The Japan Thrombosis Registry for Atrial Fibrillation, Coronary or Cerebrovascular Events (J-TRACE) — A Nation-Wide, Prospective Large Cohort Study; The Study Design —

Hideki Origasa, PhD; Shinya Goto, MD*; Shinichiro Uchiyama, MD**; Kazuyuki Shimada, MD†; Yasuo Ikeda, MD††
on behalf of the J-TRACE Investigators

Background A previous history of myocardial infarction (MI), stroke, and the presence of atrial fibrillation (AF) are known risk factors for the onset of arterial thromboembolic events such as MI and ischemic stroke. To clarify the rate of incidence of such events for these high-risk patients in Japan, a nation-wide cohort study was conducted that was named the ‘Japan Thrombosis Registry of Atrial Fibrillation, Coronary and Cerebrovascular Events’ (ie, J-TRACE) [UMIN Registered ID C000000189].

Methods and Results In the J-TRACE registry, a total of 8,093 Japanese patients with either a history of stroke and/or MI or patients with non-valvular AF were registered. This registry was developed by specialists in cardiology and neurology, physicians working at general hospitals, as well as general practice physicians, from whole regions of Japan, possibly reflecting the real-world medical practice. Recruited patients will be followed up for 2–3 years. Medical history, accompanying risk factors, demographic characteristics, and information regarding the use of medications were collected for these patients at baseline. Cardiovascular ischemic events and serious adverse experiences, including cerebral bleedings, which occur during the follow-up period will be recorded over a maximum of 3 years.

Conclusion The J-TRACE offers an opportunity to provide fundamental information regarding the incidence of cardiovascular ischemic events by a stratum of the risk factor profile and current medical treatment for Japanese patients at high risk for thromboembolic diseases. (Circ J 2008; 72: 991–997)

Key Words: Cohort studies; Prevention; Thrombosis; Trials

Thromboembolism causes serious clinical manifestations in several ways, such as non-fatal myocardial infarction (MI), ischemic stroke and cardiovascular death. The morbidity and mortality of thromboembolic diseases have substantially worsened in the past few decades, as shown recently in the United States1 Thus, these facts are now recognized to be the most significant burden for our societies. Cardiovascular diseases affect 1 in 3 Americans, and it is an underlying cause of death in 36.3% of all cases in the United States2 Although a limited amount of data has been accumulated in Japan,3 comparable data are necessary to confirm that this problem is similarly applicable to Japan.

As there is a different cultural background and regulatory system in Japan, most of the important clinical studies do not include Japan as a participating country. An unknown cardiovascular event rate and, presumably, higher rate of bleeding complications in Japanese may be other important reasons why Japan has been excluded in many of the internationally collaborative researches for the clinical development of important antithrombotic agents, such as clopidogrel2-5 Despite recent data demonstrating that the Japanese have a similar risk for cardiovascular disease as the rest of world and a lower rate of bleeding complications in patients at high risk for atherothrombotic disease2 a certain percentage of physicians still believe that the incidence of cardiovascular events is far less in Japanese patients6 We need to clarify the real incidence of both thromboemboli and bleeding events in Japanese patients at high risk for thromboembolic diseases; otherwise, we will be unable to participate in any of the international clinical researches, especially those that focus on the clinical development of antithrombotic agents.

As there are not enough data on the incidence and prevalence of thromboemboli and bleeding events in Japanese patients at high risk for cardiovascular ischemic events, we have planned a large prospective cohort study with a maximum 3-year follow-up period. Our plan is to register patients with non-valvular atrial fibrillation (AF; primary prevention), as well as those with established atherosclerotic diseases such as MI and stroke (secondary prevention), and...
follow them for the occurrence of cardiovascular ischemic events. The planning and, indeed, the conducting of such a large-scale patient registry, such as the Japan Thrombosis Registry of Atrial Fibrillation, Coronary and Cerebrovascular Events (J-TRACE) cohort study, will provide important epidemiological data of cardiovascular ischemic event rates within a few years for both primary and secondary prevention for Japanese patients. Therefore, we will be able to compare the findings with data from other countries.

The study objectives of the J-TRACE are to establish a large-scale database consisting of a broad range of patients at high risk for cardiovascular ischemic events from all geographical regions in Japan, and to estimate the incidence of cardiovascular death, non-fatal MI and ischemic or hemorrhagic stroke among them. Second, multivariate analysis of the database generated by the J-TRACE would provide fundamental information regarding the contribution of risk factors for and treatment strategies against the onset of cardiovascular ischemic events in Japanese patients at high risk for thromboembolic diseases.

### Methods

#### Study Design

The J-TRACE is a large nationwide prospective observational patient registry for following clinical events within a 3-year follow-up period (Table 1). Recruitment started in February 2005 and ceased in January 2007 (Fig 1). Two interim analyses based on the data of 1-year and 2-year follow up are planned, and the study will be completed at the end of 2009. J-TRACE, Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events; MI, myocardial infarction.

#### Study Population

Patients aged 20–90 years were eligible for enrolment in the J-TRACE, if at least 1 of the following 3 criteria were satisfied: a history of stroke and/or MI, and non-valvular AF, as shown in Table 2. Any admitted acute phase patients were ineligible for the study, where acute phase means that...
there is a short period from the onset of MI or stroke and the patient’s clinical condition is unstable and vitally critical. We did not specify the day from the onset. We devoted it to the physician in charge. Patients were attempted to be recruited consecutively at each site to ensure the study’s results could be generalized to the Japanese target population. Between February 2005 and January 2007, a total of 8,093 patients were registered. A monthly increment of the registration is shown in Fig 1.

A broad range of physicians were involved in the recruitment of eligible patients. A detailed classification according to their specialty is shown in Fig 2. They comprised cardiologists (58.6%), followed by neurologists or neurosurgeons (34.9%) and internists (3.3%). The involvement of family and general practitioners was only 3.1%. First, we selected several coordinators in each region (see Appendix). These coordinators then selected physicians to participate in the study. We did not select physicians and patients equally from the region by design. And yet, patients were selected almost equally from all regions of Japan.

**Evaluations**

At the time of enrolment, patients were assessed for demographics, medical history, risk factors, co-morbidity, and current medications, as shown in Table 3. Medical history asked the time lapse between an initial occurrence and recurrence. An ischemic or hemorrhagic stroke was documented by either CT or MRI. MI was documented by ECG, biochemical tests, or emergency PCI. Current AF was documented by ECG, as shown in Table 2. Risk factors or co-morbidity involved hypertension, diabetes, hypercholesterolemia, valvular diseases, heart failure, cancer, smoking, and drinking. Regular use of any of the following were investigated at baseline: antiplatelets, anticoagulants, drugs for hypercholesterolemia, antihypertensives, and hypoglycemic drugs. Clinical events, such as stroke, MI and death, will be evaluated at 12±6, 24±6, and 36±6 months with information of the incidence date. Causes of death will be classified as either stroke, MI, or others.

**Study Outcomes**

The study outcomes that will be evaluated are summarized in Table 4. Primary outcome is a composite of all-cause death, or non-fatal stroke, or MI within a maximum follow-up period of 3 years. Stroke will be diagnosed when the patient has acute onset of focal neurological manifestation and the responsible lesion is confirmed by brain CT or MRI. Diagnosis of MI will be confirmed by the following 2 items. First, biochemical markers such as CK-MB and troponin will be applied. Second, at least one of the following items will be applied: ischemic symptoms, development of abnormal Q waves, ST segment elevation or depression,

**Table 2 Inclusion and Exclusion Criteria for the J-TRACE Cohort Study**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects aged 20–90 years with at least 1 of the following 3 criteria:</td>
<td>Any admitted acute phase patients were ineligible for the study, where acute phase means that there is a short period from the onset of MI or stroke and the patient’s clinical condition is unstable and vitally critical</td>
</tr>
<tr>
<td>Previous ischemic or hemorrhagic stroke diagnosed by CT or MRI</td>
<td></td>
</tr>
<tr>
<td>Previous MI diagnosed by ECG (ST elevation or depression, or abnormal Q wave) and biochemical markers</td>
<td></td>
</tr>
<tr>
<td>Chronic, persistent, or paroxysmal AF diagnosed by ECG</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3 Evaluations at Baseline and at 1-, 2-, 3-Year Follow-up Visits**

<table>
<thead>
<tr>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Date of birth, gender, height, weight, BMI</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Previous stroke and/or MI, current AF</td>
</tr>
<tr>
<td>Risk factors/co-morbidity</td>
</tr>
<tr>
<td>Hypertension, diabetes, hypercholesterolemia, valvular disease/valve replacement, heart failure, cancer, smoking, drinking</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Antplatelets drugs, anticoagulant drugs, hypoglycemic drugs, drugs for hypercholesterolemia, anti-hypertensive drugs</td>
</tr>
</tbody>
</table>

**At 1-, 2- and 3-years’ follow up**

<table>
<thead>
<tr>
<th>Clinical events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (ischemic/hemorrhagic)</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Death (stroke, MI, other)</td>
</tr>
<tr>
<td>Bleeding events</td>
</tr>
<tr>
<td>Loss to follow up</td>
</tr>
</tbody>
</table>

BMI, body mass index. Other abbreviations see in Tables 1, 2.
and coronary artery intervention. Basically, we adopted the criteria that described in the relevant clinical practice guidelines. We did not establish the endpoint adjudication committee for this study. A final decision was given by the physician in charge.

Secondary outcomes are all-cause death, non-fatal MI, non-fatal stroke separately, and any drop-outs from the study, and the incidence of cerebral hemorrhage, any other bleedings, or serious adverse experiences leading to admission.

**Study Organization and Sites**

The J-TRACE has a steering committee consisting of 5 members and 41 regional coordinators, who were selected from 10 areas of Japan (see Appendix). The steering committee members are responsible for the study design, study progress management, statistical analysis, and preparation for publication. Regional coordinators consisted of cardiologists and neurologists. Their roles were to nominate the study hospitals within their region, and to promote the recruitment and communication among the study hospitals.

A total of 185 clinics from 10 regional areas of Japan participated in the J-TRACE. From these clinics, a total of 359 investigators (see Appendix) have registered all the J-TRACE participants.

**Data Management**

We have developed a website for the J-TRACE study (http://www.j-trace.com) to collect all patient data through the Internet. For security purposes, all investigators received their own ID and password to access the study website after completing the study participation process. A crypto-communication (SSL128bit) was used as well. As all the case report forms were automatically exposed to a logical check at the time of data entry, correctly completed case report forms were sent to the central secretariat only. The data management group of the secretariat performed an appropriate quality assurance of the data on a regular basis. Via the website, each of the investigators will be reminded at 1 month before the required scheduled follow-up assessment for each patient.

**Statistical Analysis**

Data will be presented using the mean, median, SD, range, and interquartile range for continuous data, and counts or percentages for categorical data. Statistical significance will be defined as 2-sided at the 5% level. The annual incidence rate and its 95% confidence interval (CI) will be computed by the approximate Poisson method. The 95% CI of the incidence rate ratio of a target population against a control (least risky subgroup) will be computed also by the approximate Poisson method. In addition, Logistic and Cox regression will be performed to detect any possible risk fac-
tors for the incidence of clinical outcomes after an appropriate covariate adjustment.

**Sample Size Determination**

It was assumed that the J-TRACE would follow a total of 10,000 patients for a follow-up period of 2–3 years. Attrition was assumed to be 10% at 1 year, 15% at 2 years, and 20% at 3 years. With these assumptions, the relative precision of an incidence estimate is ±6% (2.81–3.19%) if the annual incidence rate is supposed to be 3%. The odds ratio to be detected would be 1.6 or greater with 80% power when the 3-year follow up is completed. A summary of the statistical considerations is shown in Table 5. However, only a total of 8,093 patients were registered, indicating that the precision and power of this study will be weaker than our initial intention.

**Primary or Secondary Hypothesis**

The J-TRACE has a primary hypothesis that there might be a significant difference in annual rates of subsequent cardiovascular events between the primary prevention of patients with AF and the secondary prevention of patients with a history of MI and/or stroke. As a secondary hypothesis, we would detect any significant difference in the rates of subpopulations defined by diabetes, hypertension, obesity, and other risk factors during the follow-up period. We will also develop a risk prediction model for the Japanese patients based on the risk scores derived from these analyses.

**Discussion**

We focused basically on the secondary prevention with a history of MI and/or stroke. We also actively registered patients with non-valvular AF as a primary prevention stratum because a previous investigation revealed a high risk of ischemic events that was similar to the secondary prevention cohort represented by MI and stroke. On the other hand, the REACH did not actively register such AF patients. Although the REACH involved high-risk patients, such as those with diabetes and/or metabolic syndrome, the J-TRACE did not actively register such patients. This is a core difference in the eligibility criteria between the REACH and the J-TRACE. Furthermore, the prevalence of AF is increasing and it is a known factor in inducing cardiogenic embolism. According to the Japanese clinical data, AF is highly prevalent in patients with ischemic stroke. The NIPPON-DATA 80 has also demonstrated that patients with AF strongly have an effect on stroke mortality. Also, our data might be compared with the recently demonstrated trial of J-RHYTHM, which compared the rate with rhythm control in patients with AF. Thus, J-TRACE will enable us to generate a suitable database to further clarify the incidence of thromboembolic diseases in Japanese patients by including a primary prevention stratum composed of AF patients.

We have excluded acute phase patients admitted to hospital because we know that the risk of cardiovascular events and bleeding complications are extremely high in these patients and differ from hospital to hospital due to the difficulty in the standardization of acute care, especially vascular intervention. Therefore, we have included only those patients with stable conditions to maintain the homogeneity of the target population that would be recruited in this study.

Although recent studies have demonstrated the importance of metabolic syndrome in the onset of atherosclerotic disease, we have not included the waist circumference as a required item in this study because the body mass index (BMI) might be replaced by the waist circumference, and its measurement was considered to be troublesome in the clinical practice. Furthermore, the BMI is still important, as seen in the evidence of a previous study, which demonstrated a higher prevalence of diabetes mellitus even patients with a lower BMI. Among patients with a BMI of >30, only 3.7% of Japanese were found to be obese. Yet, although a large proportion of Japanese are not obese, they might still be prone to developing the onset of diabetes mellitus. The cohort of J-TRACE could answer such a question. Epidemiological data, such as incidence of cardiovascular events in patients with AF or previous MI/stroke, are quite limited in Japan. Such basic data are necessary for initiating more stringent clinical studies, such as randomized controlled trials, as it is necessary to obtain background data on the incidence of a targeted disease on an annual basis. When considering that the J-TRACE will follow approximately 10,000 patients for a period of 2–3 years, the annual incidence estimated from J-TRACE would be sufficiently reliable.

Disease prevention has become more important in recent years. Mortality and morbidity is much higher in patients who are diagnosed late with a disease such as MI or stroke compared with those diagnosed much earlier. Therefore, it is necessary for us to establish a strategy for preventing such episodes. Through the J-TRACE data, we would construct a risk prediction model for a relatively short-term future. This model could be adapted to the strategic plan of health promotion in Japan and enables us to compare with the models applied to Western countries.

There are many advantages to comparing the medication patterns between Japan and the rest of world, as the J-TRACE collects currently prescribed medications exclusively at baseline. They include a variety of drugs such as antiplatelets, anticoagulants, and drugs for hypertension, hypercholesterolemia, and diabetes. It will be useful to compare medication patterns among physician specialties, regions, and underlying diseases. In particular, patients with worsening diabetes and hypercholesterolemia were shown to be undertreated with respect to drug therapy. It is worth noting that the J-TRACE will be unable to clarify the importance of continuation of participants’ medication since it did not investigate medication compliance during the follow-up period. However, we could compare the prognosis between adequately treated and undertreated patients using the baseline information. Although the clinical effectiveness of the medications cannot be directly compared in observational studies due to the bias in medication selection, recently developed methods, such as propensity score analysis or instrumental variables analysis, may help us in challenging this problem.

**Acknowledgments**

The execution of this study has been and will be supported by the Japan Heart Foundation in Tokyo. Design consideration and preparation of this manuscript were done exclusively by the 5 authors listed for this article. There is no conflict of interest to declare.

**References**

2. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenland K, et al; American Heart Association Statistics Committee and Stroke Statis-


Study Design of the J-TRACE Cohort

Hisakazu Fuji, Katsuji Hashimoto, Hiroyuki Hashimoto, Kinji Ishikawa, Kazuo Kitagawa, Yoshihiro Koretsune, Akio Kohama, Yoshiyuki Kijima, Shinsuke Nanto, Katsunori Nao, Yoshiyuki Nagai, Keiko Nagano, Osaka Police Hospital's Cardiology, Yutaka Okazaki, Masafumi Tagaya, Tsutomu Takahashi


Kyusyu: Yutaka Akatsuka, Yoshihiro Fukumoto, Yasuo Fukuda, Takako Fujiki, Yuji Fukutome, Koji Hiymamuta, Rikuzo Hamada, Yasuo Hayashi, Youichi Hohezu, Yoichiro Hashimoto, Yoshifumi Hirata, Tadashi Hamada, Takeshi Ideguchi, Takuroh Imamura, Masatoshi Koga, Junji Kawagoe, Sunao Kojima, Shigehiro Kumate, Ikuo Misumi, Junno Mashiba, Takashi Matsuura, Hiroshi Nakane, Toshifusa Ogata, Hirokuni Obha, Shuichi Okamatsu, Hideki Oka, Yoshisato Shibata, Satoko Saito, Ichiro Shimada, Kazuhito Tsuruta, Kazuhiro Tashima, Yoshihide Taniwaki, Satoshi Terai, Takeshi Yamada, Hitoshi Yasumoto, Akira Yamada, Tohru Yamawaki