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Epidemiology of Second Attack of Cardiovascular Events in Patients with Type 2 Diabetes

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Abstract

The incremental risks of cardiovascular disease (CVD) after the first CVD event remain unclear because of the difficulty of assessing how risks changed from the pre-event to the post-event period. A long-term follow-up study was conducted in patients with type 2 diabetes. The endpoints were CVD, defined as ischemic stroke (IS) or coronary artery disease (CAD), and all-cause mortality. Two cohorts were defined: the pre-event and post-event cohorts. The incidence was analyzed using the Kaplan–Meier method, and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. The post-event cohort was further stratified by the type of the first event (IS or CAD). Among 2535 participants, 317 had a first CVD event, and 293 were included in the post-event cohort. Compared with the pre-event cohort, the post-event cohort had significantly higher risks of recurrent CVD (adjusted HR 2.24, 95% CI 1.63–3.06) and all-cause mortality (adjusted HR 2.07, 95% CI 1.59–2.69). Within the post-event cohort, recurrent CVD risk showed no difference between the IS and CAD groups, but all-cause mortality was significantly higher in the IS group. Patients with type 2 diabetes who experienced a first CVD event had a twofold increased risk of recurrent CVD events and all-cause mortality.

Keywords: cardiovascular disease; ischemic stroke; coronary artery disease; type 2 diabetes; recurrence; prognosis; epidemiology

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1. Introduction

Cardiovascular disease (CVD) is a major complication of atherosclerosis and remains a leading cause of death and disability worldwide [1,2]. After a first CVD event, recurrent events or events involving other vascular territories are common [3,4]. Despite contemporary secondary prevention [5,6], the residual risk of recurrent CVD events among patients with prior CVD remains a clinical challenge.

Most cohort studies assessed the risk of CVD events separately in individuals with or without previous events. For example, the Framingham Heart Study and the EPIC-Norfolk Study were population-based cohorts that investigated first CVD events in individuals without previous CVD [7,8], while the UCC-SMART Study and the RESRISK Cohort Study investigated recurrent events in individuals with established CVD [9,10]. In contrast, some large cohorts included both individuals with and without previous CVD events within a single cohort. The REACH Registry was a cohort study with this type of design, in which patients with previous symptomatic CVD had a higher risk of CVD events than those with risk factors only [11]. Even in such cohorts that enrolled both patients with and without previous events, patients were classified by baseline CVD status; thus, the actual elevation in risk after the first event was not directly observed due to selection bias or confounding by treatment variations. As a result, the natural course from the pre-event state through the first event and to recurrence remains uncertain.

To address these issues, we evaluated the effect of a first CVD event on long-term prognosis by following patients within a single cohort from an event-free period through the occurrence of the first and recurrent events, thereby enabling a within-cohort comparison of CVD incidence before and after the first event.

2. Materials and Methods

2.1. Study Design and Population

This study compared the incidences of CVD events between patients without previous events and those who had a first CVD event within a single cohort of a randomized clinical trial. Differences in outcomes between those with a coronary artery disease (CAD) and those with an ischemic stroke (IS) as their first event were also assessed. The data were derived from the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, which was a multicenter, randomized, standard care–controlled, open-label, blinded end-point trial conducted at 163 institutions in Japan to evaluate the effect of low-dose aspirin on the prevention of CVD events in patients with type 2 diabetes [12,13]. The eligibility criteria and procedures for the JPAD trial have been described previously. Briefly, the inclusion criteria were type 2 diabetes, age between 30 and 85 years, and the ability to provide informed consent. The exclusion criteria included established CVD or peripheral vascular disease, significant electrocardiographic abnormalities, atrial fibrillation, pregnancy, use of antiplatelet or anticoagulant therapy, severe gastrointestinal ulcer, advanced hepatic or renal dysfunction, and aspirin allergy. Patients were randomly allocated in a 1:1 ratio to receive aspirin (81 mg of unbuffered, uncoated aspirin or 100 mg of enteric-coated aspirin daily) or no aspirin. Patients were allowed to receive any concurrent treatment. After the trial completion in 2008, all participants were prospectively followed until 5 February 2022. During the follow-up period, the decision to administer low-dose aspirin was made by each treating physician.

2.2. Measurements

Baseline demographic and clinical characteristics were assessed at enrolment in the JPAD trial. Baseline characteristics included age, sex, duration of diabetes, smoking status, and the presence of hypertension, dyslipidemia, and microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy). Family histories of diabetes, coronary artery disease, and stroke were also recorded. Body mass index and blood pressure were measured. Laboratory tests included hemoglobin A1c (HbA1c), lipid profiles, serum creatinine, and estimated glomerular filtration rate (eGFR). Information on the use of oral antihyperglycemic agents, insulin, statins, and antihypertensive agents was documented.

The duration of follow-up was defined as the time from the index day to the date of endpoint occurrence or the final visit, whichever came first.

2.3. Endpoints and Event Adjudication

The endpoints were CVD events and all-cause mortality. CVD events comprised IS (ischemic stroke or transient ischemic attack) and CAD (acute myocardial infarction, unstable angina, or newly diagnosed exertional angina). CVD events were categorized as first and second events. All CVD events and deaths were adjudicated by a central independent committee during the study period.

2.4. Cohorts

We set the two cohorts based on the occurrence and timing of CVD events. (1) The pre-event cohort comprised all patients enrolled in the JPAD trial, who were followed until the first CVD event, death, or censoring without a CVD event or death. The index day was the day of enrolment in the JPAD trial. (2) The post-event cohort comprised patients who had a first CVD event during the follow-up period of the JPAD trial and survived the event. The index day was the date of the first CVD event, and patients were followed from that date until the second CVD event, death unrelated to the corresponding CVD event, or censoring without a second CVD event or death. The post-event cohort was further stratified by the type of the first event (IS or CAD).

2.5. Statistical Analyses

Categorical variables were presented as numbers (percentages) and continuous variables as means (standard deviations) or medians (interquartile ranges), as appropriate. Between-group comparisons were performed using the chi-square test or the Fisher's exact test for categorical variables and Student's *t*-test or the Wilcoxon rank-sum test for continuous variables.

We estimated the incidence rates of endpoints with cases per 1000 patient-years for each cohort. We estimated the cumulative incidences of endpoints with the Kaplan–Meier method and compared them with the log-rank test between the cohorts. Cox proportional hazards models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We adjusted for age, sex, systolic blood pressure, HbA1c, low-density lipoprotein cholesterol, eGFR, and aspirin use at baseline in the multivariable Cox proportional hazards models. We used the variable data at enrolment of the JAPD trial, other than age, which was adjusted for the index day for the post-event cohort.

We conducted additional analyses comparing patients with IS and those with CAD as the index event. The same statistical tests were applied: Kaplan–Meier estimates with log-rank tests for cumulative incidences, and Cox proportional hazards models to calculate HRs and 95% CIs, adjusted for the same covariates as in the main analyses. To account for the possible competing risk of death, we added a Fine–Gray model to estimate the subdistribution HR for recurrent CVD events.

As sensitivity analyses, we estimated the cumulative incidences of endpoints with the Kaplan–Meier method and compared them with the log-rank test under two other time conditions to address the systematic difference in age at the index day between the pre-event and post-event cohorts. First, we restricted the post-event cohort to individuals whose first event occurred within 2 years of enrolment. Second, we shifted the index day of the pre-event cohort forward by the median duration from enrolment to the first CVD event derived from the entire study dataset.

All reported p-values were two-sided, and p-values < 0.05 were considered statistically significant. Analyses were conducted with JMP 18.2.1 (JMP Statistical Discovery LLC, Cary, NC, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Study Population

Of 2535 participants, 317 experienced a first CVD event during follow-up (Figure 1). After excluding 24 deaths at the first CVD event (IS, 11; CAD, 13), 293 survivors were included in the post-event cohort (IS, 134; CAD, 159). Compared with the pre-event cohort, the post-event cohort was older, included more men, and had a longer duration of diabetes. They also had a higher prevalence of diabetic nephropathy and impaired renal function, with higher serum creatinine levels and lower eGFR. In addition, HbA1c and triglyceride levels were higher, high-density lipoprotein cholesterol levels were lower, and the use of calcium channel blockers was more frequent in the post-event cohort. The median follow-up durations were 9.7 and 5.1 years for the pre-event and post-event cohorts, respectively. The median duration from enrolment to the first CVD event was 5.8 years in the pre-event cohort (Table 1).

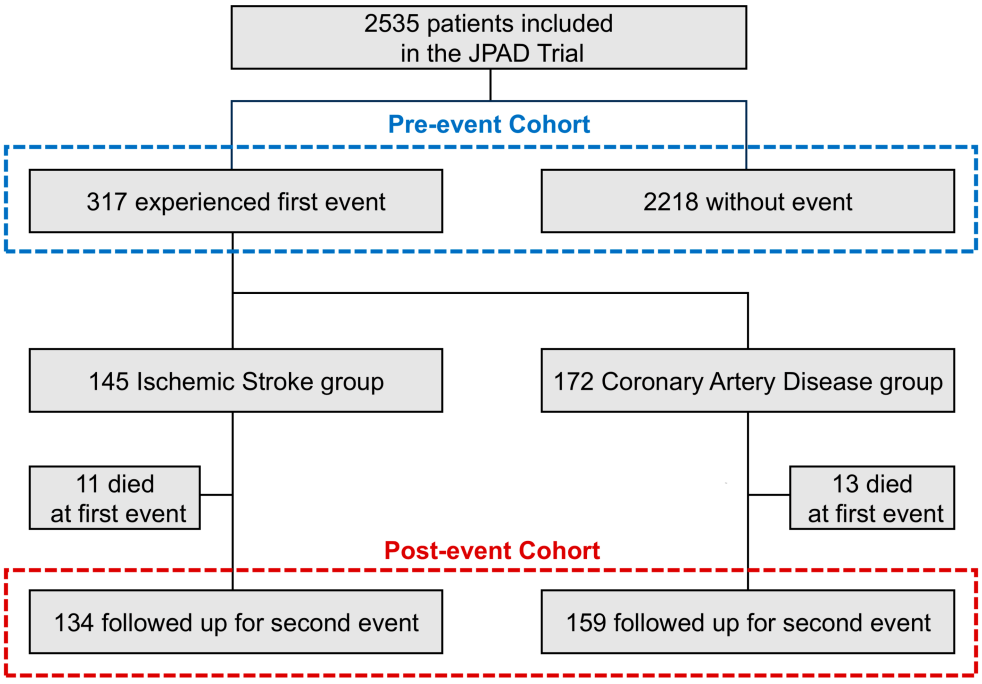


Figure 1. Study flow chart. JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes.

Table 1. Comparison of baseline patient characteristics between pre-event cohort and post-event cohort.

Variables	Pre-Event Cohort (n = 2535)	Post-Event Cohort (n = 293)	p-Value
Age, mean (SD), years	65 (9.9)	66 (9.8)	0.03
Male, n (%)	1386 (55)	184 (63)	0.008
Body mass index, mean (SD), kg/m^2	24 (3.6)	24 (3.3)	0.92
Duration of diabetes, median (IQR), years	7.0 (2.9–12)	8.3 (4.0–14)	0.005
Systolic blood pressure, mean (SD), mmHg	135 (15)	136 (15)	0.16

Table 1. *Cont.*

Variables	Pre-Event Cohort (n = 2535)	Post-Event Cohort (n = 293)	p-Value
Diastolic blood pressure, mean (SD), mmHg	77 (9.4)	77 (9.6)	0.77
Presence of hypertension, n (%)	1470 (58)	184 (63)	0.11
Presence of dyslipidemia, n (%)	1343 (53)	172 (59)	0.06
Current or past smoking, n (%)	1057 (42)	135 (46)	0.15
Diabetic microvascular complications, n (%)			
Retinopathy	365 (14)	52 (18)	0.13
Nephropathy	332 (13)	53 (18)	0.01
Neuropathy	300 (12)	46 (16)	0.06
Family history, n (%)			
Diabetes mellitus	1037 (41)	115 (39)	0.58
Coronary artery disease	289 (11)	38 (13)	0.43
Stroke	526 (21)	68 (23)	0.33
Laboratory data			
Hemoglobin A1c level, median (IQR), %	7.2 (6.6–8.1)	7.4 (6.7–8.3)	0.03
Fasting plasma glucose, median (IQR), mg/dL	136 (115–165)	140 (118–177)	0.08
Total cholesterol, median (IQR), mg/dL	200 (179–221)	203 (179–222)	0.25
Triglyceride, median (IQR), mg/dL	114 (80–163)	121 (87–180)	0.03
HDL cholesterol, median (IQR), mg/dL	53 (44–63)	52 (44–61)	0.04
LDL cholesterol, median (IQR), mg/dL	119 (100–139)	123 (102–142)	0.11
Creatinine, median (IQR), mg/dL	0.74 (0.60–0.90)	0.80 (0.69–0.93)	<0.0001
eGFR, median (IQR), mL/min/1.73 m^2	72 (60–87)	69 (58–81)	0.002
Medications, n (%)			
Aspirin	1258 (50)	143 (49)	0.79
Statin	650 (26)	74 (25)	0.89
Antihyperglycemic medications, n (%)			
Sulfonylurea	1445 (57)	174 (59)	0.43
α-glucosidase inhibitor	835 (33)	94 (32)	0.77
Biguanide	353 (14)	43 (15)	0.73
Insulin	326 (13)	47 (16)	0.13
Thiazolidine	127 (5.0)	16 (5.5)	0.74
Medications for hypertension, n (%)			
Calcium channel blocker	873 (34)	124 (42)	0.01
Angiotensin II receptor blocker	532 (21)	63 (22)	0.84
Angiotensin converting enzyme inhibitor	373 (14)	53 (18)	0.13
β-blocker	162 (6.4)	17 (5.8)	0.70
α-blocker	91 (3.6)	9 (3.0)	0.65
Duration of follow-up, median (IQR), years	9.7 (5.3–16)	5.1 (1.3–9.5)	<0.0001
Duration from enrolment to first cardiovascular event, median (IQR), years	5.8 (2.5–9.8)	NA	NA
Age at index day, mean (SD), years	65 (9.9)	72 (9.7)	NA

Duration of follow-up, duration from enrolment to first cardiovascular event, and age at index day in the post-event cohort were calculated after the entire cohort dataset was established. All other variables were collected at enrolment in the original randomized clinical trial. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NA, not applicable; SD, standard deviation.

Among the first CVD events, 145 were IS (fatal ischemic stroke, 11; non-fatal ischemic stroke, 112; transient ischemic attack, 22), and 172 were CAD (fatal CAD, 13; non-fatal myocardial infarction, 61; unstable angina, 32; newly developed exertional angina, 66) (Table 2).

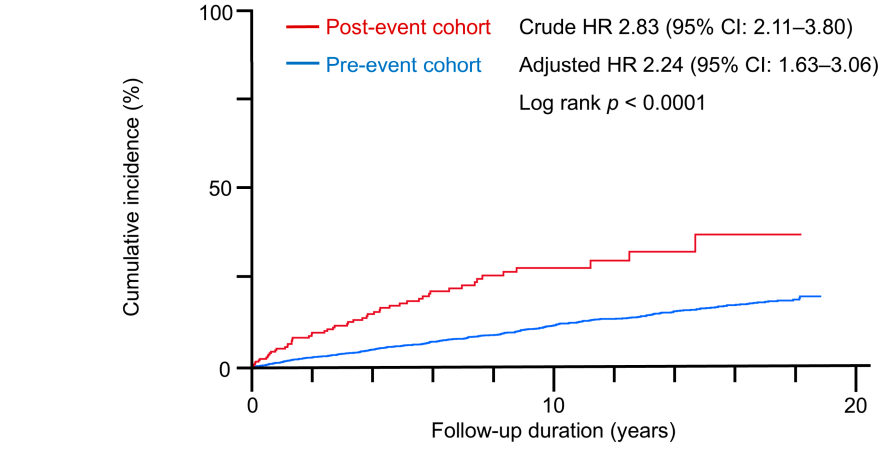
Table 2. Types of events in pre-event and post-event cohorts.

Type of Events	First Event in Pre-Event Cohort (n = 317)	Second Event in Post-Event Cohort	
		IS Group (n = 21)	CAD Group (n = 32)
Ischemic Stroke, n (%)	145 (46)	15 (71)	7 (22)
Fatal Ischemic Stroke, n (%)	11 (3.7)	2 (9.5)	0 (0)
Non-fatal Ischemic Stroke, n (%)	112 (35)	13 (62)	7 (22)
Transient Ischemic Attack, n (%)	22 (7.0)	0 (0)	0 (0)
Coronary Artery Disease, n (%)	172 (54)	6 (29)	25 (78)
Fatal Coronary Artery Disease, n (%)	13 (4.1)	2 (9.5)	1 (3.1)
Non-fatal Myocardial Infarction, n (%)	61 (19)	3 (14)	7 (22)
Unstable Angina, n (%)	32 (10)	0 (0)	7 (22)
Newly Developed Exertional Angina, n (%)	66 (21)	1 (4.8)	10 (31)

CAD, coronary artery disease; IS, ischemic stroke.

3.2. Pre-Event vs. Post-Event

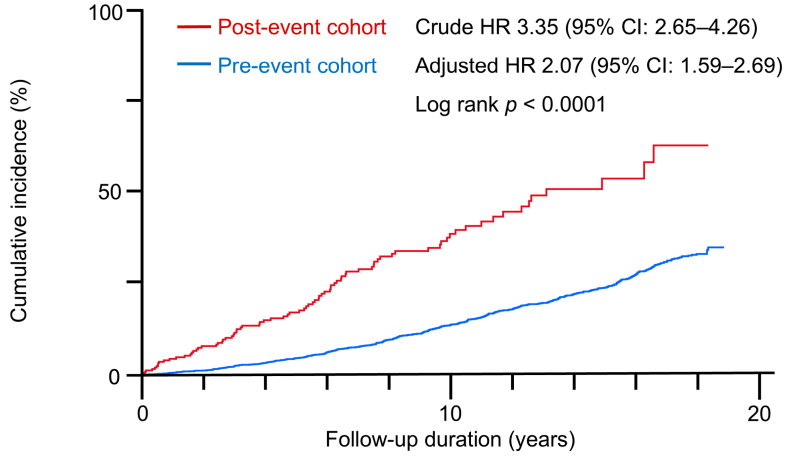
The incidences of CVD events were 12.1 vs. 35.4 per 1000 patient-years in the pre-event and post-event cohorts, respectively. Compared with the pre-event cohort, the post-event cohort had a higher 10-year cumulative incidence of CVD events (12% vs. 28%; crude HR, 2.83 [95% CI, 2.11–3.80]; adjusted HR, 2.24 [95% CI, 1.63–3.06]; log-rank $p < 0.0001$) (Figure 2a). The incidences of all-cause mortality were 19.8 and 48.1 per 1000 patient-years in the pre-event and post-event cohorts, respectively, and the 10-year all-cause mortalities were higher in the post-event cohort (14% vs. 39%; crude HR, 3.35 [95% CI, 2.65–4.26]; adjusted HR, 2.07 [95% CI, 1.59–2.69]; log-rank $p < 0.0001$) (Figure 2b).



Post-event cohort										
Number at risk, n	293	191	146	111	75	49	32	17	8	1
Cumulative events, n	0	23	33	43	48	50	51	52	53	53
Cumulative incidence, %	0	9.7	14.9	21.3	25.8	27.9	30.0	32.5	37.3	37.3
Pre-event cohort										
Number at risk, n	2535	2370	2183	1809	1491	1237	1042	863	678	253
Cumulative events, n	0	69	120	166	200	241	265	289	306	315
Cumulative incidence, %	0	2.8	4.9	7.1	9.0	11.7	13.5	15.7	17.4	19.0

(**a**)

Figure 2. *Cont.*



Post-event cohort										
Number at risk, *n*	293	206	166	133	92	60	42	24	13	2
Cumulative events, *n*	0	19	34	48	63	70	75	79	80	82
Cumulative incidence, %	0	7.8	15.0	22.8	32.5	38.7	44.8	51.0	53.9	63.1
Pre-event cohort										
Number at risk, *n*	2535	2370	2183	1809	1491	1237	1042	863	678	253
Cumulative events, *n*	0	27	77	135	194	256	311	360	414	457
Cumulative incidence, %	0	1.1	3.2	6.1	9.1	13.5	17.6	22.2	27.1	32.7

(**b**)

Figure 2. Incidence of endpoints in pre-event cohort vs. post-event cohort. (**a**) Cardiovascular events; (**b**) all-cause mortality. CI, confidence interval; HR, hazard ratio.

3.3. Post-IS vs. Post-CAD in the Post-Event Cohort

Among the post-event cohort, the IS group had slightly higher diastolic blood pressure and more frequent use of β-blockers, while the CAD group more often received α-glucosidase inhibitors. Other clinical characteristics and laboratory findings were comparable between the two groups. The median follow-up duration was significantly shorter in the IS group (3.8 vs. 6.4 years) (Table 3). Among the second CVD events, the IS group experienced 15 IS events (fatal, 2) and 6 CAD events (fatal, 2), while the CAD group experienced 7 IS events (fatal, 0) and 25 CAD events (fatal, 1) (Table 2). The 10-year incidence of CVD events did not significantly differ between the IS and CAD groups (28% vs. 28%; crude HR, 1.02 [95% CI, 0.59–1.79]; adjusted HR, 1.03 [95% CI, 0.58–1.82]; log-rank $p = 0.93$) (Figure 3a). In contrast, the 10-year all-cause mortality was higher in the IS group than in the CAD group (47% vs. 33%; crude HR, 1.89 [95% CI, 1.23–2.94]; adjusted HR, 1.69 [95% CI, 1.05–2.70]; log-rank $p = 0.03$) (Figure 3b). The Fine–Gray model showed a consistent result for recurrent CVD events (subdistribution HR, 0.90 [95% CI, 0.52–1.58]).

Table 3. Comparison of baseline patient characteristics between ischemic stroke and coronary artery disease groups in post-event cohort.

Variables	IS Group ($n = 134$)	CAD Group ($n = 159$)	*p*-Value
Age, mean (SD), years	67 (9.2)	65 (10)	0.06
Male, *n* (%)	86 (64)	98 (62)	0.65
Body mass index, mean (SD), kg/m^2	24 (3.2)	24 (3.4)	0.70
Duration of diabetes, median (IQR), years	7.0 (3.3–14)	9.5 (5.0–14)	0.13
Systolic blood pressure, mean (SD), mmHg	138 (16)	135 (15)	0.06
Diastolic blood pressure, mean (SD), mmHg	78 (10)	76 (9.2)	0.03

Table 3. *Cont.*

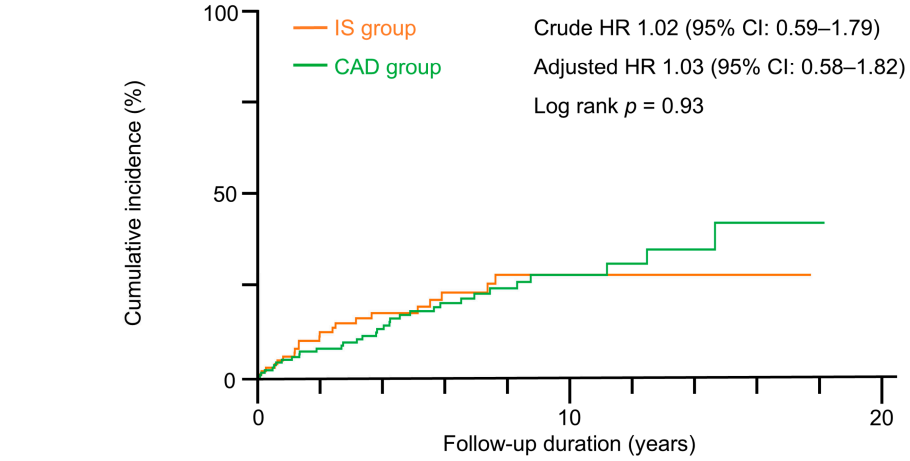
Variables	IS Group (n = 134)	CAD Group (n = 159)	p-Value
Presence of hypertension, n (%)	87 (65)	97 (61)	0.49
Presence of dyslipidemia, n (%)	72 (54)	100 (63)	0.11
Current or past smoking, n (%)	61 (46)	74 (47)	0.86
Diabetic microvascular complications, n (%)			
Retinopathy	27 (20)	25 (16)	0.32
Nephropathy	27 (20)	26 (16)	0.40
Neuropathy	17 (13)	29 (18)	0.20
Family history, n (%)			
Diabetes mellitus	47 (35)	68 (43)	0.18
Coronary artery disease	14 (10)	24 (15)	0.24
Stroke	32 (24)	36 (23)	0.80
Laboratory data			
Hemoglobin A1c level, median (IQR), %	7.3 (6.8–8.3)	7.5 (6.7–8.2)	0.95
Fasting plasma glucose, median (IQR), mg/dL	143 (120–175)	139 (114–178)	0.92
Total cholesterol, median (IQR), mg/dL	200 (175–221)	204 (186–224)	0.22
Triglyceride, median (IQR), mg/dL	128 (85–180)	112 (87–182)	0.64
HDL cholesterol, median (IQR), mg/dL	51 (43–61)	53 (44–60)	0.80
LDL cholesterol, median (IQR), mg/dL	120 (100–139)	124 (105–142)	0.24
Creatinine, median (IQR), mg/dL	0.80 (0.70–0.90)	0.80 (0.70–1.0)	0.92
eGFR, median (IQR), mL/min/1.73 m^2	67 (59–79)	69 (57–83)	0.73
Medications, n (%)			
Aspirin	64 (48)	79 (50)	0.74
Statin	30 (22)	44 (28)	0.30
Antihyperglycemic medications, n (%)			
Sulfonylurea	80 (60)	94 (59)	0.92
α-glucosidase inhibitor	35 (26)	59 (37)	0.04
Biguanide	23 (17)	20 (13)	0.27
Insulin	22 (16)	25 (16)	0.87
Thiazolidine	7 (5.2)	9 (5.7)	0.87
Medications for hypertension, n (%)			
Calcium channel blocker	62 (46)	62 (39)	0.21
Angiotensin II receptor blocker	30 (22)	33 (21)	0.73
Angiotensin converting enzyme inhibitor	25 (19)	28 (18)	0.82
β-blocker	12 (9.0)	5 (3.1)	0.03
α-blocker	6 (4.5)	3 (1.9)	0.31
Duration of follow-up, median (IQR), years	3.8 (0.5–7.6)	6.4 (2.6–9.9)	<0.0001
Age at index day, mean (SD), years	73 (9.9)	72 (9.5)	0.18

Duration of follow-up and age at index day were calculated after the entire cohort dataset was established. All other variables were collected at enrolment in the original randomized clinical trial. CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; IS, ischemic stroke; LDL, low-density lipoprotein; SD, standard deviation.

3.4. Sensitivity Analyses

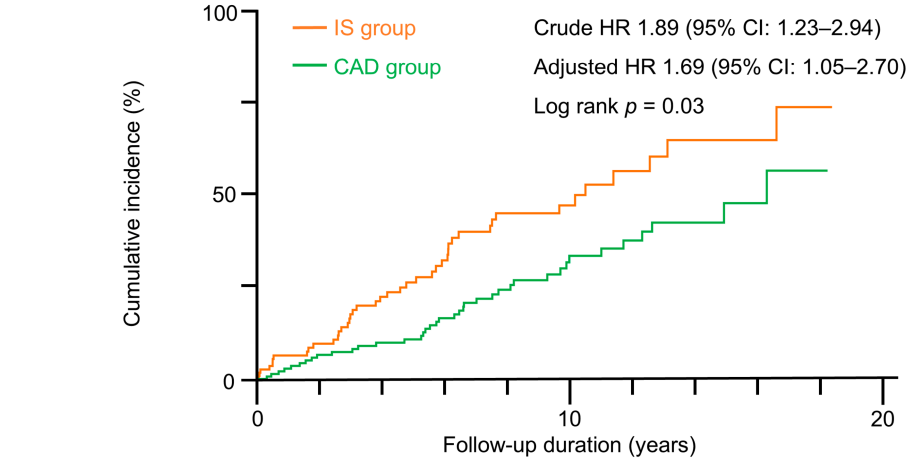
In the comparison between the pre-event cohort and the subset of the post-event cohort whose first event occurred within the first 2 years of enrolment, the post-event cohort had a higher incidence of both CVD events (crude HR, 2.24 [95% CI, 1.26–3.99]; log-rank $p = 0.006$) (Supplementary Figure S1a) and all-cause mortality (crude HR, 3.17 [95% CI, 2.14–4.71]; log-rank $p < 0.0001$) (Supplementary Figure S1b). Similarly, when the index day of the pre-event cohort was shifted forward by 5.8 years, the post-event cohort had a higher incidence of CVD events (crude HR, 2.92 [95% CI, 2.13–4.00]; log-rank $p < 0.0001$)

(Supplementary Figure S2a) and all-cause mortality (crude HR, 1.90 [95% CI, 1.49–2.44]; log-rank $p < 0.0001$) (Supplementary Figure S2b) than the pre-event cohort. These results were consistent with those of the main analyses.



IS Group										
Number at risk, *n*	134	74	55	39	29	19	11	7	4	0
Cumulative events, *n*	0	13	16	19	21	21	21	21	21	21
Cumulative incidence, %	0	12.3	17.5	23.0	27.8	27.8	27.8	27.8	27.8	27.8
CAD Group										
Number at risk, *n*	159	117	91	72	46	30	21	10	4	1
Cumulative events, *n*	0	11	17	24	27	29	30	31	32	32
Cumulative incidence, %	0	7.8	13.1	20.2	24.2	27.8	31.0	34.8	42.0	42.0

(**a**)



IS Group										
Number at risk, *n*	134	82	63	45	32	21	12	9	5	1
Cumulative events, *n*	0	10	21	28	36	37	40	42	42	43
Cumulative incidence, %	0	9.5	22.2	33.5	44.7	46.8	56.1	64.5	64.5	73.4
CAD Group										
Number at risk, *n*	159	124	102	87	59	38	29	15	7	1
Cumulative events, *n*	0	9	13	20	27	33	35	37	38	39
Cumulative incidence, %	0	6.5	9.8	16.4	24.1	33.2	37.4	42.2	47.4	56.2

(**b**)

Figure 3. Incidence of endpoints in ischemic stroke and coronary artery disease groups in post-event cohort. (**a**) Cardiovascular events; (**b**) all-cause mortality. CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; IS, ischemic stroke.

4. Discussion

This study directly compared the risks of CVD events between the pre-event and post-event patients within a single cohort prospectively followed for up to 18 years. We demonstrated that the risks of both CVD events and all-cause mortality were approximately twofold higher after the first CVD event. Furthermore, among patients with a first CVD event, the mortality risk was higher in patients after IS than after CAD, while no difference in the risk of a second CVD event was observed between patients after IS and CAD. The strength of this study lies in its ability to compare pre-event and post-event periods using identical criteria within a single cohort prospectively enrolled before the first CVD event. This study enabled a more accurate quantification of the impact of the initial event itself on subsequent prognosis. This comparison was different from that of conventional cohort studies, which compared individual populations with and without previous events.

Established risk prediction models, using baseline characteristics of our cohorts, estimated 10-year CVD risks for the first event of 22.1% (ACC/AHA Pooled Cohort Equations) and 19.9% (QRISK3 algorithm) [14,15], while the observed 10-year incidence in this study was 11.7%. For recurrent events, the SMART risk score estimated 23.2% for patients with prior CAD and 38.1% for those with prior IS [16], while the observed 10-year incidence in this study was 27.9%. The lower risks of CVD events in this study compared with the predicted risks in Western countries reflected the ethnic differences in cardiovascular risk profiles and the absolute incidence of CVD in Japanese populations [17,18]. Because the patients in this study were originally enrolled in a clinical trial, such voluntarily enrolled patients could have a generally lower risk of CVD events, and their risk factors were generally well managed. Nevertheless, the approximately twofold increase in the risk of CVD events from the pre-event cohort to the post-event cohort was consistent with these previous model predictions [17,18].

Several mechanisms could explain the increased risk of recurrent CVD events after the first event. First, atherosclerotic risk factors were accumulated over time, and the risk was already increased at the time of the first CVD event. Since a median of 5.8 years had elapsed between enrolment and the first event, clinical characteristics, including cardiometabolic risk factors and medication use, might change during this period. Therefore, the observed increase in CVD risk might partly reflect these longitudinal changes rather than the occurrence of the first event itself. Previous imaging studies indicated that atherosclerotic disease in the coronary and cerebral circulations often coexists [19,20]. These findings supported the premise that atherosclerotic disease in one vascular territory frequently coexists with subclinical lesions in others, reflecting a systemic burden. Second, the overall decline in the patients' health status following the first event could increase the risk of recurrent events. Established CVD risk factors, such as functional decline [21], diminished physical activity and fitness [22], and frailty [23], could develop or worsen after the first event. Third, functional decline after the first event could be accompanied by weakened or withheld secondary prevention. The AVAIL registry reported that patients with higher modified Rankin Scale scores were less likely to persist with preventive medications 3 months after hospitalization [24]. This suggested that patients with severe functional decline following the first event should face a disadvantage in terms of not only their physical condition but also their treatment patterns. Collectively, these multiple mechanisms were contribute to the increased risk of subsequent events.

In the post-event cohort, the IS group had higher all-cause mortality than the CAD group. This difference likely reflected the poorer post-event prognosis after IS. Prior studies comparing stroke and MI reported greater declines in physical and cognitive function among stroke survivors [25,26]. Stroke survivors also had lower medication adherence and

receipt of guideline-concordant secondary prevention than MI survivors [27,28]. These features could contribute to the higher mortality in the IS group.

If poorer post-stroke function and less intensive secondary prevention explained the higher all-cause mortality in the IS group, recurrent CVD events should also be more frequent in the IS group than in the CAD group. However, in our study, the incidence of recurrent CVD events was not significantly different between the groups. The small sample size in the post-event cohort could miss the possible differences, if any. Another explanation could be differences in the likelihood of early censoring, with earlier loss to follow-up in the IS group. To account for such early censoring in the IS group, we added analyses incorporating the competing risk of death and found consistent findings with those of the primary analyses. Severe functional decline after stroke could necessitate long-term care or nursing home placement, which often resulted in discontinuation of follow-up. If such high-risk patients were disproportionately censored early in the post-event period, the risks of recurrent CVD events and mortality would be underestimated. A similar trend might occur in the comparison between the pre-event and post-event cohorts.

Our study has several limitations. First, patient characteristics and medication use were not repeatedly measured during follow-up. Therefore, some adjusting variables could be different from their baseline values in patients in the post-event cohort. These unmeasured longitudinal changes could introduce residual confounding and partly contribute to the observed increase in CVD risk after the first event. Second, the comparison between the pre-event and post-event cohorts might be affected by survivor selection bias and immortal time bias. The results of the sensitivity analyses using alternative cohort definitions were consistent with those of the primary analyses; however, these approaches could not fully eliminate these biases. Third, heterogeneity in secondary prevention strategies could affect the results. In particular, treatment patterns could change during the long-term follow-up, and thus the observed cardiovascular risk could be different from the truth. However, all patients in this cohort were initially enrolled in a clinical trial, in which physicians were asked to follow the standard secondary prevention strategies. Therefore, the deviation from the truth should not be large enough to change the findings if such heterogeneity occurred. Fourth, the small sample size in the post-event cohort could reduce the statistical power and precision, particularly in the comparison between the IS and CAD groups. Therefore, the absence of a statistically significant difference should not be interpreted as evidence of equivalent recurrent CVD risk. Finally, because this trial was started in 2002 and conducted exclusively in Japan, caution is warranted regarding the generalizability of our findings. Importantly, recent advances in CVD prevention, including the introduction of SGLT2 inhibitors and GLP-1 receptor agonists, could alter the magnitude of the observed increase in CVD risk following the first event in contemporary clinical practice.

5. Conclusions

The increase in CVD event risk and mortality following the first CVD event suggested that the first CVD event identified a transition to a markedly higher-risk clinical state, especially following IS. Physicians should be aware of the increased risks of second CVD events and mortality in patients with type 2 diabetes who survived their first CVD event, and strengthen the management of modifiable risk factors. To address the limitations of this study, future investigations should collect longitudinal data on physiological indicators and treatment intensity to explore optimal targets for risk management.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcdd13110586/s1, Figure S1: Incidence of endpoints in pre-event cohort vs. subset of post-event cohort whose first event occurred within 2 years of enrolment;

Figure S2: Incidence of endpoints in subset of pre-event cohort whose index day was shifted forward vs. post-event cohort.

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Institutional Review Board Statement: The studies were conducted in accordance with the latest versions of the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. The protocols of the JPAD trial and its follow-up study were approved by the ethics committees of the participating institutions. The protocol for the present analyses was approved by the Ethics Committee of Hyogo Medical University (25 January 2025, No. 4929).

Informed Consent Statement: Written informed consent was obtained for the JPAD trial, and for the follow-up study, it was also verbally obtained, according to the approval from the corresponding ethics committees.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author on reasonable request.

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Abbreviations

The following abbreviations are used in this manuscript:

CAD	Coronary artery disease
CI	Confidence interval
CVD	Cardiovascular diseases

eGFR	Estimated glomerular filtration rate
HbA1c	Hemoglobin A1c
HR	Hazard ratio
IS	Ischemic stroke
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes

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