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ORIGINAL RESEARCH ARTICLE

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Elderly Japanese Patients with Atherosclerotic Risk Factors: Subanalysis of a Randomized Clinical Trial (JPPP-70)

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Abstract

Introduction This post hoc subanalysis of the randomized Japanese Primary Prevention Project investigated whether once-daily low-dose aspirin versus no aspirin reduced the risk of cardiovascular events (CVEs) in patients aged ≥ 70 years with atherosclerotic risk factors.

Methods Patients aged < 70 years (young-old) or ≥ 70 years (old) with hypertension, dyslipidemia, or diabetes participated between 2005 and 2007. Patients were randomized 1:1 to receive 100 mg enteric-coated aspirin once daily or no aspirin plus standard of care. The primary outcome was a composite of death from cardiovascular causes plus nonfatal stroke and nonfatal myocardial infarction. The secondary outcome was a composite of the primary outcome plus transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring medical or surgical intervention. Old ($n = 7971$) and young-old ($n = 6493$) patients were followed up for a median 5.02 years.

Results Aspirin did not reduce the risk of primary (hazard ratio [HR] 0.92 [95% confidence interval {CI} 0.74–1.16]; $P = 0.50$) or secondary (0.85 [0.70–1.04]; $P = 0.11$) outcomes in patients aged ≥ 70 years. In old men with high-density lipoprotein < 40 mg/dL, treatment with low-dose aspirin was associated with a reduction in the incidence of the primary endpoint compared with the group not receiving aspirin (10/260 vs 22/250; HR 0.44 [95% CI 0.20–0.93]; $P = 0.03$). This subgroup was also found to contain significant larger proportions of patients with elevated body mass index, patients with diabetes mellitus, and smokers ($P < 0.001$). Old patients also showed differences in bleeding outcomes. Serious extracranial hemorrhage requiring transfusion or hospitalization occurred significantly more frequently in the aspirin-treated group than in the non–aspirin-treated group (35 [0.88%] vs 18 [0.45%]; HR 1.96 [1.11–3.46]; $P = 0.020$). Gastrointestinal hemorrhage occurred significantly more frequently in the aspirin-treated group than the non–aspirin-treated group (63 [1.58%] vs 18 [0.45%]; relative risk [RR] 3.5 [2.08–5.90]; $P < 0.0001$). Cerebral hemorrhage (intracranial hemorrhage) tended to occur more frequently in the aspirin-treated group than the non–aspirin-treated group (22 [0.55%] vs 11 [0.28%]; RR 2.01 [0.97–4.14]; $P = 0.058$). Cerebral hemorrhage occurred significantly more frequently in old patients than in young-old patients (33 [0.41%] vs 10 [0.15%]; HR 2.7 [1.34–5.53]; $P = 0.0055$). Gastrointestinal hemorrhage occurred in a slightly higher proportion of old patients compared with young-old patients (81 [1.02%] vs 53 [0.82%]; RR 1.2 [0.88–1.76]; $P = 0.21$).

Discussion/Conclusions Aspirin did not reduce the risk of the primary or secondary outcomes in old patients. Aspirin treatment may have reduced CVEs within a high CVE risk elderly population subgroup. Aspirin treatment in such a group requires caution, because of the increased risk of intracranial hemorrhage, severe extracranial hemorrhage requiring hospitalization or transfusion, and gastrointestinal bleeding in old patients receiving aspirin therapy.

Clinical Trial Registration The study is registered at ClinicalTrials.gov [NCT00225849].

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Extended author information available on the last page of the article

Key Points

This post hoc subanalysis of the randomized Japanese Primary Prevention Project [NCT00225849] investigated the effect of once-daily low-dose aspirin versus no aspirin on cardiovascular event (CVE) risk in patients aged ≥ 70 years with atherosclerotic risk factors.

The primary outcome was death from cardiovascular causes plus nonfatal stroke and nonfatal myocardial infarction. The secondary outcome was a composite of the primary outcome plus transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring medical or surgical intervention.

Once-daily low-dose aspirin did not reduce the risk of CVEs in Japanese patients aged ≥ 70 years with atherosclerotic risk factors.

1 Introduction

Cardiovascular disease is the leading cause of death, accounting for 31% of deaths worldwide in 2012 [1]. Of the estimated 17.5 million cardiovascular-related deaths in 2012, the most common causes were coronary heart disease (42.3%) and stroke (38.3%) [1]. The number of deaths from cardiovascular diseases has been predicted to rise to over 22 million per year by 2030 [2]. In Japan, the risk of cardiovascular mortality per 1000 person-years increases from 10.81 in men and 6.97 in women aged 60–69 years to 37.61 in men and 31.33 in women aged 70 years and older (data from 1980–1999) [3]. Japan has an aging population, and one-third of the inhabitants are predicted to be aged ≥ 65 years by 2030 [4]. Additionally, the prevalence of risk factors for cardiovascular disease, such as obesity, glucose intolerance, and hypercholesterolemia, is increasing in this group [5], meaning that prevention of cardiovascular events (CVEs) in the elderly is a public health issue in Japan.

Treatment with low-dose aspirin for the primary prevention of cardiovascular disease has been widely investigated. However, the results of studies have been conflicting and, as a result, guidelines on the use of aspirin for primary prevention vary substantially [6]. In a meta-analysis of six primary prevention trials, the Antithrombotic Trialists' Collaboration (ATTC) found that low-dose aspirin reduced the occurrence of nonfatal myocardial infarction (MI) by 20% and that of serious vascular events by 12% [7]. More recent meta-analyses have shown that although aspirin may significantly reduce the risk of a first MI, its role in the prevention of stroke or cardiovascular-related death is unclear [6]. Furthermore, low-dose aspirin has been shown to increase the risk of gastrointestinal bleeding (GIB) and hemorrhagic stroke in both real-world and controlled-trial settings [7, 8]. However, in patients aged ≥ 70 years, the US Preventive Services Task Force (USPSTF) has recently reported that there is currently insufficient evidence to assess the balance of benefit versus harm of using aspirin for the primary prevention of cardiovascular disease, and additional evidence in this age group is needed [9]. However, recent Japanese studies, such as the Japanese Primary Prevention Project (JPPP) [10] and Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) [11] trials, did not demonstrate the overall merit of low-dose aspirin for primary prevention. Ten-year follow-up of JPAD subjects also indicated similar results [12].

The JPPP investigated the role of aspirin in the primary prevention of cardiovascular disease in more than 14,000 Japanese patients aged ≥ 60 years who had any combination of risk factors for atherosclerosis including hypertension, dyslipidemia, and/or diabetes mellitus [10]. The JPPP found that although daily, low-dose aspirin significantly reduced the incidence of nonfatal MI and transient ischemic attack, it did not reduce the incidence of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal MI; however, event rates in the study were low and the study was terminated early owing to likely futility [10]. While event rates between patients aged ≥ 70 years versus those aged < 70 years were similar, results of regression analyses suggested that the risk of reaching the primary endpoint—a composite of death from CVEs, nonfatal stroke, and nonfatal MI—was higher in patients aged ≥ 70 years (parameter estimate 0.92; hazard ratio [HR] 2.51 [95% confidence interval {CI} 2.00–3.14]; $P < 0.001$) [10].

This study (JPPP-70) was a post hoc subanalysis of the original JPPP study to determine whether low-dose aspirin reduced the risk of CVEs versus no aspirin, in Japanese patients aged ≥ 70 years with atherosclerotic risk factors.

2 Methods

2.1 Patient Selection

The JPPP was a multicenter, randomized, open-label, parallel-group clinical study. The study is registered at ClinicalTrials.gov [NCT00225849], and full details of the methods and study design have been published previously [10, 13]. Briefly, patients were eligible for the JPPP if they met the Japanese criteria for hypertension (2006 guidelines), dyslipidemia (2002), or diabetes (2004; full definitions have been provided by Ikeda and colleagues [10]) [14–16]. Patients with a medical history of coronary artery disease, cerebrovascular disease, atherosclerotic disease

requiring medical or surgical intervention, atrial fibrillation, peptic ulcer, or bleeding disorders or abnormalities (e.g., clotting factor deficiencies) were excluded. Patients were excluded if they were receiving antiplatelet therapy, anticoagulants, or nonsteroidal anti-inflammatory drugs, or if they had previously had an adverse reaction to aspirin or salicylic acid. Patients were recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007.

For the purposes of this subanalysis, patients were stratified into two groups: those aged ≥ 70 years and those aged < 70 years.

2.2 Study Design

Throughout the study, all patients received standard of care treatment to control hypertension, dyslipidemia, or diabetes in accordance with Japanese guidelines [14–16]. Patients were randomized 1:1 to receive either a 100-mg tablet of enteric-coated aspirin or no aspirin following a screening visit. A central computerized system was used to generate the random allocation sequence, and treatment allocations were disseminated to study investigators via the study website or by fax. Disease outcomes, adverse events, self-reported treatment adherence, blood pressure, serum lipid levels, blood glucose levels, smoking status, and body weight were assessed at each visit. Patients were followed up until withdrawal of consent or death. If the cause of death was unclear, the patient's death certificate was obtained with the permission of the Japanese government. The causes of all deaths were verified by the end of April 2014. Members of the study committees and details of investigator locations are available in the online supplementary material. Informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the human research committee of the Japan Physicians Association.

2.3 Study Endpoints

The primary endpoint was a composite of death from cardiovascular causes (MI, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal MI. The secondary endpoint was a composite of the primary endpoint plus transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring medical or surgical intervention.

2.4 Statistical Methods

The statistical analyses and sample size calculations used in the main JPPP have been described previously [10, 11]. For this subanalysis, the test hypothesis was that treatment with aspirin reduces the incidence of the primary or secondary endpoints in study participants aged ≥ 70 years with a high risk of a CVE compared with patients aged < 70 years. The test hypothesis was confirmed by rejecting the null hypothesis that aspirin does not have a preventive effect on cardiovascular outcome in patients aged ≥ 70 years with or without additional cardiovascular risk factors compared with those aged < 70 years. Between-group differences in the primary endpoint were assessed using the stratified log-rank test, with stratification for underlying disease characteristics (hypertension, dyslipidemia, or diabetes mellitus) with a two-sided significance level of $\alpha = 0.05$. HRs were calculated using the Cox proportional hazards model. For exploratory analyses, patients were further stratified according to known cardiovascular risk factors (sex, systolic blood pressure, high-density lipoprotein [HDL], body mass index [BMI], smoking status, and diabetes mellitus status). Two-sided stratified log-rank tests and Cox proportional hazards models were performed as above.

3 Results

3.1 Patients

Of the 14,464 patients who completed the main JPPP study, 7971 (3118 men [39.1%] and 4853 women [60.9%]) were aged ≥ 70 years (Fig. 1). These patients were included in this subanalysis investigating the efficacy of aspirin in the primary prevention of CVEs in patients aged ≥ 70 years compared with patients aged < 70 years (JPPP-70). Patients were randomized between March 2005 and June 2007, and the study was terminated following interim analysis in May 2011, owing to likely futility. The median follow-up time for this cohort was 5.02 years.

Compared with patients aged < 70 years, patients aged ≥ 70 years were more likely to be female, have hypertension, and have lower levels of triglycerides and total cholesterol levels (Table 1). Patients in the older age group were also less likely to be overweight, smoke, or have a family history of cardiovascular disease than younger patients. Among older patients, baseline characteristics were similar in the treatment and control groups, with the exception of glycated hemoglobin (HbA1c) levels, which were significantly higher in the control group (Table 1); the frequency of non-adherence in the intervention group (i.e., patients who did not take aspirin) was 28.0% ($n = 1118$), and the frequency of contamination of the control group (i.e., by patients who took

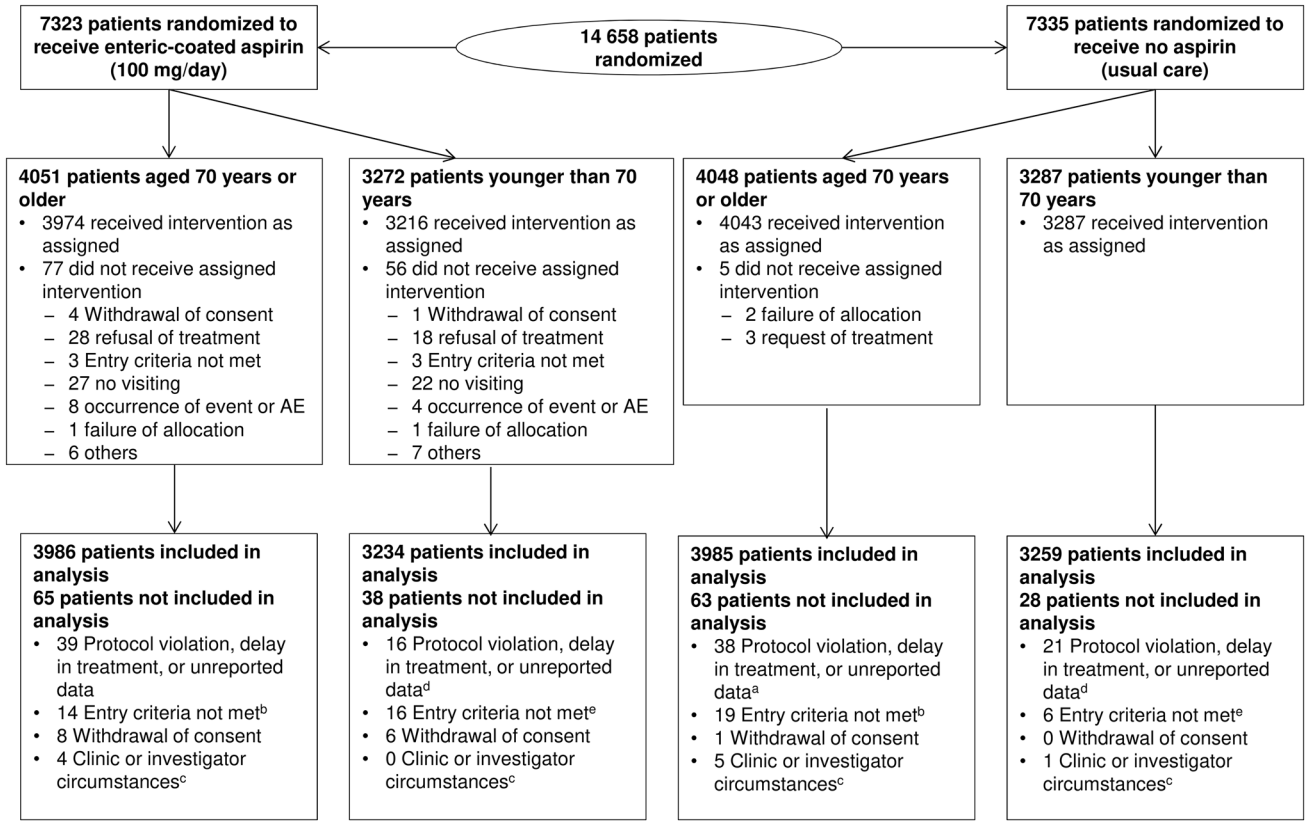

Fig. 1 Flow of patients through the Japanese Primary Prevention Project-70 (JPPP-70) subanalysis. *AE* adverse event. Age 70 years or older: [a]Protocol violations (aspirin, $n = 15$; no aspirin, $n = 16$); delay in start of treatment (aspirin, $n = 10$; no aspirin, $n = 10$); unreported data by investigators in the clinics (aspirin, $n = 14$; no aspirin, $n = 12$). [b]Reasons for not meeting inclusion criteria were serious blood abnormalities (aspirin, $n = 1$), history of prohibited drugs (aspirin, $n = 4$; no aspirin, $n = 13$), cerebrovascular disease (aspirin, $n = 4$; no aspirin, $n = 6$), atrial fibrillation (aspirin, $n = 1$), hypersensitivity to aspirin (aspirin, $n = 3$), or atherosclerotic disease (aspirin, $n = 1$). [c]Clinic or investigator circumstances were closure of clinic and investigator death. Younger than 70 years: [d]Protocol violations (aspirin, $n = 4$; no aspirin, $n = 6$); delay in start of treatment (no aspirin, $n = 5$); unreported data by investigators in the clinics (aspirin, $n = 12$; no aspirin, $n = 10$). [e]Reasons for not meeting inclusion criteria were serious blood abnormalities (aspirin, $n = 1$), history of prohibited drugs (aspirin, $n = 8$; no aspirin, $n = 5$), cerebrovascular disease (aspirin, $n = 2$; no aspirin, $n = 1$), atrial fibrillation (aspirin, $n = 2$), peptic ulcer (aspirin, $n = 2$), or long-term use of nonsteroidal anti-inflammatory drugs (aspirin, $n = 1$)

at least one dose of aspirin) was 5.2% ($n = 206$). The number and proportion of non-adherent patients in the aspirin group were calculated from patients stating that they were "not taking aspirin" as responses for current medication at any of the once-annual follow-up examinations. Adverse events ($n = 517$) represented the major reason for stopping aspirin treatment, with gastrointestinal discomfort as the most frequently occurring adverse event. Patients in the control group who took aspirin on at least one occasion represented contamination of this group. Of the 206 patients so classified, 104 took aspirin in association with occurrence of an event, and another 19 took aspirin on their own volition.

3.2 Effectiveness

3.2.1 Primary Outcomes

The rates of primary events per 1000 person-years were as follows (Table 2): total cohort 5.88 (men 7.48; women 4.73); patients aged ≥ 70 years 7.93 (men 10.01; women 6.62); and patients aged < 70 years 3.41 (men 4.90; women 2.15). In the older group, event rates per 1000 person-years were 7.60 in patients receiving aspirin and 8.25 in patients not receiving aspirin.

More primary endpoint CVEs occurred in patients aged ≥ 70 years than in those aged < 70 years (295 vs 105 events) (Table 3). Both fatal and nonfatal primary endpoint CVEs occurred more frequently in the older age group (92 vs 20 and 203 vs 85 events, respectively). Overall, in patients

Table 1 Baseline characteristics (modified intention-to-treat population)

Characteristic	Age					
	≥ 70 years ($n=7971$)	< 70 years ($n=6493$)	*P* value	≥ 70 years ($n=7971$)		
				Aspirin ($n=3986$)	No aspirin ($n=3985$)	*P* value
Patient demographics						
Age, mean (SD), years	75.2 (3.9)	64.8 (2.8)	< 0.0001	75.2 (3.9)	75.2 (3.9)	0.822
Male, *n* (%)	3118 (39.1)	3005 (46.3)	< 0.0001	1555 (39.0)	1563 (39.2)	0.847
Waist circumference, mean (SD), cm	84.9 (10.2)	85.0 (9.7)	0.764	84.9 (10.1)	84.9 (10.1)	0.715
Weight, mean (SD), kg	56.6 (9.9)	61.2 (10.4)	< 0.0001	56.7 (9.9)	56.6 (9.9)	0.668
BMI, mean (SD), kg/m^2	23.9 (3.4)	24.5 (3.4)	< 0.0001	23.9 (3.4)	23.9 (3.4)	0.787
BMI ≥ 25 kg/m^2, *n* (%)	2653 (33.3)	2593 (39.9)	< 0.0001	1326 (33.3)	1327 (33.3)	0.975
Risk factors for vascular events, *n* (%)						
HT	6916 (86.8)	5362 (82.6)	< 0.0001	3459 (86.8)	3457 (86.8)	0.970
DL	5565 (69.8)	4833 (74.4)	< 0.0001	2791 (70.0)	2774 (69.6)	0.691
DM	2597 (32.6)	2306 (35.5)	0.0002	1297 (32.5)	1300 (32.6)	0.937
HT and DL	4664 (58.5)	3876 (59.7)	0.150	2340 (58.7)	2324 (58.3)	0.726
DL and DM	1853 (23.2)	1739 (26.8)	< 0.0001	928 (23.3)	925 (23.2)	0.942
HT and DM	2117 (26.6)	1754 (27.0)	0.539	1058 (26.5)	1059 (26.6)	0.974
HT, DL, and DM	1527 (19.2)	1361 (21.0)	0.0069	765 (19.2)	762 (19.1)	0.936
Blood pressure, mmHg						
Systolic	137.7 (15.3)	136.5 (16.1)	< 0.0001	137.6 (15.3)	137.9 (15.4)	0.390
Diastolic	76.3 (10.2)	79.4 (10.3)	< 0.0001	76.1 (10.2)	76.4 (10.1)	0.223
Currently smoking, *n* (%)	784 (9.8)	1109 (17.1)	< 0.0001	399 (10.0)	385 (9.7)	0.601
Family history of premature CV disease, *n* (%)						
No	4497 (56.4)	3647 (56.2)	< 0.0001	2244 (56.3)	2253 (56.5)	0.975
Yes	2080 (26.1)	1883 (29.0)	–	1042 (26.1)	1038 (26.0)	–
Unknown	1394 (17.5)	963 (14.8)	–	700 (17.6)	694 (17.4)	–
Laboratory values, mean (SD)						
Cholesterol, mg/dL						
Total	200.7 (32.4)	206.4 (32.9)	< 0.0001	200.4 (32.5)	201.0 (32.3)	0.420
Low-density lipoprotein[a]	118.3 (29.8)	121.0 (31.1)	< 0.0001	118.1 (29.7)	118.5 (29.9)	0.551
High-density lipoprotein	57.5 (15.3)	58.6 (16.3)	< 0.0001	57.3 (15.4)	57.8 (15.1)	0.162
Triglycerides	126.9 (68.6)	138.1 (83.8)	< 0.0001	127.8 (69.6)	125.9 (67.6)	0.209
Fasting blood glucose, mg/dL	106.8 (29.5)	108.9 (34.0)	< 0.0001	107.1 (30.2)	106.4(28.7)	0.312
HbA1c, %[b]	5.6 (0.9)	5.7 (1.1)	< 0.0001	5.6 (0.9)	5.7 (1.1)	< 0.0001

SI conversion factors: To convert total, low-density lipoprotein, and high-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113; to convert glucose to mmol/L, multiply by 0.0555

BMI body mass index (calculated as weight in kg divided by height in m^2), *CV* cardiovascular, *DL* dyslipidemia, *DM* diabetes mellitus, *HbA1c* glycated hemoglobin, *HT* hypertension, *SD* standard deviation

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

[b]National Glycohemoglobin Standardization Program method

aged < 70 years, the event rate was 1.6% in both the group receiving aspirin and the group receiving no aspirin. In patients aged ≥ 70 years, the event rate was 3.5% in the group receiving aspirin and 3.9% in the group receiving no aspirin.

Aspirin was not associated with a reduction in risk of the primary outcome measure versus no aspirin in patients aged ≥ 70 years (HR 0.92 [95% CI 0.74–1.16]; $P=0.50$). Comparisons of the aspirin and non–aspirin-treated populations in this study were expected to be possible because they were both subgroups of randomized and comparable populations. However, data were analyzed with a Cox proportional hazards model comprising the characteristics in Table 1 (age, sex, BMI, hypertension, dyslipidemia, diabetes mellitus, smoking status, family history of cardiovascular disease, HDL, low-density lipoprotein [LDL], and triglycerides, fasting blood glucose, and HbA1c

Table 2 Primary event rates (modified intention-to-treat population)

Group	Primary events	Event rate/1000 person-years
Men	213	7.48
Women	187	4.73
Total (both sexes)	400	5.88
≥ 70 years		
Men	144	10.01
Women	151	6.62
Total (both sexes)	295	7.93
Aspirin	141	7.60
Non-aspirin	154	8.25
< 70 years		
Men	69	4.90
Women	36	2.15
Total (both sexes)	105	3.41

levels). This analysis yielded an adjusted HR of 0.92 (95% CI 0.73–1.16; $P = 0.49$), which was almost unchanged from that in crude analysis. A similar result—an HR of 0.93 (95% CI 0.67–1.29; $P = 0.68$)—was obtained in sensitivity analysis in which groups were compared using propensity score with an inverse probability weighted method.

While the number of fatal CVEs was the same ($n = 46$) in the groups aged ≥ 70 years receiving aspirin or no aspirin, the number of fatal cerebral infarction or subarachnoid hemorrhage events was lower in the group receiving aspirin (one vs five cases and one vs four cases, respectively). However, the number of "other" fatal CVEs was higher in the group receiving aspirin (35 cases vs 26 cases). In patients aged < 70 years, the number of each type of fatal event was broadly the same in the group receiving aspirin and the group receiving no aspirin. There was a suggestion that aspirin was associated with a reduction in the number of nonfatal MIs compared with no aspirin (13 vs 29 events) in patients aged ≥ 70 years; however, more nonfatal intracranial hemorrhage (ICH) occurred in aspirin-treated patients (17 vs six events). Survival curves present the differences in primary and secondary outcomes between aspirin-treated and non–aspirin-treated patients (Online Resource 1, see the electronic supplementary material).

In patients aged ≥ 70 years, analysis of subgroups based on common risk factors for CVEs suggested that having an HDL level of < 40 mg/dL (HR 1.72 [95% CI 1.30–2.27]; $P = 0.0001$), smoking (HR 1.66 [95% CI 1.30–2.13]; $P < 0.0001$), or having diabetes mellitus (HR 1.63 [95% CI 1.33–1.99]; $P < 0.0001$) was associated with occurrence of the primary outcome measure (Online Resource 2). However, there was no difference in the incidence of primary outcome events between patients receiving aspirin and those not receiving aspirin in the older patient subgroup (Online Resource 3). In men aged ≥ 70 years with HDL levels of < 40 mg/dL, treatment with low-dose aspirin was associated with a reduction in the incidence of the primary endpoint compared with the group not receiving aspirin (10/260 vs 22/250; HR 0.44 [95% CI 0.20–0.93]; $P = 0.03$) (Table 4). This cohort comprised 3.5% of the original JPPP study population.

Predicted 10-year atherosclerotic cardiovascular disease (ASCVD) risks are presented in Online Resource 4. Aspirin tended to be more effective in a high-risk population (there was no significant interaction). Although the number of events was small and the difference was not significant, the HR for aspirin-treated patients versus non–aspirin-treated patients was low, at 0.651, among patients aged ≥ 70 years with an ASCVD risk of ≥ 15%. Furthermore, the event rates in all patients with an ASCVD risk of ≥ 15% were high, at 11.2% for aspirin-treated patients and 16.7% for non–aspirin-treated patients. The ASCVD risk ≥ 15% subgroup also showed a small number of primary endpoint events in patients aged < 70 years, in five cases against 70 cases in patients aged ≥ 70 years.

The mean 10-year ASCVD risk for men aged ≥ 70 years with HDL < 40 mg/dL was 14.6%, signifying a high-risk population (for ASCVD). In an evaluation of background characteristics, this subgroup was also found to contain significant larger proportions of patients with elevated BMI, dyslipidemia, and diabetes mellitus, and those who were smokers ($P < 0.001$) (Online Resource 5).

3.2.2 Secondary Outcomes

Similar to the primary endpoint, the number of secondary endpoint events was higher in patients aged ≥ 70 years than in those aged < 70 years (1285 vs 612 events) (Table 3). Overall, aspirin treatment was not associated with a reduced risk of atherosclerotic events or CVEs in patients aged ≥ 70 years compared with no aspirin (HR 0.85 [95% CI 0.70–1.04]; $P = 0.11$). However, in patients aged ≥ 70 years, there were fewer cases of nonfatal MI (13 vs 29 events), angina pectoris (20 vs 30 events), and arteriosclerotic disease requiring treatment (36 vs 53 events) in the group that received aspirin compared with those who received no aspirin. In both age groups, aspirin was associated with a reduced risk of transient ischemic attack (< 70 years 4 vs 13 events; ≥ 70 years 15 vs 21 events), but with an increased risk of serious extracranial hemorrhage (ECH) requiring transfusion or hospitalization (< 70 years 27 vs 16 events; ≥ 70 years 35 vs 18 events).

In patients aged ≥ 70 years, having an HDL level of < 40 mg/dL (HR 1.62 [95% CI 1.29–2.03]; $P < 0.0001$), smoking (HR 1.50 [95% CI 1.22–1.85]; $P = 0.0001$), or having diabetes mellitus (HR 1.58 [95% CI 1.35–1.87]; $P < 0.0001$) was also associated with the occurrence of

Table 3 Primary and secondary endpoints for patients aged 70 years and older and patients aged < 70 years (modified intention-to-treat population)

Endpoint	No. of events				Interaction[b] *P* value
	< 70 years		≥ 70 years		
	Aspirin (*n* = 3234)	No aspirin (*n* = 3259)	Aspirin (*n* = 3986)	No aspirin (*n* = 3985)	
Primary endpoint					
Fatal:nonfatal events	10:42	10:43	46:95	46:108	–
Cerebral infarction	1:24	2:27	1:59	5:67	–
Intracranial hemorrhage	0:6	0:4	5:17	5:6	–
Subarachnoid hemorrhage	1:4	0:0	1:4	4:4	–
Myocardial infarction	3:7	3:9	4:13	6:29	–
Other (fatal)/undefined (nonfatal) cardiovascular events	5:1	5:3	35:2	26:2	–
Total primary events	52	53	141	154	0.745
Secondary endpoint					
Any atherosclerotic or cardiovascular event[a]	96	102	184	217	0.524
Death from cardiovascular disease	10	10	48	47	0.968
Death from causes other than cardiovascular disease	66	62	173	184	0.545
Nonfatal cerebrovascular disease (ischemic or hemorrhagic)	35	34	82	80	0.970
Nonfatal myocardial infarction	7	9	13	29	0.362
Transient ischemic attack	4	13	15	21	0.205
Angina pectoris	26	24	20	30	0.225
Arteriosclerotic diseases requiring surgery or intervention	39	32	36	53	0.662
Severe extracranial hemorrhage requiring transfusion or hospitalization	27	16	35	18	0.748
Total secondary events (first event)[c]	310 (181)	302 (172)	606 (370)	679 (399)	– (0.300)

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

[b]Test for heterogeneity among treatment vs control hazard ratios between patients aged ≥ 70 years and those aged < 70 years

[c]Owing to some patients experiencing multiple secondary events in this study, the test for heterogeneity was performed using data on those secondary events that occurred first in each patient

secondary endpoint events (Online Resource 1). The incidence of secondary outcome events in older patients was similar with and without aspirin treatment (Online Resource 2).

3.3 Safety and Tolerability

GIB occurred in 63 patients (1.6%) aged ≥ 70 years who received aspirin, compared with 18 patients (0.5%) in the same age group who did not receive aspirin ($P < 0.0001$) (Table 5). Patients aged ≥ 70 years treated with aspirin also seemed to be at increased risk of developing peptic ulcers, heartburn, stomach/abdominal pain, and stomach/abdominal discomfort compared with those not treated with aspirin. In the men aged ≥ 70 years with HDL levels of < 40 mg/dL, there were no cases of severe ECH requiring transfusion or hospital admission, such as GIB, in the aspirin-treated groups (Table 4).

Evaluations of patients aged ≥ 70 years revealed the following. Fatal ICH occurred in two aspirin-treated and two non–aspirin-treated men, and three aspirin-treated and three non–aspirin-treated women. Nonfatal ICH occurred in four aspirin-treated and two non–aspirin-treated men, and 13 aspirin-treated and four non–aspirin-treated women. This yielded totals of 22 and 11 ICHs in aspirin-treated and non–aspirin-treated patients, respectively, involving ten men and 23 women. More detailed evaluations were attempted by risk-factor subgrouping for fatal and nonfatal ICH event rates in patients aged ≥ 70 years. As shown in Online Resource 6, event rates tended to be high within the following subgroups: female, LDL < 140 mg/dL, BMI < 25, and family CVD history.

Table 4 Primary and secondary endpoints in men aged ≥ 70 years with high-density lipoprotein levels < 40 mg/dL (modified intention-to-treat population)

Endpoint	No. of events	
	Aspirin ($n=260$)	No aspirin ($n=250$)
Primary endpoint		
Fatal events	2	5
Cerebral infarction	0	1
Intracranial hemorrhage	0	0
Subarachnoid hemorrhage	0	1
Myocardial infarction	0	1
Other fatal cardiovascular events	2	2
Nonfatal events	8	17
Cerebral infarction	5	8
Intracranial hemorrhage	1	1
Subarachnoid hemorrhage	0	0
Myocardial infarction	2	8
Undefined cerebrovascular events	0	0
Total primary events	10	22
Secondary endpoint		
Any atherosclerotic or cardiovascular event	9	14
Angina pectoris	0	2
Arteriosclerotic diseases requiring surgery or intervention	8	11
Severe extracranial hemorrhage requiring transfusion or hospitalization	0	1
Total secondary events	17	28

Table 5 Incidence of prespecified gastrointestinal adverse events in patients aged ≥ 70 years with cardiovascular risk factors receiving aspirin or no aspirin (randomized population)

	Aspirin ($n=3986$) *n* (%)	No aspirin ($n=3985$) *n* (%)	*P* value
Stomach/abdominal discomfort	199 (5.0)	95 (2.4)	< 0.0001
Heartburn	112 (2.8)	84 (2.1)	0.043
Gastroduodenal ulcer	106 (2.7)	46 (1.2)	< 0.0001
Reflux esophagitis	83 (2.1)	72 (1.8)	0.373
Stomach/abdominal pain	78 (2.0)	33 (0.8)	< 0.0001
Gastrointestinal bleeding	63 (1.6)	18 (0.5)	< 0.0001
Erosive gastritis	43 (1.1)	27 (0.7)	0.0719
Nausea	38 (1.0)	25 (0.6)	0.100
Stomach/abdominal pressure	17 (0.4)	11 (0.3)	0.256

Fatal ICH occurred in six aspirin-treated patients and four non–aspirin-treated patients. Patients aged ≥ 70 years requiring hospitalization or transfusion for serious ECH were also evaluated (Table 3). There were 35 such cases among aspirin-treated patients and 18 among non–aspirin-treated patients. As shown in Online Resource 6, risk-factor subgroup analyses revealed high incidences in the male, hypertension, and family CVD history subgroups. Among men aged ≥ 70 years with HDL < 40 mg/dL, no fatal ICH occurred in either aspirin-treated or non–aspirin-treated patients, and one case of nonfatal ICH per group occurred for both aspirin-treated and non–aspirin-treated patients. Severe ECH requiring hospitalization or transfusion occurred with low incidence, zero and one in aspirin-treated patients and non–aspirin-treated patients, respectively. GIB occurred more frequently in aspirin-treated patients, at six cases (2.3%), than in non–aspirin-treated patients, at one case (0.4%).

GIB occurred more frequently in patients aged ≥ 70 years than in patients aged < 70 years, in whom the incidence was 40 cases (1.2%) with aspirin treatment and 13 (0. 4%) with no aspirin treatment.

4 Discussion

JPPP-70 is a subanalysis of the JPPP, investigating the efficacy of low-dose aspirin for primary prevention of cardiovascular disease in Japanese patients aged ≥ 70 years with atherosclerotic risk factors. As in the main JPPP study [10], the findings confirmed that low-dose aspirin did not reduce the incidence of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal MI in patients aged ≥ 70 years compared with those aged < 70 years. This is in line with findings of the ATTC meta-analysis, which showed no evidence of an age interaction [17]. Stratification by common cardiovascular risk factors suggested that low-dose aspirin was associated with a reduction in the incidence of CVEs in men aged ≥ 70 years who also had low levels of HDL (< 40 mg/dL). An HDL level of < 40 mg/dL is a known risk factor for cardiovascular disease; furthermore, registry data from the USA show that the prevalence of HDL levels of < 40 mg/dL is approximately three times higher in men than in women (29.5% vs 9.7%, respectively) [15]. Thus, further investigation of the role of low-dose aspirin for primary prevention of CVEs in men with an HDL level of < 40 mg/dL may be warranted in Japanese and non-Japanese patients.

We previously reported that nonfatal ICH and subarachnoid hemorrhage were more common in patients who received aspirin than in those who did not receive aspirin [10]. Additionally, more recent subanalyses of the JPPP cohort have shown that aspirin did not change the rate of fatal or nonfatal stroke [18]. In JPPP-70, there was a suggestion that aspirin was associated with an increased incidence of nonfatal ICH in individuals aged ≥ 70 years, but not in the younger age group. In contrast, aspirin may be associated with an increased incidence of subarachnoid hemorrhage in patients aged < 70 years only. This differs from UK registry data that suggest that aspirin does not affect the risk of ICH, but reduces the risk of subarachnoid hemorrhage; the mean ages at diagnosis in these groups were 70.8 years and 57.7 years, respectively [19].

The occurrence of GIB, peptic ulcer, and stomach/abdominal discomfort or pain was significantly increased in patients aged ≥ 70 years who received aspirin compared with those who did not. Indeed, it has been reported previously that low-dose aspirin is associated with an increased risk of GIB and ICH in men older than 70 years [8, 20]. Furthermore, increasing age is an independent risk factor for major bleeding events, including ICH [21, 22]. However, in this study the proportions of aspirin-treated patients aged ≥ 70 years who experienced these bleeding events were still low, ranging from 1.6% for GIB to 5.0% for stomach/abdominal discomfort.

In a cohort of nearly 2000 patients with an ST segment elevation MI, nearly 70% had not been previously diagnosed with cardiovascular disease, despite the presence of known risk factors (e.g., hypertension, dyslipidemia, and diabetes mellitus) in a high proportion of them [23]. Multiple trials and meta-analyses [7, 24–27], including the original JPPP study [10], have found that aspirin reduces the risk of nonfatal MI. However, given the increased risk of bleeding adverse events, current guidelines only recommend the use of aspirin for primary prevention of cardiovascular disease in patients with risk factors for cardiovascular or cerebrovascular disease [6].

Current US guidelines propose that low-dose aspirin is suitable for patients with a 10-year CVE risk of 10% or greater (or a 10-year risk of 5–10% in patients with type 2 diabetes [28]) [9, 29, 30]; UK guidelines suggest that patients with a 10-year CVE risk of 20% may be treated with low-dose aspirin; however, primary prevention of CVD is not a licensed indication for aspirin in the UK [30]. There are currently no Japanese guidelines for the use of aspirin for the primary prevention of cardiovascular disease. Our data suggest that, similar to American and European guidelines, aspirin should only be used for the primary prevention of cardiovascular disease in Japanese patients who are at high risk of experiencing a CVE.

The limitations of this subanalysis (JPPP-70) are similar to those of the original JPPP study, which was terminated early owing to unexpectedly low rates of events and likely futility [10]. In addition, the post hoc subanalyses reported here were performed on relatively small patient subgroups and are considered to be exploratory. Furthermore, decreasing adherence levels in the group receiving aspirin and the increasing uptake of aspirin in the group not randomized to receive aspirin during the 5-year trial may have confounded between-group differences [10]. In addition, due to the open-label nature of the trial, patients receiving aspirin may have been more likely to report the occurrence of adverse events than those not receiving aspirin [10]. Finally, the subgroup that appeared to benefit from aspirin treatment, namely men aged ≥ 70 years with HDL levels of < 40 mg/dL, was small, comprising just 3.5% of the original JPPP cohort; therefore, the possibility that these results occurred owing to chance cannot be ruled out. However, the mean 10-year ASCVD risk for this subgroup was 14.6%, signifying a high-risk population. Background characteristics were assessed for this group, revealing significant high proportions of patients with diabetes mellitus and smokers. Low HDL, diabetes mellitus, and smoking were noted as significant risk factors for CVEs in patients aged ≥ 70 years,

and this subgroup was a population with each of these risk factors. Smoking is known to decrease HDL levels. In diabetes mellitus, triglycerides are increased and HDL level is decreased through the decline in insulin action. The fact that the subgroup of men aged ≥ 70 years with low HDL levels represented a high-risk population for CVEs may explain the significant difference obtained for aspirin-treated patients. The low incidences of the ICH and severe ECH in this subgroup were attributed to the low proportions of patients with high HDL, patients with low LDL, and non-smokers that were more common in both groups in this study. In patients aged ≥ 70 years, ICH occurred in 22 aspirin-treated patients and 11 non–aspirin-treated patients; severe ECH requiring hospitalization or transfusion occurred in 35 aspirin-treated patients and 18 non–aspirin-treated patients. GIB occurred in 63 aspirin-treated patients (1.6%) and 18 non–aspirin-treated patients (0.5%). Incidences were significantly higher in aspirin-treated patients for each of these events. Furthermore, intracranial and severe ECH increase with age at 70 years and above. In this subgroup, GIB was noted more frequently among aspirin-treated patients than in non–aspirin-treated patients (six cases, 2.3%, vs one case, 0.4%). In light of these findings, it is considered that aspirin treatment should be approached with caution in such a high-risk population. A meta-analysis of eight primary prevention trials of low-dose aspirin in patients < 70 years showed that, whereas aspirin-treated patients have an increased risk of severe bleeding, the advantages of aspirin treatment outweigh the disadvantages in patients with a > 10% 10-year ASCVD risk [31, 32]. Recently, three primary prevention studies of aspirin treatment have been reported. The risk of major bleeding events was significantly increased with aspirin treatment—with an HR of 1.38—in the ASPREE study in elderly patients (mainly in patients aged ≥ 70 years; mean age 74 years) [32, 33]. Major bleeding events also occurred significantly more frequently with aspirin treatment, with a relative risk (RR) of 1.29, in the ASCEND study in patients with diabetes aged ≥ 40 years without cardiovascular disease [34]. The risk was similarly elevated in the present study (JPPP-70), with an RR of 1.82.

Hemorrhagic stroke requires particular consideration. However, reported incidences of hemorrhagic stroke in aspirin-treated versus non–aspirin-treated populations were 0.13% versus 0.18% during 5 years of follow-up in the ARRIVE study in patients with a CVD risk factor (men aged ≥ 55 years and women aged ≥ 60 years; mean age 64 years) [35], 0.3% versus 0.3% in the 7.4-year follow-up period in the ASCEND study, and 0.5% versus 0.4% in the 4.7-year follow-up period in the ASPREE study. The incidences were lower in these three studies than in the present study (JPPP-70), in which the corresponding incidence in aspirin-treated versus non–aspirin-treated patients during the 5.2-year follow-up period was 0.83% versus 0.58%. However, this finding was considered to reflect the high mean age in this study (75 years) and the higher incidence of stroke in the Japanese population compared with that in European and North American populations.

ICHs are common in hypertension patients, and hypertension was present in 52 of the 53 patients with serious ECH in this study. Accordingly, aspirin treatment may be useful in non-hypertensive patients with a high ASCVD risk, who have a low risk of bleeding. Furthermore, among such high-risk patients, cases of advanced coronary lesions may not be common. The required therapeutic strategy involves ankle-brachial index and carotid ultrasonography, coronary computed tomography (CT), cardiac catheterization in some cases, objective assessments of coronary lesions in individual patients, and, where necessary, coronary angioplasty and bypass surgery.

In practice, patients on aspirin-based antiplatelet therapy but not receiving standard proton pump inhibitor (PPI) therapy have higher risk of major bleeding in the long term, and this is more persistent in older patients than in younger patients in previous trials.

Routine co-prescription is recommended because 50% of the major bleeding events in patients aged 75 years or older were upper gastrointestinal in origin, and thus the projected number of those needing PPI treatment to prevent such bleeding is low [33, 34]. It is considered that PPIs should be administered as concomitant medication for elderly patients taking low-dose aspirin to prevent GIB.

Further analyses of the JPPP cohort are in progress, including investigations into the role of aspirin in the prevention of cancer-associated deaths, in order to identify patients in Japan who may benefit most from aspirin treatment.

5 Conclusion

Low-dose aspirin did not significantly reduce the risk of cardiovascular death, nonfatal stroke, or nonfatal MI in Japanese patients aged ≥ 70 years. However, low-dose aspirin may reduce the risk of these CVEs in Japanese men aged ≥ 70 years who also have HDL levels of < 40 mg/dL. This subgroup included high proportions of patients with diabetes mellitus and smokers and had a mean 10-year ASCVD risk of 14.6%, signifying that this was a high-risk population. In patients aged ≥ 70 years, aspirin treatment yielded significantly higher incidences of serious ECH requiring transfusion or hospitalization and gastrointestinal hemorrhage, and tended to yield a higher incidence of cerebral hemorrhage. Cerebral hemorrhage was significantly more frequent and gastrointestinal hemorrhage was proportionally slightly more frequent in patients aged ≥ 70 years

than in those aged < 70 years. Patients aged ≥ 70 years had a greater incidence of CVEs than those aged < 70 years, and were considered to represent a population with a higher risk of hemorrhage. The risk factors for ICH and serious ECH differed from those for CVEs.

In light of these findings, aspirin treatment for such high-risk population should be approached with caution. We consider it important to perform ankle-brachial index testing, carotid ultrasonography, coronary computed tomography angiography (CCTA), and, in some cases, heart catheterization, to make objective assessments of coronary lesions, and according to individual needs and where necessary, to provide appropriate treatment with aspirin.

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Compliance with Ethical Standards

Conflict of interest TY reports receiving personal fees from AstraZeneca, Dainippon Sumitomo, Shionogi, and Takeda. TT reports receiving grant support from Daiichi Sankyo, Eli Lilly, Kowa, Shionogi, and Takeda; speaker fees from Amgen Astellas BioPharma, Astellas, Bayer, Daiichi Sankyo, Kissei, Kowa, Pfizer, Sanofi, and Takeda; and department endowments from Aska, Astellas, Bayer, Kissei, Kowa, and MSD. SO reports receiving personal fees from Astellas, Bayer, Daiichi Sankyo, Kyowa Hakko Kirin, Mochida, MSD, and Takeda. SU reports receiving speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Dainihon Sumitomo, Otsuka, Shionogi, Takeda, and Tanabe Mitsubishi. KA reports receiving speaker fees from Bayer, Daiichi Sankyo, Mochida, MSD, and Torii Pharmaceutical. NI reports being a former employee of Sanofi-Aventis. MM reports receiving grant support from Bayer, Daiichi Sanko, Pfizer, Sanofi-Aventis, and Taisho-Toyama, and personal fees from Dainihon-Sumitomo, Otsuka, and Taisho-Toyama. KY reports grants from Nippon Shinyaku, Bristol-Myers Squibb, Chugai, Takeda, Pfizer, Kyowa Hakko Kirin, and Eisai, and personal fees from Nippon Shinyaku, Celgene Japan, Bayer, Bristol-Myers Squibb, Novartis, Takeda, Pfizer, Kyowa Hakko Kirin, and Otsuka. YU reports receiving grants from the JPPP study secretariat. YI reports receiving fees for medical advice from AstraZeneca, Bayer, Daiichi Sankyo, GlaxoSmithKline, and Sanofi-Aventis. MS, YG, and KS declare no conflicts of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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