Original Investigation

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors
A Randomized Clinical Trial

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IMPORTANCE Prevention of atherosclerotic cardiovascular diseases is an important public health priority in Japan due to an aging population.

OBJECTIVE To determine whether daily, low-dose aspirin reduces the incidence of cardiovascular events in older Japanese patients with multiple atherosclerotic risk factors.

DESIGN, SETTING, AND PARTICIPANTS The Japanese Primary Prevention Project (JPPP) was a multicenter, open-label, randomized, parallel-group trial. Patients (N = 14 464) were aged 60 to 85 years, presenting with hypertension, dyslipidemia, or diabetes mellitus recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007, and were followed up for up to 6.5 years, with last follow-up in May 2012. A multidisciplinary expert panel (blinded to treatment assignments) adjudicated study outcomes.

INTERVENTIONS Patients were randomized 1:1 to enteric-coated aspirin 100 mg/d or no aspirin in addition to ongoing medications.

MAIN OUTCOMES AND MEASURES Composite primary outcome was death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. Secondary outcomes included individual end points.

RESULTS The study was terminated early by the data monitoring committee after a median follow-up of 5.02 years (interquartile range, 4.55–5.33) based on likely futility. In both the aspirin and no aspirin groups, 56 fatal events occurred. Patients with an occurrence of nonfatal stroke totaled 114 in the aspirin group and 108 in the no aspirin group; of nonfatal myocardial infarction, 20 in the aspirin group and 38 in the no aspirin group; of undefined cerebrovascular events, 3 in the aspirin group and 5 in the no aspirin group. The 5-year cumulative primary outcome event rate was not significantly different between the groups (2.77% [95% CI, 2.40%-3.20%] for aspirin vs 2.96% [95% CI, 2.58%-3.40%] for no aspirin; hazard ratio [HR], 0.94 [95% CI, 0.77-1.15]; *P* = .54). Aspirin significantly reduced incidence of nonfatal myocardial infarction (0.30 [95% CI, 0.19-0.47] for aspirin vs 0.58 [95% CI, 0.42-0.81] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; *P* = .02) and transient ischemic attack (0.26 [95% CI, 0.16-0.42] for aspirin vs 0.49 [95% CI, 0.35-0.69] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; *P* = .04), and significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (0.86 [95% CI, 0.67-1.11] for aspirin vs 0.51 [95% CI, 0.37-0.72] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; *P* = .004).

CONCLUSIONS AND RELEVANCE Once-daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

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Editorial

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The World Health Organization estimates that annual global mortality due to cardiovascular diseases (including myocardial infarction and stroke) will approach 25 million by 2030.[1] A recent study of secular trends in cardiovascular disease in Japan indicated that, from 1960 to 2000, the prevalence of smoking decreased and blood pressure control among hypertensive individuals improved significantly. Conversely, a steep increase in the prevalence of glucose intolerance, hypercholesterolemia, and obesity was observed,[2] probably due to the adoption of Western diets and lifestyles. Over this period, a decreasing trend in stroke incidence has slowed, and the incidence of myocardial infarction has not changed.[2] By 2030, it is estimated that 32% of the Japanese population will be 65 years or older.[3] This aging population, combined with the increasing prevalence of well-documented risk factors, means that the prevention of atherosclerotic disease remains an important public health challenge in Japan.

In 2009, the Antithrombotic Trialists' Collaboration (ATTC) reviewed the benefit-risk profile of low-dose aspirin for the primary prevention of vascular disease in a meta-analysis of 6 primary prevention trials. Use of low-dose aspirin was associated with a 12% proportional reduction in serious vascular events compared with no aspirin (annual event rate, 0.51% for aspirin and 0.57% for no aspirin; *P* = .001), mainly due to a reduction in nonfatal myocardial infarction of approximately 20%.[4] Aspirin increased major gastrointestinal and extracranial bleeding compared with control (annual increase, 0.10% for aspirin and 0.07% for control; *P* < .001).[4]

In Japan, the use of aspirin for primary prevention of ischemic heart disease has not been widespread.[5,6] The Japanese Primary Prevention Project (JPPP) was designed to determine whether once-daily, low-dose, enteric-coated aspirin reduces the total number of atherosclerotic events (ischemic heart disease and stroke) compared with no aspirin in Japanese patients 60 years or older with hypertension, dyslipidemia, or diabetes mellitus.

Methods

Patient Selection

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Studies and was approved by the institutional review board of each participating center. Details of the study design and methods have been published previously.[7]

This multicenter, randomized, open-label, parallel-group clinical trial was conducted at 1007 clinics in the 47 prefectures of Japan that routinely offer outpatient care for hypertension, hyperlipidemia, or diabetes. Patients were recruited consecutively at each clinic by primary care physicians between March 2005 and June 2007. The last included patient completed follow-up in May 2012.

Patients were screened when they attended their local clinic on a routine visit if they were aged 60 to 85 years and had not been diagnosed with atherosclerotic disease. Patients were eligible if, at screening, they met Japanese guideline criteria for hypertension (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg),[8] dyslipidemia (total cholesterol ≥220 mg/dL or low-density lipoprotein [LDL] cholesterol ≥140 mg/dL or high-density lipoprotein [HDL] cholesterol <40 mg/dL or triglycerides ≥150 mg/dL; to convert total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113),[9] or diabetes mellitus (fasting morning blood glucose ≥126 mg/dL or any blood glucose ≥200 mg/dL or 2-hour blood glucose ≥200 mg/dL in the 75-g glucose tolerance test, or glycated hemoglobin ≥6.5%; to convert glucose to millimoles per liter, multiply by 0.0555).[10]

Key exclusion criteria were a history of coronary artery disease or cerebrovascular disease (including transient ischemic attack [TIA]), atherosclerotic disease requiring surgery or intervention, or atrial fibrillation (confirmed or suspected). Patients with peptic ulcer or conditions associated with bleeding (eg, von Willebrand disease) and those with serious blood abnormalities (eg, clotting factor deficiencies) were also excluded. In addition, patients with aspirin-sensitive asthma or those with a history of hypersensitivity to aspirin or salicylic acid could not participate, nor could patients who were receiving antiplatelet agents, anticoagulants, or long-term treatment with nonsteroidal anti-inflammatory drugs. The use of antiplatelet (eg, ticlopidine, cilostazol, dipyridamole, trapidil) and anticoagulant agents (eg, warfarin) was prohibited after enrollment.
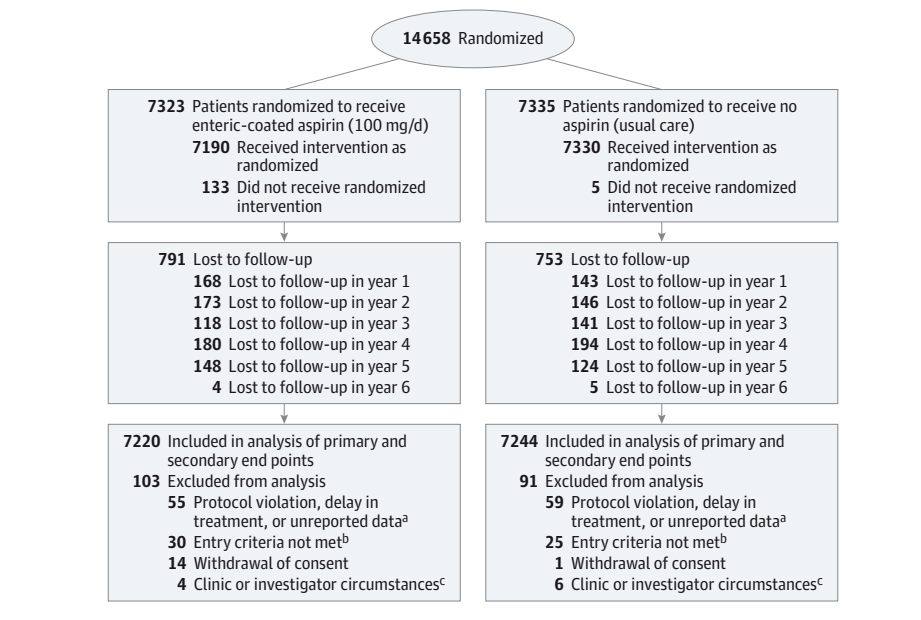
Study Design

Treatment to control hypertension, dyslipidemia, or diabetes (ie, the underlying risk factors for vascular events) was administered to all eligible patients at the screening visit and, in principle, throughout the study, in accordance with Japanese therapeutic guidelines.[9-11]

Approximately 1 month after the screening visit, patients returned for a baseline evaluation and were randomized 1:1 to receive either a 100-mg tablet of enteric-coated aspirin once daily or no aspirin, in addition to any ongoing medication (**Figure 1**). Randomization was stratified by the 3 underlying disease risk factors for atherosclerotic events (hypertension, dyslipidemia, or diabetes). Seven strata were used to account for all the different combinations of the 3 underlying disease risk factors because patients could have single or multiple risk factors (eg, diabetes mellitus, but no hypertension or dyslipidemia; diabetes and hypertension, but no dyslipidemia). The minimization method was applied to balance for sex and age within each stratum (eMethods in the Supplement). Pseudorandom numbers were generated using the Mersenne Twister method with a seed of 4989.[12] The study statistician generated the random allocation sequence using a central computerized system and study physicians were informed of treatment assignments via the study website or by fax.

At baseline and at each annual study assessment, the following variables were evaluated in the clinic when patients met

Figure 1. Flow of Patients Through the Japanese Primary Prevention Project (JPPP)

14658 Randomized

7323 Patients randomized to receive enteric-coated aspirin (100 mg/d)
7190 Received intervention as randomized
133 Did not receive randomized intervention

7335 Patients randomized to receive no aspirin (usual care)
7330 Received intervention as randomized
5 Did not receive randomized intervention

791 Lost to follow-up
168 Lost to follow-up in year 1
173 Lost to follow-up in year 2
118 Lost to follow-up in year 3
180 Lost to follow-up in year 4
148 Lost to follow-up in year 5
4 Lost to follow-up in year 6

753 Lost to follow-up
143 Lost to follow-up in year 1
146 Lost to follow-up in year 2
141 Lost to follow-up in year 3
194 Lost to follow-up in year 4
124 Lost to follow-up in year 5
5 Lost to follow-up in year 6

7220 Included in analysis of primary and secondary end points
103 Excluded from analysis
55 Protocol violation, delay in treatment, or unreported data[a]
30 Entry criteria not met[b]
14 Withdrawal of consent
4 Clinic or investigator circumstances[c]

7244 Included in analysis of primary and secondary end points
91 Excluded from analysis
59 Protocol violation, delay in treatment, or unreported data[a]
25 Entry criteria not met[b]
1 Withdrawal of consent
6 Clinic or investigator circumstances[c]

Data on patients assessed for eligibility are not available.

[a] Protocol violations (aspirin, n=19; no aspirin, n=22); delay in start of treatment (aspirin, n=10; no aspirin, n=15); unreported data by investigators in the clinics (aspirin, n=26; no aspirin, n=22).

[b] Reasons for not meeting inclusion criteria were serious blood abnormalities (aspirin, n = 2), history of prohibited drugs (aspirin, n = 12; no aspirin, n = 18), cerebrovascular disease (aspirin, n = 6; no aspirin, n = 7), atrial fibrillation (aspirin, n = 3), hypersensitivity to aspirin (aspirin, n = 3), peptic ulcer (aspirin, n = 2), atherosclerotic disease (aspirin, n = 1), or long-term use of nonsteroidal anti-inflammatory drugs (aspirin, n = 1).

[c] Clinic or investigator circumstances were closure of clinic and investigator death.

with the study physician: disease outcomes, adverse events, adherence with treatment (self-reported by patients), blood pressure, serum lipids, blood glucose, smoking status, and body weight.

To minimize loss of patients to follow-up, every effort was made to contact patients, including telephone calls, postcards, and visits from a traveling clinical research coordinator. Follow-up of patients ceased in the event of death or withdrawal of consent. If a patient was lost to follow-up because of death but the reason was unclear, the cause of death was established by obtaining the death certificate with permission from the Japanese government; this process was completed in April 2014.

The study was designed and overseen by a steering committee and decisions to amend or discontinue the study were made with advice from an independent data monitoring committee (DMC). Study end points were assessed centrally and biannually by an expert, multidisciplinary event adjudication committee that was blinded to treatment assignments in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) trial design.[13] A placebo-controlled study design was not used because the Japan Pharmaceutical Affairs Law limits the use of placebo in large, physician-led studies of approved products such as aspirin. Members of study committees and details of study clinic locations and investigators are provided in the eMethods in the Supplement.

Study End Points

The primary outcome was a composite of death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. The first secondary end point was also a composite that included the same events as the primary end point, plus TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention. Other secondary end points were death from cardiovascular disease, death from noncardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, TIA, angina pectoris, arteriosclerotic disease requiring surgery or intervention, and serious extracranial hemorrhage requiring transfusion or hospitalization.

Physicians at each study clinic diagnosed myocardial infarction according to the European Society of Cardiology and American College of Cardiology guidelines.[14] Imaging evidence of cerebral infarction or intracerebral hemorrhage accompanied by an acute regional neurological deficit maintained for 24 hours was required for a diagnosis of ischemic stroke.

The main assessment of safety was the secondary end point of serious extracranial hemorrhage requiring transfusion or hospitalization. However, data on the occurrence of the following prespecified gastrointestinal adverse events associated with aspirin were also collected for safety and tolerability analyses: gastrointestinal hemorrhage; gastroduodenal ulcer; reflux esophagitis; erosive gastritis; stomach or abdominal discomfort, pain, or pressure; heartburn; and nausea. The overall incidence of adverse events was not a primary or secondary end point of the study. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), Japanese version 16.0J. Each clinic provided case report forms via the study website or faxed the forms to a central data center for input into the study database.

Statistical Analyses

Based on Japanese epidemiological and interventional studies,[15-23] annual mortality due to cardiovascular causes, nonfatal strokes, and myocardial infarction was expected to be approximately 1.5% to 2% in individuals not receiving aspirin. Accordingly, a sample size of 10 000 patients was determined to be sufficient to provide 80% power to detect a relative risk reduction of 20% in the aspirin group compared with the no aspirin group over a mean follow-up period of 4 years at a 2-sided significance level of α = .05. However, a pre-planned review at the first annual general examination in July 2006 showed that the incidence of primary outcome events (14 events among 6745 enrolled patients) was much lower than originally estimated.

Therefore, based on the reduced observed event rate, which determined both the sample size and the timing of the final study analyses, the sample size and study duration were reestimated. Assuming that the maximum frequency of events in both groups was 0.79%, it was estimated that enrollment in the study would need to be increased to 14 960 patients for 624 primary end point events to occur over an extended follow-up of up to 6.5 years. The final analyses were to be performed when 624 events had occurred if this was sooner than the maximum follow-up period of 6.5 years. Using these revised assumptions, a reduction in the annual frequency of events from 0.87% with no aspirin to 0.70% with aspirin would be required to detect a 20% difference between the aspirin and no aspirin groups at the α = .05 significance level with 80% power.

The primary objective was to test the hypothesis that treatment with once-daily, low-dose aspirin significantly prolongs the time to occurrence of the composite primary end point event compared with no aspirin treatment. Accordingly, the null hypothesis was that the time until such an event does not differ significantly between the 2 study groups. Time until onset of events was estimated using the Kaplan-Meier method in each study group. Between-group differences in the primary end point were assessed using the stratified log-rank test in all patients meeting the inclusion criteria, with stratification for underlying disease (hypertension, dyslipidemia, or diabetes) and a 2-sided significance level of α = .05. Hazard ratios (HRs) were calculated using the Cox proportional hazards model and 95% CIs were determined; there was no evidence of violation of proportionality. Adjustment for factors used in the allocation of patients to the study groups and biased background variables were incorporated as needed.

The same statistical methods were used to evaluate between-group differences for each of the secondary end points. Prospectively defined subgroup analyses of the composite primary outcome measure were conducted in subgroups of patients defined by disease and patient demographic risk factors. Interactions between each of the subgroups and aspirin treatment were assessed by the likelihood ratio test in the Cox model. The risk of a primary end point event was also compared between subgroups (eg, in patients with hypertension vs without hypertension) and an estimate of the relative risk of occurrence of a primary end point event (a "parameter estimate") was calculated for each subgroup using Cox regression fitted to the primary end point. A total risk score for an individual patient was then calculated as the sum of the risk factors. Based on the subgroup parameter estimates, men were allocated a rounded risk score value of +1; 70 years or older, +3; smoker, +1.5; hypertension, +1; and diabetes mellitus, +1.5. The primary end point event rate and HR for aspirin compared with no aspirin were then determined in patients with risk score of less than the median value (ie, patients considered at low risk of primary end point events) or more than the median value (ie, high-risk patients).

All primary, secondary, and subgroup analyses were assessed using a modified intention-to-treat population. A modified population was used because a post hoc central assessment had to be performed after randomization to ensure that all randomized patients were eligible for, and actively participating in, the study. As a result of this assessment, the modified intention-to-treat population excluded the following patients: those who were randomized in error (did not meet the study entry criteria or had withdrawn consent), patients who could not be followed up owing to investigator or clinic circumstances (death of investigators or clinical closures), and patients with certain major systematic protocol violations or deviations. Protocol violations included lack of adherence to allocation by the site investigator and patients who had no follow up after randomization and for whom survival status could not be established; protocol deviation was delay in treatment initiation. Patients who were lost to follow-up were treated as censored cases at the last date at which survival had been verified if no primary or secondary end point event had occurred; missing data were not imputed.

The incidence of gastrointestinal adverse events was estimated in the randomized population using the precise CIs determined from the binomial distribution, and between-group differences were tested using the Fisher exact method. All statistical analyses were performed using SAS (SAS Institute), version 9.4.

Interim Analysis and Guidelines for Study Discontinuation

The independent DMC, which included medical experts and a statistician, regularly monitored the results of the trial in a blinded manner. Interim analyses were conducted at yearly intervals between 6 months after the end of patient enrollment and the final study analysis. Following review of each interim analysis, the DMC assessed whether the study should proceed or whether the study protocol should be amended. The study was to be discontinued if a significant difference in favor of aspirin compared with no aspirin was demonstrated for the primary end point at any of the interim analyses time points or if the DMC judged that there was very low likelihood of observing a significant difference if the study was continued.[7] The DMC could also recommend study discontinuation owing to the occurrence of unexpected or serious adverse reactions or an incidence of adverse reactions that was higher than expected, although there were no formal conditions for such decisions. The

other prespecified criteria for discontinuing the study or amending the protocol were publication of similar study results and ethical issues generated by changes in the social environment.

Results

Patients

A total of 14 658 patients were randomized between March 2005 and June 2007, and all were included in the safety analyses. For analyses of the primary and secondary end points, 194 patients (1.3%) were excluded from the randomized population owing to protocol violations or deviations (untraceable patients, nonadherence, or delayed start of treatment), not meeting the inclusion criteria, withdrawal of consent, or clinic or investigator circumstances (Figure 1); the remaining 14 464 patients comprised the modified intention-to-treat population.

Baseline characteristics have been reported in detail previously and were balanced between the 2 study groups for patient demographics and disease risk factors.[7] The values reported in **Table 1** differ slightly from those reported previously because the modified intention-to-treat population had not been fixed at the time that the baseline characteristics were originally reported.

Based on the rate of primary end point events at the interim analyses in May 2008 and May 2011, the committee decided that the study was unlikely to show a difference in event rate if follow-up was continued for the maximum of 6.5 years. At the time of the second interim analysis in May 2011, only 290 of the 624 estimated primary end point events (46.5%) had occurred and the estimated HR for aspirin vs no aspirin was 0.95 (99.80% CI, 0.66-1.37). Therefore, the study was terminated prematurely owing to futility; it was judged that statistical power to detect a between-group difference in the primary end point would not be reached and continuing could put participants at unnecessary risk of drug-related adverse events. At the recommendation of the DMC, the final analysis was conducted at the next annual study assessment when patients had been followed up for a median 5.02 years (interquartile range, 4.55-5.33 years); the median follow-up period was similar in the aspirin and no aspirin groups (5.01 years for aspirin and 5.02 years for no aspirin).

Most patients were adherent with aspirin therapy. A total of 88.9% of patients reported that they were adherent in year 1; this value decreased to 76.0% in year 5 (eTable 1 in the Supplement). In the no aspirin group, the proportion of patients who started to take daily low-dose aspirin increased each year from 1.5% in year 1 to 9.8% in year 5. Most patients did not receive medicines (antiplatelet or anticoagulant agents) that had been, in principle, prohibited after enrollment; however, the proportion of patients receiving these prohibited medications increased over time in both the aspirin group (1.3% in year 1, 10.5% in year 5) and the no aspirin group (1.4% in year 1, 10.4% in year 5) (eTable 1 in the Supplement).

Effectiveness

Composite Primary End Point

There was no statistically significant difference between the 2 groups in time to the primary end point—a composite of

Table 1. Baseline Characteristics for Japanese Patients Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Patient demographics		
Age, mean (SD), y	70.6 (6.2)	70.5 (6.2)
Age, No. (%)		
<70 y	3234 (44.8)	3259 (45.0)
≥70 y	3986 (55.2)	3985 (55.0)
Men, No. (%)	3055 (42.3)	3068 (42.4)
Waist circumference, mean (SD), cm	85.2 (9.9)	84.7 (10.0)
Weight, mean (SD), kg	58.7 (10.4)	58.6 (10.3)
BMI ≥25, No. (%)	2644 (36.6)	2604 (35.9)
Risk factors for vascular events, No. (%)		
HT	6133 (84.9)	6145 (84.8)
DL	5198 (72.0)	5200 (71.8)
DM	2445 (33.9)	2458 (33.9)
HT and DL	4276 (59.2)	4264 (58.9)
DL and DM	1794 (24.8)	1798 (24.8)
HT and DM	1932 (26.8)	1939 (26.8)
HT, DL, and DM	1446 (20.0)	1442 (19.9)
BMI, mean (SD)	24.2 (3.5)	24.2 (3.4)
Blood pressure, mm Hg		
Systolic	137.1 (15.8)	137.2 (15.6)
Diastolic	77.7 (10.4)	77.6 (10.2)
Currently smoking, No. (%)	959 (13.3)	934 (12.9)
Family history of premature CV disease, No. (%)		
No	4058 (56.2)	4086 (56.4)
Yes	1981 (27.4)	1982 (27.4)
Unknown	1181 (16.4)	1176 (16.2)
Laboratory values, mean (SD)		
Cholesterol, mean (SD), mg/dL		
Total	202.9 (32.9)	203.6 (32.5)
Low-density lipoprotein[a]	119.2 (30.5)	119.8 (30.3)
High-density lipoprotein	57.8 (15.8)	58.2 (15.7)
Triglycerides, mean (SD), mg/dL	132.8 (76.0)	131.0 (75.9)
Fasting blood glucose, mean (SD), mg/dL	107.8 (31.2)	107.7 (32.0)
HbA$_{1c}$, mean (SD), %[b]	6.1 (1.0)	6.0 (1.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CV, cardiovascular; DL, dyslipidemia; DM, diabetes mellitus; HbA$_{1c}$, glycated hemoglobin; HT, hypertension.

SI conversion factors: To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

[a] Calculated based on the Friedewald formula and direct measurements.

[b] National Glycohemoglobin Standardization Program method.

Table 2. Fatal and Nonfatal Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Fatal events	56	56
Cerebral infarction	2	7
Intracranial hemorrhage	5	5
Subarachnoid hemorrhage	2	4
Myocardial infarction	7	9
Other fatal cardiovascular events	40	31
Nonfatal events	137	151
Cerebral infarction	83	94
Intracranial hemorrhage	23	10
Subarachnoid hemorrhage	8	4
Myocardial infarction	20	38
Undefined cerebrovascular events	3	5

Figure 2. Time to Primary End Point Composite Event[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin vs No Aspirin (Modified Intention-to-Treat Population)

No. at risk							
Aspirin	7220	7021	6771	6583	6322	3639	169
No aspirin	7244	7073	6861	6645	6359	3711	182

HR indicates hazard ratio. The P value was determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). The HRs were calculated using the Cox proportional hazards model.
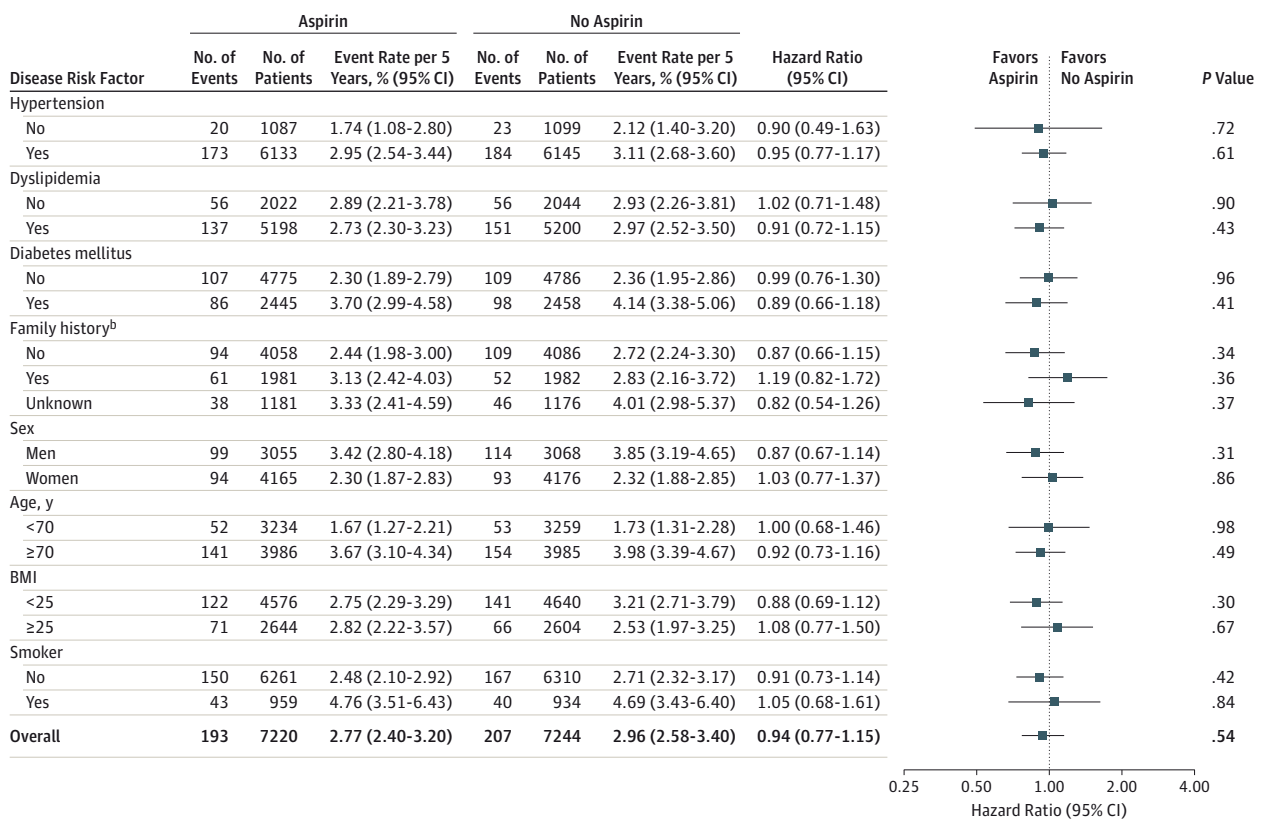
[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction (**Table 2** and **Figure 2**). The estimated HR for aspirin vs no aspirin was 0.94 (95% CI, 0.77-1.15; P = .54). At 5 years after randomization, the cumulative primary event rate was similar in participants in the aspirin group (2.77% [95% CI, 2.40%-3.20%]) and those in the no aspirin group (2.96% [95% CI, 2.58%-3.40%]). Overall, few deaths from cardiovascular causes or nonfatal stroke or myocardial infarction were reported with aspirin (n = 193) or no aspirin (n = 207) (Table 2).

Assessment of the primary end point in subgroups of patients defined by the presence or absence of 8 different disease or demographic risk factors (hypertension, dyslipidemia, diabetes mellitus, male sex, aged at least 70 years, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] of 25 or higher, smoking, or family history of premature cardiovascular disease) did not reveal significant differences between study groups; detailed results from these subgroup analyses are reported in **Figure 3**.

Regression analyses indicated that the risk of a primary end point event was higher in patients 70 years or older vs those younger than 70 years (parameter estimate, 0.92; HR, 2.51 [95% CI, 2.00-3.14]; P < .001), in patients with diabetes mellitus vs those without diabetes mellitus (parameter estimate, 0.52; HR, 1.68 [95% CI, 1.38-2.06]; P < .001), in patients who were smoking vs nonsmoking (parameter estimate, 0.53; HR, 1.70 [95% CI, 1.31-2.20]; P < .001), in men vs women (parameter estimate, 0.34; HR, 1.41 [95% CI, 1.14-1.74]; P = .002), and in patients with hypertension vs those without hypertension (parameter estimate, 0.42; HR, 1.52 [95% CI, 1.10-2.09]; P = .01). The risk of a primary end point event was not increased in patients with dyslipidemia vs those without dyslipidemia (parameter estimate, 0.13; HR, 1.13 [95% CI, 0.91-1.42]; P = .27) or in patients with a BMI of 25 or higher vs those with a BMI lower than 25 (parameter estimate, −0.13; HR, 0.88 [95% CI, 0.72-1.09]; P = .24). The risk of a primary end point event was also not significantly
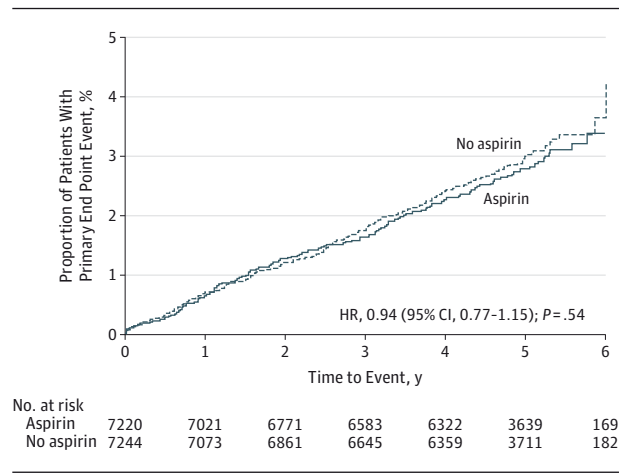
lower with aspirin vs no aspirin, irrespective of whether patients had a risk score lower than 4 (1.53% [95% CI, 1.14%-2.05%] for aspirin vs 1.47% [95% CI, 1.08%-1.98%] for no aspirin; HR, 1.09 [95% CI, 0.72-1.63]; P = .69) or a risk score of 4 or higher (3.79% [95% CI, 3.21%-4.46%] for aspirin vs 4.19% [95% CI, 3.59%-4.90%] for no aspirin; HR, 0.90 [95% CI, 0.72-1.13]; P = .35).

Secondary Outcomes

When TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention were added to the composite primary end point, the difference between the aspirin group (event rate, 4.00% [95% CI, 3.55%-4.50%]) and no aspirin group (event rate, 4.59% [95% CI, 4.11%-5.13%]) remained nonsignificant (HR, 0.89 [95% CI, 0.75-1.04]; P = .14) (**Figure 4**). There were also no significant differences between the 2 study groups for time to any cause of death (event rate, 4.29% [95% CI, 3.83%-4.82%] for aspirin vs 4.11% [95% CI, 3.66%-4.62%] for no aspirin; HR, 0.99 [95% CI, 0.85-1.17]; P = .93), death from cardiovascular disease (event rate, 0.86% [95% CI, 0.66%-1.12%] for aspirin vs 0.78% [95% CI, 0.60%-1.02%] for no aspirin; HR, 1.03 [95% CI, 0.71-1.48]; P = .89), death from causes other than cardiovascular disease (event rate, 3.46% [95% CI, 3.04%-3.94%] for aspirin vs 3.36% [95% CI, 2.94%-3.83%] for no aspirin; HR, 0.99 [95% CI, 0.82-1.18]; P = .87), nonfatal cerebrovascular disease (ischemic or hemorrhagic) (event rate, 1.65% [95% CI, 1.37%-1.99%] for aspirin vs 1.64% [95% CI, 1.36%-1.98%] for no aspirin; HR, 1.04 [95% CI, 0.80-1.34]; P = .78), angina pectoris (event rate, 0.66% [95% CI, 0.49%-0.89%] for aspirin vs 0.81% [95% CI, 0.61%-1.07%] for no aspirin; HR, 0.86 [95% CI, 0.58-1.28]; P = .46), and arteriosclerotic diseases requiring surgery or intervention (event rate, 1.08%

Figure 3. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for the Primary Composite Outcome Measure[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

	Aspirin			No Aspirin						
Disease Risk Factor	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	Hazard Ratio (95% CI)	Favors Aspirin / Favors No Aspirin		P Value
Hypertension										
No	20	1087	1.74 (1.08-2.80)	23	1099	2.12 (1.40-3.20)	0.90 (0.49-1.63)			.72
Yes	173	6133	2.95 (2.54-3.44)	184	6145	3.11 (2.68-3.60)	0.95 (0.77-1.17)			.61
Dyslipidemia										
No	56	2022	2.89 (2.21-3.78)	56	2044	2.93 (2.26-3.81)	1.02 (0.71-1.48)			.90
Yes	137	5198	2.73 (2.30-3.23)	151	5200	2.97 (2.52-3.50)	0.91 (0.72-1.15)			.43
Diabetes mellitus										
No	107	4775	2.30 (1.89-2.79)	109	4786	2.36 (1.95-2.86)	0.99 (0.76-1.30)			.96
Yes	86	2445	3.70 (2.99-4.58)	98	2458	4.14 (3.38-5.06)	0.89 (0.66-1.18)			.41
Family history[b]										
No	94	4058	2.44 (1.98-3.00)	109	4086	2.72 (2.24-3.30)	0.87 (0.66-1.15)			.34
Yes	61	1981	3.13 (2.42-4.03)	52	1982	2.83 (2.16-3.72)	1.19 (0.82-1.72)			.36
Unknown	38	1181	3.33 (2.41-4.59)	46	1176	4.01 (2.98-5.37)	0.82 (0.54-1.26)			.37
Sex										
Men	99	3055	3.42 (2.80-4.18)	114	3068	3.85 (3.19-4.65)	0.87 (0.67-1.14)			.31
Women	94	4165	2.30 (1.87-2.83)	93	4176	2.32 (1.88-2.85)	1.03 (0.77-1.37)			.86
Age, y										
<70	52	3234	1.67 (1.27-2.21)	53	3259	1.73 (1.31-2.28)	1.00 (0.68-1.46)			.98
≥70	141	3986	3.67 (3.10-4.34)	154	3985	3.98 (3.39-4.67)	0.92 (0.73-1.16)			.49
BMI										
<25	122	4576	2.75 (2.29-3.29)	141	4640	3.21 (2.71-3.79)	0.88 (0.69-1.12)			.30
≥25	71	2644	2.82 (2.22-3.57)	66	2604	2.53 (1.97-3.25)	1.08 (0.77-1.50)			.67
Smoker										
No	150	6261	2.48 (2.10-2.92)	167	6310	2.71 (2.32-3.17)	0.91 (0.73-1.14)			.42
Yes	43	959	4.76 (3.51-6.43)	40	934	4.69 (3.43-6.40)	1.05 (0.68-1.61)			.84
Overall	**193**	**7220**	**2.77 (2.40-3.20)**	**207**	**7244**	**2.96 (2.58-3.40)**	**0.94 (0.77-1.15)**			**.54**

Hazard Ratio (95% CI): 0.25 0.50 1.00 2.00 4.00

BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared). Data shown for the overall population and for subgroups defined by disease risk factor and by patient characteristics. The P values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

[b] History of premature cardiovascular disease.

[95% CI, 0.86%-1.36%] for aspirin vs 1.24% [95% CI, 0.99%-1.55%] for no aspirin; HR, 0.89 [95% CI, 0.65-1.21]; *P* = .46) (Figure 4). However, compared with no aspirin, aspirin significantly reduced the risk of nonfatal myocardial infarction (event rate, 0.30% [95% CI, 0.19%-0.47%] for aspirin vs 0.58% [95% CI, 0.42%-0.81%] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; *P* = .02) and TIA (event rate, 0.26% [95% CI, 0.16%-0.42%] for aspirin vs 0.49% [95% CI, 0.35%-0.69%] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; *P* = .04). Conversely, the risk of extracranial hemorrhage requiring transfusion or hospitalization was higher with aspirin than with no aspirin (event rate, 0.86% [95% CI, 0.67%-1.11%] for aspirin vs 0.51% [95% CI, 0.37%-0.72%] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; *P* = .004).

Exploratory Analysis

A post hoc exploratory analysis was conducted at the time of study discontinuation (1 year after the second interim analysis) when 400 primary end point events had occurred. It showed that the predictive probability of reaching a signifi-

cant difference in favor of aspirin over no aspirin was 28% if the study had continued until it was adequately powered (ie, 624 events had occurred).
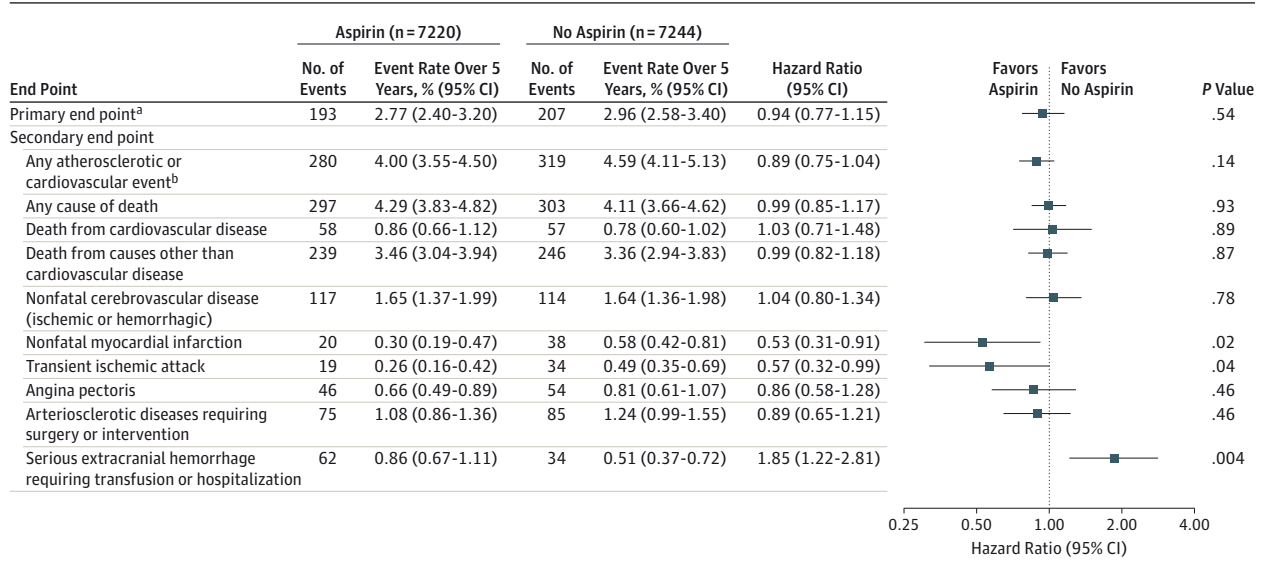
Safety and Tolerability

Analysis of gastrointestinal adverse events of interest indicated that these events were reported in a higher proportion of patients receiving daily low-dose aspirin than in those not receiving aspirin (**Table 3**).

Discussion

This study was designed to assess whether primary prevention with once-daily, low-dose aspirin would reduce the combined risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction in Japanese patients (aged ≥60 years) with hypertension, dyslipidemia, or diabetes mellitus. The study was terminated early based on a futility assessment, but an exploratory analysis sug-

Figure 4. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for Secondary End Points Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

End Point	Aspirin (n = 7220)		No Aspirin (n = 7244)					P Value
	No. of Events	Event Rate Over 5 Years, % (95% CI)	No. of Events	Event Rate Over 5 Years, % (95% CI)	Hazard Ratio (95% CI)	Favors Aspirin	Favors No Aspirin	
Primary end point[a]	193	2.77 (2.40-3.20)	207	2.96 (2.58-3.40)	0.94 (0.77-1.15)			.54
Secondary end point								
Any atherosclerotic or cardiovascular event[b]	280	4.00 (3.55-4.50)	319	4.59 (4.11-5.13)	0.89 (0.75-1.04)			.14
Any cause of death	297	4.29 (3.83-4.82)	303	4.11 (3.66-4.62)	0.99 (0.85-1.17)			.93
Death from cardiovascular disease	58	0.86 (0.66-1.12)	57	0.78 (0.60-1.02)	1.03 (0.71-1.48)			.89
Death from causes other than cardiovascular disease	239	3.46 (3.04-3.94)	246	3.36 (2.94-3.83)	0.99 (0.82-1.18)			.87
Nonfatal cerebrovascular disease (ischemic or hemorrhagic)	117	1.65 (1.37-1.99)	114	1.64 (1.36-1.98)	1.04 (0.80-1.34)			.78
Nonfatal myocardial infarction	20	0.30 (0.19-0.47)	38	0.58 (0.42-0.81)	0.53 (0.31-0.91)			.02
Transient ischemic attack	19	0.26 (0.16-0.42)	34	0.49 (0.35-0.69)	0.57 (0.32-0.99)			.04
Angina pectoris	46	0.66 (0.49-0.89)	54	0.81 (0.61-1.07)	0.86 (0.58-1.28)			.46
Arteriosclerotic diseases requiring surgery or intervention	75	1.08 (0.86-1.36)	85	1.24 (0.99-1.55)	0.89 (0.65-1.21)			.46
Serious extracranial hemorrhage requiring transfusion or hospitalization	62	0.86 (0.67-1.11)	34	0.51 (0.37-0.72)	1.85 (1.22-2.81)			.004

Hazard Ratio (95% CI): 0.25 0.50 1.00 2.00 4.00

Data shown for the overall population. The P values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

[b] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention.

Table 3. Incidence of Prespecified Gastrointestinal Adverse Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Randomized Population)

	No. (%) [95% CI]		P Value
	Aspirin (n = 7323)	No Aspirin (n = 7335)	
Stomach/abdominal discomfort	335 (4.57) [4.11-5.08]	175 (2.39) [2.05-2.76]	<.001
Heartburn	202 (2.76) [2.40-3.16]	137 (1.87) [1.57-2.20]	<.001
Gastroduodenal ulcer	191 (2.61) [2.26-3.00]	91 (1.24) [1.00-1.52]	<.001
Stomach/abdominal pain	168 (2.29) [1.96-2.66]	81 (1.10) [0.88-1.37]	<.001
Reflux esophagitis	160 (2.18) [1.86-2.55]	125 (1.70) [1.42-2.03]	.04
Gastrointestinal hemorrhage	103 (1.41) [1.15-1.70]	31 (0.42) [0.29-0.60]	<.001
Erosive gastritis	89 (1.22) [0.98-1.49]	40 (0.55) [0.39-0.74]	<.001
Nausea	79 (1.08) [0.85-1.34]	50 (0.68) [0.51-0.90]	.01
Stomach/abdominal pressure	31 (0.42) [0.29-0.60]	21 (0.29) [0.18-0.44]	.17

gested a 28% probability of finding a significant difference in favor of aspirin had the study been continued through the planned number of events. Therefore, there remains a possibility that the statistically nonsignificant reduction in the risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction was due to the study being inadequately powered, rather than an absence of beneficial effect of aspirin. However, even if the result had become statistically significant through prolongation of the study, the clinical importance of aspirin in the primary prevention of cardiovascular events would have been less than originally assumed. Therefore, it appears that aspirin is unlikely to show a clinically important benefit in the overall population included in this study. We plan to

conduct further analyses to establish whether aspirin had beneficial effects in particular subgroups of patients or if there were beneficial effects with respect to cancer prevention.

Study limitations need to be considered. Assessments of between-group differences in any end point in this study were confounded by a decreasing level of adherence with daily low-dose aspirin in the aspirin group (dropping to 76% in year 5) and increasing uptake of daily aspirin in the no aspirin group (reaching 10% in year 5). In addition, the number of patients lost to follow-up could be considered a limitation of large trials conducted in a real-world setting. However, use of Kaplan-Meier time-to-event analyses limits the effect of missing data, and the proportion of patients lost to

follow-up in this study (10.5%) was consistent with that reported for an earlier Japanese study (7.6%) with a similar design, but a shorter follow-up period.[24] This earlier study, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study[24] among patients with type 2 diabetes, also had lower than planned power (because of low event rates). It is possible that the low incidence of fatal and nonfatal cardiovascular events is due to the characteristics of Japanese patients. Compared with other relevant studies (eg, JPAD, the Prevention of Progression of Arterial Disease and Diabetes [POPADAD] study,[25] and the Aspirin for Asymptomatic Atherosclerosis Trial [AAAT][26]), baseline characteristics in the JPPP study are broadly similar, except for an apparent lower prevalence of current smoking in JPPP (13.1% in JPPP vs 21%-32% in the other studies) and a lower mean BMI compared with POPADAD (24.2 in JPPP vs 28.7-29.2 in POPADAD), although this is likely to reflect a Japanese population compared with a Western population, because BMI was similar in JPPP and JPAD.[25,26]

The PROBE study design could be considered a limitation, because it does not have all the advantages of a double-blind, randomized, placebo-controlled trial. However, adjudication of end points was performed centrally by an expert committee blinded to treatment assignments. The PROBE design does not control for lack of ascertainment.

Because the study participants were unblinded, it is possible that patients receiving aspirin were more likely to report adverse events believed to be related to aspirin treatment than those not receiving treatment. In addition, it is possible that enrollment in the study led to patients having more physician contact, resulting in better control of risk factors than the general population; if so, this might account for the low observed event rates.

It is likely that some deaths occurred among participants lost to follow-up. However, the potential effect of this under-ascertainment on the study outcomes is likely to be small. Similarly, although exclusion of nonadherent persons after randomization could have biased the findings away from the null (in either direction), the magnitude of any such bias would be expected to be small.

Hemorrhagic stroke is more common in Japanese populations than in Western populations.[27] In this study, no increase was observed in fatal hemorrhagic strokes (intracerebral and subarachnoid) for aspirin vs no aspirin. However, more patients treated with aspirin had nonfatal intracerebral hemorrhage (23 patients) or subarachnoid hemorrhage (8 patients) than those not receiving aspirin (10 patients for nonfatal intracerebral hemorrhage and 4 patients for subarachnoid hemorrhage).

More recent meta-analyses than the ATTC,[4] not using patient-level data, also included studies completed since 2009 (JPAD, POPADAD, and AAAT)[28-30] and suggested beneficial effects for aspirin in the primary prevention of cardiovascular events. In the meta-analysis performed by Raju and colleagues,[29] primary prevention with aspirin, compared with nonuse of aspirin, was associated with a reduction in all-cause mortality (relative risk [RR], 0.94 [95% CI, 0.88-1.00]), myocardial infarction (composite of fatal and nonfatal; RR, 0.83 [95% CI, 0.69-1.00]), ischemic stroke (RR, 0.86 [95% CI, 0.75-0.98]), and the composite of myocardial infarction, stroke, and cardiovascular death (RR, 0.88 [95% CI, 0.83-0.94]). Bartolucci and colleagues[28] reported in their meta-analysis that aspirin significantly decreased the risk of total cardiovascular events (odds ratio [OR], 0.87 [95% CI, 0.80-0.93]; $P = .001$) and nonfatal myocardial infarction (OR, 0.81 [95% CI, 0.67-0.99]; $P = .042$), compared with no aspirin. In the third meta-analysis, conducted by Seshasai and colleagues,[30] the association of aspirin (compared with no aspirin) with a significant reduction in the risk of cardiovascular events (OR, 0.90 [95% CI, 0.85-0.96]) was primarily accounted for by a large reduction in the risk of nonfatal myocardial infarction (OR, 0.80 [95% CI, 0.67-0.96]). No effect on fatal myocardial infarction was observed, but a modest nonsignificant reduction was apparent for all-cause mortality.

Despite inconsistent evidence for the benefit of aspirin in primary prevention of cardiovascular events, the benefits in secondary prevention are well documented, including in Japanese patients.[31-33] There is also a growing body of evidence to suggest benefits for aspirin in the prevention of colorectal and other cancers,[34,35] and the prevention of cancer recurrence, including in the Japanese population.[36] Reduction in the incidence of colorectal cancer may influence the overall benefit-risk profile of aspirin. Further analyses of the JPPP study data are planned, including analysis of deaths associated with cancers, to allow more precise identification of the patients for whom aspirin treatment may be most beneficial. In addition, other primary prevention studies using aspirin, such as ARRIVE,[37] ASCEND,[38] ASPREE,[39] and ACCEPT-D,[40] are in progress; however, these are being conducted in predominantly Western populations.

Conclusions

Once-daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

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REFERENCES

1. World Health Organization. Atlas of heart disease and stroke. http://www.who.int/cardiovascular _diseases/resources/atlas/en/. Accessed May 29, 2014.

2. Hata J, Ninomiya T, Hirakawa Y, et al. Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961-2009). *Circulation*. 2013;128(11):1198-1205.

3. Ministry of Health Labour and Welfare Japan. Ministry of Health, Labour, and Welfare report: 2014 [in Japanese]. http://www.mhlw.go.jp/wp /hakusyo/kousei/14/. Accessed October 6, 2014.

4. Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet*. 2009;373(9678):1849-1860.

5. Bhatt DL, Steg PG, Ohman EM, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295(2):180-189.

6. Yamazaki T, Goto S, Shigematsu H, et al; REACH Registry Investigators. Prevalence, awareness, and treatment of cardiovascular risk factors in patients at high risk of atherothrombosis in Japan. *Circ J*. 2007;71(7):995-1003.

7. Teramoto T, Shimada K, Uchiyama S, et al. Rationale, design, and baseline data of the Japanese Primary Prevention Project (JPPP)—a randomized, open-label, controlled trial of aspirin vs no aspirin in patients with multiple risk factors for vascular events. *Am Heart J*. 2010;159(3):361-369.e4.

8. Japanese Society of Hypertension. Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2004). *Hypertens Res*. 2006;29(suppl):S1-S105.

9. Japan Atherosclerosis Society. Japan Atherosclerosis Society (JAS) guidelines for diagnosis and treatment of atherosclerotic cardiovascular diseases. http://www.researchgate .net/publication/246586151_1FSO3-4_Japan _atherosclerosis_society_(JAS)_guidelines_for _diagnosis_and_treatment_of_atherosclerotic _cardiovascular_diseases. Accessed October 23, 2014.

10. The Japan Diabetes Society. *Evidence-Based Practice Guideline for the Treatment of Diabetes in Japan* [in Japanese]. Tokyo: Nankodo Co Ltd; 2004.

11. Japanese Society of Hypertension. Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2004). *Hypertens Res*. 2006;29(suppl):S1-S105.

12. Matsumoto M, Nishimura T. Mersenne Twister: a 623-dimensionally equidistributed uniform psuedo-random number generator. http://diyhpl.us /~bryan/papers2/paperbot/Mersenne%20twister %3A%20a%20623 -dimensionally%20equidistributed%20uniform %20pseudo-random%20number %20generator.pdf. Accessed November 4, 2014.

13. Hansson L, Hedner T, Dahlöf B. Prospective Randomized Open Blinded End Point (PROBE) study: a novel design for intervention trials: Prospective Randomized Open Blinded End-Point. *Blood Press*. 1992;1(2):113-119.

14. Luepker RV, Apple FS, Christenson RH, et al; AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108 (20):2543-2549.

15. Baba S; J-MIND Study Group. Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. *Diabetes Res Clin Pract*. 2001;54(3):191-201.

16. Ishii M, Goto Y. The Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients [in Japanese]. *Junkankika*. 2004;55:471-476.

17. Kyushu Lipid Intervention Study Group. Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. *J Atheroscler Thromb*. 2000;7 (2):110-121.

18. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111(2):383-390.

19. Matsuzaki M, Kita T, Mabuchi H, et al; J-LIT Study Group. Japan Lipid Intervention Trial. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. *Circ J*. 2002;66(12):1087-1095.

20. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. *Hypertension*. 1999;34(5):1129-1133.

21. Ogihara T; PATE-Hypertension Study Group in Japan. Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension (The PATE-Hypertension Study) in Japan. *Am J Hypertens*. 2000;13(5 pt 1):461-467.

22. Takishita S, Kawano Y, Omae T. Results of Japanese Trial on the Efficacy of Antihypertensive Treatment in the Elderly (JATE) and the Survey of Physician's Attitude to JATE and Large-Scaled Clinical Trials [in Japanese]. *Rinshou-iyaku.* 2000; 16:1363-1376.

23. Study Group on Long-term Antihypertensive Therapy. A 12-month comparison of ACE inhibitor and CA antagonist therapy in mild to moderate essential hypertension—the GLANT study. *Hypertens Res*. 1995;18(3):235-244.

24. Ogawa H, Nakayama M, Morimoto T, et al; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;300(18):2134-2141.

25. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomized placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.

26. Fowkes FG, Price JF, Stewart MC, et al; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA*. 2010;303(9): 841-848.

27. Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation*. 2008;118(25):2702-2709.

28. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol*. 2011;107(12):1796-1801.

29. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med*. 2011;124(7):621-629.

30. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172(3):209-216.

31. Shinohara Y, Katayama Y, Uchiyama S, et al; CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomized noninferiority trial. *Lancet Neurol*. 2010;9(10):959-968.

32. Yasue H, Ogawa H, Tanaka H, et al; Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. *Am J Cardiol*. 1999;83(9):1308-1313.

33. Yokoyama M, Origasa H, Matsuzaki M, et al; Japan EPA Lipid Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded end point analysis. *Lancet*. 2007;369(9567):1090-1098.

34. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med*. 2013;159(2):77-85.

35. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of 5 randomized trials. *Lancet*. 2010;376(9754):1741-1750.

36. Ishikawa H, Mutoh M, Suzuki S, et al. The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumors in Asian patients: a randomized trial. *Gut*. 2014;63(11):1755-1759.

37. clinicaltrials.gov. A study to assess the efficacy and safety of enteric-coated acetylsalicylic acid in patients at moderate risk of cardiovascular disease (ARRIVE). https://clinicaltrials.gov/ct2/show /NCT00501059?term=ARRIVE+aspirin&rank=1. Accessed October 9, 2014.

38. clinicaltrials.gov. ASCEND: a study of cardiovascular events in diabetes. https: //clinicaltrials.gov/ct2/show/NCT00135226?term =ascend+aspirin&rank=1. Accessed October 9, 2014.

39. clinicaltrials.gov. Aspirin in Reducing Events in the Elderly (ASPREE). https://clinicaltrials.gov/ct2 /show/NCT01038583. Accessed October 9, 2014.

40. ISRCTN Register. Aspirin and simvastatin combination for cardiovascular events prevention trial in diabetes. http://www.controlled-trials.com /isrctn48110081/48110081. Accessed October 9, 2014.