

ORIGINAL RESEARCH

Comprehensive Prestroke Risk Factor Control and Functional Outcomes After Acute Ischemic Stroke

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BACKGROUND: Whether comprehensive prestroke risk factor (RF) management—defined by the extent to which existing major RFs meet prespecified treatment and biomarker criteria—is associated with 3-month functional outcomes after ischemic stroke remains unclear.

METHODS: We analyzed patients with ischemic stroke from the CRCS-K-NIH (Clinical Research Collaborations for Stroke in Korea-National Institutes for Health) registry (2011–2022), a multicenter stroke registry in Korea. Hypertension, diabetes, dyslipidemia, and atrial fibrillation were considered as major RFs for ischemic stroke. Comprehensive prestroke RF management was categorized as well controlled (all present RFs meeting study-defined control criteria), partially controlled (some RFs meeting this criteria), or poorly controlled (no RFs meeting this criteria). The primary outcome was 3-month modified Rankin Scale score of 0 to 2, indicating functional independence (good outcome).

RESULTS: Among 63570 patients with ≥ 1 major RFs, 28.6% were poorly controlled, 35.6% partially controlled, and 35.8% well controlled. The rate of 3-month good outcome was 66.0% among those with 1 RF, 60.8% in 2, and 55.0% in ≥ 3 . After multivariable adjustment, both well-controlled and partially controlled groups had significantly higher odds of achieving good 3-month outcomes compared with poorly controlled patients, consistently across RF burden strata (well controlled: adjusted odds ratio, 1.16 [95% CI, 1.08–1.25] for 1 RF, 1.34 [95% CI, 1.21–1.48] for 2, and 1.23 [95% CI, 1.03–1.48] for ≥ 3 ; partially controlled: 1.16 [95% CI, 1.06–1.26] for 2; 1.22 [95% CI, 1.05–1.42] for ≥ 3) and in the overall cohort (well controlled: 1.22 [95% CI, 1.15–1.29], partially controlled: 1.14 [95% CI, 1.07–1.22]).

CONCLUSIONS: Comprehensive prestroke RF management, defined by study-specific treatment- and biomarker-based criteria, was independently associated with a higher likelihood of favorable 3-month outcomes across levels of RF burden. These findings suggest that effective prestroke management of existing RFs may improve poststroke functional outcomes, regardless of the number of RFs present.

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Key Words: acute ischemic stroke ■ comprehensive risk factor control ■ functional outcome ■ risk factor ■ risk factor burden

CLINICAL PERSPECTIVE

What Is New?

- In a large nationwide stroke registry, comprehensive prestroke management of major modifiable risk factors—hypertension, diabetes, dyslipidemia, and atrial fibrillation—was independently associated with more favorable 3-month functional outcomes after ischemic stroke, regardless of the number of risk factors present.
- The degree of prestroke risk factor management, rather than risk factor burden alone, showed a consistent association with poststroke functional independence across different levels of risk factor burden.

What Are the Clinical Implications?

- These findings suggest that effective prestroke management of existing risk factors may improve functional recovery after ischemic stroke, highlighting the importance of sustained, comprehensive risk factor management beyond the prevention of stroke occurrence itself.

Nonstandard Abbreviations and Acronyms

mRS	modified Rankin Scale
RF	risk factor

Cardiovascular risk factors (RFs) are associated not only with the occurrence of stroke but also with poststroke outcomes.^{1,2} Major modifiable RFs, including hypertension, diabetes, dyslipidemia, and atrial fibrillation (AF), are well-established determinants of stroke severity, functional outcome, and mortality.³ Effective prestroke management of individual RFs has been shown to improve poststroke outcomes; for example, prestroke statin use has been associated with reduced stroke severity and better functional outcomes, and poor glycemic control has been linked to higher mortality and worse outcomes after ischemic stroke.^{4,5} Similarly, oral anticoagulant therapy in patients with AF was associated with more favorable outcomes.⁶

Emerging evidence suggests that prestroke medication use may influence poststroke outcomes; however, these findings are largely limited by a focus on individual medications rather than the effectiveness of comprehensive RF control.⁷ In clinical practice, patients often present

with multiple coexisting RFs, and multimorbidity itself has been associated with poorer functional recovery after stroke.^{8,9} Beyond individual RFs, the combined burden and management of multiple RFs may play a critical role in determining poststroke outcomes.

Despite the recognized importance of RF management, few studies have evaluated whether the comprehensive prestroke management of multiple major RFs—rather than RF burden alone—is associated with 3-month functional outcomes following ischemic stroke. In addition, it remains unclear whether the degree of comprehensive RF control confers prognostic value across different levels of RF burden.

In this registry-based study, prestroke RF control reflects study-defined, treatment- and biomarker-based management status rather than true physiologic control or medication adherence. Accordingly, associations observed in this study should be interpreted in the context of prestroke RF management, rather than direct measures of biologic control.

Therefore, this study aimed to evaluate whether comprehensive prestroke RF management, classified as well controlled, partially controlled, or poorly controlled based on prespecified criteria, is associated with 3-month functional outcomes after ischemic stroke. We further investigated whether comprehensive RF management, regardless of the numbers of RFs present, contributes to improved 3-month poststroke functional outcomes.

METHODS

Subjects

This study analyzed data from patients with acute cerebrovascular events enrolled in the CRCS-K-NIH (Clinical Research Collaborations for Stroke in Korea-National Institutes for Health), a multicenter, prospective stroke registry in Korea, between January 2011 and December 2022.¹⁰ Details of the registry have been described in previous studies.^{11,12} Among these, we included patients with acute ischemic stroke who were admitted within 7 days of onset and had complete information on vascular RFs. Patients without data on admission glycated hemoglobin, low-density lipoprotein cholesterol, or glucose levels, as well as those without a 3-month mRS assessment, were excluded from the analysis (Figure S1).

Data Availability

The data used in this study are available upon reasonable request following the submission of a

legitimate academic research proposal to be assessed by the CRCS-K-NIH steering committee.

Data Collection

Demographic, clinical, imaging, and laboratory data were prospectively collected. Ischemic stroke subtypes were classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria, which were refined to incorporate additional information based on modern imaging studies.^{13,14}

Risk Burden and Its Control

The 4 major modifiable RFs selected for this study were hypertension, diabetes, dyslipidemia, and AF, as they are key contributors to ischemic stroke. Patients were categorized according to the number of the 4 major RFs present: no RF, 1 RF, 2 RFs, or ≥ 3 RFs. The numbers of RFs were considered by treating each factor as equally weighted.

The definitions of comprehensive prestroke RF control in patients with ≥ 1 RFs were prespecified based on clinical relevance, as follows; patients were assigned to the well-controlled status if all major RFs present in the patients met the criteria for individual well-controlled RF. Those for whom only a subset of present RFs met the well-controlled criteria were categorized into the partially-controlled status, and patients for whom none of the RFs were well controlled were classified into the poorly-controlled status.

Individual RF control status was considered based on the clinical relevance and previous literature.^{15–18} RFs meeting study-defined control criteria at the time of index stroke were defined as follows: well-controlled hypertension as recent prior antihypertensive medication, well-controlled diabetes as both prior antidiabetic medication and glycated hemoglobin $<7.0\%$ on admission, well-controlled dyslipidemia as both recent prior statin medication and low-density lipoprotein cholesterol $<100\text{mg/dL}$ on admission, and well-controlled AF as the presence of AF and prior oral anticoagulant medication. Prior medication use was defined as the use of relevant drugs for at least 1 month before stroke onset, confirmed by self-reports, medical records, or prescription data. For each RF, the rate of well-controlled status was defined as the proportion of patients with that RF who met the criteria for well-controlled status. Detailed descriptions are provided in the Supplemental Methods.

Primary Outcome

At 3 months after initial ischemic stroke admission, patients were followed up by trained research coordinators in face-to-face or telephone interviews based on a standardized interview protocol.^{11,12} To ensure

consistency in assessment, the evaluators underwent validated training and testing for modified Rankin Scale (mRS) evaluation and were certified. The primary outcome was defined as an mRS score of 0 to 2 at 3 months, indicated by a good functional outcome (functional independence). The secondary outcomes included an mRS score of 0 to 1 (excellent outcome, no or minimal disability) at 3 months, analysis of the ordinal mRS, and 3-month mortality.

Statistical Analysis

Patient baseline characteristics are presented as means $\pm$ SD or medians with interquartile ranges for continuous variables and numbers and percentages for categorical variables. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, and continuous variables were analyzed using analysis of variance or the Kruskal–Wallis test, as appropriate. Given the low proportion of missing baseline data, single imputation using the median was performed for continuous variables. For categorical variables, missing entries were replaced with a reference or absence category. The following parameters had missing data and the proportion of missing values was as follows: height (1.8%), weight (1.3%), creatinine (0.6%), blood urea nitrogen (0.5%), hemoglobin (0.3%), platelet count (0.6%), white blood cell count (0.2%), glucose ($<0.1\%$), and TOAST subtypes ($<0.1\%$).

Binary logistic regression analysis was performed to explore the relationships between RF control status (only patients with ≥ 1 major RFs) and dichotomized clinical outcomes and ordinal logistic regression analysis was applied to investigate the relationship between RF control status and 3-month mRS score distribution within each numbers of present RFs and across all levels of RF presence. Variables for adjustment in multivariable models were predefined on clinical relevance and prior literatures as follows: age, male, prestroke disability, initial National Institutes of Health Stroke Scale score, glucose, TOAST subtypes, history of stroke, history of coronary artery disease, hypertension, dyslipidemia, diabetes, AF, prior antiplatelet, prior statin, large artery steno-occlusion, reperfusion therapy, and systolic blood pressure. Odds ratios (ORs) and 95% CIs were estimated. All statistical analyses were performed using SAS software (Version 9.4, SAS Institute Inc, Cary, NC, USA).

Standard Protocol Approvals, Registrations, and Patient Consents

Clinical information was collected from the CRCS-K-NIH registry with approval from the local institutional review boards of all the participating centers. A waiver for informed consent was provided because of study subject anonymity and minimal risk to the participants. The institutional review boards also approved the

Table 1. General Characteristics of Subjects According to the Control Status Across All Levels of Risk Factor Presence

	Total	Poorly controlled	Partially controlled	Well controlled	P value*	P trend†
No.	63 570	18 192	22 614	22 764		
Age, y, mean±SD	69.9±12.1	65.6±13.4	71.6±11.1	71.8±11.2	<0.001	<0.001
Male sex, n (%)	36 948 (58.1)	11 892 (65.4)	12 239 (54.1)	12 817 (56.3)	<0.001	<0.001
Arrival within 24 h	44 922 (70.7)	12 777 (70.2)	16 245 (71.8)	15 900 (69.8)	<0.001	0.24
Height, cm	162.3±9.0	163.9±8.9	161.7±8.9	161.5±9.0	<0.001	<0.001
Weight, kg	63.2±12.1	64.1±12.5	63.5±12.1	62.3±11.6	<0.001	<0.001
Body mass index	23.9±3.6	23.7±3.6	24.2±3.7	23.8±3.5	<0.001	0.343
National Institutes of Health Stroke Scale score, median (interquartile range)	3 (1–8)	3 (1–7)	4 (2–9)	3 (1–7)	<0.001	<0.001
National Institutes of Health Stroke Scale score 0–4	37 362 (58.8)	10 882 (59.8)	12 316 (54.5)	14 164 (62.2)	<0.001	<0.001
Pre-modified Rankin Scale score 0–1, n (%)	54 877 (86.3)	16 530 (90.9)	19 000 (84.0)	19 347 (85.0)	<0.001	<0.001
Trial of Org 10172 in Acute Stroke Treatment, n (%)					<0.001	0.846
Large-artery atherosclerosis	21 908 (34.5)	5984 (32.9)	7001 (31.0)	8923 (39.2)		
Small-vessel occlusion	10 951 (17.2)	3837 (21.1)	3000 (13.3)	4114 (18.1)		
Cardioembolism	14 745 (23.2)	4057 (22.3)	7510 (33.2)	3178 (14.0)		
Other determined cause	1624 (2.6)	573 (3.1)	344 (1.5)	707 (3.1)		
Undetermined cause	14 342 (22.6)	3741 (20.6)	4759 (21.0)	5842 (25.7)		
History of transient ischemic attack	1172 (1.8)	246 (1.4)	442 (2.0)	484 (2.1)	<0.001	<0.001
History of stroke	14 370 (22.6)	2271 (12.5)	5634 (24.9)	6465 (28.4)	<0.001	<0.001
History of coronary artery disease	6632 (10.4)	971 (5.3)	2952 (13.1)	2709 (11.9)	<0.001	<0.001
History of peripheral artery disease	588 (0.9)	131 (0.7)	256 (1.1)	201 (0.9)	<0.001	0.151
Hypertension	50 483 (79.4)	9797 (53.9)	21 180 (93.7)	19 506 (85.7)	<0.001	<0.001
Well-controlled hypertension	38 129 (75.5)	0 (0.0)	18 623 (87.9)	19 506 (100.0)	<0.001	<0.001
Diabetes	25 857 (40.7)	5095 (28.0)	13 747 (60.8)	7015 (30.8)	<0.001	0.542
Well-controlled diabetes	13 870 (48.1)	0 (0.0)	5825 (39.0)	8045 (100.0)	<0.001	<0.001
Dyslipidemia	23 758 (37.4)	6380 (35.1)	12 207 (54.0)	5171 (22.7)	<0.001	<0.001
Well-controlled dyslipidemia	8938 (37.6)	0 (0.0)	3767 (30.9)	5171 (100.0)	<0.001	<0.001
AF	15 740 (24.8)	4209 (23.1)	8862 (39.2)	2669 (11.7)	<0.001	<0.001
Well-controlled AF	3904 (24.8)	0 (0.0)	1235 (13.9)	2669 (100.0)	<0.001	<0.001
Current smoker	13 765 (21.7)	5647 (31.0)	4108 (18.2)	4010 (17.6)	<0.001	<0.001
Prior antiplatelet	20 140 (31.7)	2659 (14.6)	9343 (41.3)	8138 (35.7)	<0.001	<0.001
Prior anticoagulant	4551 (7.2)	112 (0.6)	1411 (6.2)	3028 (13.3)	<0.001	<0.001
Prior statin	16 315 (25.7)	1271 (7.0)	7684 (34.0)	7360 (32.3)	<0.001	<0.001
Prior antihypertension	2495 (3.9)	344 (1.9)	1418 (6.3)	733 (3.2)	<0.001	<0.001
Prior antidiabetes	18 938 (29.8)	2579 (14.2)	10 647 (47.1)	5712 (25.1)	<0.001	<0.001
Large artery steno-occlusion					<0.001	0.927
No	30 163 (47.4)	9194 (50.5)	9932 (43.9)	11 037 (48.5)		
Mild (<50%)	5759 (9.1)	1543 (8.5)	2102 (9.3)	2114 (9.3)		
Significant (>50%)	11 165 (17.6)	2852 (15.7)	3969 (17.6)	4344 (19.1)		
Occlusion	16 483 (25.9)	4603 (25.3)	6611 (29.2)	5269 (23.1)		
Reperfusion therapy					<0.001	<0.001
No	52 521 (82.6)	14 867 (81.7)	18 291 (80.9)	19 363 (85.1)		
IVT only	5340 (8.4)	1681 (9.2)	2007 (8.9)	1652 (7.3)		
EVT only	3179 (5.0)	827 (4.5)	1247 (5.5)	1105 (4.9)		
Combined IVT+EVT	2530 (4.0)	817 (4.5)	1069 (4.7)	644 (2.8)		

(Continued)

Table 1. Continued

	Total	Poorly controlled	Partially controlled	Well controlled	P value*	P trend†
White blood cells	8.3±3.7	8.3±3.5	8.4±3.5	8.1±3.9	<0.001	<0.001
Serum urea nitrogen, mg/dL	18.0±9.3	16.4±7.9	19.1±10.2	18.1±9.3	<0.001	<0.001
Creatinine, mg/dL	1.04±0.94	0.94±0.69	1.12±1.08	1.04±0.97	<0.001	<0.001
Hemoglobin	13.6±2.1	14.1±2.0	13.4±2.0	13.2±2.0	<0.001	<0.001
Low-density lipoprotein, mg/dL	105.0±38.9	119.1±39.7	104.1±39.3	94.6±34.1	<0.001	<0.001
Platelet count	228.3±73.5	231.2±69.9	227.4±72.1	227.0±77.5	<0.001	<0.001
Glycated hemoglobin, %	6.5±1.5	6.7±1.8	6.9±1.5	5.9±0.5	<0.001	<0.001
Glucose, mg/dL	150.7±66.8	155.6±76.8	166.1±74.5	131.4±40.0	<0.001	<0.001
Systolic blood pressure, mmHg	150.0±28.2	153.9±30.8	149.9±27.7	146.9±26.0	<0.001	<0.001
Diastolic blood pressure, mmHg	85.2±16.6	88.8±18.3	84.7±16.2	82.7±15.1	<0.001	<0.001

*P value by chi-square test, ANOVA, and Kruskal–Wallis test.

†P value by Cochran–Armitage trend test, Cochran–Mantel–Haenszel test, and linear contrasts test in ANOVA.

AF indicates atrial fibrillation; EVT, endovascular treatment; and IVT, intravenous thrombolysis.

specific use of the registry database and additional review of medical records for this study.

RESULTS

General Characteristics

A total of 75 815 patients (mean age 68.8±13 years; male 59%) with a median National Institutes of Health Stroke Scale score of 3 (interquartile range, 1–7) were analyzed. Among them, 16.2% (n=12 245) had no major RF, 32.1% (n=24 350) had 1 RF, 32.9% (n=24 918) had 2 RFs, and 18.9% (n=14 302) had ≥3 RFs. Detailed characteristics and functional outcomes at 3 months according to numbers of RFs are presented in Tables S1 and S2 and Figures S2 and S3.

Of the 63 570 patients with ≥1 major RFs (mean age 69.9±12 years; male 58.1%), 28.6% (n=18 192) were poorly controlled, 35.6% (n=22 614) were partially controlled, and 35.8% (n=22 764) were well controlled. Patients with poorly controlled status were younger, had lower prestroke morbidity (prestroke mRS score>1), and were less likely to have a history of stroke or coronary artery disease compared with those with well-controlled status (Table 1).

Numbers of Risk Burdens and Control Status of RFs

Key characteristics according to control status (well, partially, or poorly controlled) within each number of present RFs are presented in Table S3. The well-controlled status was 52.4% with 1 RF, 30.0% with 2 RFs, and 16.8% with ≥3 RFs. In contrast, the poorly controlled status was 47.6%, 21.2%, and 9.2%, respectively (Figure 1A). The percentage of well-controlled status for each individual RF is presented in Figure 1A, and the contribution of each RF to the respective risk burdens is illustrated in Figure 1B. As the numbers of risk burdens increased,

the proportion of well-controlled status for each RF increased numerically (Figure 1C). Overall, Figure 1 shows the distribution of prestroke RF control status across different levels of RF burden at the patient level (Figure 1A and 1B), while also illustrating individual RF-level control rates for each individual RF (Figure 1C), thereby providing context for subsequent analyses of functional outcomes.

Functional Outcomes According to the Control Status by Each Number of Risk Burdens

According to the number of present RFs, the proportion of patients with a good 3-month outcome was 64.7% in those with 1 RF, 61.6% in those with 2 RFs, and 56.1% in those with ≥3 RFs. Crude good outcome rates were paradoxically higher in the poorly controlled group than the well-controlled group among patients with 1 RF (67.4% versus 64.7%, $P<0.001$), but the difference was not significant after adjustment (57.6% versus 61.2%, $P=0.09$). For 2 RFs, adjusted good outcome rates increased with better control (59.8%, 63.2%, and 66.5% for poorly, partially, and well-controlled groups; $P<0.001$). Among those with ≥3 RFs, good outcome rates also trended higher with better control (61.3%, 54.0%, and 56.1%), though not statistically significant ($P=0.053$). Crude and adjusted outcomes by numbers of risk burden are detailed in Table 2 and Table S4.

Associations of 3-month functional outcomes and the control status of present RFs by numbers of RFs are shown in Table 3. Among patients with 1 RF, the well-controlled group was associated with greater odds for achieving a good outcome (adjusted OR [aOR], 1.16 [95% CI, 1.08–1.25]), excellent outcome (aOR, 1.15 [95% CI, 1.09–1.23]), and better functional outcome (aOR, 1.10 [95% CI, 1.05–1.16]) at 3 months, compared with the poorly controlled group. Among those with 2 RFs, the well-controlled group and partially controlled group,

Table 2. Functional Outcomes at 3 Month According to the Control Status of Each Number of Present Risk Factors Among Patients With ≥ 1 Risk Factors, Adjusted Analysis

	1 risk factor		P value	2 risk factors			P value	≥ 3 risk factors			P value
	Poorly controlled	Well controlled		Poorly controlled	Partially controlled	Well controlled		Poorly controlled	Partially controlled	Well controlled	
mRS score 0–2	57.6 (54.4–60.7)	61.2 (58.2–64.2)	0.099	59.8 (57.9–61.6)	63.2 (62.1–64.4)	66.5 (65.1–68.0)	<0.001	61.8 (56.6–66.8)	66.3 (62.3–70.2)	66.7 (62.2–70.8)	0.156
mRS score 0–1	32.2 (29.4–35.1)	35.4 (32.5–38.4)	0.126	34.7 (33.1–36.3)	38.7 (37.5–39.9)	41.6 (40.1–43.1)	<0.001	36.9 (32.2–42.0)	41.8 (37.4–46.2)	43.9 (39.2–48.8)	0.048
mRS score distribution											
0	13.5 (11.7–15.4)	14.4 (12.6–16.3)	0.507	13.2 (12.3–14.2)	15.3 (14.5–16.1)	16.3 (15.3–17.3)	<0.001	13.6 (10.7–16.5)	14.5 (11.9–17.2)	16.9 (13.7–20.1)	0.133
1	20.2 (17.8–22.5)	22.6 (20.1–25.2)	0.161	23.3 (21.9–24.7)	25.2 (24.2–26.2)	27.2 (25.9–28.5)	<0.001	25.3 (20.9–29.7)	29.6 (25.5–33.8)	28.9 (24.5–33.4)	0.257
2	23.1 (20.6–25.7)	23.4 (20.8–25.9)	0.905	23.0 (21.6–24.4)	22.3 (21.4–23.3)	22.6 (21.4–23.8)	0.660	23.0 (18.8–27.2)	22.3 (18.8–25.8)	20.8 (17.1–24.4)	0.428
3	21.6 (19.1–24.2)	19.8 (17.4–22.1)	0.285	18.9 (17.5–20.2)	18.3 (17.4–19.2)	15.8 (14.8–16.9)	<0.001	16.8 (13.3–20.3)	15.4 (12.6–18.1)	15.6 (12.6–18.7)	0.630
4	13.2 (11.4–15.0)	11.8 (10.1–13.4)	0.252	14.1 (12.9–15.3)	11.9 (11.2–12.6)	11.2 (10.3–12.1)	<0.001	14.1 (10.8–17.3)	11.8 (9.5–14.1)	11.9 (9.4–14.5)	0.307
5	4.8 (3.9–5.6)	4.3 (3.5–5.0)	0.381	4.5 (3.9–5.0)	3.8 (3.4–4.1)	3.8 (3.4–4.2)	0.052	4.7 (3.3–6.1)	3.6 (2.8–4.5)	3.6 (2.6–4.6)	0.223
6	3.5 (2.9–4.2)	3.8 (3.1–4.4)	0.614	3.1 (2.6–3.5)	3.1 (2.8–3.4)	3.1 (2.7–3.5)	0.929	2.6 (1.7–3.5)	2.7 (2.0–3.3)	2.3 (1.6–2.9)	0.573
Mortality	3.2 (2.7–3.8)	3.6 (3.0–4.2)	0.331	2.8 (2.5–3.2)	3.1 (2.9–3.4)	3.2 (2.8–3.5)	0.211	2.5 (1.8–3.4)	2.7 (2.2–3.5)	2.3 (1.8–3.1)	0.796

Adjusted proportion (%; 95% CI) and P value by logistic regression. Adjusted variables: age, male, prestroke disability, initial National Institutes of Health Stroke Scale score, glucose, Trial of Org 10172 in Acute Stroke Treatment subtypes, history of stroke, history of coronary artery disease, hypertension, dyslipidemia, diabetes, atrial fibrillation, prior antiplatelet, prior statin, large artery steno-occlusion, reperfusion therapy, and systolic blood pressure. mRS indicates modified Rankin Scale.

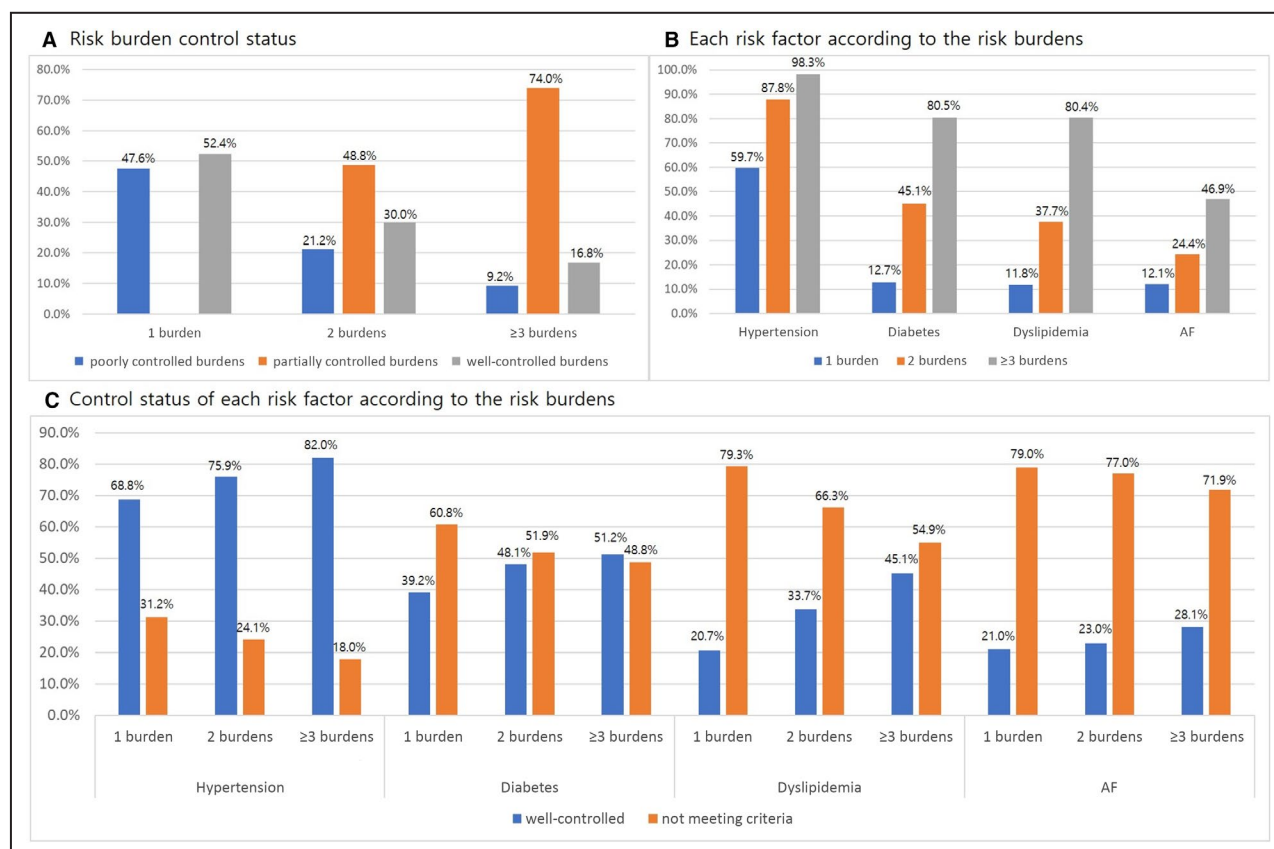


Figure 1. Distribution of prestroke RF control according to RF burden.

A, Patient-level prestroke RF control status—classified as well-controlled, partially-controlled, or poorly-controlled—according to the number of major RFs present. **B**, Contribution of each major RF to overall RF burden across control status categories. **C**, RF-level control rates for each individual RF across increasing RF burden. At the RF level, individual RFs are classified as meeting or not meeting the study-defined control criteria. AF indicates atrial fibrillation; and RF, risk factor.

compared with the poorly controlled group, were significantly associated with greater chance of achieving a 3-month good (aOR, 1.34 [95% CI, 1.21–1.48] and 1.16 [95% CI, 1.06–1.26], well-controlled and partially controlled groups, respectively) and excellent (aOR, 1.34 [95% CI, 1.22–1.47] and 1.19 [95% CI, 1.10–1.29], respectively) functional outcomes and better functional outcome (aOR 1.25 [95% CI, 1.16–1.34] and 1.15 [95% CI, 1.08–1.22], respectively) at 3 months. Among those with ≥3 RFs, similar associations were observed in well-controlled and partially controlled groups. Forest plots for associations of 3-month functional outcomes with controlled status of RFs according to the risk burdens (numbers of RFs) are shown in Figure 2 and Figure S4.

Functional Outcomes at 3 Months According to the Control Status of All Levels of RFs

Across all levels of RF presence, the proportions of patients with good functional outcomes at 3 months were 66.1% in the poorly controlled group, 56.5% in the partially controlled group, and 62.8% in the

well-controlled group (Table S5 and Figure 3). After adjustments of relevant variables, adjusted rates of 3-month good outcome were 59.8% (95% CI, 58.7–60.9), 62.9% (95% CI, 62.0–63.9), and 64.4% (95% CI, 63.5–65.3) in poorly, partially, and well-controlled groups, respectively. Overall, compared with poorly controlled status, well-controlled status and partially controlled status were significantly associated with higher odds for 3-month good, excellent, and better functional outcomes (Table 3; Figure 2; Figure S4).

DISCUSSION

In our analysis of >75 000 patients with stroke, among patients with ≥1 major RFs, both well-controlled and partially controlled groups were consistently associated with higher odds of achieving good or excellent functional outcomes at 3 months compared with poorly controlled patients, across different levels of RF burden. These findings suggest that the degree to which existing RFs are managed before stroke, rather than RF burden alone, is associated with early post-stroke functional outcomes.

Table 3. Associations of 3-Month Functional Outcomes (mRS Score 0–2, mRS Score 0–1, and mRS Distributions) and Risk Factor Control Status by Each Number of Risk Factors

	mRS score 0–2 at 3 mo				mRS score 0–1 at 3 mo				mRS score distribution*			
	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P value	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P value
1 risk factor												
Poorly-controlled	Reference		Reference		Reference		Reference		Reference		Reference	
Well controlled	0.89 (0.84–0.94)	<0.001	1.16 (1.08–1.25)	<0.001	0.88 (0.84–0.93)	<0.001	1.15 (1.09–1.23)	<0.001	0.88 (0.84–0.92)	<0.001	1.10 (1.05–1.16)	<0.001
2 risk factors												
Poorly controlled	Reference		Reference		Reference		Reference		Reference		Reference	
Partially controlled	0.79 (0.74–0.85)	<0.001	1.16 (1.06–1.26)	0.001	0.82 (0.77–0.88)	<0.001	1.19 (1.10–1.29)	<0.001	0.82 (0.77–0.87)	<0.001	1.15 (1.08–1.22)	<0.001
Well controlled	0.89 (0.83–0.96)	0.002	1.34 (1.21–1.48)	<0.001	0.91 (0.85–0.98)	0.01	1.34 (1.22–1.47)	<0.001	0.91 (0.85–0.96)	0.002	1.25 (1.16–1.34)	<0.001
≥3 risk factors												
Poorly controlled	Reference		Reference		Reference		Reference		Reference		Reference	
Partially controlled	0.74 (0.66–0.83)	<0.001	1.22 (1.05–1.42)	0.01	0.80 (0.71–0.90)	<0.001	1.22 (1.06–1.41)	0.005	0.76 (0.69–0.84)	<0.001	1.12 (1.01–1.25)	0.04
Well controlled	0.81 (0.70–0.92)	0.002	1.23 (1.03–1.48)	0.02	0.91 (0.80–1.04)	0.17	1.34 (1.13–1.58)	<0.001	0.88 (0.79–0.99)	0.04	1.24 (1.10–1.41)	<0.001
≥1 risk factors												
Poorly controlled	Reference		Reference		Reference		Reference		Reference		Reference	
Partially controlled	0.67 (0.64–0.70)	<0.001	1.14 (1.07–1.22)	<0.001	0.69 (0.66–0.72)	<0.001	1.15 (1.08–1.22)	<0.001	0.68 (0.66–0.71)	<0.001	1.10 (1.05–1.15)	<0.001
Well controlled	0.87 (0.83–0.90)	<0.001	1.22 (1.15–1.29)	<0.001	0.88 (0.85–0.92)	<0.001	1.21 (1.15–1.28)	<0.001	0.88 (0.85–0.91)	<0.001	1.15 (1.10–1.20)	<0.001

Adjusted variables; age, male, prestroke disability, initial National Institutes of Health Stroke Scale score, glucose, Trial of Org 10172 in Acute Stroke Treatment subtypes, history of stroke, history of coronary artery disease, hypertension, dyslipidemia, diabetes, atrial fibrillation, prior antiplatelet, prior statin, large artery steno-occlusion, reperfusion therapy, and systolic blood pressure. mRS indicates modified Rankin Scale.

*Ordinal shift across the range of mRS scores toward lower values.

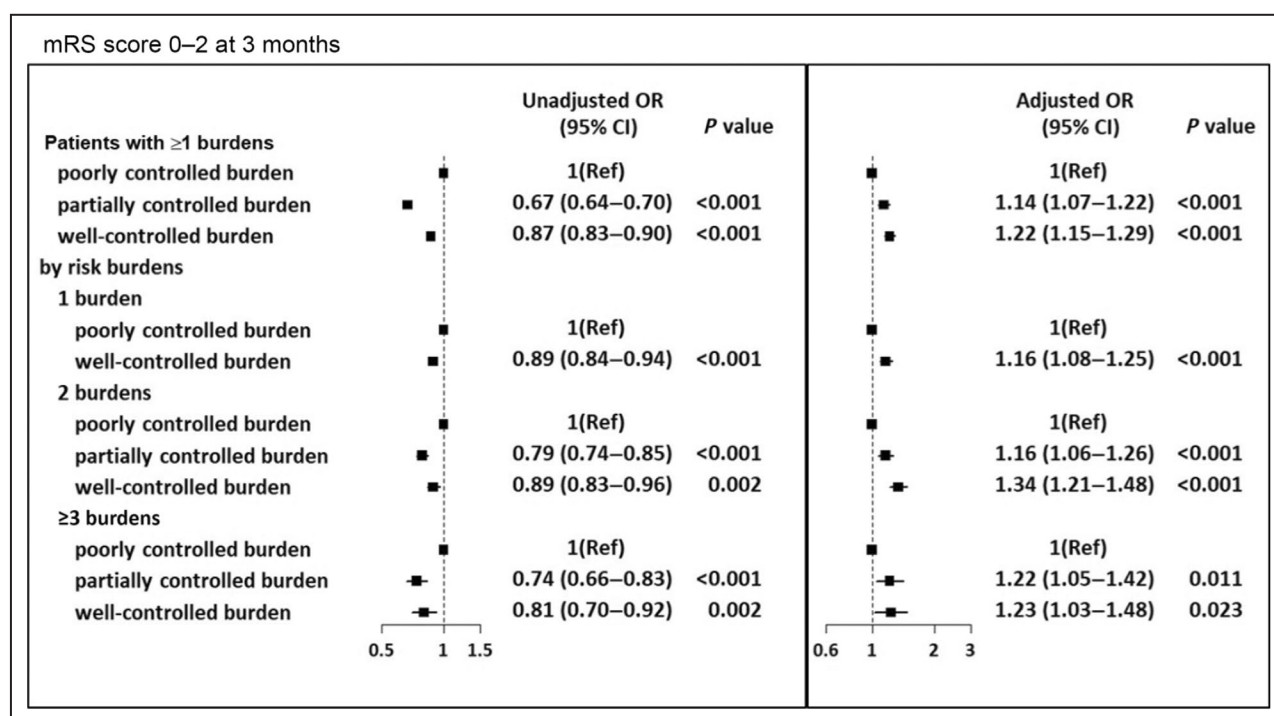


Figure 2. Associations of 3-month good outcomes (mRS score 0–2) with controlled status according to each number (burden) of present risk factors and across all levels of risk factor presence. mRS indicates modified Rankin Scale; and OR, odds ratio.

In this study, comprehensive prestroke RF control was operationally defined according to whether existing major RFs—hypertension, diabetes, dyslipidemia, and AF—met prespecified treatment- and biomarker-based criteria. These 4 RFs were selected because they are among the most consistently established, treatment-modifiable determinants of ischemic stroke occurrence and outcomes in contemporary clinical practice.^{19,20} Patients were categorized as well controlled if all present RFs met these criteria, partially controlled if some RFs met the criteria, and poorly controlled if none did. Other RFs, such as smoking or obesity, were not included because they lack standardized treatment- or biomarker-based criteria for defining prestroke “control” in registry-based data. In particular, smoking status is typically self-reported and does not have a clear threshold for adequate control comparable to pharmacologically managed RFs. However, smoking status was included as a covariate in the multivariable analyses to account for its potential confounding effects.

An interesting and seemingly counterintuitive finding was that the proportions of both poorly controlled and well-controlled statuses decreased as the number of RFs increased, whereas individual RF control rates tended to improve with higher RF burden. This pattern likely reflects increased contact with health care systems among patients with multiple comorbidities, leading to more frequent monitoring, treatment initiation, and optimization of individual RF management.

Notably, patients in the poorly controlled group tended to be younger, had better premorbid functional status, and were less likely to have a history of stroke or coronary artery disease compared with those in the well- or partially controlled groups. Despite these seemingly favorable baseline characteristics, poorly controlled patients experienced worse 3-month functional outcomes after multivariable adjustment. Rather than focusing solely on individual RFs, our findings suggest that considering how multiple coexisting RFs are managed before stroke may provide additional context for understanding early functional outcomes after stroke. In this context, future studies should explore strategies—such as integrated care pathways or multidisciplinary prevention programs—that may help extend effective RF management to patients with lower levels of health care engagement.

In our study, patients with stroke without any of the 4 major RFs were younger, predominantly male, and presented with less severe stroke, as reflected by lower National Institutes of Health Stroke Scale scores at admission. This observation is consistent with prior evidence suggesting that the presence of major RFs is associated with greater stroke severity.²¹ In the INTERSTROKE (International Case-Control Study of Risk Factors for First Acute Stroke) substudy, hypertension, AF, and smoking were more strongly associated with severe stroke presentations compared with nonsevere strokes.²² Accordingly, although patients

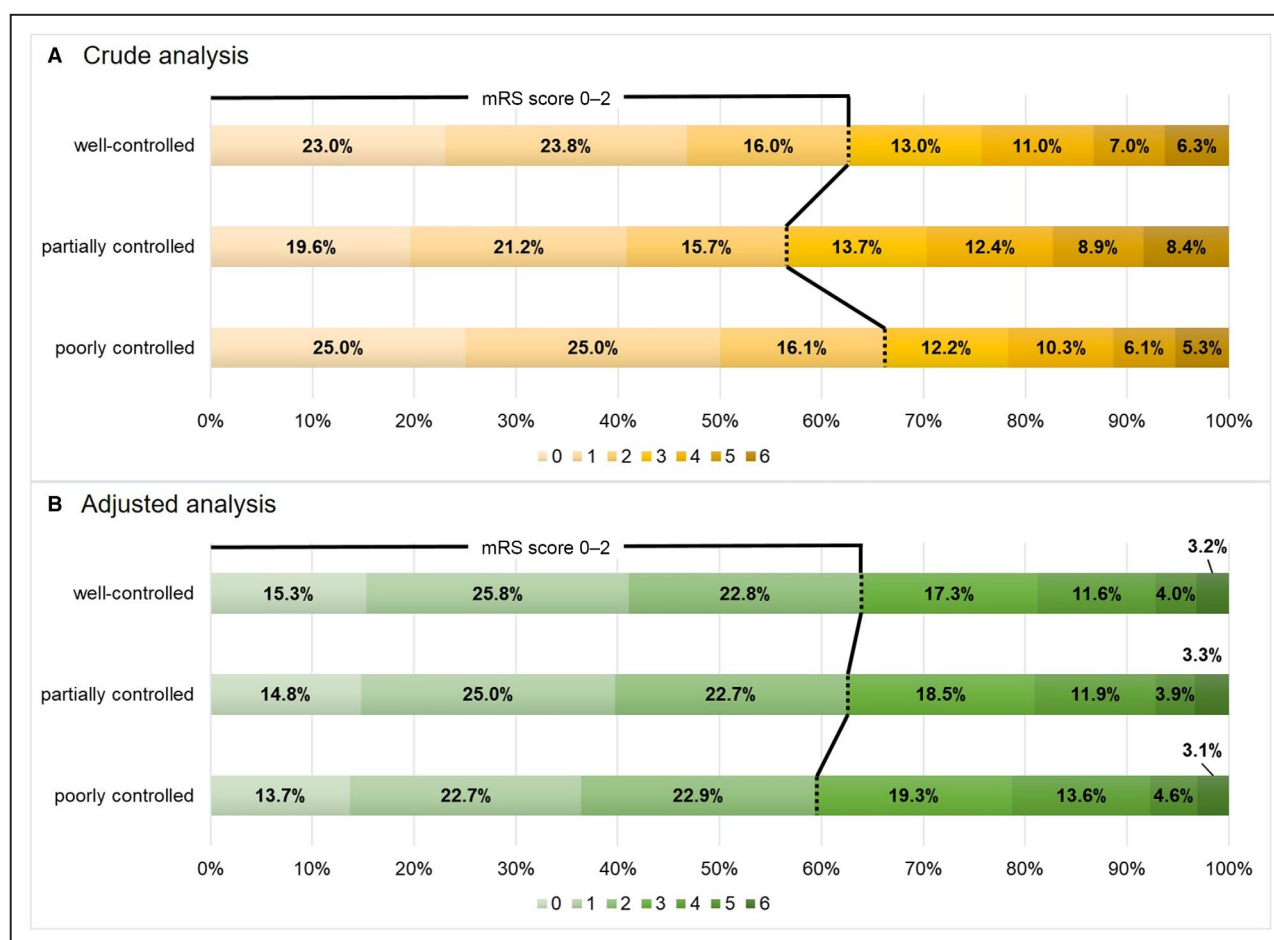


Figure 3. The unadjusted (A) and adjusted (B) distributions of mRS scores at 3 months according to the control status of all present risk factors.

mRS indicates modified Rankin Scale.

with no or lower risk burden showed more favorable 3-month outcomes and lower mortality in crude analysis, adjusted analyses revealed that those with higher risk burdens had more favorable functional outcomes. This pattern differs from findings of the Riksstroke registry, in which patients without standard modifiable stroke RFs had lower mortality than those with ≥ 1 standard modifiable stroke RFs.²¹ However, our analysis primarily focused more on the impact of prestroke RF control among patients with ≥ 1 RFs rather than on the presence or absence of RFs alone. Further studies are needed to clarify the independent and interactive effects of RF burden and control on poststroke outcomes.

Several limitations of this study should be acknowledged. First, as the analysis was restricted to patients who experienced an index ischemic stroke, the findings are subject to index event bias,²³ and caution is warranted when interpreting associations between prestroke RF profiles and poststroke outcomes. Second, the selection and operational definition of RF and their control status were study specific. Control status as primarily defined based on medication use and admission

biomarker levels, which may not fully reflect true physiologic control or medication adherence. For hypertension and AF, control status was defined by medication use alone, given the lack of reliable prestroke blood pressure data and the absence of established biomarkers for anticoagulation adequacy with non-vitamin K antagonist oral anticoagulants. These definitions may have led to misclassification of RF control status. Third, although smoking is commonly included in standard modifiable RF frameworks,^{24,25} we prioritized AF because of its strong and direct association with ischemic stroke outcomes and its treatment-modifiable nature.²¹ This choice should be considered when comparing our findings with studies using alternative RF definitions. Fourth, information on prior medication use, including dosage, duration, and adherence, was limited. In addition, the equal weighting of individual RFs in our composite control classification may not fully capture their differential impact on functional outcomes. Fifth, given the large sample size, even small differences without clear clinical significance could yield statistically significant results (P value < 0.05), necessitating careful interpretation.

Finally, although this is a multicenter prospective registry study, its conduct in South Korea limits generalizability. Findings may vary across different populations, and the retrospective nature of the analysis makes it difficult to fully control for unmeasured confounders and selection bias. In addition, information on health care use and socioeconomic status was not available in the registry, which may have influenced both prestroke RF management and poststroke outcomes. Despite these limitations, the study benefits from a robust analysis using a large prospective stroke registry, which enhances its value.

CONCLUSIONS

In conclusion, our study found that comprehensive prestroke RF controls, defined by treatment- and biomarker-based management criteria, was associated with more favorable 3-month functional outcomes after ischemic stroke, irrespective of RF burden. These findings suggest that effective prestroke management of existing RFs can improve outcomes regardless of how many are present, underscoring the importance of not only identifying but also effectively managing them to enhance poststroke functional independence. Risk prevention strategies should emphasize not only identifying high-risk individuals but also achieving optimal control of existing RFs. Future studies would be warranted to investigate the optimal strategies for integrated RF control and to evaluate their impact on long-term outcomes in diverse patient populations.

ARTICLE INFORMATION

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Disclosure

None.

Supplemental Material

Tables S1–S5

Figures S1–S4

Supplemental Method

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