Clinical evidence for Japanese population based on prospective studies—Linking clinical trials and clinical practice

Hisao Ogawa (MD, PhD, FJCC)*, Sunao Kojima (MD, PhD)

Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto City 860-8556, Japan

Received 4 May 2009; accepted 7 May 2009
Available online 12 June 2009

Summary „Evidence-based medicine (EBM)‟ implies effective and high quality practice for patients based on well-grounded medical science. The success of clinical trials in Japan is essential to build original evidence specific for Japanese patients. Based on this concept, we have performed several large-scale clinical trials to provide EBM, including the Japanese Antiplatelets Myocardial Infarction Study [JAMIS; clinical improvement in acute myocardial infarction (AMI) patients with antiplatelet therapy], the Japanese ß-Blockers and Calcium Antagonists Myocardial Infarction (JBCMI; comparison of the effects of ß-blockers and calcium antagonists on cardiovascular events in post-AMI patients), a multicenter study for aggressive lipid-lowering strategy by HMG-CoA reductase inhibitors in patients with AMI (MUSASHI; effects of statin therapy on cardiovascular events in patients with AMI), and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD trial; efficacy of low-dose aspirin therapy for primary prevention of atherosclerotic events in type 2 diabetic patients). The results of these prospective studies were directly linked with clinical practice. We have acquired the know-how of large-scale clinical trials; an important point is to have passion for „buildup evidence specific for the Japanese‟ and to recruit subjects for enrollment after explaining the significance of „clinical trials for the Japanese‟.

© 2009 Japanese College of Cardiology. Published by Elsevier Ireland Ltd. All rights reserved.
Introduction

"Evidence-based medicine (EBM)" implies providing effective and high quality clinical practice for patients based on well-grounded medical science. Our group has completed several large-scale clinical trials to provide EBM. In Japan, evidence-based guidelines for the management of cardiovascular disease were previously prepared, however, such guidelines cited mainly work that originated in western countries. There is no doubt that the western data cannot be applied blindly to different ethnic groups with heart disease. Therefore, evidence for Japanese is required for the clinical setting. In the past several years, the strategy used for the treatment of heart disease has been changing constantly based on well-established large-scale clinical trials that were performed mainly in western countries. Recent years have witnessed the birth of Japanese clinical trials and the results have been published gradually.

In this article, we summarize and review several prospective clinical trials including the latest ones from our group on cardiovascular diseases.

Prospective randomized clinical trials with regard to secondary prevention of acute myocardial infarction

It is well known that the Japanese population has lower mortality from coronary artery disease compared with western countries [1]. This difference between Japanese and Caucasians may be due to racial or ethnic differences in the response to drugs, probably related to differences in the distribution of polymorphisms of drug-metabolizing enzymes, drug receptors, and environmental factors [2–4]. However, well-established medical strategies were not available in the past for the secondary prevention of acute myocardial infarction (AMI) in Japanese patients. Therefore, prospective randomized clinical trials are indispensable for the preparation of guidelines in the Japanese clinical setting.

Significance of antiplatelet therapy in Japanese AMI patients: the Japanese Antiplatelets Myocardial Infarction Study (JAMIS)

The multicenter study, the Japanese Antiplatelets Myocardial Infarction Study (JAMIS) [5] was performed to determine the effects of aspirin or trapidil on clinical outcome compared with no antiplatelet treatment in patients with AMI. The JAMIS was a multicenter open-label randomized controlled trial of aspirin 81 mg/day, trapidil 300 mg/day, and no antiplatelet treatment in patients with AMI admitted within 1 month from the onset of symptoms. The study patients were recruited from 70 hospitals in 18 prefectures from October 1994 to March 1996. The primary objective was to compare the effect of these three regimens on cardiovascular events, such as cardiovascular death (including sudden death), reinfarction, uncontrolled unstable angina requiring admission to hospital, and nonfatal ischemic stroke. A total of 723 patients were randomly assigned to the aspirin group (n=250), trapidil group (n=243) and control group (n=230). There were no significant differences among the three groups with respect to age, gender, time from onset to admission, the frequency of performed
emergency coronary angiography, index AMI location, types of Q-wave AMI and non-Q-wave AMI, and the frequency of previous myocardial infarction. The frequencies of reperfusion therapy, such as thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), and thrombolysis and PTCA, and that of other medications (nitrates, calcium antagonists, β-blockers, and angiotensin-converting-enzyme inhibitors) were also distributed equally among the three groups. Follow-up data were available for 100% of the patients at 3 months and 98.2% at the end of the study period. Thirteen patients (1.8%) were lost to follow-up (2 in the aspirin group, 5 in the trapidil group, and 6 in the control group). The mean follow-up period was 475 days (1.3 years), and the maximum was 970 days. Reinfarction occurred in 5 patients of the aspirin group, 9 of the trapidil group, and 17 of the control group. The relative risk of reinfarction in the aspirin group compared with the control group was 0.271 (95% confidence interval [CI] 0.101–0.722, p = 0.0045) (Fig. 1A), and that for the trapidil group compared with the control group was 0.501 (95% CI 0.228–1.101, p = 0.0810) (Fig. 1B). The number of patients with cardiovascular death (aspirin group: 6; trapidil group: 4; control group: 5) and non-cardiac death (aspirin group: 3; trapidil group: 4; control group: 2) was about the same in the three groups. Cardiovascular events occurred in 36 patients of the aspirin group, 22 of the trapidil group, and 42 of the control group. The relative risk of developing cardiovascular events in the aspirin group compared with the control group was 0.789 (95% CI 0.525–1.185, p = 0.1961) (Fig. 1C). On the other hand, that for the trapidil group compared with the control group was 0.496 (95% CI 0.306–0.804, p = 0.0039) (Fig. 1D). Analyses of the primary endpoints showed that the incidence of reinfarction was lower in the aspirin group compared with the control group and that of cardiovascular events was lower in the trapidil group compared with the control group. Adverse effects were observed in the aspirin group (n = 7) and trapidil group (n = 16). These included minor side effects, which disappeared after discontinuation of the drugs.

The JAMIS demonstrated that long-term daily use of 81 mg aspirin reduced the incidence of recurrent AMI compared with the group receiving no antiplatelets after AMI and that the incidence of

Figure 1 (A) Kaplan–Meier plot of reinfarction observed in the aspirin and control groups. (B) Kaplan–Meier plot of reinfarction observed in the trapidil and control groups. (C) Kaplan–Meier plot of cardiovascular events observed in the aspirin and control groups. (D) Kaplan–Meier plot of cardiovascular events observed in the trapidil and control groups.
cardiovascular events was reduced in the group receiving 300 mg trapidil daily compared with the group receiving no antiplatelets.

Comparison between β-blockers and calcium antagonists in preventing cardiovascular events in Japanese AMI patients: the Japanese β-Blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Study

The Japanese β-Blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Study compared the effects of β-blockers and calcium antagonists on cardiovascular events in Japanese post-AMI patients [6]. The study was a multicenter, open-label, controlled, randomized clinical trial. A total of 1090 patients were consecutively enrolled at 90 hospitals in 28 prefectures of Japan between December 1998 and October 2000. Patients were eligible for the study if they presented within 1 month of the onset of symptoms of AMI. Randomization was conducted during first day to 1 month after the attack. Of these patients, 545 were randomized into the β-blocker group, and 545 into the calcium antagonist group. The β-blockers administered were atenolol, bisoprolol, calvedilol, and metoprolol. Calcium antagonists were those of slow-release or long-acting dihydropyridines including amlodipine, manidipine, slow-release nifedipine, and nisoldipine. The choice of the drugs of each class and the dose were at the discretion of each attending physician. The primary endpoint was defined as the combination of cardiovascular death, nonfatal reinfarction, uncontrolled unstable angina including coronary spastic angiina, and nonfatal stroke.

Thirty-one (5.7%) patients of the β-blocker group and 22 (4.0%) patients of the calcium antagonist group were not treated with assigned therapy. Sixty-four (11.8%) patients of the β-blocker group were classified as Killip class I. The rate of reperfusion therapies was 85.1% for the β-blocker group and 80.6% for the calcium antagonist group. PCI was performed in 77.6% and 75.5% of the β-blocker group and the calcium antagonist group, respectively. The rate of revascularization with thrombolysis in myocardial infarction (TIMI) grade 3 was 83.4% in the β-blocker group and 84.4% in the calcium antagonist group. Almost all patients received aspirin (97.8% vs. 98.0%) and the administration rate of angiotensin-converting-enzyme inhibitors (62.9% vs. 63.8%) was also high. The period from onset of attack to enrollment was 0–30 (median 13) days for the β-blockers group and 0–30 (median 12) days for the calcium antagonists group. The average follow-up period was 454 ± 274 days.

There was no significant difference in the primary endpoint or total cardiovascular events between the β-blocker group (14.3% [n = 78]) and calcium antagonist group (13.2% [n = 72]) (p = 0.349). There were no significant differences in the incidence of cardiovascular death (1.7% [n = 9] vs. 1.1% [n = 6], p = 0.377) (Fig. 2A), nonfatal infarction (0.9% [n = 5] vs. 1.3% [n = 7], p = 0.698) (Fig. 2B), unstable angina (11.0% [n = 60] vs. 10.6% [n = 58], p = 0.572) (Fig. 2C), or nonfatal stroke (0.7% [n = 4] vs. 0.2% [n = 1], p = 0.148) (Fig. 2D) between the two groups. However, the rates of occurrence of heart failure (4.2% [n = 23] vs. 1.1% [n = 6], p = 0.001) (Fig. 3A) and coronary spasm (1.3% [n = 7] vs. 0.2% [n = 1], p = 0.027) (Fig. 3B) were significantly higher in the β-blocker blocker group than in the calcium antagonist group.

The JBCMI study found no significant differences in the incidence of cardiovascular events including cardiac death, nonfatal AMI, uncontrolled unstable angina, and nonfatal stroke between the β-blocker group and calcium antagonist group. Heart failure occurred earlier in the β-blocker group probably because the dose was not necessarily titrated.

Effectiveness of lipid-lowering therapy with early administration of statins in Japanese AMI patients: multicenter study for aggressive lipid-lowering strategy by HMG-CoA reductase inhibitors in patients with AMI (MUSASHI-AMI)

The multicenter study for aggressive lipid-lowering strategy by HMG-CoA reductase inhibitors in patients with AMI (MUSASHI) investigated the effects of statin therapy on cardiovascular events including heart failure in Japanese AMI patients with ST elevation after percutaneous coronary intervention (PCI) [7]. Between February 2002 and September 2004, 486 eligible consecutive patients with AMI who were admitted to 54 medical centers in 28 prefectures of Japan were enrolled. Acute phase reperfusion therapy included PCI and/or thrombolysis after admission when needed. Study patients were randomly assigned within 96 h after symptom onset with stratification by center to the standard therapy, which included open-label treatment with any of the statins available in Japan during the recruitment period (pravastatin, atorvastatin, fluvastatin, simvastatin, or pitavastatin),
Clinical evidence for the Japanese

Figure 2 (A) Kaplan–Meier plot of cardiovascular death in the β-blocker and calcium antagonist groups. (B) Kaplan–Meier plot of uncontrolled unstable angina requiring hospitalization in the β-blocker and calcium antagonist groups. (C) Kaplan–Meier plot of nonfatal myocardial infarction in the β-blocker and calcium antagonist groups. (D) Kaplan–Meier plot of nonfatal stroke in the β-blocker and calcium antagonist groups.

or to the control group (standard AMI therapy without statins). Treating physicians were allowed to change the dosage of statin during the study period. The primary endpoint was defined as combination of cardiovascular death, nonfatal AMI, recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization, congestive heart failure requiring emergency

Figure 3 (A) Kaplan–Meier plot of heart failure in the β-blocker and calcium antagonist groups and (B) Kaplan–Meier plot of coronary spasm in the β-blocker and calcium antagonist groups.
rehospitalization, and nonfatal stroke. Patients were monitored for events during 24 months after randomization.

A total of 486 patients were enrolled; 241 were randomly assigned to receive discretionat statins and 245 to receive standard AMI therapy without statins. Fatal complications such as left-ventricular free wall rupture occurring within 7 days after symptom onset were excluded from the analysis. Demographic and clinical characteristics of survivors of acute-phase complications (from data available for 237 patients of the statin and 244 of the non-statin group) were similar at baseline. ST elevation was seen in about 90% of the study patients and the two groups included substantial numbers of smokers. Coronary angioplasty was selected as the reperfusion therapy in more than 90% of those patients. Bare metal stents, but not drug-eluting stents, were used in most patients because the latter was not available in Japan at the time of the study.

At the time of randomization, serum lipid levels were nearly equal in both groups (Fig. 4A–D). In all randomized patients, the mean total cholesterol levels were 207 mg/dL, low-density lipoprotein (LDL) cholesterol levels were 133 mg/dL, mean triglyceride levels were 134 mg/dL, and high-density lipoprotein cholesterol levels were 46 mg/dL. In the statin group, total and LDL cholesterol levels decreased by 13% and 24% by 6 months after randomization, 14% and 27% by 1 year, and 17% and 25% by 2 years, respectively. In contrast, in the non-statin group, total and LDL cholesterol levels decreased by 1% and 4% by 6 months, 1% and 6% by 1 year, and 3% and 8% by 2 years, respectively.

During the follow-up period, primary endpoint events occurred in 15 patients (5.9%) of the statin group (2 cardiovascular death, 3 nonfatal acute myocardial infarction, 6 symptomatic myocardial ischemia requiring emergency rehospitalization, 1 heart failure requiring urgent rehospitalization, and 3 stroke) and 29 (11.9%) of the non-statin group (1 cardiovascular death, 17 symptomatic myocardial ischemia requiring emergency rehospitalization, 9 heart failure requiring urgent rehospitalization, and 2 stroke), with an absolute difference of 5.2%. Statin treatment significantly reduced the risk of the primary combined endpoints during a mean follow-up period of 416 ± 11 days (Fig. 5A). There were no significant differences in risk of death, nonfatal AMI, and stroke between the statin and non-statin groups. In contrast, the statin group had a lower risk of congestive heart failure requiring urgent rehospitalization. The effect of statins in preventing heart failure became evident at 6 months after randomization (Fig. 5B). Furthermore, symptomatic myocardial ischemia requiring emergency rehospitalization was more frequent in the statin group compared to the non-statin group (Fig. 5C).

**Figure 4** Serum lipid levels in statin vs. non-statin groups. Data are mean value. Total cholesterol (A), low-density lipoprotein cholesterol (B), high-density lipoprotein cholesterol (C), and triglycerides (D). ***p < 0.0001, **p < 0.001, *p < 0.05. HDL, high-density lipoprotein; LDL, low-density lipoprotein.
The MUSASHI-AMI trial demonstrated that a lipid-lowering strategy with statins decreased subsequent cardiovascular events, in particular, congestive heart failure and unstable angina in Japanese patients with AMI.

**Novel strategies for primary prevention of atherosclerotic events in patients with diabetes mellitus**

Patients with diabetes are at high risk of fatal and nonfatal macrovascular events. The risk of myocardial infarction in diabetic patients without previous myocardial infarction is as high as for nondiabetic patients with previous myocardial infarction [8]. The Kumamoto study indicated that intensive glycemic control by multiple insulin injection therapy can delay the onset and progression of diabetic retinopathy, nephropathy, and neuropathy [9]. On the other hand, the UK Prospective Diabetes Study reported that intensive blood-glucose control with sulfonylureas or insulin substantially reduced the risk of microvascular complications but not macrovascular disease [10]. Therefore, novel medical treatment in addition to anti-diabetic agents is important to prevent the development and progression of cardiovascular complications in diabetic patients.

**Low-dose aspirin for primary prevention of atherosclerotic events in patients with diabetes mellitus: the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) Study**

The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial was undertaken to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in type 2 diabetic patients [11]. This multicenter, prospective, randomized, open-label blinded-endpoint study was conducted from December 2002 through April 2008 in 163 institutions throughout Japan. The study screened 2567 type 2 diabetic patients without history of atherosclerotic disease, including cardiovascular disease, stroke, and peripheral vascular disease. Six patients who withdrew their informed consent were excluded. Twenty-two patients met the exclusion criteria (10 with history of atherosclerotic disease, 10 aged >85 years, 1 no diabetes, and 1 receiving warfarin). A total of 2539 patients were randomly assigned into the following two groups: 1262 patients in the aspirin group (81 or 100 mg/day) and 1277 patients in the non-aspirin group. The primary endpoint was any atherosclerotic event, which was a composite of sudden death, death from coronary, cerebrovascular, and aortic causes, nonfatal acute myocardial infarction, unstable
angina, newly developed exertional angina, non-fatal ischemic and hemorrhagic stroke, transient ischemic attack, or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) during the follow-up period. Key secondary endpoints were each and combinations of primary endpoints and death from any cause. Further, adverse events analyzed in that study included gastrointestinal (GI) events and any hemorrhagic events other than hemorrhagic stroke. The median follow-up period was 4.37 years. A total of 193 patients were lost to follow-up, and data for those patients were censored at the day of last follow-up.

All baseline clinical characteristics including treatments for diabetes, hypertension, and dyslipidemia, and diabetic microvascular complications, were similar between the two groups. The mean age of the whole group was 65 ± 10 years and 55% of the patients were men. The median history of diabetes was 7.3 years in the aspirin group and 6.7 years in the non-aspirin group. Diabetes was well controlled in both arms: glycosylated hemoglobin level was 7.1 ± 1.4% in the aspirin arm and 7.0 ± 1.2% in the non-aspirin arm. The prevalence of hypertension and dyslipidemia in the entire population was 58% and 53%, respectively. The systolic/diastolic blood pressure was well controlled in both arms: 136 ± 15/77 ± 9 mmHg in the aspirin arm and 134 ± 15/76 ± 9 mmHg in the non-aspirin arm.

A total of 154 atherosclerotic events occurred in that study. The incidence of the primary endpoint of any atherosclerotic event, a composite of sudden death, death from cardiovascular or aortic causes, nonfatal acute myocardial infarction, unstable angina, exertional angina, nonfatal ischemic and hemorrhagic stroke, transient ischemic attack, or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) was not significantly different in the aspirin group (68 events, 5%) than the non-aspirin group (86 events, 7%) [hazard ratio (HR), 0.80; 95% CI, 0.58–1.10; log-rank test, p = 0.16] (Fig. 6A). The combined fatal coronary events and fatal cerebrovascular events occurred in 1 (stroke) patient in the aspirin group and 10 patients (5 fatal MI and 5 fatal stroke) in the non-aspirin group for a 90% relative risk reduction (HR, 0.10; 95% CI, 0.01–0.79, p = 0.004) (Fig. 6B). Other secondary coronary, cerebrovascular, and peripheral vascular disease endpoints are listed in Table 1; there were no significant differences between the aspirin and the non-aspirin arms in these endpoints. There was no significant difference in cardiovascular mortality; two deaths due to aortic dissection were recorded in the low-dose aspirin arm. Hemorrhagic strokes occurred in 13; the incidences in each group were similar (6 in the aspirin group and 7 in the non-aspirin group). One fatal hemorrhagic stroke was recorded in the aspirin group and 4 in the non-aspirin group. Death from any cause

![Figure 6](image-url) (A) Kaplan–Meier estimates of primary endpoint of total atherosclerotic events and (B) Kaplan–Meier estimates of combined endpoint of fatal coronary and fatal cerebrovascular events. CI, confidence interval.
Table 1  Baseline characteristics of patients in the aspirin and non-aspirin treatment groups.

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Aspirin Group</th>
<th>Non-aspirin Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint: all atherosclerotic events</td>
<td>68 (5.4)</td>
<td>86 (6.7)</td>
<td>0.80 (0.58—1.10)</td>
<td>0.16</td>
</tr>
<tr>
<td>Coronary and cerebrovascular events (fatal - nonfatal)</td>
<td>17 (1.3)</td>
<td>23 (1.9)</td>
<td>0.76 (0.47—1.23)</td>
<td>0.27</td>
</tr>
<tr>
<td>Coronary heart disease event</td>
<td>10 (0.8)</td>
<td>30 (2.4)</td>
<td>1.84 (1.19—2.83)</td>
<td>0.003</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>9 (0.7)</td>
<td>10.3 (7.3—13.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Myocardial infarction (fatal)</td>
<td>0</td>
<td>10 (0.8)</td>
<td>0.39 (0.13—1.16)</td>
<td>0.12</td>
</tr>
<tr>
<td>Stable angina</td>
<td>12 (0.9)</td>
<td>31 (2.5)</td>
<td>0.49 (0.21—1.13)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cerebrovascular disease (fatal - nonfatal)</td>
<td>28 (2.2)</td>
<td>32 (2.5)</td>
<td>0.84 (0.53—1.32)</td>
<td>0.44</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>22 (1.7)</td>
<td>24 (1.9)</td>
<td>1.00 (0.59—1.67)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ischemic</td>
<td>15 (1.2)</td>
<td>13 (1.0)</td>
<td>1.15 (0.63—2.10)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>7 (0.6)</td>
<td>11 (0.9)</td>
<td>0.64 (0.25—1.65)</td>
<td>0.35</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>5 (0.4)</td>
<td>6 (0.5)</td>
<td>1.00 (0.19—5.39)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CI, confidence interval.

In the 1363 patients aged ≥65 years (719 in the aspirin group and 644 in the non-aspirin group), the incidence of atherosclerotic events was significantly lower in the aspirin group (45 events, 6%) than in the non-aspirin group (59 events, 9%) (HR, 0.68; 95% CI, 0.46—0.99, p=0.047) (Fig. 7). In the 1176 patients <65 years of age, the incidence of atherosclerotic events was not significantly different between the aspirin group (23; 4%) and the non-aspirin group (27; 4%) (HR, 1.0; 95% CI, 0.57—1.70, p=0.98). Interaction with age was not significant (p=0.27). There were no significant differences between the aspirin group and non-aspirin group in other subgroup analyses, as shown in Fig. 8: including men, women, hypertensive, normotensive, current or past smoker, nonsmoker, and dyslipidemia, and normolipidemia.

The hemorrhagic events consisted of GI bleeding in 12 patients of the aspirin group and 4 of the non-aspirin group, and retinal hemorrhage in 8 patients of the aspirin group and 4 of the non-aspirin group. In the aspirin group, there were 4 patients who developed serious adverse events that needed blood transfusion; while none of the patients of the non-aspirin group required transfusion. Another 13 patients of the aspirin group had minor bleeding. There was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding, which occurred in 10 patients of the aspirin group and in 7 patients of the non-aspirin group.

In summary, in the JPAD trial, the first prospectively designed trial to evaluate the effects of low-dose aspirin in type 2 diabetic patients free of cardiovascular disease, showed that low-dose aspirin as primary prevention does not reduce the risk of cardiovascular events. Aspirin was well tol-
erated in these patients, as there was no increase in hemorrhagic stroke and only a small increase in serious GI hemorrhagic events. These findings should be interpreted in concert with the low incidence of atherosclerotic disease in Japan and the current management practice for cardiovascular risk factors, and further studies of larger population are warranted to confirm the effects of aspirin in primary prevention of cardiovascular disease in diabetics [12].

**Conclusions**

The success of clinical trials in Japan is essential to build evidence based on Japanese populations. The above-mentioned trials were successful and several clinical trials are currently underway. These include candesartan for prevention of cardiovascular events after Cypher or Taxus coronary stenting trial (4C), valsartan in cardiovascular disease with renal dysfunction (V-CARD) study, and olmesartan and calcium antagonists randomized (OSCAR) study. The latter showed satisfactory prognosis after lipid-lowering therapy consisting of early administration of statins in Japanese patients with coronary heart disease and diabetes mellitus, representing a sub-analysis of the MUSASHI (MUSASHI-DM) [13] study, a prospective observational study in patients with AMI (New Japanese acute coronary syndrome study [JACSS]). We have the know-how of large-scale clinical trials acquired empirically to date. First of all, a sense of purpose regarding clinical trials, understanding of study protocol, and elucidation of details of trials are very important before recruitment of large numbers of participants across Japan. Good mutual communication between participants and the regional research office is indispensable. As for surveys, a great number of headings should be avoided and the form of registration should be simple yet accurate. A study conference should be held periodically and the state of registration and the trials still in progress should be presented to participants. We also make every effort to increase the motivation of participants. We provide incentives to participants such as the chance of presentation of common data. To put it concretely, JACSS data were analyzed and presented in national and international scientific meetings by each participant and a total of 13 articles [14–26] have been published so far. Moreover, it is essential that the chief researcher has accurate grasp of the entire operation including all participating institutions and is close to the participants. This is a part of the reason why clinical trials are going well. In conclusion, the most important point for researchers is to have passion for "buildup evidence specific for the Japanese" and to recruit subjects for enrollment after explaining the significance of "clinical trials for the Japanese".

**Acknowledgments**

The authors’ work presented in this article was supported in part by grants-in-aid from Cardiovascular Disease (6A-1) from the Japanese Ministry of Health and Welfare, Tokyo, Japan, Cardiovas-
Clinical evidence for the Japanese


The authors thank Ms Yuko Kuratsu and Ms Yukari Hirata for secretarial assistance.

Disclosures: None.

References


