European Heart Journal (2012) **33**, 2761–2763
doi:10.1093/eurheartj/ehs260

High resting heart rate predicts mortality, disability, and cognitive decline in patients after ischaemic stroke: time for additional selective $I_{(f)}$ channel inhibitor trials?

Sverre E. Kjeldsen[1]* and Peter M. Okin[2]

[1]Department of Cardiology, University of Oslo at Ullevaal Hospital, N-0407 Oslo, Norway; and [2]Department of Cardiology,Weill Cornell Medical College, New York, NY, USA

Online publish-ahead-of-print 26 August 2012

This editorial refers to 'Impact of resting heart rate on mortality, disability, and cognitive decline in patients after ischaemic stroke'†, by M. Böhm *et al.*, on page 2804

Michael Böhm and co-workers[1] have reported on the relationship of cardiovascular and neurological outcomes to baseline heart rate after ischaemic stroke in 20 165 patients (mean age 66.1, SD 8.6 years) with baseline heart rate data assigned to the treatment arms of the PRoFESS trial. Patients were grouped by quintiles of baseline heart rate and were evaluated for a primary outcome of recurrent stroke, a secondary outcome of the composite of recurrent stroke, myocardial infarction, or death from a vascular cause, and were further assessed for new or worsening heart failure and non-vascular death. Additional pre-defined endpoints were disability after recurrent stroke, assessed with the modified Rankin scale (mRS) and Barthel index at 3 months, and cognitive function, assessed with the Mini-Mental State Examination (MMSE) score at 4 weeks after randomization and at the penultimate visit.

Although there was no significant relationship of recurrent stroke, new myocardial infarction, or the composite secondary endpoint to baseline heart rate, these findings further support the strong relationship of heart rate to mortality. Patients in the two highest quintiles of heart rate (77–82 and >82 b.p.m.) were at higher risk for total death [hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.19–1.69; and HR 1.74, 95% CI 1.48–2.06, $P < 0.0001$] compared with patients in the lowest quintile. Risk of vascular death (starting at heart rates from 71 to ≤76 b.p.m., HR 1.39, 95% CI 1.11–1.74, $P < 0.0001$) and non-vascular death (from >82 b.p.m., HR 1.66, 95% CI 1.29–2.13, $P = 0.0016$) was also strongly associated with higher baseline heart rate. Importantly, increased mortality risk persisted after adjusting for multiple confounders including baseline blood pressure. Perhaps most interesting, in the group of patients with recurrent stroke, lower baseline heart rate was associated with better neurological outcomes as measured with the Barthel index and mRS score, and with less cognitive decline according to an MMSE score ≤ 24 points at 1 month and at the penultimate visit or a decline of ≥ 2 points between these two time periods. Thus, a high baseline heart rate is a risk indicator for mortality in patients with stroke and, importantly, low heart rate is associated with better functional outcome and less cognitive decline after ischaemic stroke.

The evidence that heart rate predicts hypertension and cardiovascular disease is strong; to date, most of the data supporting this relationship have come from epidemiological observations or cross-sectional studies with single measurements of heart rate at the beginning of the study.[2–8] However, two large randomized clinical trials in hypertension with repeated measurements of heart rate recently added substantial evidence to the heart rate story in hypertension.[9–12]

The relationship of in-treatment heart rate over time based on annual electrocardiograms (ECGs) to incident heart failure was evaluated in 9024 hypertensive patients without heart failure at baseline who were treated with losartan- or atenolol-based regimens in the LIFE study.[9] During 4.7 ± 1.1 years mean follow-up, heart failure developed in 285 patients (3.2%). In multivariate Cox analyses that adjusted for randomized treatment, baseline risk factors for heart failure, baseline and in-treatment blood pressure, QRS duration, and ECG left ventricular hypertrophy, higher in-treatment heart rate predicted a 45% higher adjusted risk of new heart failure for every 10 b.p.m. higher heart rate (95% CI 34–57%) or 159% higher risk of heart failure in patients with persistence or

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +47 22119100, Fax: + 47 22119181, Email: s.e.kjeldsen@medisin.uio.no

† doi:10.1093/eurheartj/ehs250.

development of a heart rate ≥ 84 b.p.m. (95% CI 88–257%). With adjustment for the same covariates, baseline heart rate as a continuous variable was a significantly less powerful predictor of new heart failure (HR 1.15 per 10 b.p.m., 95% CI 1.03–1.28), and a baseline heart rate ≥ 84 b.p.m. did not predict new heart failure (HR 1.00, 95% CI 0.63–1.58). Thus, higher in-treatment heart rate on serial ECGs predicts greater risk of incident heart failure during antihypertensive treatment, independent of covariates, in hypertensive patients with ECG left ventricular hypertrophy. These data add to previous observations from LIFE that a higher in-treatment heart rate over time is associated with increased risk of cardiovascular and all-cause mortality and incident atrial fibrillation in patients with hypertension and left ventricular hypertrophy.[10,11]

The predictive value of heart rate in patients with high risk hypertension was further evaluated in a pre-planned secondary analysis of data from the VALUE Trial.[12] Participants were 15 193 hypertensive patients randomized in the trial and followed for 5 years. Heart rate was assessed from ECG recordings obtained annually throughout the study. The primary endpoint was time to cardiac events. After adjustment for confounders, the HR of the composite cardiac primary endpoint for a 10 b.p.m. increase from baseline heart rate was 1.16 (95% CI 1.12–1.20). Compared with the lowest heart rate quintile, the adjusted HR in the highest quintile was 1.73 (95% CI 1.46–2.04). Compared with the pooled lower quintiles of baseline heart rate, the annual incidence of the primary endpoint in the top baseline quintile was higher in each of the 5 years of the study (all $P < 0.05$). The adjusted HR for the primary endpoint in the highest in-trial heart rate quintile vs. the lowest quintile was 1.53 (95% CI 1.26–1.85). The incidence of primary endpoints in the highest in-trial heart rate group compared with the pooled four lower quintiles was 53% greater in patients with well controlled blood pressure ($P < 0.001$) and 34% greater in those with uncontrolled blood pressure ($P = 0.002$). These data provide evidence that increased heart rate is a long-term predictor of cardiovascular events in patients with high risk hypertension and that this effect is not modified by good blood pressure control.

The study by Böhm *et al.* has several limitations that warrant mention. First, as the authors note,[1] they were unable to evaluate the predictive value of serial measures of heart rate over time during the study. This may in part explain the lack of association with heart failure[1] given the less powerful association of baseline heart rate with incident heart failure among hypertensive patients in the LIFE study.[9] In addition, patients could be enrolled in PRoFESS during up to 120 days after their qualifying stroke, with some patients being enrolled while still in the hospital from their stroke. Given that heart rate may vary significantly over this time period and that there was no attempt to control statistically for time from stroke to initial heart rate determination, this may have impacted on the prognostic value of heart rate in an unpredictable fashion. Finally, increased heart rate is strongly associated with incident atrial fibrillation,[11] which may have an independent impact on cardiovascular outcomes. However, incident atrial fibrillation was not determined or controlled for in the study of Böhm *et al.*[1]

Similarly to the PRoFESS data,[1] the prognostic impact of high heart rate is strong and independent of co-variables including high blood pressure. The exciting news with the current PRoFESS data, however, is that that the prognostic impact of a high heart rate is brought forward into a population of stroke survivors. While the prognostic influence on cardiovascular disease and mortality was not unexpected, the prognostic relationship of heart rate to disability and early cognitive decline after recurrent stroke is a major new finding.[1] With the ageing of the population, the number of people surviving strokes who will suffer subsequent cognitive decline is increasing and, to date, there has been little in the way of meaningful findings with respect to either prognostic markers or treatment. The significant relationship of neurological function after recurrent stroke to heart rate suggests a relationship with the cardiovascular system; raised heart rate could be a marker of underlying cardiovascular disease or high blood pressure that is not yet detected in stroke survivors (e.g. ambulatory hypertension or high out-of-office blood pressure). High heart rate could, on the other hand, be a marker of sympathetic overactivity and/or untoward parasympathetic withdrawal,[7] or a marker for subclinical left ventricular dysfunction.[9]

It is not yet known whether therapeutic reduction of heart rate can improve cardiovascular prognosis. The randomized, double-blind placebo-controlled BEAUTIFUL trial showed that reducing heart rate with the selective $I_{(f)}$ channel inhibitor, ivabradine, did not reduce hospitalization for new or worsening heart failure in patients with stable coronary disease and left ventricular dysfunction at higher risk due to a baseline heart rate ≥70 b.p.m.[13] However, in the randomized, placebo-controlled SHIFT trial, ivabradine significantly reduced the composite endpoint of cardiovascular death and hospitalization for worsening heart failure in patients with chronic heart failure at baseline.[14,15] In light of the recent finding of the prognostic importance of increased baseline heart rate in stroke survivors,[1] and the benefit of ivabradine in heart failure patients,[14,15] randomized, controlled trials of this compound in stroke survivors as well as in hypertensive people[9–12] with controlled blood pressure and residual heart rate elevation may be warranted.

Conflicts of interest: S.E.K. and P.M.O. were in the leadership of the LIFE and VALUE studies, supported by Merck and Novartis.

References

1. Böhn M, Cotton D, Foster L, Custodis F, Laufs U, Sacco R, Bath PMW, Yusuf S, Diener H-C. Impact of resting heart rate on mortality, disability, cognitive decline in patients after ischaemic stroke. *Eur Heart J* 2012;**33**:2804–2812.
2. Levy RL, White PD, Stroud WD, Hillman CCI. Transient tachycardia: prognostic significance alone and in association with transient hypertension. *JAMA* 1945;**129**:585–588.
3. Dyer A, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiological studies. *Am J Epidemiol* 1980;**112**:736–749.
4. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: The Framingham Study. *Am Heart J* 1987;**113**:1489–1494.
5. Gillum RF, Makuc DM, Feldman JJ. Pulse rate coronary heart disease, death: the NHANES I epidemiologic follow-up study. *Am Heart J* 1991;**121**:172–177.
6. 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.
7. Julius S, Jamerson K, Mejia A, Krause L, Schork N, Jones K. The association of borderline hypertension with target organ changes higher coronary risk. Tecumseh Blood Pressure Study. *JAMA* 1990;**264**:354–358.
8. Selby JV, Friedman GD, Quesensberry P. Precursor of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol and other serum chemistries. *Am J Epidemiol* 1990;**131**:1017–1027.

9. Okin PM, Kjeldsen SE, Julius S, Hille DA, Dahlöf B, Devereux RB. Effect of changing heart rate during treatment of hypertension on incidence of heart failure. *Am J Cardiol* 2012;**109**:699–704.
10. Okin PM, Kjeldsen SE, Julius S, Hille DA, Dahlöf B, Edelman JM, Devereux RB. All-cause, cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. *Eur Heart J* 2010;**31**:2271–2279.
11. Okin PM, Wachtell K, Kjeldsen SE, Julius S, Lindholm LH, Dahlöf B, Devereux RB. Incidence of atrial fibrillation in relation to changing heart rate over time in hypertensive patients: the LIFE study. *Circ Arrhythmia Electrophysiol* 2008;**1**:337–343.
12. 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. Heart rate predicts cardiac events in treated high risk hypertension. *Am J Cardiol* 2012;**109**:685–692.
13. Fox K, Ford I, Tendera M, Ferrari R, on behalf of the BEAUTIFUL investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:807–816.
14. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubrost-Brama A, Lerebours G, Tavazzi L, on behalf of the SHIFT Investigators. 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.
15. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubrost-Brama A, Lerebours G, Tavazzi L, on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.

CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehs088
Online publish-ahead-of-print 3 May 2012

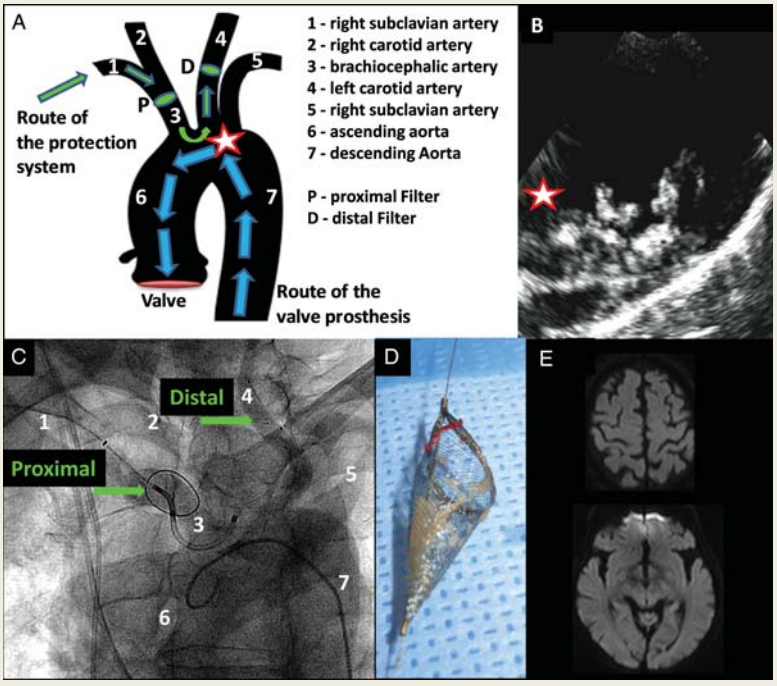
Catch me, if you can!

Alexander Ghanem[1]*, Eberhard Grube[1], Andreas Müller[2], Georg Nickenig[1], and Jan-Malte Sinning[1]

[1]Department of Medicine/Cardiology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany and [2]Department of Radiology, University of Bonn, Bonn, Germany

* Corresponding author. Tel: +49 228 28715507, Fax: +49 228 28711631, Email: ghanem@uni-bonn.de

A 78-year-old gentleman with symptomatic aortic valve stenosis (EuroSCORE: 26.9%) was referred for transcatheter aortic valve implantation (TAVI). Open heart surgery was denied due to a floating thrombus in the aortic arch near the origin of the left common carotid artery, considered as a source of two left-sided ischaemic strokes 3 months prior to TAVI (*Panels A* and *B*; see Supplementary material online, *Video S1*). The patient underwent transfemoral TAVI with the peri-procedural use of a cerebral protection device (CE Pro™ Claret Medical Inc., Santa Rosa, CA, USA), deployed via the right brachial artery. The filters were deployed within the brachiocephalic and left carotid artery, respectively (*Panel C*). As the system was retrieved after successful TAVI, a significant amount of debris was found within the filters (*Panel D*). In post-procedural transoesophageal echocardiography, the thrombus was not detectable (see Supplementary material online, *Video S2*). Diffusion-weighted magnetic resonance imaging ruled out silent cerebral embolism (*Panel E*). The use of a dedicated cerebral protection device might reduce peri-interventional embolic burden in patients undergoing TAVI.



Supplementary material is available at *European Heart Journal* online.