Clinical Studies

Design and Rationale of the Japanese Coronary Artery Disease (JCAD) Study
A Large-scale, Multicentered Prospective Cohort Study

JCAD study Investigators and Operation Secretariat headed by
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SUMMARY

Since there is insufficient evidence on patients with coronary artery disease in Japan, the Japanese Coronary Artery Disease (JCAD) Study, in which 217 institutions participate, was designed to collect basic data based on evidence-based medicine (EBM). In this study, cardiac catheterization is performed on all cases to select study subjects confirmed as having CAD diagnosed based on the criteria that he or she has stenosis in at least one branch of a coronary artery to the extent of 75% or higher according to the AHA classification. Data including background information, risk factors, clinical management, and medication are to be collected over the web. The follow-up arm of the study consists of following each subject for three years to obtain data on the long-term prognosis of patients with CAD while the other arm is for enrolling new subjects every six months who will be followed for six months only for the purpose of determining the latest trend in patients. The two arms of the study have been ongoing since April 2000. As of September 30, 2003, 15,506 subjects have been enrolled in the follow-up arm and the follow-up data have been entered in the database. The authors plan to report data showing any correlation between incidence rate, focusing mainly on cerebrocardiovascular events, and other factors such as the management of risk factors, and type and dosage of medications obtained in the largest cohort ever studied in Japan of patients with a coronary artery lesion confirmed by cardiac catheterization. (Jpn Heart J 2004; 45: 895-911)

Key words: Coronary artery disease, Coronary risk factors, Japanese prospective cohort, Major cardiovascular event (MACE), Pharmacological treatment, Registration via Web

DYNAMIC statistics of the Japanese population in 19991) show that the number of deaths from heart disease amounts to 151,079 a year, which corresponds to 15.4% of all deaths, and is second to only those from malignant neoplasms. Considering that coronary artery disease (CAD) is responsible for the majority of deaths from heart disease, seeking an approach to the trends in patients with CAD
and the coronary risk factors behind it is one of the most important tasks for clinicians.

In European countries as well as in the USA, the frequency of occurrence of CAD has traditionally been high and many cohort studies such as the Framingham Study\(^2\) have been conducted. These studies have shown that the combination of various factors including smoking, hypertension, diabetes and hypercholesterolemia is responsible for the onset of CAD. Based on these findings, many related societies and organizations have issued various guidelines,\(^3\)-\(^6\) aiming at helping people properly manage known risk factors, and these have resulted in a certain level of success. In Japan too, several important cohort studies such as the Hisayama Study,\(^7\) Hiroshima-Nagasaki Study,\(^8\) and J-LIT\(^9\) were published. Based on the findings of these studies, various guidelines were prepared and attempts have been made to apply these guidelines to day-to-day clinical practice. However, the guidelines were, in fact, prepared by importing European and American guidelines without substantial modification due to the shortage in absolute quantity of data accumulated in Japan as a whole which determines treatment. Further, taking into account the report\(^10\) that according to the data obtained so far in Japan, the mortality of CAD is one-third to one-fifth as much as that in Europe and the USA, for both physicians and patients, it may not be easy to comply with the Japanese guidelines prepared by referring to European and America guidelines.

However, as Japanese people continue to increasingly adopt a Western lifestyle, it is believed the incidence of CAD will increase in Japan in the near future as it has in Europe and the USA. It is conceivable that before long Japanese clinicians will find themselves in an environment demanding they focus more on the prevention and treatment of CAD. Therefore, it is a matter of urgent necessity to construct an original database that will serve as the basis of clinical practice which incorporates disease structures peculiar to Japan, including the facts that there are more cases of cerebrovascular disease than those of CAD, and that the incidence of hypertension is overwhelmingly higher than other diseases.

This study was planned to offer guidance for the preparation of treatment guideline(s) for Japanese patients, by way of investigating the current status of medical treatment and management of risk factors in CAD patients, and grasping the correlation between background factors and the occurrence of cerebrocardiovascular events. To be more specific, this is a large-scale, multicentered prospective cohort study (observational study) aiming at a total enrollment of approximately 20,000 subjects. Fifty-five advisors and administrators were selected from major regional hospitals performing many cardiac catheterization procedures. In total, 217 institutions have participated in the study.
PURPOSE

The JCAD Study aims at offering fundamental data which can contribute to evidence-based medicine (EBM) for the treatment and management of patients with CAD by investigating sequentially how CAD patients are treated and how their risk factors are managed in Japan, and further, by gaining information on the incidence of major cerebrocardiovascular events.

STUDY DESIGN AND SUBJECTS

This study has two concurrently ongoing arms, one following the same subjects for three years with a follow-up examination every six months (Follow-up Study), the other enrolling new subjects every six months with a follow-up period of six months (Trend Study) (see Figure 1). For both the Follow-up and Trend Studies, at the time of performing cardiac catheterization during the enrollment period, patients having significant stenosis of at least 75% according to the AHA classification in one or more branches of a coronary artery and whose clinical information six months later is available to investigators were continuously enrolled until the target number of cases allocated to each institution was achieved. Subjects were enrolled regardless of age or sex. Subjects whose cerebrocardiovascular event, including death was confirmed within six months of enrollment were included in the study, even though their clinical information six months later was not available.

Follow-up Study (to follow the same subjects for three years. Simultaneously serves as the first enrollment of the Trend Study):

i) Age/sex: no preference.
ii) To enroll all the subjects who have received cardiac catheterization during a one-year period from April 2000 through March 2003 and who meet all of the following three conditions:
   (1) Subjects who have significant stenosis of at least 75% according to the AHA classification in a coronary artery at the time of cardiac catheterization;
   (2) Subjects who are retained as outpatients of the same institution six months after cardiac catheterization; and
   (3) Subjects who are not retained as outpatients of the institution but whose cardiac event (including death) is confirmed within six months of cardiac catheterization.

Trend Study (to enroll subjects every six months who are not enrolled in the Follow-up Study to follow them for six months only.):

i) Age/sex: no preference.
ii) To enroll subjects who have undergone cardiac catheterization during the following period. Other criteria are the same as for the Follow-up Study.
A: Follow-up Study

Patient enrollment period

April 2000 March 2001

CAG

\[ \text{at the time of discharge after CAG} \]

\[ \begin{array}{cccccc}
0 & 6 & 12 & 18 & 24 & 30 & 36 (M) \\
\end{array} \]

\[ \uparrow \text{Investigation by CRC (Data collection from each patient's record)} \]

\[ \ast \text{Investigation is performed every six months compiling data obtained during the previous months.} \]

B: Trend Study

Patient enrollment period

(2nd to 6th stage)

CAG

\[ \begin{array}{cccc}
0 & 6 & (M) \\
\end{array} \]

\[ \uparrow \ast \]

*Investigation is performed six months after enrollment compiling data obtained during the previous months.

Figure 1. Schematic representation of the Follow-up (A) and Trend (B) Studies.

**METHOD, PROTECTION OF PRIVACY, AND ETHICS**

An enrollment system was established within the University Hospital Medical Information Network (UMIN) and subjects were enrolled through the web by participating institutions located throughout Japan. For security purposes, an ID
and password used exclusively by a responsible investigator at each institution and a cryptocommunication system (SSL128bit) were employed. To protect subject privacy, only the system manager was allowed access to case card numbers and birth dates which identify the individual patients. Other participants, including the secretariat and administrators of the study, were denied access to such information. Access to individual patient data was given only to the attending physician in charge of each patient. Further, in principle, case records were to be prepared by physicians themselves or by a Clinical Research Coordinator (CRC) being overseen by physicians. In addition, each physician was to confirm whether the data had been entered correctly.

**Table I. JCAD Study Items to be Investigated (A: Follow-up Study, B: Trend Study)**

A: Follow-up Study (Following-up each patient for 3 years)

<table>
<thead>
<tr>
<th>Background</th>
<th>CAG*</th>
<th>6M</th>
<th>12M</th>
<th>18M</th>
<th>24M</th>
<th>30M</th>
<th>36M</th>
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<td>Lifestyle improvement therapy Y/N</td>
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<td>Event</td>
<td>○ (observation throughout the study period)</td>
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The investigation items have to be determined on the date defined above or before/after one month from the date.

B: Trend Study (enrolling new patients every six months, following the patients only for six months thereafter)

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<td>Event</td>
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The investigation items have to be determined on the date defined above or before/after one month from the date.

* At the time of CAG: values obtained on the latest date before discharge (during hospitalization for check-up) have to be entered.
1) Clinical Research Review Board
   In principle, the Clinical Research Review Board of each participating institution reviews and approves the study protocol and other documents, and evaluates the study on an ongoing basis.

2) Informed Consent
   In principle, each attending physician explains the study to each candidate patient and obtains his or her voluntary written informed consent prior to enrollment.

3) Confidentiality of Data
   In reporting the data collected, the physician, CRC, staff members of the Study Secretariat, and others use a case card number or subject number (designated by UMIN after enrollment).

PARAMETERS TO BE DETERMINED

For the subjects who were enrolled after cardiac catheterization, data on medications administered before cardiac catheterization, risk factors, and results of the catheterization procedure, diagnosis at the time of catheterization procedure, previous disease (treatment), if any, site of stenosis, extent of stenosis, treatment performed after catheterization procedure (percutaneous transluminal angioplasty, coronary artery bypass, etc.) were recorded. Further information regarding how coronary risk factors such as hyperlipidemia, impaired glucose tolerance, hypertension, smoking, and drinking are managed, as well as laboratory data obtained at that time regarding total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low density lipoprotein cholesterol (LDL-C; Friedewald formula), fasting blood glucose (FBG), HbA1c, blood pressure, body mass index (BMI), uric acid (UA), lipoprotein small a (Lp (a)), C-reactive protein (CRP), and cardiac failure, if any, were collected at enrollment and every six months thereafter. In the case of acute disease such as myocardial infarction, hematological data obtained during a stable phase were recorded. These data were to be entered every six months (see Table I).

With the endpoint being all cerebrocardiovascular events, in case such an event should occur after enrollment, a description of the event, treatment, and outcome were recorded any time such an event occurred. "Event" is defined as the case where the subject develops a new cerebrocardiovascular disease or experiences a recurrence of such a disease after the cardiac catheterization procedure or treatment performed following such a procedure. If there are no symptoms of ischemia and restenosis is confirmed by regular cardiac catheterization, such a case is to be excluded from “event”.
ANALYSES

In the Follow-up and Trend Studies, enrolled cases will be analyzed by the “intention-to-treat” method. The following analyses are planned for each of the studies:

**Follow-up study:** How the risk factors each CAD patient with stenosis of 75% according to the AHA classification has are managed during the three-year period and how such management influences the endpoint are to be analyzed. The chi-square test is used for qualitative data, while the \( t \)-test is used for quantitative data in the case of a comparison between two groups. In the case of comparison among three or more groups such data are subjected to variance analysis, and if there is any significant difference, Scheffe’s post hoc analysis is also to be performed. The \( \chi^2 \) test is used for any change in risk factors, while changes in parameters are to be evaluated by variance analysis and then subjected to Scheffe’s multiple comparison. Relation between the endpoint and the presence (or absence) of any risk factors, such as treatment after cardiac catheterization procedure, medication administered, risk factor parameter, and expenses incurred (in treatment, drugs, etc.) are to be analyzed by multivariate studies based on Cox’s proportional hazard model. Further, multiple regression analysis based on these factors is to be performed in an attempt to construct a linear model to forecast the occurrence of cardiovascular events.

**Trend study:** The trend in the selection of treatment for CAD patients in Japan for each six-month period is to be investigated and how the difference in the selection of treatment correlates with the endpoint is to be studied. The risk factors for each subject and the changes in parameters are to be studied using the same analytical methods as in the Follow-up Study. Analysis of events is to be performed in the same manner as in the Follow-up Study. In addition, relative risk is to be calculated for every six-month period, and how the occurrence of cardiovascular events is influenced by the presence (or absence) of any of the risk factors, medication administered, and changes in risk factor parameters is to be studied.

**FUTURE SCHEDULE**

Enrollment began in April 2000 and the initial enrollment of 15,506 cases for the Follow-up Study ended on September 30, 2003. In the Follow-up Study, the patient enrollment procedure was completed by the end of March, 2004 and the data entry period will expire as of the end of September 2004. In April 2005, how risk factors and treatment given to each patient correlate with the recurrence
rate of CAD will be reported based on the Follow-up Study and background fac-
tors of Japanese CAD patients, while how they are treated and the change in the
recurrence rate of short-term cerebrocardiovascular events will be reported based
on the Trend Study.

Subsequently, various subanalyses, including analysis by sex, existence of
concomitant coronary risk factors, treatment following the cardiac catheterization
procedure, and a cost versus benefit study will be performed and the results will
be reported at a later date.

ACKNOWLEDGEMENT

The study has 55 advisors selected from major regional hospitals throughout Japan.
Participating institutions and physicians are shown below:
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Akita Endo, Hiroyuki Kita, Hisataka Sasao
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