

Low-Dose Aspirin Therapy in Patients With Type 2 Diabetes and Reduced Glomerular Filtration Rate

Subanalysis from the JPAD trial

YOSHIHIKO SAITO, MD, PHD¹
 TAKESHI MORIMOTO, MD, PHD²
 HISAO OGAWA, MD, PHD³
 MASAFUMI NAKAYAMA, MD, PHD³
 SHIRO UEMURA, MD, PHD¹
 NAOFUMI DOI, MD, PHD¹
 HIDEAKI JINNOUCHI, MD, PHD⁴
 MASAKO WAKI, MD, PHD⁵

HIROFUMI SOEJIMA, MD, PHD³
 SEIGO SUGIYAMA, MD, PHD³
 SADANORI OKADA, MD¹
 YASUHIRO AKAI, MD, PHD¹
 ON BEHALF OF THE JAPANESE PRIMARY
 PREVENTION OF ATHEROSCLEROSIS WITH
 ASPIRIN FOR DIABETES (JPAD) TRIAL
 INVESTIGATORS*

OBJECTIVE—Type 2 diabetes accompanied by renal damage is a strong risk factor for atherosclerotic events. The purpose of this study was to investigate the efficacy of low-dose aspirin therapy on primary prevention of atherosclerotic events in patients with type 2 diabetes and coexisting renal dysfunction.

RESEARCH DESIGN AND METHODS—The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was a prospective, randomized, open-label trial conducted throughout Japan that enrolled 2,539 type 2 diabetic patients without a history of atherosclerotic diseases. Patients were assigned to the aspirin group (81 mg/day or 100 mg/day) or the nonaspirin group and followed for a median of 4.37 years. The primary end points were atherosclerotic events of fatal and nonfatal ischemic heart disease, stroke, and peripheral arterial disease.

RESULTS—The analysis included 2,523 patients who had serum creatinine measured. In 1,373 patients with baseline estimated glomerular filtration rate (eGFR) 60–89 mL/min/1.73 m², the incidence of primary end points was significantly lower in the aspirin group than in the nonaspirin group (aspirin, 30/661; nonaspirin, 55/712; hazard ratio 0.57 [95% CI 0.36–0.88]; *P* = 0.011). Low-dose aspirin therapy did not reduce primary end points in patients with eGFR ≥90 mL/min/1.73 m² (aspirin, 9/248; nonaspirin, 11/270; 0.94 [0.38–2.3]) or those with eGFR <60 mL/min/1.73 m² (aspirin, 29/342; nonaspirin, 19/290; 1.3 [0.76–2.4]). The Cox proportional hazard model demonstrated a significant interaction between mild renal dysfunction (eGFR 60–89 mL/min/1.73 m²) and aspirin (*P* = 0.02).

CONCLUSIONS—These results suggest a differential effect of low-dose aspirin therapy in diabetic patients with eGFR 60–89 mL/min/1.73 m².

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D diabetes is a strong risk factor for cardiovascular (CV) events. However, the primary prevention strategy for CV events remains to be established (1). In patients with type 2 diabetes, the presence of coexisting renal damage is associated with an increased incidence of CV events (2–4). Although diabetic

nephropathy is diagnosed by pathological examination, the presence of albuminuria is clinically adopted as pathognomonic manifestation of diabetic nephropathy.

Recently, the National Kidney Foundation (5) defines chronic kidney disease as persistent kidney damage of any underlying cause, as reflected by estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² for more than 3 months. eGFR <60 mL/min/1.73 m² is the cutoff because it has been identified as a predictor of CV events in the general population (6), in patients with diabetes (3,4), and in patients with other CV risk factors (6,7). Given that nearly two thirds of diabetic patients with eGFR <60 mL/min/1.73 m² have normal albuminuria (8), American Diabetes Association (ADA) guidelines (9) recommend that serum creatinine should be measured at least annually and used to calculate eGFR in all diabetic patients, regardless of the degree of albuminuria (8,9). Thus, to establish the primary prevention strategy for diabetic patients with renal damage, a GFR-based approach might be helpful.

Low-dose aspirin therapy has previously been recommended by several key guidelines for primary prevention of CV events in patients with diabetes, although with some inconsistencies (1,9). In 2010, the ADA, the American Heart Association, and the American College of Cardiology Foundation convened a group of experts to create updated recommendations for the primary prevention strategy of low-dose aspirin use in patients with diabetes (1). They performed a new meta-analysis that included two recent randomized controlled trials of aspirin, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial (10), and the Prevention of Progression of Arterial Diseases and Diabetes (POPADAD) trial (11). Both trials enrolled only patients with diabetes and neither showed any significant effect of aspirin to prevent atherosclerotic events.

Based on the currently available evidence (12,13), aspirin appears to have a

From the ¹First Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan; the ²Center for Medical Education, Kyoto University Graduate School of Medicine, Kyoto, Japan; the ³Department of Cardiovascular Medicine, Graduate Medical School of Medical Science, Kumamoto University, Kumamoto, Japan; ⁴Jinnouch Hospital, Kumamoto, Japan; and the ⁵Division of Endocrinology and Metabolism, Department of Internal Medicine, Shizuoka City Hospital, Shizuoka, Japan.

Corresponding author: Yoshihiko Saito, yssaito@naramed-u.ac.jp.

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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 m² 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 m²), 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 m²) 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 m² variable. The included variables were aspirin, dummy variable for eGFR 60–89 mL/min/1.73 m² (relative to eGFR ≥90 mL/min/1.73 m²), dummy variable for eGFR <60 mL/min/1.73 m² (relative to eGFR ≥90), interaction variable between eGFR 60–89 mL/min/1.73 m² 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 m².

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 m² 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 m², 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 \geq 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 \geq 90 mL/min/1.73 m² 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 m² (HR 1.6 [95% CI 1.0–2.7]; $P = 0.048$) and in patients with eGFR <60 mL/min/1.73 m² (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 m² (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. 1B). The Cox proportional hazard model demonstrated significant

interaction between mild renal dysfunction (eGFR 60–89 mL/min/1.73 m²) and aspirin use ($P = 0.02$). However, there was no significant difference in the incidence of primary end points in patients with eGFR \geq 90 mL/min/1.73 m² (nine events in the aspirin group and 11 events in the nonaspirin group; 0.94 [0.38–2.3]) (Fig. 1A), or those with eGFR <60 mL/min/1.73 m² (29 events in the aspirin group and 19 in the nonaspirin group; 1.3 [0.76–2.4]) (Fig. 1C). 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 m² (0.53 [0.34–0.83]; $P = 0.0052$), and not in patients with eGFR \geq 90 or <60 mL/min/1.73 m² (eGFR \geq 90 mL/min/1.73 m²: 0.87 [0.36–2.14]; eGFR <60 mL/min/1.73 m²: 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 m² (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 m² (1.15 [0.45–2.95]; $P = 0.76$) and those with eGFR <60 mL/min/1.73 m² (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 m², low-dose aspirin

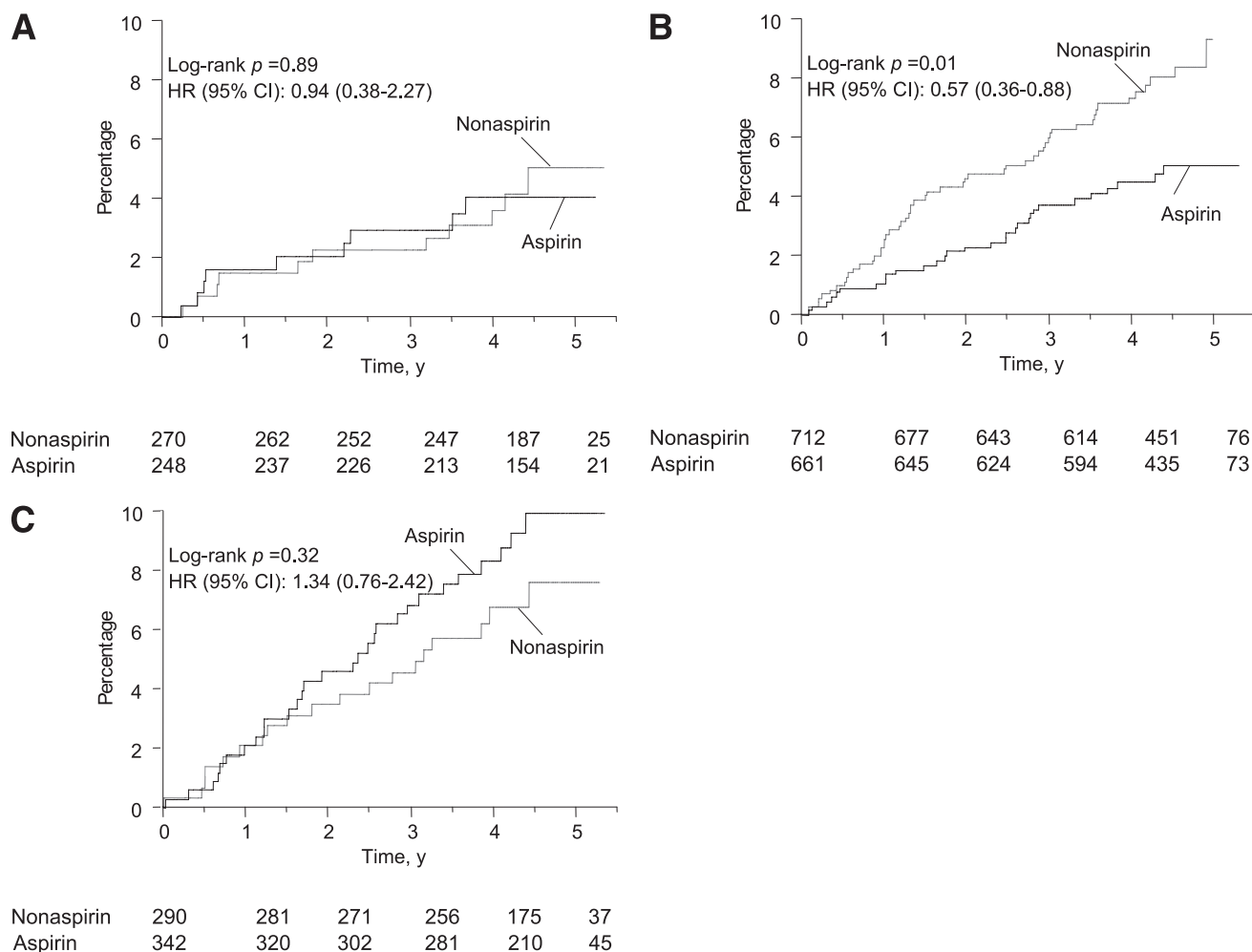


Figure 1—Percentage of primary end points by category of patients with eGFR of at least 90 mL/min/1.73 m² (A), 60–89 mL/min/1.73 m² (B), or <60 mL/min/1.73 m² (C).

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 m².

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 m², but not in those with either eGFR <60 mL/min/1.73 m² or at least 90 mL/min/1.73 m². In the subgroup of patients with eGFR 60–89 mL/min/1.73 m², 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 sub-analysis 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,

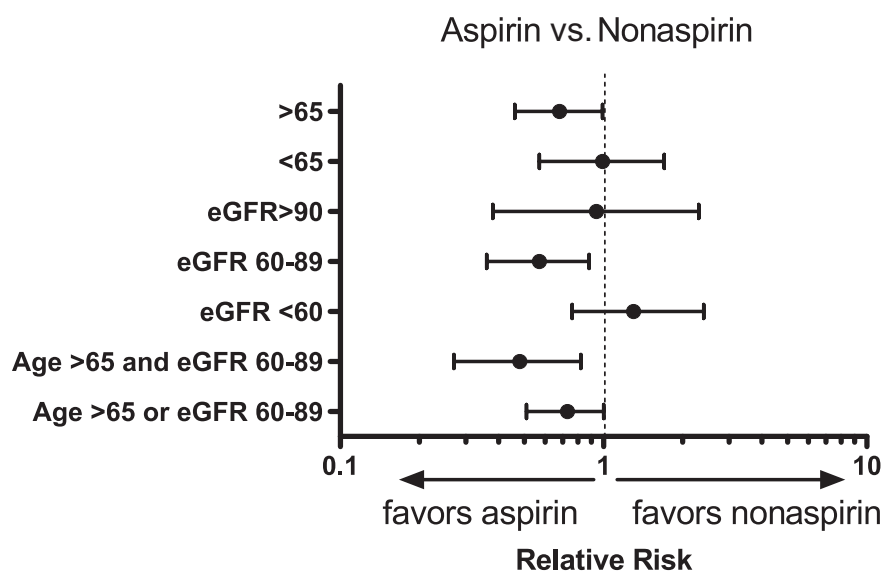


Figure 2—Subgroup analysis of incidence of primary end points.

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 m², 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 m². 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/1.73m² (aspirin, 11/264; placebo 32/272; HR 0.34 [95% CI 0.17–0.67]), and not in those with eGFR ≥60 mL/min/1.73m² (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 m² 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 m² 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 m²—a usual cutoff value—was associated with increased atherosclerotic risk, but in addition, eGFR 60–89 mL/min/1.73 m² 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 m² 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 m². 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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