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Resting heart rate and ischemic stroke in patients with heart failure

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Abstract

Background—Although high resting heart rate (RHR) is known to be associated with increased risk of mortality and hospital admission in patients with heart failure, the relationship between

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Disclosures

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RHR and ischemic stroke remains unclear. This study aimed to investigate the relationship between RHR and ischemic stroke in patients with heart failure in sinus rhythm.

Methods—We examined 2060 patients with systolic heart failure in sinus rhythm from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial. RHR was determined from baseline electrocardiogram and was examined as a continuous variable, and also as a categorical variable using quartiles. Ischemic strokes were identified during follow-up and adjudicated by physician review.

Results—During 3.5±1.8 years of follow-up, 77 patients [5.3% from Kaplan Meier (KM) curve] experienced an ischemic stroke. The highest incidence of ischemic stroke [21/503 (KM 6.9%)] was observed in the lowest RHR quartile (RHR <64 beats/min) compared to other groups; 22/573 (KM 5.3%) in 64–70 beats/min, 13/465 (KM 3.5%) in 71–79 beats/min, and 21/519 (KM 5.4%) in RHR >79 beats/min (p=0.693). Multivariable Cox proportional hazards analysis revealed that RHR was significantly associated with ischemic stroke (hazard ratio per unit decrease: 1.07, 95% confidence interval: 1.02 to 1.13, when RHR <64/beats/min; p=0.038), along with history of stroke or transient ischemic attack and left ventricular ejection fraction.

Conclusions—In contrast to its beneficial effect on mortality and hospital re-admissions, lower RHR may increase the risk of ischemic stroke in patients with systolic heart failure in sinus rhythm.

Keywords

beta-blocker; heart failure; ischemic stroke; resting heart rate; sinus rhythm; WARCEF trial

Introduction

Approximately 5.7 million adults are living with heart failure in United States, and the prevalence is increasing [1]. Among heart failure patients, approximately half have reduced left ventricular ejection fraction (LVEF). Heart failure with reduced LVEF (HFrEF) is a major cause of mortality and hospital admission and a high resting heart rate (RHR) is a strong predictor of mortality and hospital re-admission in patients with HFrEF [2–4]. Beta-adrenoceptor-blocking agents (beta-blockers) are now well established as mandatory therapy in patients with HFrEF [5–8], and part of their beneficial effect may depend on RHR reduction [9–11]. However, the relationship between RHR and ischemic stroke risk in HFrEF is still unclear although HFrEF is associated with an increased risk for cardioembolic stroke [12,13]. The aim of this study was to investigate the relationship between RHR and ischemic stroke in HFrEF patients in sinus rhythm who were treated with beta-blockers.

Methods

Patients

We analyzed data from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, which compared warfarin and aspirin in a double-blind, randomized design [14]. The results of the primary analysis have been previously published [15]. WARCEF obtained data from 168 centers in 11 countries, and enrolled 2,305 patients with follow-up periods of up to 6 years (mean, 3.5±1.8 years). Patients were >18 years of age and had normal sinus rhythm and LVEF ≤35% within 3 months before randomization. All patients were treated with guideline-recommended medical treatment. Since approximately 90% of patients were treated with beta-blockers, which affect RHR, we limited our analysis to these patients, therefore excluding 243 patients who were not treated with beta-blockers. Two others were excluded because they did not have RHR information. The final sample for analysis thus included 2,060 patients. RHR was obtained from the baseline electrocardiogram. The study was approved by the institutional review boards and ethics boards of participating centers.

Assessment of established and potential risk factors of ischemic stroke

Clinical characteristics included in our study were age, sex, hypertension, diabetes mellitus, current smoking status and alcohol consumption, history of myocardial infarction (MI), history of atrial fibrillation (AF), prior stroke/transient ischemic attack (TIA), education level, New York Heart Association (NYHA) class, systolic and diastolic blood pressure (BP), pulse pressure, medications, implantable cardioverter defibrillator, and LVEF. LVEF on either quantitative echocardiography, radionuclide or contrast ventriculography was obtained in all patients within 3 months before randomization.

Follow-up

Follow-up was performed monthly by telephone or in person. An in-person assessment was conducted quarterly for clinical evaluation. Stroke was defined as a clinically relevant new lesion detected on computed tomography or magnetic resonance imaging or, in the absence of a new lesion, clinical findings that were consistent with the occurrence of clinical stroke and that lasted for longer than 24 hours.

Statistical analysis

Categorical variables are presented as number/total number (%) and compared by quantiles of RHR using Chi-squared test or Fisher exact test. Continuous variables are presented as mean ± standard deviation and compared using the ANOVA F-test. Kaplan Meier (KM) estimates for ischemic stroke stratified by quartiles of RHR were also calculated. Univariable and multivariable linear regression analyses were conducted to determine the variables independently associated with RHR. Univariable and multivariable Cox proportional hazards regression analyses were then performed to identify the association between RHR and ischemic stroke. The linearity of associations was assessed using restricted cubic splines and, if a trend of non-linearity was found ($p<0.10$), a linear spline or quadratic or cubic polynomial transformation was chosen based on the univariable Akaike's Information Criterion (AIC). To compare the association of RHR with ischemic stroke in aspirin- and warfarin-treated subgroups, we added treatment and its interaction with RHR to the Cox models. Multivariable analyses were performed in 2 models. Model 1: adjustment by variables with significant association with ischemic stroke in univariable Cox proportional hazard analysis, and Model 2: adjustment as in Model 1 plus variables with significant association with RHR in univariable linear regression analysis. Missing values for the covariates were imputed using means for continuous variables and modal values for categorical variables. Differences were considered significant at $p<0.05$ two-sided. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Results

The study sample had a mean age of 60±11 years and a mean heart rate of 71 beats/min (median=70 beats/min, 25th–75th percentile 64–80 beats/min). Baseline characteristics stratified by RHR quartiles are shown in Table 1. The factors independently associated with RHR in a multivariable linear regression analysis were age (β-coefficient −0.132, p<0.001), diabetes mellitus (β-coefficient 2.188, p<0.001), current smoking (β-coefficient 2.614, p<0.001), current alcohol consumption >2oz/day (β-coefficient −2.037, p<0.001), history of MI (β-coefficient −2.085, p<0.001), history of AF (β-coefficient −3.448, p=0.008), NYHA class (β-coefficient 1.609, p=0.003), diastolic BP (β-coefficient 0.169, p<0.001), pulse pressure (β-coefficient −0.061, p=0.001), diuretics (β-coefficient: 2.037, p=0.002) and LVEF (β-coefficient −0.134, p<0.001; Table 2).

During 3.5±1.8 years of follow-up, 77 patients (5.3% from KM curve) developed ischemic stroke. The highest incidence of ischemic stroke [21/503 (KM 6.9%)] was observed in the lowest RHR quartile (RHR <64 beats/min) compared to other groups; 22/573 (KM 5.3%) in 64–70 beats/min, 13/465 (KM 3.5%) in 71–79 beats/min, and 21/519 (KM 5.4%) in RHR >79 beats/min (p=0.693).

A trend of nonlinear association between RHR and stroke was found (p=0.08), and linear spline with knot at RHR=64 beats/min was selected as the best model based on AIC. The hazard ratio plot is displayed in Figure 1. Results from Cox models are presented in Table 3. Overall, low RHR was a significant predictor of stroke (adjusted p=0.044 in model 1). In particular, the risk of stroke increased with decreasing RHR for RHR values <64 beats/min (adjusted HR: 1.07, p=0.013), while was unaffected above that value (adjusted HR: 0.99, p=0.355). Ischemic stroke was also significantly associated with history of stroke or TIA (adjusted HR: 3.42, p<0.001) and LVEF (quadratic model, overall p<0.001, 75th vs. 25th percentile adjusted HR: 0.82). Even after adjustment for additional variables with significant association with RHR (age, diabetes mellitus, current smoking, current alcohol consumption, history of MI, history of AF, NYHA class, diastolic BP, pulse pressure, diuretics, and statin), RHR remained significantly associated with ischemic stroke (Table 3 model 2).

Table 4 shows relationship between RHR and stroke risk in warfarin- and aspirin-treated subgroups. The interaction model results showed that lower RHR was significantly associated with ischemic stroke among patients randomized to aspirin (p=0.039), whereas there was no relationship in those randomized to warfarin (p=0.408). This result persisted after adjustment for the variables with significant association with RHR (Table 4 model 2). In patients with RHR <64 beats/min, significantly lower ischemic stroke rate was observed in the warfarin group than in the aspirin group [5/235 (KM 4.4%) vs. 16/268 (KM 9.2%), p=0.034], whereas ischemic stroke rate did not differ between the 2 treatment groups in patients with RHR ≥64 beats/min [22/790 (KM 3.6%) vs. 34/767 (KM 6.0%), p=0.086].

Discussion

This study demonstrates for the first time that low RHR is associated with a higher incidence of ischemic stroke among patients with HFrEF who are in sinus rhythm and are treated with currently recommended medical regimen, including beta-blockers.

In patients with HFrEF who are in sinus rhythm, a high RHR is associated with increased mortality and hospital re-admissions [2–4], and beta-blockers substantially improve outcome [5–8]. Although the benefits of beta-blockers may not be entirely related to RHR reduction, several meta-analyses have shown a stronger effect on survival for RHR rather than the beta-blockers dose achieved [9–11]. As a result, it has become a common clinical assumption that the beneficial effect of beta-blockers depends on, or is heralded by, their RHR-lowering effect: the slower the RHR, the greater the benefit. However, although HFrEF is associated with an increased risk for cardioembolic stroke [12,13], the relationship between RHR and ischemic stroke has not been fully investigated in patients with HFrEF in sinus rhythm. Here, we report for the first time that low RHR was associated with higher incidence of ischemic stroke in patients with HFrEF in sinus rhythm. Our finding was unexpected, because low RHR is usually associated with lower mortality and rate of hospital admission in these patients [2–4]. The relationship between heart rate and stroke still remains unclear in other clinical settings, where conflicting results have been reported [16–21]. Mao et al. showed that high resting heart rate increased the risk of stroke in 169,871 general Chinese adults ≥40 years [18]. Similarly, data from patients with stable coronary artery disease and hypertension demonstrated that high resting heart rate was associated with an increased risk of stroke [19,20]. More recently, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study conducted in 24,730 subjects without history of stroke showed that each 10 beats/min increase in heart rate was associated with a 10% increase in the risk of stroke [21]. In contrast, reports from the general French population and the Women's Health Initiative Study did not show an association between resting heart rate and stroke [16,17].

The underlying mechanisms of our finding are unclear, but several potential explanations can be hypothesized. Recent studies have reported that low RHR is associated with higher incidence of AF development in various populations [22–24]. Bohn et al. reported that RHR lower than 60 beats/min was associated with increased incidence of AF in 27,064 patients with high cardiovascular risk during a mean follow-up period of 4.7 years [22]. Wesley et al. also reported that RHR lower than 60 beats/min was an independent risk for AF development in 5,226 elderly individuals from the general population [23]. In our study, patients with low RHR may have more frequently developed transient episodes of AF during follow-up, which might be involved in their higher risk for ischemic stroke. Another possible mechanism could be an increase in central aortic pressure secondary to heart rate lowering. Bradycardia leads to dyssynchrony or uncoupling between outgoing and reflected wave, thereby elevating central aortic pressure. In the Conduit Artery Functional Evaluation (CAFE) study [25], significantly higher central aortic systolic blood pressure was observed with beta-blocker treatment compared with calcium channel blocker treatment despite similar effect on peripheral blood pressure, resulting in higher incidence of stroke in patients with hypertension. Finally, an increase in pulse pressure may also be involved in the development of stroke in HFrEF patients with low RHR. Because mean arterial pressure is a product of cardiac output (heart rate × stroke volume) and peripheral vascular resistance, low RHR should result in higher stroke volume to maintain cardiac output. A higher stroke volume, in turn, causes elevated pulse pressure which has been recognized as an independent predictor of stroke [26,27]. Indeed, RHR was negatively correlated with pulse pressure in our population. However, pulse pressure was not significantly associated with ischemic stroke.

Interestingly, when patients were divided into subgroups on the basis of assigned antithrombotic treatment, low RHR was associated with ischemic stroke in the aspirin group, but not in the warfarin group. In patients with RHR <64 beats/min, patients treated with warfarin had significantly lower ischemic stroke rate than those with aspirin. This result suggests that systemic anticoagulation may counteract the risk of stroke associated with low RHR, also suggesting a potential thromboembolic component for the stroke mechanism. Furthermore, it may indicate that warfarin treatment may be preferable to aspirin for stroke prevention in patients with low RHR.

Among medications that affect heart rate, ivabradine is a novel HF medication that specifically inhibits the I_f current in the sinoatrial node, thereby lowering heart rate without affecting other aspects of cardiac function [28]. In SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial), RHR reduction with ivabradine was associated with 26% risk reduction of first HF hospitalization, and 11% risk reduction of first all-cause hospitalization [29]. Because of the study period of WARCEF trial (from October 2002 through January 2010), ivabradine was not used. Future studies are needed to investigate the association of RHR with ischemic stroke in patients treated with ivabradine.

Study limitations

Our study has several limitations. Because we enrolled patients with HFrEF in sinus rhythm at enrollment, the results may not be generalizable to patients with HF with preserved LVEF and to those with AF. Because of the absence of information on beta-blocker dose, we cannot evaluate a possible effect of different doses on our results. However, several meta-analyses have shown a stronger relationship between the RHR and prognosis in HF than between beta-blockers dose and prognosis [9–11]. Finally, although we performed multivariable analyses adjusting for ischemic stroke risk factors and variables associated with RHR, we cannot rule out the possibility of unmeasured confounders playing a role in the observed associations.

Conclusions

In contrast to the beneficial effect of lower RHR on mortality and hospital admissions, lower RHR increased the risk of ischemic stroke in HFrEF patients in sinus rhythm treated with beta-blockers. Further studies are required to evaluate the mechanisms for the increased risk of ischemic stroke in patients with low RHR.

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References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. Circulation. 2016; 133:e38–60. [PubMed: 26673558]
2. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006; 27:65–75. [PubMed: 16219658]
3. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010; 376:886–894. [PubMed: 20801495]
4. Li SJ, Sartipy U, Lund LH, Dahlstrom U, Adiels M, Petzold M, Fu M. Prognostic significance of resting heart rate and use of beta-blockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: Findings from the Swedish heart failure registry. Circ Heart Fail. 2015; 8:871–879. [PubMed: 26243796]
5. The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomised trial. Lancet. 1999; 353:9–13. [PubMed: 10023943]
6. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999; 353:2001–2007. [PubMed: 10376614]
7. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344:1651–1658. [PubMed: 11386263]
8. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002; 106:2194–2199. [PubMed: 12390947]
9. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol. 2008; 101:865–869. [PubMed: 18328855]
10. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: Beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med. 2009; 150:784–794. [PubMed: 19487713]
11. Cullington D, Goode KM, Clark AL, Cleland JG. Heart rate achieved or beta-blocker dose in patients with chronic heart failure: Which is the better target? Eur J Heart Fail. 2012; 14:737–747. [PubMed: 22622001]
12. Kalaria VG, Passannante MR, Shah T, Modi K, Weisse AB. Effect of mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. Am Heart J. 1998; 135:215–220. [PubMed: 9489967]
13. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. J Am Coll Cardiol. 1999; 33:1424–1426. [PubMed: 10193748]

14. Pullicino P, Thompson JL, Barton B, Levin B, Graham S, Freudenberger RS. Warfarin versus aspirin in patients with reduced cardiac ejection fraction (WARCEF): Rationale, objectives, and design. J Card Fail. 2006; 12:39–46. [PubMed: 16500579]
15. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012; 366:1859–1869. [PubMed: 22551105]
16. Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a french population: Role of age, gender, and blood pressure. Hypertension. 1999; 33:44–52. [PubMed: 9931080]
17. Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, Hendrix SL, Robinson JG, LaCroix AZ, Manson JE. Resting heart rate as a low tech predictor of coronary events in women: Prospective cohort study. BMJ. 2009; 338:b219. [PubMed: 19193613]
18. Mao Q, Huang JF, Lu X, Wu X, Chen J, Cao J, Li J, Gu D. Heart rate influence on incidence of cardiovascular disease among adults in China. Int J Epidemiol. 2010; 39:1638–1646. [PubMed: 20719745]
19. Julius S, Palatini P, Kjeldsen SE, Zanchetti A, Weber MA, McInnes GT, Brunner HR, Mancia G, Schork MA, Hua TA, Holzhauer B, Zappe D, Majahalme S, Jamerson K, Koylan N. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. Am J Cardiol. 2012; 109:685–692. [PubMed: 22169130]
20. Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, Yusuf S, Bohm M. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: An analysis of ONTARGET/TRANSCEND. Clin Res Cardiol. 2014; 103:149–159. [PubMed: 24356937]
21. O'Neal WT, Qureshi WT, Judd SE, Meschia JF, Howard VJ, Howard G, Soliman EZ. Heart rate and ischemic stroke: The reasons for geographic and racial differences in stroke (REGARDS) study. Int J Stroke. 2015; 10:1229–1235. [PubMed: 26306564]
22. Bohm M, Schumacher H, Linz D, Reil JC, Ukena C, Lonn E, Teo K, Sliwa K, Schmieder RE, Sleight P, Yusuf S. Low resting heart rates are associated with new-onset atrial fibrillation in patients with vascular disease: Results of the ONTARGET/TRANSCEND studies. J Intern Med. 2015; 278:303–312. [PubMed: 25872921]
23. O'Neal WT, Almahmoud MF, Soliman EZ. Resting heart rate and incident atrial fibrillation in the elderly. Pacing Clin Electrophysiol. 2015; 38:591–597. [PubMed: 25690400]
24. Morseth B, Graff-Iversen S, Jacobsen BK, Jorgensen L, Nyrnes A, Thelle DS, Vestergaard P, Lochen ML. Physical activity, resting heart rate, and atrial fibrillation: The Tromsø study. Eur Heart J. 2016; 37:2307–2313. [PubMed: 26966149]
25. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the conduit artery function evaluation (CAFE) study. Circulation. 2006; 113:1213–1225. [PubMed: 16476843]
26. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension : Prognostic information provided by pulse pressure. Hypertension. 1999; 34:375–380. [PubMed: 10489379]
27. Fyhrquist F, Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Hille DA, Lyle PA, Edelman JM, Snapinn SM, Wedel H. Pulse pressure and effects of losartan or atenolol in patients with hypertension and left ventricular hypertrophy. Hypertension. 2005; 45:580–585. [PubMed: 15790960]
28. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. Pharmacol Res. 2006; 53:399–406. [PubMed: 16638640]
29. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet. 2010; 376:875–885. [PubMed: 20801500]

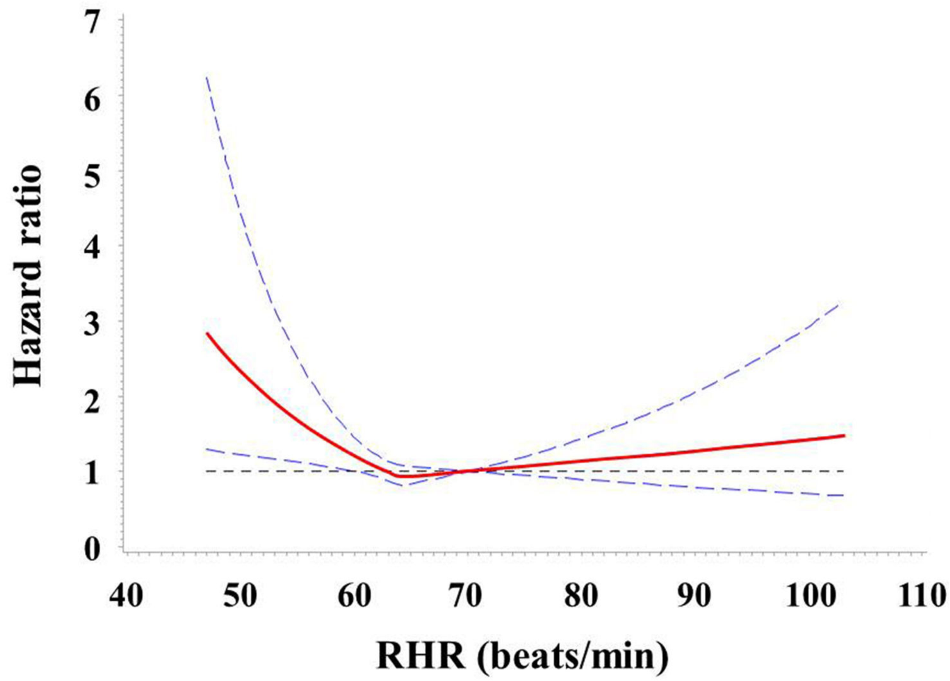

Figure 1.

Risk of ischemic stroke by RHR. Each hazard ratio was computed with the median heart rate value of 70 beats/min as the reference (red solid line). Blue dashed-lines represent the 95% confidence interval and black dashed-line represents hazard ratio 1.0. RHR = resting heart rate.

Table 1

Baseline characteristics stratified by RHR.

	RHR<64 beats/min (N=503)	64–70 beats/min (N=573)	71–79 beats/min (N=465)	RHR>79 beats/min (N=519)	p value
Age, years	62.8±11.4	62.4±10.9	59.4±11.1	56.9±10.7	<0.001
Male gender, n (%)	415/503 (82.5)	439/573 (76.6)	373/465 (80.2)	433/519 (83.4)	0.021
Hypertension, n/total n (%)	283/488 (58.0)	346/558 (62.0)	311/454 (68.5)	299/505 (59.2)	0.004
Diabetes mellitus, n/total n (%)	139/503 (27.6)	179/572 (31.3)	167/464 (36.0)	172/518 (33.2)	0.040
Current smoking, n/total n (%)	64/503 (12.7)	85/573 (14.8)	94/465 (20.2)	120/518 (23.2)	<0.001
Current alcohol consumption>2oz/day, n/total n (%)	154/503 (30.6)	147/573 (25.7)	103/465 (22.2)	108/518 (20.8)	0.002
History of MI, n/total n (%)	293/503 (58.3)	286/572 (50.0)	217/464 (46.8)	207/518 (40.0)	<0.001
History of AF, n/total n (%)	25/503 (5.0)	23/572 (4.0)	17/464 (3.7)	11/519 (2.1)	0.107
Prior stroke or TIA, n/total n (%)	65/503 (12.9)	79/573 (13.8)	52/464 (11.2)	56/518 (10.8)	0.401
Education level, n/total n (%)					0.649
<High school	216/503 (42.9)	251/572 (43.9)	206/464 (44.4)	214/517 (41.4)	
High school graduate or some college	200/503 (39.8)	241/572 (42.1)	195/464 (42.0)	221/517 (42.7)	
College graduate or post graduate	87/503 (17.3)	80/572 (14.0)	63/464 (13.6)	82/517 (15.9)	
NYHA class					0.001
I, n/total n (%)	78/500 (15.6)	61/573 (10.6)	62/464 (13.4)	66/516 (12.8)	
II, n/total n (%)	294/500 (58.8)	325/573 (56.7)	251/464 (54.1)	267/516 (51.7)	
III, n/total n (%)	128/500 (25.6)	180/573 (31.4)	146/464 (31.5)	168/516 (32.6)	
IV, n/total n (%)	0/0 (0.0)	7/573 (1.2)	5/464 (1.1)	15/516 (2.9)	
Systolic BP, mmHg	122.2±19.2	124.4±18.0	125.3±19.2	123.6±19.1	0.064
Diastolic BP, mmHg	71.1±10.9	74.0±10.9	74.9±11.0	76.7±12.1	<0.001
Pulse pressure, mmHg	51.1±15.1	50.5±13.8	50.3±14.4	46.8±13.7	<0.001
Medication					
ACEI or ARB, n/total n (%)	497/503 (98.8)	563/572 (98.4)	458/465 (98.5)	513/519 (98.8)	0.912
Calcium channel blocker, n/total n (%)	41/502 (8.2)	50/571 (8.8)	46/465 (9.9)	35/519 (6.7)	0.343
Diuretics, n/total n (%)	380/503 (75.5)	465/573 (81.2)	386/465 (83.0)	452/519 (87.1)	<0.001
Statin, n/total n (%)	344/395 (87.1)	353/420 (84.0)	289/351 (82.3)	279/351 (79.5)	0.043
ICD, n/total n (%)	103/503 (20.5)	110/572 (19.2)	88/464 (19.0)	89/519 (17.1)	0.596
LV ejection fraction, %	25.6±7.5	25.1±7.2	24.6±7.4	23.5±7.6	<0.001

ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin receptor blocker, BP = blood pressure, ICD = implantable cardioverter defibrillator, LV = left ventricle, MI = myocardial infarction, NYHA = New York Heart Association, RHR= resting heart rate, and TIA = transient ischemic attack.

Table 2

Univariable and multivariable linear regression analysis for the determinants of RHR.

	For a change of	Univariable		Multivariable	
		β-coefficient (95 CI)	p value	β-coefficient (95 CI)	p value
Age, years	1 unit increase	−0.222 (−0.266,−0.177)	<0.001	−0.132 (−0.179,−0.085)	<0.001
Male gender		0.121 (−1.175,1.418)	0.855		
Hypertension		0.179 (−0.882,1.240)	0.740		
Diabetes mellitus		1.220 (0.120,2.319)	0.030	2.188 (1.116,3.259)	<0.001
Current smoking		3.148 (1.808,4.487)	<0.001	2.614 (1.321,3.907)	<0.001
Current alcohol consumption>2oz/day		−2.723 (−3.904,−1.542)	<0.001	−2.037 (−3.165,−0.908)	<0.001
History of MI		−3.326 (−4.342,−2.310)	<0.001	−2.085 (−3.105,−1.064)	<0.001
History of AF		−3.424 (−6.141,−0.707)	0.014	−3.448 (−6.004,−0.892)	0.008
Prior stroke or TIA		−1.098 (−2.662,0.467)	0.169		
Education level	Ref:<High school		0.522		
High school graduate or some college		0.255 (−0.858,1.368)			
College graduate or post graduate		−0.640 (−2.171,0.891)			
NYHA class III or IV		2.363 (1.264,3.463)	<0.001	1.609 (0.553,2.665)	0.003
Systolic BP, mmHg	1 unit increase	0.012 (−0.015,0.039)	0.380		
Diastolic BP, mmHg	1 unit increase	0.190 (0.146,0.234)	<0.001	0.169 (0.126,0.212)	<0.001
Pulse pressure, mmHg	1 unit increase	−0.100 (−0.136,−0.065)	<0.001	−0.061 (−0.097,−0.025)	0.001
ACEI or ARB		1.009 (−3.420,5.438)	0.655		
Calcium channel blocker		−0.750 (−2.603,1.104)	0.428		
Diuretics		3.268 (1.950,4.587)	<0.001	2.037 (0.757,3.318)	0.002
Statin		−1.986 (−3.549,−0.423)	0.013	−0.785 (−2.296,0.727)	0.309
ICD		−1.250 (−2.558,0.058)	0.061		
LV ejection fraction, %	1 unit increase	−0.194 (−0.262,−0.126)	<0.001	−0.134 (−0.200,−0.068)	<0.001

ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin receptor blocker, BP = blood pressure, CI = confidence interval, ICD = implantable cardioverter defibrillator, LV = left ventricle, MI = myocardial infarction, NYHA = New York Heart Association, RHR= resting heart rate, and TIA = transient ischemic attack.

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Table 3

Univariate and multivariate Cox proportional-hazards regression analysis for ischemic stroke.

	For a change of	Univariable		Multivariable model 1		Multivariable model 2	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
RHR, beats/min	Linear Spline		0.034		0.044		0.038
	1 unit decrease when RHR< 64	1.07 (1.02, 1.12)	0.009	1.07 (1.01, 1.12)	0.013	1.07 (1.02, 1.13)	0.011
	1 unit decrease when RHR≥ 64	0.99 (0.96, 1.01)	0.325	0.99 (0.97, 1.01)	0.355	0.99 (0.96, 1.01)	0.271
Age, years	1 unit increase	1.01 (0.99, 1.03)	0.374			1.01 (0.98, 1.03)	0.605
Male gender		0.88 (0.52, 1.52)	0.655				
Hypertension		0.95 (0.60, 1.50)	0.829				
Diabetes mellitus		1.27 (0.80, 2.03)	0.306			1.16 (0.71, 1.91)	0.555
Current smoking		1.03 (0.58, 1.83)	0.928			0.99 (0.55, 1.81)	0.986
Current alcohol consumption		0.80 (0.46, 1.38)	0.415			0.81 (0.46, 1.44)	0.479
History of MI		1.37 (0.88, 2.16)	0.166			1.29 (0.79, 2.08)	0.309
History of AF		1.10 (0.35, 3.48)	0.876			1.21 (0.38, 3.91)	0.744
Prior stroke or TIA		3.22 (1.98, 5.25)	<0.001	3.42 (2.09, 5.59)	<0.001	3.36 (2.04, 5.54)	<0.001
Education level	Ref: <High school		0.891				
High school graduate or some college		1.05 (0.64, 1.73)					
College graduate or post graduate		1.17 (0.62, 2.20)					
NYHA class III or IV		1.03 (0.63, 1.66)	0.913			0.90 (0.55, 1.48)	0.673
Systolic BP, mmHg	1 unit increase	1.00 (0.99, 1.01)	0.880				
Diastolic BP, mmHg	1 unit increase	1.00 (0.98, 1.02)	0.772			1.00 (0.98, 1.02)	0.853
Pulse pressure, mmHg	1 unit increase	1.00 (0.98, 1.02)	0.970			1.00 (0.98, 1.01)	0.727
ACEI or ARB		1.17 (0.16, 8.38)	0.879				
Calcium channel blocker		0.42 (0.13, 1.34)	0.143				
Diuretics		1.04 (0.58, 1.86)	0.889			1.06 (0.58, 1.93)	0.848
Statin		0.94 (0.43, 2.06)	0.870			0.88 (0.39, 1.98)	0.761
ICD		0.59 (0.30, 1.19)	0.140				
LV ejection fraction, %	Quadratic		<0.001		<0.001		<0.001
	75^{th} vs. 25^{th} percentiles	0.85 (0.66, 1.11)		0.82 (0.63, 1.07)		0.83 (0.63, 1.09)	

ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin receptor blocker, BP = blood pressure, CI = confidence interval, HR = hazard ratio, ICD = implantable cardioverter defibrillator, LV = left ventricle, MI = myocardial infarction, NYHA = New York Heart Association, RHR= resting heart rate, and TIA = transient ischemic attack.

Table 4

Unadjusted and adjusted Cox proportional-hazards regression analysis for ischemic stroke in warfarin and aspirin subgroup.

	For a change of	Univariable		Multivariable model 1		Multivariable model 2	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
RHR (warfarin group), beats/min	Linear Spline		0.402		0.408		0.304
	1 unit decrease when RHR< 64	1.04 (0.93, 1.15)	0.484	1.04 (0.93, 1.15)	0.529	1.04 (0.93, 1.16)	0.520
	1 unit decrease when RHR≥ 64	0.97 (0.93, 1.01)	0.180	0.97 (0.93, 1.01)	0.181	0.97 (0.93, 1.01)	0.123
RHR (aspirin group), beats/min	Linear Spline		0.032		0.039		0.037
	1 unit decrease when RHR< 64	1.08 (1.01, 1.14)	0.017	1.07 (1.01, 1.13)	0.023	1.08 (1.01, 1.14)	0.018
	1 unit decrease when RHR≥ 64	1.00 (0.97, 1.03)	0.872	1.00 (0.97, 1.03)	0.992	1.00 (0.97, 1.03)	0.865
Warfarin by RHR interaction			0.340		0.318		0.259
Age, years	1 unit increase					1.01 (0.99, 1.03)	0.469
Diabetes				1.16 (0.70, 1.91)	0.559		
Current smoking				1.01 (0.56, 1.84)	0.968		
Current alcohol consumption				0.79 (0.45, 1.40)	0.424		
History of MI				1.28 (0.79, 2.07)	0.317		
History of AF				1.35 (0.42, 4.36)	0.611		
Prior stroke or TIA		3.52 (2.15, 5.77)	<0.001	3.50 (2.12, 5.80)	<0.001		
NYHA class III or IV				0.91 (0.55, 1.50)	0.716		
Diastolic BP, mmHg	1 unit increase			1.00 (0.98, 1.02)	0.694		
Pulse pressure, mmHg	1 unit increase			1.00 (0.98, 1.01)	0.650		
Diuretics				1.08 (0.59, 1.97)	0.800		
Statin				0.88 (0.39, 1.99)	0.759		
LV ejection fraction, %	Quadratic		<0.001		<0.001		
	75^{th} vs. 25^{th} percentiles	0.82 (0.63, 1.07)		0.83 (0.63, 1.09)			

AF = atrial fibrillation, BP = blood pressure, CI = confidence interval, HR = hazard ratio, LV = left ventricle, MI = myocardial infarction, NYHA = New York Heart Association, RHR= resting heart rate, and TIA = transient ischemic attack.