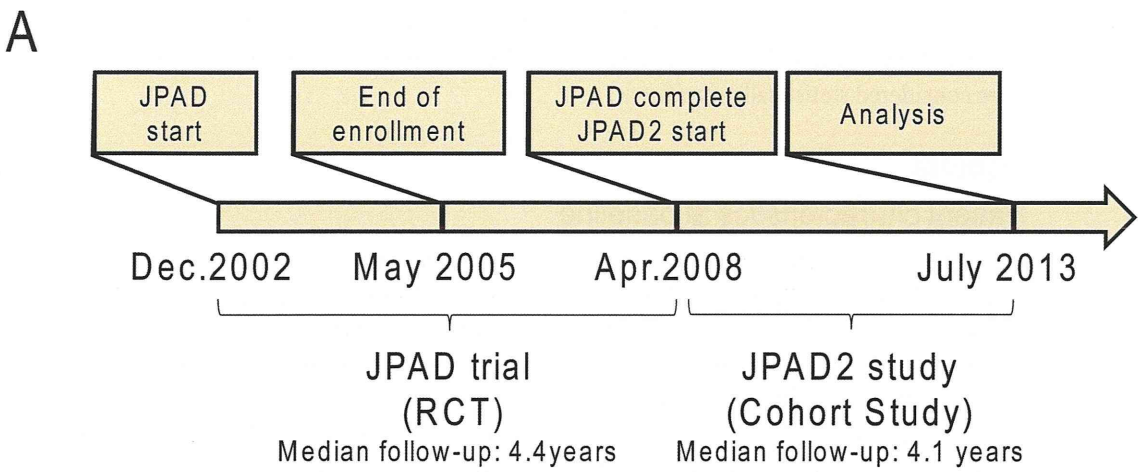

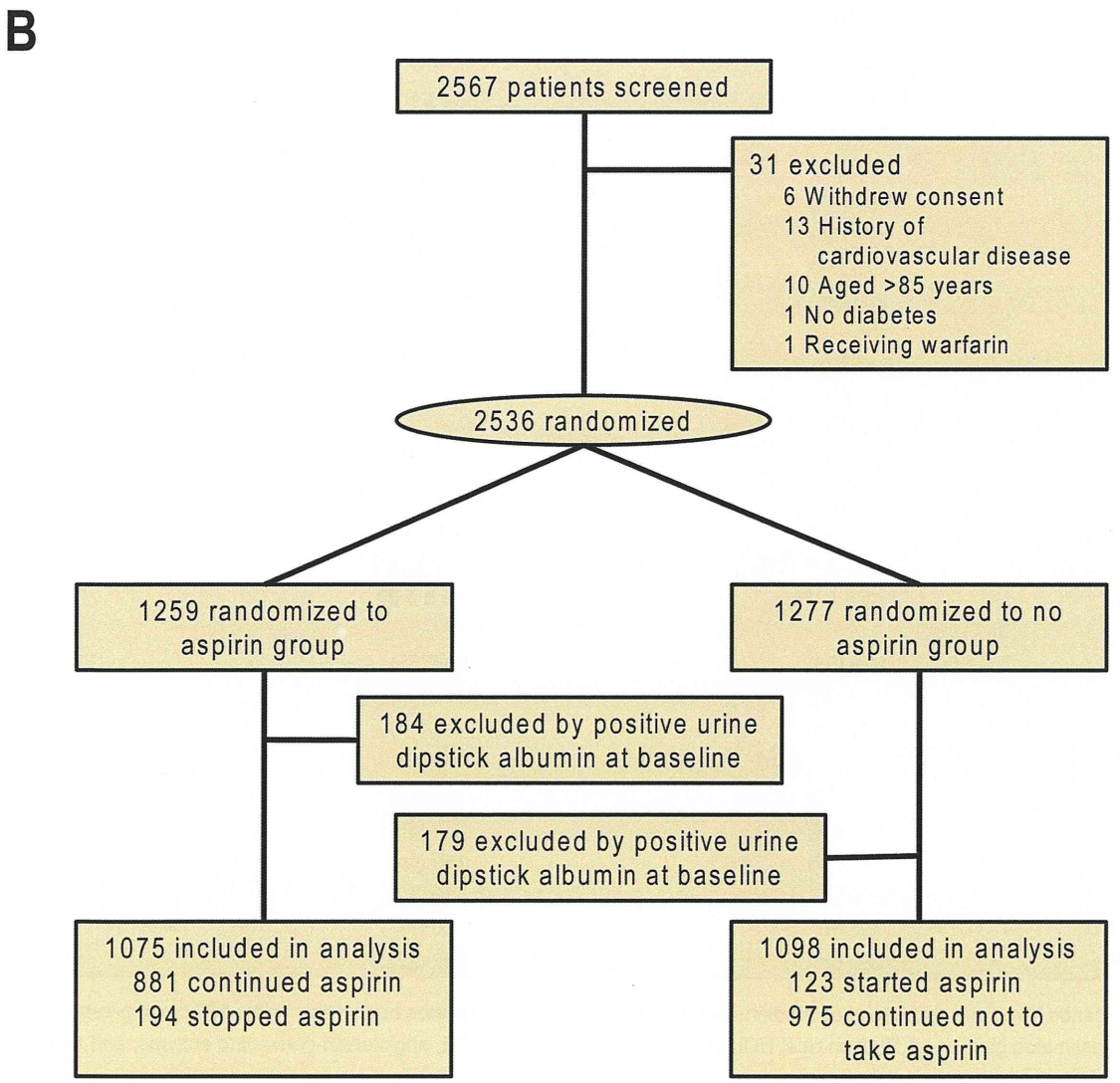

Fig 1. Timeline of the JPAD2 cohort study. A, The timeline of the JPAD trial and the JPAD2 cohort study. RCT indicates randomized controlled trial. **B,** The flow chart of the JPAD trial and the JPAD2 cohort study.

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Statistical analyses were conducted by an independent statistician (T.M.) with the use of JMP 8.0 (SAS Institute, Cary, NC) and SAS 9.4 (SAS Institute) software. *P* values less than 0.05 were considered statistically significant.

Results

Patient characteristics at baseline

We included 2,173 patients with negative urine dipstick albumin at baseline of the original JPAD trial (Table 1). There were 1,075 patients in the aspirin group and 1,098 patients in the no aspirin group. The mean age ± SD was 65 ± 10 years in the aspirin group and 64 ± 10 years in the no aspirin group ($P = 0.01$). The aspirin group had a slightly higher mean serum creatinine level than the no aspirin group (aspirin group, 68 ± 19 μmol/L; no aspirin group, 66 ± 18 μmol/L; $P = 0.04$), but there were no significant differences in eGFR at baseline (aspirin group, 74.0 ± 19.3 ml/min/1.73m^2; no aspirin group, 75.6 ± 20.0 ml/min/1.73m^2; $P = 0.06$).

Table 1. Patients' characteristics at baseline of the original JPAD trial.

	Aspirin	No aspirin	*P* value
N	1075	1098	
Age, y	65 ± 10	64 ± 10	0.01
Male	592 (55)	573 (52)	0.2
BMI, kg/m^2	24 ± 4	24 ± 4	0.4
Duration of diabetes, y	7.2 (2.8–12.2)	6.5 (2.9–12.1)	0.4
Hypertension	604 (56)	605 (55)	0.6
Dyslipidemia	578 (54)	568 (52)	0.3
History of smoking	234 (22)	210 (19)	0.1
Systolic BP, mmHg	135 ± 15	134 ± 14	0.06
Diastolic BP, mmHg	77 ± 9	76 ± 9	0.03
FPG, mmol/L	8.1 ± 2.7	8.0 ± 2.6	0.7
HbA1c, %	7.5 ± 1.4	7.4 ± 1.2	0.09
Serum creatinine, μmol/L	0.77 ± 0.22	0.75 ± 0.20	0.04
eGFR, ml/min/1.73m^2	74.0 ± 19.3	75.6 ± 20.0	0.06
Total cholesterol, mmol/L	5.22 ± 0.88	5.17 ± 0.88	0.1
Fasting triglycerides, mmol/L	1.28 (0.89–1.78)	1.25 (0.89–1.81)	0.5
HDL cholesterol, mmol/L	1.45 ± 0.41	1.45 ± 0.39	0.9
Medications			
Sulfonylurea	619 (58)	604 (55)	0.2
α-glycosidase inhibitor	353 (33)	363 (33)	0.9
Biguanide	134 (12)	156 (14)	0.2
Thiazolidinedione	51 (5)	49 (4)	0.8
Insulin	138 (13)	130 (12)	0.5
Calcium channel blocker	344 (32)	358 (33)	0.8
ACE inhibitor	145 (13)	159 (14)	0.5
ARB	209 (19)	210 (19)	0.9
β-blocker	61 (6)	76 (7)	0.2
Statin	266 (25)	292 (27)	0.3

Duration of diabetes and fasting triglyceride levels are expressed as medians (interquartile range). BMI indicates body mass index; BP, blood pressure; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HDL, high- density lipoprotein; ACE, angiotensin-converting enzyme; and ARB, angiotensin II type 1 receptor blocker.

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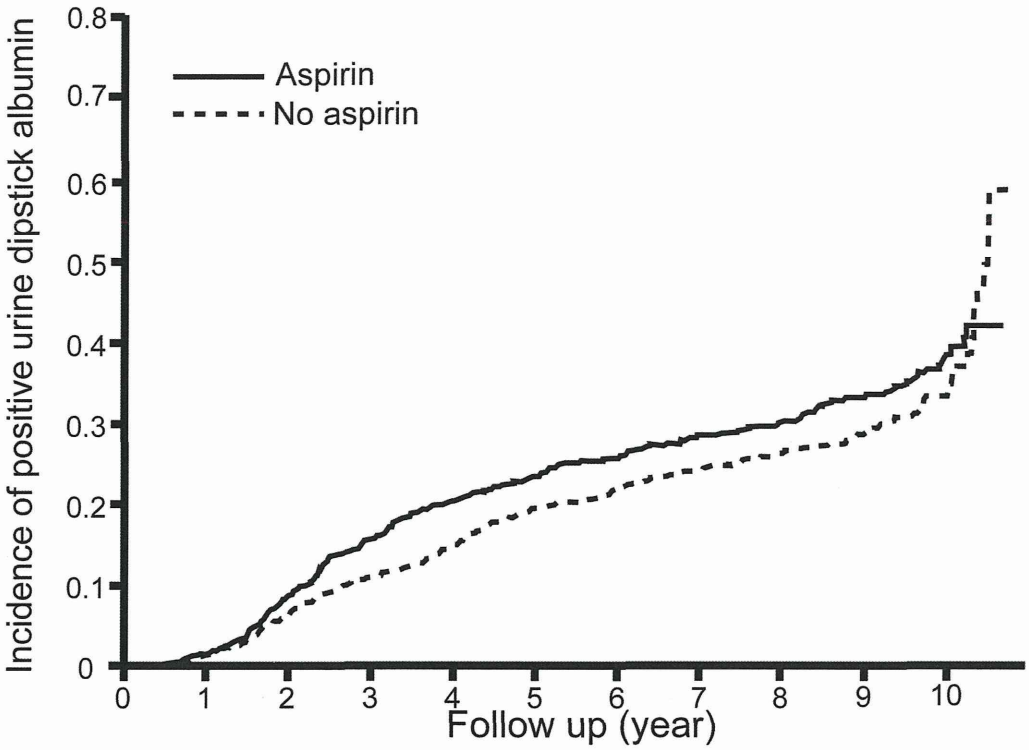

No. at risk											
Aspirin	1075	983	869	759	675	591	532	451	393	297	79
No aspirin	1098	1013	922	841	761	662	611	533	462	337	101

Incidence										
Aspirin	0.02	0.09	0.16	0.21	0.24	0.26	0.29	0.31	0.34	0.39
No aspirin	0.02	0.07	0.11	0.15	0.20	0.22	0.25	0.27	0.29	0.34

Fig 2. Incidence of positive urine dipstick albumin in patients on long-term low-dose aspirin therapy in the intention-to-treat analysis. Positive urine dipstick albumin developed in 297 patients in the aspirin group and 270 patients in the no aspirin group. The intention-to-treat analysis showed that low-dose aspirin did not increase the incidence of positive urine dipstick albumin (HR, 1.17; 95% CI, 0.995 to 1.38; log-rank $P = 0.057$)

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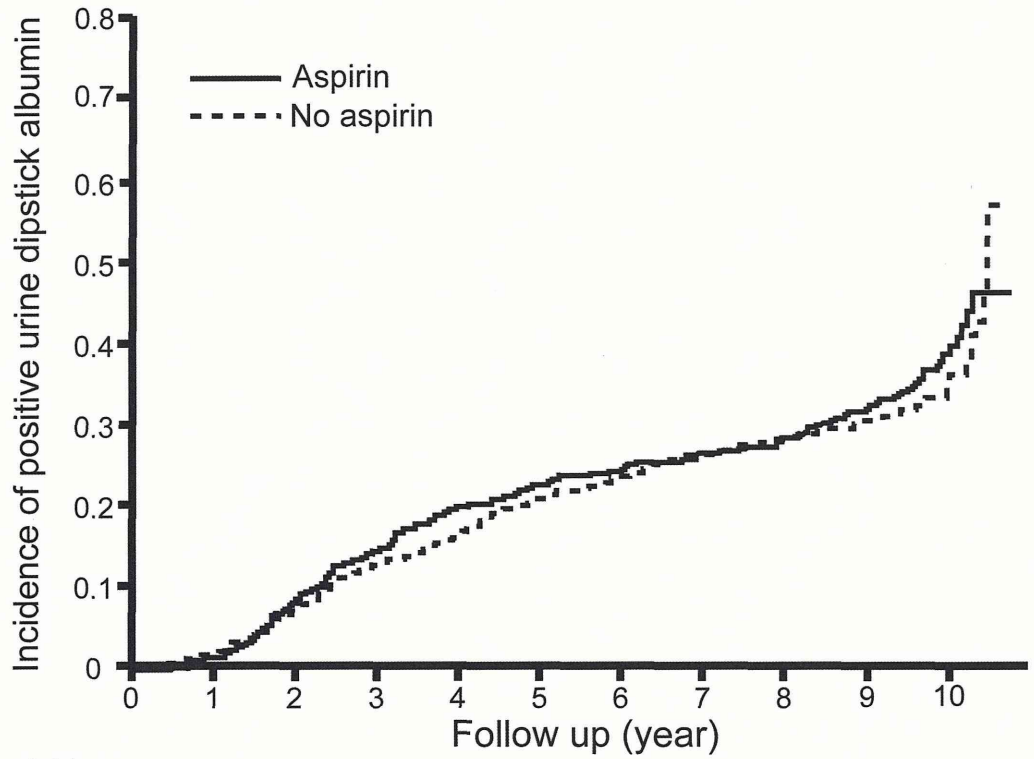
Diastolic blood pressure was significantly higher by 1 mmHg in the aspirin group (aspirin group, 77 ± 9 mmHg; no aspirin group, 76 ± 9; $P = 0.03$). There were no differences in systolic blood pressure, prevalence of hypertension, and use of antihypertensives.

Effect of low-dose aspirin on the incidence of positive urine dipstick albumin

The median duration of follow-up was 8.5 years (95% CI, 8.3 to 8.7 years), which includes the RCT period of the JPAD trial. During the follow-up period, positive urine dipstick albumin developed in 297 patients in the aspirin group and 270 patients in the no aspirin group. Kaplan-Meier curves based on the intention-to-treat principle showed that low-dose aspirin does not increase the incidence of positive urine dipstick albumin (HR, 1.17; 95% CI, 0.995 to 1.38; log-rank $P = 0.057$; Fig 2).

Since the JPAD2 cohort study was a cohort study, the use of low-dose aspirin was based on each treating physician's clinical judgment after the RCT period of the JPAD trial. In July 2013 survey, 881 (82%) patients in the aspirin group and 123 (11%) in the no aspirin group were taking low-dose aspirin (Fig 1B). When we took into account the actual use of low-dose aspirin



No. at risk											
Aspirin	1004	920	816	719	636	559	506	436	375	291	72
No aspirin	1169	1076	975	881	800	694	637	548	480	343	108

Incidence										
Aspirin	0.02	0.09	0.15	0.20	0.23	0.25	0.27	0.29	0.32	0.39
No aspirin	0.02	0.07	0.13	0.16	0.21	0.24	0.26	0.29	0.31	0.34

Fig 3. Incidence of positive urine dipstick albumin in patients on long-term low-dose aspirin therapy in the on-treatment analysis. In the on-treatment analysis, low-dose aspirin had no effect on the incidence of positive urine dipstick albumin (HR, 1.08; 95% CI, 0.92 to 1.28; log-rank $P = 0.32$).

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(on-treatment analysis), the incidence of positive urine dipstick albumin was not associated with the use of low-dose aspirin (HR, 1.08; 95% CI, 0.92 to 1.28; log-rank $P = 0.32$; Fig 3).

Multivariable analysis of the incidence of positive urine dipstick albumin

The multivariable Cox proportional hazards models were performed in 2,159 patients, since there were 14 missing data in serum creatinine at baseline. The multivariable analyses showed that low-dose aspirin was not associated with the incidence of positive urine dipstick albumin in the intension-to-treat analysis (HR, 1.12; 95% CI, 0.95 to 1.32) and the on-treatment analysis (HR, 1.08; 95% CI, 0.92 to 1.27) (Table 2). The incidence of positive urine dipstick albumin was higher among the elderly (≥65 years old) and those with elevated serum creatinine, high HbA1c (≥7.2%), or high blood pressure in both analyses.

Annual changes in eGFR

The analysis of annual changes in eGFR included 1,574 patients (aspirin group, 766; no aspirin group, 808), because there were 599 missing data in eGFR at follow-up. The annual change in

Table 2. Multivariable analysis of the incidence of positive urine dipstick albumin.

	HR	95% CI		
Intention-to-treat analysis				
Aspirin use	1.12	0.95	to	1.32
Age ≥65 years	1.23	1.04	to	1.46
Male sex	0.95	0.79	to	1.15
Serum creatinine	2.59	1.71	to	3.93
HbA1c ≥7.2%	1.38	1.16	to	1.63
Systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg	1.78	1.48	to	2.13
ACE inhibitor or ARB use at baseline	1.11	0.91	to	1.35
ACE inhibitor / ARB use at the time of the follow-up survey in 2009	0.98	0.81	to	1.18
On-treatment analysis				
Aspirin use	1.08	0.92	to	1.27
Age ≥65 years	1.24	1.04	to	1.46
Male sex	0.95	0.79	to	1.15
Serum creatinine	2.61	1.72	to	3.96
HbA1c ≥7.2%	1.38	1.16	to	1.63
Systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg	1.80	1.50	to	2.15
ACE inhibitor or ARB use at baseline	1.10	0.91	to	1.33
ACE inhibitor / ARB use at the time of the follow-up survey in 2009	0.99	0.82	to	1.19

BP indicates blood pressure; ACE, angiotensin-converting enzyme; and ARB, angiotensin II type 1 receptor blocker.

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eGFR was −0.8 ± 2.9 ml/min/1.73m^2/year in the aspirin group, and −0.9 ± 2.5 ml/min/1.73m^2/year in the no aspirin group. There was no significant difference in the both group ($P = 0.2$).

Discussion

Low-dose aspirin therapy is recommended for preventing CVD in high-risk patients with diabetes [14, 15]. However, it remained uncertain whether long-term low-dose aspirin use affects renal function in patients with diabetes. Also in people without diabetes, the association between aspirin and the risk of CKD was controversial.

Previous case-control studies that estimated the cumulative aspirin dose in patients with CKD and those without CKD have produced conflicting results. Some case-control studies have found a positive association between aspirin use and CKD prevalence [4, 5], while other studies have found no association [6, 7].

Several large cohort studies were conducted to examine whether long-term aspirin use affects renal function in healthy people and patients with CKD. One cohort study in healthy people was based on the Physicians' Health Study. In this study, a total of 11,032 initially healthy men were followed for 14 years. The association between renal function based on serum creatinine and creatinine clearance and cumulative aspirin dose was not observed [8]. Another cohort study analyzed the association between changes in eGFR over 11 years and cumulative aspirin dose among 1,697 initially healthy women from the Nurses' Health Study. The study concluded that long-term aspirin use was not associated with renal dysfunction [10]. On the other hand, a cohort study of 19,163 patients with newly diagnosed CKD in Taiwan found that aspirin use was associated with an increased risk of ESRD [11]. The effect of aspirin on renal dysfunction in healthy individuals and patients with CKD may differ.

Most clinical studies evaluated renal function using serum creatinine, creatinine clearance, or eGFR, not albuminuria nor proteinuria. Recently, a nationwide cross-sectional study based on data from the National Health and Nutrition Examination Survey analyzed the association between habitual analgesic use and albuminuria prevalence in 8,057 US adults [13]. It showed that the prevalence of albuminuria (urinary albumin-to-creatinine ratio of 30 mg/g or greater) was similar in people with habitual aspirin use and those without habitual use of any analgesics. Since albuminuria and proteinuria occur before eGFR declines in some conditions such as diabetes [17], this study was notable in using albuminuria as a marker of renal dysfunction. However, this study was a cross-sectional study. Prospective studies were needed to assess the effect of low-dose aspirin on albuminuria or proteinuria.

A previous prospective study reported 'high-dose' aspirin reduced proteinuria in patients with diabetes. This study showed that 6 weeks of aspirin (990 mg/day) and dipyridamole (225 mg/day) reduced urinary protein excretion without changes in blood pressure and plasma glucose levels in 16 patients with type 1 diabetes [23]. Although the sample size was small, the results suggested that short-term high-dose aspirin had beneficial effects on proteinuria in patients with diabetes. Subsequently, more prospective studies were conducted to examine whether 'low-dose' aspirin affects albuminuria in patients with diabetes. These studies recruited patients with diabetes and microalbuminuria (urinary albumin excretion of 30 to 300 mg/day), who were then treated with low-dose aspirin (150 mg/day) for 4 weeks. There were no changes in urinary albumin excretion and eGFR [24, 25], suggesting that low-dose aspirin therapy does not affect albuminuria in patients with diabetes. However, these studies had relatively short follow-up periods. Long-term studies were required to evaluate the effect of low-dose aspirin on albuminuria or proteinuria in patients with diabetes.

The present study assessed for the first time whether long-term low-dose aspirin affects the incidence of positive urine dipstick albumin in patients with type 2 diabetes. Both intention-to-treat analysis and on-treatment analysis showed that low-dose aspirin did not increase the incidence of positive urine dipstick albumin for a median follow-up of 8.5 years. The multivariable Cox proportional hazards models also showed that low-dose aspirin did not increase the risk of positive urine dipstick albumin, adjusting age, sex, serum creatinine, hemoglobin A1c, blood pressure, blood pressure, and treatment with ACE inhibitors and ARBs.

Our study has several limitations. First, we did not have data about habitual analgesic use. Habitual analgesic use might affect the relationship between low-dose aspirin and renal function. Second, we did not quantify the degree of albuminuria. It is possible that we underestimated the effect of aspirin on renal function, because albuminuria is a very early change in diabetic nephropathy. Third, we measured urine dipstick albumin, not by evaluating the urinary albumin–creatinine ratio. Dipstick-positivity may be affected by various conditions, such as sample volume and urine specific gravity. Finally, the JPAD2 cohort study was a cohort study after the RCT period. However, over 80% of patients remained in the original allocation for aspirin as of the 2013 follow-up. The on-treatment analysis and multivariable analysis also showed similar results.

We concluded that low-dose aspirin therapy does not affect eGFR and the incidence of positive urine dipstick albumin during a median follow-up of 8.5 years. Although aspirin is a type of cyclooxygenase inhibitor, our findings suggest that long-term low-dose aspirin therapy is safe with respect to renal function for patients with type 2 diabetes.

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Membership of the JPAD trial / the JPAD2 cohort study

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Independent Statistical Analysis: Dr Morimoto is a statistician at Department of Clinical Epidemiology, Hyogo College of Medicine

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Author Contributions

Conceived and designed the experiments: SO TM HO MS HS MN YS. Analyzed the data: SO TM YS. Contributed reagents/materials/analysis tools: SO HO HS HJ MW YA HI YS. Wrote the paper: SO TM YS.

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Original Article

Impact of Total Risk Management on Coronary Plaque Regression in Diabetic Patients with Acute Coronary Syndrome

- Sub Analysis of JAPAN-ACS Study -

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Aim: Diabetic patients with coronary artery disease have a high incidence of cardiovascular events, which was associated with increased coronary plaque volume. Low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) play pivotal roles in the progression of coronary plaque. Several trials have shown that intervention for a single risk factor reduced the development of coronary plaque progression. However, it remained uncertain whether total risk management for LDL-C, BP, and glycosylated Hb (HbA1c) has a beneficial effect on coronary plaque volume in diabetic patients.
Methods: This study was a sub-study of the JAPAN-ACS that was a prospective, randomized, open-label trial that evaluated the impact of intensive lipid-lowering therapy on coronary plaque volume in patients with acute coronary syndrome (ACS). Among a total of 252 patients, 73 diabetic patients were analyzed. We examined the impact of total risk management (LDL-C <80 mg/dL, systolic BP <130 mmHg, and HbA1c <6.5%) on changes in coronary plaque volume. The patients were divided into four groups according to the number of risk factors that achieved the target value.
Results: Baseline characteristics were similar among the groups. The degree of coronary plaque regression was greater in patients who achieved total risk management. The number of risk factors that achieved the target level was associated with the extent of the coronary plaque volume reduction in a dose-dependent manner.
Conclusion: Total risk management that focused on LDL-C, BP, and HbA1c had a beneficial impact on the coronary plaque regression in diabetic patients with ACS.

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Key words: Diabetes mellitus, Total risk management, Intravascular ultrasound, Coronary plaque, Statin

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Introduction

Diabetes mellitus is associated with increased adverse cardiovascular events in patients with coronary artery disease (CAD)[1-4]. Large clinical trials failed to show the efficacy of intensive glucose control in reduc-