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Title	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( 本文 (Fulltext) )
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# 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;<sup>1–4</sup> however, these trials were performed 30 years ago or more<sup>2–4</sup> and do not completely reflect the recent progression of both medical and CABG therapies, which for medical therapy has been dramatic during the past 30 years and the recent long-term prognosis of patients with low-risk CAD has also improved.<sup>5</sup> 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 ( $\geq 75\%$  stenosis according to the American Heart Association classification) of 3-vessel disease or ostial lesions of LAD, or LMT lesions ( $\geq 50\%$  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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**Table 1 Classification of Severity of Angina**

Class 0: No angina even during strenuous or prolonged physical activity
Class 1: Angina only during strenuous or prolonged physical activity
Class 2: Angina only during vigorous physical activity (ie, slight limitation)
Class 3: Symptoms during occasional ADL (ie, mild limitation)
Class 4: Symptoms during ADL (ie, moderate limitation)
Class 5: Unable to perform any activity without angina or angina at rest (ie, severe limitation)

ADL, activities of daily living.

**Table 2 Patient Characteristics**

	Medical	CABG
Total no. of patients	77	99
Gender (ratio of male)	72.7%	74.7%
Averaged age (years)	69.6±9.5	68.5±7.8
Patients older than 65 years	74.0%	72.3%
Mean value of initial symptom grade	1.7±1.5	1.8±1.4
% of patients with culprit in LMT	29.9%	35.4%
% of stenosis in LMT culprit lesion	60.2±15.4	64.4±16.3

Values are mean±SD.

CABG, coronary artery bypass grafting; LMT, left main trunk.

**Table 3 Underlying Diseases**

	Medical (%)	CABG (%)
Hypertension	59.7	53.0
Diabetes mellitus	44.2	45.8
Hyperlipidemia	50.6	53.0
Hyperuricemia	10.4	7.2
Old myocardial infarction	42.9	41.0

Abbreviation see in Table 2.

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

**Table 4 Medications**

	Medical (%)	CABG (%)
Antiplatelets	85.7	78.3
Anticoagulants	14.3	27.7
Ca antagonists	53.2	53.9
KATP-channel opener	24.7	19.3
β-blockers	42.9	25.3
Nitrates	67.5	62.7
ACEI	39.0	27.7
ARB	13.0	16.9
Statin	41.6	43.3

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. Other abbreviations see in Table 2.

**Table 5 Changes in the Severity of Angina After 1 Year**

	Medical		CABG	
	Initial entry	1 year later	Initial entry	1 year later
Overall	1.7±1.5	→ 1.0±1.2	1.8±1.4	→ 0.3±0.7*
Severity of angina: 0–2	0.8±0.8	→ 0.6±0.7	1.0±0.9	→ 0.2±0.5
Severity of angina: 3–5	3.6±0.7	→ 1.8±1.5	3.6±0.7	→ 0.6±0.9*

See Table 1 for classification of angina severity.

\**p*<0.05 vs Medical-preceding group.

Abbreviation see in Table 2.

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 arteriography (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).

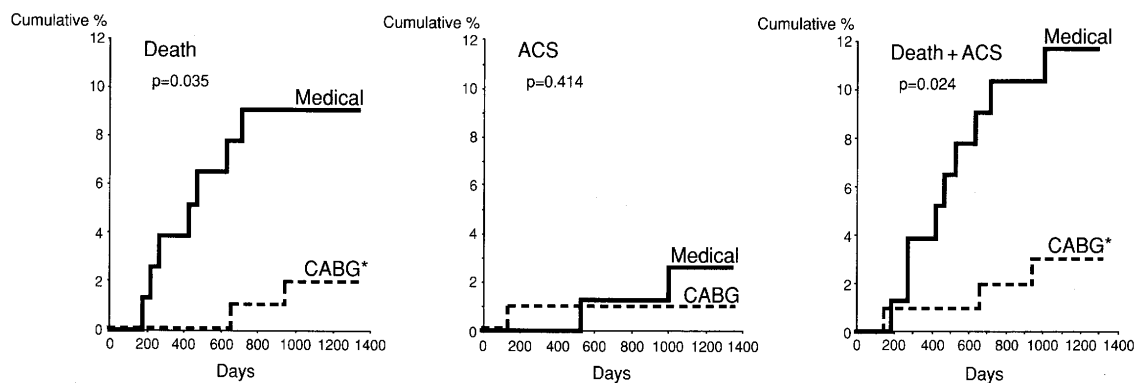
Only 10 patients (13.0%) in the Medical group had additional PCI (average: 1.5±0.8, range 1–3 times), whereas 11 (11.1%) in the CABG group had additional PCI and/or CABG (1.9±1.3, 1–6 times).

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

### A: Patients with high-risk CAD



### B: Patients with LMT disease

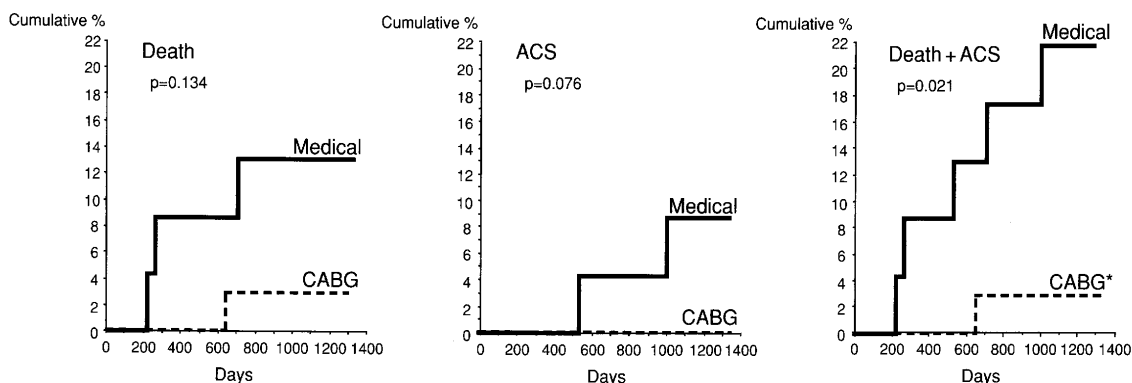


Fig 1. Kaplan-Meier curves showing the primary endpoints during the 3.4-years of follow-up. (A) In patients with high-risk CAD (LMT disease and 3-vessel disease), the rate of cardiac death in the medical-preceding group was significantly higher than in the CABG-preceding group. The rates of non-fatal 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. (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.

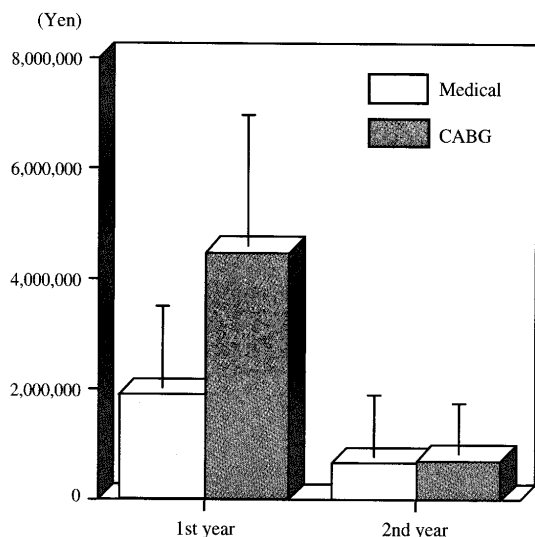


Fig 2. Total cost during the 1st and the 2nd years. Averaged annual medical cost per patient was markedly cheaper in the medical-preceding group (Medical) than in the coronary artery bypass grafting-preceding group (CABG), 2.3-fold cheaper during first year. However, the cost during the second year was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

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 (2.6% [Medical] vs 1.0%) (Fig 1A). Thus, the overall rates of cardiac death and non-fatal ACS were significantly lower in the CABG (3.0%) than in the Medical group (11.7%) (Fig 1A). Non-cardiac death rates were similar between the 2 groups: Medical group (5.2%, 4 of 77 patients: 2 gastric cancer, 1 renal failure, 1 pneumonia) and CABG group (2.0%, 2 of 99 patients: 1 lung cancer, 1 pneumonia) ( $p = 0.250$ ).

In patients with disease of the LMT (23 of 77 patients in the Medical group, and 35 of 99 patients in the CABG group) during the 3.4-year follow-up, the rates of cardiac death and non-fatal ACS (Fig 1B) were similar between 2 groups. However, the overall rates of cardiac death and non-fatal ACS in patients with disease of the LMT were significantly lower in the CABG group (2.9%) than in the Medical group (21.7%) (Fig 1B).

#### Total Cost During the First and Second Years

The total cost per patient in the Medical and CABG groups during the first year was  $1,908,230 \pm 1,606,810$  yen and  $4,474,450 \pm 2,491,600$  yen, respectively, and  $685,700 \pm$

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 the data from Western countries previously reported 30 or more years ago<sup>2-4</sup> 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<sup>6</sup> or our data<sup>5,7</sup> 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<sup>4</sup> 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<sup>4</sup> 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<sup>8</sup> and Western countries;<sup>9</sup> 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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## Appendix 1

### Study Participants

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