Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

10-Year Follow-Up of a Randomized Controlled Trial

BACKGROUND: The long-term efficacy and safety of low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus are still inconclusive.

METHODS: The JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) was a randomized, open-label, standard care–controlled trial examining whether low-dose aspirin affected cardiovascular events in 2539 Japanese patients with type 2 diabetes mellitus and without preexisting cardiovascular disease. Patients were randomly allocated to receive aspirin (81 or 100 mg daily; aspirin group) or no aspirin (no-aspirin group) in the JPAD trial. After that trial ended in 2008, we followed up with the patients until 2015, with no attempt to change the previously assigned therapy. Primary end points were cardiovascular events, including sudden death, fatal or nonfatal coronary artery disease, fatal or nonfatal stroke, and peripheral vascular disease. For the safety analysis, hemorrhagic events, consisting of gastrointestinal bleeding, hemorrhagic stroke, and bleeding from any other sites, were also analyzed. The primary analysis was conducted for cardiovascular events among patients who retained their original allocation (a per-protocol cohort). Analyses on an intention-to-treat cohort were conducted for hemorrhagic events and statistical sensitivity.

RESULTS: The median follow-up period was 10.3 years; 1621 patients (64%) were followed up throughout the study; and 2160 patients (85%) retained their original allocation. Low-dose aspirin did not reduce cardiovascular events in the per-protocol cohort (hazard ratio, 1.14; 95% confidence interval, 0.91–1.42). Multivariable Cox proportional hazard model adjusted for age, sex, glycemic control, kidney function, smoking status, hypertension, and dyslipidemia showed similar results (hazard ratio, 1.04; 95% confidence interval, 0.83–1.30), with no heterogeneity of efficacy in subgroup analyses stratified by each of these factors (all interaction $P>0.05$). Sensitivity analyses on the intention-to-treat cohort yielded consistent results (hazard ratio, 1.01; 95% confidence interval, 0.82–1.25). Gastrointestinal bleeding occurred in 25 patients (2%) in the aspirin group and 12 (0.9%) in the no-aspirin group ($P=0.03$), and the incidence of hemorrhagic stroke was not different between groups.

CONCLUSIONS: Low-dose aspirin did not affect the risk for cardiovascular events but increased risk for gastrointestinal bleeding in patients with type 2 diabetes mellitus in a primary prevention setting.

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Clinical Perspective

What Is New?

- In the median 10-year follow-up of the JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) and the JPAD2 study, long-term therapy with low-dose aspirin did not affect cardiovascular events in Japanese patients with type 2 diabetes mellitus and without preexisting atherosclerotic cardiovascular disease.
- In analyses stratified by age, sex, presence of hypertension and dyslipidemia, smoking status, hemoglobin A_{1c}, and estimated glomerular filtration rate, there was no significant difference in the efficacy of low-dose aspirin between the aspirin and no-aspirin groups.
- Long-term therapy with low-dose aspirin increased the hazard for gastrointestinal bleeding, but no significant differences in the incidence of hemorrhagic stroke were observed.

What Are the Clinical Implications?

- On the basis of the absence of cardiovascular efficacy coupled with significantly increased gastrointestinal bleeding risk, low-dose aspirin is not recommended for Japanese patients with type 2 diabetes mellitus in the absence of prevalent atherosclerotic cardiovascular disease.
- Whether these findings are broadly applicable to other patient populations remains uncertain, with international trials presently underway evaluating the utility of low-dose aspirin for primary cardiovascular prevention in patients with type 2 diabetes mellitus.

Diabetes mellitus is a strong risk factor for cardiovascular events.[1,2] Platelet activation plays a causative role in the development of cardiovascular events in the setting of type 2 diabetes mellitus in which platelet activation and aggregation are exaggerated.[3–5] Guidelines published in the early 2000s recommended the use of low-dose aspirin for primary prevention in patients with diabetes mellitus over a certain age or in the presence of concomitant cardiovascular risk factors.[6–8] This recommendation was based largely on results from randomized clinical trials that showed a positive effect of low-dose aspirin in healthy volunteers,[9–11] in patients with hypertension,[12] and for secondary prevention in patients after myocardial infarction.[13] During that period, however, very little evidence directly supported the use of low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes mellitus.

In this context, we designed and conducted the JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) to evaluate the efficacy of low-dose aspirin on the primary prevention of cardiovascular events. The study population was 2539 Japanese patients with type 2 diabetes mellitus who were enrolled beginning in 2002, and we reported the original results in 2008 after a median follow-up of 4.4 years.[14] Low-dose aspirin therapy did not increase adverse events such as hemorrhagic stroke or gastrointestinal bleeding, and although the efficacy results were not statistically significantly different, the point estimate of the effect on the primary composite cardiovascular outcome was a 20% reduction (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58–1.10).[14] The reason why the JPAD trial results did not demonstrate a benefit of aspirin was unclear. Possible explanations included a lower observed event rate than expected, yielding limited statistical power and the chance for type II error, or that low-dose aspirin is not effective in reducing cardiovascular events in patients with type 2 diabetes mellitus in a primary prevention setting.

In addition to the JPAD trial, another randomized clinical trial investigated the efficacy of low-dose aspirin therapy on the primary prevention of cardiovascular events in patients with diabetes mellitus and likewise did not demonstrate the efficacy of aspirin, although its follow-up period was 6.7 years.[15] After the results of these trials were published, guidelines were revised to de-emphasize the use of aspirin for primary cardiovascular disease risk prevention in diabetes mellitus.[2,16] Around the same time, it became evident that posttrial observational studies are useful to examine the effect of an intervention on the prevention of cardiovascular events because long-term follow-up can strengthen statistical power.[17–19]

With these findings taken into account, the follow-up of the JPAD trial was extended to elucidate the efficacy and safety of long-term therapy with low-dose aspirin in patients with type 2 diabetes mellitus.

METHODS

The JPAD trial was a multicenter, randomized, standard care–controlled, open-label, blinded end-point trial conducted at 163 institutions throughout Japan to evaluate the effect of low-dose aspirin on cardiovascular events in patients with type 2 diabetes mellitus and no preexisting cardiovascular diseases.[14] Patient enrollment in the JPAD trial started in December 2002 and was completed in May 2005. After the JPAD trial was completed in April 2008, all patients were followed up biennially until July 2015. The JPAD trial and its follow-up period together constitute the JPAD2 study (Figure 1).

The JPAD trial and the JPAD2 study were performed according to the Declaration of Helsinki and were approved by the ethics committee of each participating hospital (Nara Medical University Ethics Committee and Graduate School of Medical Science, Kumamoto University Ethics Committee). Written informed consent was obtained from each participant before participation in the JPAD trial. In the JPAD2 study, the revised study protocol was approved by each ethics committee (Nara Medical University Ethics Committee and

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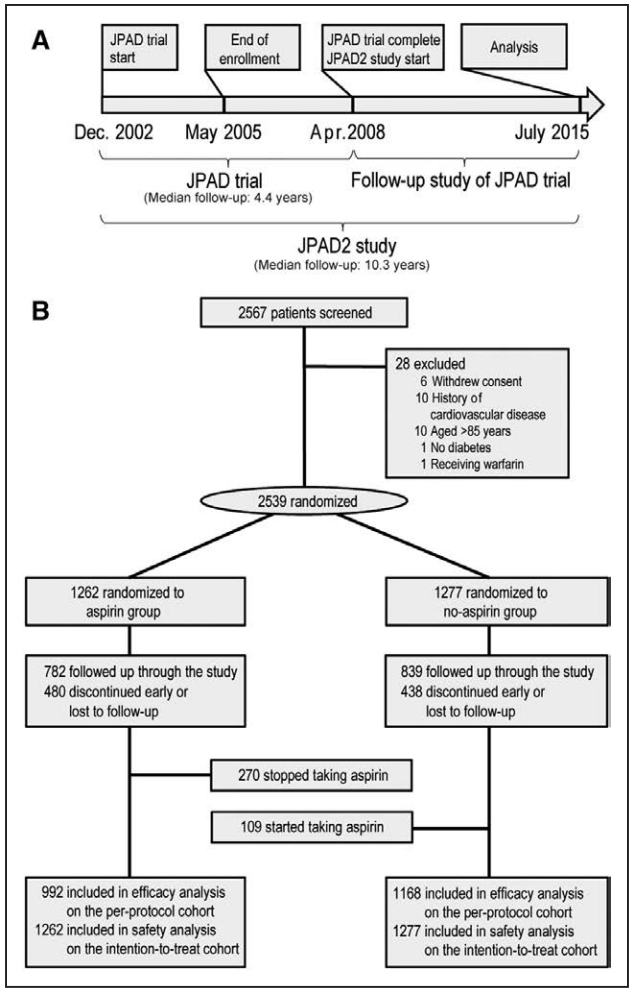

Figure 1. Flowcharts of the JPAD2 study (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) and follow-up.
A, In the JPAD trial, patient enrollment started in December 2002 and was completed in May 2005. After the JPAD trial was completed in April 2008, we followed up all patients meeting JPAD2 criteria until July 2015. The median total follow-up duration (JPAD trial+follow-up) was 10.3 years (95% confidence interval, 10.2–10.5). **B**, During the follow-up period, 270 patients in the aspirin group stopped taking low-dose aspirin, and 109 patients in the no-aspirin group started taking aspirin. Overall, 2160 patients (85%) retained their original allocation for aspirin (the per-protocol cohort). They were included in the primary efficacy analysis for cardiovascular events. Safety analysis was conducted for hemorrhagic events on the intention-to-treat cohort.

Graduate School of Medical Science, Kumamoto University Ethics Committee), and verbal informed consent was again obtained from each participant. The study protocol for the JPAD trial was registered at clinicaltrials.gov with the identifier NCT00110448.

Sample Size Calculations

In the design of the JPAD trial, it was estimated that 52 primary outcome events per 1000 patients would occur annually. On the basis of a 2-sided α level of 0.05, a power of 0.95, an enrollment period of 2 years, and a follow-up period of 3 years after the last enrollment, we estimated that 2450 patients would need to be enrolled to detect a 30% relative risk reduction in cardiovascular events by the low-dose aspirin therapy. A final total of 2539 patients were enrolled.

Study Patients

In the JPAD2 study, we recruited all patients who did not meet the primary end point of the JPAD trial. The JPAD inclusion criteria were diagnosis of type 2 diabetes mellitus, age of 30 to 85 years, and ability to provide informed consent. Exclusion criteria were electrocardiographic abnormalities consisting of ischemic ST-segment depression, ST-segment elevation, or pathological Q waves; a history of coronary artery disease confirmed by coronary angiography; a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or transient ischemic attack; a history of peripheral atherosclerotic disease necessitating medical treatment; atrial fibrillation; pregnancy; use of antiplatelet or antithrombotic therapy; a history of severe gastric or duodenal ulcer; severe liver dysfunction; severe kidney dysfunction; and allergy to aspirin.

Intervention

In the JPAD trial, patients were randomly allocated (1:1) to receive aspirin (either 81 mg unbuffered, uncoated aspirin or 100 mg enteric-coated aspirin daily; aspirin group) or no aspirin (no-aspirin group). The randomization was performed as nonstratified randomization from a random-number table. Personnel at the central trial coordinating center prepared sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites. All patients were allowed to undergo any concurrent treatments. At the end of the JPAD trial, patients were administered low-dose aspirin therapy (at either 81 or 100 mg daily) according to the decision of each physician during the follow-up period. We checked whether the patients were administered low-dose aspirin in the biennial follow-ups.

Primary and Secondary End Points

The primary and secondary end points were the time to first occurrence of any cardiovascular event during the JPAD trial or the JPAD2 extension study.

The primary end point was a composite of the following cardiovascular events: sudden death; death resulting from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; and nonfatal aortic and peripheral vascular disease.

The secondary end points were each cardiovascular event and the combinations of cardiovascular events as follows: Coronary artery events were a composite of death resulting from coronary causes, nonfatal acute myocardial infarction, unstable angina, and newly developed exertional angina. Cerebrovascular events were a composite of death resulting from cerebrovascular causes, nonfatal ischemic and hemorrhagic stroke, and transient ischemic attack. Vascular events

were a composite of death from aortic causes and nonfatal aortic and peripheral vascular disease.

Hemorrhagic events consisted of gastrointestinal bleeding, hemorrhagic stroke, and bleeding from any other sites.

All potential end points and hemorrhagic events were adjudicated by a central independent committee blinded to group assignments in the both the JPAD trial and the JPAD2 study.

Statistical Analyses

The primary analyses were based on the per-protocol principle because the JPAD2 study was a follow-up study of the randomized controlled trial, and the decision to continue the original allocation was at the discretion of the patients and their physicians. Patients who withdrew the original allocation were excluded from the per-protocol analyses. As the sensitivity analyses, we conducted the primary analyses on the basis of the intention-to-treat principle according to original JPAD randomization assignment to evaluate robustness.

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean±SD or median (interquartile range). On the basis of their distribution, continuous variables were compared by use of the Student *t* test or Wilcoxon rank-sum test as appropriate.

We followed up the patients until the day of the first cardiovascular event or July 2015 if patients did not have a cardiovascular event. If patients were not followed up until July 2015, they were censored on the day of their last visit. Efficacy comparisons were based on time to the first event. The cumulative incidence of each end point was estimated with the Kaplan-Meier method in each group, and differences between groups were assessed with the log-rank test. We constructed Cox proportional hazard models to estimate the HR and 95% CI of the efficacy of low-dose aspirin therapy in terms of the incidence of the composite primary end point. We developed multivariable Cox proportional hazard models adjusted for age, sex, baseline hemoglobin A_{1c} (HbA_{1c}), estimated glomerular filtration rate (eGFR), history of smoking, and presence of hypertension and dyslipidemia. These factors were considered to affect the incidence of cardiovascular events in patients with diabetes mellitus on the basis of previous studies.[20–22] In these models, age was dichotomized by 65 years, and HbA_{1c} was dichotomized by a median value of 7.2%. eGFR was calculated by a Japanese equation for eGFR[23] and dichotomized by 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. In subgroup analyses, we stratified the patients by age (≥65 or <65 years), sex, presence of hypertension and dyslipidemia at baseline, smoking status (current/past smoking or not), baseline HbA_{1c} (≥7.2% or <7.2%), and baseline eGFR (≥90, 60–89, or <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$). We conducted interaction analyses in each subgroup to evaluate heterogeneity.

Hemorrhagic events were analyzed on the intention-to-treat cohort because hemorrhagic events were major causes of discontinuing low-dose aspirin therapy. For adjusting the influence of age, presence of hypertension, and concomitant use of antiulcer medications, we developed multivariable Cox proportional hazard models. To evaluate the effect of hemorrhagic events on discontinuing low-dose aspirin therapy, we also analyzed hemorrhagic events in the per-protocol cohort.

Statistical analyses were conducted by an independent statistician (T.M.) using JMP 9.0 (SAS Institute, Cary, NC) and SAS 9.4 (SAS Institute, Cary, NC). Two-tailed values of $P<0.05$ were considered statistically significant.

RESULTS

The median follow-up period was 10.3 years (95% CI, 10.2–10.5), and 1621 patients (64%) were followed up until the day of the first cardiovascular event or July 2015 (Figure 1). During the follow-up period, 270 patients in the aspirin group stopped taking low-dose aspirin, and 109 patients in the no-aspirin group started taking aspirin. These 379 patients (15%) were excluded from the per-protocol analysis at the time their aspirin treatment changed, and 2160 patients (85%) who retained their original allocation were included in the per-protocol analysis.

Baseline Characteristics in the Aspirin and No-Aspirin Groups

Baseline characteristics are presented by initial randomized treatment assignment in Table 1. The mean age of the entire population at baseline was 65±10 years, and 55% of the patients were men. The mean body mass index was 24±4 kg/m^2. The median duration of diabetes mellitus was 7.1 years. The prevalence of diabetic microvascular complications was 15% for retinopathy, 13% for nephropathy, and 12% for neuropathy. Hypertension and dyslipidemia were present in more than half of the patients (hypertension, 58%; dyslipidemia, 53%). Mean levels of HbA_{1c} and eGFR were 7.5±1.3% and 74.1±20.6 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, respectively.

In the per-protocol cohort, there were slight but significant differences between the aspirin and no-aspirin groups in terms of age, blood pressure, HbA_{1c}, and creatinine at baseline (Table 1). The aspirin group was older and had higher blood pressure; however, the prevalence of hypertension was not significantly different between the groups. The HbA_{1c} level was higher in the aspirin group. The creatinine level was slightly higher in the aspirin group, but eGFR was not significantly different between the 2 groups.

We analyzed the differences in baseline characteristics between patients who were followed up through the entire study duration and those who discontinued early or were lost to follow-up. There were no overt differences between the groups (Table I in the online-only Data Supplement).

The Efficacy of Low-Dose Aspirin Therapy on Primary Prevention of Cardiovascular Events

A total of 317 cardiovascular events occurred in the overall population (aspirin group, 151 events; no-aspirin group, 166 events; Table 2). The incidence of the primary end point was not significantly different between the aspirin and no-aspirin groups (log-rank $P=0.2$; Figure 2), and the HR of aspirin was 1.14 (95% CI, 0.91–1.42).

Table 1. Baseline Characteristics of the Per-Protocol Cohort

	Aspirin Group (n = 992)	No-Aspirin Group (n = 1168)	*P* Value
Age, mean (SD), y	65 (10)	64 (10)	0.002
Men, n (%)	564 (57)	631 (54)	0.2
Body mass index, mean (SD), kg/m^2	24 (3)	24 (4)	0.5
Duration of diabetes mellitus, median (IQR), y	7.6 (2.9–12.5)	6.7 (3.0–12.3)	0.2
Systolic blood pressure, mean (SD), mm Hg	136 (16)	134 (15)	0.007
Diastolic blood pressure, mean (SD), mm Hg	77 (9)	76 (9)	0.03
Presence of hypertension, n (%)	582 (59)	660 (57)	0.3
Presence of dyslipidemia, n (%)	542 (55)	602 (52)	0.2
Smoking status, n (%)			
Current	233 (23)	226 (19)	0.02
Past	217 (22)	228 (20)	0.2
Diabetic microvascular complications, n (%)			
Retinopathy	156 (16)	170 (15)	0.4
Nephropathy	134 (14)	146 (13)	0.5
Neuropathy	134 (14)	129 (11)	0.08
Family history, n (%)			
Diabetes mellitus	415 (42)	466 (40)	0.4
Coronary artery disease	121 (12)	125 (11)	0.3
Stroke	218 (22)	227 (19)	0.1
Laboratory data			
HbA_{1c}, mean (SD), %	7.5 (1.4)	7.4 (1.2)	0.01
Fasting plasma glucose, mean (SD), mg/dL	148 (50)	145 (48)	0.2
Total cholesterol, mean (SD), mg/dL	202 (33)	200 (33)	0.1
Fasting triglycerides, median (IQR), mg/dL	115 (79–162)	114 (81–163)	0.8
HDL cholesterol, mean (SD), mg/dL	55 (15)	55 (16)	0.99
LDL cholesterol, mean (SD), mg/dL	121 (31)	119 (31)	0.2
Creatinine, mean (SD), mg/dL	0.79 (0.37)	0.77 (0.23)	0.03
eGFR, mean (SD), mL·min^{-1}·1.73 m^{-2}	73.3 (20.2)	74.8 (21.0)	0.09
Hemoglobin, mean (SD , g/dL	14.2 (1.5)	14.1 (1.5)	0.04
Urinary protein (≥30 mg/dL), n (%)	132 (14)	156 (14)	0.98
Antihyperglycemic medications, n (%)			
Sulfonylurea	570 (57)	657 (56)	0.6
α-Glucosidase inhibitor	326 (33)	377 (32)	0.8
Biguanide	136 (14)	168 (14)	0.7
Thiazolidinedione	45 (5)	60 (5)	0.5
Insulin	138 (14)	145 (12)	0.3
Medications for hypertension or dyslipidemia, n (%)			
Calcium channel blocker	345 (35)	395 (34)	0.6
AT_1 receptor blocker	214 (22)	234 (20)	0.4
ACE inhibitor	148 (15)	172 (15)	0.9
α-Blocker	58 (6)	77 (7)	0.5
Statins	255 (26)	293 (25)	0.7
Antiulcer medications, n (%)	106 (11)	112 (10)	0.4

ACE indicates angiotensin-converting enzyme; AT_1, angiotensin II type 1; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein. Body mass index was calculated as weight in kg divided by height in m^2. LDL cholesterol was estimated with the Friedewald equation.

Multivariable Cox proportional hazard modeling also showed no difference in the incidence of the primary end point between groups (adjusted HR, 1.04; 95% CI, 0.83–1.30; Table 3). The cardiovascular events comprised 125 coronary artery events, 133 cerebrovascular events, and 45 vascular events. There were no significant differences in any of the secondary end points between the aspirin and no-aspirin groups (Table 2).

In patients who switched their original allocation for aspirin, 16 patients (6%) of the aspirin group and 5 patients (5%) of the no-aspirin group had the primary end points. Sensitivity analyses using intention-to-treat methods showed similar results (HR, 1.01; 95% CI, 0.82–1.25; log-rank *P*=0.9; Figure 3). The number (incidence) of occurrences of the primary end point were 167 (16.5 per 1000 person-years) in the aspirin group and 171 (16.3 per 1000 person-years) in the no-aspirin group. Details of the first cardiovascular events in the intention-to-treat cohort are presented in Table II in the online-only Data Supplement. Multivariable Cox proportional hazard modeling showed no difference in the incidence of the primary end point between groups also in the intention-

Table 2. Details of the First Cardiovascular Events in the Per-Protocol Cohort

	Aspirin Group			No-Aspirin Group			Hazard Ratio	95% CI	Log-Rank *P* Value
	n	%	n/1000 Person-y	n	%	n/1000 Person-y			
Primary end point	151	15.2	20.3	166	14.2	17.8	1.14	0.91–1.42	0.2
Coronary artery events	57	5.7	7.7	68	5.8	7.3	1.06	0.74–1.49	0.8
Fatal myocardial infarction	3	0.3	0.4	6	0.5	0.6	0.61	0.13–2.32	0.5
Nonfatal myocardial infarction	22	2.2	3.0	22	1.9	2.4	1.26	0.70–2.29	0.4
Unstable angina	9	0.9	1.2	14	1.2	1.5	0.80	0.33–1.83	0.6
Stable angina	23	2.3	3.1	26	2.2	2.8	1.11	0.63–1.95	0.7
Cerebrovascular events	61	6.1	8.2	72	6.2	7.7	1.06	0.75–1.49	0.8
Fatal stroke	9	0.9	1.2	8	0.7	0.9	1.44	0.55–3.84	0.4
Nonfatal stroke									
Ischemic	37	3.7	5.0	45	3.9	4.8	1.02	0.66–1.58	0.9
Hemorrhagic	7	0.7	0.9	9	0.8	1.0	0.98	0.35–2.63	0.97
Transient ischemic attack	8	0.8	1.1	10	0.9	1.1	0.98	0.37–2.48	0.96
Vascular events	26	2.6	3.5	19	1.6	2.0	1.71	0.95–3.14	0.07
Sudden death	7	0.7	0.9	7	0.6	0.8	1.30	0.45–3.80	0.6

CI indicates confidence interval. The primary and secondary end points were the time to first occurrence of any cardiovascular event during the JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) or the JPAD2 extension study.

to-treat cohort (adjusted HR, 0.94; 95% CI, 0.76–1.17; Table III in the online-only Data Supplement).

We analyzed the incidence of primary end point divided by in-trial and posttrial periods on the per-protocol cohort (Figure I in the online-only Data Supplement). Low-dose aspirin did not reduce the risk for the primary end point in either the in-trial (ie, JPAD) or posttrial (ie, follow-up of JPAD) period (in-trial period: HR, 0.99; 95% CI, 0.73–1.34; posttrial period: HR, 1.34; 95% CI, 0.97–1.84).

Subgroup Analyses

We conducted subgroup analyses stratified by age, sex, presence of hypertension and dyslipidemia at baseline,

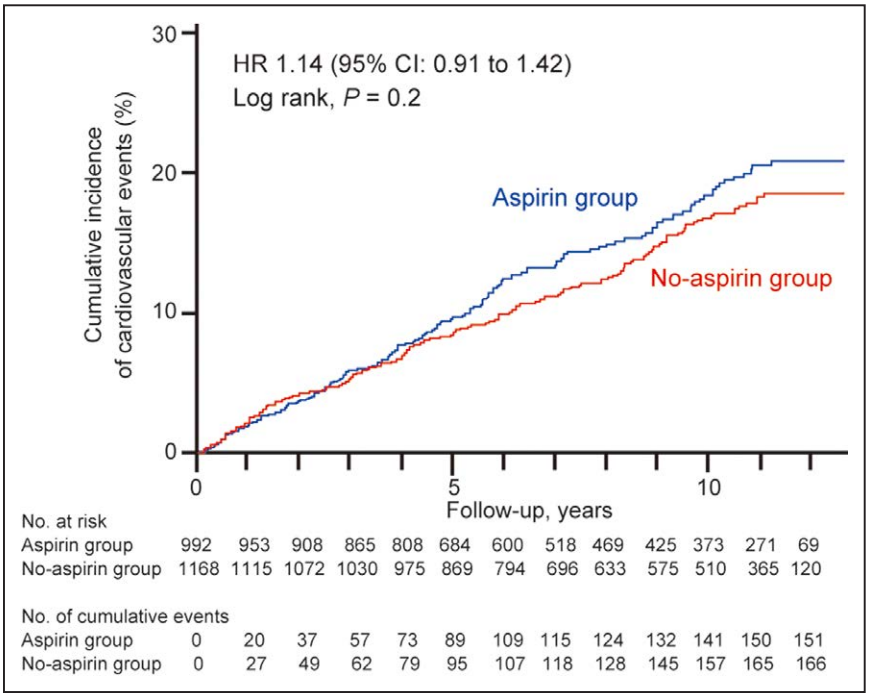

Figure 2. The efficacy of low-dose aspirin therapy on primary prevention of cardiovascular events.
A total of 317 cardiovascular events occurred (aspirin group, 151 events; no-aspirin group, 166 events). The incidence of the primary end point was not statistically different between the aspirin group and no-aspirin group (hazard ratio [HR], 1.14; 95% confidence interval [CI], 0.91–1.42; log-rank *P*=0.2).

Table 3. Multivariable Analyses on the Per-Protocol Cohort for Risk of the Primary Composite Cardiovascular Outcome

	Hazard Ratio	95% CI	*P* Value	χ^2 Score
Age ≥65 y	1.92	1.51–2.45	<0.0001	28.2
HbA_{1c} ≥7.2%	1.79	1.43–2.25	<0.0001	25.1
Men	1.57	1.17–2.09	0.002	9.3
Dyslipidemia	1.28	1.02–1.61	0.03	4.6
Hypertension	1.22	0.97–1.55	0.09	2.8
eGFR ≥60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	0.81	0.64–1.04	0.1	2.8
Current or past smoking	1.06	0.81–1.41	0.7	0.2
Low-dose aspirin	1.04	0.83–1.30	0.7	0.1

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; and HbA_{1c}, hemoglobin A_{1c}.

smoking status, baseline HbA_{1c}, and baseline eGFR. In all subgroups, there were no significant differences in the efficacy of low-dose aspirin therapy between the aspirin and no-aspirin groups (Figure 4). The interaction analyses showed no heterogeneity of efficacy in all subgroups.

Hemorrhagic Events

We analyzed hemorrhagic events on the intention-to-treat cohort to avoid underestimation of the adverse events owing to low-dose aspirin because the low-dose aspirin therapy was often stopped in patients who experienced hemorrhagic events. In the present study, 13 of 270 patients who stopped taking low-dose aspirin in the aspirin group had a gastrointestinal bleeding event, although no patients did among 109 patients who started taking low-dose aspirin originally assigned to the no-aspirin group.

Overall, hemorrhagic events occurred in 80 patients (6%) in the aspirin group and 67 patients (5%) in the no-aspirin group (*P*=0.2; Table 4). Gastrointestinal bleeding occurred more frequently in the aspirin group (aspirin group, 25 events [2%]; no-aspirin group, 12 events [0.9%]; *P*=0.03); however, there were no significant differences in the frequency of hemorrhagic stroke (aspirin group, 11 events [0.9%]; no-aspirin group, 15 events [1.2%]; *P*=0.4). Multivariable Cox proportional hazard modeling, adjusted for age, presence of hypertension, and concomitant use of antiulcer medications, also showed that low-dose aspirin increased the incidence of gastrointestinal bleeding (adjusted HR, 2.14; 95% CI, 1.10–4.42; *P*=0.03) but did not affect the incidence of total hemorrhagic events (adjusted HR, 1.22; 95% CI, 0.88–1.69; *P*=0.2) and hemorrhagic stroke (adjusted HR, 0.71; 95% CI, 0.32–1.55; *P*=0.4).

The incidence of gastrointestinal bleeding was not statistically different between the aspirin and no-aspirin groups in the per-protocol cohort (Table IV in the online-only Data Supplement).

DISCUSSION

After the JPAD trial was completed in 2008, 2160 patients (85%) retained their original allocation for low-dose aspirin. The JPAD2 study showed that over the 10-year trial plus posttrial follow-up, low-dose aspirin therapy

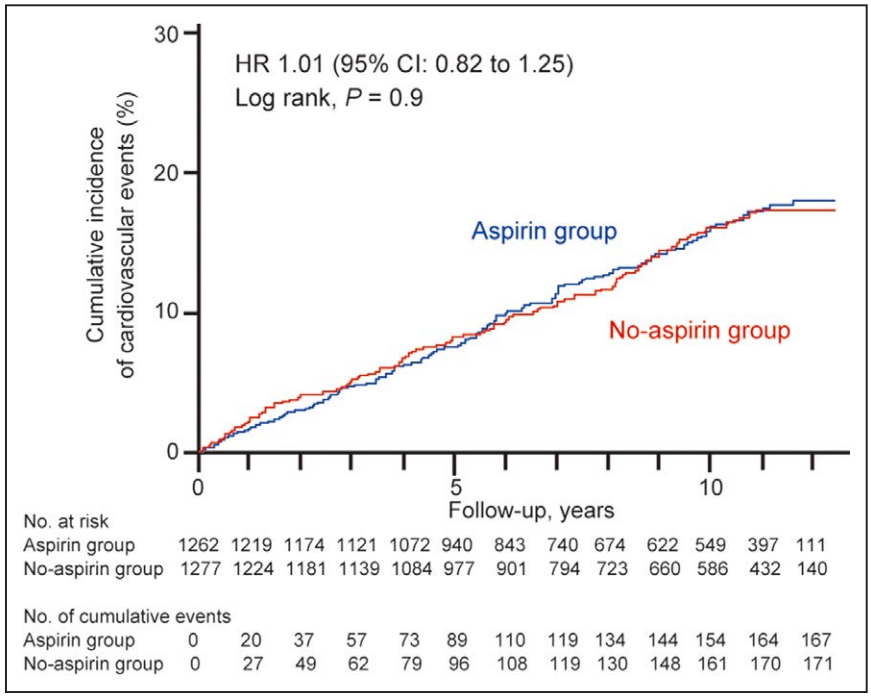

Figure 3. Sensitivity analyses for the efficacy of low-dose aspirin on cardiovascular events based on the intention-to-treat cohort. Sensitivity analyses on the intention-to-treat cohort showed that low-dose aspirin did not affect cardiovascular events (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.82–1.25; log-rank *P*=0.9).

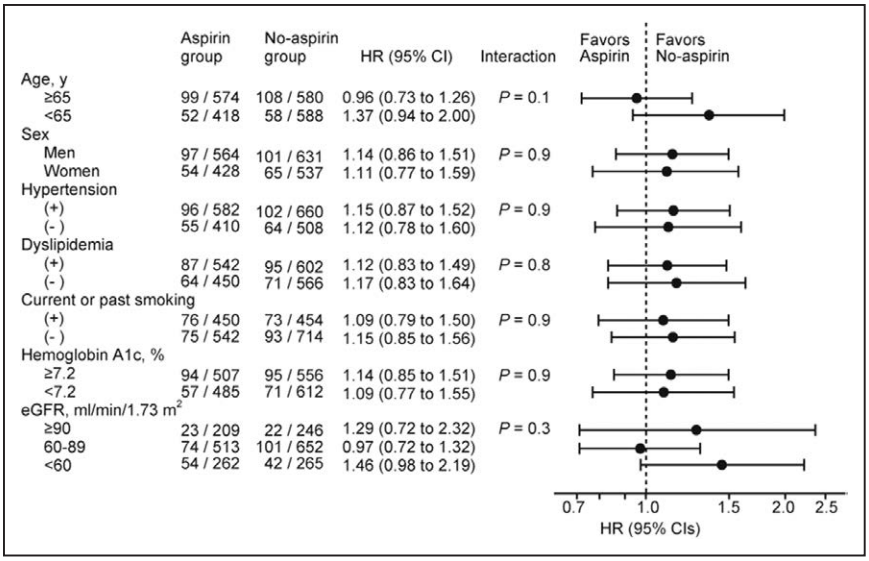

Figure 4. Subgroup analyses on the per-protocol cohort.
Subgroup analyses, stratified by age, sex, presence of hypertension and dyslipidemia at baseline, smoking status, baseline hemoglobin A_{1c}, and baseline estimated glomerular filtration rate (eGFR), did not show significant differences between the aspirin and no-aspirin groups in the efficacy of low-dose aspirin therapy. The interaction analyses showed no heterogeneity of efficacy in all subgroups. CI indicates confidence interval; and HR, hazard ratio.

did not reduce cardiovascular events in Japanese patients with type 2 diabetes mellitus and no preexisting cardiovascular diseases. Hemorrhagic stroke was not increased by the low-dose aspirin therapy, but gastrointestinal bleeding occurred more frequently in the aspirin group. Both the JPAD trial and the JPAD2 study showed consistent results for the lack of efficacy of aspirin on primary prevention of cardiovascular events. Long-term follow-up results were consistent with the randomized trial findings that low-dose aspirin is not effective in reducing cardiovascular events in patients with type 2 diabetes mellitus without prevalent atherosclerotic vascular disease.

In general populations, previous clinical trials for primary prevention with aspirin have demonstrated the beneficial effects of aspirin on preventing cardiovascular events.[9–11,24] Recent meta-analyses also indicated the benefit of aspirin for primary prevention, especially in people with high cardiovascular risk.[25,26] According to these results, low-dose aspirin is beneficial for primary prevention in general populations. Recently, the US Preventive Services Task Force recommended low-dose aspirin therapy for primary prevention of cardiovascular events in adults 50 to 59 years of age who have a ≥10% 10-year cardiovascular disease risk and are not at increased risk for bleeding.[27] In patients with diabetes mellitus, however, the JPAD2 study could not demonstrate the benefit of aspirin for primary prevention. Meta-analyses in patients with diabetes mellitus have reported that aspirin has a smaller benefit for primary prevention than in general populations,[26,28,29] although patients with diabetes mellitus are at high risk for cardiovascular events. It seems that there are differential effects of low-dose aspirin therapy on preventing cardiovascular events in patients with and without diabetes mellitus. Platelet dysfunction,[5] increased platelet turnover,[30] or aspirin resistance[31,32] in diabetes mellitus might diminish the benefit of aspirin, although the precise mechanism is not clear at present. Increased dose of aspirin and twice-daily low-dose aspirin therapy could be possible therapeutic options for cardiovascular prevention in patients with diabetes mellitus, but the clinical implication of these aspirin regimens remains uncertain in the absence of data from randomized trials assessing such strategies.[33]

Table 4. Hemorrhagic Events in the Intention-to-Treat Cohort

	Aspirin Group, n (%) (n=1262)	No-Aspirin Group, n (%) (n=1277)	*P* Value
Total	80 (6)	67 (5)	0.2
Gastrointestinal bleeding	25 (2)	12 (0.9)	0.03
Hemorrhagic stroke	11 (0.9)	15 (1.2)	0.4
Other site of bleeding	45 (4)	42 (3)	0.7

A possible cause of the negative result in the JPAD2 study was the progress of preventive medicines such as the development and clinical prescription of intense-dose statins. Most evidence for the value of aspirin therapy for primary prevention was documented in the 20th century,[9,10,12,24] when intense-dose statins were not yet widely used, clinical targets of low-density lipoprotein cholesterol level were not as aggressive as contemporary practice, smoking was more prevalent, and blood pressure was not intensively controlled. Recent clinical trials, including the JPAD trial, could not demonstrate the efficacy of aspirin in the setting of primary prevention for patients with or without diabetes mellitus.[14,15,34,35] State-of-the-art medicines might make it difficult to detect the efficacy of low-dose aspirin therapy on primary prevention of cardiovascular events in the present day.

Overall, hemorrhagic events occurred numerically more frequently in the aspirin group, although the absolute difference over the median 10.3-year follow-up

was only 1%, with gastrointestinal bleeding statistically more frequent in the aspirin group with an absolute difference of 1.1%. In the JPAD trial, there were 12 cases (1.0%) of gastrointestinal bleeding in the aspirin group and 4 (0.3%) in the no-aspirin group, but the difference was not statistically significant. Prolonged therapy with low-dose aspirin and aging of the study patients might increase gastrointestinal bleeding caused by aspirin.[36] A previous meta-analysis of hemorrhagic events with aspirin therapy revealed that low-dose aspirin increased the frequency of gastrointestinal bleeding, and comorbidity with diabetes mellitus was a significant risk.[37] A population-based study of aspirin-related bleeding showed that aspirin did not increase gastrointestinal bleeding even in patients with diabetes mellitus, although patients with diabetes mellitus had a higher rate of bleeding than those without diabetes mellitus.[38] In the JPAD2 study, long-term follow-up revealed that low-dose aspirin certainly increased the rate of gastrointestinal bleeding in patients with diabetes mellitus.

A chemopreventive effect of aspirin on cancer has been suggested by a series of observations over the past few decades, as has been recently reviewed.[39] Results from several meta-analyses demonstrated that long-term therapy with low-dose aspirin is beneficial for prevention of cancer, especially colorectal cancer.[40,41] The US Preventive Services Task Force recommended the use of low-dose aspirin therapy for prevention of colorectal cancer in selected patients.[27] In the JPAD trial, we reported that low-dose aspirin therapy tended to reduce deaths caused by cancer with a median follow-up of 4.4 years (HR, 0.80; 95% CI, 0.40–1.57).[42] We are planning to analyze the long-term efficacy of low-dose aspirin on cancer prevention in the JPAD2 study, but those data are not currently available.

The strength of the JPAD2 study was long duration (median, 10.3 years) of follow-up (JPAD trial+follow-up), the importance of the clinical question, and the systematic collection/central blinded adjudication of the primary cardiovascular outcomes. On the other hand, there are several limitations. First, the JPAD2 study was a follow-up study of a randomized controlled trial. We used per-protocol analyses instead of intention-to-treat analyses because the JPAD2 study was not a randomized study but a cohort study. However, per-protocol analyses compromise to some degree randomization that is captured more accurately in intention-to-treat methods, especially in the present context in which the occurrence of either a cardiovascular event or a bleeding event would affect clinical prescription for aspirin and introduce informed censoring into the analyses. In fact, 270 patients, including 13 patients with gastrointestinal bleeding, stopped taking low-dose aspirin in the aspirin group, and 109 patients, including 5 patients with cardiovascular events, started taking low-dose aspirin in the no-aspirin group during the follow-up. Consequently, the remaining 2160 patients who retained their original allocation for aspirin were analyzed in the per-protocol setting. However, there were slight but significant differences in baseline characteristics between the per-protocol aspirin and no-aspirin groups (Table 1). We conducted a multivariable Cox proportional hazard model on the per-protocol cohort that adjusted for important confounders (Table 3). In addition, we performed sensitivity analyses using the Kaplan-Meier method (Figure 3) and multivariable Cox proportional hazard modeling (Table III in the online-only Data Supplement) using the intention-to-treat cohort. These analyses yielded consistent results. Second, a substantial portion of patients (36%) were not followed up throughout the study period. As described in Methods, these patients were censored on the day of their last visit. The baseline characteristics were similar between patients who discontinued early or were lost to follow-up and those who were followed up throughout the study, as shown in Table I in the online-only Data Supplement. Third, the prescription of low-dose aspirin might have been revised on the basis of the results of the original JPAD trial. For example, we reported the potential benefit of low-dose aspirin therapy for patients ≥65 years of age in the subgroup analysis of the JPAD trial.[14] In the per-protocol cohort of the JPAD2 study, the prescription frequencies of low-dose aspirin were 50% in patients ≥65 years of age and 42% in those <65 years of age.

CONCLUSIONS

The posttrial follow-up of the JPAD trial, comprising a mean observation during and after the trial of >1 decade, indicated that long-term therapy with low-dose aspirin is not associated with lower cardiovascular events in Japanese patients with type 2 diabetes mellitus in a primary prevention setting. On the other hand, low-dose aspirin therapy was associated with and significantly increased the incidence of gastrointestinal bleeding.

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FOOTNOTES

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Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: 10-Year Follow-Up of a Randomized Controlled Trial

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For the JPAD Trial Investigators

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Differences in baseline characteristics between follow-up patients and lost to follow-up patients

	Overall			Aspirin group			No-aspirin group		
	Follow-up	Lost to follow-up	*P* value	Follow-up	Lost to follow-up	*P* value	Follow-up	Lost to follow-up	*P* value
N	1621	918		782	480		839	438	
Age, y, mean (SD)	65 (10)	64 (10)	0.07	65 (9)	64 (10)	0.09	64 (10)	64 (11)	0.3
Men, n (%)	904 (56)	483 (53)	0.1	447 (57)	259 (54)	0.3	457 (54)	224 (51)	0.3
BMI, kg/m^2, mean (SD)	24 (4)	24 (4)	0.6	24 (4)	24 (4)	0.7	24 (4)	24 (4)	0.8
Duration of diabetes, y, median (IQR)	7.0 (3.0 to 12.4)	6.9 (2.8 to 12.3)	0.5	7.5 (3.2 to 12.2)	6.6 (2.4 to 12.4)	0.3	6.5 (3.0 to 12.5)	7.1 (3.1 to 11.8)	0.9
Systolic blood pressure, mmHg, mean (SD)	135 (15)	135 (15)	0.5	135 (15)	137 (16)	0.1	134 (15)	134 (14)	0.5
Diastolic blood pressure, mmHg, mean (SD)	77 (9)	77 (9)	0.1	77 (10)	78 (9)	0.4	76 (9)	77 (9)	0.2
Presence of hypertension, n (%)	940 (58)	533 (58)	0.97	454 (58)	288 (60)	0.5	486 (58)	245 (56)	0.5
Presence of dyslipidemia, n (%)	834 (51)	511 (56)	0.04	398 (51)	282 (59)	0.007	436 (52)	229 (52)	0.9
Smoking status									
Current, n (%)	346 (21)	191 (21)	0.7	185 (24)	104 (22)	0.4	161 (19)	87 (20)	0.8
Past, n (%)	364 (22)	158 (17)	0.002	186 (24)	90 (19)	0.04	178 (21)	68 (16)	0.01
Diabetic microvascular complications									
Retinopathy, n (%)	234 (14)	131 (14)	0.9	124 (16)	63 (13)	0.2	110 (13)	68 (16)	0.2
Nephropathy, n (%)	206 (13)	116 (13)	0.95	104 (13)	65 (14)	0.9	102 (12)	51 (12)	0.8
Neuropathy, n (%)	197 (12)	103 (11)	0.5	108 (14)	55 (11)	0.2	89 (11)	48 (11)	0.8
Family history, n (%)									
Diabetes	657 (41)	382 (42)	0.6	321 (41)	205 (43)	0.6	336 (40)	177 (40)	0.9
Coronary artery disease	171 (11)	119 (13)	0.07	83 (11)	64 (13)	0.1	88 (10)	55 (13)	0.3
Stroke	348 (21)	178 (19)	0.2	178 (23)	97 (20)	0.3	170 (20)	81(18)	0.5
Laboratory data									
HbA1c, %, mean (SD)	7.4 (1.3)	7.5 (1.4)	0.2	7.5 (1.4)	7.6 (1.6)	0.1	7.4 (1.2)	7.4 (1.2)	0.8
Fasting plasma glucose, mg/dl, mean (SD)	146 (48)	149 (51)	0.2	146 (49)	150 (52)	0.2	145 (47)	147 (50)	0.6
Total cholesterol, mg/dl, mean (SD)	200 (34)	203 (35)	0.08	201 (35)	204 (34)	0.2	199 (33)	202 (36)	0.3
Fasting triglyceride, mg/dl, median (IQR)	112 (80 to 159)	118 (81 to 170)	0.08	114 (84 to 172)	120 (84 to 172)	0.05	111 (81 to 160)	116 (80 to 167)	0.6
HDL-cholesterol, mg/dl, mean (SD)	55 (15)	55 (15)	0.6	55 (15)	55 (16)	0.9	56 (16)	55 (15)	0.5
LDL-cholesterol, mg/dl, mean (SD)	119 (31)	121 (31)	0.3	120 (32)	121 (31)	0.7	118 (31)	120 (32)	0.3
Creatinine, mg/dll, mean (SD)	0.8 (0.2)	0.8 (0.4)	0.7	0.8 (0.2)	0.8 (0.5)	0.4	0.8 (0.2)	0.8 (0.2)	0.4
eGFR, ml/min/1.73 m^2, mean (SD)	73.9 (20.5)	73.9 (20.8)	0.9	72.9 (19.7)	72.9 (21.1)	0.99	74.8 (21.3)	75.1 (20.4)	0.8
Hemoglobin, g/dl, mean (SD)	14.1 (1.5)	14.2 (1.5)	0.3	14.2 (1.5)	14.3 (1.5)	0.046	14.1 (1.5)	14.1 (1.5)	0.6
Urinary protein (≥30 mg/dl), n (%)	221 (14)	125 (14)	0.9	108 (14)	68 (14)	0.9	113 (14)	57 (13)	0.8

We followed the patients until the day of the first cardiovascular event or July 2015, if patients did not have cardiovascular event (follow-up patients). If patients were not followed-up until July 2015, they were censored on the day of their last visit (lost to follow-up patients).

BMI was calculated as weight in kg divided by height in m^2. LDL-cholesterol was estimated by using the Friedewald equation.

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

Supplementary Table 2. Details of the first cardiovascular events in the intention-to-treat cohort

	Aspirin group		No-aspirin group			
	n (%)	No. per 1000 person-years	n (%)	No. per 1000 person-years	HR (95% CI)	Log-rank *P* value
Primary end point	167 (13.2)	16.5	171 (13.4)	16.3	1.01 (0.82 to 1.25)	0.9
Coronary artery events	63 (5.0)	6.2	70 (5.5)	6.7	0.93 (0.66 to 1.31)	0.7
Fatal myocardial infarction	3 (0.2)	0.3	6 (0.5)	0.6	0.51 (0.11 to 1.94)	0.3
Nonfatal myocardial infarction	25 (2.0)	2.5	23 (1.8)	2.2	1.13 (0.64 to 2.01)	0.7
Unstable angina	9 (0.7)	0.9	14 (1.1)	1.3	0.67 (0.28 to 1.52)	0.3
Stable angina	26 (2.1)	2.6	27 (2.1)	2.6	1.00 (0.58 to 1.72)	0.99
Cerebrovascular events	66 (5.2)	6.5	73 (5.7)	7.0	0.94 (0.67 to 1.31)	0.7
Fatal stroke	10 (0.8)	1.0	8 (0.6)	0.8	1.31 (0.52 to 3.43)	0.6
Nonfatal stroke						
Ischemic	38 (3.0)	3.8	46 (3.6)	4.4	0.85 (0.55 to 1.31)	0.5
Hemorrhagic	8 (0.6)	0.8	9 (0.7)	0.9	0.92 (0.35 to 2.41)	0.9
Transient ischemic attack	10 (0.8)	1.0	10 (0.8)	1.0	1.03 (0.42 to 2.51)	0.95
Vascular events	31 (2.5)	3.1	20 (1.6)	1.9	1.61 (0.92 to 2.87)	0.09
Sudden death	7 (0.6)	0.7	8 (0.6)	0.8	0.92 (0.32 to 2.57)	0.9

The primary and secondary end points were the time to first occurrence of any cardiovascular event during the JPAD trial or the JPAD2 extension study.

Supplementary Table 3. Multivariable analyses on the intention-to-treat cohort

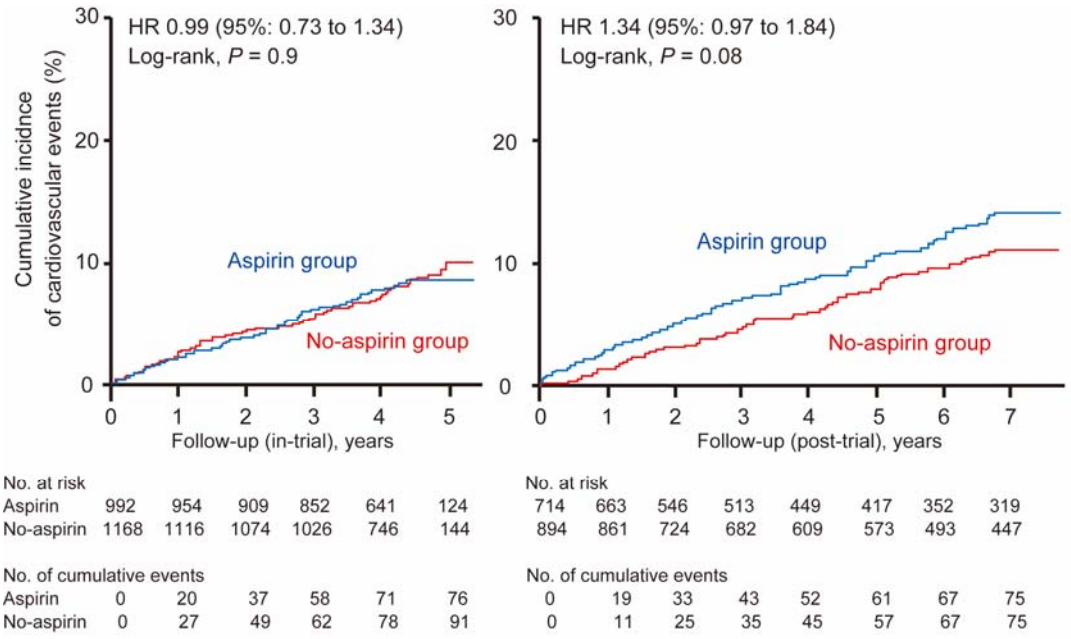
	HR	95% CI	*P* value	Chi-square score
Age ≥65 years	1.84	1.46 to 2.33	<0.0001	26.7
HbA1c ≥7.2%	1.75	1.40 to 2.18	<0.0001	24.7
Men	1.60	1.20 to 2.12	0.001	10.6
Dyslipidemia	1.27	1.02 to 1.58	0.04	4.4
Hypertension	1.19	0.95 to 1.49	0.1	2.2
eGFR ≥60 ml/min/1.73 m^2	0.84	0.67 to 1.07	0.2	2.0
Low-dose aspirin	0.94	0.76 to 1.17	0.6	0.3
Current or past smoking	1.05	0.81 to 1.38	0.7	0.1

Abbreviations: HR, hazard ratio; CI, confidence interval; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate.

Supplementary Table 4. Hemorrhagic events in the per-protocol cohort

	Aspirin group, n (%) (n = 992)	No-aspirin group, n (%) (n = 1168)	*P* value
Total	48 (5)	64 (5)	0.5
Gastrointestinal bleeding	12 (1.2)	12 (1.0)	0.7
Hemorrhagic stroke	9 (0.9)	15 (1.3)	0.4
Other site of bleeding	28 (3)	39 (3)	0.5

Supplementary Figure 1. Incidence of primary end point in in-trial and post-trial periods



We analyzed the incidence of primary end point divided by in-trial and post-trial period on the per-protocol cohort. The in-trial period was from the enrollment of the JPAD trial to April 2008. The post-trial period was from May 2008 to July 2015. Low-dose aspirin did not reduce primary end point both in-trial and post-trial periods (in-trial period: hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.73 to 1.34; log-rank, *P* = 0.9; post-trial period: HR, 1.34; 95% CI, 0.97 to 1.84; log-rank, *P* = 0.08).

Supplementary Appendix

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Dr. Lam: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the Journal and its editors. I'm Dr. Carolyn Lam, associate editor from the National Heart Center and Duke National University of Singapore. Our podcast is taking us to Japan today where we will be talking about aspirin for primary prevention in patients with diabetes. First, here's your summary of this week's issue.

The first study provides insight into the development of neurologic injury in patients with single ventricles undergoing staged surgical reconstruction. In this paper by Dr. Fogel and colleagues from the Children's Hospital of Philadelphia, the authors recognize that single ventricle patients experience greater survival with staged surgical procedures culminating in the Fontan operation, but experience high rates of brain injury and adverse neurodevelopmental outcome. They therefore studied 168 single ventricle patients with MRI scans immediately prior to bi-directional Glenn, prior to the Fontan, and then three to nine months after the Fontan reconstruction. They found that significant brain abnormalities were frequently present in these patients and that the detection of these lesions increased as children progressed through staged surgical reconstruction. In addition, there was an inverse association of various indices of cerebral blood flow with these brain lesions. This study therefore suggests that measurement of cerebral blood flow and identification of brain abnormalities may enhance recognition of single ventricle patients at risk for poor outcomes, and possibly facilitate early intervention.

The next paper uncovers a unique mechanism underlying arrhythmogenesis and suggests that the anti-epileptic drug valproic acid may possibly be repurposed for anti-arrhythmic applications. In this paper by first authors Dr. Chowdhury and Liu and corresponding author Dr. Wang and colleagues from University of Manchester UK. The authors used mouse models and human induced pluripotent stem cells derived cardiomyocytes to discover a new mechanism linking mitogen activated kinase-kinase 7 deficiency with increased arrhythmia vulnerability in pathologically remodeled hearts. Mechanistically, mitogen activated kinase-kinase-7 deficiency in the hypertrophied hearts left histone deacetylase-2 unphosphorylated, and filamin A accumulated in the nucleus, which then formed an association with kruppel-like factor 4 preventing its transcriptional regulation. Diminished potassium channel reserve caused repolarization delays resulting in ventricular arrhythmias, and the histone deacetylase-2 inhibitor, valproic acid restored potassium channel expression abolishing the ventricular arrhythmias. This study therefore provides exciting insights in developing a new class of anti-arrhythmics specifically targeting signal transduction cascades to replenish repolarization reserve, all for the treatment of ventricular arrhythmias.

Does the Mediterranean diet improve HDL function in high risk individuals? Well, the next paper by first author Dr. Hernaiz, corresponding author Dr. Fito and colleagues from Hospital Del Mar Medical Research Institute in Barcelona, Spain addresses this questions. The authors looked at a large sample of 296 volunteers from the PREDIMED study and compared the effects of two traditional Mediterranean diets, one enriched with virgin olive oil, and the other with nuts to a low-fat control diet. They looked at the

effects of these diets on the role of HDL particles on reverse cholesterol transport, HDL antioxidant properties, and HDL vasodilatory capacity after one year of dietary intervention. They found that both Mediterranean diets increased cholesterol efflux capacity and improved HDL oxidative status relative to the baseline. In particular, the Mediterranean diet enriched with virgin olive oil decreased cholesterol ester transfer protein activity, and increased HDL ability to esterify cholesterol, paraoxonase-1, arylesterase activity, and HDL vasodilatory capacity. They therefore concluded that adherence to a traditional Mediterranean diet, particularly when enriched with virgin olive oil, improves HDL function in humans.

The final study tells us that among hospitalized medically ill patients, extended duration Betrixaban reduces the risk of stroke compared to standard dose enoxaparin. In this retrospective sub-study of the APEX trial, Dr. Gibson and colleagues from Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, Massachusetts randomized 7,513 hospitalized acutely ill patients in a double-dummy, double-blind fashion to either extended duration of the oral Factor Xa inhibitor Betrixaban at 80 mg once daily for 35 to 42 days, or standard dose subcutaneous enoxaparin at 40 mg once daily for 10 days all for venous thromboprophylaxis. They found that the extended duration Betrixaban compared with enoxaparin reduced all cause stroke by almost one half with a relative risk of 0.56 equivalent to an absolute risk reduction of 0.43 percent and number needed to treat of 232. The effect of Betrixaban on stroke was explained by a reduction in ischemic stroke with no difference in hemorrhagic stroke. The reduction in ischemic stroke was confined to patients hospitalized with acute heart failure or non-cardioembolic ischemic stroke.

This paper is accompanied by an editorial by Drs. Quinlan, Eikelboom, and Hart in which they articulate three reasons that they think these results are important. First, the results demonstrated an unexpectedly high rate of new or recurrent ischemic stroke during the first three months in hospitalized medical patients receiving standard enoxaparin prophylaxis, the rate being even higher in patients presenting with heart failure or ischemic stroke. Secondly, the data demonstrated for the first time that a NOAC reduces the risk of ischemic strokes in patients without known atrial fibrillation. Thirdly, the effects of Betrixaban on stroke were dose dependent, all of the benefits were seen in those who received the 80 mg dose, whereas the 40 mg dose did not provide advantages compared with enoxaparin or placebo. While these results are encouraging, the editorialists also warn that these are based on a post-hoc analysis and should be considered hypothesis generating.

Well, that brings it to the end of our summaries. Now for our feature discussion.

Today our feature discussion focuses on the exciting 10-year follow up results of the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes, or JPAD trial. I am simply delighted to have with me first and corresponding author Dr. Yoshihiko Saito from Nara Medical University, Japan. As well as a familiar voice on this podcast, Dr. Shinya Goto associate editor of Circulation from Tokai University in Japan. Welcome gentlemen!

Dr. Goto: I am very pleased to have this opportunity. I am always enjoy listening your podcast, and this is very interesting topic of aspirin in prevention cardiovascular event in patients with diabetes, type II diabetes.

Dr. Lam: I couldn't agree more, because the burden of cardiovascular disease globally is actually shifting to Asia, and the burden of diabetes especially, is one of the fastest growing in Asia. So a very, highly relevant topic indeed. Could I start, Yoshi, by asking you: these are the 10 year follow up results, what inspired you to take a re-look at the original JPAD results and to report this 10 year result?

Dr. Saito: The American guidelines said that low-dose aspirin is recommended to the type II diabetes patient for the primary prevention of cardiovascular events who are older than 30 years old, and who are not contraindicated to aspirin. That meant that almost all type II diabetes patients were recommended to low dose aspirin. However, at that time there was no direct [inaudible 00:09:49] evidence for it. So we connected the prospective randomized control trial that examined the effects of the low dose aspirin on primary prevention of cardiovascular events in type II diabetes patients without preexisting cardiovascular disease. The name of this trial, JPAD trial, that stand for the Japanese Primary Prevention of Atherosclerosis with aspirin in Diabetes. We enrolled 2,539 patients who were assigned to the low dose asprin group or the no aspirin group. So we followed them with a median follow up period of 4.4 years.

The results of the original JPAD trial were that low dose aspirin reduced CV events by about 20%, but the reduction could not reach statistical significance. So I don't know the exact reason, but one is the reason is low statistical power, because event rate was about one-third of the anticipated. Another reason is that low dose aspirin really could not reduce cardiovascular events. So we decided the extension of the follow up of the JPAD trial to elucidate the efficacy and safety of long term therapy with low dose aspirin in type II diabetes patients. This extension study was named the JPAD 2 study. We followed them up to the median follow up period of more than 10 years.

In this time the JPAD trial study, we analyzed the patients in a pod protocol method because the randomized control trial was ended after 2008. Finally, we analyzed the 992 patients in the aspirin group, and 1,168 patients in the no aspirin group who retained the original allocations throughout the study period. The primary endpoint were composite endpoint of cardiovascular events including sudden cardiac death, the fatal and the non-fatal coronary artery disease, fatal and non-fatal stroke, peripheral vascular disease, and aortic dissection. This end point is the same as the original JPAD trial. The main results are the primary endpoints, 15.2% of patients occurred primary endpoints in aspirin group, and 14.2% in the no aspirin group occurred in the primary endpoints. So the primary endpoints rate is singular in both groups, with the hazard ratio is 1.14 with a 95% CI is 0.91 to 1.42 with a p value of 0.2 by log-rank test. So the low dose aspirin therapy could not reduce cardiovascular events in the type II diabetes mellitus.

We also analyzed these data by intention to treat analysis, the results is singular. Again, the low dose aspirin therapy could not reduce the cardiovascular event in type II diabetes mellitus. However, I was told the hemorrhagic events, total hemorrhagic

events was singular in both groups, but gastrointestinal bleeding of about 2% in the aspirin group but only 0.9% in no aspirin group. That means our gastrointestinal bleeding is doubled in the aspirin group compared with no aspirin group. This is the main outcome of the JPAD and JPAD-2 trials.

Dr. Lam: Thank you so much Yoshi, and really congratulations on such a tremendous effort. I completely applaud the idea of looking at the 10 year follow up trying to address the issue of whether or not it was a lack of power that limited JPAD-1, but what you found really reinforced what you found in JPAD-1, which is low dose aspirin did not reduce cardiovascular events in the diabetic group. They're still huge numbers, I'm so impressed that 85% of the treatment assignment was retained. Then furthermore you even showed increased gastrointestinal bleeding with aspirin. So really remarkable results. Can I just ask, are you surprised by the results, and how do you reconcile it with what was found in the general population studies like the Physician Health Study, or the US Preventive Services Task Force, where they really seem to say that primary prevention aspirin works in the general population when your risk is a certain amount?

Dr. Saito: I think that we studied only the type II diabetes patients, so it is not clear that our results are applied to the general population, but our results is very much similar to the current European guidelines and American guidelines.

Dr. Lam: That's a very interesting point about diabetic versus non-diabetic population and the utility of low dose aspirin. Shinya, you brought this up before. What do you think?

Dr. Goto: For the primary prevention population cohort study, aspirin demonstrated 25% reduction of cardiovascular event. We are not recommending aspirin for primary prevention due to the balance of bleeding and cardiovascular protection, absolute risk. In Yoshi's paper, in patients with type II diabetes aspirin evened that [inaudible 00:16:13], and that is very important message he had shown in this long term outcome randomized trial.

Dr. Lam: Do you think that there are some pathophysiologic differences when you study a diabetic versus non-diabetic population?

Dr. Goto: Yes, that is a very important topic, and we have very nice review paper by Dr. Domenico and Fiorito. In patients with diabetes the platelet time over becomes relatively rapid as compared to general population. New platelets come to blood and COX-1 inhibition by aspirin cannot reach to enough level in diabetes patient. Still, this [inaudible 00:16:57] hypothesis, very interesting hypothesis.

Dr. Saito: I think so, I think so. That review that proposed the same concept, their higher dose of aspirin as possibly effective for diabetic patient.

Dr. Lam: That's interesting. Are you planning any future studies Yoshi?

Dr. Saito: Yeah, maybe two times study.

Dr. Goto: But anyway, the event rate is currently very low than the old [inaudible 00:17:28]. So the sample size should be huge. Huge sample size is needed for the primary prevention setting to analyze the effect of aspirin, so the number needed to treat in the primary prevention setting is more than 1000. If diabetes patient, aspirin is resistant to aspirin so the number needed to treat is getting larger. So the sample size is getting larger and larger. That is not practical to perform that clinical trial.

Dr. Lam: That's a very good point that the contemporary trials like yours are really challenged by the low event rates because of improved preventive treatment across the board like high dose statins, like very, very low LDL targets, and so on. That's a good point. Actually, could I ask both of you gentlemen, and maybe Shinya you can start, can you let us know what is it like to perform such a large rigorous clinical trial in Japan? It must be a lot of effort. Could you give us an idea?

Dr. Goto: In Japan, medical care system is a little bit different from the U.S. Every patient covered by the homogeneous health care system so it means it is rather difficult to conduct a clinical trial. I appreciate the effort by Professor Saito, Yoshi, it is extremely difficult to conduct the study. Japan is relatively small island, patient stick to the clinic so the long term follow up with relatively low follow up can be expected. [inaudible 00:19:15] number of patients is a challenge, and Yoshi did succeed it. We can do that and due to the baseline therapy is quite homogenous, impact of the clinical care like this has very strong impact.

Dr. Lam: Exactly, and I share your congratulations once again to Yoshi for really tremendous effort, important results. Thank you so much Shinya for helping with this paper, and for really highlighting how really important it is. Did anyone have anything else to add?

Dr. Saito: Yes, I have one thinking, in respect to the Japanese clinical trials. I think the Japanese evidence, as derived from Japanese clinical studies is getting better and better in quality. Almost all Japanese clinical trials enrolled only Japanese patients, so the way the Japanese not so good at to organize the international clinical trial because of the, one is the language problem, and the other is funding problem. In Japanese funding agency, the AMED, that is similar to the NIH in United States, but AMED is not so strong as NIH so that they cannot give a bigger budget to the Japanese clinicians. That is another problem to organize a big clinical trial. The funding [inaudible 00:20:49] apprenticeship without holding investigators are very, very important to be better clinical situation in Japan, I think so.

Dr. Lam: Thank you for listening to Circulation on the Run, don't forget to tune in next week.