Differential Effect of Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Diabetes Management

A subanalysis of the JPAD trial

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OBJECTIVE—Recent reports showed that low-dose aspirin was ineffective in the primary prevention of cardiovascular events in diabetic patients overall. We hypothesized that low-dose aspirin would be beneficial in patients receiving insulin therapy, as a high-risk group.

RESEARCH DESIGN AND METHODS—This study is a subanalysis of the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial—a randomized, controlled, open-label trial. We randomly assigned 2,539 patients with type 2 diabetes and no previous cardiovascular disease to the low-dose aspirin group (81 or 100 mg daily) or to the no-aspirin group. The median follow-up period was 4.4 years. We investigated the effect of low-dose aspirin on preventing atherosclerotic events in groups receiving different diabetes management.

RESULTS—At baseline, 326 patients were treated with insulin, 1,750 with oral hypoglycemic agents (OHAs), and 463 with diet alone. The insulin group had the longest history of diabetes, the worst glycemic control, and the highest prevalence of diabetic microangiopathies. The diet-alone group had the opposite characteristics. The incidence of atherosclerotic events was 26.6, 14.6, and 10.4 cases per 1,000 person-years in the insulin, OHA, and diet-alone groups, respectively. In the insulin and OHA groups, low-dose aspirin did not affect atherosclerotic events (insulin: hazard ratio [HR] 1.19 [95% CI 0.60−2.40]; OHA: HR 0.84 [0.57−1.24]). In the diet-alone group, low-dose aspirin significantly reduced atherosclerotic events, despite the lowest event rates (HR 0.21 [0.05−0.64]).

CONCLUSIONS—Low-dose aspirin reduced atherosclerotic events predominantly in the diet-alone group and not in the insulin or OHA groups.

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Cardiovascular disease is one of the major prognostic factors in patients with diabetes (1,2). Accumulated evidence has shown that low-dose aspirin is effective in the secondary prevention of cardiovascular events (3). Previous studies have suggested that low-dose aspirin is beneficial for primary prevention in members of the general population who are at high risk (4–8); however, its efficacy for patients with diabetes remains controversial (9).

Recently, two large clinical trials—the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial (10) and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial (11)—investigated whether low-dose aspirin reduced cardiovascular events in patients with diabetes but without cardiovascular disease. The JPAD trial, which was conducted by our research group, examined the efficacy of low-dose aspirin for primary prevention of atherosclerotic events in 2,539 Japanese patients with type 2 diabetes. The trial demonstrated that low-dose aspirin reduced atherosclerotic events by 20%, but statistical significance was not reached (10). The overall event rate was 17 cases per 1,000 person-years, which was one-third of the expected event rate at the start of the trial (10). Thus there might have been too few events to precisely estimate the effect of aspirin. The POPADAD trial, which registered 1,276 patients with either type 1 or type 2 diabetes in Scotland, also failed to document an effect of aspirin (11). It was determined that the POPADAD trial was inconclusive because of insufficient cardiovascular events and low compliance with aspirin therapy.

Recently, the American Diabetes Association (ADA), the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) jointly recommended the use of low-dose aspirin for primary prevention of cardiovascular

events only in high-risk diabetic patients (12). Previous epidemiological studies have reported that diabetic patients undergoing insulin therapy have increased mortality compared with those receiving therapy with oral hypoglycemic agents (OHAs) or diet alone (13,14). Therefore, patients treated with insulin, defined to be a high-risk group, are considered to be the most likely to benefit from low-dose aspirin therapy.

In this subanalysis of the JPAD trial, we hypothesized that low-dose aspirin would be most beneficial for primary prevention in diabetic patients receiving insulin therapy. We investigated the effect of low-dose aspirin on preventing atherosclerotic events in groups categorized according to type of diabetes management at baseline.

RESEARCH DESIGN AND METHODS

Study design
The JPAD trial was a multicenter, prospective, randomized, open-label, blinded, end point trial conducted at 163 institutions throughout Japan. This trial was performed according to the Declaration of Helsinki and approved by the institutional review board at each participating hospital. Written informed consent was obtained from each participant before the trial.

The detailed design of the JPAD trial has been previously described (10). In brief, we enrolled 2,539 patients, aged between 30 and 85 years, with type 2 diabetes and no history of cardiovascular disease. The participants were randomly assigned to the aspirin group or the no-aspirin group. The 1,262 patients in the aspirin group were assigned to take 81 mg or 100 mg of aspirin once daily. The 1,277 patients in the no-aspirin group were allowed to use antiplatelet therapy, including aspirin, if needed. All patients were allowed to use any concurrent treatments.

In this subanalysis, we classified all participants into three subgroups according to the diabetes management at baseline: insulin, OHA, or diet alone. Patients with insulin and OHA combination therapy were included in the insulin group. The diet-alone group consisted of patients who used neither insulin nor OHAs. The median follow-up period was 4.4 years. A total of 193 patients were lost to follow-up, and data for those patients were censored at the day of last follow-up.

The Consolidated Standards of Reporting Trials (CONSORT) diagram for the JPAD trial was presented previously (10).

Definition of atherosclerotic events
The primary end point was the occurrence during the follow-up period of any atherosclerotic event, which was a composite of the following: death 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. All potential end points and hemorrhagic events (gastrointestinal bleeding and hemorrhagic stroke) were adjudicated by an independent committee that was blinded to the group assignments.

Presentation of hemoglobin A_{1c} level
Hemoglobin A_{1c} (HbA_{1c}) values were converted from the Japanese Diabetes Society (JDS) values used in the main analysis of the JPAD trial (10) into National Glycohemoglobin Standardization Program (NGSP) equivalent values. NGSP equivalent values were calculated using the following formula: NGSP equivalent value (%) = JDS value (%) + 0.4 (15).

Statistical analyses
Categorical variables were expressed as number and percentage and were compared with the χ^2 test. Continuous variables were expressed as mean values ± SDs unless otherwise indicated. Based on their distribution, continuous variables were compared using the Student t test or Wilcoxon rank sum test for two-group comparisons and ANOVA or Kruskal-Wallis test for three-group comparisons. Cumulative incidence was estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test.

Efficacy comparisons were performed on the basis of time to the first event according to the intention-to-treat principle, with all patients included in the group to which they were randomized and with patients lost to follow-up censored at the day of the last visit. Cumulative incidences of end points were estimated by the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. We used the Cox proportional hazard model to estimate the hazard ratio (HR) of aspirin use along with the 95% CI. We also developed multivariable Cox proportional hazard models to assess the effects of aspirin on atherosclerotic events adjusting for age (≥65 years), hypertension, dyslipidemia, and history of smoking to evaluate the robustness.

Statistical analyses were conducted by an independent statistician (T.M.) with the use of JMP 8.0 (SAS Institute, Cary, NC) software and SAS 9.2 (SAS Institute). P values of less than 0.05 were considered statistically significant.

RESULTS

Baseline clinical characteristics
At baseline, 326 patients were treated with insulin, 1,750 with OHAs, and 463 with diet alone (Table 1). The mean age was slightly lower in the insulin group (62 years) than the other groups (65 years). Mean BMI was lowest in the insulin group (23 kg/m^2) and highest in the diet-alone group (25 kg/m^2). Median duration of diabetes was longest in the insulin group: 13.0 years in the insulin group, 7.2 years in the OHA group, and 3.5 years in the diet-alone group. Mean levels of HbA_{1c} and fasting plasma glucose (FPG) were 8.1% and 8.77 mmol/L in the insulin group, 7.6% and 8.27 mmol/L in the OHA group, and 6.7% and 7.22 mmol/L in the diet-alone group. The prevalence of diabetic microangiopathies was highest in the insulin group (retinopathy, 43%; nephropathy, 20%; neuropathy, 32%) and lowest in the diet-alone group (retinopathy, 4%; nephropathy, 8%; neuropathy, 4%).

The frequency of other cardiovascular risk factors was also investigated at baseline (Table 1). The prevalence of hypertension and dyslipidemia was significantly higher in the diet-alone group (hypertension, 72%; dyslipidemia, 56%) than in the other two groups. The use of statins was low in all groups: 18, 27, and 24% in the insulin, OHA, and diet-alone groups, respectively. Smoking history and family history of cardiovascular diseases were similar among groups.

Atherosclerotic events in each diabetes management
The incidence of atherosclerotic events was 26.6, 14.6, and 10.4 cases per 1,000 person-years in the insulin, OHA, and diet-alone groups, respectively (Supplementary Table 1). Both coronary artery and cerebrovascular events occurred most frequently in the insulin group (coronary artery events, 12.1; cerebrovascular events, 12.1 cases per

Table 1—*Baseline characteristics by diabetes management*

Diabetes management	Insulin	OHA	Diet alone	P value
n	326	1,750	463	
Age (years)	62 (10)	65 (10)	65 (10)	<0.0001
Male, n (%)	184 (56)	952 (54)	251 (54)	0.8
BMI (kg/m^2)	23 (4)	24 (4)	25 (4)	<0.0001
Duration of diabetes (years)	13.0 (7.7–19.1)	7.2 (3.3–12.1)	3.5 (1.0–7.6)	<0.0001
HbA$_{1c}$ (%)	8.1 (1.5)	7.6 (1.3)	6.7 (0.8)	<0.0001
FPG (mmol/L)	8.77 (3.16)	8.27 (2.78)	7.22 (1.78)	<0.0001
Serum creatinine (μmol/L)	71 (27)	71 (27)	71 (18)	0.8
Proteinuria, n (%)	58 (18)	240 (14)	48 (10)	0.01
Diabetic retinopathy, n (%)	140 (43)	205 (12)	20 (4)	<0.0001
Diabetic nephropathy, n (%)	66 (20)	220 (13)	36 (8)	<0.0001
Diabetic neuropathy, n (%)	104 (32)	176 (10)	20 (4)	<0.0001
Diabetes medications, n (%)				
Sulfonylurea	27 (8)	1,420 (81)	0 (0)	<0.0001
α-Glycosidase inhibitor	88 (27)	748 (43)	0 (0)	<0.0001
Biguanide	37 (11)	317 (18)	0 (0)	<0.0001
Thiazolidinedione	9 (3)	119 (7)	0 (0)	<0.0001
Insulin	326 (100)	0 (0)	0 (0)	–
Family history of diabetes, n (%)	153 (47)	731 (42)	155 (33)	0.0003
Complications of other cardiovascular risk factors, n (%)				
Hypertension	156 (48)	983 (56)	334 (72)	<0.0001
Dyslipidemia	132 (40)	953 (54)	260 (56)	<0.0001
History of smoking	146 (45)	731 (42)	182 (39)	0.3
Family history of cardiovascular diseases, n (%)				
Coronary artery disease	38 (12)	198 (11)	54 (12)	0.96
Stroke	71 (22)	360 (21)	95 (21)	0.9

Data are mean (SD) or n (%); duration of diabetes data are median (interquartile range). BMI was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or therapy with antihypertensive agents. Dyslipidemia was defined as total cholesterol level ≥5.7 mmol/L, fasting triglyceride level ≥1.7 mmol/L, or therapy with antilipidemic agents.

1,000 person-years). There was a low incidence of peripheral vascular events among the three groups (insulin, 2.4; OHA, 1.7; diet alone, 1.6 cases per 1,000 person-years). Survival analysis showed that the rate of atherosclerotic events was significantly higher in the insulin group than those in the other groups (log-rank test, P = 0.0013; Fig. 1).

Efficacy of low-dose aspirin in each diabetes management
Participants were randomly assigned to the aspirin group or the no-aspirin group (Supplementary Table 2). In the insulin group, low-dose aspirin did not affect the incidence of atherosclerotic events (HR 1.19 [95% CI 0.60–2.40]; log-rank test, P = 0.61; Fig. 2A). Similar results were observed in the OHA group (HR 0.84 [0.57–1.24]; log-rank test, P = 0.38; Fig. 2B). On the other hand, in the diet-alone group, low-dose aspirin significantly reduced atherosclerotic events despite the fact that this group had the lowest atherosclerotic event rate (HR 0.21 [0.05–0.64]; log-rank test,

P = 0.0069; Fig. 2C). Adjusting for age, hypertension, dyslipidemia, and history of smoking, low-dose aspirin significantly reduced atherosclerotic events in the diet-alone group (HR 0.20 [0.06–0.68]; log-rank test, P = 0.0099) but not in the insulin or OHA groups (insulin: HR 1.0 [0.50–2.00], log-rank test, P = 1.0; OHA: HR 0.77 [0.52–1.14], log-rank test, P = 0.20).

Hemorrhagic events
The number of gastrointestinal bleeding and hemorrhagic strokes was very low overall and seemed similar between the aspirin and no-aspirin groups in each diabetes management. The number of gastrointestinal bleeding was one in the insulin group (this patient took aspirin) and seven in the OHA group (four in the aspirin group and three in the no-aspirin group). In the diet-alone group, no patients suffered from gastrointestinal bleeding. The number of hemorrhagic stroke was two in the insulin group (one in the aspirin group and one in the no-aspirin group), nine in the OHA group (five in the aspirin group and four in the

no-aspirin group), and two in the diet-alone group (all in the no-aspirin group).

CONCLUSIONS—The major findings of this subanalysis were as follows: Japanese patients with type 2 diabetes receiving insulin therapy had a high incidence of atherosclerotic events and low-dose aspirin reduced atherosclerotic events not in patients receiving insulin therapy but in patients treated with diet alone. These results were unchanged after adjusting for other cardiovascular risk factors.

The patients' baseline characteristics categorized by diabetes management obviously demonstrated the difference in diabetes status (Table 1). The insulin group was characterized by the youngest mean age (62 years) and the longest median duration of diabetes (13.0 years), which meant that patients in the insulin group developed diabetes at the youngest age among the three groups. In contrast, patients in the diet-alone group developed diabetes in recent years and at older age. The slightly but significantly low BMI in the insulin group (mean BMI, 23 kg/m^2)
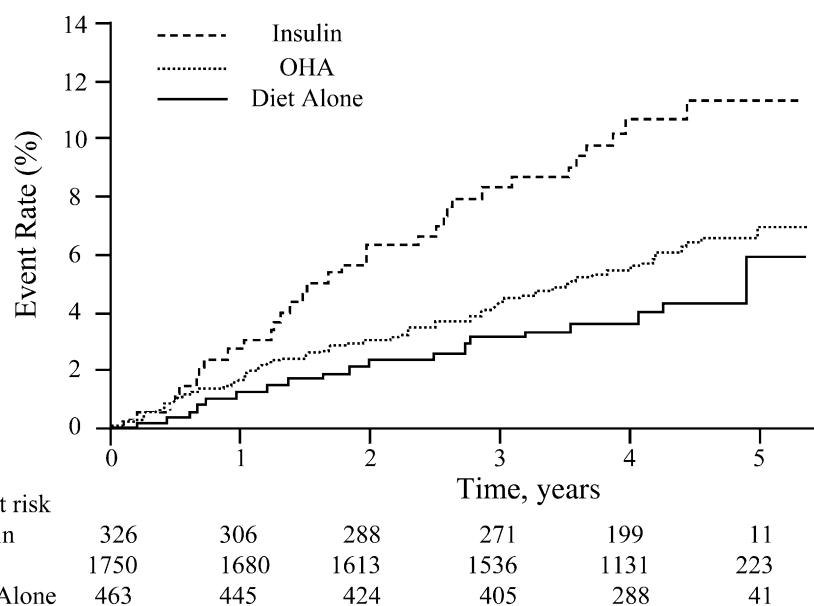
No. at risk

Insulin	326	306	288	271	199	11
OHA	1750	1680	1613	1536	1131	223
Diet Alone	463	445	424	405	288	41

Figure 1—*Incidence of atherosclerotic events in each diabetes management. Survival analysis showed that the rate of atherosclerotic events was significantly higher in the insulin group (log-rank test,* P = 0.0013).

might be a reflection of insufficient insulin secretion. The glycemic control was worst in the insulin group (mean levels of HbA_{1c} and FPG, 8.1% and 8.77 mmol/L) and best in the diet-alone group (mean levels of HbA_{1c} and FPG, 6.7% and 7.22 mmol/L). The prevalence of diabetic microangiopathies was highest in the insulin group ($\geq 20\%$) and lowest in the diet alone group ($<10\%$). There are no definitive criteria defining clinical stages of diabetes; however, it is usually classified according to the extent of vascular complications or the level of glycemic control. Thus we could regard the insulin group as demonstrating an advanced clinical stage of diabetes and the diet-alone group as demonstrating a less advanced or earlier clinical stage of diabetes than the insulin and OHA groups. Our results might indicate that low-dose aspirin was most beneficial in early clinical stages of diabetes, despite the lowest event rates.

Recently, we reported that a subanalysis of the JPAD trial showed a difference in low-dose aspirin effect on primary prevention of atherosclerotic events in renal function (16). In the study, reduced renal function in diabetic patients was significantly associated with high incidence of atherosclerotic events. Low-dose aspirin did not prevent atherosclerotic events in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (HR 1.3 [95% CI 0.76−2.4]). On the other hand, in the patients with an eGFR of 60

to 89 mL/min/1.73 m^2, low-dose aspirin significantly reduced atherosclerotic events, despite low event rates (HR 0.57 [0.36−0.88]) (16). As in the current study, low-dose aspirin was not beneficial in patients with advanced stages of renal dysfunction and with high event rates but rather in those with early stages of renal dysfunction and with low event rates. These results suggest that progression of diabetes and diabetes complications (renal dysfunction) might attenuate the effect of low-dose aspirin.

The current recommendation of the ADA, AHA, and ACCF regarding the preventative use of aspirin in high-risk diabetic patients is based on the number of cardiovascular events prevented by low-dose aspirin (relative risk reduction of ~10%) being greater than the number of hemorrhagic events (1−5 cases per 1,000 person-years) (12). Therefore, low-dose aspirin use depends on individual cardiovascular risk. Because diabetic patients with higher cardiovascular risk should have greater absolute benefit from low-dose aspirin, our findings were unexpected and inconsistent with the recommendation. To confirm whether low-dose aspirin is really effective in high-risk or low-risk diabetic patients, further investigations are needed.

One possible mechanism of our findings is that events in patients with advanced clinical stages of diabetes are unpreventable because of overly advanced atherosclerotic

lesions. Another possible mechanism is aspirin resistance in diabetic patients with poor glycemic control. Aspirin resistance is often described as a phenomenon whereby patients develop cardiovascular disease despite aspirin intake. The details surrounding aspirin resistance remain obscure, but it is thought to be affected by underlying interindividual variability (17). Increased platelet aggregation has been observed in patients with diabetes (18). Several studies have reported that aspirin's antiplatelet function is lower in diabetic patients than in nondiabetic patients (19) and that the frequency of aspirin resistance is positively correlated with the levels of HbA_{1c} and FPG (20). Higher aspirin doses have been shown to improve aspirin resistance in patients with diabetes (19). In our study, poor glycemic control in the insulin group might diminish the effects of aspirin via commonly occurring aspirin resistance. Increasing aspirin dosage may improve antiplatelet function, but there are insufficient data regarding the effect of high-dose aspirin on the prevention of cardiovascular events at this time (12). Combination therapy with aspirin and other antiplatelet agents, such as clopidogrel, suppresses platelet aggregation more strongly (19), but the benefit of dual antiplatelet therapy on primary prevention is also inconclusive (21).

The differing prevalence of other cardiovascular risk factors among patients in the various diabetic treatment groups might alter the low-dose aspirin effect on primary prevention of atherosclerotic events. In the diet-alone group, a high prevalence of hypertension (72%) and dyslipidemia (56%), high age (mean age, 65 years), mild overweight (mean BMI, 25 kg/m^2), and mild glucose intolerance (mean levels of HbA_{1c} and FPG, 6.7% and 7.22 mmol/L) might indicate that these patients could be considered to have multiple cardiovascular risk factors rather than overt diabetes. In fact, previous clinical trials of primary prevention in patients with multiple cardiovascular risk factors showed that low-dose aspirin reduced cardiovascular events (5–7), whereas no trial provided a definitive conclusion regarding patients with diabetes (9–11). The Primary Prevention Project (PPP) trial reported a difference in the effect of low-dose aspirin on primary prevention between patients with and without overt diabetes (22). The PPP trial enrolled 4,495 patients with at least one major cardiovascular risk factor,
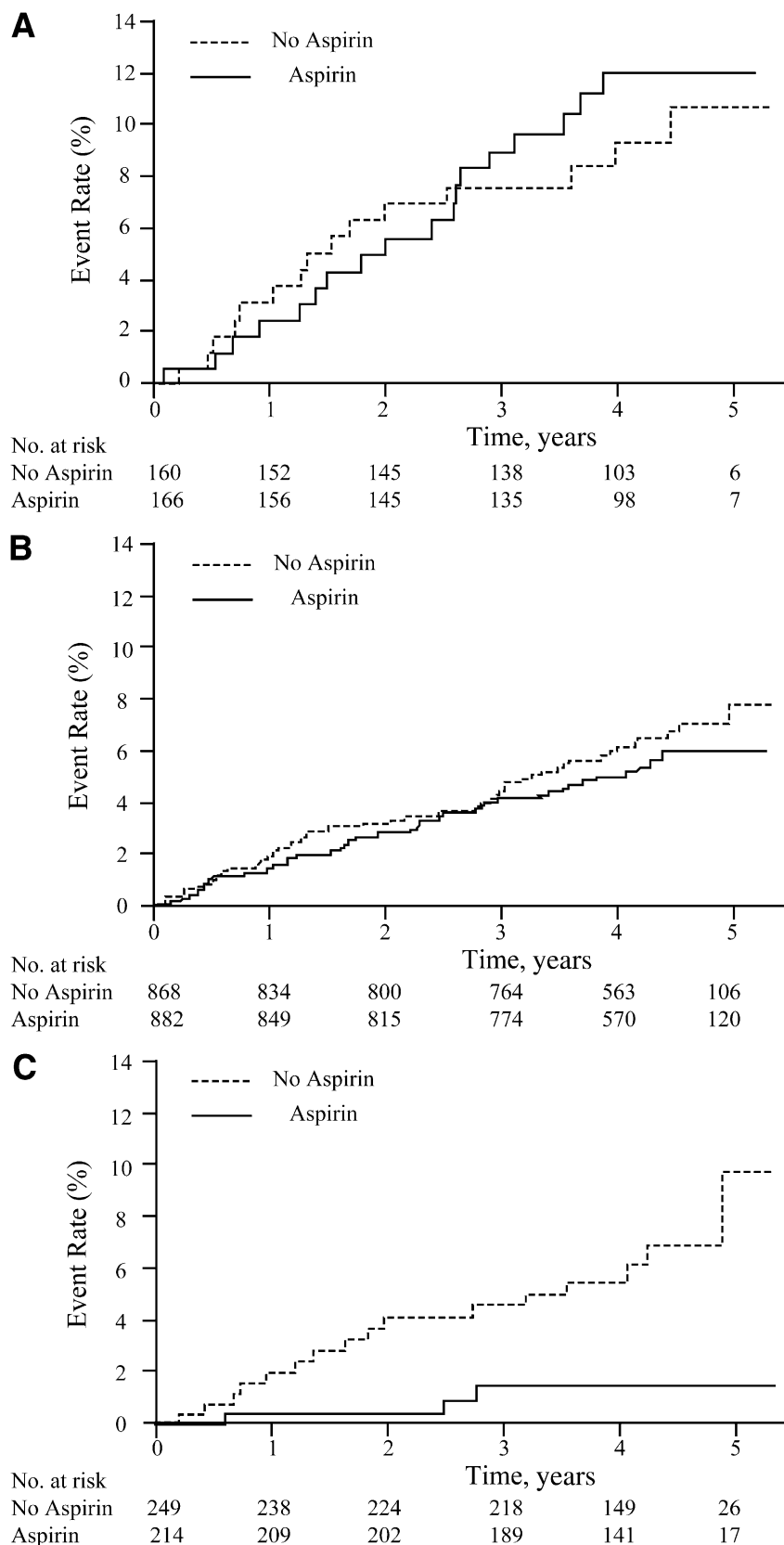
Figure 2—*Efficacy of low-dose aspirin on primary prevention of atherosclerotic events in each diabetes management. A and B: In the insulin (A) and OHA (B) groups, low-dose aspirin did not affect the incidence of atherosclerotic events (insulin: HR 1.19 [95% CI 0.60−2.40]; log-rank test, P = 0.61; OHA: HR 0.84 [0.57−1.24]; log-rank test, P = 0.38). C: In the diet-alone group, low-dose aspirin significantly reduced atherosclerotic events despite the lowest event rates (HR 0.21 [0.05−0.64]; log-rank test, P = 0.0069).*

including 1,031 patients with overt diabetes (FPG ≥7.8 mmol/L or treated with OHAs). This trial showed that low-dose aspirin lowered the incidence of cardiovascular events by 33% in total (7); however, in the diabetic group, low-dose aspirin did not reduce cardiovascular events despite 50% higher event rates (22). These reports might confirm that low-dose aspirin was beneficial in the diet-alone group, as a subset of patients in the early clinical stages of diabetes and with comorbid other cardiovascular risk factors.

Recent meta-analyses, including data from the JPAD trial, reported that low-dose aspirin is not effective in the primary prevention of cardiovascular events in patients with diabetes (9,23). Patients treated with insulin are at high risk for cardiovascular events; however, our findings indicated that low-dose aspirin reduced atherosclerotic events not in the insulin group but in the diet-alone group. These results suggest that low-dose aspirin therapy is most beneficial in early clinical stages of diabetes. When clinicians use low-dose aspirin in diabetic patients to prevent cardiovascular events, they should take into account not only conventional cardiovascular risk factors but also the clinical stage of diabetes. Further studies are needed to assess the effect of low-dose aspirin at each clinical stage of diabetes.

Study strengths and limitations

Our project is the first report to estimate the effect of low-dose aspirin on the primary prevention of atherosclerotic events in groups undergoing various diabetes management strategies. Our results suggest that the clinical impact of low-dose aspirin depends on the clinical stage of diabetes. However, this subanalysis has several limitations in addition to those reported in the main JPAD report (10).

First, we used the management of diabetes at baseline as a subgrouping variable. As with other variables, the management modality could change over time. Such changes could be especially frequent in the diet-alone and OHA groups as they begin to require more intensive treatment, and as a result the subgrouping might not be valid. Second, the small number of patients in each treatment group, especially in the insulin group, limited the certainty with which we could formulate conclusions regarding aspirin's effect. Larger studies are needed for definitive evaluation of the effect of aspirin in

patients treated with insulin. Third, several OHAs are reported to be beneficial for preventing cardiovascular events (e.g., metformin [24] and pioglitazone [25]), but we analyzed the OHA group without taking specific drug properties into account. Since most patients (81%) in the OHA group took sulfonylurea at baseline, we could not assess the single-agent effects of the cardioprotective OHAs. Finally, the number of hemorrhagic events was very low in both the aspirin and no-aspirin groups; however, the sample sizes were too small to estimate aspirin's side effects in the JPAD trial. Therefore, we could not make firm conclusions about the safety of low-dose aspirin based on our results.

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