with the progression of medical treatment, as well as surgical procedure, because improvement was observed in patients with medical-preceding therapy and there was no significant difference in medical treatment between the Medical and CABG groups.

Total Cost

Total cost was markedly lower in the Medical group than the CABG group during the first year, but the cost during the second year was similar between the 2 groups. However, CABG-preceding therapy is recommended in patients with high-risk CAD because of the better long-term prognosis.

Study Limitations

In this study, randomization was retrospectively performed using consecutive patients with high-risk CAD treated by medical-preceding therapy that had been selected by consensus between the doctor and patient, although the long-term outcomes were surveyed prospectively for an average of 3.4 years. Therefore, the most important limitation is that the subjects were not general patients with high-risk CAD. Second, the improvement of angina symptoms in the short term after treatment was not examined. Finally, this study compared the prognosis and costs between medical- and CABG-preceding therapy, but PCI was not referred. Thus, a comparative study of CABG and PCI in patients with LMT disease is warranted.

Conclusion

CABG-preceding therapy in patients with high-risk CAD is more advantageous than medical-preceding therapy from the perspective of long-term prognosis.

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References


Appendix 1

Study Participants

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