Effect of Heart Rate Variabilities on Outcome After Acute Intracerebral Hemorrhage: A Post Hoc Analysis of ATACH-2

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BACKGROUND: To explore how the clinical impact of heart rate (HR) and heart rate variabilities (HRV) during the initial 24 hours after acute intracerebral hemorrhage (ICH) contribute to worse clinical outcomes.

METHODS AND RESULTS: In the ATACH-2 (Antihypertensive Treatment in Intracerebral Hemorrhage 2) trial, the HR was recorded for every 15 minutes from baseline to 1 hour and hourly during the initial 24 hours post-randomization. We calculated the following: mean, standard deviation, coefficient of variation, successive variation, and average real variability (ARV). Outcomes were hematoma expansion at 24 hours and unfavorable functional outcome, defined as modified Rankin Scale score 4 to 6 at 90 days. Of the 1000 subjects in ATACH-2, 994 with available HR data were included in the analyses. Overall, 262 experienced hematoma expansion, and 362 had unfavorable outcomes. Increased mean HR was linearly associated with unfavorable outcome (per 10 bpm increase adjusted odds ratio [aOR], 1.31, 95% CI, 1.14–1.50) but not with hematoma expansion, while HR-ARV was associated with hematoma expansion (aOR, 1.06, 95% CI, 1.01–1.12) and unfavorable outcome (aOR, 1.07, 95% CI, 1.01–1.3). Every 10-bpm increase in mean HR increased the probability of unfavorable outcome by 4.3%, while every 1 increase in HR-ARV increased the probability of hematoma expansion by 1.1% and unfavorable outcome by 1.3%.

CONCLUSIONS: Increased mean HR and HR-ARV within the initial 24 hours were independently associated with unfavorable outcome in acute ICH. Moreover, HR-ARV was associated with hematoma expansion at 24 hours. This may have future therapeutic implications to accommodate HR and HRV in acute ICH.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT01176565.

Key Words: heart rate ■ heart rate variabilities ■ intracerebral hemorrhage ■ randomized controlled trial ■ stroke
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What Is New?
- Higher heart rate (HR) and impaired HR variabilities in the setting of acute stroke reflect not only various stress conditions but also post-stroke cardiosympathetic-vagal dysregulations; however, its prognostic values for patients with acute intracerebral hemorrhage remain unclear.
- HR average real variability within 24 hours after intracerebral hemorrhage had a consistent association with hematoma expansion at 24 hours and functional 3-month outcomes.
- In addition, increased mean HR was linearly associated with subsequent functional disability.

What Are the Clinical Implications?
- HR average real variability could represent more physiologically relevant HR variation attributable to concomitant autonomic dysfunction.
- It would be important to ensure that HR control is smooth and sustained in the hyperacute phase of intracerebral hemorrhage.
- Future studies are expected to investigate the clinical implications and optimal HR management strategies in the acute period of intracerebral hemorrhage.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| ARV          | average real variability |
| ICH          | intracerebral hemorrhage |
| mRS          | modified Rankin Scale |
| NIHSS        | National Institute of Health Stroke Scale |

CLINICAL PERSPECTIVE

Acute stroke remains unclear. Possibly, the effect of brain-heart interaction, such as cardiosympathetic-vagal dysregulation, which reflects the post-stroke dysregulation of the autonomic nervous system with excess sympathetic activity, would affect the cardiac ability to accommodate instantaneously according to circulatory changes. Consequently, the discordant HR fluctuation is manifested as impaired HR variabilities (HRV). Impaired HRV has been shown to be an independent predictor of mortality not only in the general population but also in patients with cardiac diseases. To date, however, studies investigating the association between clinical outcomes after stroke and whole spectrum of HR measures are scarce, leaving limited elucidation of the impact of HRV, particularly in patients on acute treatment for ICH. The overarching hypothesis was that impaired HRV in acute ICH would have a clinical impact on hematoma expansion at 24 hours and functional outcome at 3 months. We therefore performed an exploratory analysis of the ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage) trial data focusing on patients with acute ICH.

METHODS

Study Design and Inclusion Criteria
The whole data set of ATACH-2 is currently open to the public and is available upon request to the National Institute of Neurological Disorders and Stroke. We conducted a post hoc analysis of the ATACH-2 trial, an international, randomized, open-label trial to determine the efficacy of rapidly lowering systolic blood pressure in patients with acute supratentorial ICH within 4.5 hours of onset of <60 mL who also had elevated systolic BP (>180 mm Hg), the details of which have been described elsewhere. Participants were randomized to intensive treatment (target systolic BP, 110–139 mm Hg within 2 hours) or standard treatment (target systolic BP, 140–179 mm Hg within 2 hours) using intravenous nicardipine.

Standard Protocol Approvals, Registrations, and Patient Consents
The ATACH-2 study is registered with ClinicalTrials.gov (NCT01176565) and the University Hospital Medical Information Network clinical trial registry in Japan (UMIN 000006526), approved by ethical committees/competent authorities in all participating sites. Informed consent was obtained from each subject, her/his legally authorized representative, or a relative.

Heart Rate Monitoring and Heart Rate Parameters
The ATACH-2 trial recorded the maximum and minimum HR for every 15 minutes for the first hour after randomization and every hour thereafter between 1 and 24 hours in the acute period (27 measurements altogether). We focused on the maximum HR because prior studies showed that higher HR has clinical impact on functional outcomes and mortality. We calculated 5 HR measures: mean, SD, coefficient of variation (defined as SD/mean×100%), successive variation, and average real variability (ARV) during the initial 24-hour post-randomization. Successive variation is the average squared difference between the consecutive order of individual measurements \( \left( \frac{1}{n-1} \sum_{i=1}^{n-1} |x_{i+1} - x_i|^2 \right) \).
ARV is calculated as the average absolute difference between the consecutive order of individual HR measurements \( \left( \frac{1}{n-1} \sum_{i=1}^{n-1} |x_{i+1} - x_i| \right) \).

**Clinical Outcomes**

Following the criteria used in ATACH-2, the predefined outcome was unfavorable functional outcome, defined as a modified Rankin Scale (mRS) score of 4 to 6, at 90 days after randomization. Moreover, hematoma expansion, which is a neuroimaging marker of primary brain injury and a factor associated with unfavorable outcome, was defined as >33% or >6 mL increase in volume on the computed tomographic scan obtained at 24 hours compared with the baseline scan, or surgical evacuation of hematoma within 24 hour regardless of post-surgery hematoma volume.

**Statistical Analysis**

The demographic and baseline characteristics of the study subjects were summarized as mean±SD for continuous variables, number of patients (%) for categorical variables, and median with interquartile range for ordinal variables, as appropriate. We tested for differences with Student t test for continuous variables, chi-square test for binary variables, and the Wilcoxon Rank-sum test for ordinal variables. There were no significant differences in hematoma expansion and unfavorable outcome between randomized treatment groups, thus we combined both groups into a single cohort to assess the association between HR parameters and clinical outcomes for the present analyses. We used single imputation for missing HR measurements using regression analyses. We modelled each HR measure as continuous variables and also categorized those into quartile groups. The multivariable analysis was adjusted for the established predictors of outcome: age, sex, prior antihypertensive medication, initial National Institutes of Health Stroke Scale (NIHSS), hematoma location (lobar versus non-lobar) at baseline, hematoma volume at baseline, and systolic blood pressure at presentation in the emergency department. Our model was also adjusted for the treatment allocation and mean maximum dose of nicardipine. Multivariable analysis was performed separately for each HR measure. Models are evaluated using the Akaike Information Criterion (AIC), where smaller values indicate better model fit. Testing for interaction was used to determine heterogeneity in the associations of HR measures with outcomes between the treatment groups. We further tested margin plot analyses along with a quadratic term, only if the significant associations appeared in the logistic regression model. We also performed restricted cubic spline analyses with 3-knots to flexibly display the relationship between HR measures and clinical outcomes.

All P values were two sided, and a P value of <0.05 was considered statistically significant. Analysis was performed using STATA (version 16, StataCorp LP, College Station, TX).

**RESULTS**

The baseline characteristics of the study group were previously described. Among 1000 patients enrolled in ATACH-2, baseline HR data were available for 998 participants. For the entire cohort, patients who died within the initial 24 hours (n=4) were excluded, leaving 994 patients for further investigation (Table 1). Of these, there were missing data for 43 patients with hematoma expansion and 38 with unfavorable outcomes at 90 days, respectively. Altogether, 262 (27%) patients experienced hematoma expansion and 362 (37%) had unfavorable outcomes at 90 days (mRS 4–6), including death (mRS 6) in 63 (6.6%).

| Table 1. Baseline Characteristics |
|-------------------------------|
| Variable                      | All (n=994) |
| Age, y                        | 62 [52–71] |
| Male                          | 615 (62)   |
| Asian                         | 534 (54)   |
| Hypertension                  | 788 (79)   |
| Premorbid antihypertensive medication, (n=987) | 490 (50) |
| SBP at initial presentation, mm Hg | 200±27    |
| DBP at initial presentation, mm Hg | 111±20   |
| Prior stroke                  | 164 (16)   |
| Atrial fibrillation, (n=984)  | 35 (3.5)   |
| Ischemic heart disease        | 43 (4.3)   |
| Dyslipidemia                  | 240 (24)   |
| Baseline NIHSS score          | 11 [6–16]  |
| Baseline Glasgow coma score   | 15 [12–15] |
| Lobar ICH                     | 116 (11)   |
| Left-sided ICH                | 519 (52)   |
| ICH volume, mL                | 10.2 [5.1–18.4] |
| Intensive SBP control randomization arm | 495 (50) |
| Mean maximum nicardipine infusion rate, mg/h | 3.7 [1.7–6.9] |
| Hydrocephalus, (n=985)        | 132 (13)   |
| Evacuation surgery            | 44 (4.4)   |
| Mean HR, median [IQR], range, bpm | 86 [77–96], (53–134) |
| HR-SD, bpm                    | 8.9 [6.8–11.4] |
| HR-CV, %                      | 10.3 [7.9–13.3] |
| HR-SV, bpm                    | 8.5 [6.2–11.3] |
| HR-ARV, bpm                   | 6.2 [4.6–8.2] |

Values are presented as frequencies (percentages), means±SD, or median [interquartile ranges], as appropriate. ARV indicates average real variability; CV, coefficient of variation; DBP, diastolic blood pressure; HR, heart rate; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; and SV, successive variation.
The study population included 26838 HR measurements (ie, 994x27) of 994 subjects at 24 hours intervals. Of these, we imputed 570 HR measurements (2%). The median values of mean HR within 24 hours after ICH were 86 (IQR: 77–96, range: 53–134) bpm. The median values of mean HR for the first 24 hours after randomization according to the treatment group are shown in Figure S1. The median value of HR-ARV was 6.2 (IQR: 4.6–8.2) bpm. There was no significant difference in the value between mean HR, HR-ARV and treatment allocations (Table S1).

Heart Rate Variabilities and Hematoma Expansion

Among the HR measures, only HR-ARV was modestly associated with hematoma expansion in multivariable analysis (odds ratio [OR] 1.06; 95% CI 1.01–1.12, \(P=0.029\)) (Table 2). The adjusted model minimized the AIC (unadjusted model: 951, adjusted model: 935, \(\Delta\text{AIC}=−26\)). HR-ARV had a significant association with hematoma expansion (the highest quartile of HR-ARV, adjusted OR 1.64; 95% CI 1.07–2.51; \(P\) trend =0.016; Figure 1A). The adjusted restricted cubic spline model shows that higher HR-ARV was associated with a linear rise in the risk of hematoma expansion (Figure 2A). The probability of hematoma expansion increased from 24% at 4 of HR-ARV to 33% at 12 of HR-ARV, resulting in a 1.1% increased probability of hematoma expansion per 1 increase in HR-ARV (Figure 2B). There was no significant interaction between HR-ARV and treatment allocation (\(P=0.591\)).

Heart Rate and Unfavorable Functional Outcome

Increasing mean HR (per 10 bpm) was significantly associated with unfavorable functional outcome in the fully adjusted model (OR 1.31; 95% CI 1.14–1.50, \(P<0.001\)) (Table 3). The adjusted model minimized the AIC (unadjusted model: 1143, adjusted model: 812, \(\Delta\text{AIC}=−331\)). The quartiles of mean HR were associated with the outcome in a linear fashion (the highest quartile of mean HR; OR 2.81; 95% CI 1.73–4.58, \(P<0.001\)) (Figure 1B). The adjusted restricted cubic spline model shows that higher mean HR associated with a linear rise in the risk of unfavorable outcome (Figure 3A). The probability of unfavorable functional outcome increased from 22% at 60 bpm of mean HR to 48% at 120 bpm of mean HR, resulting in a 4.3% increased probability of worse functional outcome per 10-bpm increase in mean HR (\(P=0.001\)) (Figure 3B). There was no significant interaction between mean HR and treatment allocation (\(P=0.82\)).

Heart Rate Variabilities and Unfavorable Functional Outcome

HR-ARV were independently associated with unfavorable outcome in the fully adjusted model (OR 1.07; 95% CI 1.01–1.13, \(P=0.023\)) (Table 3). The adjusted model minimized the AIC (unadjusted model: 1158, adjusted model: 824, \(\Delta\text{AIC}=−334\)). HR-ARV had a significant association with unfavorable outcome (the highest quartile of HR-ARV; adjusted OR 1.75; 95% CI 1.09–2.83; \(P\) trend =0.016; Figure 1B). The adjusted restricted cubic spline model shows that higher HR-ARV was associated with a linear rise in the risk of unfavorable outcome (Figure 4A). The probability of unfavorable functional outcome increased from 35% at 6 of HR-ARV to 43% at 12 of HR-ARV, resulting in a 1.3% increased probability of worse functional outcome per 1 increase in HR-ARV (Figure 4B). There was a marginal effect modification between HR-ARV and treatment allocation (\(P=0.10\)). In the intensive treatment arm, the probability of worse functional outcome increased from 32% at 6 of HR-ARV to 36% at 12 of HR-ARV, resulting in a 0.6% increased probability of

### Table 2. Logistic Regression Models Showing the Effect of Heart Rate Parameter Predictors on the Odds Ratio of Hematoma Expansion at 24 Hours

|                     | Unadjusted |              |       | Adjusted |              |       |
|---------------------|------------|--------------|-------|----------|--------------|-------|
|                     | OR         | 95% CI       | \(P\) Value | OR      | 95% CI       | \(P\) Value |
| Mean HR, per 10 bpm | 1.01       | 0.99–1.16    | 0.275 | 1.05     | 0.93–1.18    | 0.434 |
| HR-SD               | 1.02       | 0.98–1.05    | 0.337 | 1.01     | 0.97–1.05    | 0.484 |
| HR-CV               | 1.00       | 0.97–1.04    | 0.535 | 1.00     | 0.97–1.04    | 0.656 |
| HR-SV               | 1.04       | 1.00–1.07    | 0.042*| 1.03     | 0.99–1.07    | 0.126 |
| HR-ARV              | 1.06       | 1.01–1.12    | 0.012*| 1.06     | 1.01–1.12    | 0.029*|

Adjusted for age, sex, treatment arm, baseline NIHSS, premorbid antihypertensive medication, location of ICH, mean max nicardipine, SBP at presentation in emergency department, ICH volume, and atrial fibrillation. ARV indicates average real variability; bpm, beats per minute; CV, coefficient of variation; HR, heart rate; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; and SV, successive variability.

*\(P<0.05\).
whereas in the standard treatment, the probability of outcome increased from 39.2% at 6 of HR-ARV to 52.6% at 12 of HR-ARV, resulting in a 2.2% increased probability of worse functional outcome per 1 increase in HR-ARV (Figure 4C).

Figure 1. The odds ratio according to quartiles of heart rate (HR) measures. A, for hematoma expansion at 24 hours; (B) for unfavorable functional outcome at 90 days. Lowest quintile is reference. ARV indicates average real variability; CV, coefficient of variation; and SV, successive variation.

Figure 2. Associations between heart rate-average real variability (HR-ARV) and hematoma expansion at 24 hours. A, The adjusted cubic spline model. This curve (black line) displays that higher HR-ARV appears to be associated with a rise in the risk of outcome. The dotted curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1. B, Probability of hematoma expansion with margins plot, including 95% CIs. Every 1 increase in HR-ARV is associated with an absolute increase in the probability of hematoma expansion by 1.1%.
For the separate components of the functional outcome, HR and HR fluctuations were not associated with death at 90 days (mRS 6) in the fully adjusted model (data not shown).

**DISCUSSION**

In the post hoc analysis of the ATACH-2 trial, a major finding is that increased mean HR and HR-ARV within 24 hours after ICH are associated with subsequent functional disability. HR-ARV had a consistent association with hematoma expansion at 24 hours and functional 3-month outcomes. We found evidence for effect modification according to the treatment group, such that the association of HR-ARV with worse functional outcome remained significant. In contrast, mean HR within 24 hours after ICH was associated with functional outcomes but not hematoma expansion.

Numerous studies in the general population and those in patients with coronary heart disease have demonstrated associations between increased HR levels and cardiovascular events and mortality.\(^{13–15}\)

Regarding the absolute HR levels as the prognostic possibilities after stroke, higher HR (≥85 bpm) at baseline was linked to mortality and unfavorable functional outcome both in 5606 patients with acute ischemic stroke in the VISTA study and in 3185 patients with acute ICH in the INTERACT 1 and 2.\(^{4,11}\)

Because various kinds of antihypertensive medications were used in acute ICH in the latter,\(^{11}\) the

### Table 3. Logistic Regression Models Showing the Effect of Heart Rate Parameter Predictors on the Odds Ratio of Unfavorable Functional Outcome (mRS4–6 at 90 Days)

|                  | Unadjusted |            | Adjusted |            |
|------------------|------------|------------|----------|------------|
|                  | OR 95% CI  | P Value    | OR 95% CI| P Value    |
| Mean HR, per 10 bpm | 1.24 1.12–1.37 <0.001* | 1.31 1.14–1.50 <0.001* |
| HR-SD            | 1.01 0.98–1.05 0.428 | 1.01 0.97–1.06 0.515 |
| HR-CV            | 0.98 0.98–1.02 0.318 | 0.98 0.94–1.02 0.211 |
| HR-SV            | 1.05 1.01–1.08 0.03† | 1.04 0.99–1.09 0.063 |
| HR-ARV           | 1.07 1.03–1.13 0.001† | 1.07 1.01–1.13 0.023† |

Adjusted for age, sex, treatment arm, baseline NIHSS, premorbid antihypertensive medication, location of ICH, mean max nicardipine, SBP at presentation in emergency department, ICH volume, and atrial fibrillation. ARV indicates average real variability; bpm, beats per minute; CV, coefficient of variation; HR, heart rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; and SV, successive variability.

*\(P<0.01.\)
†\(P<0.05.\)

**Figure 3.** Associations between mean-heart rate (HR) and unfavorable functional outcome.

A. The adjusted cubic spline model. This curve (black line) displays that higher mean HR appears to be associated with a rise in risk of outcome. The dotted curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1.

B. Probability of unfavorable functional outcome with margins plot, including 95% CIs. Every 10-bpm increase in the mean HR was associated with an absolute increase in the probability of unfavorable functional outcome by 4.3%.
The present study is partially in line with the results of the ENOS sub-analysis, showing the positive association between higher HR, HRV (represented by SD of HR), and unfavorable outcome in the setting of all types of acute stroke. Our study confirmed and reinforced the prognostic significance of an increased HR and HRV in a large population with acute ICH of the controlled trial.

Underlying stress conditions related to acute stroke typically cause impaired HR control. Acute stroke per se can commonly provoke autonomic imbalance with activation of the sympathetic nervous system and decreased vagal tone. This sympathetic-vagal dysregulation provokes increased HR and blood pressure, and impaired HRV. Other clinical manifestations have been reported, such as cardiac dysfunction, arrhythmias, hyperglycemia, blood pressure variability, and immunodepression, which lead to worse functional outcome and increased mortality. Also, putative mechanisms of sympathetic-vagal dysregulation on the cerebrovascular system have been reported impaired cerebral autoregulation, secondary brain injury due to inflammation, and blood–brain barrier disruption. In particular, lesions involving the insula may disrupt connections to the hypothalamic paraventricular nucleus, although the apparent evidence of relevant localization remains inconclusive.

Furthermore, there is more vigorous use of antihypertensive therapy in the acute period after ICH onset, making the analysis of HR parameters potentially confounded by medication effects. Nicardipine can cause sympathetic activation and reflex sympathetic tachycardia as well-described side effects. However, mean HR and HRV are each associated with clinical outcome independent of intravenous nicardipine. Consequently, HRV represents an inadequate response of the autonomic nervous system insult from acute ICH or other mechanisms and might be used as a potential prognostic indicator in acute ICH.

We showed a linear association between higher mean HR and unfavorable outcomes, which has not been demonstrated previously. Several observational studies in patients with coronary heart disease suggested a J-shaped association, while whether the J-shaped association between HR and mortality is a prevalent phenomenon across different populations is yet to be established. It is possible that patients with presence of coma with lower HR who may represent the Cushing reflex and typically require surgical evacuation were excluded, thus making them underrepresented in the ATACH-2 trial. Prior studies also have demonstrated associations between HR and mortality in the setting of any stroke. Only 6.6% of participants included in our analyses died at 3 months and may have lacked sufficient power to detect an association.

In contrast, HR-ARV remained associated with both the outcomes. HR-ARV consists of absolute difference between consecutive measurements, which could represent more physiologically relevant HR variation related to concomitant autonomic dysfunction. Also, patients with higher HRV under intensive treatment for elevated BP were more likely to have a moderate risk for worse functional outcome, suggesting that the

Figure 4. Associations between heart rate- average real variability (HR-ARV) and unfavorable functional outcome. A. The adjusted cubic spline model. This curve (black line) displays that higher HR-ARV appears to be associated with a rise in the risk of outcome. The dotted curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1. B, Probability of unfavorable functional outcome with margins plot, including 95% CIs. Every 1 increase in HR-ARV was associated with an absolute increase in the probability of unfavorable functional outcome by 1.3%. C, Probability of unfavorable functional outcome, according to the treatment arm. In the intensive treatment arm, there was a 0.6% increased probability of worse functional outcome per 1 increase in HR-ARV. Whereas in the standard treatment, there was a 2.2% increased probability of it.
potential association might be mediated by intensive BP control. No previous study has focused on the acute term influence of HRV for the outcomes in acute ICH setting, thus limiting comparisons. Collectively, we have interpreted the association between HR-ARV levels, hematoma expansion, and subsequent worse functional outcome manifested as representing a more severe ICH which concomitantly causes more severe autonomic dysfunctions.

The present study focused on intermittent, long-term (1-hour frequency) HRV in the acute stages. Most studies assessing HRV examined beat-to-beat HRV obtained by 24-hour electrocardiographic monitoring.22,23 The prognostic implications of HRV depend on the measurement method and sampling frequency. It is still uncertain whether a clinical significance of long-term HRV is equivalent to that of beat-to-beat HRV. However, several population-based studies provided evidence that the predictive power of increased long-term HRV obtained every 30 minutes or 1 hour is an independent predictor of cardiovascular events and mortality.24,25 Therefore, it is possible that intermittent HR monitoring (1-hour frequency) may be effective in predicting prognostic values in clinical settings.

The strength of this study was high frequency sampling of 27 measurements, particularly during the acute phase for the initial 24 hours, which enabled a detailed assessment of intermittent HR fluctuations. This study also has limitations. First, although based on prospectively collected data of a randomized clinical trial, our analysis was post hoc and therefore prone to confounding. Second, selection bias could be considered because of exclusion of patients with huge hematoma from registration, limiting the strength of association and generalizability. Third, reverse causality cannot be excluded in this observational analysis because the more severe ICH subjects with a worse prognosis might give rise to greater HR rather than HR per se causing poor outcome. The independent contribution of HRV even after adjustment for stroke severity argues against, but does not rigorously exclude, reverse causality. Fourth, while we acknowledge the over-inflation of type I error probability from multiple testing, since this work is considered as hypothesis generating.

In conclusion, increased mean HR and HR-ARV within 24 hours after ICH can be an important determinant of outcome. It would be important not only to rapidly reduce high HR but also to ensure that HR control is smooth and sustained in the hyperacute phase of ICH. However, it remains unknown whether modulation of HR could improve prognosis after ICH. Further studies are necessary to confirm our findings and to investigate the clinical implications and optimal HR management strategies in the acute period after ICH.

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Table S1. Baseline HR measures between the treatment allocation.

|                          | the intensive-treatment group | the standard-treatment group | p      |
|--------------------------|-------------------------------|-------------------------------|--------|
| Mean HR, bpm             | 87 [77–96]                    | 85 [76–96]                    | 0.053  |
| HR-SD, bpm               | 8.8 [6.7–11.2]                | 8.9 [6.8–11.7]                | 0.302  |
| HR-CV, %                 | 10.0 [7.8–13.1]               | 10.5 [8.2–13.6]               | 0.032* |
| HR-SV, bpm               | 8.3 [6.2–11.2]                | 8.5 [6.3–11.5]                | 0.365  |
| HR-ARV, bpm              | 6.2 [4.6–8.1]                 | 6.1 [4.7–8.2]                 | 0.445  |

Values are presented as median [interquartile ranges].

HR, heart rate; ARV, average real variability; CV, coefficient of variation; and SV, successive variation.

*p < 0.05.
Figure S1. Within group median mean-HR during the first 24 h after randomization and interquartile range.

The red line (median) and dots (IQR) represent intensive treatment group. The blue line (median) and dots (IQR) represent the standard treatment group.