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ORIGINAL RESEARCH

Persistent Beta-Blocker Therapy Reduces Long-Term Mortality in Patients With Acute Ischemic Stroke With Elevated Heart Rates

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BACKGROUND: Elevated heart rate in patients with acute ischemic stroke is associated with increased risk of mortality. Beta-blocker therapy is well known to reduce heart rate.

METHODS AND RESULTS: This study was a post hoc analysis of patients with acute ischemic stroke with maximum heart rates ≥100 bpm. Beta-blocker use, assessed on the eighth day after the index stroke, was categorized as persistent or nonpersistent based on usage up to 39 months. The primary outcome was a composite of stroke recurrence, myocardial infarction, and mortality within the first year. Long-term mortality, a secondary outcome, was tracked for up to 10 years. Among 5049 patients (women, 38%; mean age, 68.5 years), 32.1% were prescribed beta blockers by the eighth day after stroke, and 99% had prior beta-blocker use. One-year cumulative incidences of the primary outcome, stroke recurrence, and death were 27.8%, 3.5%, and 25.8%, respectively. Persistent beta-blocker use was associated with a significant reduction in the primary outcome (adjusted hazard ratio [HR], 0.81 [95% CI, 0.68–0.97]) and mortality (adjusted HR, 0.80 [95% CI, 0.69–0.94]) from 2 months to 1 year. Extended analysis of mortality for up to 10 years showed long-term benefits of beta-blocker use. Analyses subdividing patients into persistent users, discontinuers, and never-users suggested higher early mortality risk among discontinuers and potential late survival benefits for persistent users. Subgroup analyses demonstrated greater benefits in patients <75 years, and those with atrial fibrillation, coronary heart disease, and higher mean heart rates.

CONCLUSIONS: Our study shows that continuation of beta-blocker therapy in patients with acute ischemic stroke with tachycardia significantly reduces long-term mortality.

Key Words: beta blocker ■ heart rate ■ ischemic stroke

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CLINICAL PERSPECTIVE

What Is New?

- Our study evaluated the impact of persistent beta-blocker use on long-term outcomes in patients with acute ischemic stroke with elevated heart rates.
- Persistent beta-blocker therapy was associated with significant reductions in long-term mortality, particularly in high-risk subgroups such as younger patients and those with atrial fibrillation, coronary heart disease, or higher mean heart rates.
- Nonpersistent beta-blocker use, especially discontinuation, was associated with higher early mortality risks compared with never-users.

What Are the Clinical Implications?

- Persistent beta-blocker therapy should be considered as a long-term strategy to reduce mortality in patients with acute ischemic stroke with elevated heart rates.
- These findings highlight the potential value of continuation of beta-blocker therapy and may guide treatment decisions in high-risk populations with acute ischemic stroke.
- Future randomized trials are needed to explore the potential benefits of initiating beta-blocker therapy de novo in patients with stroke with tachycardia.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
IPTW	inverse probability of treatment weighting
K-NHIS	Korea National Health Insurance Service

Heart rate is increasingly recognized as a prognostic indicator for outcomes following a stroke, as elevated levels are associated with an increased risk of major vascular events. Early evidence from a post hoc analysis of the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial underscored a correlation between higher heart rates and increased mortality after stroke.[1] However, the applicability of the findings was limited by the inclusion of patients outside the acute phase of ischemic stroke and the exclusion of those with cardioembolic strokes.

Subsequent research has broadened the scope of investigation to include patients with atrial fibrillation (AF)-related strokes[2] and a more diverse patient population with acute ischemic stroke (AIS).[2,3] Notably, the latter study showed that patients with AIS with heart rates exceeding 100 bpm between the fourth and seventh days post- stroke had a 1.8-fold greater risk of major clinical events, including recurrent stroke, myocardial infarction, and death, and more than double the risk of mortality within 1 year.[3]

Despite these associations, the benefits of pharmacologically reducing heart rate in this context remain underexplored. Some observational studies suggest that beta blockers may offer a mortality benefit in patients who have had a stroke.[4,5] However, these studies may be limited by small sample sizes, single-center settings, or a lack of focus on long-term effects. Moreover, the most recent meta-analysis of patients with stroke or transient ischemic attack treated with beta blockers versus placebo did not find significant differences in outcomes that included recurrent stroke and all-cause mortality.[6]

Current guidelines no longer recommend beta blockers as a first-choice medication for treatment of hypertension treatment[7,8] but do endorse their use after myocardial infarction.[9–11] Given these uncertainties and the limited role of beta blockers in managing hypertension, our study investigates the effectiveness of beta-blocker therapy in reducing major vascular events and death among patients with AIS presenting with elevated heart rates during the acute phase—a group known to be at higher risk of mortality.

METHODS

Data Availability and Ethics Statement

The data will not be available to other researchers for the purpose of reproducing the results because of local legal regulations of the Korea National Health Insurance Service (K-NHIS) regarding access to patient-level data. Informed consent was obtained from all participants for data collection and subsequent linkage to administrative databases, including the K-NHIS claims database. Furthermore, this study received approval from the institutional review board of each participating center. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Study Design and Rationale for Participant Selection

This post hoc analysis used a prospectively collected cohort from the CRCS-K-NIH (Clinical Research Collaboration for Stroke in Korea-National Institute of Health) registry. This nationwide, multicenter stroke registry includes patients with AIS from 14 hospitals enrolled between January 2011 and October 2018.

Detailed methodologies of the registry have been previously described.[12–14] Patients who consented to allow data linkage had their records linked to the K-NHIS database, covering approximately 97% of the population,[15] permitting comprehensive claims data analysis.

Drawing upon findings from prior investigations,[2,3] we selected a subset of patients exhibiting a maximum heart rate of 100 bpm or higher during the period from the fourth to the seventh day after stroke (Figure S1). This participant group was identified as being at elevated risk for the composite outcome of stroke recurrence, myocardial infarction, and all-cause mortality, positioning them as potential candidates who might benefit from beta-blocker therapy.

Data Collection and Outcome Definitions

Data including demographics, initial stroke severity (National Institutes of Health Stroke Scale), vascular risk factors, and stroke characteristics (stroke subtype classified by the TOAST [Trial of Org 10 172 in Acute Stroke Treatment] criteria modified using a magnetic resonance imaging-based algorithm)[16,17] were directly obtained from the registry database. Information about heart rate was collected during routine in-hospital clinical encounters and was extracted retrospectively from the electronic medical record systems of participating centers. Information on beta-blocker use and clinical indications such as ischemic heart disease, AF, or atrial flutter, and heart failure in the year before the index stroke was sourced from the K-NHIS database.[18]

The primary outcome was defined as a composite of stroke recurrence, myocardial infarction, and all-cause mortality, representing the first occurrence of any of these events within the first year following the index stroke. Secondary outcomes included individual occurrence of recurrent stroke, myocardial infarction, and mortality within 1 year after the index stroke. These data were prospectively collected via structured telephone interviews or during routine follow-up visits at outpatient clinics, occurring at 3 months and 1 year after stroke.[12–14]

Regarding mortality, the follow-up was extended to 10 years, using mortality data from the K-NHIS database. The follow-up extended to December 2022, providing a median follow-up duration of 4.2 years, with an interquartile range from 0.9 to 6.2 years. This long-term mortality served as the key secondary outcome measure.

Definition of Beta-Blocker Use

Beta-blocker usage, as defined using the K-NHIS database, commenced from the eighth day after the index stroke. Compliance was tracked monthly during the first year and quarterly up to 39 months. Observations beyond 39 months were excluded due to a low number of cases. Patients prescribed beta blockers on the eighth day post stroke and who consistently received them at each respective time point were categorized as "persistent users."[19] Those who never initiated or discontinued therapy before these time points were labeled as "nonpersistent users."

For the analysis of primary and secondary outcomes within 1 year, persistent use was defined monthly up to 6 months after the index stroke. For analyses of long-term mortality, persistent beta-blocker use was defined monthly throughout the first year and then quarterly.

Statistical Analysis

We noted significant variability in beta-blocker use during the first year following the index stroke. Specifically, 28% of patients discontinued beta blockers within 30 days, and only 31% continued beyond 10 months (Figure S2). To address this variability and its potential impact on outcomes, we carried out a landmark analysis, a method that allows for dynamic categorization of study participants based on their ongoing treatment status at specified time points. This approach facilitated a more precise evaluation of the effects of persistent beta-blocker use on outcomes.[19,20]

Initially, we compared primary and secondary outcomes within the first year between patients prescribed beta blockers within 8 days of their index stroke and those who were not, using the log-rank test. To identify differences in baseline characteristics between the 2 groups, we employed various statistical tests; the chi-square test for categorical variables, Student's *t* test for continuous variables, and Mann–Whitney *U* test for ordinal variables. We then applied propensity score analysis with inverse probability of treatment weighting (IPTW) to balance baseline characteristics between the groups, followed by outcome comparisons using the log-rank test. Hazard ratios (HRs) and 95% CIs were estimated for these comparisons.

Patients categorized as persistent users, who received beta blockers consistently from the eighth day and were defined monthly up to 6 months, were compared with nonpersistent users. We analyzed the cumulative incidences of primary and secondary outcomes using the log-rank test and estimated HRs and CIs using multivariable marginal Cox models, accounting for the effect of the admitting hospital. The Cox proportional hazards assumption was evaluated using tests based on weighted Schoenfeld residuals.

For long-term mortality, the key secondary outcome, we compared persistent users at multiple time points (eighth day, 2 months, 6 months, 1 year, 2 years, 3 years) against nonpersistent users, estimating HRs and CIs of persistent use, determined monthly during the first year and then quarterly up to 39 months.

To estimate the effects of discontinuation and persistent use versus never-use, we subdivided nonpersistent users into "discontinuers" and "never-users" and compared the cumulative incidence of long-term mortality across 3 groups: discontinuers, persistent users, and never-users. HRs and 95% CIs for discontinuation

Table 1. Baseline Characteristics of the Patients (n=5049)

Variable	Beta-blocker user n=1623	Beta-blocker nonuser n=3426	*P* value
Age, y, mean±SD	73.0±11.0	70.7±13.0	<0.01
Male sex, N (%)	768 (47.3)	1860 (54.3)	<0.01
Onset to arrival time (min), median (IQR)	222 (76–1111)	400 (113–1752)	<0.01
Premorbid mRS score			0.04
0	1190 (73.3)	2404 (70.2)	
1	127 (7.8)	254 (7.4)	
2	87 (5.4)	217 (6.3)	
3	121 (7.5)	262 (7.6)	
4	59 (3.6)	172 (5.0)	
5	39 (2.4)	117 (3.4)	
Premorbid mRS score, median (IQR)	0 (0–1)	0 (0–1)	0.01
Initial National Institutes of Health Stroke Scale score, median (IQR)	10 (4–16)	7 (3–14)	<0.01
Trial of Org 10 172 in Acute Stroke Treatment classification, N (%)			<0.01
Large artery atherosclerosis	304 (18.7)	1117 (32.6)	
Small vessel occlusion	63 (3.9)	363 (10.6)	
Cardioembolism	902 (55.6)	1029 (30.0)	
Other or undetermined	354 (21.8)	917 (26.8)	
Risk factors			
Hypertension, N (%)	1290 (79.5)	2242 (65.4)	<0.01
Diabetes, N (%)	593 (36.5)	1206 (35.2)	0.35
Hyperlipidemia, N (%)	433 (26.7)	878 (25.6)	0.43
Previous stroke or transient ischemic attack, N (%)	360 (22.2)	720 (21.0)	0.35
Coronary artery disease, N (%)	807 (49.7)	963 (28.1)	<0.01
Arrhythmia, N (%)	1112 (68.5)	1309 (38.2)	<0.01
Atrial fibrillation or atrial flutter, N (%)	1059 (65.2)	1227 (35.8)	<0.01
Other arrhythmia, N (%)	53 (3.3)	82 (2.4)	0.07
Heart failure, N (%)	660 (40.7)	606 (17.7)	<0.01
Current smoking, N (%)	201 (12.4)	677 (19.8)	<0.01
Reperfusion therapy			
Intravenous thrombolysis, N (%)	339 (20.9)	614 (17.9)	0.01
Endovascular thrombectomy, N (%)	347 (21.4)	451 (13.2)	<0.01
Prior use of beta blockers, N (%)	1601 (98.6)	1357 (39.6)	<0.01
Concurrent use of antiarrhythmic agents, N (%)	278 (17.1)	267 (7.8)	<0.01
Discharge antiplatelet, N (%)			<0.01
No	803 (49.5)	1120 (32.7)	
Single antiplatelet	463 (28.5)	1155 (33.7)	
Combined antiplatelet	357 (22.0)	1151 (33.6)	
Discharge anticoagulation, N (%)			<0.01
No	894 (55.1)	2596 (75.8)	
Non-vitamin K antagonist oral anticoagulants	374 (23.0)	357 (10.4)	
Other anticoagulants	355 (21.9)	473 (13.8)	
Discharge statin, N (%)	1270 (78.3)	2770 (80.9)	0.03
Symptomatic steno-occlusion, N (%)	1052 (64.8)	2039 (59.5)	<0.01
Mean systolic blood pressure during d 4–7 after stroke onset, mm Hg (SD)	135.4±16.0	136.3±15.9	0.06

IQR indicates interquartile range; and mRS, modified Rankin Scale.;

and persistent use relative to never-use were then calculated. Subgroup analyses were conducted to verify the consistency of beta-blocker effects on long-term mortality across different factors, such as age, sex, history of AF, heart failure, and coronary heart disease, and the class of beta blocker (beta-1 selective versus non-beta-1 selective; third generation versus first and second generation).

For sensitivity analysis, we redefined persistent use at several key time points and estimated corresponding mortality outcomes for each interval: from the eighth day to 2 months, from 2 months to 1 year, from 1 year to 2 years, and from 2 years or more. Survival curves for persistent and nonpersistent users within each interval were compared using the log-rank test. Adjusted HRs with 95% CIs for persistent use at the start of each interval were estimated using both the traditional multivariable marginal Cox model and the propensity score analysis with IPTW. E-values were also calculated to assess the presence of unmeasured confounding.[21] In addition, patients were subdivided based on the median of the mean heart rate (87 bpm) recorded between the fourth and seventh days after stroke to examine whether the effect of persistent beta-blocker use was strengthened in patients with persistent or more severe tachycardia.

Covariates in our multivariable marginal Cox models were predetermined based on our knowledge about outcome determinants, including demographic, clinical, and treatment variables relevant to stroke outcomes.[3] These included age, sex, symptom onset to arrival time, premorbid modified Rankin scale, initial National Institutes of Health Stroke Scale score, stroke subtype, vascular risk factors (hypertension, diabetes, hyperlipidemia, prior history of stroke or transient ischemic attack, coronary heart disease, arrhythmia, heart failure, current smoking), acute reperfusion treatment (intravenous thrombolysis or endovascular treatment), concurrent use of antiarrhythmic agents, use of antiplatelet agents, anticoagulants or statin drugs during the acute period, steno-occlusion of the intra- or extracranial artery relevant to the acute ischemic lesions, and mean systolic blood pressure levels between the fourth and seventh day after symptom onset.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A 2-sided P value of <0.05 was used to determine statistical significance.

RESULTS

Baseline Characteristics and Outcomes

We analyzed 5049 patients with AIS identified with a maximum heart rate of 100 bpm or higher between the fourth and seventh day post stroke (Figure S1). Patients prescribed beta blockers by the eighth day post stroke were typically older and had more severe neurological deficits and a higher prevalence of cardiac comorbidities including coronary artery disease, arrhythmia, and heart failure compared with those who did not receive beta blockers (Table 1). Notably, 99% of those on beta blockers between the fourth day and seventh day post stroke were already receiving these medications before the index stroke.

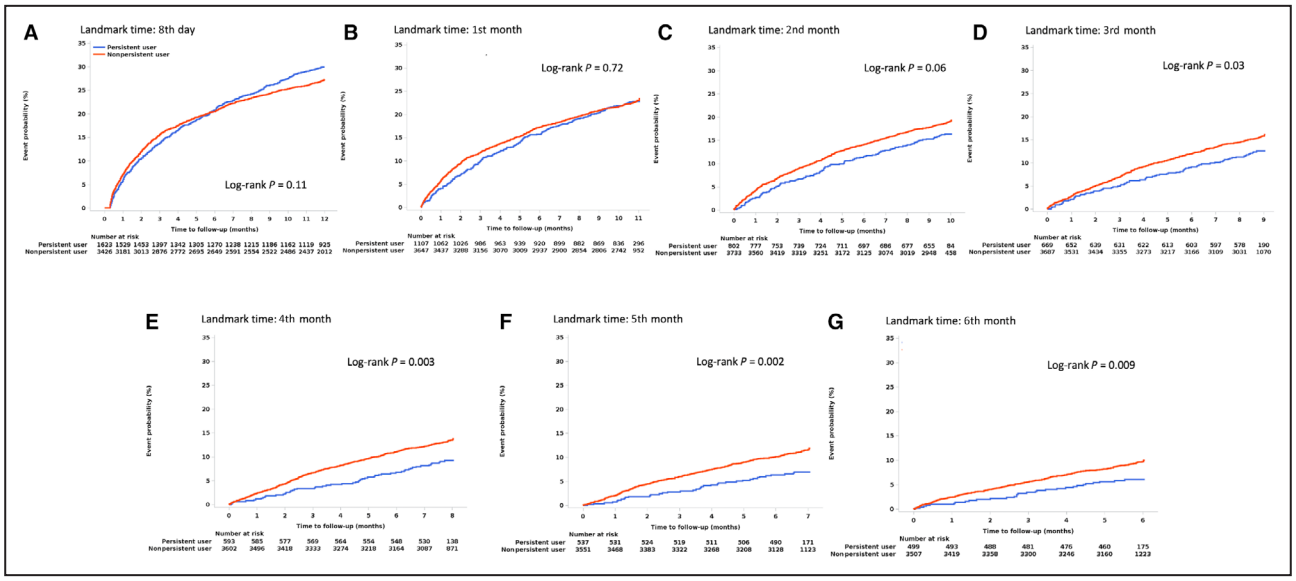

Figure 1. Cumulative incidence of the primary outcome (composite of stroke recurrence, myocardial infarction, and all-cause mortality) up to 1 year after symptom onset by landmark time points for persistent use of beta-blockers.
A, Eighth day, **B**, First month, **C**, Second month, **D**, Third month, **E**, Fourth month, **F**, Fifth month, **G**, Sixth month.

A comparison with a cohort of 17 519, who were registered in the CRCS-K-NIH registry but excluded from the analysis for not meeting the heart rate criterion, showed that individuals who were excluded were younger, were less severely affected by stroke, and had fewer cardiac comorbidities (Table S1).

During the first year after the index stroke, 179 recurrent strokes, 19 myocardial infarctions, and 1304 deaths were recorded. The 1-year cumulative incidence of the primary outcome was 27.8%. The rate of recurrent stroke and all-cause mortality was 3.5%, and 25.8%, respectively. No significant differences were observed in these outcomes between the beta-blocker and non-beta-blocker groups (Figure S3). However, propensity score analysis with IPTW showed a transient early benefit in reduction of the primary outcome and all-cause mortality within 1 year among beta-blocker users, although this benefit dissipated over time (Figure S4).

Landmark Analysis for the Persistent Use of Beta-Blockers

Landmark analysis revealed that persistent beta-blocker use, starting from 3 months post stroke, was associated with significantly lower incidence of the primary outcome and all-cause mortality but not with stroke recurrence within 1 year after stroke (Figure 1, Figures S5 and S6). Adjusted HRs for persistent use assessed at 2 months were 0.81 (95% CI, 0.68–0.97) for the primary outcome and 0.80 (95% CI, 0.69–0.94) for all-cause mortality (Figure 2).Extended follow-up

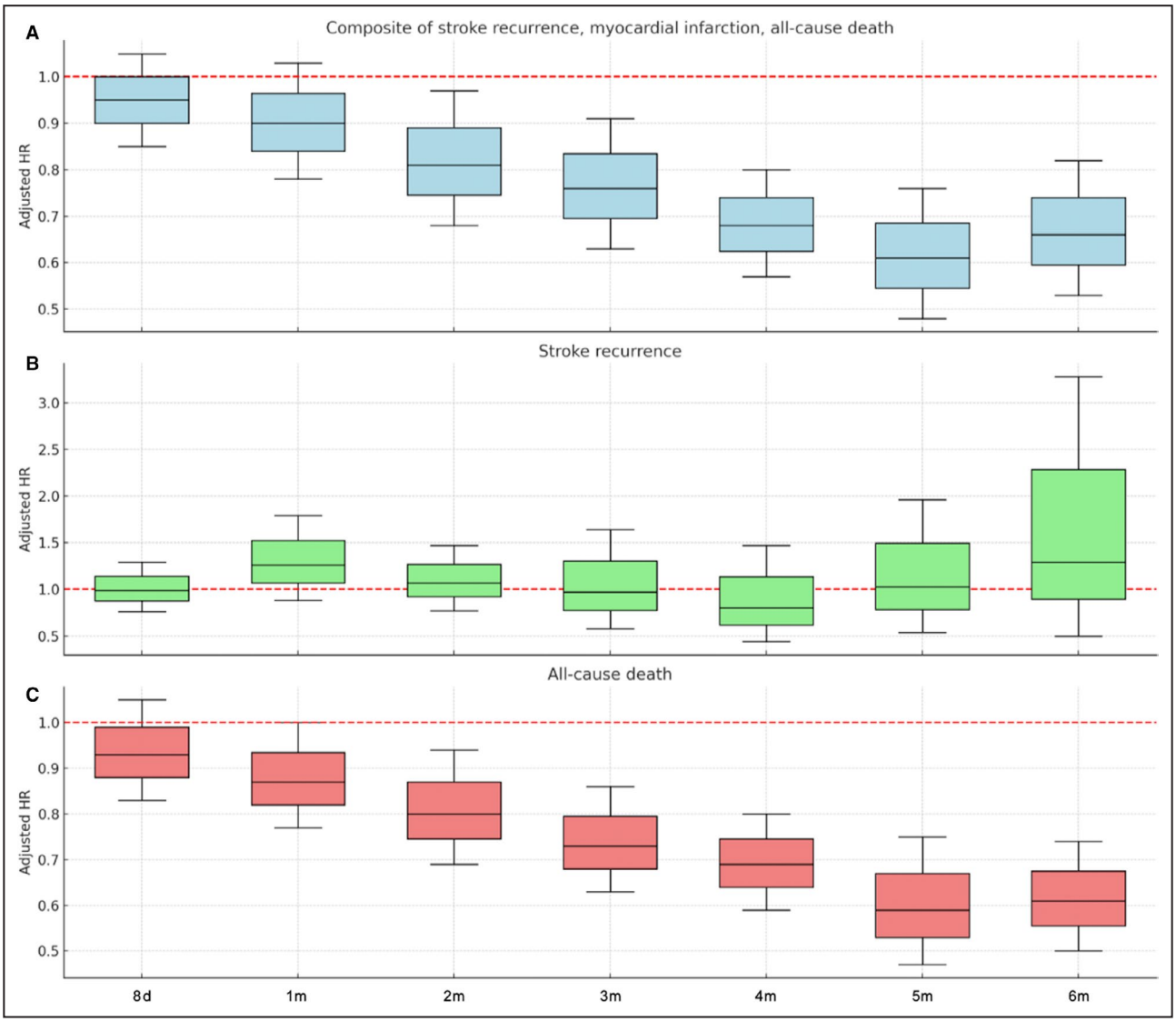

Figure 2. Hazard ratios and 95% CIs for persistent use of beta blockers defined monthly up to 6 months post stroke.
A, A composite of stroke recurrence, myocardial infarction, all-cause mortality. **B**, Stroke recurrence. **C**, All-cause mortality within 1 year after stroke onset. *Hazard ratios and 95% CIs were estimated by the multivariable marginal Cox model to address for center effect along with predetermined covariates. HR indicates hazard ratio.

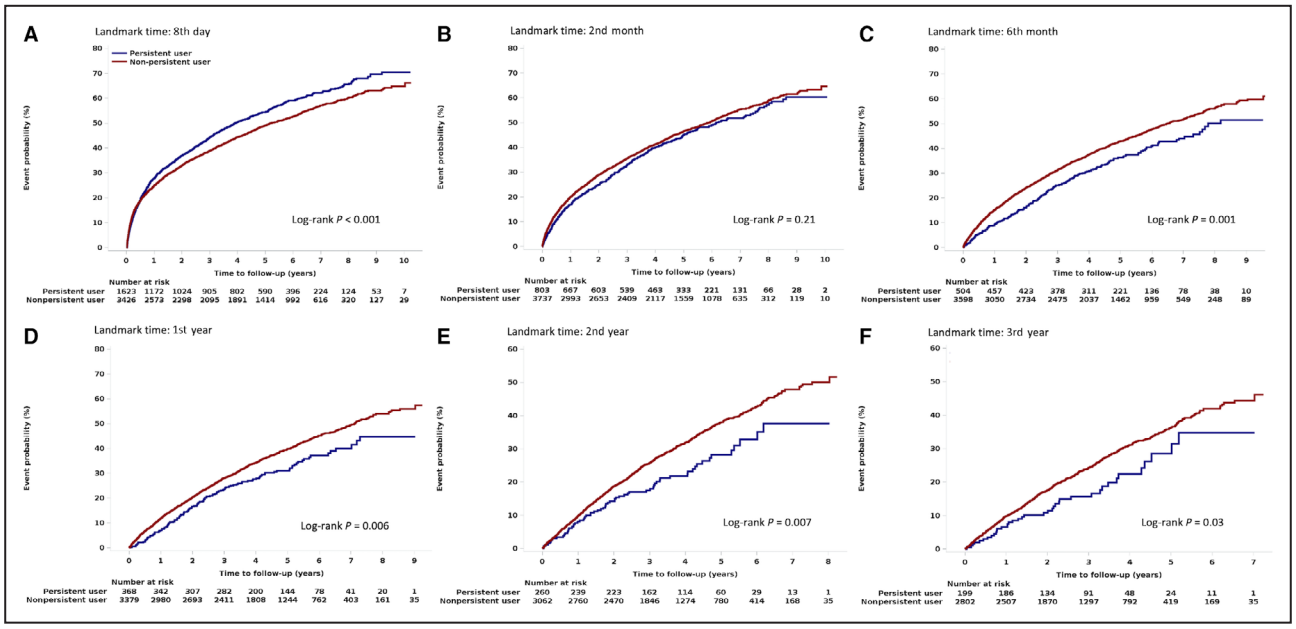

Figure 3. Cumulative incidences of long-term mortality up to 10 years post stroke according to persistent use vs nonpersistent use defined at each time point.
A, Eighth day, **B**, Second month, **C**, Sixth month, **D**, First year, **E**, Second year, **F**, Third year.

to 10 years showed a 10-year cumulative incidence of mortality at 66.6% (95% CI, 64.4%–68.7%). Persistent users at 6 months, 1 year, 2 years, and 3 years after stroke had significantly lower mortality rates than nonpersistent users (*P* values <0.05 on the log-rank test, Figure 3). Adjusted HRs for persistent use at 2 and 36 months were 0.88 (95% CI, 0.78–0.99) and 0.69 (95% CI, 0.50–0.96), respectively, with most HRs for persistent users remaining below the null value (Figure 4A).Comparisons of long-term mortality among persistent users, discontinuers, and never-users revealed consistently higher incidence of long-term mortality in discontinuers compared with other groups from 2 months to 3 years (*P* values <0.001 on log-rank tests, Figure 5). The adjusted HR for discontinuers compared with never-users was 1.17 (95% CI, 1.04–1.31) at 1 month with the risk diminishing over time (Figure S7). Additionally, the survival benefit of persistent beta-blocker use over never-use became evident over time and reached statically significance at 30 months after stroke (adjusted HR 0.69 [95% CI, 0.50–0.97]).

Predetermined Subgroup and Sensitivity Analysis

Subgroup analyses suggested that benefits of persistent beta-blocker use were more pronounced in younger individuals (less than 75 years), those with AF, and those with coronary heart disease (Table 2, Figures S8 and S9). However, the reduction in long-term mortality did not significantly differ across beta-blocker class (Figure S10).

Sensitivity analyses confirmed that persistent beta-blocker use consistently reduced mortality across various time intervals (Figure 4B), with robust E-values supporting these findings (Figure 4C). The robustness of these findings is further supported by that the observed survival benefits were more noticeable in patients with a higher mean heart rate (Figure S11). Propensity score analysis with IPTW showed similar point estimates but wider CIs at later time points due to substantial imbalances in group sizes (Figure 4C).

Lastly, a significant difference was observed in the 10-year cumulative incidence of mortality between the study group and those excluded for a maximum heart rate <100 bpm (66.6% versus 39.0%, *P*<0.001 on the log-rank test, Figure S12).

DISCUSSION

Our study highlights the potential of persistent beta-blocker use to reduce long-term mortality in patients with AIS with tachycardia, as indicated by heart rates >100 bpm. In our analysis of >5000 patients from a national, multicenter, prospective registry linked with the national claims database, we observed a consistent 10% to 30% reduction in long-term mortality with persistent beta-blocker use starting from 2 months after stroke. Notably, mortality differences between persistent users and never-users became more pronounced

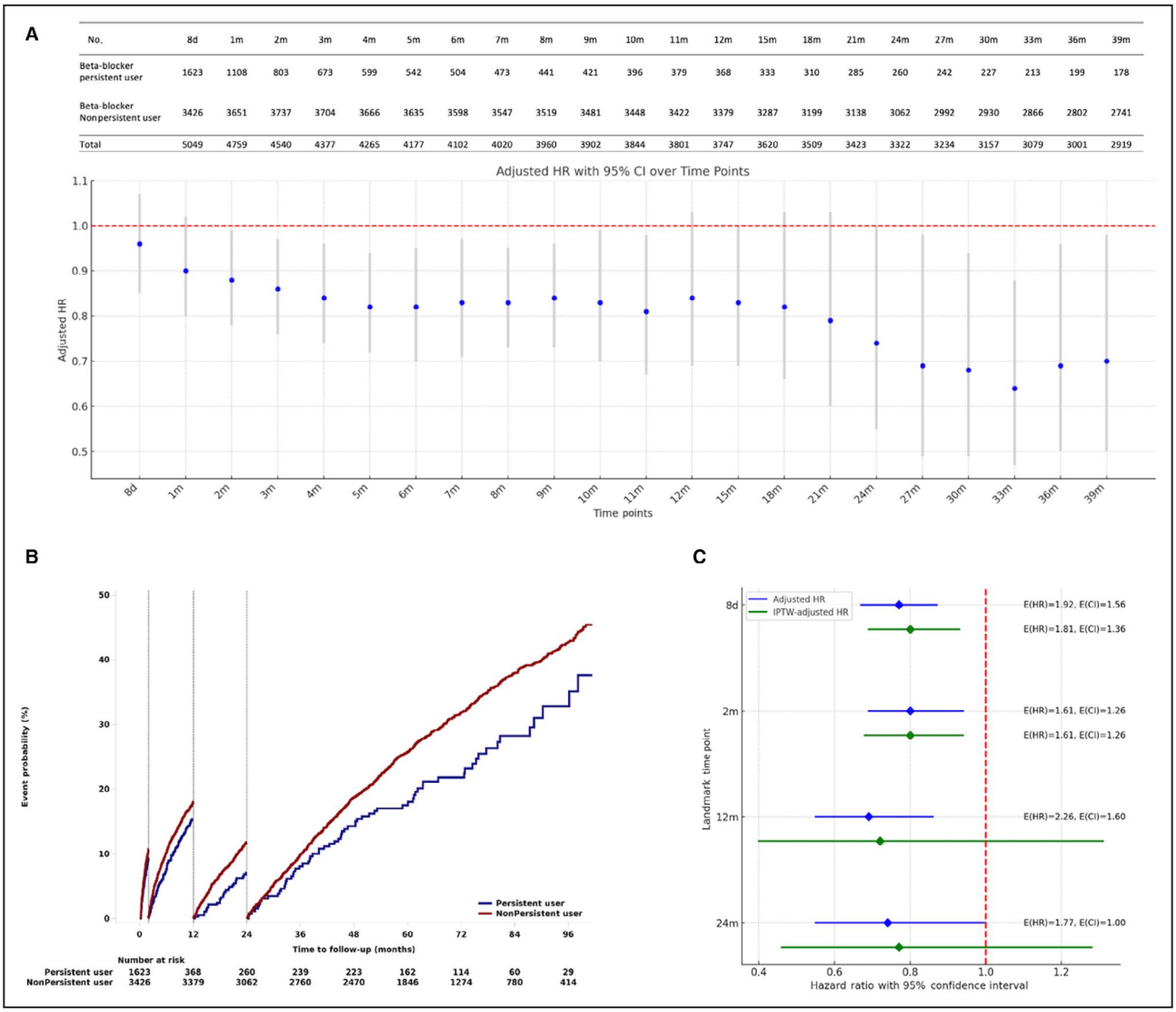

Figure 4. Comparisons of long-term mortality according to persistent use of beta blockers.
A, Hazard ratios and 95% CIs for persistent use defined at each time point up to 39 months after stroke. **B**, Cumulative incidence of events among persistent and nonpersistent beta-blocker users calculated within the intervals defined by landmark time points (eighth day, 2 months, 1 year, and 2 years). **C**, Adjusted hazard ratios and 95% CIs from pre-IPTW and IPTW-applied analyses, with corresponding E-values for hazard ratios nearest to the null. HR indicates hazard ratio; and IPTW, inverse probability of treatment weighting.

over time, whereas the differences between discontinuers and never-users diminished.

Despite current guidelines supporting beta-blocker use in patients with coronary heart disease,[11,22,23] their efficacy in patients with stroke remains inconclusive.[5,6,24] Our findings contribute to the controversy over beta-blocker use after stroke by showing a benefit in high-risk patients with AIS selected based on a simple, clinically applicable criterion of heart rate measurement between the fourth and seventh day after stroke. Moreover, 99% of patients prescribed beta blockers by the eighth day were already using these medications before their stroke. Thus, most patients in our study received beta blockers as continuation therapy rather than as initial therapy. Importantly, there was a higher observed mortality risk in patients who discontinued beta blockers, potentially due to adverse outcomes such as the resurgence of coronary heart disease or sudden death associated with the upregulation of beta-adrenergic receptors.[25,26]

Our study uniquely focuses on patients with AIS with high heart rates, a high-risk population that is more likely to benefit from beta-blocker therapy, contrary to some previous studies that reported no significant benefits.[6,24] Among the 24 424 patients with AIS with available data in our study, over one fifth experienced tachycardia, and their 10-year mortality rates were significantly higher—67% compared with 39% for

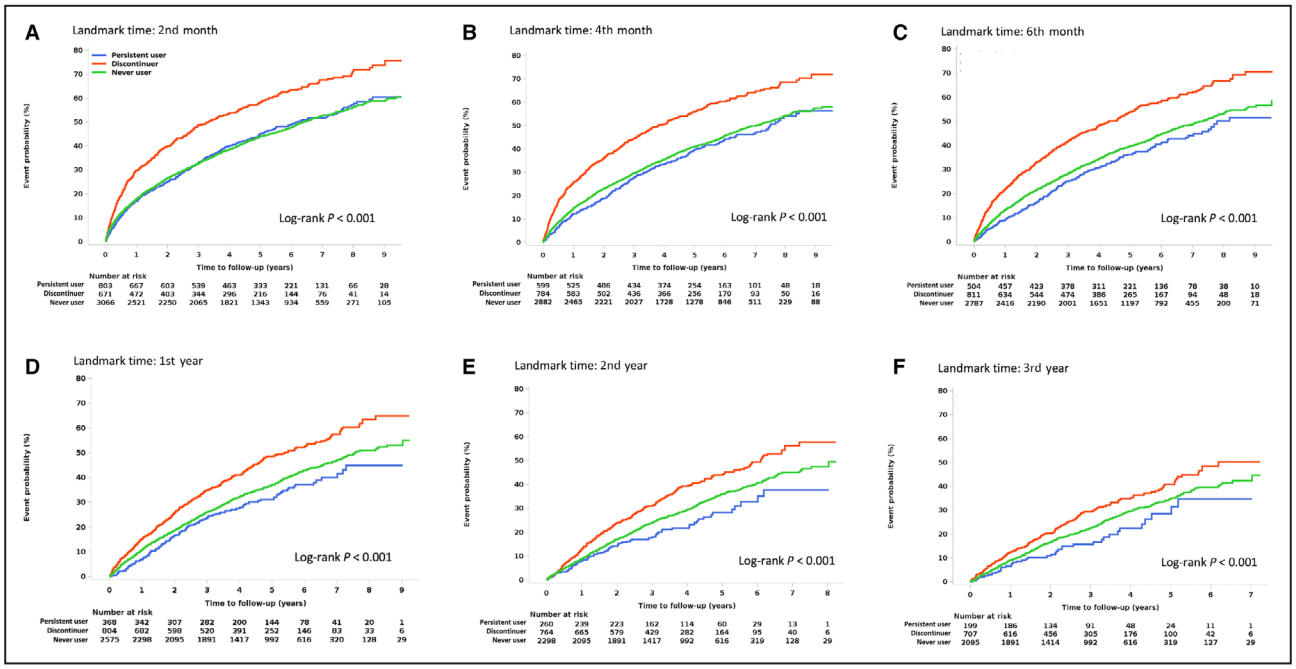

Figure 5. Cumulative incidences of long-term mortality up to 10years post stroke according to persistent users vs discontinuers vs never-users defined at each time point.
A, Second month, **B**, Fourth month, **C**, Sixth month, **D**, First year, **E**, Second year, **F**, Third year.

those with lower heart rates. This aligns with findings from the PRoFESS trial, which reported an HR of 1.74 for all-cause mortality in the highest quintile of heart rate relative to the lowest.[1] Furthermore, our selection criterion, employing a maximum heart rate between the fourth and seventh day after stroke, was based on

Table 2. Hazard Ratios and 95% CIs of Long-Term Mortality for Persistent Use of Beta Blockers Compared With Nonpersistent Use According to Age, Presence of Coronary Heart Disease, or Atrial Fibrillation at Each Landmark Time Point

Landmark time point	Adjusted HR (95% CI)		*P* for interaction	Adjusted HR (95% CI)		*P* for interaction	Adjusted HR (95% CI)		*P* for interaction
	Age<75 y	Age≥75 y		Without coronary heart disease	With coronary heart disease		Without atrial fibrillation or atrial flutter	With atrial fibrillation or atrial flutter	
Eighth day	0.86 (0.66–1.11)	1.02 (0.92–1.12)	0.21	0.98 (0.86–1.12)	0.93 (0.78–1.10)	0.54	1.04 (0.86–1.24)	0.91 (0.77–1.07)	0.32
First month	0.78 (0.65–0.95)	0.98 (0.86–1.12)	0.04	0.97 (0.81–1.15)	0.85 (0.74–0.98)	0.22	0.97 (0.76–1.25)	0.87 (0.76–0.99)	0.45
Second month	0.77 (0.60–0.98)	0.96 (0.85–1.09)	0.11	0.90 (0.78–1.03)	0.87 (0.75–1.01)	0.76	1.06 (0.83–1.36)	0.80 (0.69–0.94)	0.09
Third month	0.75 (0.59–0.95)	0.95 (0.84–1.08)	0.08	0.95 (0.82–1.10)	0.80 (0.70–0.92)	0.02	1.02 (0.80–1.31)	0.79 (0.67–0.93)	0.13
Fourth month	0.71 (0.56–0.90)	0.96 (0.81–1.14)	0.06	0.96 (0.82–1.12)	0.76 (0.67–0.87)	0.002	1.01 (0.76–1.34)	0.78 (0.67–0.90)	0.14
Fifth month	0.71 (0.54–0.94)	0.92 (0.76–1.11)	0.20	0.97 (0.81–1.17)	0.72 (0.62–0.83)	0.001	1.03 (0.76–1.38)	0.74 (0.65–0.84)	0.05
Sixth month	0.70 (0.54–0.91)	0.92 (0.74–1.15)	0.16	0.92 (0.76–1.11)	0.74 (0.61–0.91)	0.07	1.00 (0.70–1.43)	0.74 (0.65–0.84)	0.12
12th month	0.68 (0.49–0.94)	1.00 (0.77–1.29)	0.07	0.89 (0.69–1.16)	0.81 (0.62–1.05)	0.53	0.89 (0.56–1.39)	0.82 (0.68–0.99)	0.75
24th month	0.60 (0.43–0.85)	0.91 (0.65–1.26)	0.03	0.71 (0.45–1.11)	0.77 (0.57–1.04)	0.72	0.87 (0.48–1.60)	0.68 (0.48–0.98)	0.52
36th month	0.54 (0.36–0.81)	0.90 (0.60–1.34)	0.05	0.76 (0.52–1.12)	0.64 (0.45–0.91)	0.34	0.84 (0.50–1.43)	0.63 (0.40–0.99)	0.44

HR indicates hazard ratio. HRs and 95% CIs were derived by multivariable marginal Cox model in order to consider the effect of the hospitalized center.

earlier research[3] and suggests that a single heart rate measurement >100 bpm can effectively predict mortality risk and serve as a viable criterion for selecting participants in future observational and trial studies.

Although our study suggests a potential delayed survival benefit for persistent beta-blocker users compared with never-users, our power to detect these differences was limited by the decreasing number of persistent users over time. The adjusted HRs for persistent users versus never-users were statistically insignificant before 30 months but began showing potential benefits thereafter. Recently, questions have emerged regarding the long-term mortality benefit of beta-blocker therapy after acute myocardial infarction.[27] These findings combined with our results, highlight the need for future research to explore the initiation of beta blockers in high-risk patients with AIS to evaluate long-term mortality benefits.

In subgroup analyses, we observed no heterogeneity in the effects of beta blockers across different cardiac indications or beta-blocker classes. However, we identified some heterogeneity favoring younger patients and those with coronary heart disease or AF. A meta-analysis of 21 clinical trials reported differential benefits of beta blockers in reducing cardiovascular risk by age, notably favoring patients <60 years.[28] This could be attributed to decreased beta-adrenergic responsiveness in the older people.[29] Future research should clarify the differential impacts, particularly concerning age-specific responses to beta-blocker therapy.

Our study leverages a high-quality registry database linked with national claims data, allowing for extensive data collection and a long follow-up period. This comprehensive data set enhances the reliability of our findings, which show a consistent reduction in mortality among beta-blocker users, evident in both unadjusted and adjusted analyses. Such depth and breadth of data collection strengthen the robustness of our results and provide a solid foundation for our conclusions.

However, there are several limitations to our study. Beta-blocker users in our cohort had more cardiovascular comorbidities, predisposing them to a higher mortality risk. Despite the higher baseline risk, our analysis shows a consistent reduction of mortality, supporting the robustness of our findings. Furthermore, although we used propensity scores, IPTW, and E-values to adjust for potential confounders and enhance the credibility of our analysis, the potential for residual confounding remains. In addition, the exclusion of patients who did not consent to data linkage could introduce selection bias (Table S2). However, the high consent rate (93.5%) likely mitigates this concern. Also, most data were sourced from academic hospitals, which might limit the generalizability of our findings. Nevertheless, the alignment with national stroke audit data suggests that our results may have broader applicability.[30] Finally, we lacked direct measures of drug adherence, relying instead on registry data and national claims databases to estimate beta-blocker use. Although these sources are robust, they may not capture every nuance of patient adherence or compliance.

CONCLUSIONS

Our study confirms that in patients with AIS who exhibit a maximum heart rate of ≥100 bpm, continuing previously prescribed beta-blocker therapy is associated with a significant reduction in long-term mortality. Additionally, our results reveal a potential delayed survival benefit for those who persistently use beta blockers compared with those who do not use them at all. Thus, initiating beta-blocker therapy de novo in similar patients with AIS might also be advantageous and merits further study. Given the substantial gaps in our current understanding of beta-blocker therapy for tachycardia after AIS, there is a need for a clinical trial to strengthen the evidence base, refine therapeutic strategies, and ultimately clarify the long-term outcomes for high-risk patients.

ARTICLE INFORMATION

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Disclosures

Dr Gorelick reports serving on major adverse cardiac events adjudication committees for industry (AstraZeneca, UCB, IQVIA), data monitoring committees for AMGEN and Sanofi, and as a consultant to NeuroX (telemedicine)

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Supplemental Material

Tables S1–S2
Figures S1–S12

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