

SUPPLEMENTAL MATERIAL

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Table S1. Cumulative incidence of outcomes by mean heart rate deciles

	Cumulative incidence (%) (95% CI)			
	Day 23	Day 83	Day 173	Day 358
Composite of stroke recurrence, myocardial infarction and all-cause mortality				
1 st decile	1.77 (0.85 - 2.69)	4.34 (2.91 - 5.77)	6.20 (4.50 - 7.90)	7.82 (5.92 - 9.72)
2 nd decile	2.13 (1.13 - 3.13)	4.28 (2.87 - 5.69)	5.97 (4.32 - 7.63)	8.15 (6.21 - 10.08)
3 rd decile	1.52 (0.66 - 2.37)	3.68 (2.37 - 5.00)	5.39 (3.81 - 6.98)	8.88 (6.84 - 10.91)
4 th decile	2.02 (1.04 - 3.00)	3.92 (2.57 - 5.28)	5.49 (3.89 - 7.09)	6.95 (5.16 - 8.74)
5 th decile	2.04 (1.05 - 3.02)	5.40 (3.81 - 6.98)	6.75 (4.98 - 8.52)	9.83 (7.70 - 11.97)
6 th decile	3.05 (1.85 - 4.25)	7.29 (5.47 - 9.11)	10.18 (8.05 - 12.31)	12.87 (10.50 - 15.24)
7 th decile	2.77 (1.63 - 3.91)	7.36 (5.54 - 9.18)	10.13 (8.01 - 12.25)	14.02 (11.56 - 16.48)
8 th decile	3.67 (2.36 - 4.98)	7.01 (5.22 - 8.80)	10.52 (8.35 - 12.69)	14.91 (12.35 - 17.47)
9 th decile	6.04 (4.39 - 7.70)	13.16 (10.79 - 15.53)	17.65 (14.95 - 20.35)	23.38 (20.35 - 26.41)
10 th decile	12.74 (10.42 - 15.07)	25.09 (22.05 - 28.12)	32.20 (28.91 - 35.50)	38.68 (35.21 - 42.14)
All-cause mortality				
1 st decile	0.88 (0.23 - 1.53)	2.68 (1.55 - 3.81)	4.14 (2.74 - 5.55)	5.09 (3.53 - 6.64)
2 nd decile	1.13 (0.40 - 1.87)	2.02 (1.04 - 2.99)	2.93 (1.75 - 4.11)	4.61 (3.11 - 6.11)
3 rd decile	0.88 (0.23 - 1.54)	2.67 (1.54 - 3.80)	3.72 (2.39 - 5.05)	6.05 (4.35 - 7.75)
4 th decile	0.76 (0.15 - 1.36)	1.64 (0.76 - 2.53)	3.21 (1.97 - 4.45)	4.01 (2.62 - 5.39)
5 th decile	1.02 (0.32 - 1.72)	2.96 (1.77 - 4.15)	3.91 (2.54 - 5.28)	6.30 (4.55 - 8.04)
6 th decile	1.78 (0.86 - 2.71)	4.99 (3.47 - 6.52)	6.96 (5.17 - 8.75)	8.83 (6.83 - 10.84)
7 th decile	1.64 (0.75 - 2.52)	5.08 (3.55 - 6.62)	7.33 (5.50 - 9.16)	10.56 (8.38 - 12.74)
8 th decile	2.66 (1.54 - 3.78)	5.10 (3.56 - 6.64)	7.66 (5.78 - 9.54)	11.64 (9.33 - 13.94)
9 th decile	5.29 (3.73 - 6.85)	11.89 (9.62 - 14.16)	15.56 (13.00 - 18.12)	20.76 (17.85 - 23.66)
10 th decile	11.98 (9.72 - 14.24)	23.44 (20.47 - 26.40)	30.98 (27.71 - 34.25)	36.76 (33.33 - 40.18)

Stroke recurrence				
1 st decile	0.89 (0.23 - 1.55)	1.81 (0.87 - 2.75)	2.22 (1.18 - 3.27)	3.07 (1.83 - 4.30)
2 nd decile	1.00 (0.31 - 1.69)	2.41 (1.34 - 3.48)	3.34 (2.08 - 4.61)	4.32 (2.88 - 5.77)
3 rd decile	0.89 (0.23 - 1.54)	1.41 (0.58 - 2.24)	2.08 (1.07 - 3.09)	3.60 (2.23 - 4.97)
4 th decile	1.39 (0.58 - 2.21)	2.42 (1.34 - 3.49)	2.55 (1.45 - 3.66)	3.38 (2.10 - 4.66)
5 th decile	1.15 (0.40 - 1.89)	2.73 (1.58 - 3.89)	3.44 (2.14 - 4.74)	4.17 (2.73 - 5.61)
6 th decile	1.28 (0.49 - 2.06)	2.74 (1.58 - 3.89)	3.99 (2.59 - 5.39)	4.88 (3.32 - 6.44)
7 th decile	1.14 (0.40 - 1.88)	2.32 (1.26 - 3.38)	3.15 (1.91 - 4.40)	4.02 (2.61 - 5.43)
8 th decile	0.90 (0.23 - 1.56)	1.84 (0.88 - 2.79)	3.14 (1.87 - 4.40)	3.73 (2.35 - 5.12)
9 th decile	1.41 (0.58 - 2.24)	2.52 (1.40 - 3.64)	3.30 (2.00 - 4.60)	5.14 (3.46 - 6.81)
10 th decile	1.23 (0.43 - 2.03)	2.49 (1.32 - 3.66)	3.57 (2.13 - 5.02)	5.26 (3.42 - 7.09)
Composite of stroke recurrence, myocardial infarction and vascular death				
1st decile	1.39 (0.58 - 2.21)	2.56 (1.45 - 3.67)	3.38 (2.10 - 4.65)	4.21 (2.78 - 5.64)
2nd decile	1.26 (0.48 - 2.03)	2.54 (1.44 - 3.63)	3.73 (2.40 - 5.06)	4.71 (3.20 - 6.21)
3rd decile	0.76 (0.15 - 1.37)	1.54 (0.67 - 2.40)	2.21 (1.17 - 3.25)	4.00 (2.56 - 5.44)
4th decile	1.64 (0.76 - 2.53)	2.79 (1.64 - 3.94)	3.32 (2.07 - 4.58)	4.28 (2.85 - 5.72)
5th decile	1.40 (0.58 - 2.22)	3.12 (1.89 - 4.34)	3.82 (2.45 - 5.18)	4.69 (3.17 - 6.21)
6th decile	1.66 (0.77 - 2.56)	3.11 (1.89 - 4.34)	4.50 (3.02 - 5.98)	5.53 (3.88 - 7.18)
7th decile	1.26 (0.48 - 2.04)	3.09 (1.87 - 4.31)	3.93 (2.55 - 5.31)	5.36 (3.74 - 6.97)
8th decile	1.90 (0.95 - 2.85)	3.09 (1.87 - 4.31)	4.66 (3.15 - 6.17)	5.40 (3.77 - 7.03)
9th decile	3.53 (2.25 - 4.82)	5.43 (3.83 - 7.03)	6.50 (4.73 - 8.26)	8.76 (6.67 - 10.84)
10th decile	5.19 (3.62 - 6.76)	7.97 (6.01 - 9.93)	9.34 (7.19 - 11.48)	10.92 (8.55 - 13.30)

Table S2. Piecewise hazard ratios for the primary outcome before and after 30 days since outcome ascertainment

Heart rate parameter	Time from outcome ascertainment			
	0 to 30 days		31 to 358 days	
	Adjusted HR* (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Mean heart rate (per 10 bpm increase)	1.31 (1.23-1.40)	<.0001	1.24 (1.18-1.31)	<.0001
Time-weighted average heart rate (per 10 bpm increase)	1.33 (1.24-1.42)	<.0001	1.26 (1.19-1.33)	<.0001
Maximum heart rate (per 10 bpm increase)	1.17 (1.13-1.21)	<.0001	1.12 (1.09-1.15)	<.0001
Minimum heart rate (per 10 bpm increase)	1.16 (1.07-1.27)	0.0004	1.13 (1.06-1.21)	0.0002

* Derived from multivariable time dependent Cox model. HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure. Predetermined covariates included age, sex, time from symptom onset to hospital arrival, initial stroke severity, history of hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, previous history of stroke or transient ischemia attack, premorbid modified Rankin's scale, current smoking, whether the patient received recanalization therapy (intravenous thrombolysis or endovascular treatment), antithrombotic (antiplatelet agents and/or anticoagulants) and statin administration at discharge, symptomatic steno-occlusion of the intra- or extracranial major cerebral arteries, initial SBP, mean value of SBP between the 4th and 7th days after symptom onset, initial glucose level, and ischemic stroke subtype.

Figure S1. Patient selection

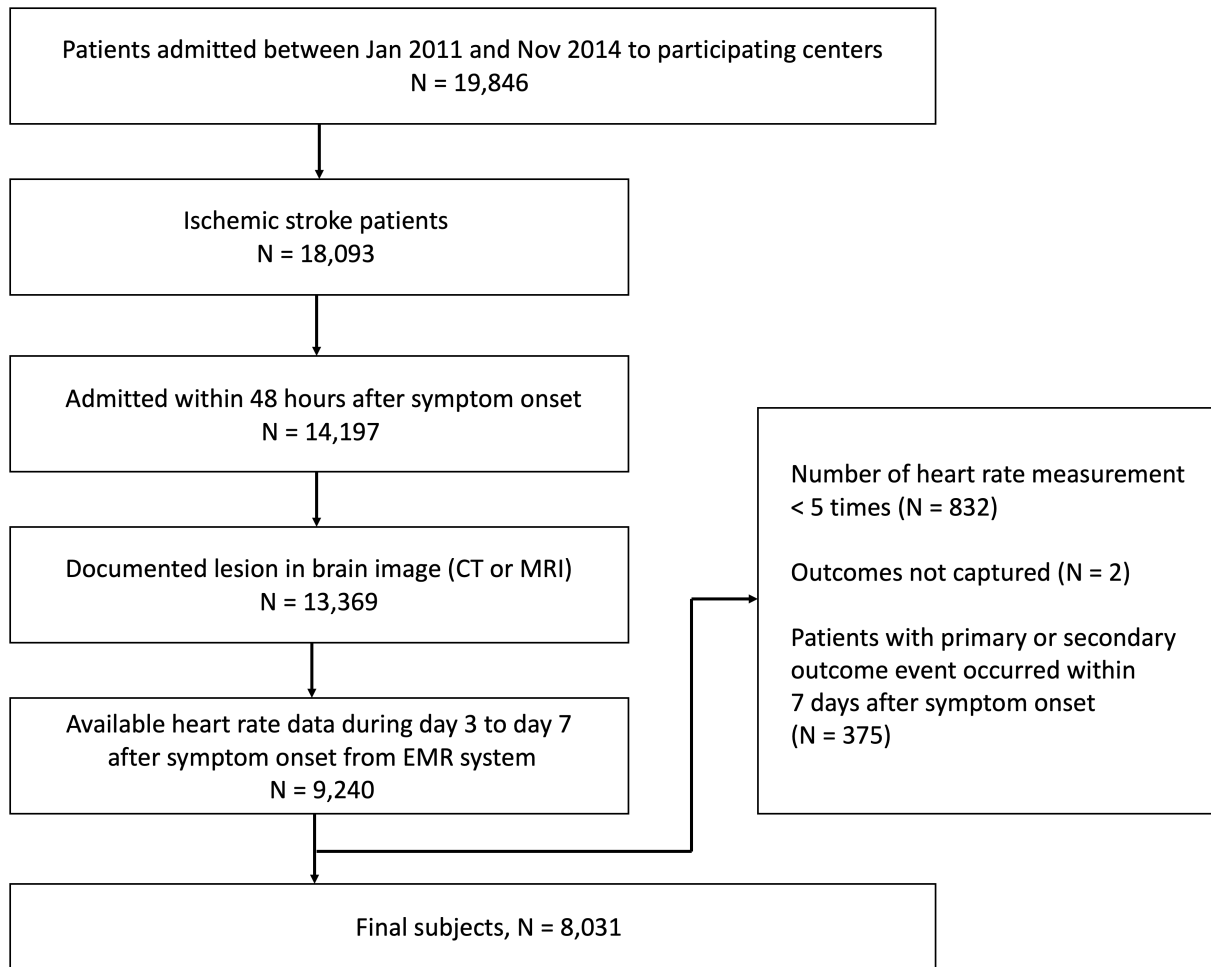


Figure S2. Histogram of heart rate parameters

(A) Mean heart rate (B) time weighted average heart rate (C) Maximum heart rate (D) Minimum heart rate

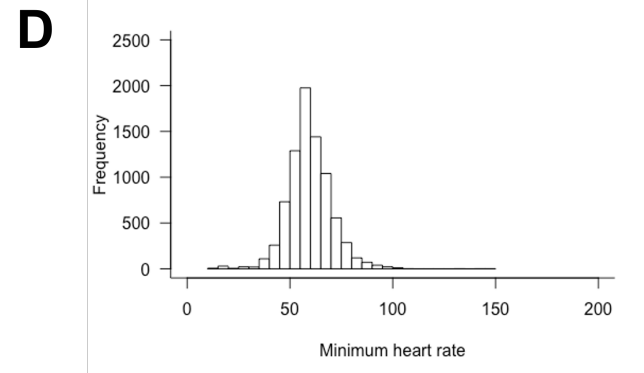
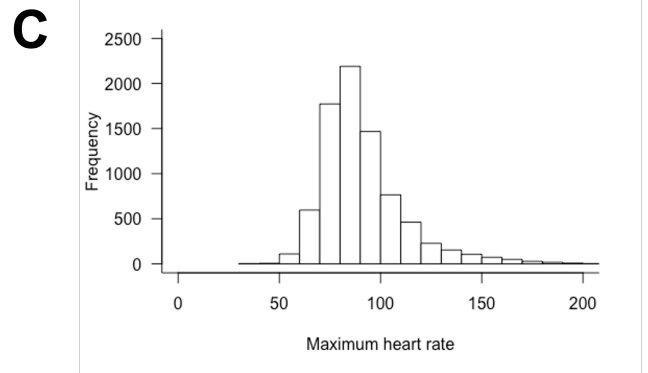
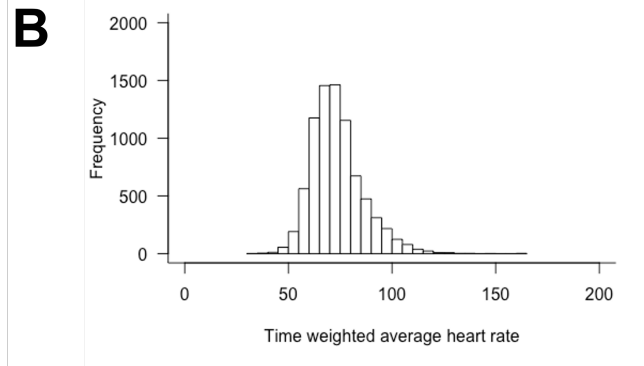
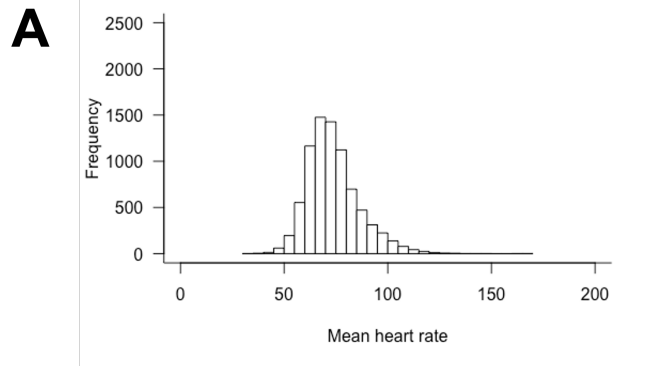


Figure S3. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) according to mean systolic blood pressure level during day 4 to day 7 after stroke onset

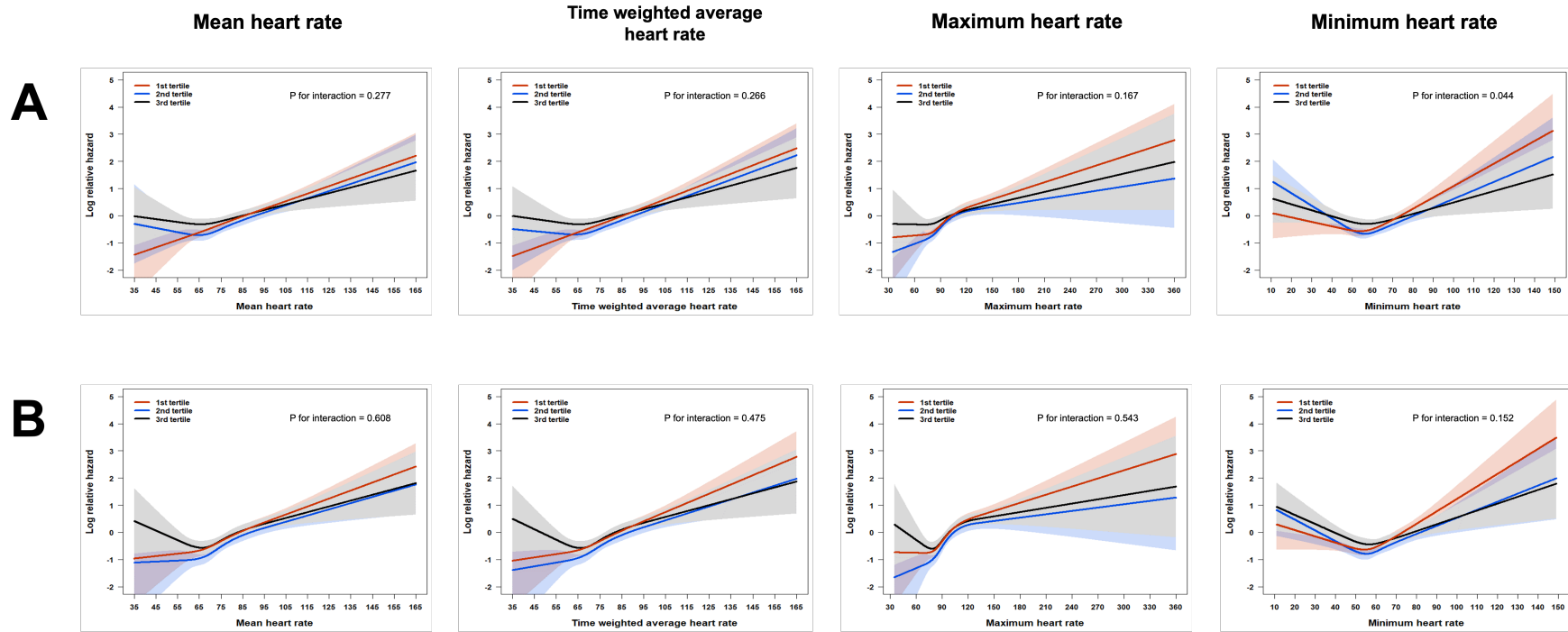


Figure S4. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in patients with and without hypertension

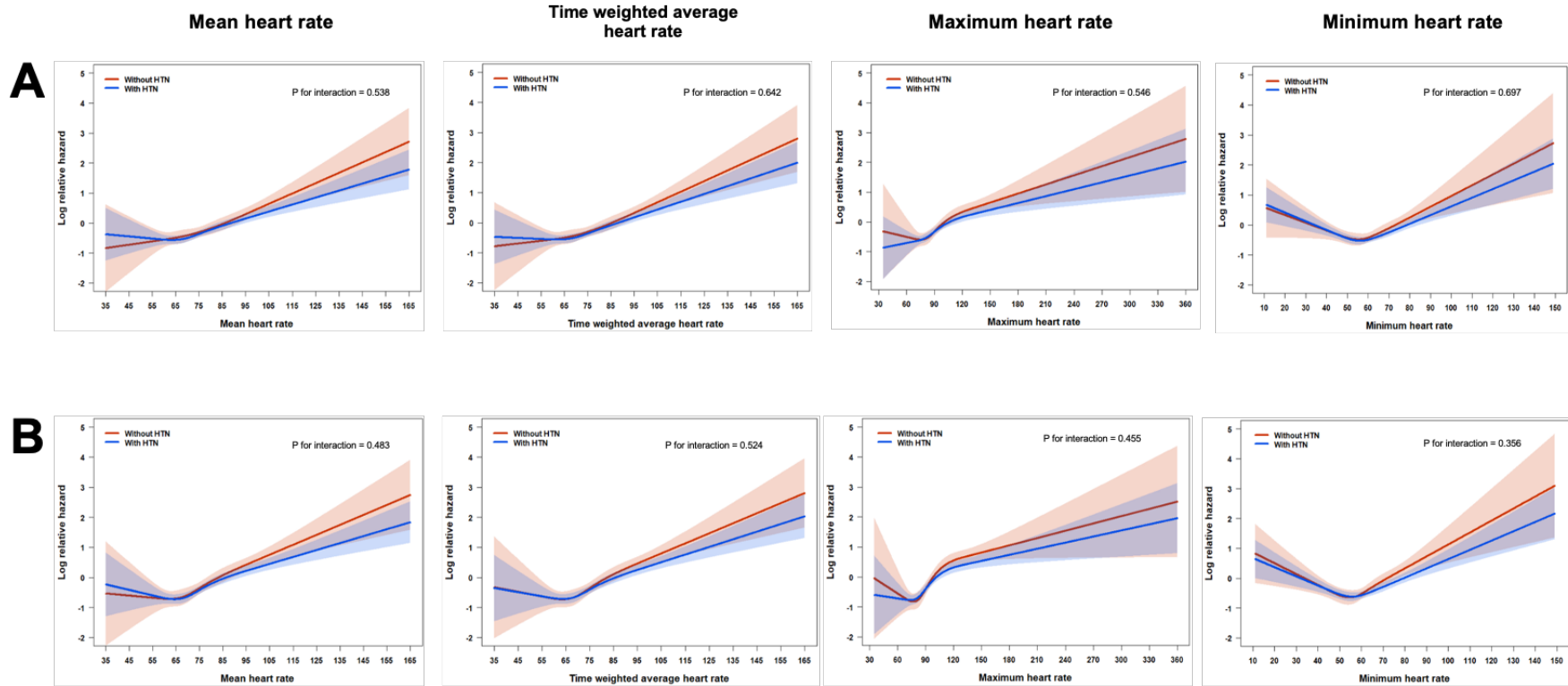


Figure S5. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in patients with and without atrial fibrillation

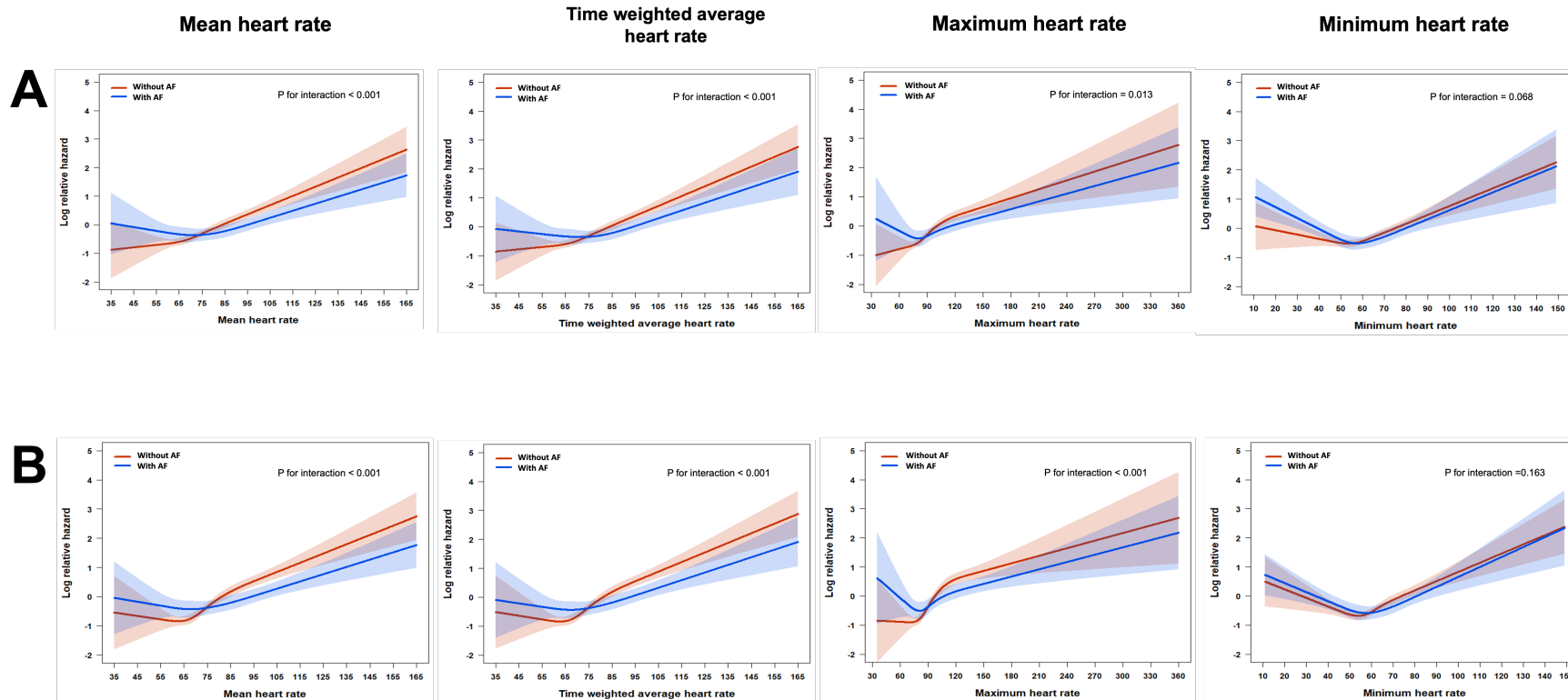


Figure S6. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in patients with age older than 70 years and 70 years or younger

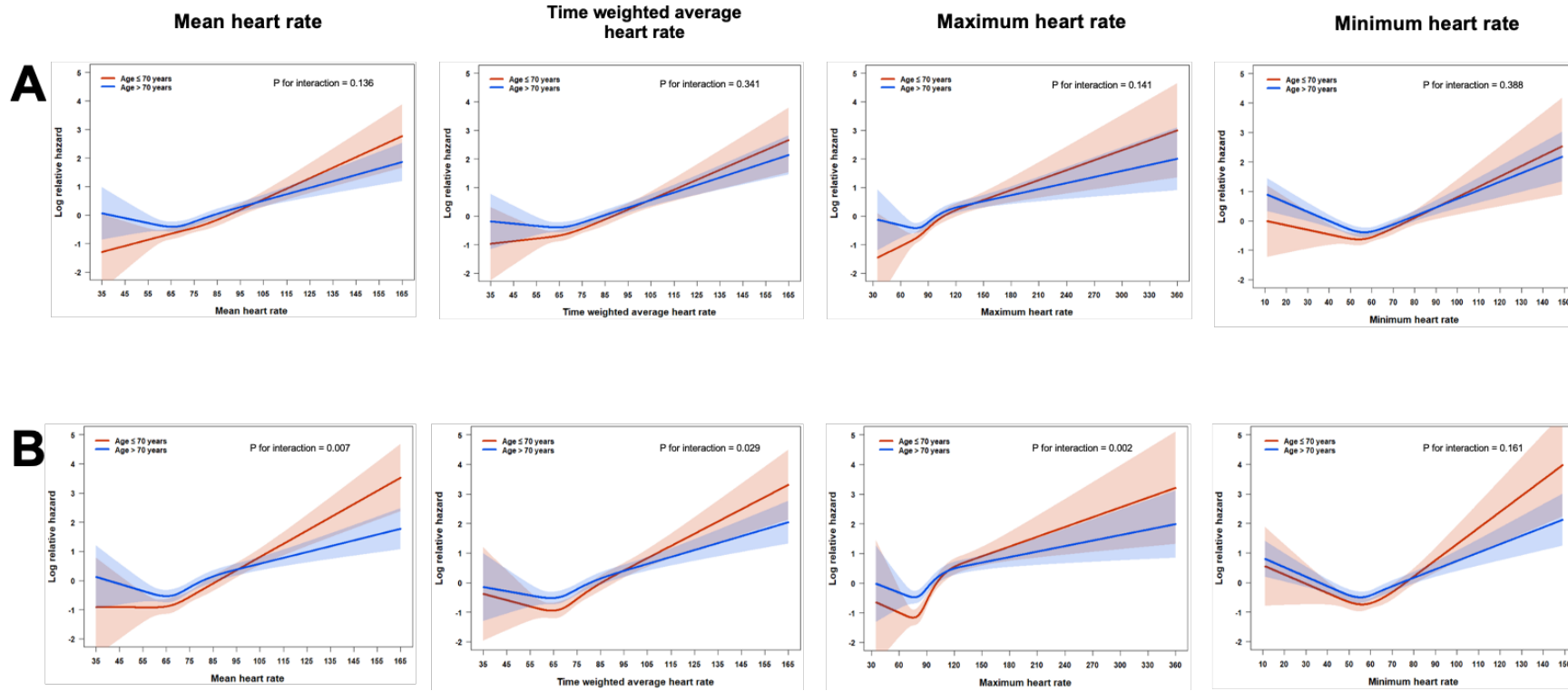


Figure S7. Kaplan-Meier survival curve and piecewise hazard ratios for the primary outcome before and after 30 days since outcome ascertainment according to heart rate cutoffs

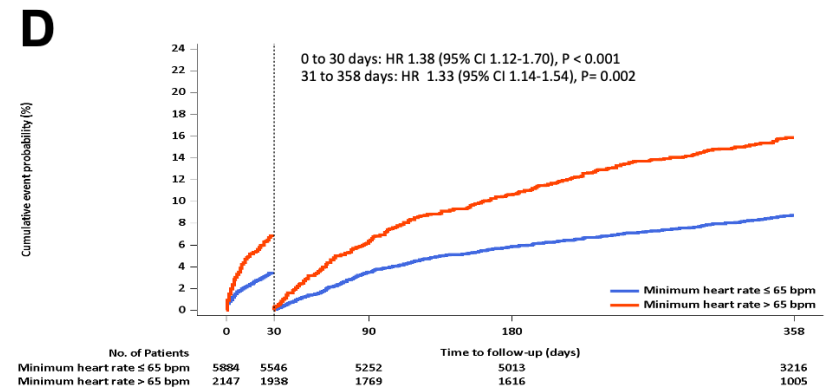
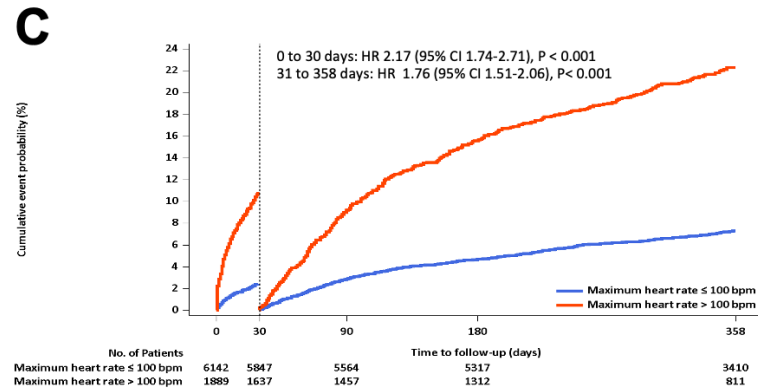
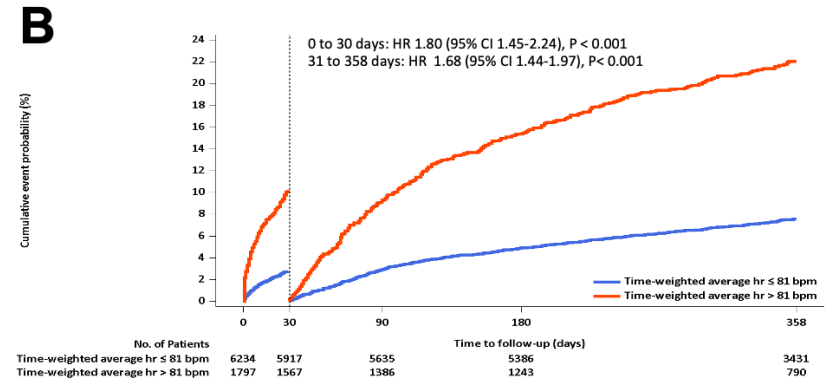
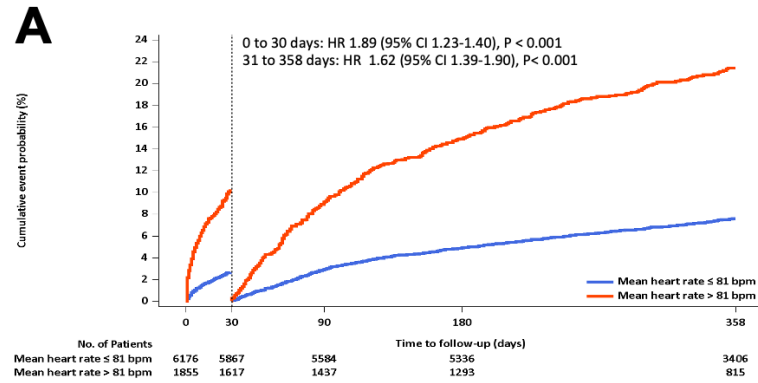


Figure S8. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in the validation dataset

