Efficacy of Low-Dose Aspirin Therapy for the Primary Prevention of Atherosclerotic Events in Type 2 Diabetic Patients: The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial

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***On behalf of all JPAD Investigators**

Disclosure Information

Hisao Ogawa, MD, PhD

- Efficacy of Low-Dose Aspirin Therapy for the Primary Prevention of Atherosclerotic Events in Type 2 Diabetic Patients

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Background

- Risk of CV events is increased from 2- to 4-fold in type 2 diabetes[1]
- Aspirin is recommended for primary prevention in patients with type 2 diabetes in many guidelines, including AHA[2,3]
- Previous aspirin primary prevention trials have had diabetic subgroups but data from European and North American populations were limited[4,5] and nonexistent from Japan

1. Haffner SM, et al. *N Engl J Med*. 1998;339:229-234; 2. American Diabetes Association. *Diabetes Care*. 2007;30(suppl 1):S4-S41; 3. AHA/ADA Scientific Statement. *Circulation*. 2007;115:114-126; 4. Antithrombotic Trialists' Collaboration. *BMJ.* 2002;324:71-86; 5. Sacco M, et al. *Diabetes Care.* 2003;26: 3264-3272.

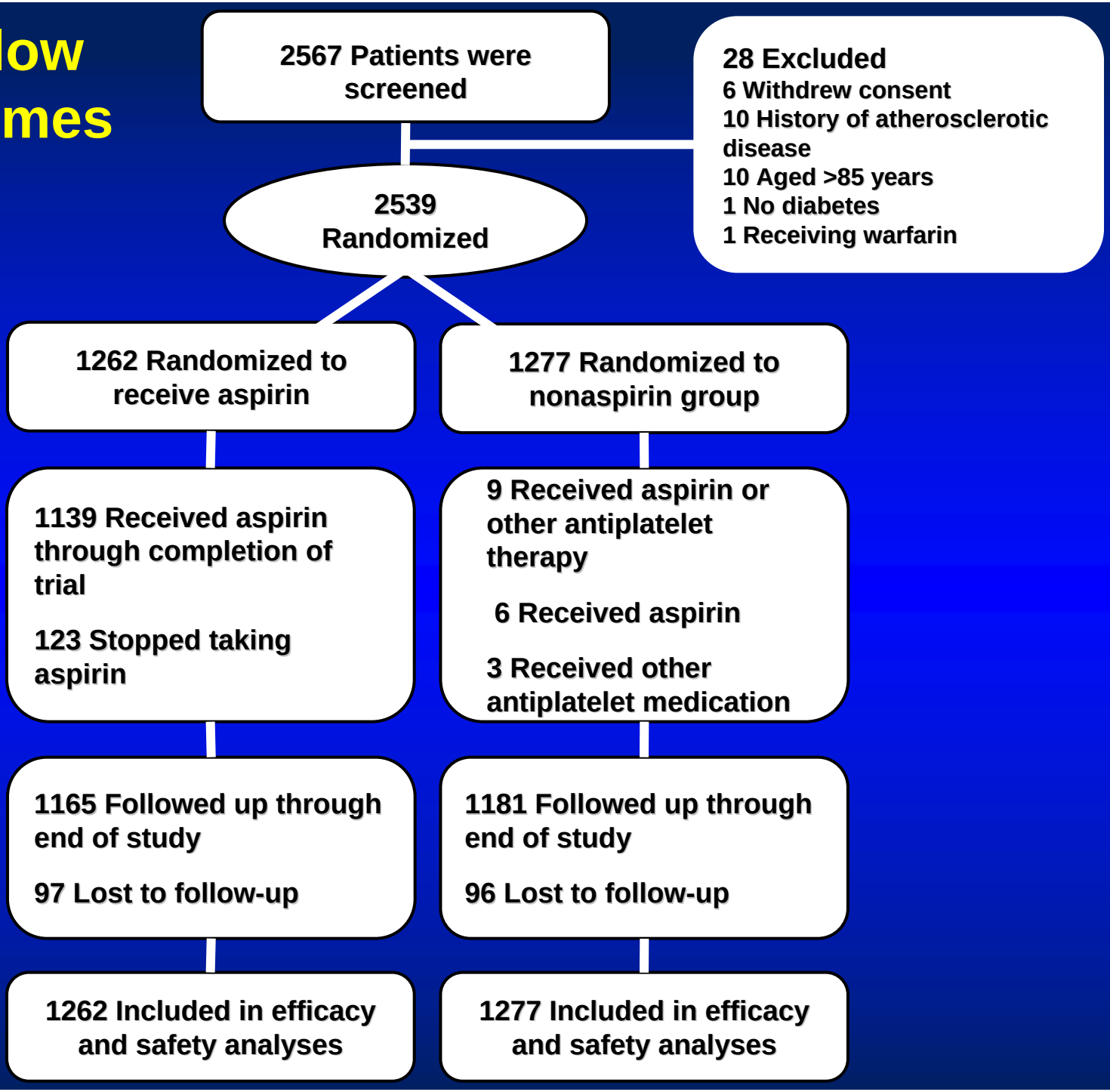
JPAD Overview

- Design: Prospective, randomized, open-label, controlled trial with blinded end point assessment (PROBE)
  - Patients randomized to low-dose aspirin group (81 or 100 mg/day) or nonaspirin group
  - Conducted at 163 institutions in Japan from December 2002 to May 2005 with follow-up to April 2008
- Inclusion Criteria: Type 2 diabetes between ages 30 and 85 years
- Exclusion Criteria: Coronary, cerebrovascular, or other arteriosclerotic disease, atrial fibrillation, history of severe gastric or duodenal ulcer, and use of antiplatelet or antithrombotic medication

JPAD End Points

- Primary end point: any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis)
- Secondary end points: Each primary end point and combinations of primary end points and death from any cause
- Adverse events analyzed included gastrointestinal events and any hemorrhagic events other than hemorrhagic stroke

Patient Flow and Outcomes

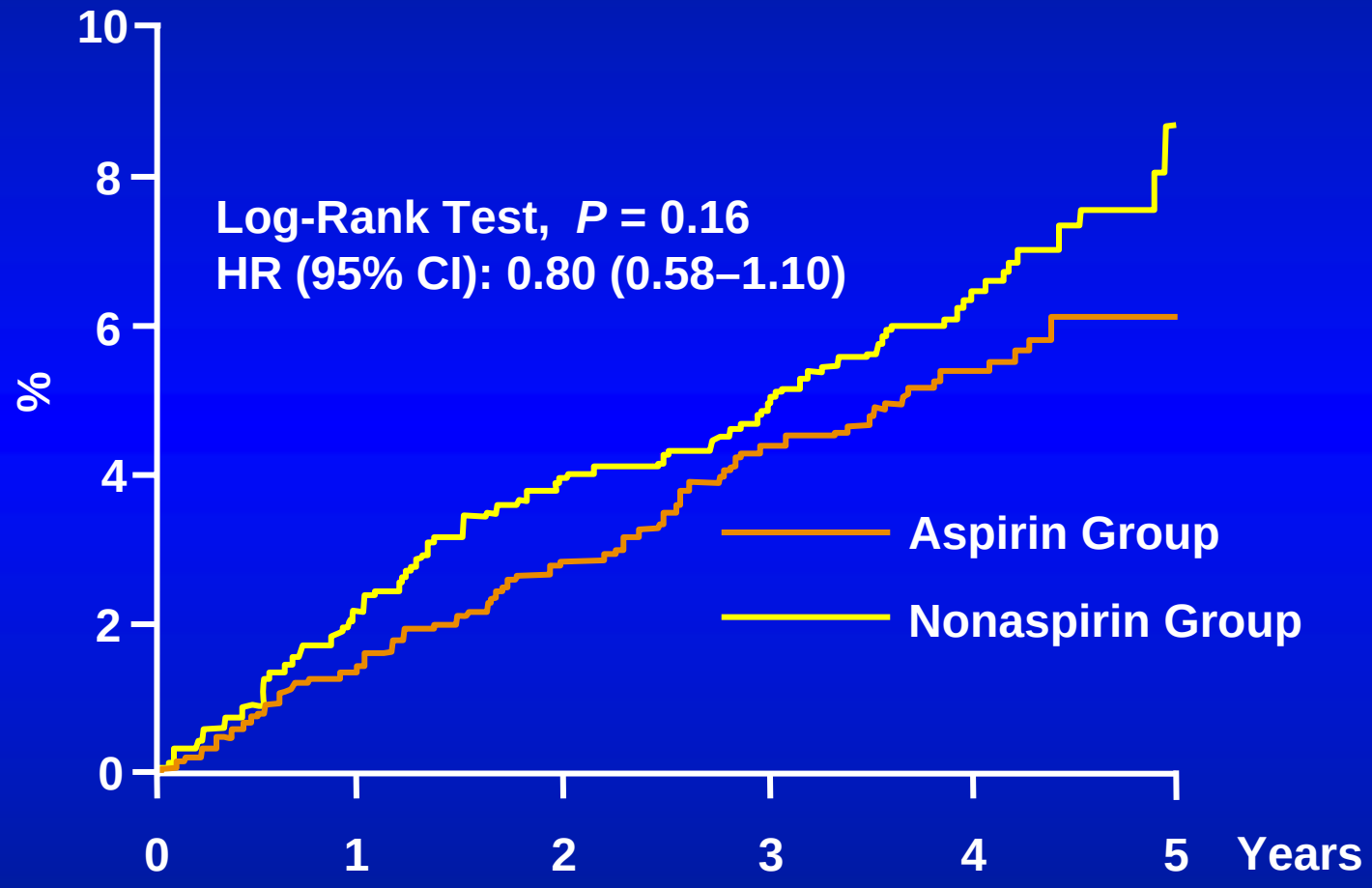


Baseline Clinical Characteristics

Characteristic	Aspirin Group (n = 1262)	Nonaspirin Group (n = 1277)
Age (y)*	65 ± 10	64 ± 10
Male, n (%)	706 (56)	681 (53)
Current smoker, n (%)	289 (23)	248 (19)
Body mass index (kg/m^2)*	24 ± 4	24 ± 4
Hypertension, n (%)	742 (59)	731 (57)
Dyslipidemia, n (%)	680 (54)	665 (52)
Duration of diabetes (y), median (IQR)	7.3 (2.8-12.3)	6.7 (3.0-12.5)
Systolic blood pressure (mm Hg)*	136 ± 15	134 ± 15
Diastolic blood pressure (mm Hg)*	77 ± 9	76 ± 9

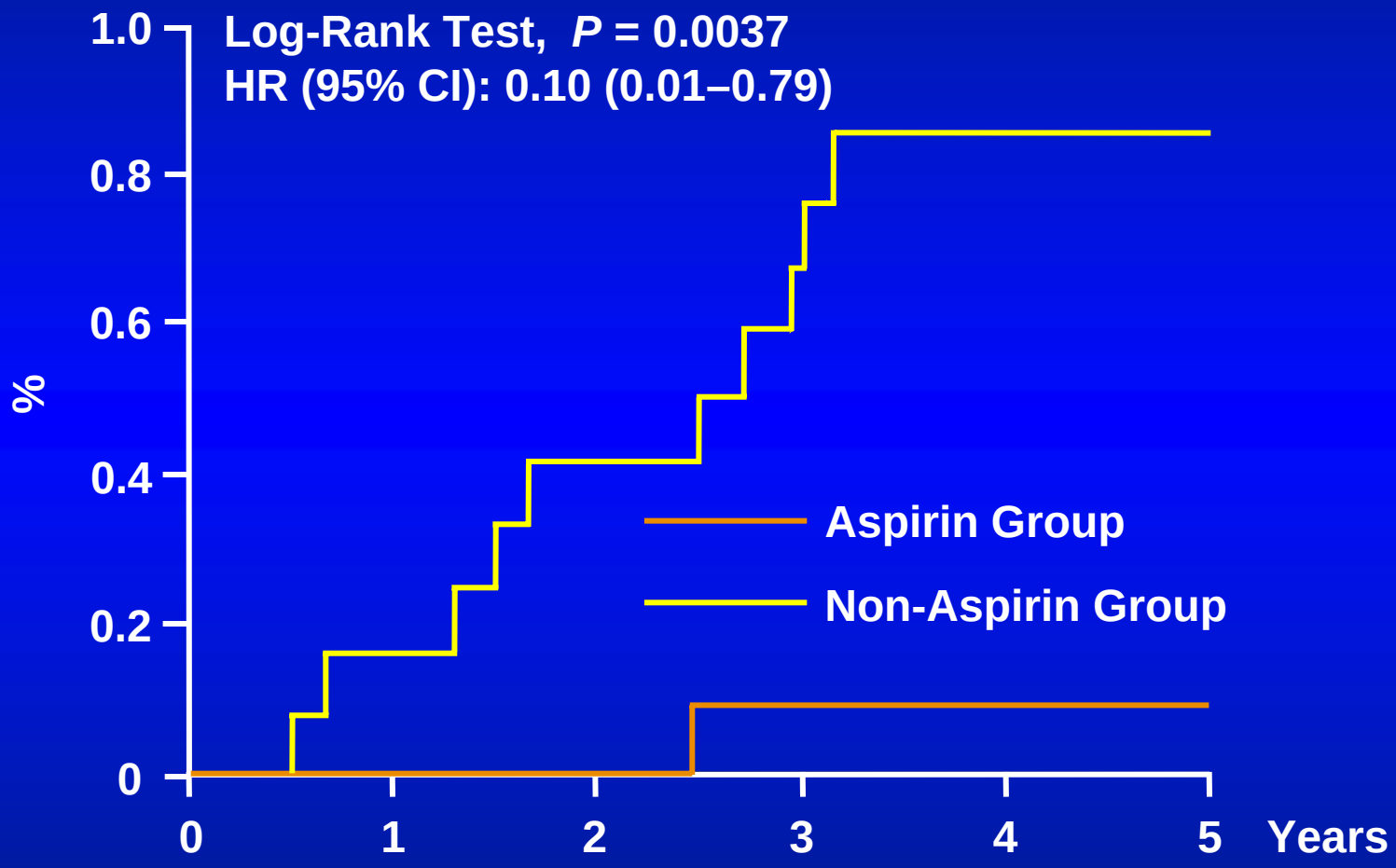
*Mean ± SD.

Primary End Point: Total Atherosclerotic Events According to the Treatment Groups



Nonaspirin Group (n)	1277	1220	1165	1117	813	135
Aspirin Group (n)	1262	1210	1159	1095	806	140

Fatal Coronary and Cerebrovascular Events According to the Treatment Groups



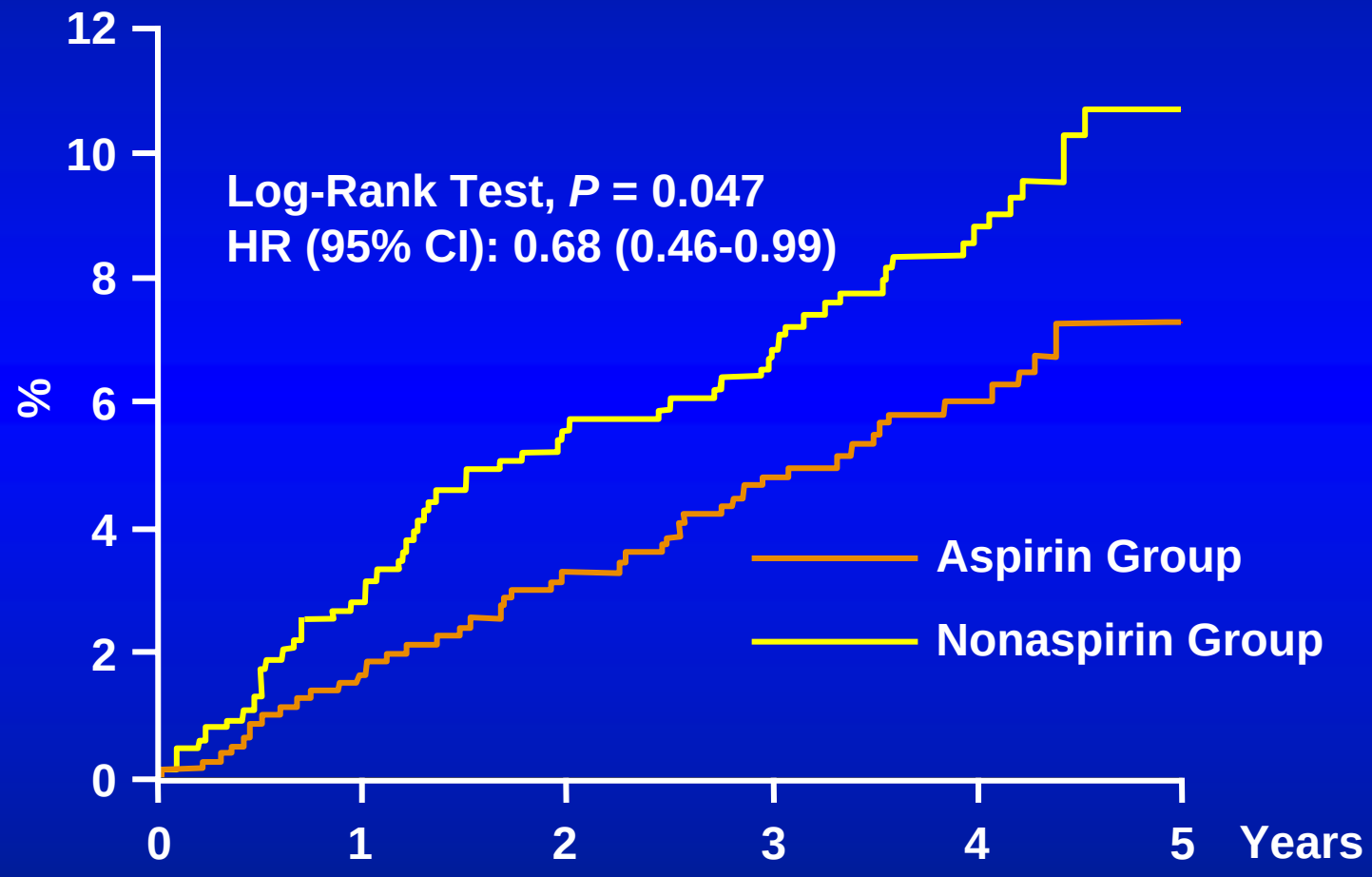
Nonaspirin Group (n)	1277	1220	1165	1117	813	135
Aspirin Group (n)	1262	1210	1159	1095	806	140

Other End Points

	Aspirin Group n (%)	Nonaspirin Group n (%)	HR	95% CI	*P* Value
CHD events (fatal + nonfatal)	28 (2.2)	35 (2.7)	0.81	0.49–1.33	0.40
Fatal MI	0 (0)	5 (0.4)			
Nonfatal MI	12 (1.0)	9 (0.7)	1.34	0.57–3.19	0.50
Unstable angina	4 (0.3)	10 (0.8)	0.40	0.13–1.29	0.13
Stable angina	12 (1.0)	11 (0.9)	1.10	0.49–2.50	0.82
Stroke (fatal + nonfatal)	28 (2.2)	32 (2.5)	0.84	0.53–1.32	0.44
Fatal stroke	1 (0.08)	5 (0.4)	0.20	0.024–1.74	0.15
Nonfatal stroke (ischemic)	22 (1.7)	24 (1.9)	0.93	0.52–1.66	0.80
Nonfatal stroke (hemorrhagic)	5 (0.4)	3 (0.2)	1.68	0.40–7.04	0.48
Transient ischemic attack	5 (0.4)	8 (0.6)	0.63	0.21–1.93	0.42
Peripheral artery disease*	7 (0.6)	11 (0.9)	0.64	0.25–1.65	0.35
Total mortality	34 (2.7)	38 (3.0)	0.90	0.57–1.14	0.67

*Arteriosclerosis obliterans (5 in aspirin group and 8 in nonaspirin group); aortic dissection (2 fatal in the aspirin group and 1 nonfatal in the nonaspirin group); mesenteric artery thrombosis (1 in the nonaspirin group) and retinal artery thrombosis (1 in the nonaspirin group).

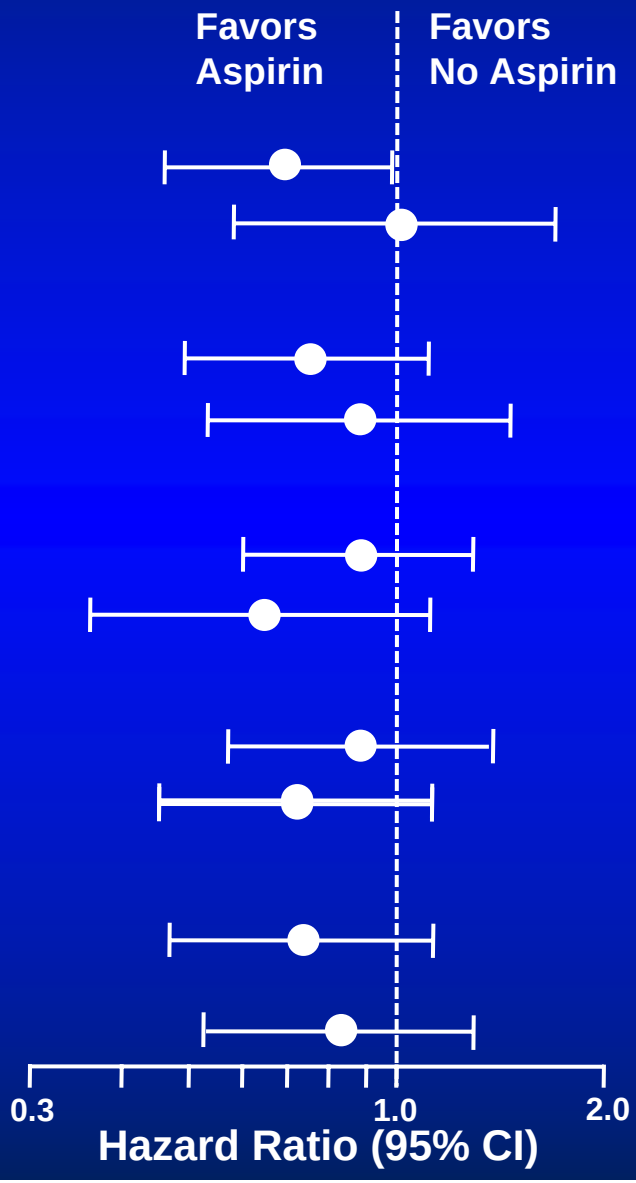
Total Atherosclerotic Events According to the Treatment Groups: Subgroup—Aged 65 Years or Older



Nonaspirin Group (n)	644	612	582	553	396	73
Aspirin Group (n)	719	683	656	619	452	77

Subgroup Analysis

	Events, No./Total No.		
	Aspirin Group	Nonaspirin Group	Hazard Ratio (95% CI)
Age, y			
≥65	45/719	59/644	0.68 (0.46–0.99)
<65	23/543	27/633	1.0 (0.57–1.70)
Gender			
Male	40/706	51/681	0.74 (0.49–1.12)
Female	28/556	35/596	0.88 (0.53–1.44)
Hypertensive Status			
Hypertensive	49/742	55/731	0.88 (0.60–1.30)
Normotensive	19/520	31/546	0.64 (0.36–1.13)
Lipid Status			
Dyslipidemia	38/680	43/665	0.88 (0.57–1.37)
Normolipidemia	30/582	43/612	0.71 (0.45–1.14)
Smoking			
Current or past smoker	36/565	42/494	0.73 (0.47–1.14)
Nonsmoker	32/697	44/783	0.83 (0.53–1.31)



Adverse Events

- No difference between aspirin group (10 patients) and nonaspirin group (7 patients) for composite of hemorrhagic stroke and severe GI bleeding
  - 4 cases of severe gastrointestinal (GI) bleeding that required transfusion in aspirin group
  - 6 hemorrhagic strokes (1 fatal) in aspirin group and 7 hemorrhagic strokes (4 fatal) in nonaspirin group

Summary

- In JPAD, low-dose aspirin was associated with an important, but not statistically significant reduction in the primary end point of total atherosclerotic events
- Secondary end point of coronary and cerebrovascular mortality was reduced significantly by low-dose aspirin
- For other coronary, cerebrovascular, and peripheral vascular end points, aspirin did not have a statistically significant effect
- Aspirin was associated with a large, statistically significant reduction in total events in the subgroup of patients ≥65 years old
- Aspirin was well tolerated with no increase in fatal hemorrhagic strokes and a small nonsignificant increase in serious GI hemorrhages
- In a Japanese population where hemorrhagic strokes are more common, low-dose aspirin did not increase the risk of hemorrhagic strokes

Conclusions

- JPAD was the largest primary prevention trial of aspirin in type 2 diabetes
- Although the effect of low-dose aspirin was not statistically significant for the primary end point, a significant effect was demonstrated on fatal coronary and fatal cerebrovascular events. The trial also suggests that low-dose aspirin might reduce total events in older patients.
- JPAD supports the safety of using low-dose aspirin in diabetics for primary prevention

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

A Randomized Controlled Trial

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Context Previous trials have investigated the effects of low-dose aspirin on primary prevention of cardiovascular events, but not in patients with type 2 diabetes.

Objective To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

Design, Setting, and Participants Multicenter, prospective, randomized, open-label, blinded, end-point trial conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2539 patients with type 2 diabetes without a history of atherosclerotic disease and had a median follow-up of 4.37 years.

Interventions Patients were assigned to the low-dose aspirin group (81 or 100 mg per day) or the nonaspirin group.

Main Outcome Measures Primary end points were atherosclerotic events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary end points included each primary end point and combinations of primary end points as well as death from any cause.

Results A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the nonaspirin group (17.0 per 1000 person-years) (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, $P=.16$). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; $P=.0037$). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, $P=.67$). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.

Conclusion In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

Trial Registration clinicaltrials.gov Identifier: NCT00110448

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DIABETES MELLITUS IS A POWERful risk factor for cardiovascular events. The Framingham Heart Study reported that diabetes was associated with odds ratios for coronary heart disease of 1.5 and 1.8 for men and women, respectively, and relative risks for stroke of 1.4 and 1.7 for men and women, respectively.[1-3] Individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular events than those without diabetes.[4]

Several earlier investigations have shown that aspirin therapy is established as a secondary prevention strategy for cardiovascular events.[7-9] Clinical guidelines have recommended that individuals with risk factors for coronary heart disease should take aspirin for primary prevention and for secondary prevention; in particular, those with diabetes were considered good candidates for aspirin except for those with contraindications.[10-13] The American Diabetes Association recommends use of aspirin as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk, including those who are older than 40 years or who have additional risk factors, such as family history of coronary heart disease, hypertension, smoking, dyslipidemia, or albuminuria.[14] Nonetheless, the clinical trial data for aspirin in primary preven-

For editorial comment see p 2180.

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JPAD Statistics and Sample Size

- Efficacy comparisons were performed on the basis of the time to the first event, according to the intention-to-treat principle, including patients lost to follow-up censored at the time of the last visit
- Safety analyses were performed on data from all enrolled patients
- Sample size estimates based on adjusted event rates from epidemiologic studies in Japan (Hisayama and Funagata[1,2])
- Sample size estimated for 2450 patients based on a two-sided alpha level of 0.05; power 0.95; enrollment period of 2 years; follow-up period of 3 years after the last enrollment; and 30% risk reduction for an occurrence of atherosclerotic disease by aspirin

1. Fujishima M, et al. *Diabetes*. 1996;45(suppl 3):S14-S16; 2. Tominaga M, et al. *Diabetes Care*.1999;22:920-924.

Concomitant Medications

Characteristic	Aspirin Group (n = 1262)	Nonaspirin Group (n = 1277)
Treatment for Diabetes, n (%)		
Sulfonylureas	737 (58)	710 (56)
Alpha-glucosidase inhibitors	422 (33)	414 (32)
Biguanides	168 (13)	186 (15)
Insulin	166 (13)	160 (13)
Thiazolidinediones	63 (5)	65 (5)
Treatment for Hypertension and Dyslipidemia, n (%)		
Calcium channel blockers (CCB)	436 (35)	440 (34)
Angiotensin-II receptor antagonists	269 (21)	266 (21)
Angiotensin-converting enzyme inhibitors	178 (14)	195 (15)
Beta-blockers	75 (6)	87 (7)
Alpha-blockers	53 (4)	38 (3)
Statins	322 (26)	328 (26)

Baseline Clinical Laboratory Measurements

Characteristic	Aspirin Group (n = 1262)	Nonaspirin Group (n = 1277)
Clinical Laboratory Data, mean ± SD		
Hemoglobin A_{1c} level (%)	7.1 ± 1.4	7.0 ± 1.2
Fasting plasma glucose level (mg/dL)	148 ± 50	146 ± 48
Total cholesterol level (mg/dL)	202 ± 34	200 ± 34
Fasting triglyceride level (mg/dL)	135 ± 88	134 ± 89
HDL-cholesterol level (mg/dL)	55 ± 15	55 ± 15
Blood urea nitrogen level (mg/dL)	16 ± 5	16 ± 5
Serum creatinine level (mg/dL)	0.8 ± 0.3	0.8 ± 0.2
Red blood cells ($x10^5$/mL)	45.2 ± 4.7	45.0 ± 4.8
White blood cells ($x10^3$/mL)	6.2 ± 1.6	6.1 ± 1.7
Hemoglobin level (g/dL)	14.0 ± 1.5	14.0 ± 1.5

Adverse Events

	Aspirin Group	Nonaspirin Group
Bleeding, gastrointestinal*		
Hemorrhagic gastric ulcer	5	3
Bleeding from esophageal varices	1	0
Bleeding from colon diverticula	2	0
GI bleeding due to cancer	2	0
GI bleeding (unknown)	1	1
Hemorrhoids bleeding	1	0
Bleeding, other		
Retinal bleeding	8	4
Bleeding after tooth extraction	1	0
Subcutaneous hemorrhage	3	0
Hematuria	2	1
Nose bleeding	6	1
Chronic subdural hematoma	2	0
Nonbleeding, gastrointestinal event		
Nonhemorrhagic gastritis	3	0
Nonhemorrhagic gastric ulcer	17	3
Nonhemorrhagic duodenal ulcer	1	1
Only GI symptom	26	0

*In the aspirin group, there were 4 cases of severe GI bleeding that required transfusion.