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IMPACT OF HEART RATE ON ADMISSION ON MORTALITY AND MORBIDITY IN ACUTE ISCHEMIC STROKE PATIENTS – Results from VISTA

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Abstract

Background –Elevated heart rate (HR) is associated with worse outcomes in patients with cardiovascular disease. Its predictive value in acute stroke patients is less well established.

Aims – We investigated the effects of HR on admission in acute ischemic stroke.

Methods – Using the Virtual International Stroke Trials Archive (VISTA) database, we analyzed the association between HR in acute stroke patients without atrial fibrillation and the predefined composite endpoint of (recurrent) ischemic stroke, transient ischemic attack (TIA), myocardial infarction (MI) and vascular death within 90 days.

Predefined secondary outcomes were the composite endpoint components and any death, decompensated heart failure and degree of functional dependence according to modified Rankin Scale (mRS) after 90 days. HR was analyzed as categorical variable (quartiles).

Results – We had 5606 patients for analysis (mean NIHSS: 13; mean age: 67years; mean HR: 77bpm; 44% female) among whom the composite endpoint occurred in 620 patients (11.1%). Higher HR was not associated with the composite endpoint.

The frequencies of secondary outcomes were 3.2% recurrent stroke (N=179), 0.6% TIA (N=35), 1.8% MI (N=100), 6.8% vascular death (N=384), 15.0% any death (N=841), and 2.2% decompensated heart failure (N=124). Patients in the highest quartile (HR>86bpm) were at increased risk for any death [adjusted Hazard Ratio (95% Confidence Interval)=1.40 (1.11-1.75)], decompensated heart failure [adjusted Hazard Ratio=2.20 (1.11-4.37)] and worse mRS [adjusted Odds Ratio=1.29 (1.14-1.52)].

Conclusions – In acute stroke patients, higher HR (>86bpm) is linked to mortality, heart failure and higher degree of dependence after 90 days but not to recurrent stroke, TIA or MI.

BACKGROUND:

Heart rate (HR) is an easily accessible clinical variable and HR monitoring is an essential part of stroke unit management (1). Resting HR is an important marker of stress-induced vascular damage (2). Current data leave little doubt that higher HR is an independent prognostic indicator for cardiovascular mortality. Higher resting HR was positively associated with all cause death, sudden death, and hospitalization due to congestive heart failure in healthy men, the elderly and patients with severe hypertension, metabolic syndrome, heart failure and coronary artery disease (3–8).

With regard to outcome in stroke patients, data on frequency and significance of higher HR are scarce (3,9–10). Some studies suggest that higher HR is related to poor outcome after stroke (9-11). Unfortunately, sizes of study populations did not always allow adjustment for stroke severity and co-morbidities (especially hypertension and antihypertensive medication e.g. beta-blockers or verapamil). Previous studies did not use time-to-event analysis (10,11). Others included patients with sub-acute and chronic stroke only (qualifying event up to 120 days before study inclusion) (9,12).

In addition to poor outcome, higher HR was associated with cognitive decline in a post-hoc analysis of the PRoFESS Study (9). The mediating mechanisms remained unclear. (Recurrent) stroke or TIA are candidates to mediate cognitive decline and a higher degree of dependency.

The aim of this study was to analyse the effect of HR on the day of admission for acute stroke (onset less than 24 hrs before admission) on cardiovascular and neurological events (including stroke and TIA) as well as mortality after ischemic stroke in the Virtual International Stroke Trials Archive (VISTA) on time-to-event basis in patients with

METHODS:

Data Source and Patients

We collected demographics, clinical data, and functional outcome measures from trials in ischemic stroke conducted from 1998 to 2012 and held within VISTA. The Virtual International Stroke Trials Archive (VISTA) collates individual patient data from completed clinical trials and provides access to anonymized data for novel exploratory analyses. VISTA has been described in more detail elsewhere (13).

Only trials were chosen, that included acute ischemic stroke patients (onset within 24hrs before trial inclusion). Besides, we only included trials that offered all relevant predefined baseline and outcome information: HR on admission in particular, occurrence of outcome events, and modified Rankin Scale (mRS) at day 90. Outcome measures were

retrieved from AE and SAE data reports. Patients with atrial fibrillation were excluded because atrial fibrillation can lead to both brady- and tachycardia making interpretation more difficult. In addition, patients with cardio-embolic stroke due to atrial fibrillation may constitute a special entity. Patients' data were anonymized in relation to patients and trials. According to study protocols, heart rate was obtained within 24h after stroke onset and on hospital admission in all five trials included. Heart rate was obtained from ECG by a central reader in two trials, and obtained by pulse measurement in supine position in the other trials. All trials lodged in VISTA already had local institutional review board approved procedures in accordance with the Declaration of Helsinki. Hence, our analysis did not require a new study approval. Conduct and reporting are in accordance with the STROBE guidelines for cohort studies.

Outcome measures

Outcome measures and statistical approach were pre-specified within the application to the VISTA steering committee and approved by the committee prior to analysis. Outcomes were evaluated according to quartiles of HR at baseline. Primary outcome was the composite endpoint of major vascular outcomes [(recurrent) ischemic stroke, transient ischemic attack (TIA), myocardial infarction (MI) or vascular deaths]. The composite endpoint was chosen according to previous studies (9,12). Secondary endpoints were the composite endpoint components: occurrence of either (recurrent) stroke/TIA, MI, as well as any death, and decompensated heart failure until day 90(time-to-event), and modified Rankin Scale (mRS) Score at 90 days.

Statistics

For all descriptive analyses percentages, means with standard deviation (SD) or median with interquartile ranges (IQR) of the variables were reported depending on scale and distribution. To compare patients' characteristics between different trials within this study Chi-square-test for comparison of categorical variables, one-way ANOVA for comparison of sufficiently normally distributed data, Kruskal-Wallis-test for non-normally distributed data and ordinal regression analysis for ordinal data were used (table 1). For bivariate analysis of associations of HR and different patients characteristics or outcomes HR was divided in four groups of similar size (quartiles: Q1: <67bpm, Q2: 67-76bpm, Q3: 77-86 bpm, Q4: >86 bpm). Differences were tested using bivariate ordinal regression analysis with random effects to

account for the heterogeneity between the trials (random intercept models, used software: SAS 9.3, PROC GLIMMIX) (table 2).

Hazard ratios were calculated on time-to-event basis by using Cox proportional hazard regression analyses with random effects to account for heterogeneity between trials (R package ordinal, command: clmm). We used HR of 67-76 bpm as reference category because of U-shaped distribution of the composite endpoint with regard to HR (figure 1). To test the association of HR and mRS we conducted ordinal regression analysis with random effects. Co-variates for adjustment were pre-specified within the proposal handed in to the VISTA collaborators and included the Essen Risk Score parameters (14): age (categorized as <65years, between 65 and 75 and age>75), smoking-status, arterial hypertension, diabetes mellitus, previous MI, other cardiovascular diseases, previous TIA or stroke in addition to qualifying event. Furthermore, we defined National Institutes of Health Stroke Scale (NIHSS) on admission, gender, blood glucose on admission [mmol/l], blood-pressure on admission [mmHg], use of beta-blockers before stroke, and use of verapamil before stroke as potential confounders. Additionally we accounted for the clustering of patients in trials by using regression models with random effects.

Results are expressed as hazard ratios with 95% confidence intervals (95% CI) when using Cox regression on time to event basis and as odds ratios with 95% confidence intervals (95% CI) for ordinal regression for mRS on day 90.

SPSS 19.0.0.1, SAS 9.3 and R 3.1.1 were used for data analysis.

RESULTS:

A total of 5606 patients from five distinct studies were available for analysis (mean (SD) NIHSS: 13 (6); age: 67 (13) years, HR: 77 (15) bpm, 44% female). Demographics and co-morbidities for the total cohort as well as for each individual trial are reported in table 1. Trials differed significantly for almost all patient characteristics. Beta-blocker and verapamil use was especially high in trial D.

On follow-up, a feature of the composite endpoint was recorded in 620 patients (11.1%). Recordings of secondary (single) outcomes were: 179 recurrent strokes (3.2%), 35 TIAs (0.6%), 100 myocardial infarctions (1.8%), 384 vascular deaths (6.8%), 841 any deaths (15.0%), and 124 exacerbation of heart failure (2.2%). In patients experiencing more than one endpoint component, the first event was considered.

Unadjusted ordinal regression analysis did not show a significant association between HR and the composite endpoint (p=0.336, table 2).

On the contrary, unadjusted ordinal regression analyses showed significant associations of higher HR on admission and a higher probability for occurrence of MI (p=0.014), any death (p=0.025), occurrence of decompensated heart failure (p=0.026) and higher degree of dependency (worse mRS Score; p=0.026) (table 2). With regard to co-variates and confounding factors, bivariate analysis also showed that female stroke patients had more often a higher HR than male stroke patients (p=0.002), that patients with a higher HR where younger compared to those with normal or lower HR (p<0.001). In addition higher HR was associated with higher glucose (p<0.001), higher systolic and diastolic blood pressure (both p<0.001), higher body temperature (p<0.001), was more frequent in patients with diabetes (p<0.001), but less frequent in patients with history of MI (p<0.001) and in patients who used beta-blockers (p<0.001). Essen Risk Score was higher in the lowest HR quartile (p<0.001) (table 2).

The distribution of the composite endpoint, vascular death or any death according to HR suggested a U- or J-shaped relation and the second quartile was therefore chosen as reference in the multiple Cox regression models (table 2, Figure 1). Cox proportional regression models demonstrated a significantly higher risk of any death in patients with HR>86 bpm compared to patients in the second quartile [HR (67-76bpm)] [adjusted Hazard Rate (95%CI): 1.40 (1.11-1.75)] (table 3). Similarly, patients with HR>86 bpm had a higher risk of exacerbation of heart failure [adjusted Hazard Rate (95%CI): 2.20 (1.11-4.37)]. The association between HR>86 bpm and death from vascular cause just failed statistical significance after adjustment [adjusted Hazard Rate (95%): 1.33 (0.98-1.81); p=0.065]. Adjusted ordinal regression analysis revealed a significantly worse mRS score at day 90 for patients with HR>86 bpm compared to the reference HR (67-76bpm) [adjusted OR (95%CI): 1.29 (1.10-1.52)].

Neither higher nor lower HR was significantly associated with occurrence of (recurrent) stroke/TIA or MI. Moreover, HR was also not significantly associated with the composite endpoint when applying the time-to-event approach (table 3).

DISCUSSION:

Our study found an independent association between the highest quartile of HR on admission (>86 bpm) and any deaths, exacerbation of heart failure, and a higher degree of dependence as defined by the mRS in acute stroke patients without atrial fibrillation. In contrast, higher HR was not significantly associated with the composite endpoint of stroke, TIA, MI and vascular deaths nor the composite endpoint components recurrence of stroke/TIA or MI alone. Our findings in acute ischemic stroke patients are corroborated by a number of previous

studies in healthy men and patients with severe hypertension, with heart failure, and with coronary artery disease emphasizing the predictive value of HR for overall mortality (3,5–8). Moreover, there was no significant association of HR with occurrence of stroke in patients with stable coronary heart disease, acute coronary syndrome or chronic stroke (9,15,16). Finally other studies did not find an association between higher heart rate and MI (12,15).

Previous data on stroke patients have predominantly been reported for the non-acute setting and in mildly affected patients. Our study reports on very acute (included <24h after onset) and severely affected stroke patients (mean NIHSS=13). The predictive value of HR could have been different in this special subgroup of patients.

The PRoFESS and PERFORM studies on sub-acute and chronic stroke patients showed a significant association between higher HR and mortality, too. Up to date, the predictive value of HR for death seems well established for several populations, including acute and non-acute stroke patients as well as in-hospital mortality and mortality within the first three months following the initial event (9,12,18).

Moreover, our study further supports the relevance of HR in predicting decompensated heart failure. The association of higher HR and decompensated heart failure is recognised from patients with known heart failure with and without coronary artery disease and from patients with suspected or proven coronary artery disease (5,17,19). Our study extends this finding to acute stroke patients where this aspect has not been studied before.

Decompensated heart failure may have contributed to both mortality and the third finding of our analysis: the association with higher degree of disability as quantified by the mRS. Mediating mechanisms leading to higher mortality in patients with heart failure are well described (20). Pathophysiological explanations for the association between higher heart rate and worse disability are less well understood (21). Heart failure may contribute by restricting patients' mobility (worsening disability). Interestingly, there is an association of heart rate and cognitive decline in patients with high cardiovascular risk (after MI or survived stroke) (22). Cognitive decline may also contribute to a higher degree of disability. However, following our analysis of VISTA, although higher HR predicts decompensated heart failure, and heart failure increases stroke risk, one cannot assume an increased stroke risk when finding higher HR alone. Besides, our analysis does not support the hypothesis, that clinically manifest (recurrent) stroke/TIA are relevant contributors to the cognitive decline observed in these patients.

Our study benefits from the large sample size including comprehensive adjustments for confounding factors (including beta-blockers and verapamil) and accounting for clustering of

patients in trials, pre-defined primary and secondary outcomes. There are inherent limitations in the retrospective design and the sampling of trial populations including divergences in obtaining heart rate.

Conclusion

Our analysis extends the evidence for an impact of elevated HR on mortality and morbidity to patients with an acute cerebral ischemic event and major neurological deficits. In acute stroke patients, higher HR indicates higher risk of any death, decompensated heart failure, and higher degree of dependency on follow up but higher HR does not predict (recurrent) cerebral ischemic events.

Conflicts of interest: None declared.

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Author contributions statement:

CHN, KRL and ME conceived the study. UG, AS, SKP provided statistical guidance, and performed all statistical work for the study. PMB and CHD and KRL are members of the VISTA group, the data source for the present study, and represent the VISTA investigators on this project. CHN drafted the manuscript and all authors contributed substantially to its revision. CHN takes responsibility for the paper as a whole.

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Table 1: Sample description for the whole study and for the five different trials from the VISTA project. Mean ± SD, median (IQR) or percentages.

Trial	N	Age	Sex (female)	NIHSS; N=5605	Diabetes mellitus; N=5481	Arterial Hypert. N=5481	Heart Rate [bpm]	Smoking Never / stopped / current; N=5477	Beta-Blocker use	Vera-pamil use	Glucose (basel.) [mmol/l] ; N=5034	Systolic Blood pressure [mmHg]	Essen Risk Score sum
Total	5606	67 (13)	43.6 %	12.8 (5.5)	24.5%	72.1%	77 (15)	49.4%/16.4%/34.2%	19.3%	2.0%	6.6 (5.8 – 8.2)	155 (26)	2.9 (1.5) s
A	1282	67 (12)	42.4%	12.2 (5.2)	20.0%	67.2%	77 (15)	55.3%/19.0%/25.8%	12.1%	1.1%	6.6 (5.8 - 8.1)	156 (26)	2.6 (1.5)
B	2331	67 (13)	42.4%	12.4 (5.4)	25.5%	74.8%	77 (15)	51.1%/22.3%/26.6%	17.2%	1.3%	6.7 (5.7 – 8.2)	154 (26)	2.9 (1.5)
C	429	69 (13)	50.1%	16.2 (5.1)	23.8%	71.3%	80 (17)	45.5%/ 31.5%/23.1%	11.0%	1.6%	6.4 (5.6 – 8.2)	154 (25)	2.7 (1.3)
D	552	69 (13)	43.7%	14.5 (4.3)	22.8%	68.3%	77 (16)	0.5% / 0.0% /99.5%	17.4%	1.4%	6.7 (5.8 – 8.3)	156 (25)	3.3 (1.4)
E	1012	68 (13)	44.8%	12.1 (6.1)	29.4%	75.0%	77 (15)	68.8%/ 0.0%/31.2%	37.7%	5%	Not available	153 (25)	Not available
P		<0.001[b]	0.041 [a]	<0.001 [b]	<0.001 [a]	<0.001 [a]	0.028 [b]	<0.001 [d]	<0.001 [a]	<0.001[a]	0.470 [c]	0.035 [b]	<0.001 [b]

[a] χ-square-test; [b] one-way ANOVA; [c] Kruskal-Wallis-Test; [d] ordinal regression

Table 2: Characteristics of study participants by resting heart rate (in quartiles), bivariate test results using ordinal regression with random effects.

HR (Quartiles)	Total N=5606	Q1 (<67bpm) N=1427	Q2 (67-76 bpm) N=1492	Q3 (77-86 bpm) N=1324	Q4 (>86 bpm) N=1363	P
Gender (female)	43.6%	41.7%	41.1%	45.6%	46.2%	0.002 [a]
Age [years]; Mean (SD)	67 (13)	69 (12)	67 (13)	67 (13)	66 (13)	<0.001[a]
NIHSS on admission; Mean (SD); N=5605	12.8 (5.5)	13.0 (5.5)	12.9 (5.6)	12.4 (5.5)	12.9 (5.5)	0.206
Right hemisphere N=5598	51.8%	53.6%	51.2%	51.1%	51.0%	0.179 [a]
Glucose on admission [mmol/l]; Median [IQR]; N=4022	6.6 [5.8 – 8.2]	6.5 [5.6-7.8]	6.6 [5.7-8.1]	6.6 [5.7-8.2]	6.9 [5.9-9.1]	<0.001 [b]
Systolic blood pressure on admission [mmHg]; Mean (SD); N=5603	155 (26)	152 (26)	154 (25)	156 (25)	157 (27)	<0.001 [a]
Diastolic blood pressure on admission [mmHg]; Mean (SD); N=5601	82 (16)	78 (15)	82 (15)	84 (16)	87 (17)	<0.001 [a]
Temperature on admission [°C]; Mean (SD); N=4394	36.8 (0.6)	36.6 (0.6)	36.8 (0.5)	36.9 (0.5)	36.9 (0.6)	<0.001 [a]
Arterial hypertension at baseline; N=5481	72.1%	73.5%	71.0%	71.0%	73.0%	0.760 [a]
Diabetes mellitus; N=5481	24.5%	20.8%	23.8%	26.2%	27.3%	<0.001 [a]

Smoking						
never,	49.4%	48.6%	49.1%	53.2%	46.9%	0.666 [a]
stopped,	16.4%	17.6%	17.1%	12.7%	17.9%	
current	34.2%	33.8%	33.8%	34.2%	35.2%	
N=5477						
Hx of heart failure; N=4165	5.5%	5.0%	5.7%	4.8%	6.6%	0.234 [a]
Hx of myocardial infarction; N=5481	14.9%	17.8%	14.6%	14.1%	12.8%	<0.001[a]
Hx of Stroke; N=5529	23.3%	24.9%	21.7%	24.9%	22.0%	0.293 [a]
Hx of TIA; N=4374	9%	7.6%	9.4%	9.2%	9.6%	0.134 [a]
B-Blocker on admission	19.3%	27.3%	18.5%	15.8%	15.2%	<0.001 [a]
Verapamil on admission	2.0%	1.8%	1.8%	2.6%	1.7%	0.684 [a]
Treatment with rTPA	36.4%	38.4%	35.9%	34.2%	36.9%	0.261 [a]
Essen Risk Score Sum Mean (SD); N=4590	2.9 (1.5)	3.0 (1.5)	2.8 (1.5)	2.8 (1.5)	2.8 (1.4)	<0.001 [a]
Essen Risk Score > 2; N=4590	58.5%	61.9%	59.1%	56.7%	56.0%	0.002 [a]
OUTCOME	% (events)					
Composite outcome [c]	11.1% (N=620)	11.4%	10.3%	10.0%	12.7%	0.336 [a]
Secondary Outcomes	3.2%	3.4%	3.2%	3.2%	3.1%	0.693 [a]
Recurrent Stroke	(N=179)					
TIA	0.6% (N=35)	0.8%	0.6%	0.6%	0.5%	0.410 [a]

MI	1.8% (N=100)	1.2%	1.9%	1.4%	2.6%	**0.014** [a]
Vascular death	6.8% (N=384)	7.8%	6.3%	5.9%	8.9%	0.383 [a]
Any death	15.0% (N=841)	15.3%	13.2%	13.1%	18.6%	**0.025** [a]
Exacerbation of heart failure	2.2% (N=124)	1.9%	2.1%	1.5%	3.4%	**0.026** [a]
Modified Rankin Scale Score at day 90; mean; median (IQR) N=5417	2.9; 3.0 (1-4)	3.0; 3.0 (1-4)	2.8; 3.0 (1-4)	2.8; 3.0 (1-4)	3.1 3.0 (1-5)	**See table 3**

[a] ordinal regression with random effects

[b] ordinal regression with random effects of log-transformed values

[c] the composite endpoint is less than the sum of its components, because patients my have suffered more than one endpoint.

Table 3: Adjusted and unadjusted Hazard ratios for the primary and secondary endpoints in relation to resting HR (in quartiles).

Outcome Total: N=4015	**Q1 (<67pbm)** Hazard Ratio [95% CI] (p)	**Q2 67-76bpm**	**Q3 77-86 bpm** Hazard Ratio [95% CI] (p)	**Q4 >86 bpm** Hazard Ratio [95% CI] (p)
Primary, composite endpoint,				
n=509 events; adjusted [a]	1.07 [0.84 – 1.37] (0.590)	Reference	0.95 [0.73 – 1.24] (0.730)	1.25 [0.98 – 1.60]* (0.073)
unadjusted	1.13 [0.89 – 1.44] (0.300)	Reference	0.92 [0.71 – 1.19] (0.530)	1.25 [0.98 – 1.59] (0.068)
Secondary (single) Outcomes:				
Recurrent stroke or TIA				
n=171 events; adjusted [a]	1.07 [0.71 – 1.46] (0.750)	Reference	0.93 [0.61 - 1.44] (0.750)	0.93 [0.60 - 1.43] (0.730)
unadjusted	1.09 [0.72 – 1.63] (0.690)	Reference	0.95 [0.62 – 1.45] (0.800)	0.93 [0.61 – 1.43] (0.750)
Myocardial infarction,				
n=68 events; adjusted [a]	0.49 [0.24 – 1.01] (0.052)	Reference	0.53 [0.25 – 1.14] (0.100)	1.37 [0.76 – 2.48] (0.300)
Unadjusted	0.58 [0.29 – 1.18] (0.130)	Reference	0.54 [0.25 – 1.14] (0.110)	1.28 [0.72 – 2.28] (0.410)
Death from cardiovascular				
causes, n=333 events; adjusted [a]	1.11 [0.82 - 1.50] (0.510)	Reference	1.01 [0.72 - 1.40] (0.970)	1.33 [0.98 - 1.81] (0.065)

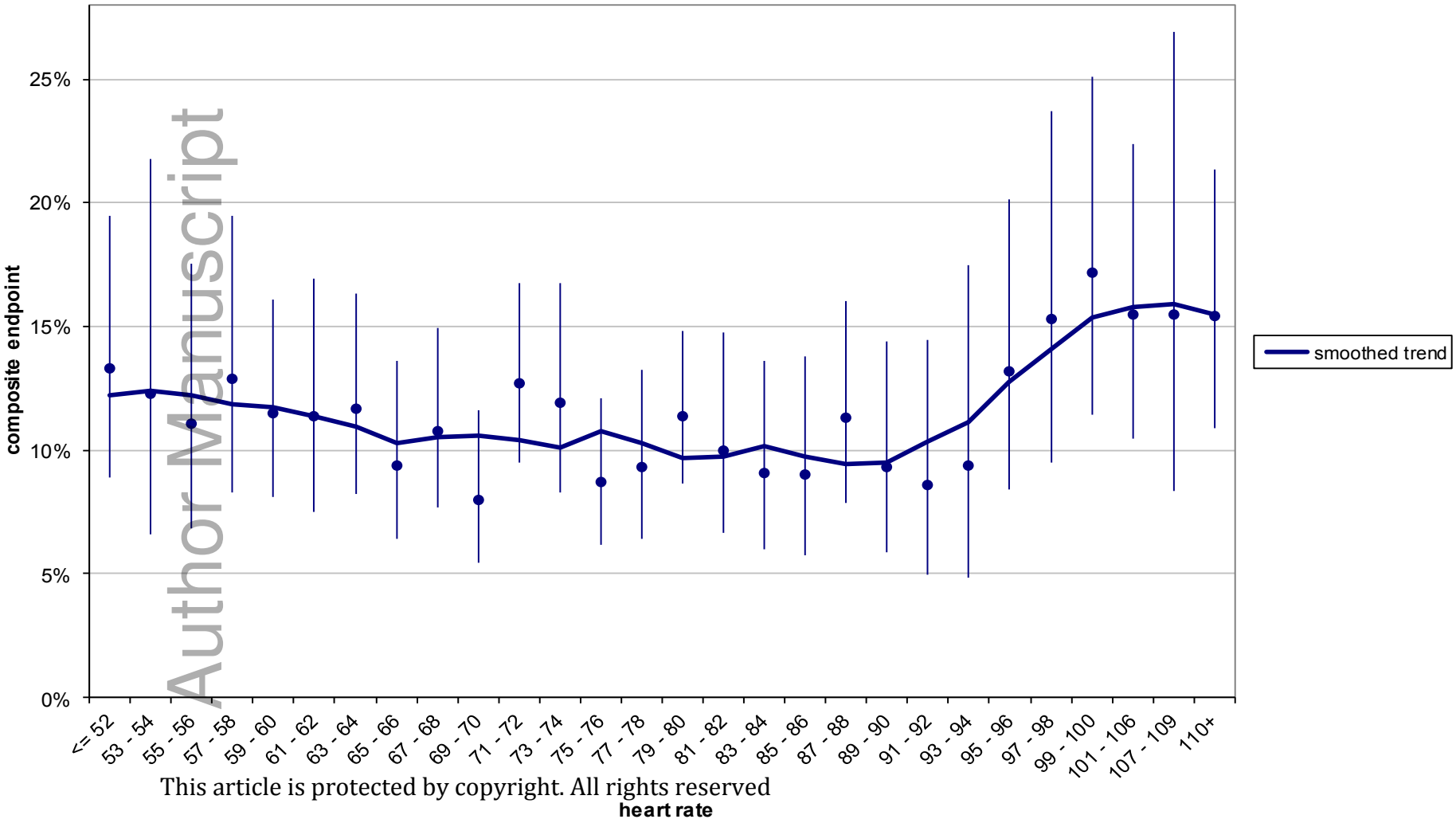
Unadjusted	1.20 [0.89 - 1.62] (0.230)	Reference	0.92 [0.67 - 1.28] (0.640)	**1.36 [1.01 - 1.83] (0.042)**
Any death, n=592 events; adjusted [a]	0.98 [0.78-1.24] (0.890)	Reference	1.00 [0.78-1.27] (0.980)	**1.40 [1.11-1.75] (0.004)**
Unadjusted	1.01 [0.78-1.24] (0.670)	Reference	0.91 [0.72-1.16] (0.460)	**1.32 [1.06-1.65] (0.013)**
Exacerbation of heart failure[b] n=67 events; adjusted [a]	1.19 [0.57-2.47] (0.640)	Reference	1.18 [0.54-2.58] (0.670)	**2.20 [1.11-4.37] (0.024)**
Unadjusted	1.35 [0.65-2.77] (0.420)	Reference	1.14 [0.53-2.46] (0.740)	**2.01 [1.02-3.95] (0.042)**
Modified Rankin Scale Score at 90 days (Odds Ratio) adjusted [a]	1.07 [0.91-1.25] (0.409)	Reference	1.12 [0.95-1.31] (0.173)	**1.29 [1.10-1.52] (0.002)**
unadjusted	1.14 [0.98-1.33] (0.080)	Reference	1.00 [0.85-1.17] (0.960)	**1.26 [1.08-1.47] (0.004)**

[a] adjusted for the Essen Risk Score parameters: age between 65 and 75, age>75, Smoker, Arterial hypertension, Diabetes, previous myocardial infarction, other cardiovascular diseases (except myocardial infarction or atrial fibrillation), previous TIA or stroke in addition to qualifying event and furthermore NIHSS on admission, Blood glucose on admission (mmol/l), use of beta-blockers before stroke

[b] In patients without known congestive heart failure before index stroke.

Figure Legends

Figure 1: Prevalence and 95%CI of composite endpoint (recurrent ischemic stroke, TIA, myocardial infarction and vascular death within 90 days) after index stroke by resting HR.



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