modest effect on CV events, with an absolute decrease in events depending on the underlying CV disease risk. They jointly stated the recommendation that low-dose aspirin use for prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CV disease risk, but not for adults with low risk. Those adults with diabetes at increased CV disease risk include most of men over age 50 years and women over age 60 years who have one or more of following additional risk factors: smoking, hypertension, dyslipidemia, family history of premature CV disease, and albuminuria (1). Probably because there are sufficient data concerning eGFR, they did not mention eGFR as an additional risk.

The aim of this study was to determine whether GFR-dependent risk stratification affects the efficacy of low-dose aspirin therapy for primary prevention of atherosclerotic events in patients with diabetes in the JPAD trial.

RESEARCH DESIGN AND METHODS—The objectives and methods of the JPAD trial have been described previously (10). In brief, the JPAD trial randomly assigned 2,539 patients with type 2 diabetes without any history of atherosclerotic diseases between the ages of 30 and 85 years to the aspirin or nonaspirin group. Patients in the aspirin group were assigned to take 81 mg or 100 mg of aspirin once daily. The dosage of aspirin (81 mg or 100 mg) was chosen by each physician. JPAD was a prospective, nonblinded, randomized clinical trial; event adjudication was done by an independent end point committee blinded to treatment assignment. Japanese Pharmaceutical Affairs Law prohibits the use of placebo in large physician-conducted studies.

The primary end point was 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, and mesenteric arterial thrombosis) during the follow-up period. Secondary end points were combinations of events: atherosclerotic/ischemic (death from coronary, cerebrovascular causes; nonfatal acute myocardial infarction; unstable angina, newly developed exertional angina; nonfatal ischemic stroke; transient ischemic attack; or nonfatal peripheral vascular disease), structural (aortic dissection), and hemorrhagic events (hemorrhagic stroke). Adverse events analyzed included gastrointestinal events and hemorrhagic stroke.

We performed a post hoc subgroup analysis to analyze the relationship between renal function and atherosclerotic events and the effect of aspirin in patients with normal and reduced renal function; eGFR was calculated for patients whose serum creatinine was available. The baseline eGFR (mL/min/1.73 m^2 of body surface area) was calculated by the new three-variable Japanese equation for GFR (eGFR = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 [if female]) instead of the Modification of Diet in Renal Disease equation, because in a Japanese population this equation is more accurate than the other equations when compared with measured GFR computed from inulin clearance (14). Those patients without creatinine values at baseline were excluded from this analysis.

Statistical analysis

Efficacy comparisons were performed based on the time to the first event, according to the intention-to-treat principle, including patients lost to follow-up who were censored at the time of the last visit. We first divided all patients into three groups based on eGFR (≥90, 60–89, <60 mL/min/1.73 m^2), according to the guidelines of the National Kidney Foundation (5). We assessed the difference in baseline characteristics among eGFR groups by *t* test or Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables. We evaluated the effects of the baseline eGFR groups on the cumulative incidences of the primary end point by the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. We used the Cox proportional hazards model to estimate hazard ratios (HRs) and their CIs. We also assessed the effects of aspirin on primary end points stratified by combinations of eGFR groups and age at baseline.

Stratified by eGFR groups, the study population was assessed for the effects of aspirin on atherosclerotic events. We developed Cox proportional hazard models in each stratum of eGFR groups. On the basis of the hypothesis that mild renal dysfunction (eGFR 60–89 mL/min/1.73 m^2) has an interaction with aspirin, we developed a Cox proportional hazard model with the interaction variable between aspirin and eGFR 60–89 mL/min/1.73 m^2 variable. The included variables were aspirin, dummy variable for eGFR 60–89 mL/min/1.73 m^2 (relative to eGFR ≥90 mL/min/1.73 m^2), dummy variable for eGFR <60 mL/min/1.73 m^2 (relative to eGFR ≥90), interaction variable between eGFR 60–89 mL/min/1.73 m^2 and aspirin. We also developed multivariable Cox proportional hazard models to assess the effects of aspirin on primary end points adjusting for age, hypertension, dyslipidemia, and history of smoking to see the robustness.

Differences in adverse events, including any hemorrhagic events and gastrointestinal bleeding according to eGFR, were assessed by χ^2 test or Fisher exact test. Patients with missing values for any selected variable were excluded from the analyses that used the variable. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). *P* values <0.05 were considered statistically significant.

RESULTS—Because 16 patients were excluded from the analysis as a result of the lack of availability of the baseline serum creatinine level, 2,523 of the 2,539 patients originally enrolled in the JPAD trial were included in the current study, as shown in Supplementary Fig. 1. The baseline demographics by eGFR are shown in Supplementary Table 1. The mean (SD) serum creatinine level at baseline was 0.8 (0.3) mg/dL and the mean eGFR was 74 (21) mL/min/1.73 m^2.

As shown in Table 1, there were no significant differences in baseline demographics between the aspirin group and the nonaspirin group. There were also no significant differences in each category of patients stratified by eGFR, except in the group with eGFR ≥90 mL/min/1.73 m^2 patients, who were significantly older in the aspirin group than in the nonaspirin group, and in the group with eGFR 60–89 mL/min/1.73 m^2, whose diastolic blood pressure was slightly but significantly higher in the aspirin group than in the nonaspirin group and whose incidence of history of smoking was significantly higher in the aspirin group than in the nonaspirin group.

Relation between eGFR and primary end points

Incidence of primary end points significantly increased with declining eGFR

Table 1—*Baseline demographics by treatment*

	eGFR ≥90 mL/min/1.73 m^2			eGFR 60–89 mL/min/1.73 m^2			eGFR <60 mL/min/1.73 m^2		
	Aspirin	Nonaspirin	*P*	Aspirin	Nonaspirin	*P*	Aspirin	Nonaspirin	*P*
n	248	270		661	712		342	290	
Age (years), mean (SD)	61 (9)	58 (10)	0.0001	65 (10)	65 (10)	0.6	68 (9)	69 (8)	0.7
Male, *n* (%)	127 (51)	130 (48)	0.5	386 (58)	398 (56)	0.4	184 (54)	150 (52)	0.6
Hypertension, *n* (%)	120 (48)	131 (49)	0.97	376 (57)	399 (56)	0.8	242 (71)	198 (68)	0.5
Dyslipidemia, *n* (%)	140 (56)	132 (49)	0.09	339 (51)	362 (51)	0.9	195 (57)	168 (58)	0.8
Laboratory measurements									
Glycated hemoglobin (%), mean (SD)	7.5 (1.7)	7.4 (1.4)	0.3	7.0 (1.3)	6.9 (1.2)	0.2	7.0 (1.3)	6.9 (1.1)	0.1
Serum creatinine level (mg/dL), mean (SD)	0.5 (0.09)	0.5 (0.1)	0.2	0.7 (0.1)	0.7 (0.1)	0.8	1.1 (0.5)	1.0 (0.2)	0.2
Dipstick-positive proteinuria, *n* (%)	32 (13)	35 (13)	0.96	68 (10)	72 (10)	0.9	76 (23)	63 (22)	0.9
Blood pressure (mmHg), mean (SD)									
Systolic	134 (16)	134 (16)	0.6	135 (14)	134 (14)	0.07	138 (15)	136 (15)	0.1
Diastolic	77 (10)	77 (10)	0.9	77 (9)	76 (9)	0.01	77 (9)	76 (10)	0.1
Medications for diabetes, *n* (%)									
Sulfonylurea	145 (58)	146 (54)	0.3	384 (58)	382 (54)	0.1	205 (60)	177 (61)	0.8
α-Glucosidase inhibitor	90 (36)	80 (30)	0.1	222 (34)	238 (33)	0.95	105 (31)	94 (32)	0.6
Biguanides	38 (15)	56 (21)	0.1	82 (12)	96 (13)	0.6	47 (14)	34 (12)	0.4
Insulin	42 (17)	46 (17)	0.97	87 (13)	80 (11)	0.3	36 (11)	34 (12)	0.6
Thiazolidinediones	10 (4)	23 (9)	0.04	31 (5)	31 (4)	0.8	21 (6)	11 (4)	0.2
Medication for hypertension and dyslipidemia, *n* (%)									
Calcium channel blocker	73 (29)	75 (28)	0.7	214 (32)	239 (34)	0.6	149 (44)	123 (42)	0.8
Angiotensin receptor blocker	36 (15)	41 (15)	0.8	135 (20)	137 (19)	0.6	94 (27)	88 (30)	0.4
Angiotensin-converting enzyme inhibitor	30 (12)	39 (14)	0.4	96 (15)	104 (15)	0.96	52 (15)	52 (18)	0.4
β-Blocker	10 (4)	14 (5)	0.5	40 (6)	49 (7)	0.5	25 (7)	24 (8)	0.7
α-Blocker	4 (1.6)	5 (1.9)	1	25 (4)	22 (3)	0.5	24 (7)	11 (4)	0.08
Statins	69 (28)	61 (23)	0.2	159 (24)	179 (25)	0.6	91 (27)	87 (30)	0.3
History of smoking, *n* (%)	113 (46)	109 (40)	0.2	311 (47)	282 (40)	0.005	140 (41)	100 (34)	0.1

(P = 0.03), as shown in Supplementary Fig. 2. The group of patients with eGFR ≥90 mL/min/1.73 m^2 was used as the reference group in the analysis of the association between the level of eGFR and primary end points. The incidence of primary end points was significantly higher in patients with mildly reduced eGFR 60–89 mL/min/1.73 m^2 (HR 1.6 [95% CI 1.0–2.7]; P = 0.048) and in patients with eGFR <60 mL/min/1.73 m^2 (2.0 [1.2–3.5]; P = 0.0066).

Efficacy of low-dose aspirin therapy on primary and secondary end points in diabetic patients with reduced GFR

In 1,373 patients with eGFR 60–89 mL/min/1.73 m^2 (661 patients in the aspirin group and 712 patients in the nonaspirin group), a total of 85 primary end points (any atherosclerotic event) occurred: 30 in the aspirin group and 55 in the nonaspirin group (HR 0.57 [95% CI 0.36–0.88]; P = 0.011) (Fig. 1*B*). The Cox proportional hazard model demonstrated significant interaction between mild renal dysfunction (eGFR 60–89 mL/min/1.73 m^2) and aspirin use (P = 0.02). However, there was no significant difference in the incidence of primary end points in patients with eGFR ≥90 mL/min/1.73 m^2 (nine events in the aspirin group and 11 events in the nonaspirin group; 0.94 [0.38–2.3]) (Fig. 1*A*), or those with eGFR <60 mL/min/1.73 m^2 (29 events in the aspirin group and 19 in the nonaspirin group; 1.3 [0.76–2.4]) (Fig. 1*C*). Adjusting for age, hypertension, dyslipidemia, and history of smoking, low-dose aspirin significantly reduced primary end points in patients with eGFR 60–89 mL/min/1.73 m^2 (0.53 [0.34–0.83]; P = 0.0052), and not in patients with eGFR ≥90 or <60 mL/min/1.73 m^2 (eGFR ≥90 mL/min/1.73 m^2: 0.87 [0.36–2.14]; eGFR <60 mL/min/1.73 m^2: 1.24 [0.69–2.23]).

The secondary end point of atherosclerotic/ischemic events occurred in 26 patients in the aspirin group and in 50 patients in the nonaspirin group, among the patients with eGFR 60–89 mL/min/1.73 m^2 (HR 0.54 [0.33–0.86]; P = 0.010) (Supplementary Table 2). The incidence of atherosclerotic/ischemic events was similar between the aspirin and nonaspirin groups in both categories of patients with eGFR of at least 90 mL/min/1.73 m^2 (1.15 [0.45–2.95]; P = 0.76) and those with eGFR <60 mL/min/1.73 m^2 (1.29 [0.70–2.43]; P = 0.42) (Supplementary Table 2). In the structural and hemorrhagic events, the benefit of aspirin was not observed in any category of patients stratified by eGFR.

Efficacy of low-dose aspirin therapy on primary end points in subgroups

As reported previously, the incidence of primary end points was significantly lower in the aspirin group than in the nonaspirin group in the subgroup of patients aged 65 years or older (Fig. 2) (10). In the subgroups of patients aged 65 years or older whose eGFR was 60–89 mL/min/1.73 m^2, low-dose aspirin

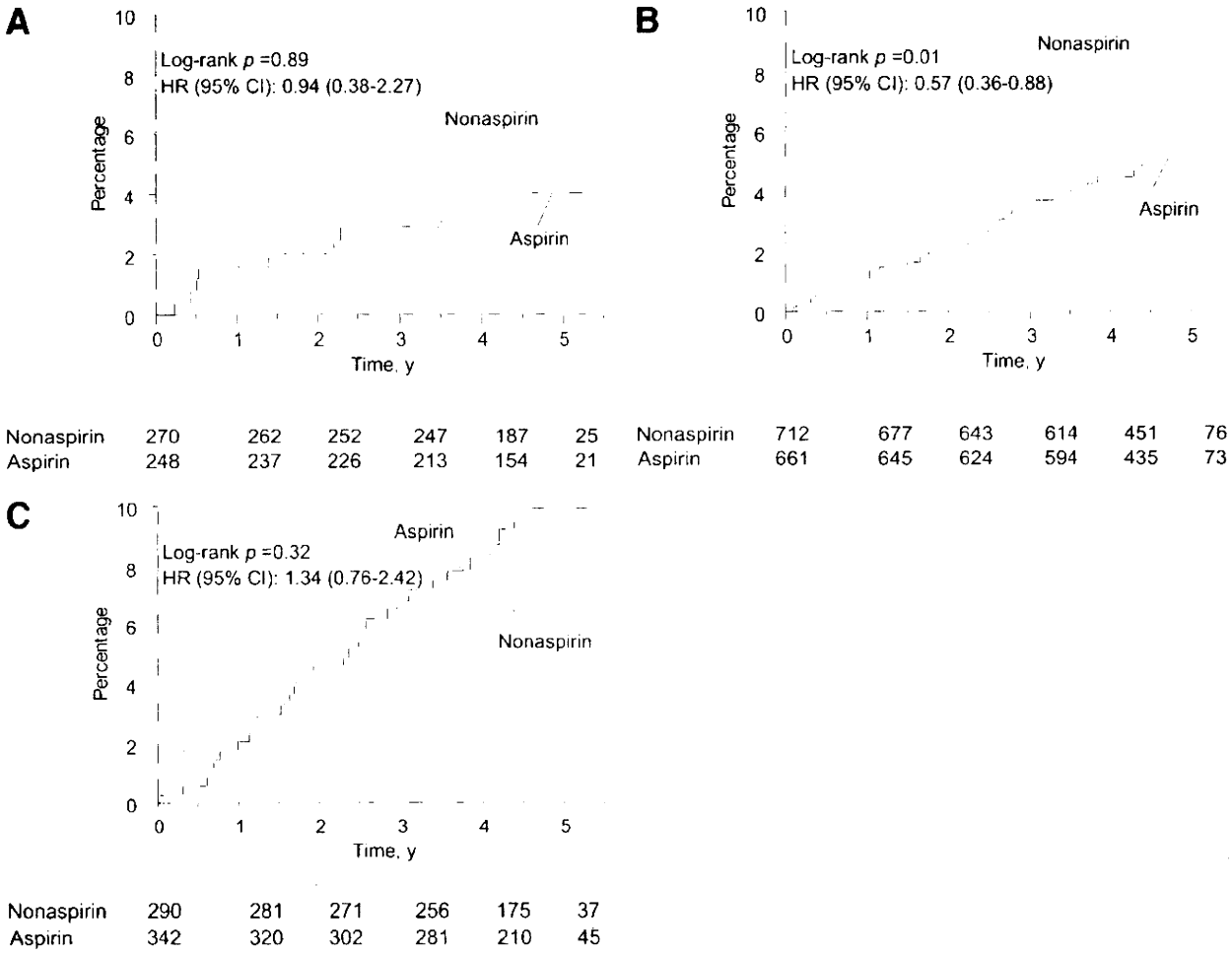

Figure 1—*Percentage of primary end points by category of patients with eGFR of at least 90 mL/min/1.73 m^2 (A), 60–89 mL/min/1.73 m^2 (B), or <60 mL/min/1.73 m^2 (C).*

therapy reduced primary end points by 52% (HR 0.48 [95% CI 0.27–0.82]; P = 0.007) (Fig. 2). In the subgroups of male or female, there was no significant difference in the primary end point between the aspirin and nonaspirin group (data not shown).

Safety

Incidence of the composite of gastrointestinal bleeding and cerebral bleeding was very low and was similar between the aspirin (three gastrointestinal bleeding events and four cerebral bleeding events) and nonaspirin (two gastrointestinal bleeding events and four cerebral bleeding events) groups in the group of patients with eGFR 60–89 mL/min/1.73 m^2.

CONCLUSIONS—In the present subgroup analysis of JPAD, a prospective, randomized, clinical trial of low-dose aspirin versus nonaspirin groups for primary prevention in Japanese type 2 patients with diabetes, low-dose aspirin therapy reduced the incidence of atherosclerotic events in diabetic patients with eGFR 60–89 mL/min/1.73 m^2, but not in those with either eGFR <60 mL/min/1.73 m^2 or at least 90 mL/min/1.73 m^2. In the subgroup of patients with eGFR 60–89 mL/min/1.73 m^2, there was no increase in serious gastrointestinal and cerebral bleeding in the aspirin group compared with the nonaspirin group.

There has been rapidly growing interest in the relation between renal dysfunction and atherosclerotic events in general populations as well as patients at risk for CV events. This is the first subanalysis to clarify the efficacy of aspirin in reducing atherosclerotic risk in patients stratified according to eGFR in patients with diabetes. The current study provides new information that eGFR may be useful to identify candidates for aspirin therapy among Japanese patients with diabetes. We used the new three-variable Japanese equation for GFR, which is more closely correlated with the inulin clearance than the Modification of Diet in Renal Disease equation in the Japanese population (14). It is not clear, however, that eGFR-based identification can be applied to the Caucasian population, because GFR in the Japanese population is lower than that in Caucasians (15). Furthermore, some previous studies in Western populations had reported that Modification of Diet in Renal Disease equation or Cockcroft-Gault formula underestimated GFR in patients with diabetes, and that eGFR was not a predictor of mortality (16,17). Further studies are therefore necessary to confirm the usefulness of eGFR in this strategy.

The progressive increase in CV risk with worsening eGFR found in Japanese patients with diabetes in this study is consistent with previous data (8,18). It has been hypothesized to be related to factors associated with renal damage,

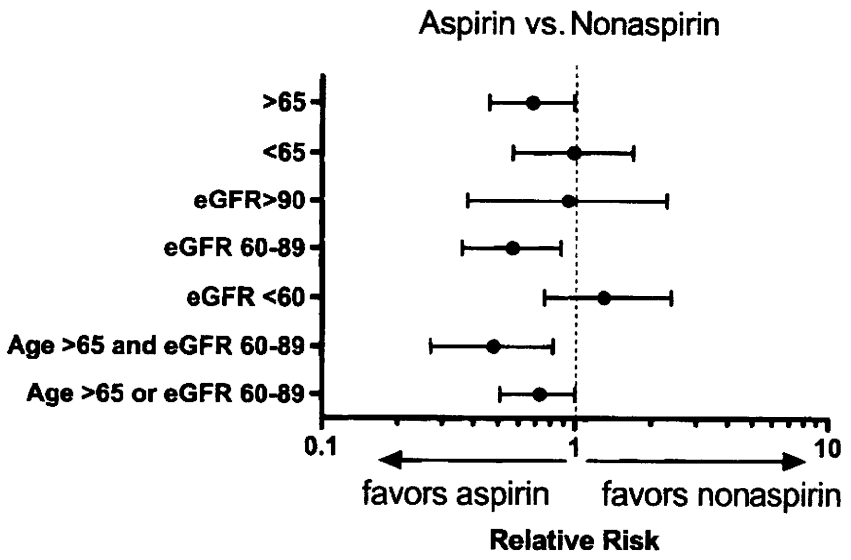

Figure 2—*Subgroup analysis of incidence of primary end points.*

including anemia, oxidative stress, derangements in calcium-phosphate homeostasis, inflammation and conditions promoting coagulation (18). The possible mechanism for the beneficial effect of low-dose aspirin therapy on the prevention of atherosclerotic events in the subgroup of patients with eGFR 60–89 mL/min/1.73 m^2, is inhibition of thrombus formation via blocking thromboxane-dependent platelet activation. Recently, aspirin also has been found to have protective effects on oxidative stress-induced endothelial dysfunction in vivo, which may be involved in the prevention of atherosclerotic events (19,20). However, it is not clear why low-dose aspirin therapy could not prevent atherosclerotic events in the subgroup of patients with eGFR <60 mL/min/1.73 m^2. Given that aspirin in a daily dose of 100 mg or less is associated with a higher incidence of aspirin resistance in patients with diabetes or renal dysfunction (21,22), one possible explanation is that the dose of aspirin is too low to inhibit platelet activation in these patients. Another possible explanation is that in patients with advanced kidney disease, atherosclerotic events are predominantly caused by factors such as renal anemia, derangement of calcium-phosphate homeostasis, and other unknown renal-related factors that are not influenced by aspirin.

During preparation of this manuscript, the subanalysis of the Hypertension Optimal Treatment (HOT) study was published about the efficacy of the low-dose aspirin for primary prevention in patients with chronic kidney disease (23). This study showed that low-dose aspirin is beneficial for preventing major CV disease in patients with eGFR <45 mL/min/1.73m^2 (aspirin, 11/264; placebo 32/272; HR 0.34 [95% CI 0.17–0.67]), and not in those with eGFR ≥60 mL/min/1.73m^2 (aspirin, 233/7517; placebo, 252/7461; 0.91 [0.76–1.09]) (23). The result seems inconsistent with our result; however, the HOT study enrolled patients with diastolic hypertension, and the rate of diabetic patients was only 8%. The underlying mechanisms were unclear, but the difference in patients' characteristics, especially coexisting with diabetes, might affect the aspirin effect.

Along with progression of renal damage in diabetes, GFR is normal or increases to above the normal level in the early period and then gradually decreases. The proportion of patients with eGFR of at least 90 mL/min/1.73 m^2 in the JPAD trial was 21% of the total patients enrolled, which was higher than the 13% prevalence for this eGFR category observed in the general Japanese population (15). The proportion with eGFR <60 mL/min/1.73 m^2 in the JPAD trial was 25%, which was also higher than the 16% prevalence in the general population (15). This distributional difference in eGFR is probably explained by the characteristic progression pattern of diabetic renal damage. In the current study, eGFR <60 mL/min/1.73 m^2—a usual cutoff value—was associated with increased atherosclerotic risk, but in addition, eGFR 60–89 mL/min/1.73 m^2 was also associated with increased risk for any atherosclerotic events.

This study has a few limitations. With the nonblinded design, differential ascertainment is possible; however, end point classification was conducted by a blinded, independent committee that was unaware of the group assignments. Second, we used the eGFR instead of direct measurement of GFR using an exogenous marker, such as inulin clearance. Equations for estimating GFR have limited precision compared with measured GFR. However, for practical reasons, many large trials have used eGFR calculated by the Modification of Diet in Renal Disease equation or Cockcroft-Gault formula. Third, our population enrolled only 20 patients with eGFR <30 mL/min/1.73 m^2 and no patients receiving hemodialysis, so we could not analyze the effect of aspirin in these categories of patients. Finally, we did not measure the rate of urinary albumin excretion, a factor that may drive the documented independent effect of the baseline eGFR on CV outcomes.

In conclusion, the current study demonstrated that low-dose aspirin therapy reduced the risk of atherosclerotic events in type 2 diabetic patients with eGFR 60–89 mL/min/1.73 m^2. The results suggest that eGFR may be useful for risk stratification in the primary prevention strategy with aspirin. However, as these results are from a post hoc subgroup analysis, they should be viewed as hypothesis generating and should be investigated further in additional studies.

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Y.S. conducted the trial, interpreted and analyzed data, and wrote the manuscript. T.M. performed all statistical analyses. H.O. conducted the trial, contributed to discussion, and reviewed and edited the manuscript. M.N., S.U., N.D., H.J., M.W., H.S., and S.S. researched data. S.O. contributed to discussion and reviewed and edited the manuscript. Y.A. reviewed and edited the manuscript.

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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.[1-5] Individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular events than those without diabetes.[6]

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.[10-15] 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.[16] Nonetheless, the clinical trial data for aspirin in primary preven-

For editorial comment see p 2180.

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tion are limited. Several large trials of aspirin for primary prevention have examined its effects in subgroups with diabetes; these subgroup analyses did not demonstrate a significant effect on reducing vascular events because they were underpowered.[17-21] Thus, a primary prevention trial of aspirin for diabetic patients is needed.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was undertaken to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

METHODS

The JPAD trial was a prospective, randomized, open-label, controlled trial with blinded end-point assessment. Patient enrollment started in December 2002 and was completed in May 2005; patients were followed up until April 2008. Patients were enrolled and followed up at 163 institutions throughout Japan. The institutional review board at each participating hospital approved this trial, and written informed consent was obtained from each patient.

Trial Population

The inclusion criteria were diagnosis of type 2 diabetes mellitus, age between 30 and 85 years, and ability to provide informed consent. The exclusion criteria were electrocardiographic changes consisting of ischemic ST-segment depression, ST-segment elevation, or pathologic Q waves; a history of coronary heart disease confirmed by coronary angiography; a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack; a history of arteriosclerotic disease necessitating medical treatment; atrial fibrillation; pregnancy; use of antiplatelet or antithrombotic therapy, defined as aspirin, ticlopidine, cilostazol, dipyridamole, trapidil, warfarin, and argatroban; a history of severe gastric or duodenal ulcer; severe liver dysfunction; severe renal dysfunction, and allergy to aspirin.

Trial Protocol

Enrolled patients were randomly assigned to the aspirin group or the nonaspirin group. The randomization was performed as nonstratified randomization from a random number table. The study center prepared the sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites. Patients in the aspirin group were assigned to take 81 mg or 100 mg of aspirin once daily. Patients were followed up at each hospital visit or by telephone if necessary. Follow-up visits were scheduled every 2 weeks for patients seen in a clinic setting and every 4 weeks for patients seen in a hospital setting. Data for patients who were lost to follow-up were included at the day of last follow-up. Patients were allowed to use any concurrent treatment. Patients in the nonaspirin group were also allowed to use antiplatelet/thrombotic therapy, including aspirin, if needed and vice versa.

End Points

The primary end point was 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) during the follow-up period. Key secondary end points were each primary end point and combinations of primary end points and death from any cause. Adverse events analyzed included gastrointestinal (GI) events and any hemorrhagic events other than hemorrhagic stroke. All potential primary end points, secondary end points, and adverse events were adjudicated by an independent committee on validation of data and events that was unaware of the group assignments.

Sample Size Calculation

For sample size calculation, we first estimated the incidences of cardiovascular and cerebrovascular events among Japanese diabetic patients. The incidence of cardiovascular death, myocardial infarction, and cerebrovascular events were 7.5, 7.5, and 8.0 events per 1000 Japanese diabetic patients per year, respectively, according to the Hisayama-cho study[22] and Funagata study.[23] The total incidence of the atherosclerotic events, including peripheral arterial disease, was suggested to be 3 times the aforementioned number by the Hypertension Optimal Treatment (HOT) study.[24] Because the recent incidence of atherosclerotic events among Japanese individuals seemed relatively lower than that previously reported in Japan, we discounted 25% of the estimated 69 events that were expected to occur and estimated that 52 events per 1000 Japanese diabetic patients would occur annually.

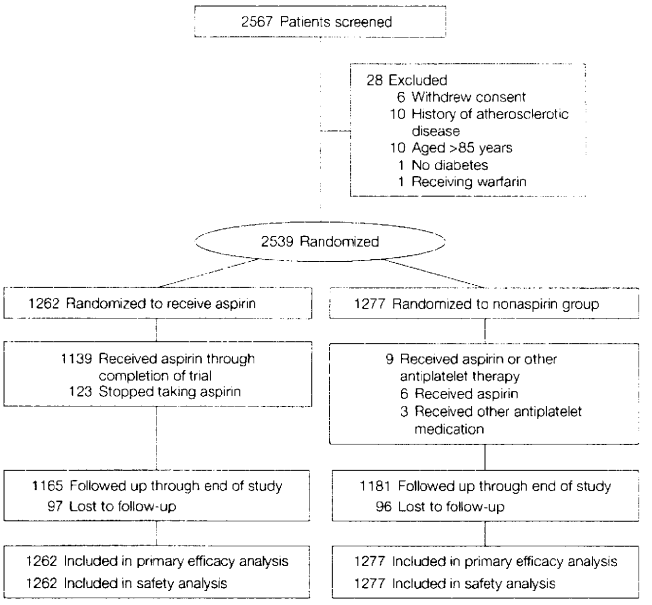
Based on a 2-sided α level of .05, a power of 0.95, an enrollment period of 2 years, and a follow-up period of 3 years after the last enrollment, we estimated that 2450 patients would need to be enrolled to detect a 30% relative risk reduction for an occurrence of atherosclerotic disease by aspirin.[19]

Statistical Analyses

Efficacy comparisons were performed on the basis of time to the first event, according to the intention-to-treat principle, including all patients in the group to which they were randomized with patients lost to follow-up censored at the day of the last visit. Safety analyses were performed on data from all enrolled patients. Following the descriptive statistics, cumulative incidences of primary and secondary 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 hazards model to estimate hazard ratios (HRs) of aspirin use along with 95% confidence intervals (CIs). We used the χ^2 test or Fisher exact test to evaluate adverse events.

We also conducted subgroup analyses for predetermined subgroups: sex (men, women); age (younger than 65 years, 65 years or older); hypertensive

Figure 1. Participation in Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial



status (hypertensive, normotensive); smoking status (current or past smoker, nonsmoker); and lipid status (hyperlipidemia, normolipidemia). Using the Cox proportional hazard model, proportional hazard assumptions were assessed on the plots of log (time) vs log [−log(survival)] stratified by index variables. Patients with missing values for any selected variable were excluded from the analyses that used the variable.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-Plus version 7.0 (Insightful Corp, Seattle, Washington). *P* values of less than .05 were considered statistically significant. An independent safety monitoring board monitored the safety and efficacy of the study after 2 years of follow-up for an interim assessment and at the end of the study.

RESULTS

Study Population

The study screened 2567 patients with type 2 diabetes mellitus without a history of atherosclerotic disease, including cardiovascular disease, stroke, and peripheral vascular disease, from December 2002 to May 2005 in 163 institutions (FIGURE 1). Six patients who withdrew their informed consent were excluded. Twenty-two patients met exclusion criteria. We randomly assigned 2539 patients as follows: 1262 patients in the aspirin group and 1277 patients in the nonaspirin group. Patients were followed up until April 2008. The median follow-up period was 4.37 years (95% CI, 4.35-4.39). A total of 193 patients were lost to follow-up, and data for those patients were censored at the day of last follow-up.

Baseline Clinical Characteristics

Baseline clinical characteristics, including treatments for diabetes, hypertension, and dyslipidemia and diabetic microvascular complications, were similar between the 2 groups (TABLE 1). Overall mean (SD) age was 65 (10) years; 55% of patients were men. Median duration of diabetes was 7.3 years in the aspirin group and 6.7 years in the nonaspirin group. Diabetes was well controlled in both groups: mean (SD) levels of glycated hemoglobin were 7.1% (1.4%) in the aspirin group and 7.0% (1.2%) in the nonaspirin group. The prevalence of hypertension and dyslipidemia was 58% and 53%, respectively. Blood pressure was well controlled in both groups: mean (SD) systolic pressure, 136 (15) mm Hg; mean (SD) diastolic pressure, 77 (9) mm Hg in the aspirin group and mean (SD) systolic pressure, 134 (15) mm Hg; mean (SD) diastolic pressure, 76 (9) mm Hg in the nonaspirin group.

By the end of the study, 123 patients (10%) in the aspirin group had stopped taking the study medication. Since aspirin therapy was allowed in the nonaspirin group, 6 patients (0.5%) had taken aspirin and 3 patients (0.2%) had taken other antiplatelet medication.

Efficacy Analysis

A total of 154 atherosclerotic events occurred (TABLE 2). The incidence of the primary end point of any atherosclerotic event, a composite of sudden death, death from cardiovascular or aortic causes, nonfatal acute myocardial infarction, unstable angina, exertional angina, nonfatal ischemic and hemorrhagic stroke, transient ischemic attack, and nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis), was not significantly different in the aspirin group (68 events, 5.4%) than in the nonaspirin group (86 events, 6.7%) (HR, 0.80; 95% CI, 0.58-1.10; log-rank test, $P=.16$) (Table 2 and FIGURE 2).

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; $P=.0037$). Other secondary coronary, cerebrovascular, and peripheral vascular disease end points are shown in Table 2; there were no significant differences between the aspirin group and the nonaspirin group in these end points. There were 2 deaths due to aortic dissection, both in the low-dose aspirin group, and 1 nonfatal aortic dissection in the nonaspirin group. A total of 13 hemorrhagic strokes occurred; the incidences in each group were similar (6 in the aspirin group and 7 in the

nonaspirin group). There was 1 fatal hemorrhagic stroke in the aspirin group and 4 in the nonaspirin group.

Death from causes other than cardiovascular events were as follows for the aspirin group and nonaspirin group, respectively: there were 15 and 19 deaths due to malignancy, 2 and 5 due to infection, 3 and 0 due to suicide, 2 and 0 due to traffic crashes, and 1 and 1 due to liver cirrhosis. Therefore, 23 patients in the aspirin group and 25 patients in the nonaspirin group died from causes other than cardiovascular events. Eight patients in the aspirin group and 3 patients in the nonaspirin group died from unknown causes. 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, $P=.67$).

Subgroup Analyses

In the 1363 patients aged 65 years or older (719 in the aspirin group and 644 in the nonaspirin group), the incidence of atherosclerotic events was significantly lower in the aspirin group (45 events, 6.3%) than in the nonaspirin group (59 events, 9.2%) (HR, 0.68; 95% CI, 0.46-0.99; $P=.047$). In the 1176 patients younger than age 65 years, there were 23 events in the aspirin group (4.2%) and 27 events in the nonaspirin group (4.3%), a difference that was not significant (HR, 1.0; 95% CI, 0.57-1.70; $P=.98$). A formal test of interaction with age did not show a significant result ($P=.27$). There were no significant differences between the aspirin group and nonaspirin group in other subgroup analyses, including men, women, hypertensive, normotensive, current or past smokers, nonsmokers, dyslipidemia, and normolipidemia (FIGURE 3).

Safety

The prespecified analysis of adverse events is shown in TABLE 3. The hemorrhagic events consisted of GI bleeding in 12 patients in the aspirin group and 4 in the nonaspirin group and retinal hemorrhage in 8 patients in the aspirin group and 4 in the nonaspirin group. In the aspirin group, 4 patients had serious adverse events that needed a transfusion; no patients in the non-

Table 1. Baseline Clinical Characteristics

Characteristic	No. (%) Aspirin Group (n = 1262)	No. (%) Nonaspirin Group (n = 1277)
Age, mean (SD), y	65 (10)	64 (10)
Male	706 (56)	681 (53)
Current smoker	289 (23)	248 (19)
Past smoker	545 (43)	482 (38)
Body mass index, mean (SD)[a]	24 (4)	24 (4)
Hypertension	742 (59)	731 (57)
Dyslipidemia	680 (54)	665 (52)
Systolic blood pressure, mean (SD), mm Hg	136 (15)	134 (15)
Diastolic blood pressure, mean (SD), mm Hg	77 (9)	76 (9)
Duration of diabetes, median (IQR), y	7.3 (2.8-12.3)	6.7 (3.0-12.5)
Diabetic microvascular complication		
Diabetic retinopathy	187 (15)	178 (14)
Diabetic nephropathy	169 (13)	153 (12)
Proteinuria, ≥15 mg/dL	222 (18)	224 (18)
Diabetic neuropathy	163 (13)	137 (11)
Dermal ulcer	6 (0.5)	6 (0.5)
Treatment for diabetes		
Sulfonylureas	737 (58)	710 (56)
α-Glucosidase inhibitors	422 (33)	414 (32)
Biguanides	168 (13)	186 (15)
Insulin	166 (13)	160 (13)
Thiazolidines	63 (5)	65 (5)
Treatment for hypertension and dyslipidemia		
Calcium channel blockers	436 (35)	440 (34)
Angiotensin-II receptor antagonists	269 (21)	266 (21)
Angiotensin-converting enzyme inhibitors	178 (14)	195 (15)
β-Blockers	75 (6)	87 (7)
α-Blockers	53 (4)	38 (3)
Statins	322 (26)	328 (26)
Family history		
Type 2 diabetes mellitus	526 (42)	513 (40)
Ischemic heart disease	147 (12)	143 (11)
Stroke	275 (22)	251 (20)
Patient medical history		
Peptic ulcer	83 (7)	96 (8)
Clinical laboratory measurements, 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, $\times 10^6$/mL	45.2 (4.7)	45.0 (4.8)
White blood cells, $\times 10^3$/mL	6.2 (1.6)	6.1 (1.7)
Hemoglobin level, g/dL	14.0 (1.5)	14.0 (1.5)

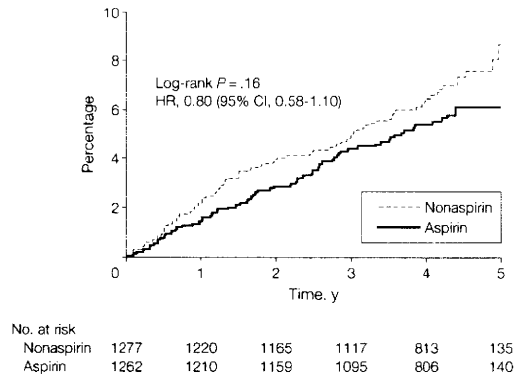
Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range.
SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; to convert total and HDL cholesterol to mmol/L, multiply by 0.0259; to convert triglyceride to mmol/L, multiply by 0.0113; to convert urea nitrogen to mmol/L, multiply by 0.357; to convert creatinine to μmol/L, multiply by 88.4.
[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Atherosclerotic Events

	Aspirin Group		Nonaspirin Group			
	No. (%)	No. per 1000 Person-Years	No. (%)	No. per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value
Primary end point: all atherosclerotic events	68 (5.4)	13.6	86 (6.7)	17.0	0.80 (0.58-1.10)	.16
Coronary and cerebrovascular mortality	1 (0.08)	0.2	10 (0.8)	2.0	0.10 (0.01-0.79)	.0037
CHD events (fatal + nonfatal)	28 (2.2)	5.6	35 (2.7)	6.9	0.81 (0.49-1.33)	.40
Fatal MI	0	0	5 (0.4)	1.0		
Nonfatal MI	12 (1.0)	2.4	9 (0.7)	1.8	1.34 (0.57-3.19)	.50
Unstable angina	4 (0.3)	0.8	10 (0.8)	2.0	0.40 (0.13-1.29)	.13
Stable angina	12 (1.0)	2.4	11 (0.9)	2.2	1.10 (0.49-2.50)	.82
Cerebrovascular disease (fatal + nonfatal)	28 (2.2)	5.6	32 (2.5)	6.3	0.84 (0.53-1.32)	.44
Fatal stroke	1 (0.08)	0.2	5 (0.4)	1.0	0.20 (0.024-1.74)	.15
Nonfatal stroke						
Ischemic	22 (1.7)	4.4	24 (1.9)	4.6	0.93 (0.52-1.66)	.80
Hemorrhagic	5 (0.4)	1.0	3 (0.2)	0.6	1.68 (0.40-7.04)	.48
Transient ischemic attack	5 (0.4)	1.0	8 (0.6)	1.6	0.63 (0.21-1.93)	.42
Peripheral artery disease[a]	7 (0.6)	1.4	11 (0.9)	2.2	0.64 (0.25-1.65)	.35

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.
[a] 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).

Figure 2. Total Percentage of Atherosclerotic Events According to Treatment Group



CI indicates confidence interval; HR, hazard ratio.

aspirin group required transfusion. Another 13 patients in the aspirin group had minor bleeding. There was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding, which occurred in 10 patients in the aspirin group and in 7 patients in the nonaspirin group.

COMMENT

Myocardial infarction and ischemic stroke are leading causes of mortality and morbidity in patients with type 2 diabetes.[25] Given the rapid increase in the number of patients with type 2 diabetes worldwide and especially in Asia, establishing effective means of primary prevention of coronary and cerebrovascular events is an important public health priority.[26] In the JPAD primary prevention trial of 2539 type 2 diabetic patients without documented cardiovascular disease, the incidence of the primary end point of total atherosclerotic events, consisting of coronary, cerebrovascular, and peripheral vascular events, was not significantly different in the group that received prophylactic aspirin (81 or 100 mg once daily) than in the nonaspirin group. With the exception of fatal coronary and cerebrovascular events, none of the prespecified secondary end points were reduced significantly in the low-dose aspirin group. The incidence of fatal coronary and cerebrovascular events, a prespecified secondary end point, was significantly reduced in the low-dose aspirin group ($P = .0037$). A benefit of low-dose aspirin on the primary end point also was suggested in the subgroup of patients aged 65 years or older, which had a significant 32% relative reduction in total atherosclerotic events ($P = .047$). The cardiovascular mortality benefit was achieved with a small increase in cases of serious GI bleeding (4 patients in the aspirin group had bleeding that required transfusion), but no excess of fatal GI or cerebral hemorrhages.

The JPAD trial enrolled 2539 diabetic patients without documented coronary or cerebrovascular complications; the sample size was the largest among the previous primary prevention studies in respect to the number of diabetic patients enrolled. However, no difference was found in the effect of aspirin on the primary end point or most secondary end points.

The interpretation of these results is challenging because the overall event rates were low: 17 in 1000 Japanese diabetic patients. This is one-third of the event rate anticipated in our sample-size calculations, which were based on the Hisayama-cho[22] and Funagata[23] epidemiologic studies conducted in Japan in the 1990s. Current treatment of cardiovascular risk factors in patients with type 2 diabetes has improved since the 1990s and may have ac-

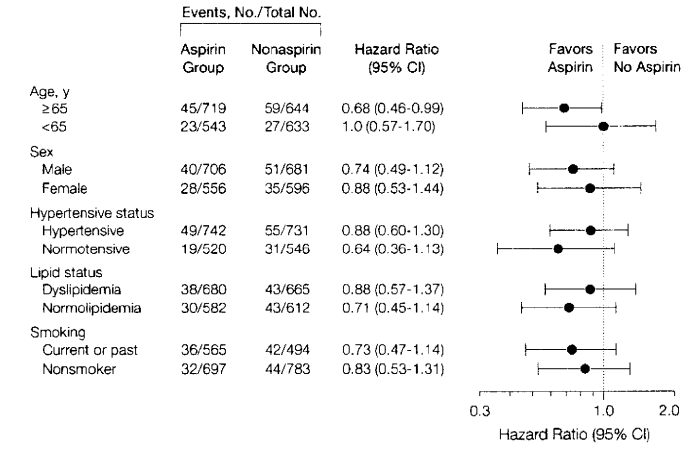
counted for the lower event rates: there is better control of glucose, blood pressure, and lipid levels in clinical practice. The baseline characteristics of patients in the JPAD trial were similar to those in previous studies except that body mass index was relatively lower in the JPAD trial than that in the previous studies, although similar to that in other studies of Japanese diabetics.[4,6,19-21,27,28]

A meta-analysis of primary prevention trials that included the British Doctors' Trial, the Physicians' Health Study, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP) trial, and the Women's Health Study showed that aspirin therapy significantly reduced the risk of total coronary heart disease, nonfatal myocardial infarction, and total cardiovascular events with a nonsignificant trend for decreased risk of stroke, cardiovascular mortality, and all-cause mortality.[29] However, the evidence for aspirin in prevention of cardiovascular events in diabetic patients has been surprisingly scant. Previous studies investigating the effects of low-dose aspirin on primary prevention of cardiovascular events did not enroll solely diabetic patients but enrolled patients with hypertension in the HOT study; patients with 1 or more cardiovascular risk factors in the Thrombosis Prevention Trial and the PPP trial; and a healthy population in the British Doctors' Trial, the Physicians' Health Study, and the Women's Health Study.

Several large primary prevention trials have included subgroup analyses of patients with diabetes. The Physicians' Health Study of 22 071 healthy men randomized to receive 325 mg of aspirin every other day or placebo showed a significant reduction in myocardial infarction for the entire population, but there was no significant difference for the small number of individuals with diabetes in the 2 treatment groups (11/275 in the aspirin group and 26/258 in the placebo group).[18] The Antithrombotic Trialists' Collaboration meta-analysis of 287 randomized trials reported effects of antiplatelet therapy (mainly aspirin) vs control in 135 000 patients and showed a nonsignificant 7% reduction in the odds for serious vascular events for the subgroup of 5126 patients with diabetes.[19]

Sacco et al[20] described the effects of aspirin on atherosclerotic disease in patients with diabetes as a subgroup of the PPP trial, which investigated the effects of aspirin and vitamin E in a 2-by-2 factorial trial of 4495 patients with at least 1 known major cardiovascular risk factor.[21] The original study was stopped on ethical grounds after a mean follow-up of 3.6 years because aspirin was associated with a lower risk of atherosclerotic disease in the overall group. The results of a subgroup analysis of 1031 diabetic patients did not

Figure 3. Subgroup Analysis of Incidence of Atherosclerotic Events



CI indicates confidence interval (shown as error bars in the plot).

Table 3. Adverse Effects

	No.	
	Aspirin Group	Nonaspirin Group
Bleeding, gastrointestinal[a]		
Hemorrhagic gastric ulcer	5	3
Bleeding from esophageal varices	1	0
Bleeding from colon diverticula	2	0
Gastrointestinal bleeding due to cancer	2	0
Hemorrhoid bleeding	1	0
Gastrointestinal bleeding (cause unknown)	1	1
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 gastrointestinal symptom	26	0
Other		
Anemia	4	0
Asthma	1	0

[a] In the aspirin group, 4 cases of severe gastrointestinal bleeding required transfusion.

reach statistical significance, possibly because of the early stopping of the trial and the subgroup size.[20] In addition, medication adherence was poor in the PPP trial: 28.2% of subjects assigned to aspirin had stopped this therapy by the conclusion of the trial. In the JPAD study, only 10% of patients in the aspirin group stopped this therapy by the end of the mean 4.37 years of follow-up.

Because of the low event rate in JPAD, our study was underpowered for demonstrating that aspirin had a significant effect on reducing total atherosclerotic events. However, the observation in the JPAD trial of an effect of aspirin on the secondary outcome of fatal cardiovascular events was also seen in the PPP trial. Aspirin did not reduce cardiovascular mortality in the HOT study, and it did not reduce fatal stroke in the Women's Health Study. The reason for the discrepancy in the preventive effect of aspirin on fatal cardiovascular events is not clear at present. The total number of fatal events was small (ranging from 13 to 49) in the JPAD trial as well as the PPP trial and in the subgroup population with diabetes in the HOT study. A larger trial is needed to determine the efficacy of low-dose aspirin on mortality.

The JPAD trial composite primary end point also included hemorrhagic stroke. The finding that aspirin did not increase the risk of hemorrhagic stroke was consistent with findings from prior reports,[21,24,30,31] although the population studied was patients with diabetes. The finding of no increase in hemorrhagic stroke in the JPAD trial is of particular clinical importance because hemorrhagic stroke is more common in Japanese populations than in the West.[32,33] Moreover, there was no fatality due to hemorrhagic events except for hemorrhagic stroke; however, the hemorrhagic events that required surgical interventions or transfusion were observed in 4 patients in aspirin group.

The study design may be considered a limitation of the JPAD trial (prospective, randomized, open-label, controlled trial with blinded end-point assessment), as it did not have the advantages of a double-blind, randomized trial. The Japanese Pharmaceutical Affairs Law limits the use of placebo in physician-initiated studies because it is an unapproved medicine. However, the end-point classification was conducted by a blinded, independent committee on validation of data and events that was unaware of the group assignments.

Previous clinical studies indicate that a cardiovascular risk reduction is difficult to achieve by aggressively controlling plasma glucose levels in diabetic patients.[34-37] These studies suggested that the contribution of lowering glucose levels to the reduction of macrovascular events appears to be minimal, at least in the first few years of treatment. Although improved glucose control can protect against the development of microvascular complications, the absence of a reduction in macrovascular events implicates an additive effect of nonglycemic risk factors that often accompany diabetes, such as hypertension, hyperlipidemia, and hypercoagulability. Additional medications such as angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, statins, and antiplatelet agents may be needed in patients with type 2 diabetes mellitus. The JPAD trial indicates that among these medications, aspirin is well tolerated for primary prevention and may provide an additional low-cost option.

In summary, in the JPAD trial, the first prospectively designed trial to evaluate low-dose aspirin in patients with type 2 diabetes without previous cardiovascular disease, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events. Despite a large sample size, the event rate in the study was lower than anticipated. Aspirin was well tolerated in these patients, as there was no increase in hemorrhagic strokes and a small increase in serious GI hemorrhagic events (4 patients required transfusion). These findings should be interpreted in context with the low incidence of atherosclerotic disease in Japan and the current management practice for cardiovascular risk factors and suggest the need to conduct additional studies of aspirin for primary prevention of cardiovascular disease in diabetic patients.

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Acquisition of data: Ogawa, Nakayama, Morimoto, Uemura, Kanauchi, Doi, Jinnouchi, Sugiyama.
Analysis and interpretation of data: Ogawa, Nakayama, Morimoto.
Drafting of the manuscript: Ogawa, Nakayama, Morimoto, Uemura.
Critical revision of the manuscript for important intellectual content: Ogawa, Nakayama, Morimoto, Kanauchi, Doi, Jinnouchi, Sugiyama, Saito.
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INTERNAL MEDICINE

CASE REPORT

Cerebral Infarction Associated with Heparin-Induced Thrombocytopenia in a Patient with Encephalitis

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Abstract

We report a patient who had cerebral infarction associated with heparin-induced thrombocytopenia (HIT) during treatment of aseptic encephalitis. In patients with intracranial inflammation, such as ours, the possibility of HIT has to be considered when heparin is used, since inflammatory cerebral lesions often cause vascular damage, which is an aggravating factor for HIT-associated thrombosis.

Key words: cerebral infarction, encephalitis, heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a life-threatening thrombotic disorder caused by antibodies (HIT-Ab) against a complex of heparin and platelet factor 4 (1). Thrombotic complications include cerebral infarction and peripheral deep vein thrombosis (DVT), often occurring 5-15 days after the start of heparin (2). Encephalitis occasionally involves cerebral arteries, leading to cerebral infarction (2). However, whether heparin use triggers cerebral infarction is unknown. We report an encephalitis patient with HIT-associated cerebral infarction.

Case Report

A 73-year-old man was admitted to a local hospital because of headache, drowsiness, and mild left hemiparesis including the facial muscles, without apparent sensory disturbance. Abnormal MRI findings (Fig. 1A, B) initially suggested cerebral infarction, and he was given heparin (10,000 IU/day) for 2 days. He had no risk factors for cerebral infarction, including hypertension, hyperlipidemia, diabetes mellitus, hereditary coagulation disorders (Protein C, Protein S, AT III deficiencies), and cardiac diseases; there was no evidence of cerebral infarction on cerebral angiography (Fig. 1C). The next day, pleocytosis (187/mm^3, 58% lymphocytes), elevated protein (159 mg/dL), and normal glucose in the CSF suggested the diagnosis of encephalitis. Heparin was stopped. The patient was transferred to our hospital on day 4. He had almost normal blood chemistry and cell counts, including a normal platelet count (192×10^3/μL). Anticoagulation testing revealed slightly elevated levels of D-dimer (6.8 μg/mL [normal <1.0 μg/mL]) and FDP (11.6 μg/mL [normal <10 μg/mL]), but normal PT and APTT levels. On CSF testing, Herpes simplex and Varicella zoster DNA were negative. Serum antibody titers excluded infection with various bacteria, fungi, and viruses. No organisms (including *Mycobacterium tuberculosis*) were cultured from the CSF. Serum auto-antibodies against the nucleus, ds-DNA, cardiolipin, galactose, RNP, Sm, SSA, SSB, and neutrophil cytoplasm were negative. These findings suggested that the patient had aseptic encephalitis. On day 8, total parenteral nutrition was started, and heparin was flushed (100 IU) once daily to maintain central catheter patency. The patient gradually recovered consciousness so that he was able to eat meals by himself, and the CSF abnormalities improved (37 cells/mm^3 and 124 mg protein/dL) on day 21. On day 23, he suddenly became semicomatose and developed right hemiplegia with total aphasia. A brain diffusion-weighted image (DWI) showed high intensity in the left basal ganglia and corona radiata (Fig. 1D, E). On MRA, the main trunk of the left middle cerebral artery was occluded (Fig. 1F). Electrocardiography (ECG) including bedside ECG monitoring showed normal sinus rhythm during the entire disease

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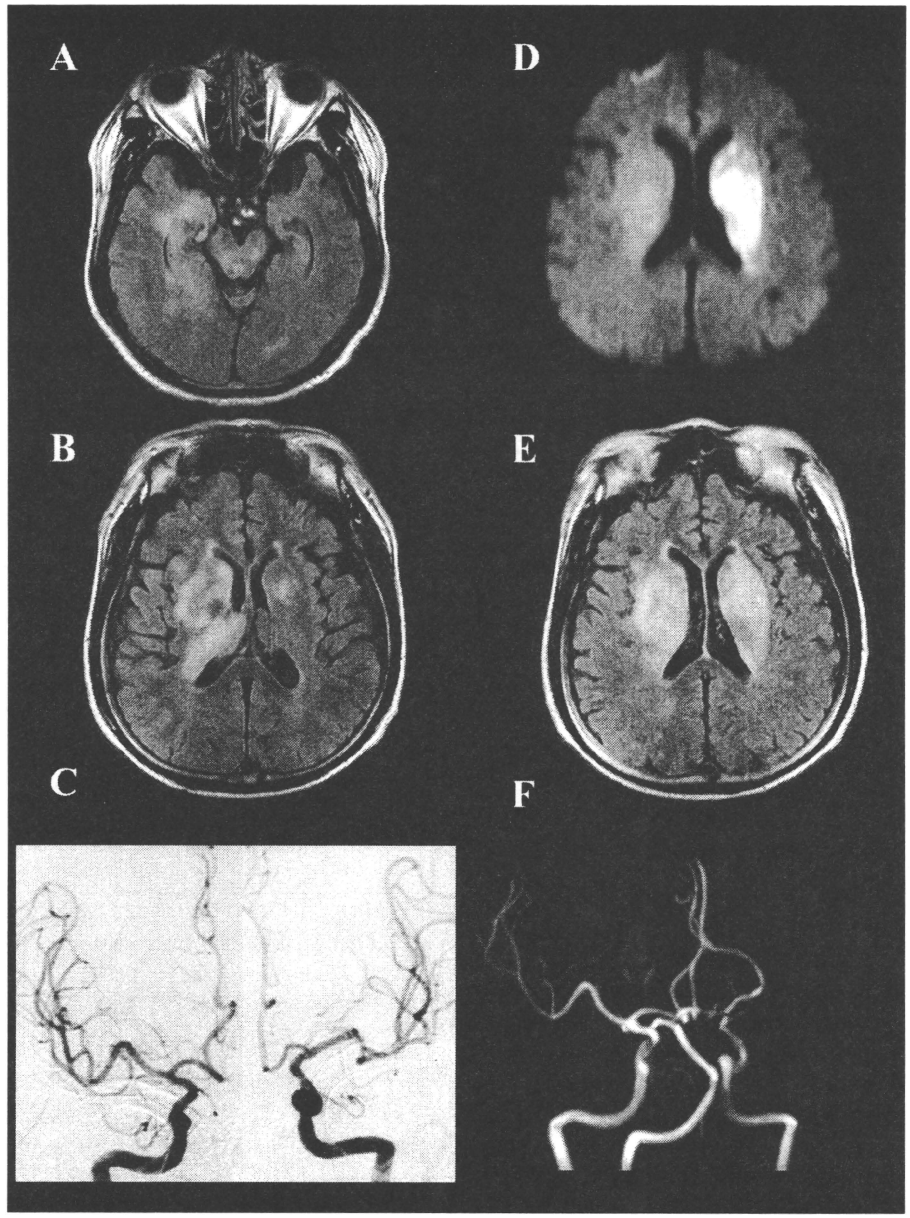

Figure 1. **Radiological findings before (A-C) and after (D-F) cerebral infarction associated with HIT. (A, B) FLAIR images (TE /TR=124/9000, 1.5-T whole-body magnetic resonance system, Magnetom Sonata A.G., Siemens, Erlangen, Germany) obtained 9 days after disease onset (day 9) show hyperintense lesions in the right hippocampus, temporal lobe, and corona radiata. (C) Cerebral angiography done 3 days after disease onset shows no stenosis or occlusion in bilateral internal carotid arteries. (D) DWI (TR/TE=180/96, b=1,000 s/mm^2, matrix 128×128, field of view 230 mm) on day 23 shows a hyperintense lesion in the left corona radiata. (E) A FLAIR image on day 23 shows a hyperintense lesion in the corona radiata bilaterally. (F) Brain MRA on day 23 shows occlusion of the main trunk of the left middle cerebral artery.**

course; transthoracic and transesophageal echocardiography revealed no cardiac thrombus, patent foramen ovale, or complicated aortic arch lesions. The platelet count remained normal (211×10^3/μL). On day 24, intravenous continuous heparin injection (8,000 IU/day) was resumed. On day 30, the platelet count decreased to 9.9×10^3/μL, with an extremely high D-dimer level (42.4 μg/mL) (Fig. 2). Venous ultrasonography showed DVT in the right popliteal vein on day 32. Since these findings suggested the possibility of HIT, we stopped heparin and started argatroban on day 34. HIT-Ab was subsequently found to be positive in the blood sample obtained at the onset of cerebral infarction (OD_{405}=0.652, normal <0.4, enzyme-linked immunosorbent assay GTI-PF4, Genetic Testing Institute, Waukesha WI, USA). According to a previous report, the clinical probability score at the onset of stroke was 4 points, indicating a intermediate probability

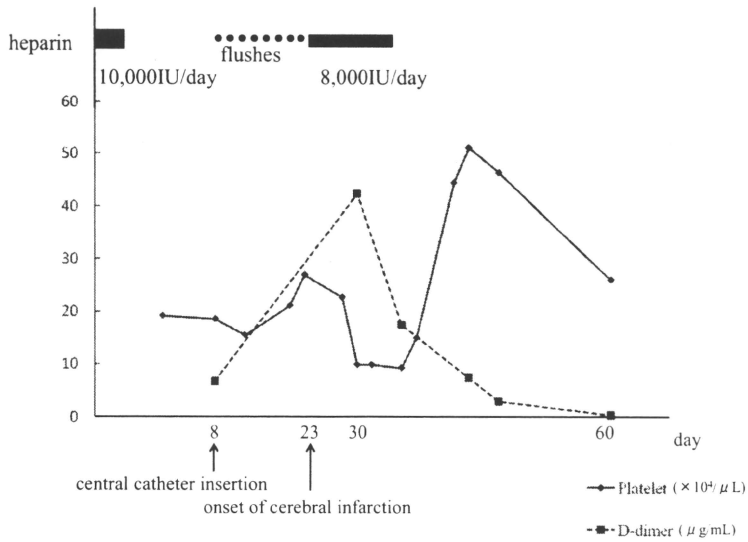

Figure 2. **Time course of the platelet count and the D-dimer level with heparin use.**

of HIT (low, 0-3; intermediate, 4-5; and high, 6-8) (3), and the score at the onset of thrombocytopenia increased to 6 points (high probability). On the other hand, the disseminated intravascular coagulation (DIC) score was 4 points, indicating a low probability of DIC. Argatroban therapy normalized the platelet count and the D-dimer level with negative HIT-Ab (OD_{405}=0.177), and the patient's condition improved within two weeks. Resolution of DVT seen on follow-up venous ultrasonography on day 56 also supported the effectiveness of argatroban.

Discussion

We report a patient with encephalitis and HIT, the combination of which has not been previously described. Even though encephalitis can cause cerebral infarction or inflammatory lesions with similar neurological deficits, the symptoms our patient which developed on day 23 were likely due to HIT-associated cerebral infarction for several reasons. First, HIT-Ab was positive with severe thrombosis and decreased platelets, and these findings were resolved by discontinuation of heparin and administration of argatroban. Second, the improved CSF findings and clinical recovery at the onset of cerebral infarction seemed to rule out aggravation of encephalitis. Furthermore, while inflammatory-associated cerebral infarction often occurs in the territories of small arteries, our patient had a new lesion in the main trunk of the left middle cerebral artery, with a high intensity DWI lesion matching the vascular territory. Development of cerebral infarction 7 days before thrombocytopenia in our patient also does not rule out HIT, since recent studies demonstrated that thrombocytopenia is often absent at the onset of thromboembolic complications and, sometimes, may be absent during the entire disease course (4). We cannot exclude the possibility that the HIT-associated cerebral infarction occurred independently of the encephalitis; however, the lack of other causes of vascular damage suggests that encephalitis may trigger or predispose to HIT-associated infarction.

The pathophysiological mechanism by which encephalitis causes HIT-associated cerebral infarction remains unknown. However, in encephalitis, vascular damage in cerebral arteries involves leukocyte infiltration into arterial walls (5). These activated leukocytes release chemokines, such as CCL 17 and CCL22, which may subsequently activate platelets, thereby releasing platelet factor 4 to form a complex with HIT-Ab and heparin (6). Thus, inflammation-mediated vascular damage in encephalitis may trigger thrombosis and subsequent HIT-associated cerebral infarction (6).

Some issues and limitations related to the present case report need to be considered. First, the dose of heparin that triggered HIT was low. A therapeutic dose (10,000 IU/day) was administered for two days, and heparin flushes (100 IU/day) were given for 15 days. It is true that HIT due to heparin flushes is rare (7), but several reports suggested a risk of HIT after exposures to small quantities of heparin from catheter flushes (8). The initial therapeutic dose may have triggered immune sensitization, and the daily small amount for heparin flush may have resulted in cerebral infarction. Second, HIT-Ab was measured by enzyme-immunoassays (EIAs) in the present case. EIAs have limited sensitivity and specificity compared to the serotonin release assay (SRA) that is considered the "gold standard" for the diagnosis of HIT (9). However, SRA is available in only a few laboratories in Japan. Although the laboratory findings (positive HIT-Ab by EIAs) did not demonstrate definite HIT in our patient, these findings in combination with a clinical score suggest the diagnosis of HIT (3). Third, the possibility of DIC and other drug-induced thrombocytopenia cannot be completely excluded. However, the low DIC score and successful treatment with argatroban, in addition to the continuation of the drugs for encephalitis, suggest that the possibil-

ity of DIC and other drug-induced thrombocytopenia was low.

Heparin is widely used as anticoagulation therapy to prevent worsening or recurrence of ischemic stroke, and it is often used as continuous infusion therapy for cardioembolic stroke. HIT sometimes causes recurrence of cerebral infarction and worsens neurological complications (10, 11). Recent reports have advocated the use of heparin to prevent DVTs in patients with a consciousness disturbance, since they have decreased spontaneous limb movements (12). However, HIT may develop with heparin therapy, especially in patients with intracranial inflammation.

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Effects of Telmisartan on Arterial Stiffness Assessed by the Cardio-Ankle Vascular Index in Hypertensive Patients

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Key Words
Albuminuria · Telmisartan · Arterial stiffness · Blood pressure · Cardio-ankle vascular index

Abstract
Background/Aims: This study was conducted to determine the effect of telmisartan on the cardio-ankle vascular index (CAVI), a novel blood pressure (BP)-independent marker for arterial stiffness in hypertensive patients. ***Methods:*** One hundred consecutive hypertensive patients were randomly assigned either to a group treated with calcium channel blocker (CCB)-based therapy or a group treated with telmisartan-based therapy. Clinical and biological parameters were then measured before and 12 months after the start of this study. ***Results:*** CAVI, the logarithm of urinary albumin excretion, and BP were reduced significantly after telmisartan-based therapy. The decreases in 24-hour diastolic BP and daytime systolic BP associated with telmisartan-based therapy were significantly greater than those associated with CCB-based therapy. Both therapies significantly and similarly decreased the clinical BP, 24-hour systolic BP, daytime diastolic BP and serum levels of low-density lipoprotein cholesterol. No significant differences in the metabolic parameters were observed between the two therapies. ***Conclusion:*** Telmisartan-based therapy had beneficial effects on arterial stiffness assessed by CAVI, albuminuria, 24-hour BP and metabolism compared with CCB-based therapy. Since these markers are known to influence the future risk of cardiovascular events, telmisartan could be a useful drug for hypertensive patients.

Introduction

Arterial stiffness is a powerful independent marker of vascular target organ damage and an independent prognostic predictor for cardiovascular morbidity and mortality [1]. In addition, arterial stiffness has been implicated as a marker for vasculature aging [2]. Its prevention and control are important in light of the growing number of patients with diabetes and hypertension. Arterial stiffness has been assessed using several methods, including pulse pressure, the augmentation index (AI) and pulse wave velocity (PWV). These parameters can easily be measured in the clinic in a matter of minutes using relatively inexpensive technology and a simple reproducible method. Each of these simple measures of arterial aging is correlated with the risk of cardiac, cerebral and vascu-

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lar events [1, 3, 4]. However, these measures cannot be used to determine whether the improvement in arterial stiffness is caused by a blood pressure (BP)-dependent effect or a BP-independent mechanism. The cardio-ankle vascular index (CAVI) is a new marker of arterial stiffness that is calculated from the PWV and adjusted according to the BP value [5]. CAVI has been shown to be closely correlated with other markers contributing to arterial stiffness, such as the carotid intima-media thickness (IMT) [6].

Several lines of experimental and clinical evidence have documented that the renin-angiotensin system (RAS) plays a key role in the pathophysiology of a number of cardiovascular diseases. Angiotensin II type 1 receptor blocker (ARB) is currently one of the most wildly used first-line antihypertensive drugs. Evidence shows that it not only reduces BP, but also has some ancillary effects on cardiovascular properties, such as the protection of heart and kidney function beyond the mere lowering of elevated BP [7]. In particular, ARB telmisartan is reported to have an agonistic activity on peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby ameliorating progression or even causing the regression of arterial stiffness [8]. In fact, treatment with telmisartan (40 mg/day for 3 months) in hypertensive patients decreased both BP and PWV [9]. However, whether telmisartan improves CAVI, which is less dependent on BP [5], remains uncertain.

The aim of this study was to assess the effects of an ARB telmisartan on markers of arterial stiffness using CAVI, AI and the maximum of the carotid intima-media thickness (MAX-IMT), along with urinary albumin excretion (UAE) and brain natriuretic peptide (BNP), which are known surrogate markers for cardiovascular morbidity and mortality in hypertensive patients [10].

Patients and Methods

Study Population and Design

The subjects of the present study were comprised of 100 consecutive patients with untreated hypertension or uncontrollable hypertension treated with medications other than RAS inhibitors. Hypertension was defined as follows. In patients without comorbid illness, hypertension was defined as a clinical systolic BP of >140 mm Hg and/or a clinical diastolic BP of >90 mm Hg at any time, and/or a systolic ambulatory BP of >130 mm Hg and/or a diastolic ambulatory BP of >85 mm Hg in the morning. In patients with diabetes mellitus, hypertension was defined as a clinical systolic BP of >130 mm Hg and/or a clinical diastolic BP of >80 mm Hg at any time.

All the patients were randomly assigned to either a group treated with calcium channel blocker (CCB)-based therapy or a group treated with telmisartan-based therapy. The randomization was performed by the envelop method. The target BP was defined as <130/85 mm Hg in patients without any complications and <130/80 mm Hg in patients with diabetes mellitus, chronic kidney disease or metabolic syndrome. Patients treated with CCB-based therapy were first treated with 20 mg/day of nifedipine, 2.5 mg/day of amlodipine, 5 mg/day of cilnidipine or 2 mg/day of benidipine for 4 weeks, and the doses of the CCBs were subsequently increased every 4 weeks until the target BP was attained (up to 60 mg/day of nifedipine, 10 mg/day of amlodipine, 20 mg/day of cilnidipine and 8 mg/day of benidipine). If the target BP was not achieved, ARBs, β-blockers, diuretics and ACE inhibitors were subsequently added. Patients treated with telmisartan-based therapy were first treated with 20 mg/day of telmisartan for 4 weeks, and the telmisartan dose was subsequently increased every 4 weeks until the target BP was attained (up to a maximum dose of 80 mg/day). The CCBs and diuretics were subsequently added unless the BP fell below the target BP. Clinical and biological parameters were measured before and 12 months after the start of this study. During the study period, previous medications and therapies other than antihypertensive drugs were continued. The subjects were not blinded to the treatment, although all measurements were performed under blind conditions.

The study was approved by the review board of Keio University Medical School Hospital and written informed consent was obtained from every subject.

Serum levels of creatinine, potassium, uric acid, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), glucose and glycoalbumin, and plasma levels of BNP, the active renin concentrations (ARC) and aldosterone (PAC) were measured in venous blood samples. The logarithm of urinary albumin excretion (log UAE) was measured in urinary samples drawn on the morning after an overnight fast on the same days as the ankle-brachial index (ABI), CAVI, AI, BP and MAX-IMT measurements were performed.

Ambulatory BP Monitoring

An oscillometric-based device (TM-2431; A&D Co., Tokyo, Japan) was used to perform 24-hour ambulatory BP monitoring. BP was measured every 30 min during the day (between 6:00 a.m. and 10:00 p.m.) and every 60 min during the night (between 10:00 p.m. and 6:00 a.m.). The mean values and the standard deviations of the ambulatory BP for each subject were calculated for a 24-hour period. The standard deviation of the ambulatory BP values was recorded as the variability of ambulatory BP in this study. The nocturnal decrease in BP was calculated as the average systolic BP during the day minus the average systolic BP during the night. The morning BP surge was calculated as the highest systolic BP during the first 2 hours after waking minus the lowest systolic BP during the night.

Cardio-Ankle Vascular Index

CAVI was measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi Co. Ltd., Tokyo, Japan), as described previously [11]. Cuffs were applied to bilateral upper arms and ankles, with the subjects lying in a supine position with their heads held along the midline. ECG electrodes were placed on both

wrists and a microphone for detecting heart sounds was placed over the sternum. The patients rested in this supine position for at least 10 min before the start of monitoring. CAVI was calculated using the following formula:

$$CAVI = a\ \{(2\rho/\Delta P) \times \ln (Ps/Pd)\ PWV^2\} + b,$$

where Ps is the systolic BP, Pd is the diastolic BP, ΔP is Ps – Pd, ρ is blood density, and a and b are constants.

Augmentation Index

AI was measured using an automated tonometric device (HEM-9000AI; Omron Healthcare Co. Ltd., Kyoto, Japan), as described previously [12]. Peripheral pressure waveforms were recorded over 30 s from the radial artery at the wrist with the subjects in a sitting position after resting for at least 5 min. AI was calculated using the following formula:

AI = (late systolic BP – diastolic BP)/(systolic BP – diastolic BP) × 100 (%).

Urinary Albumin Excretion

UAE was evaluated on the basis of the mean albumin-to-creatinine ratio in three nonconsecutive overnight urine samples. The urinary concentrations of albumin and creatinine were determined using a turbidimetric immunoassay with a Superior-Microalbumin kit (DPC Co., Tokyo, Japan) and with the Jaffé reaction using an autoanalyzer.

Carotid Intima-Media Thickness

Ultrasonography B-mode imaging of the carotid artery was performed using a PowerVision 6000 machine (Toshiba, Tokyo, Japan) at a transducer frequency of 7.5 MHz. Each subject was examined while in a supine position. Up to 4 cm of the common carotid artery and the carotid bulb were scanned bilaterally using longitudinal and transverse projections. The images were focused on the far wall of the artery. IMT was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall, and the greatest IMT value in the bilateral longitudinal projections was recorded as the maximum IMT. The IMT was measured within plaque-free areas. The mean intraobserver and interobserver coefficients of variation for the maximum IMT were 4.3 and 4.7%, respectively.

Statistical Analyses

Analyses were performed using Microsoft Office Excel 2007 and StatView 5.0. software (SAS Institute Inc., Cary, N.C., USA). Fisher's exact test was used to analyze sex and the frequency of diabetes mellitus, smoking and the use of statins. The Mann-Whitney U test was used to analyze age and body mass index. Changes in biological parameters were analyzed using Student's t test and a two-way analysis of variance for repeated measures combined with Tukey-Kramer post hoc tests. The contributions of changes in variables to changes in CAVI were tested using a regression analysis and an analysis of covariance. A p value <0.05 was considered significant. Data are presented as the means ± SD.

Table 1. Patient characteristics at baseline

Characteristics	CCB-based	Telmisartan-based	p
Number	50	50	0.999
Age, years	51.0 ± 10.0	52.4 ± 8.7	0.615
Male gender, n	35	39	0.495
BMI	25.4 ± 4.1	24.1 ± 3.7	0.412
WC, cm	86.9 ± 9.9	89.0 ± 8.1	0.452
DM, n	6	7	0.999
Smoker, n	14	14	0.999
Use of statins, n	12	10	0.810
Serum Cr, mg/dl	0.88 ± 0.34	0.84 ± 0.14	0.539
Serum K, mEq/l	4.3 ± 0.3	4.4 ± 0.4	0.062
Serum UA, mg/dl	6.2 ± 1.4	6.1 ± 1.5	0.626
Serum TG, mg/dl	165 ± 126	166 ± 128	0.964
Serum HDL-C, mg/dl	57 ± 15	53 ± 13	0.213
Serum LDL-C, mg/dl	130 ± 34	121 ± 24	0.142
GA, %	14.5 ± 1.9	14.7 ± 1.8	0.609
BNP, pg/ml	11.0 ± 8.3	11.2 ± 11.9	0.927
Plasma ARC, pg/ml	12.1 ± 17.0	9.6 ± 8.7	0.363
Log UAE	1.16 ± 0.69	1.03 ± 0.66	0.445
ABI	1.13 ± 0.13	1.16 ± 0.08	0.188
CAVI	7.8 ± 1.3	8.2 ± 1.0	0.051
AI, %	80.1 ± 16.2	83.7 ± 13.6	0.408
max IMT, mm	1.1 ± 0.8	1.2 ± 0.6	0.394

Data are the means ± SD. WC = Waist circumference; DM = diabetes mellitus; Cr = creatinine; K = potassium; UA = uric acid; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; GA = glycoalbumin.

Results

Table 1 shows that no significant differences in baseline patient characteristics were observed between the group treated with CCB-based therapy and the group treated with telmisartan-based therapy. At the end of the study, the numbers of patients in the group treated with CCB-based therapy who had been prescribed additional antihypertensive medication were as follows: 5 for losartan, 4 for valsartan, 2 for olmesartan, 7 for candesartan, 2 for enalapril, 3 for diuretics, and 10 for β-blockers. In the group treated with telmisartan-based therapy, 3 patients were additionally treated with diuretics and 17 were treated with CCB.

Table 2 shows the changes in BP during the 12-month treatment period. No significant differences in the baseline BP were observed between the group treated with CCB-based therapy and the group treated with telmisartan-based therapy. The clinical systolic BP decreased significantly after the CCB-based therapy and also de-