Resting Heart Rate and Ischemic Stroke in Patients with Heart Failure

Koki Nakanishi^a Marco R. Di Tullio^a Min Qian^b John L.P. Thompson^b
Arthur J. Labovitz^d Douglas L. Mann^e Ralph L. Sacco^f Patrick M. Pullicinoⁿ
Ronald S. Freudenberger^g John R. Teerlink^h Susan Grahamⁱ
Gregory Y.H. Lip^o Bruce Levin^b Jay P. Mohr^c Richard Buchsbaum^b
Conrado J. Estol^j Dirk J. Lok^k Piotr Ponikowski^l Stefan D. Anker^m
Shunichi Homma^a WARCEF Investigators

^aDepartment of Medicine, Division of Cardiology, Columbia University Medical Center, ^bDepartment of Biostatistics, Mailman School of Public Health, Columbia University Medical Center, ^cDepartment of Neurology, Columbia University Medical Center, New York, NY, ^dUniversity of South Florida, Tampa, FL, ^eWashington University, St. Louis, MO, ^fUniversity of Miami, Miami, FL, ^gLehigh Valley Hospital, Allentown, PA, ^hSection of Cardiology, San Francisco Veterans Affairs Medical Center and University of California San Francisco, San Francisco, CA, and ⁱSUNY Upstate Medical University, Syracuse, NY, USA; ^jCentro Neurológico de Tratamiento y Rehabilitación, Buenos Aires, Argentina; ^kDeventer Hospital, Deventer, The Netherlands; ^lMilitary Hospital, Wroclaw, Poland; ^mDepartment of Innovative Clinical Trials, University Medicine Göttingen (UMG), Göttingen, Germany; ⁿUniversity of Kent, Canterbury, Kent, and ^oUniversity of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK

Keywords

Beta-blocker · Heart failure · Ischemic stroke · Resting heart rate · Sinus rhythm · Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial

Abstract

Background: Although high resting heart rate (RHR) is known to be associated with an increased risk of mortality and hospital admission in patients with heart failure, the relationship between RHR and ischemic stroke remains unclear. This study is aimed at investigating the relationship between RHR and ischemic stroke in patients with heart failure in sinus rhythm. **Methods:** We examined 2,060 patients

with systolic heart failure in sinus rhythm from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial. RHR was determined from baseline electrocardiogram, and was examined as both a continuous variable and 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 ($p = 0.693$). Multi-variable Cox proportional hazards analysis revealed that RHR

was significantly associated with ischemic stroke (hazard ratio per unit decrease: 1.07, 95% CI 1.02–1.13, when RHR <64/ beats/min; $p = 0.038$), along with a 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.

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Introduction

Approximately 5.7 million adults are living with heart failure in the 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 a 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 $\leq 35\%$ 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 only these patients. A total of 243 patients who were not treated with beta-blockers were excluded from the study. 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

The 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 pressures (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 h.

Statistical Analysis

Categorical variables are presented as number/total number (%) and compared by quartiles of RHR using chi-square test or Fisher exact test. Continuous variables are presented as mean $\pm$ SD 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 model values for categorical variables. Differences were considered significant at $p < 0.05$ 2-sided. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

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.

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 >2 oz/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, n/total n (%)					0.001
I	78/500 (15.6)	61/573 (10.6)	62/464 (13.4)	66/516 (12.8)	
II	294/500 (58.8)	325/573 (56.7)	251/464 (54.1)	267/516 (51.7)	
III	128/500 (25.6)	180/573 (31.4)	146/464 (31.5)	168/516 (32.6)	
IV	0/0 (0.0)	7/573 (1.2)	5/464 (1.1)	15/516 (2.9)	
Systolic BP, mm Hg	122.2±19.2	124.4±18.0	125.3±19.2	123.6±19.1	0.064
Diastolic BP, mm Hg	71.1±10.9	74.0±10.9	74.9±11.0	76.7±12.1	<0.001
Pulse pressure, mm Hg	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; TIA, transient ischemic attack.

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 >2 oz/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 a linear spline with knot at RHR = 64 beats/min was selected as the best model based on AIC. The hazard ratio (HR) 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

Table 2. Univariable and multivariable linear regression analysis for the determinants of RHR

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

Fig. 1. Risk of ischemic stroke by RHR. Each HR was computed with the median heart rate value of 70 beats/min as the reference (red solid line). Blue dashed-lines represent 95% CI and black dashed-line represents HR 1.0. RHR, resting heart rate; HR, hazard ratio.

values <64 beats/min (adjusted HR 1.07, $p = 0.013$), while it was unaffected above that value (adjusted HR 0.99, $p = 0.355$). Ischemic stroke was also significantly associated with the 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 the 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 variables with significant association with RHR (Table 4, model 2).

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)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> 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
Gender, male		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, mm Hg	1 unit increase	1.00 (0.99–1.01)	0.880				
Diastolic BP, mm Hg	1 unit increase	1.00 (0.98–1.02)	0.772			1.00 (0.98–1.02)	0.853
Pulse pressure, mm Hg	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				
	75th vs. 25th percentiles	0.85 (0.66–1.11)		0.82 (0.63–1.07)	<0.001	0.83 (0.63–1.09)	<0.001

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

In patients with RHR <64 beats/min, significantly lower ischemic stroke rate was observed in the warfarin group compared to 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 the 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

Table 4. Unadjusted and adjusted Cox proportional hazards regression analysis for ischemic stroke in warfarin and aspirin subgroups

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, mm Hg	1 unit increase					1.00 (0.98–1.02)	0.694
Pulse pressure, mm Hg	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						
	75th vs. 25th percentiles			0.82 (0.63–1.07)	<0.001	0.83 (0.63–1.09)	<0.001

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

with a 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. [18] showed that high RHR increased the risk of stroke in 169,871 general Chinese adults ≥40 years. Similarly, data from patients with stable coronary artery disease and hypertension demonstrated that high RHR was associated with an increased risk of stroke [19, 20]. More recently, the Reasons for Geographic and Racial Differences in Stroke 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 RHR and stroke [16, 17].

The underlying mechanisms of our finding are unclear, but several potential explanations can be hypothe-

sized. Recent studies have reported that low RHR is associated with higher incidence of AF development in various populations [22–24]. Bohm et al. [22] 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. O'Neal et al. [23] 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. 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 waves, thereby elevating the central aortic pressure. In the Conduit Artery Functional Evaluation study [25], significantly higher central aortic systolic BP was observed with beta-blocker treatment compared with calcium channel blocker treatment despite similar effect on peripheral BP, resulting in a higher incidence of stroke in patients with

hypertension. Finally, an increase in pulse pressure may also contribute to the development of stroke in HFrEF patients with low RHR. Because the 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, and also suggests a potential thromboembolic component for the stroke mechanism. Furthermore, it may indicate that warfarin treatment may be preferable to aspirin treatment 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 the heart rate without affecting the other aspects of cardiac function [28]. In Systolic Heart failure treatment with the β -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, 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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