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BRIEF REPORT

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No beneficial effects of aspirin on secondary cardiovascular prevention in patients with type 2 diabetes using non-steroidal anti-inflammatory drugs

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Abstract

There is little evidence on whether non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin interact in secondary cardiovascular prevention in type 2 diabetic patients. This is an observational study using data from the Action to Control Cardiovascular Risk in Diabetes and Follow-on studies. Hazard ratios (HRs) for mortality with 95% confidence intervals (95% CIs) were calculated using Cox proportional hazard models to compare time to death in patients using and not using aspirin who were simultaneously using or not using NSAIDs. A total of 3600 type 2 diabetic patients with cardiovascular disease were included. During a mean follow-up period of 8.8 years, 948 patients died. After adjustments, the risk of all-cause mortality in patients not using NSAIDs was significantly lower in those using aspirin than in those not using aspirin (HR, 0.81; 95% CI, 0.70-0.93; $P = 0.004$). The risk in patients using NSAIDs did not differ significantly between the two groups. There was a significant interaction between aspirin use and NSAIDs use. In type 2 diabetic patients with cardiovascular disease, aspirin use was not beneficial for those using NSAIDs.

KEYWORDS
ACCORD, anti-inflammatory drugs, aspirin, cardiovascular events, mortality, non-cardiovascular mortality, non-steroidal secondary prevention

1 | INTRODUCTION

The benefits of aspirin use in patients with a history of cardiovascular disease are well-established in the secondary prevention of cardiovascular events.[1] Non-steroidal anti-inflammatory drugs (NSAIDs), including nonselective and cyclooxygenase (COX)-2-selective NSAIDs, increase the risk of cardiovascular and gastrointestinal events.[2–4] In addition, a previous study had suggested that both nonselective and COX-2-selective NSAIDs increase the risk of death in patients with a history of cardiovascular disease.[5] Moreover, there are pharmacodynamic concerns regarding concomitant use of NSAIDs in patients using aspirin because nonselective and COX-2-selective NSAIDs, such as ibuprofen and celecoxib, may block the access of aspirin to the acetylation site of platelet-expressed COX-1.[6,7] However, the clinical data regarding this interaction are inconsistent. Therefore, the aim of this study was to assess whether the concomitant use of aspirin and other NSAIDs may adversely affect the risk of mortality in diabetic patients with a history of cardiovascular disease. Because aspirin and NSAIDs may be associated with non-cardiovascular events such as cancer and gastrointestinal events, for example, gastrointestinal bleeding and renal failure, we further evaluated the

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associations between concomitant use of aspirin and NSAIDs and both cardiovascular and non-cardiovascular mortality.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

We used data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[8] and the Action to Control Cardiovascular Risk in Diabetes Follow-on (ACCORDION)[9] studies to assess whether aspirin use is equally effective in type 2 diabetic patients with a history of cardiovascular disease who are using and not using NSAIDs. NSAIDs in the present study did not include aspirin. The study design and patient characteristics of the ACCORD and ACCORDION studies have been previously reported. In the present study, we limited inclusion to patients with a history of clinical cardiovascular disease (n = 3611), which was defined as myocardial infarction, angina pectoris, coronary revascularization including coronary artery bypass grafting and percutaneous coronary intervention, stroke or other revascularization, such as carotid artery revascularization and peripheral artery revascularization. Patients with missing information regarding the use of aspirin and NSAIDs were excluded (n = 11), which resulted in a final sample of 3600 patients. The institutional review board of the National Center for Global Health and Medicine approved the present study. The National Heart, Lung, and Blood Institute (NHLBI) approved the use of ACCORD data.

2.2 | Outcomes and measurements

The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular and non-cardiovascular mortality and major adverse cardiovascular events (MACE). Cardiovascular death was defined as presumed cardiovascular death, unexpected death and death from myocardial infarction, congestive heart failure, arrhythmia, stroke and other cardiovascular diseases, including pulmonary emboli and abdominal aortic aneurysm rupture. MACE was defined as cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. Participants were followed for a maximum of 13 years.

All prescribed medications that participants were using regularly, including aspirin and NSAIDs, were confirmed at baseline. NSAIDs comprised both nonselective and COX-2-selective NSAIDs.

2.3 | Statistical analysis

Comparisons were made between patients using and those not using aspirin. Hazard ratios (HRs) for mortality, with 95% confidence intervals (CIs), were calculated using Cox proportional hazard models to compare the time to occurrence of outcome events in the subgroups of aspirin users and nonusers, separately in patients using and not using NSAIDs. To confirm the robustness of results, several multivariable adjustments were made. In addition, propensity score-matched analyses were performed to confirm results of the primary outcome. All statistical analyses were conducted using Stata software (version 14.1, Stata Corp, College Station, Texas). A P value of <0.05 was considered statistically significant for all tests.

3 | RESULTS

3.1 | Baseline characteristics

The present study included 3197 patients who were not using NSAIDs and 403 patients who were using NSAIDs. Among patients using NSAIDs, those using aspirin were associated with a lower proportion of women, more use of statins, and lower levels of glycated haemoglobin and low-density lipoprotein cholesterol; other characteristics were similar between those using and not using aspirin (Table 1).

3.2 | All-cause, cardiovascular and non-cardiovascular mortality

The overall mean (SD) follow-up period was 8.8 (2.5) years and 944 patients died. All-cause mortality rates (per 1000 person-year) were 30.0 and 28.0 in patients not using and those using NSAIDS, respectively. Among patients not using NSAIDs, the risk of all-cause mortality was significantly lower in those using aspirin than in those not using aspirin (Figure S1). Among patients using NSAIDs, the risk of all-cause mortality did not differ significantly between those using and those not using aspirin. After multivariable adjustments, the risk of all-cause mortality in patients not using NSAIDs was significantly lower in those using aspirin than in those not using aspirin (adjusted HR in model 1, 0.81; 95% CI, 0.70-0.93; P = 0.003; adjusted HR in model 2, 0.80; 95% CI, 0.69-0.93; P = 0.002; adjusted HR in model 3, 0.80; 95% CI, 0.69-0.93; P = 0.003) (Table 2). In patients using NSAIDs, the adjusted risk of all-cause mortality did not differ significantly between those using and those not using aspirin. There were significant interactions between the use of aspirin and the use of NSAIDs in all three multivariable models (P for all interactions <0.05). Propensity score-matched analyses with well-balanced baseline characteristics between the two groups did not alter the results (Table S1 and Figure S2). In addition, the risk of all-cause mortality in patients not using nonselective NSAIDs was significantly lower in those using aspirin than in those not using aspirin (adjusted HR in model 3, 0.81; 95% CI, 0.70–0.94; P = 0.004), whereas that in patients using nonselective NSAIDs did not differ significantly between those using and those not using aspirin (adjusted HR in model 3, 1.51; 95% CI, 0.84-2.72; P = 0.16) (P for interaction <0.05).

Similarly, the risks of cardiovascular and non-cardiovascular mortality in patients not using NSAIDs were significantly lower in those using aspirin than in those not using aspirin, whereas these risks in patients using NSAIDs did not differ significantly between the two groups (Figure S3 and Table 2).The analyses limited to patients with major cardiovascular diseases or coronary heart disease showed similar results. Regarding MACE (Figure S4), no

TABLE 1 Baseline characteristics of type 2 diabetic patients with a history of clinical cardiovascular disease using and not using nonsteroidal anti-inflammatory drugs

	NSAIDs (−)			NSAIDs (+)		
Characteristics	**Aspirin (−)**	**Aspirin (+)**	***P* value**	**Aspirin (−)**	**Aspirin (+)**	***P* value**
Number	1044	2153		136	267	
Age (years)	62.3 (8.3)	62.8 (7.8)	0.080	63.1 (7.7)	62.5 (6.6)	0.413
Female sex (%)	30.5	26.0	0.008	41.2	31.1	0.044
Race/ethnicity (%)			0.001			0.250
White	61.1	67.8		66.2	67.4	
Black	17.7	14.4		24.3	18.0	
Hispanic	9.0	6.4		5.9	7.1	
Others	12.2	11.3		3.7	7.5	
Educational level (%)			0.059			0.452
Less than high school	17.3	14.8		14.1	18.0	
High school	24.2	27.4		31.9	25.5	
Some college	34.8	32.6		37.0	36.3	
College degree or higher	23.7	25.2		17.0	20.2	
Currently smoking (%)	13.6	11.9	0.169	22.8	15.0	0.052
Body mass index (kg/m^2)[a]	31.7 (5.3)	32.0 (5.2)	0.085	33.6 (5.3)	33.3 (5.1)	0.572
Duration of diabetes (years)	11.3 (8.3)	11.7 (8.0)	0.208	12.2 (8.0)	12.6 (8.1)	0.699
Hypertension (%)	96.7	96.3	0.605	97.1	94.8	0.290
Dyslipidaemia (%)	96.9	98.2	0.024	98.5	99.3	0.490
Medications (%)						
Insulin	39.4	40.2	0.684	50.7	43.2	0.153
Metformin	57.9	63.5	0.002	57.4	61.1	0.474
Thiazolidinedione	22.6	20.6	0.199	18.4	20.2	0.660
ACE-I/ARB	71.2	73.3	0.207	76.5	72.3	0.367
CCB	11.1	14.5	0.008	16.2	12.7	0.34
Thiazide	23.3	25.6	0.155	31.6	26.6	0.289
Beta-blocker	43.5	57.5	<0.001	49.3	59.2	0.058
Statin	71.5	79.9	<0.001	63.2	79.8	<0.001
Antiplatelet agents (except aspirin)	13.8	10.4	0.004	13.2	13.5	0.945
Glycated haemoglobin (%)	8.3 (1.1)	8.3 (1.0)	0.632	8.5 (1.1)	8.2 (1.0)	0.019
LDL cholesterol (mg/dL)	103.2 (33.4)	97.5 (31.5)	<0.001	105.8 (30.5)	97.7 (29.6)	0.010
HDL cholesterol (mg/dL)	40.1 (10.5)	39.3 (9.9)	0.043	40.8 (11.5)	39.2 (10.7)	0.155
Triglyceride (mg/dL)	192.8 (127.0)	189.1 (119.0)	0.422	199.7 (126.9)	190.3 (108.5)	0.441
eGFR (mL/min/1.73 m^2)[b]	88.5 (23.4)	88.3 (22.6)	0.813	88.5 (22.6)	89.3 (22.8)	0.712
Systolic blood pressure (mm Hg)	137.7 (16.5)	134.4 (17.3)	<0.001	136.9 (15.9)	135.6 (17.1)	0.446
Diastolic blood pressure (mm Hg)	74.0 (10.7)	72.2 (10.6)	<0.001	75.0 (10.4)	73.3 (10.0)	0.103
Glycaemic control strategy						
Intensive glycaemic treatment (%)	50.7	50.4	0.884	47.8	52.4	0.378
BP control strategy						
Intensive BP treatment (%)	23.6	21.7	0.233	23.5	21.7	0.681
Lipid control strategy						
Intensive lipid treatment (%)	25.4	29.3	0.022	22.1	29.6	0.108

Data are presented as number of participants, percent or mean (standard deviation). *P* value was calculated by comparing variables in aspirin users with those in aspirin nonusers. Categorical variables were compared using chi-squared tests, and continuous variables were compared using *t*-tests.
HbA1c: 8.3% = 67 mmoL/moL; 8.5% = 69 mmoL/moL; 8.2% = 66 mmoL/moL.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BP, blood pressure; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Body mass index was calculated as weight in kilograms divided by square of height in meters.
[b]Estimated GFR was calculated using the following Modification of Diet in Renal Disease Study equation: estimated GFR (mL/min/1.73 m^2) = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 for female) × (1.212 for African American).

TABLE 2 All-cause, cardiovascular and non-cardiovascular mortality in type 2 diabetic patients with a history of clinical cardiovascular disease using and not using nonsteroidal anti-inflammatory drugs

	NSAIDs (–)			NSAIDs (+)		
Event	**Aspirin (–)**	**Aspirin (+)**	***P* value**	**Aspirin (–)**	**Aspirin (+)**	***P* value**
In patients with history of clinical CVD[a]	(n = 1044)	(n = 2153)		(n = 136)	(n = 267)	
All-cause death						
Number of events	298	544		32	70	
Event rate (per 1000 person-year)	33.3	28.5		25.8	29.1	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.84 (0.73–0.97)	0.01	1.00 (ref)	1.14 (0.75–1.73)	0.54
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.81 (0.70–0.93)	0.003	1.00 (ref)	1.28 (0.83–1.98)	0.25
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.80 (0.69–0.93)	0.002	1.00 (ref)	1.40 (0.90–2.18)	0.13
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.80 (0.69–0.93)	0.003	1.00 (ref)	1.35 (0.85–2.13)	0.20
Cardiovascular death						
Number of events	125	224		14	29	
Event rate (per 1000 person-year)	14.0	11.7		11.3	12.1	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.83 (0.67–1.04)	0.10	1.00 (ref)	1.07 (0.57–2.03)	0.82
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.78 (0.63–0.98)	0.02	1.00 (ref)	1.16 (0.60–2.23)	0.65
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.79 (0.63–0.99)	0.04	1.00 (ref)	1.12 (0.57–2.18)	0.74
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.79 (0.63–0.99)	0.04	1.00 (ref)	1.14 (0.56–2.32)	0.72
Non-cardiovascular death						
Number of events	173	320		18	41	
Event rate (per 1000 person-year)	19.3	16.7		14.5	17.1	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.85 (0.71–1.02)	0.08	1.00 (ref)	1.19 (0.68–2.07)	0.54
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.82 (0.68–0.99)	0.04	1.00 (ref)	1.46 (0.82–2.62)	0.20
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.81 (0.67–0.97)	0.02	1.00 (ref)	1.71 (0.94–3.10)	0.07
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.82 (0.68–0.99)	0.04	1.00 (ref)	1.47 (0.79–2.72)	0.22
Major adverse cardiovascular events						
Number of events	278	575		39	68	
Event rate (per 1000 person-year)	39.4	37.0		44.3	34.6	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.94 (0.81–1.08)	0.37	1.00 (ref)	0.77 (0.52–1.14)	0.19
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.90 (0.78–1.04)	0.17	1.00 (ref)	0.79 (0.52–1.18)	0.24
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.92 (0.80–1.07)	0.28	1.00 (ref)	0.80 (0.52–1.21)	0.28
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.93 (0.80–1.08)	0.33	1.00 (ref)	0.81 (0.52–1.25)	0.33
In patients with history of major CVD[b]	(n = 990)	(n = 2071)		(n = 131)	(n = 255)	
All-cause death						
Number of events	283	518		31	67	
Event rate (per 1000 person-years)	33.3	28.2		25.7	29.1	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.83 (0.72–0.96)	0.01	1.00 (ref)	1.14 (0.75–1.75)	0.54
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.80 (0.69–0.93)	0.002	1.00 (ref)	1.28 (0.82–2.00)	0.28
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.79 (0.68–0.92)	0.002	1.00 (ref)	1.34 (0.85–2.13)	0.21
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.79 (0.68–0.92)	0.002	1.00 (ref)	1.31 (0.81–2.11)	0.26

TABLE 2 (Continued)

Event	NSAIDs (−)			NSAIDs (+)		
	Aspirin (−)	Aspirin (+)	*P* value	Aspirin (−)	Aspirin (+)	*P* value
Cardiovascular death						
Number of events	119	217		14	28	
Event rate (per 1000 person-year)	14.0	11.8		11.6	12.2	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.84 (0.67–1.05)	0.11	1.00 (ref)	1.05 (0.55–2.00)	0.87
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.79 (0.63–0.99)	0.03	1.00 (ref)	1.11 (0.57–2.16)	0.75
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.79 (0.63–0.99)	0.04	1.00 (ref)	1.04 (0.53–2.05)	0.91
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.79 (0.62–0.99)	0.04	1.00 (ref)	1.09 (0.52–2.28)	0.81
Non-cardiovascular death						
Number of events	164	301		17	39	
Event rate (per 1000 person-year)	19.3	16.4		14.1	17.0	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.83 (0.69–1.00)	0.05	1.00 (ref)	1.22 (0.69–2.15)	0.50
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.81 (0.67–0.98)	0.03	1.00 (ref)	1.50 (0.81–2.77)	0.19
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.79 (0.65–0.96)	0.01	1.00 (ref)	1.70 (0.91–3.16)	0.09
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.80 (0.65–0.97)	0.02	1.00 (ref)	1.41 (0.74–2.72)	0.29
Major adverse cardiovascular events						
Number of events	267	558		39	65	
Event rate (per 1000 person-year)	39.8	37.3		45.6	34.6	
Unadjusted hazard ratio (95% CI)	1.00 (ref)	0.93 (0.81–1.08)	0.36	1.00 (ref)	0.75 (0.50–1.11)	0.15
Adjusted hazard ratio (95% CI), model 1	1.00 (ref)	0.90 (0.78–1.04)	0.16	1.00 (ref)	0.74 (0.49–1.12)	0.15
Adjusted hazard ratio (95% CI), model 2	1.00 (ref)	0.92 (0.79–1.07)	0.27	1.00 (ref)	0.75 (0.49–1.14)	0.17
Adjusted hazard ratio (95% CI), model 3	1.00 (ref)	0.92 (0.79–1.07)	0.30	1.00 (ref)	0.74 (0.47–1.15)	0.17

Data are presented as number or hazard ratio (95% CI). Model 1 included age, sex, race/ethnicity, educational level, smoking status, BMI, duration of diabetes, hypertension and dyslipidaemia. Model 2 included the potential confounders of model 1 plus glycated haemoglobin, low-density lipoprotein cholesterol, systolic blood pressure and the assigned glycaemic strategy of the ACCORD trial. Model 3 included all potential confounders of models 1 and 2 plus the use of certain types of medications (insulin, metformin, thiazolidinedione, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, thiazide, beta-blockers, statin and antiplatelet agents except aspirin), high-density lipoprotein cholesterol, log-transformed triglyceride, diastolic blood pressure, estimated glomerular filtration rate, and the assigned blood pressure and lipid strategy of the ACCORD trial.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.

[a]Clinical cardiovascular disease was defined as myocardial infarction, angina pectoris, coronary revascularization including coronary artery bypass grafting and percutaneous coronary intervention, stroke or other revascularization such as carotid artery revascularization and peripheral artery revascularization.

[b]Major cardiovascular disease was defined as coronary heart disease or stroke.

significant interactions were noted between the use of aspirin and use of NSAIDs.

4 | DISCUSSION

Aspirin acts by irreversibly acetylating the serine residue at position 529 in platelet COX-1 and inhibits thromboxane production by platelets,[6] which results in inhibition of platelet aggregation and a lower risk of cardiovascular events, particularly in patients with a history of cardiovascular disease.[1] Some,[10] but not all,[11] studies revealed that the associations between the use of aspirin and cardiovascular events may be affected by the use of NSAIDs. One possible explanation is that NSAIDs block the access of aspirin to the acetylation site of platelet-expressed COX-1.[6,7] However, the clinical data are inconsistent. Kurth et al. previously described a subgroup analysis of a 5-year randomized, double-blind, placebo-controlled trial concerning the use of 325 mg aspirin on alternate days among 22 071 apparently healthy US male physicians for whom prospective observational data on the use of NSAIDs were available.[12] The analyses suggested that regular, but not intermittent, use of NSAIDs reduced the clinical benefits of aspirin use in avoiding a first myocardial infarction. Conversely, Patel et al. demonstrated a 40% reduction in the rate of development of myocardial infarction in patients using both aspirin and ibuprofen as opposed to using aspirin alone, suggesting enhanced protection against acute myocardial infarction with co-administration of aspirin and ibuprofen.[11] In addition, no study evaluated whether NSAIDs interfere with the well-established beneficial effects of aspirin in diabetic patients with a history of cardiovascular disease. Specifically considering this patient group, the present study revealed that aspirin use was associated with lower mortality only in those not using NSAIDs; in patients using NSAIDs,

no beneficial effect of aspirin was identified. These results suggest that the effects of aspirin are attenuated by use of NSAIDs. In diabetic patients with a history of cardiovascular disease, our findings indicate that the best choice of treatment would be to minimize the use of NSAIDs. Notably, the present study also demonstrated that the use of aspirin was associated with a decreased risk of non-cardiovascular mortality that was attenuated by concomitant use of NSAIDs. Several studies have suggested that aspirin use reduces the incidence of cancer and of non-cardiovascular and cancer mortality.[13] Some studies using animal models suggested that these effects are mediated, in part, by inhibition of the COX enzymes and reduced production of inflammatory mediators.[13] NSAIDs have been associated with gastrointestinal events and renal failure, and concomitant use of aspirin and NSAIDs can in fact lead to an increased risk of gastrointestinal events relative to the use of NSAIDs alone.[14] These adverse effects of NSAIDs may also reduce the beneficial effects of aspirin. The effect of aspirin on MACE was not significantly affected by the use of NSAIDs in this study. Further, the incidence of MACE tended to be lower in patients using NSAIDs and aspirin than in those using either NSAIDs or aspirin alone. Therefore, further large-scale studies are warranted to validate the results of this study.

This study has several limitations. First, this was not a randomized trial but an observational study. Even after multivariable adjustments, residual bias, including unknown confounders and unmeasured underlying disease with chronic pain, such as rheumatoid arthritis, might have affected the results. Second, the small number of events and of patients using NSAIDs might influence the results. In addition, we could not completely assess the interactions between use of aspirin and nonselective or COX-2-selective NSAIDs (eg, celecoxib vs. naproxen) and the differential impact on results. Hence, our results should be confirmed by larger-scale studies with detailed information concerning the use of NSAIDs. Third, the management of diabetes has changed since the ACCORD study was initiated. The residual risk is decreasing because of additional effective therapies, such as increased use of statins and sodium glucose cotransporter 2 inhibitors. Thus, it remains unknown whether the same results would be obtained in a more contemporary cohort. Fourth, detailed information regarding the doses of aspirin and the doses and types of NSAIDs is lacking. A recent study revealed that low doses (75–100 mg) of aspirin were effective in preventing cardiovascular events only in patients weighing less than 70 kg, whereas high doses (≥325 mg) of aspirin were effective only in patients weighing 70 kg or more.[15] Those findings were consistent in diabetic patients. In addition, the pharmacodynamic interactions that occur in platelets may differ according to the different types of NSAIDs involved.[6,10] Moreover, the timing of aspirin and NSAIDs use may also influence the results.[6] Further studies with more detailed information about NSAIDs are needed to reveal the interactions between aspirin and NSAIDs.

In conclusion, the present study demonstrated that, in type 2 diabetic patients with a history of cardiovascular disease, aspirin use is beneficial for those who are not using NSAIDs but is not beneficial for those who are using NSAIDs. To fully derive the benefits of aspirin and avoid the increased risk of cardiovascular events, more attention should be paid to the use of NSAIDs.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

T. T. was responsible for the study concept and design, for data acquisition and for statistical analysis. T. T. and H. K. shared responsibility for analysis and interpretation of data. T. T. drafted the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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