

Supplemental Figure 1. Methods and results of validation study.

Methods

The SRICHS is an electronic chart-based stroke registry system recording clinical data of all admitted patients with a diagnosis of stroke (ICD-9-CM codes 430-437) in the Chang-Gung Healthcare System. The registered data is regularly checked for accuracy and assumed to be the gold standard in this validation study. We extracted the data of patients with the primary diagnosis of HS from both the SRICHS and NHIRD between 2009 and 2013. We then linked the two databases using date of birth, sex, primary diagnosis at discharge, admission date, and discharge date. This linking procedure helped to improve the accuracy of NHIRD by reducing bias such as incorrect coding.

Results

Among 114,219 HS patients in the NHIRD, a total of 2,343 patients in the SRICHS were matched for validation study. The positive predictive values of HS and first-ever HS were 97.98% and 90.54% in the NHIRD database, respectively (Supplemental Figure 1). Of the 16,693 eligible first-ever HS patients in the NHIRD, a total of 234 patients in the SRICHS were further matched. The mean admission systolic BP of these matched patients were 154.4 ± 24.8 , 154.3 ± 28.0 , and 137.8 ± 22.4 mmHg in the ACEI/ARB, CCB, and comparison groups ($p = 0.02$), while the diastolic BP were 91.2 ± 18.3 , 89.9 ± 16.5 , and 80.7 ± 14.1 mmHg in the ACEI/ARB, CCB, and comparison groups ($p = 0.04$), respectively.

A. Validated ICH (ICD-9 code: 431.xx) diagnoses (n = 1,634) in NHIRD

		SRICHs		
		+	-	
NHIRD	+	1,601	33	1,634 ^a
	-	-	-	

a. linked cases between NHIRD and SRICHs

PPV=1,601/1,634=97.98%

B. Validated first ever ICH diagnoses (n = 1,554) in NHIRD

		SRICHs		
		+	-	
NHIRD	+	1,407	147	1,554 ^a
	-	-	-	

a. linked cases between NHIRD and SRICHs

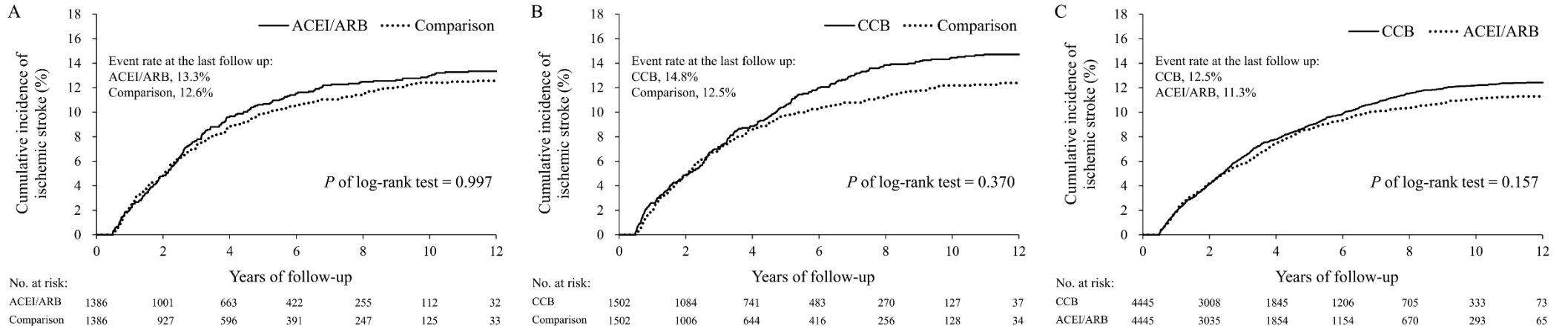
PPV=1,407/1,554=90.54%

HS, hemorrhagic stroke; ICD-9 CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHIRD, National Health Insurance Research Database; PPV, positive predictive value; SRICHs, Stroke Registry In Chang-Gung Healthcare System.

Supplemental Figure 2. Comparisons of cumulative incidence of ischemic stroke between the study groups.

The cumulative incidence compares the time to ischemic stroke between the study groups. The multivariate adjusted survival curves of the ACEI/ARB (A) and CCB (B) groups show a similar trend of ischemic stroke compared to the comparison group. The CCB and ACEI/ARB groups have similar risk of ischemic stroke throughout the follow-up period (C).

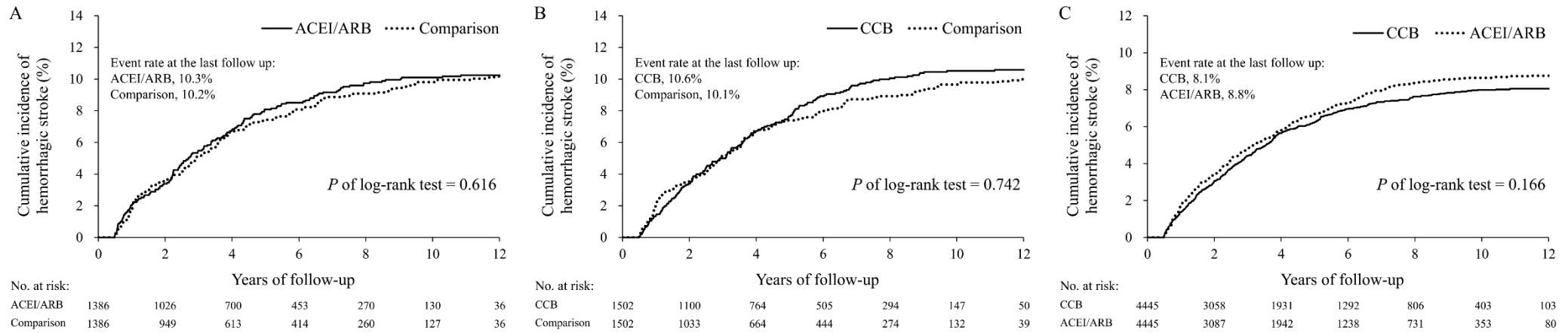
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.



Supplemental Figure 3. Comparisons of cumulative incidence of recurrent hemorrhagic stroke between the study groups.

The cumulative incidence compares the time to recurrent hemorrhagic stroke between the study groups. The multivariate adjusted survival curves of the ACEI/ARB (A) and CCB (B) groups show a similar trend of recurrent hemorrhagic stroke compared to the comparison group. The CCB and ACEI/ARB groups have similar risk of recurrent hemorrhagic stroke throughout the follow-up period (C).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.



Supplemental Table 1. ICD-9-CM code used for diagnosis in the current study

Variable	Code
Hemorrhage stroke	431.xx
Previous myocardial infarction	410.xx, 412.xx
Ischemic stroke	433.xx–435.xx, excluding 433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 434.00, 434.10, 434.90
Coronary artery disease	410.xx–414.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Hemodialysis	585.xx (Catastrophic illness certificate)
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Atrial fibrillation	427.31
Diabetes mellitus	250.xx
Dyslipidemia	272.xx
Malignancy	140.xx–208.xx (Catastrophic illness certificate)
Cirrhosis	571.2, 571.5, 571.6
Cardiovascular death	
Acute myocardial infarction	410.xx
Sudden cardiac death	427.5
Heart failure	428.xx
Cardiogenic shock	785.51
Any stroke	430.xx–437.xx
Dysrhythmia	427.xx
Pulmonary embolism	415.1, 415.11, 415.19
Aortic aneurysm dissection	441.xx
Peripheral arterial disease	443.9

Supplemental Table 2. Proportions of patients receiving non-study medications before propensity score matching

Characteristics	CCB (<i>n</i> = 10,400)	ACEI/ARB (<i>n</i> = 4,708)	Comparison (<i>n</i> = 1,585)	<i>P</i>
Non-antihypertensive medications (ATC codes)				
Anti-thrombotic agent				
Aspirin (B01AC06)	766 (7.4)	507 (10.8)	163 (10.3)	<0.001
Clopidogrel (B01AC04)	59 (0.6)	79 (1.7)	19 (1.2)	<0.001
Warfarin (B01AA)	53 (0.5)	86 (1.8)	56 (3.5)	<0.001
Lipid lowering agent				
Statin (C10AA)	686 (6.6)	590 (12.5)	106 (6.7)	<0.001
T2DM medication				
Insulin (A10A)	179 (1.7)	185 (3.9)	67 (4.2)	<0.001
Metformin (A10BA)	801 (7.7)	632 (13.4)	146 (9.2)	<0.001
Thiazolidinediones (A10BG02, A10BG03)	46 (0.4)	72 (1.5)	13 (0.8)	<0.001
Sulfonylurea (A10BB)	822 (7.9)	609 (12.9)	153 (9.7)	<0.001

CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; T2DM, Diabetes mellitus type 2; ATC code, Anatomical Therapeutic Chemical code.

Supplemental Table 3. Baseline characteristics of the study patients in the ACEI/ARB and comparison groups after propensity score matching

Characteristics	ACEI/ARB (<i>n</i> = 1,386)	Comparison (<i>n</i> = 1,386)	<i>P</i>
Age (years)	66.1±13.8	65.4±14.5	0.168
Age group			0.545
< 40	49 (3.5)	53 (3.8)	
40–75	896 (64.6)	918 (66.2)	
> 75	441 (31.8)	415 (29.9)	
Gender			0.754
Male	867 (62.6)	859 (62.0)	
Female	519 (37.4)	527 (38.0)	
Previous myocardial infarction	29 (2.1)	29 (2.1)	1.000
Previous ischemic stroke	94 (6.8)	77 (5.6)	0.180
Previous antiplatelet use	378 (27.3)	354 (25.5)	0.301
Previous anticoagulant use	63 (4.5)	59 (4.3)	0.711
Comorbidity			
Coronary artery disease	231 (16.7)	220 (15.9)	0.571
Chronic kidney disease	32 (2.3)	35 (2.5)	0.711
Hemodialysis	8 (0.6)	9 (0.6)	0.808
Chronic obstructive pulmonary disease	147 (10.6)	147 (10.6)	1.000
Atrial fibrillation	73 (5.3)	69 (5.0)	0.730
Diabetes mellitus	305 (22.0)	302 (21.8)	0.890
Dyslipidemia	186 (13.4)	179 (12.9)	0.694
Malignancy	61 (4.4)	59 (4.3)	0.852
NIHSS	15.6±7.2	15.5±7.4	0.520
NIHSS group			0.818
≤ 5	160 (11.5)	158 (11.4)	
6-13	382 (27.6)	397 (28.6)	
> 13	844 (60.9)	831 (60.0)	
Follow up years (not matched)	5.0±3.4	4.7±3.5	0.026
Anti-thrombotic agent			
Aspirin	162 (11.7)	144 (10.4)	0.275
Clopidogrel	20 (1.4)	19 (1.4)	0.872
Warfarin	38 (2.7)	38 (2.7)	1.000
Lipid lowering agent			
Statin	112 (8.1)	103 (7.4)	0.523
T2DM medication			
Insulin	57 (4.1)	56 (4.0)	0.923
Metformin	140 (10.1)	137 (9.9)	0.849
Thiazolidinediones	11 (0.8)	12 (0.9)	0.834
Sulfonylurea	150 (10.8)	139 (10.0)	0.494
Numbers of antihypertensive drug class used at baseline			0.682
1	994 (71.7)	980 (70.7)	
2	332 (24.0)	337 (24.3)	
≥ 3	60 (4.3)	69 (5.0)	
Add on within two years (not matched)			
Antihypertensive drug not of interest			
Beta-blocker	81 (5.8)	21 (1.5)	<0.001
Alpha-blocker	28 (2.0)	12 (0.9)	0.011

Other	9 (0.6)	8 (0.6)	0.808
Diuretics not of interest			
Thiazide	40 (2.9)	20 (1.4)	0.009
Loop diuretics	84 (6.1)	67 (4.8)	0.155
Spironolactone	24 (1.7)	23 (1.7)	0.883
Number of drugs used within two years			<0.001
0	163 (11.8)	239 (17.2)	
1	821 (59.2)	822 (59.3)	
≥ 2	402 (29.0)	325 (23.4)	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NIHSS, National Institutes of Health Stroke Scale; T2DM, Diabetes mellitus type 2.

Supplemental Table 4. Baseline characteristics of the study patients in the CCB and comparison groups after propensity score matching

Characteristics	CCB (<i>n</i> = 1,502)	Comparison (<i>n</i> = 1,502)	<i>P</i>
Age (years)	65.4±13.8	65.1±14.6	0.675
Age group			0.869
< 40	59 (3.9)	64 (4.3)	
40–75	995 (66.2)	985 (65.6)	
> 75	448 (29.8)	453 (30.2)	
Gender			0.385
Male	958 (63.8)	935 (62.3)	
Female	544 (36.2)	567 (37.7)	
Previous myocardial infarction	27 (1.8)	25 (1.7)	0.780
Previous ischemic stroke	90 (6.0)	83 (5.5)	0.584
Previous antiplatelet use	364 (24.2)	359 (23.9)	0.831
Previous anticoagulant use	50 (3.3)	54 (3.6)	0.690
Comorbidity			
Coronary artery disease	219 (14.6)	219 (14.6)	1.000
Chronic kidney disease	35 (2.3)	38 (2.5)	0.722
Hemodialysis	8 (0.5)	9 (0.6)	0.808
Chronic obstructive pulmonary disease	159 (10.6)	153 (10.2)	0.720
Atrial fibrillation	61 (4.1)	68 (4.5)	0.529
Diabetes mellitus	312 (20.8)	306 (20.4)	0.787
Dyslipidemia	192 (12.8)	182 (12.1)	0.581
Malignancy	69 (4.6)	69 (4.6)	1.000
NIHSS	15.8±7.2	15.7±7.3	0.700
NIHSS group			0.311
≤ 5	174 (11.6)	163 (10.9)	
6-13	376 (25.0)	412 (27.4)	
> 13	952 (63.4)	927 (61.7)	
Follow up years (not matched)	5.1±3.4	4.7±3.4	<0.001
Anti-thrombotic agent			
Aspirin	171 (11.4)	147 (9.8)	0.155
Clopidogrel	20 (1.3)	17 (1.1)	0.620
Warfarin	33 (2.2)	34 (2.3)	0.902
Lipid lowering agent			
Statin	99 (6.6)	101 (6.7)	0.884
T2DM medication			
Insulin	64 (4.3)	57 (3.8)	0.516
Metformin	148 (9.9)	140 (9.3)	0.620
Thiazolidinediones	10 (0.7)	12 (0.8)	0.669
Sulfonylurea	148 (9.9)	141 (9.4)	0.665
Numbers of antihypertensive drug class used at baseline			0.098
1	1,126 (75.0)	1,074 (71.5)	
2	316 (21.0)	357 (23.8)	
≥ 3	60 (4.0)	71 (4.7)	
Add on within two years (not matched)			
Antihypertensive drug not of interest			
Beta-blocker	93 (6.2)	27 (1.8)	<0.001
Alpha-blocker	31 (2.1)	14 (0.9)	0.011

Other	11 (0.7)	8 (0.5)	0.490
Diuretics not of interest			
Thiazide	38 (2.5)	21 (1.4)	0.025
Loop diuretics	63 (4.2)	77 (5.1)	0.226
Spironolactone	21 (1.4)	31 (2.1)	0.162
Number of drugs used within two years			<0.001
0	165 (11.0)	255 (17.0)	
1	930 (61.9)	896 (59.7)	
≥ 2	407 (27.1)	351 (23.4)	

CCB, calcium channel blocker; T2DM, Diabetes mellitus type 2; NIHSS, National Institutes of Health Stroke Scale.

Supplemental Table 5. Baseline characteristics of the study patients in the ACEI/ARB and CCB groups after propensity score matching

Characteristics	ACEI/ARB (n = 4,445)	CCB (n = 4,445)	P
Age (years)	63.0±13.6	63.1±13.6	0.770
Age group			0.759
< 40	181 (4.1)	186 (4.2)	
40–75	3,271 (73.6)	3,240 (72.9)	
> 75	993 (22.3)	1,019 (22.9)	
Gender			0.467
Male	2,846 (64.0)	2,813 (63.3)	
Female	1,599 (36.0)	1,632 (36.7)	
Previous myocardial infarction	60 (1.3)	62 (1.4)	0.855
Previous ischemic stroke	186 (4.2)	182 (4.1)	0.831
Previous antiplatelet use	1,042 (23.4)	1,047 (23.6)	0.900
Previous anticoagulant use	81 (1.8)	76 (1.7)	0.687
Comorbidity			
Coronary artery disease	546 (12.3)	521 (11.7)	0.415
Chronic kidney disease	102 (2.3)	99 (2.2)	0.831
Hemodialysis	36 (0.8)	38 (0.9)	0.815
Chronic obstructive pulmonary disease	253 (5.7)	253 (5.7)	1.000
Atrial fibrillation	133 (3.0)	142 (3.2)	0.581
Diabetes mellitus	1,021 (23.0)	1,020 (22.9)	0.980
Dyslipidemia	672 (15.1)	669 (15.1)	0.929
Malignancy	153 (3.4)	167 (3.8)	0.425
NIHSS	14.2±7.0	14.3±6.9	0.495
NIHSS group			0.738
≤ 5	552 (12.4)	531 (11.9)	
6-13	1,578 (35.5)	1,570 (35.3)	
> 13	2,315 (52.1)	2,344 (52.7)	
Follow up years (not matched)	4.5±3.3	4.6±3.4	0.227
Anti-thrombotic agent			
Aspirin	420 (9.4)	405 (9.1)	0.583
Clopidogrel	48 (1.1)	49 (1.1)	0.919
Warfarin	47 (1.1)	48 (1.1)	0.918
Lipid lowering agent			
Statin	476 (10.7)	469 (10.6)	0.810
T2DM medication			
Insulin	142 (3.2)	139 (3.1)	0.856
Metformin	544 (12.2)	548 (12.3)	0.897
Thiazolidinediones	46 (1.0)	44 (1.0)	0.832
Sulfonylurea	526 (11.8)	530 (11.9)	0.896
Antihypertensive drug not of interest			
Beta-blocker	1,478 (33.3)	1,451 (32.6)	0.542
Alpha-blocker	396 (8.9)	399 (9.0)	0.911
Other	124 (2.8)	131 (2.9)	0.656
Diuretics not of interest			
Thiazide	356 (8.0)	331 (7.4)	0.321
Loop diuretics	426 (9.6)	427 (9.6)	0.971
Spironolactone	74 (1.7)	71 (1.6)	0.802

Numbers of antihypertensive drug class used at baseline			0.636
1	2,277 (51.2)	2,276 (51.2)	
2	1,603 (36.1)	1,631 (36.7)	
≥ 3	565 (12.7)	538 (12.1)	
Add on within two years (not matched)			
Antihypertensive drug not of interest			
Beta-blocker	246 (5.5)	257 (5.8)	0.614
Alpha-blocker	86 (1.9)	84 (1.9)	0.877
Other	28 (0.6)	39 (0.9)	0.177
Diuretics not of interest			
Thiazide	108 (2.4)	101 (2.3)	0.624
Loop diuretics	188 (4.2)	179 (4.0)	0.631
Spironolactone	54 (1.2)	40 (0.9)	0.147
Number of drugs used within two years			0.912
0	370 (8.3)	381 (8.6)	
1	2,217 (49.9)	2,207 (49.7)	
≥ 2	1,858 (41.8)	1,857 (41.8)	

CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NIHSS, National Institutes of Health Stroke Scale; T2DM, Diabetes mellitus type 2.

Supplemental Table 6. Secondary outcomes in the ACEI/ARB and comparison groups after propensity score matching

Outcome	ACEI/ARB (<i>n</i> = 1,386)	Comparison (<i>n</i> = 1,386)	ACEI/ARB vs. Comparison	
			HR (95% CI) [†]	<i>p</i>
2-year follow-up				
Hemodialysis	0 (0.0)	2 (0.1)	NA	NA
Cardiovascular death	10 (0.7)	13 (0.9)	0.74 (0.32, 1.69)	0.474
Myocardial infarction	7 (0.5)	3 (0.2)	2.23 (0.58, 8.63)	0.245
5-year follow-up				
Hemodialysis	2 (0.1)	6 (0.4)	0.32 (0.06, 1.56)	0.158
Cardiovascular death	27 (1.9)	23 (1.7)	1.11 (0.63, 1.93)	0.726
Myocardial infarction	12 (0.9)	5 (0.4)	2.25 (0.79, 6.39)	0.127
At the last follow-up				
Hemodialysis	8 (0.6)	9 (0.6)	0.75 (0.28, 2.03)	0.576
Cardiovascular death	37 (2.7)	39 (2.8)	0.90 (0.57, 1.41)	0.639
Myocardial infarction	22 (1.6)	13 (0.9)	1.59 (0.80, 3.17)	0.183

HR, hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker;

[†] Propensity score is additionally treated as a covariate in the model.

Supplemental Table 7. Secondary outcomes in the CCB and comparison groups after propensity score matching

Outcome	CCB (<i>n</i> = 1,502)	Comparison (<i>n</i> = 1,502)	CCB vs. Comparison	
			HR (95% CI) [†]	<i>p</i>
2-year follow-up				
Hemodialysis	6 (0.4)	2 (0.1)	2.92 (0.59, 14.45)	0.190
Cardiovascular death	8 (0.5)	14 (0.9)	0.55 (0.23, 1.30)	0.171
Myocardial infarction	8 (0.5)	3 (0.2)	2.55 (0.68, 9.61)	0.167
5-year follow-up				
Hemodialysis	10 (0.7)	5 (0.3)	1.87 (0.64, 5.47)	0.254
Cardiovascular death	16 (1.1)	24 (1.6)	0.62 (0.33, 1.16)	0.133
Myocardial infarction	13 (0.9)	5 (0.3)	2.42 (0.86, 6.80)	0.093
At the last follow-up				
Hemodialysis	15 (1.0)	9 (0.6)	1.51 (0.66, 3.45)	0.329
Cardiovascular death	32 (2.1)	40 (2.7)	0.72 (0.45, 1.15)	0.168
Myocardial infarction	22 (1.5)	13 (0.9)	1.53 (0.77, 3.04)	0.224

HR, hazard ratio; CI, confidence interval; CCB, calcium channel blocker;

[†] Propensity score is additionally treated as a covariate in the model.

Supplemental Table 8. Secondary outcomes in the ACEI/ARB and CCB groups after propensity score matching

Outcome	ACEI/ARB (<i>n</i> = 4,445)	CCB (<i>n</i> = 4,445)	ACEI/ARB vs. CCB	
			HR (95% CI) [†]	<i>p</i>
2-year follow-up				
Hemodialysis	5 (0.1)	27 (0.6)	0.18 (0.07, 0.47)	<0.001
Cardiovascular death	32 (0.7)	25 (0.6)	1.27 (0.75, 2.14)	0.377
Myocardial infarction	18 (0.4)	11 (0.2)	1.62 (0.76, 3.43)	0.208
5-year follow-up				
Hemodialysis	13 (0.3)	47 (1.1)	0.27 (0.14, 0.49)	<0.001
Cardiovascular death	68 (1.5)	54 (1.2)	1.24 (0.87, 1.77)	0.242
Myocardial infarction	36 (0.8)	24 (0.5)	1.48 (0.88, 2.48)	0.139
At the last follow-up				
Hemodialysis	29 (0.7)	65 (1.5)	0.42 (0.27, 0.65)	<0.001
Cardiovascular death	99 (2.2)	77 (1.7)	1.29 (0.96, 1.74)	0.094
Myocardial infarction	59 (1.3)	42 (0.9)	1.42 (0.96, 2.11)	0.084

HR, hazard ratio; CI, confidence interval; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker;

[†] Propensity score is additionally treated as a covariate in the model.