ESC European Society of Cardiology

European Heart Journal (2018) **0**, 1–9
doi:10.1093/eurheartj/ehy808

Resting heart rate and cardiovascular outcomes in diabetic and non-diabetic individuals at high cardiovascular risk analysis from the ONTARGET/TRANSCEND trials

Michael Böhm[1]*, Helmut Schumacher[2], Koon K. Teo[3], Eva M. Lonn[3], Felix Mahfoud[1], Christian Ukena[1], Johannes F.E. Mann[4,5], Giuseppe Mancia[6], Josep Redon[7], Roland E. Schmieder[5], Karen Sliwa[8], Nikolaus Marx[9], Michael A. Weber[10], Bryan Williams[11], and Salim Yusuf[3]

[1]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Kirrberger Str. 1, 66421 Homburg/Saar, Germany; [2]Statistical Consultant, 55218 Ingelheim, Germany; [3]Population Health Research Institute, McMaster University, Hamilton, Ontario L8L 2X2, Canada; [4]KfH Kidney Centre, Menzinger Str. 44, 80638 München, Germany; [5]Department of Nephrology and Hypertension, University Hospital, Friedrich-Alexander University, Schlossplatz 4, 91054 Erlangen/Nuremberg, Germany; [6]University of Milano-Bicocca, Istituto Clinico Universitario Policlinico di Monza, Piazza dell'Ateneo Nuovo, 1, 20126 Milano, Italy; [7]Hypertension Unit, Hospital Clínico Universitario, University of Valencia, Av. de Blasco Ibáñez, 13, 46010 València, Spain; [8]Faculty of Health Sciences, Hatter Institute for Cardiovascular Research in Africa & IIDMM, University of Cape Town, Anzio Road, Observatory, Cape Town, 7925, South Africa; [9]Department of Internal Medicine, University Hospital RWTH Aachen, Pauwelsstraße 30, 52074 Aachen; [10]Downstate College of Medicine, State University of New York, 450 Clarkson Ave, Brooklyn, NY 11203, USA; and [11]University College London (UCL), Institute of Cardiovascular Science, National Institute for Health Research (NIHR), UCL Hospitals Biomedical Research Centre, 149 Tottenham Court Road, London W1T 7D, UK

Received 9 May 2018; revised 26 June 2018; editorial decision 5 October 2018; accepted 13 November 2018

Aims Resting heart rate (RHR) has been shown to be associated with cardiovascular outcomes in various conditions. It is unknown whether different levels of RHR and different associations with cardiovascular outcomes occur in patients with or without diabetes, because the impact of autonomic neuropathy on vascular vulnerability might be stronger in diabetes.

Methods and results We examined 30 937 patients aged 55 years or older with a history of or at high risk for cardiovascular disease and after myocardial infarction, stroke, or with proven peripheral vascular disease from the ONTARGET and TRANSCEND trials investigating ramipril, telmisartan, and their combination followed for a median of 56 months. We analysed the association of mean achieved RHR on-treatment with the primary composite outcome of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, the components of the composite primary outcome, and all-cause death as continuous and categorical variables. Data were analysed by Cox regression analysis, ANOVA, and χ^2 test. These trials were registered with ClinicalTrials.gov.number NCT00153101. Patients were recruited from 733 centres in 40 countries between 1 December 2001 and 31 July 2008 (ONTARGET) and 1 November 2001 until 30 May 2004 (TRANSCEND). In total, 19 450 patients without diabetes and 11 487 patients with diabetes were stratified by mean RHR. Patients with diabetes compared to no diabetes had higher RHRs (71.8 ± 9.0 vs. 67.9 ± 8.8, $P < 0.0001$). In the categories of <60 bpm, 60 ≤ 65 bpm, 65 ≤ 70 bpm, 70 ≤ 75 bpm, 75 ≤ 80 bpm and ≥80 bpm, non-diabetic patients had an increased hazard of the primary outcome with mean RHR of 75 ≤ 80 bpm (adjusted hazard ratio [HR] 1.17 (1.01–1.36)) compared to RHR 60 ≤ 65 bpm. For patients with in-trial RHR ≥80 bpm the hazard ratios were highest (diabetes: 1.96 (1.64–2.34), no diabetes: 1.73 (1.49–2.00), For cardiovascular death hazards were also clearly increased at RHR ≥80 bpm (diabetes [1.99, (1.53–2.58)], no diabetes [1.73 (1.38–2.16)]. Similar results were obtained for hospitalization for heart failure and all-cause death while the effect of RHR on myocardial infarction and stroke was less pronounced. Results were robust after adjusting for various risk indicators including beta-blocker use and atrial fibrillation. No significant association to harm was observed at lower RHR.

* Corresponding author. Tel: +49 6841 16 15031, Fax: +49 6841 16 15032, Email: michael.boehm@uks.eu

Conclusion Mean RHR above 75–80 b.p.m. was associated with increased risk for cardiovascular outcomes except for stroke. Since in diabetes, high RHR is associated with higher absolute event numbers and patients have higher RHRs, this association might be of particular clinical importance in diabetes. These data suggest that RHR lowering in patients with RHRs above 75–80 b.p.m. needs to be studied in prospective trials to determine if it will reduce outcomes in diabetic and non-diabetic patients at high cardiovascular risk.

Clinical Trial registration http://clinicaltrials.gov.Unique identifier: NCT00153101.

Keywords Diabetes • Cardiovascular risk • Myocardial infarction • Heart failure • Blood pressure • ONTARGET • TRANSCEND • Heart rate

Introduction

Diabetes mellitus is associated with an increased risk of cardiovascular disease,[1] in particular, in combination with hypertension.[2] Elevated blood pressure (BP) is associated with enhanced resting heart rate (RHR) in patients with diabetes.[3] Resting heart rate is a predictor of mortality and cardiovascular disease in numerous cohorts as healthy populations,[4,5] hypertensives,[6] patients at high cardiovascular risk after myocardial infarction or stroke,[7] and in heart failure patients.[8] High RHR associates with poor physical conditioning[9] and cardiovascular comorbidities, common in diabetes such as chronic kidney disease[10] and cognitive impairment.[11] Interestingly, it also associates with incident diabetes.[12] Resting heart rate is regulated by the autonomic nervous system[13] and influenced by autonomic imbalance caused by parasympathetic denervation and sympathetic overactivity in patients with diabetes.[14,15] Considering the higher cardiovascular risk in diabetes compared with no diabetes, it is important whether high RHR contributes to high risk in patients with diabetes. Furthermore, RHR lowering drugs that inhibit hyperpolarization-activated cation channels are available to potentially modify the RHR risk association and may provide a potential therapeutic tool.[16] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[17] and the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND)[18] randomized patients with high cardiovascular risk to ramipril, telmisartan, or their combination in 31 546 patients. Among those, 11 730 patients had diabetes and 19 806 patients had no diabetes. No differences between randomized groups were detected in both trials, and this allowed a direct comparison and pooling of outcome data observed in the treatment strata. The objective of this analysis was to assess the risk at different on-treatment RHR levels in patients with or without diabetes after prior stroke, myocardial infarction, peripheral artery disease, and at high-cardiovascular risk on contemporary cardiovascular treatments.

Methods

In ONTARGET/TRANSCEND, patients with a history of coronary artery disease or peripheral artery disease or transient ischaemic attack or stroke or diabetes mellitus complicated by end organ damage were included. Recruitment took place in 733 centres in 40 countries with a follow-up of a median of 56 months. Design, treatment allocations, algorithms, and results of these trials were reported previously.[17,18] Inclusion and exclusion criteria are summarized in Supplementary material online, *Table S1*. The study protocols were approved by the local Ethics Committees of all participating centres. All patients gave written informed consent. In ONTARGET, patients were randomly assigned to ramipril 10 mg daily, telmisartan 80 mg daily, or the combination of both daily in a double dummy design after a run-in period where tolerability to ramipril and telmisartan was tested. In TRANSCEND, patients were intolerant to ACE-inhibitors and were assigned to either telmisartan 80 mg qd or matching placebo. Standard treatment was provided by the treating physicians according to best clinical practice and study medication was given on top of their usual treatments. Investigators were specifically advised to adjust the existing BP medication according to their clinical practice. Visits were scheduled at 6 weeks and 6 months after randomization and every 6 months thereafter. Randomized treatments of ONTARGET showed similar results of the primary composite outcome of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure as well as on secondary outcomes (time to first event).

The primary composite outcome and the individual components between the treatment groups allowed pooling of data of all patients in order to perform an adequately powered comprehensive *post hoc* analysis of patients with diabetes and no diabetes according to on-treatment RHR. The primary objective of this study was to explore the association of RHR and cardiovascular outcomes in patients with or without diabetes. Resting heart rate and BP were taken after resting for 3 min in a sitting position using an automated validated device (Omron model HEM 757, Omron Corporation, Kyoto, Japan) in the presence of the study nurse or investigator. Only patients with complete data on RHR and BP entered the analysis. The flow of the study, the treatment allocations, and the exclusion of patients at every step of the analysis is depicted in Supplementary material online, *Figure S1*. In total, 31 546 patients were randomized into ONTARGET and TRANSCEND, 19 806 patients without and 11 730 patients with diabetes mellitus. Information on diabetes was lacking in 10 patients. Thirty-one patients did not have available baseline BP measurements. In 242 patients there was no follow-up of BP before first event. Of the remaining 31 263 patients, there were missing values of important covariates in 226 patients (BP, RHR, treatments, and others). Finally, 30 937 patients were analysed (19 450 without diabetes and 11 487 with diabetes). Allocation of patients to treatment groups of ONTARGET/TRANSCEND is displayed in Supplementary material online, *Figure S1*. An average of 8.4 ± 2.5 RHR measurements taken over 55.3 ± 10.2 months was available in patients without diabetes. In patients with diabetes an average of 8.2 ± 2.6 RHR measurements taken over 54.3 ± 11.8 months was available. Clinical diagnostic criteria for diabetes were

fasting glucose ≥7 mmol/L, elevated HbA1C to ≥110% of upper limit norm of the study centre, the initiation of insulin or oral hypoglycaemic patients and/or a 2-h glucose ≥11.1 mmol/L following a 75 g oral glucose tolerance test. For patients with diabetes only recruited into the studies, evidence of end organ damage as retinopathy, left ventricular hypertrophy, macro- or microalbuminuria, or any evidence of previous cardiac or vascular disease had to be present.

Study outcomes

The primary outcome was defined as a composite of cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure. The composite and the individual components of the composite as well as all-cause death were used in this secondary analysis. All primary and secondary outcomes events were evaluated by a blinded central committee according to standard criteria.[17,18] Patients with non-fatal events were not censored for other outcomes; e.g. patients with an MI were still on risk for stroke.

Statistical analysis

All outcome events were combined for this analysis as outcomes were not different in ONTARGET and TRANSCEND between randomized treatments. Patients with diabetes or without diabetes were divided into subgroups according to their baseline RHR and to their mean achieved in-trial RHR. The following cut-offs were chosen: <60 b.p.m., 60 b.p.m. to <65 b.p.m., 65 b.p.m. to <70 b.p.m., 70 b.p.m. to <75 b.p.m., 75 b.p.m. to <80 b.p.m., and ≥80 b.p.m. Patient characteristics are displayed according to baseline RHR (Supplementary material online, *Table S2*) as well as to mean achieved in-trial RHR (Supplementary material online, *Table S3*). Continuous data are presented as mean ± standard deviation and categorical data as percentages. Groups were tested for differences using ANOVA for continuous data and the χ^2 test for categorical data. Yearly event rates and cumulative incidence curves for the composite outcome and its individual components as well as all-cause death were presented according to the RHR criteria as described above separated by the presence of diabetes. Cumulative incidence curves were adjusted for the competing risk of death or non-cardiovascular death, whatever appropriate. Relative differences between RHR categories for patients with or without diabetes were analysed using Cox regression including the interaction between prevalence of diabetes and RHR categories. The analysis was adjusted for all variables in Supplementary material online, *Table S2*, and the competing risk of death was also considered. The results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) using non-diabetics with RHR 60 b.p.m. to <65 b.p.m. as reference. The association between hazard and mean achieved RHR as continuous variable was analysed non-parametrically using restricted cubic splines allowing for non-linear relationships.[19] Four knots (5th, 35th, 65th, and 95th percentile of in-trial RHR) were chosen for the analysis. Prevalence of diabetes and the interaction of diabetes with mean achieved RHR were included in the model. Hazard ratios and 95% confidence bands depending on mean achieved RHR and prevalence of diabetes were presented, using non-diabetics with a RHR of 60 b.p.m. as reference (HR = 1). Also in this analysis the competing risk of death was considered. All analyses were done with the SAS version 9.4 (SAS Institute, NC, USA).

Results

From the overall population of 30 937 patients, 11 487 patients with diabetes and 19 450 without diabetes were identified. Supplementary material online, *Tables S2* and *S3* show the demographic and clinical characteristics according to baseline and mean in-trial RHR in diabetes and no diabetes. Patients in the different randomization strata were similarly distributed between the RHR groups. *Figure 1* shows the distribution of mean in-trial RHR in those with or without diabetes. Patients with diabetes (red) had a slightly higher RHR compared with patients without diabetes (blue) (71.8 ± 9.0 vs. 67.9 ± 8.8, $P < 0.0001$). Females tended to have higher baseline and in-trial RHR, while males had lower baseline and in-trial RHR. This was not different between patients with or without diabetes. *Figure 2A–F* depicts the association of mean in-trial RHR in patients with and without diabetes with cardiovascular outcomes. In general, cardiovascular outcomes were more frequent in patients with diabetes independent of RHR. The primary outcome (*Figure 2A*), cardiovascular death (*Figure 2B*), hospitalization for heart failure (*Figure 2E*), and all-cause death (*Figure 2F*) were observed most frequently in those patients with a RHR ≥80 b.p.m. The difference according to the risk associated with higher RHR was greatest for the primary outcome, heart failure hospitalization, and all-cause death, while the difference was less pronounced for myocardial infarction and absent for stroke (*Figure 2C* and *D*).

Figure 3 depicts HRs (left) and yearly event rates (right) in patients with (red) and without diabetes (blue). The hazard for the primary outcome (*Figure 3A*) was generally increased in patients with diabetes, as well as in patients without diabetes but with a RHR of 75 b.p.m. to <80 b.p.m.; it was further enhanced at RHR ≥80 b.p.m., all compared with the reference group of non-diabetics with RHR of 60 b.p.m. to <65 b.p.m. Also for the other outcomes there was a general increase in hazard for patients with diabetes, and a significant effect of RHR (but less pronounced for stroke). Also non-diabetics with RHR ≥80 b.p.m. had an increased hazard compared with the reference, for the composite outcome and heart failure hospitalization already an RHR ≥75 b.p.m. led to an increased hazard, and for all-cause death the threshold was even 70 b.p.m. The tests for interaction between presence of diabetes and mean achieved in-trial RHR did not reveal significant findings. However, for the composite outcome, heart failure hospitalization and all-cause death at least there was a trend for heterogeneity (respective $P < 0.2$), meaning that the

Figure 1 Distribution of mean resting heart rate in diabetes (red) and no diabetes (blue).

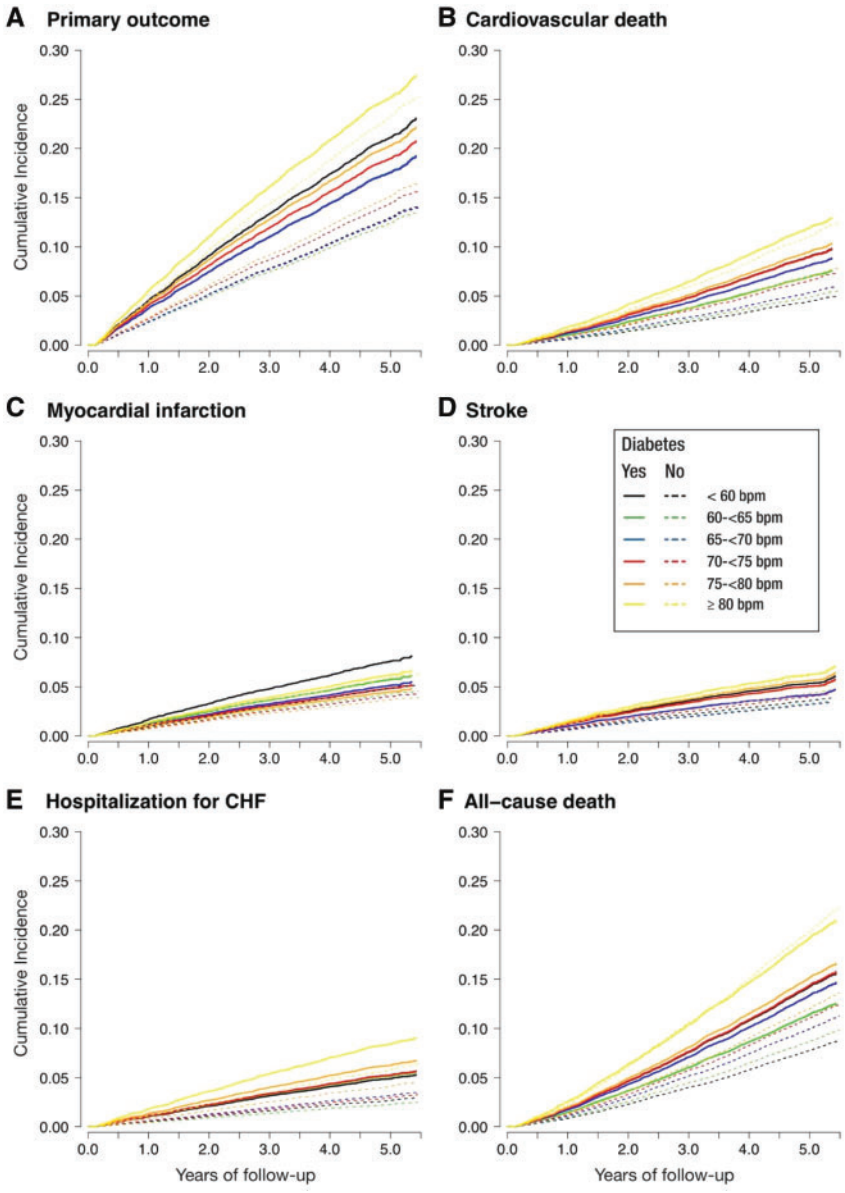


Figure 2 Cumulative incidence curves for the primary outcome (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for chronic heart failure (*E*), and all-cause death (*F*) according to mean achieved resting heart rate of the groups <60 b.p.m., 60 b.p.m. to <65 b.p.m., 65 b.p.m. to <70 b.p.m., 70 b.p.m. to <75 b.p.m., 75 b.p.m. to <80 b.p.m., and ≥80 b.p.m. The primary outcome included cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. Filled lines depict diabetes and dotted lines depict no diabetes.

impact of in-trial RHR may be different between patients without and with diabetes.

In order to add further plausibility, we evaluated patients with high-risk diabetes. Within the group of patients with diabetes a subgroup with end organ damage was identified suffering from myocardial hypertrophy, retinopathy, and macro- or microalbuminuria. In agreement with the previous finding, the hazards were further increased in patients with diabetes and complications (Supplementary material online, *Figure S2*).

There was an apparent non-linear relationship between RHR and cardiovascular outcomes, which was different between the different types of outcomes. *Figure 4* shows the relative hazard depending on presence of diabetes and in-trial RHR compared with no diabetes with 60 b.p.m. as reference. The association of risk to RHR was similar in patients with or without diabetes with a threshold of an increased risk above on treatment RHR >75 b.p.m. for the primary outcome, hospitalization for heart failure, and all-cause death and with a threshold ≥80 b.p.m. for myocardial infarction, while there was no association to stroke. A typical J-curve was not observed except for a trend for the primary outcome (*Figure 4A*) and stroke (*Figure 4D*). Over the entire mean on-treatment RHR spectrum the hazards were

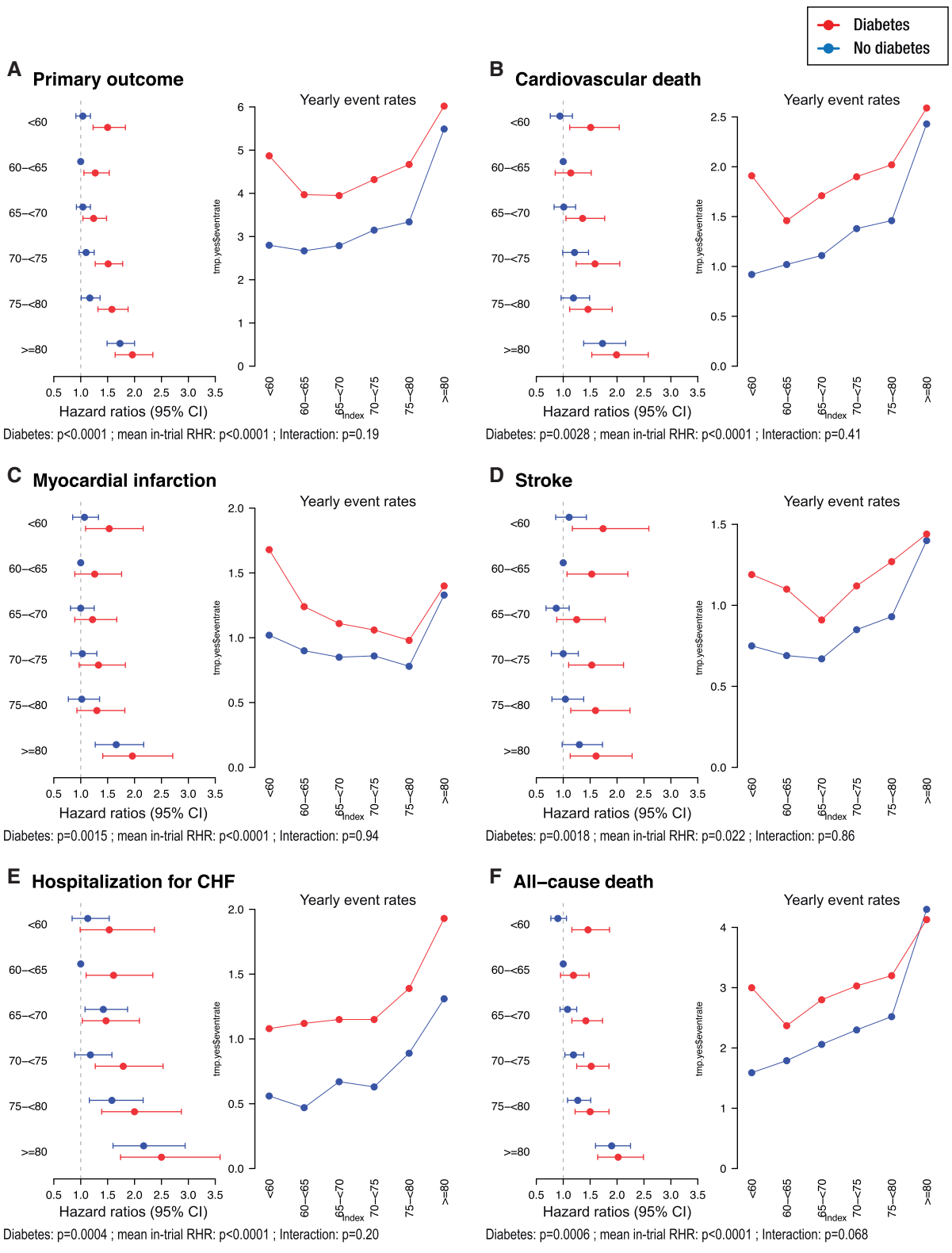


Figure 3 Hazard ratios (left) and yearly event rates (right) for mean achieved resting heart rate in diabetes (red) and no diabetes (blue) for the primary endpoint (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for chronic heart failure (*E*), and all-cause death (*F*). The primary outcomes were cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. The hazard ratios (Cox regression) were adjusted for the variables diastolic blood pressure, systolic blood pressure, heart rate at baseline, age, sex, body mass index, renal function, physical activity, education, alcohol consumption, tobacco use, history of hypertension, history of diabetes, myocardial infarction, stroke/transient ischaemic attack, heart rhythm, comedications, study, and study medications.

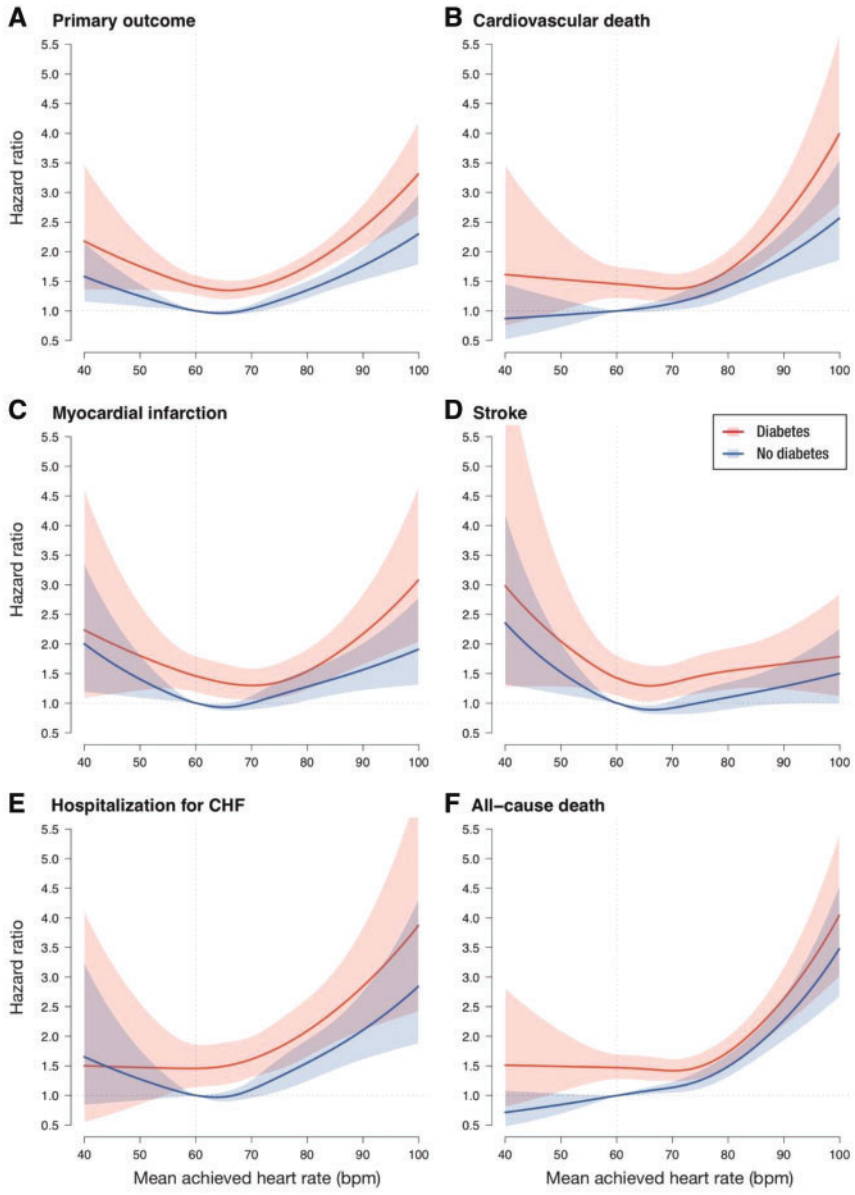


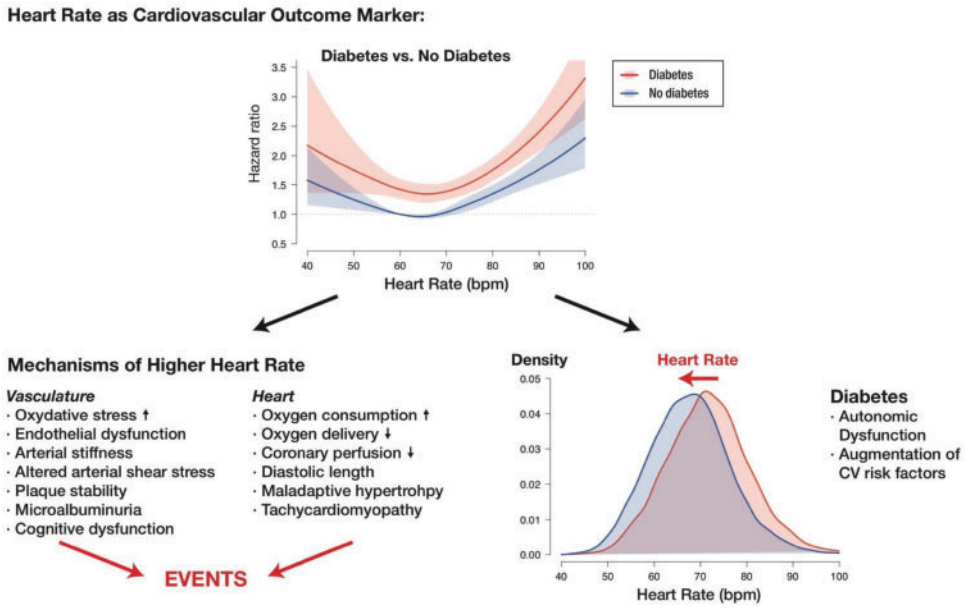
Figure 4 Hazard ratio according to mean achieved resting heart rate of the adjusted hazard ratios for the primary outcome (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for chronic heart failure (*E*), and all-cause death (*F*). The analyses used a model with restricted cubic splines and were adjusted for the same variables as described in *Figure 3*. The reference (hazard ratio = 1) is the mean achieved resting heart rate = 60 b.p.m.

higher for individuals with diabetes compared with those without diabetes (*Figure 4A–F*). All data were adjusted for risk indicators accounting also for the presence of atrial fibrillation on beta blocker use.

Discussion

The results of the present study extend prior data indicating that in patients with diabetes at high cardiovascular risk the relative hazard of outcomes associated with high RHRs is similar to patients without diabetes. However, over the whole spectrum of RHR, the absolute event rates are higher in patients with diabetes and RHRs were also higher in patients with diabetes. This is further strengthened by the higher RHR in patients with diabetes potentially related to the sympathetic activation or parasympathetic withdrawal.[14,15]

A higher RHR is associated with increased cardiovascular outcomes in seemingly healthy individuals[4,5] and in patients with hypertension,[6] high cardiovascular risk,[7] or heart failure.[8] Herein, we show that the relative RHR-risk association was not different between



Take home figure Heart rate association to cardiovascular death, myocardial infarction, stroke, and heart failure hospitalization is related to heart rate (above, *Figure 4A*). Pathophysiological mechanisms in the vasculature are oxidative stress, endothelial dysfunction, arterial stiffness, pathological shear stress, plaque instability resulting in microalbuminuria and cognitive dysfunction, and vascular events. In the heart oxygen consumption is increasing, oxygen delivery and coronary perfusion decreases by a reduction of diastolic length leading to maladaptive hypertrophy and sometimes tachycardiomyopathy.[33] Diabetes enhances event rates (right, above, *Figure 4A*) involving an augmentation of cardiovascular risk factors. Autonomic dysfunction contributes to a slightly higher heart rate in individuals with diabetes (right, below, *Figure 1*). Heart rate is a risk indicator in vascular disease in diabetes. It has to be scrutinized whether it turns into a modifiable risk factor as shown previously in heart failure and a therapeutic target to reduce events.

patients with and without diabetes, while the absolute event rate is increased over the whole spectrum of RHR except for RHR ≥80 b.p.m. for cardiovascular death, myocardial infarction, stroke, and all-cause death. The association of RHR was different according to the outcomes of interest with less strong associations for myocardial infarction and none for stroke. Cardiovascular death and all-cause death have previously been associated with RHR in high cardiovascular risk patients[7] and in the large epidemiological Melbourne Collaborative Cohort Study.[20] The close association of RHR to all-cause death and cardiovascular death in diabetes and no diabetes might be explained by the strong relationship of RHR to chronic heart failure reported herein, as well as in dedicated heart failure trials.[8] Furthermore, high RHR associates to acute, critical illness such as hypertensive crises,[21] shock,[22,23] and stroke outcomes[24] as well as intracerebral haemorrhage.[25] Beyond acute critical illness, several cardiovascular comorbidities like renal impairment,[10] cognitive impairment,[11] COPD,[26] and pulmonary hypertension[27] might contribute to the strong association between RHR and fatal outcomes. Furthermore, RHR has been associated with the development and outcome of non-cardiac diseases like cancer[28] and incident metabolic disease[12,29] indicating that RHR is a more general risk marker for cardiovascular and non-cardiovascular disease.[30] A difference between patients with and without diabetes at RHR ≥80 b.p.m. was smaller. One might speculate that this could be due to deconditioning, which has a collinear effect on outcome and global health. Furthermore, the difference between patients with and without diabetes was greater for all outcomes at low RHR <60 b.p.m. Low RHR <60 b.p.m. might select patients with concomitant sinus node or conduction disease as a reflection of higher cardiovascular impairment in diabetes mellitus explaining the higher event rates. However, there is no exercise data or Holter data available in this large overall population. The suggestion can neither be proven nor rejected.

Consistent with this suggestion, a sensitivity analysis looking at patients with diabetes and complications (retinopathy, myocardial hypertrophy, and macro- or microalbuminuria) showed higher event rates through all heart rate categories indicating that the higher event rate is causally related to diabetes and its complications.

Hospitalization for heart failure was closely associated with RHR above a threshold of 75 b.p.m. Resting heart rate reduction with the I_f-inhibitor ivabradine-reduced cardiovascular death and heart failure hospitalization outcomes in a chronic heart failure population.[31] This effect was most pronounced when RHR was above the median of 75 b.p.m.[32] This finding demonstrates that in heart failure, RHR is a modifiable risk factor rather than only a risk marker. This concept needs to be studied in conditions other than chronic heart failure.[33] In heart failure, comorbid diabetes has multiple actions like promoting fibrosis, changing Ca^{2+} and Na^{+} homeostasis, protein glycosylation, oxidative stress, and others.[34] In turn, treatment of diabetes with SGLT2-inhibitors[35,36] reduced cardiovascular outcomes, HbA1C levels and heart failure-related outcomes indicating that

there is a close crosstalk between diabetes mellitus and incident heart failure.

Interestingly, the association of RHR to myocardial infarction was less pronounced and only occurring at a RHR above 80 b.p.m. This is in line with a previous analysis from ONTARGET showing that myocardial infarction in contrast to other cardiovascular outcomes like cardiovascular death and heart failure was not associated with RHR.[7] Consistent with this observation, RHR reduction with ivabradine did not reduce non-fatal myocardial infarction in a population with stable coronary artery disease.[37] Stroke was not associated with RHR. This supported by previous analysis from the PROFESS-trial where a second stroke after an index stroke was not associated with high RHR.[24] However, neurological outcome and cognitive decline was more favourable at lower compared with higher RHR.[24] Improved cognitive function has been shown to be related to an improvement of endothelial function and collateral formation at lower RHR and after RHR reduction.[38]

Limitations

The present analysis from ONTARGET and TRANSCEND may have some limitations, but also strengths. It is a retrospective secondary analysis of a large outcome trial, which is not subject to randomization. Therefore, it is observational and hypothesis generating by nature. However, the rigorous capture of vital signs like RHR and BP as well as the large number of patients and outcome events in a broad population of patients at high cardiovascular risk and on contemporary treatments are the strengths of this analysis.

Conclusion

In conclusion, our study indicates that high mean on-treatment RHR is associated with cardiovascular death, all-cause death, and heart failure hospitalization, while it is less associated with myocardial infarction and not associated with stroke. Relative hazard according to RHR is not different between diabetes and no diabetes, but event rates in diabetes are generally higher. Furthermore, the certain degree of autonomic dysbalance involving sympathetic activation and parasympathetic withdrawal or the increasing HR strengthens the relevance of this finding. Thus, similar relative risk according to RHR within the group with diabetes translates into higher event numbers in diabetes compared with no diabetes at high RHR, which are higher in diabetes with prevalent end organ damage. The significance of this association of cardiovascular outcomes to higher RHR is further supported by the finding that patients with diabetes tend to have higher RHRs compared with patients without diabetes potentially related to sympathetic activation and/or parasympathetic withdrawal potentially involving autonomic neuropathy. Interestingly RHR is not mentioned in the ESC Guidelines on diabetes,[39] cardiovascular disease prevention,[40] or hypertension.[41] Therefore, future studies on RHR reduction may provide insights into a novel therapeutic approach to patients with a broad spectrum of cardiovascular and metabolic disease to reduce or even halt morbid and mortal events. Presently, this needs to be scrutinized by prospective intervention trials, because it is unknown whether RHR is a modifiable risk factor (like in chronic heart failure) or a risk marker in cardiovascular high-risk patients.

Supplementary material

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

Acknowledgements

The authors thank Armin Schweitzer for editorial help and artwork.

Funding

The funders of the trials had no role in the design and interpretation of this analysis. The trial was designed and conducted by the Steering Committees of ONTARGET and TRANSCEND. The authors had full access to all data of the study with final responsibility to submit this manuscript for publication. This work was supported by Deutsche Forschungsgemeinschaft [SFB TTR 219, S-01 to M.B., N.M., and F.M.].

Conflicts of interest: M.B. reports other from Astra Zeneca, Boehringer Ingelheim, Medtronic, Novartis, Vifor outside the submitted work; G.M. received personal fees from Boehringer Ingelheim, Ferrer, Medtronic, Merck, Menarini, Novartis, Recordati and Servier during the conduct of the study; F.M. is supported by Deutsche Hochdruckliga, Deutsche Gesellschaft für Kardiologie and Deutsche Forschungsgemeinschaft (SFB TRR219). F.M. received research grants and lectures fees from Medtronic and Recor; S.Y., K.T., R.S. and N.M. received grants from Boehringer Ingelheim, during the conduct of the study; M.W. received other from Boehringer Ingelheim and Johnson & Johnson outside the submitted work; B.W. received personal fees from Boehringer Ingelheim, outside the submitted work; J.R., E.L., H.S., K.S. and J.M. have nothing to disclose.

References

1. Writing Group Members; Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 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; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Executive Summary: heart disease and stroke statistics–2016 update: a Report from the American Heart Association. *Circulation* 2016;**133**:447–454.
2. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *Lancet* 2012;**380**:601–610.
3. Ferrannini E, Balkau B, Coppack SW, Dekker JM, Mari A, Nolan J, Walker M, Natali A, Beck-Nielsen H, Risc I. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. *J Clin Endocrinol Metab* 2007;**92**:2885–2892.
4. Dyer AR, 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 epidemiologic studies. *Am J Epidemiol* 1980;**112**:736–749.
5. Gillum RF, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: the NHANES I epidemiologic follow-up study. *Am Heart J* 1991;**121**:172–177.
6. Okin PM, Kjeldsen SE, Julius S, Hille DA, Dahlöf B, Edelman JM, Devereux RB. All-cause and 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.
7. Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, Yusuf S, Böhm 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.
8. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Shift I. 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.
9. Jurca R, Jackson AS, LaMonte MJ, Morrow JR Jr, Blair SN, Wareham NJ, Haskell WL, van Mechelen W, Church TS, Jakicic JM, Laukkanen R. Assessing cardiorespiratory fitness without performing exercise testing. *Am J Prev Med* 2005;**29**:185–193.

10. Böhm M, Schumacher H, Schmieder RE, Mann JF, Teo K, Lonn E, Sleight P, Mancia G, Linz D, Mahfoud F, Ukena C, Sliwa K, Bakris G, Yusuf S. Resting heart rate is associated with renal disease outcomes in patients with vascular disease: results of the ONTARGET and TRANSCEND studies. *J Intern Med* 2015;**278**: 38–49.
11. Böhm M, Schumacher H, Leong D, Mancia G, Unger T, Schmieder R, Custodis F, Diener H-C, Laufs U, Lonn E, Sliwa K, Teo K, Fagard R, Redon J, Sleight P, Anderson C, O'Donnell M, Yusuf S. Systolic blood pressure variation and mean heart rate is associated with cognitive dysfunction in patients with high cardiovascular risk. *Hypertension* 2015;**65**:651–661.
12. Carnethon MR, Yan L, Greenland P, Garside DB, Dyer AR, Metzger B, Daviglus ML. Resting heart rate in middle age and diabetes development in older age. *Diabetes Care* 2008;**31**:335–339.
13. Sabbah HN, Ilsar I, Zaretsky A, Rastogi S, Wang M, Gupta RC. Vagus nerve stimulation in experimental heart failure. *Heart Fail Rev* 2011;**16**:171–178.
14. Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nat Rev Endocrinol* 2012;**8**:405–416.
15. Xuan YL, Wang Y, Xue M, Hu HS, Cheng WJ, Li XR, Yin J, Yang N, Yan SH. In rats the duration of diabetes influences its impact on cardiac autonomic innervations and electrophysiology. *Auton Neurosci* 2015;**189**:31–36.
16. Biel M, Wahl-Schott C, Michalakis S, Zong X. Hyperpolarization-activated cation channels: from genes to function. *Physiol Rev* 2009;**89**:847–885.
17. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.
18. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008;**372**:1174–1183.
19. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med* 1989;**8**:551–561.
20. Seviiri M, Lynch BM, Hodge AM, Yang Y, Liew D, English DR, Giles GG, Milne RL, Dugué PA. Resting heart rate, temporal changes in resting heart rate, and overall and cause-specific mortality. *Heart* 2018;**104**:1076–1085.
21. Al Bannay R, Böhm M, Husain A. Heart rate differentiates urgency and emergency in hypertensive crisis. *Clin Res Cardiol* 2013;**102**:593–598.
22. Hoke RS, Muller-Werdan U, Lautenschlager C, Werdan K, Ebelt H. Heart rate as an independent risk factor in patients with multiple organ dysfunction: a prospective, observational study. *Clin Res Cardiol* 2012;**101**:139–147.
23. Sander O, Welters ID, Foex P, Sear JW. Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications. *Crit Care Med* 2005;**33**:81–88.
24. Böhm M, Cotton D, Foster L, Custodis F, Laufs U, Sacco R, Bath PM, Yusuf S, Diener HC. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *Eur Heart J* 2012;**33**:2804–2812.
25. Qiu M, Sato S, Zheng D, Wang X, Carcel C, Hirakawa Y, Sandset EC, Delcourt C, Arima H, Wang J, Chalmers J, Anderson CS; INTERACT Investigators. Admission heart rate predicts poor outcomes in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial Studies. *Stroke* 2016;**47**:1479–1485.
26. Jensen MT, Marott JL, Lange P, Vestbo J, Schnohr P, Nielsen OW, Jensen JS, Jensen GB. Resting heart rate is a predictor of mortality in COPD. *Eur Respir J* 2013;**42**:341–349.
27. Henkens IR, Van Wolferen SA, Gan CT, Boonstra A, Swenne CA, Twisk JW, Kamp O, van der Wall EE, Schalij MJ, Vonk-Noordegraaf A, Vliegen HW. Relation of resting heart rate to prognosis in patients with idiopathic pulmonary arterial hypertension. *Am J Cardiol* 2009;**103**:1451–1456.
28. Anker MS, Ebner N, Hildebrandt B, Springer J, Sinn M, Riess H, Anker SD, Landmesser U, Haverkamp W, von Haehling S. Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. *Eur J Heart Fail* 2016;**18**:1524–1534.
29. Hong JW, Noh JH, Kim DJ. The association of resting heart rate with the presence of diabetes in Korean adults: the 2010-2013 Korea National Health and Nutrition Examination Survey. *PLoS One* 2016;**11**:e0168527.
30. Böhm M. Heart rate: from heart failure to chronic diseases and cancer. Is there a role for supportive care by heart rate reduction? *Eur J Heart Fail* 2017;**19**:250–252.
31. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
32. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol* 2013;**102**:11–22.
33. Nikolovska-Vukadinović A, Vukadinović D, Borer J, Cowie M, Komajda M, Lainscak M, Swedberg K, Böhm M. Heart rate and its reduction in chronic heart failure and beyond. *Eur J Heart Fail* 2017;**19**:1230–1241.
34. Kaplan A, Abidi E, El-Yazbi A, Eid A, Booz GW, Zouein FA. Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects. *Heart Fail Rev* 2018;**23**:419–437.
35. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;**138**: 458–468.
36. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME® Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016;**37**:1526–1534.
37. Fox K, Ford I, Steg PG, Tardif J-C, Tendera M, Ferrari R; SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;**371**:1091–1099.
38. Schirmer SH, Degen A, Baumhäkel M, Custodis F, Schuh L, Kohlhaas M, Friedrich E, Bahlmann F, Kappl R, Maack C, Böhm M, Laufs U. Heart-rate reduction by I_f-channel inhibition with ivabradine restores collateral artery growth in hypercholesterolemic atherosclerosis. *Eur Heart J* 2012;**33**:1223–1231.
39. Authors/Task Force Members, Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL; ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document Reviewers, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schächinger V, Scheen A, Schirmer H, Strömberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;**34**:3035–3087.
40. , Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM; Additional Contributor: Simone Binno (Italy); Document Reviewers: De Backer G, Roffi M, Aboyans V, Bachl N, Bueno H, Carerj S, Cho L, Cox J, De Sutter J, Egidi G, Fisher M, Fitzsimons D, Franco OH, Guenoun M, Jennings C, Jug B, Kirchhof P, Kotseva K, Lip GY, Mach F, Mancia G, Bermudo FM, Mezzani A, Niessner A, Ponikowski P, Rauch B, Rydén L, Stauder A, Turc G, Wiklund O, Windecker S, Zamorano JL; Authors/Task Force Members. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016;**23**:NP1–NP96.
41. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.