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Heart rate and blood pressure interactions in the development of erectile dysfunction in high-risk cardiovascular patients

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Abstract

Aims: Erectile dysfunction (ED) is associated with cardiovascular risk factors as elevated systolic blood pressure (SBP), resting high heart rate (HR), and endothelial dysfunction and predicts cardiovascular events. However, the interaction between high HR and SBP and the development of ED remains unclear.

Methods and Results: We evaluated 1015 male patients enrolled in the ED substudy of ONTARGET and TRANSCEND, examining the influence of mean HR and mean SBP obtained over all study visits (mean 10.9±1.4 study visits) and their interaction with ED. In patients without pre-existing ED, new onset ED was detected in 29% of patients below, and 41% of patients above, the median of mean HR (OR 1.72, 95% CI 1.8–2.5, $p = 0.0047$). In patients with pre-existing ED, high HR had no add-on effect. With or without pre-existing ED, high SBP had no influence after adjustment for covariates (OR 1.03, 95% CI 0.66–1.59, $p = 0.91$). In a continuous model, it was shown that effects of high HR were prominent at low Kölner (Cologne) Evaluation of Erectile Function (KEED) score baseline values and in the presence of SBP above the median.

Conclusions: In patients at risk for cardiovascular events, high HR is associated with ED, whereas the effect of high SBP was not significant. High resting HR might represent a cardiovascular risk indicator. Whether HR represents a potential treatment target to improve ED in high-risk individuals must be scrutinized in prospective trials.

Keywords

Endothelial dysfunction, endothelial function, heart rate, high cardiovascular risk

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Introduction

Erectile dysfunction (ED) is defined as inability to perform satisfactory sexual performance due to inefficient penile erection.[1] It represents a common health problem, which is associated with age and other cardiovascular risk factors.[2–4] Furthermore, ED is associated with cardiovascular events[5,6] and may precede clinical coronary artery disease.[7,8] Elevated systolic blood pressure (SBP) has been shown to increase the risk of cardiovascular events such as stroke, coronary artery disease, heart failure, and renal failure.[9,10] High resting heart rate (HR) has been identified as an important risk

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marker for cardiovascular disease[11] and is also associated with increased risk of cardiovascular events in hypertension,[12] coronary artery disease,[13] and heart failure.[14] Penile erection is crucially dependent on endothelial function.[15] Pharmacological HR reduction improves vascular endothelial function,[16] plaque load in hypercholesterolaemia,[17] stroke size in a stress model[18] and endothelial-dependent relaxation of corpus cavernosum[19,20] in atherosclerotic animals with endothelial dysfunction. It is unclear whether HR is associated with ED in humans and whether or how HR interacts with hypertension.

Both the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)[21] and the effects of the angiotensin receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors (TRANSCEND trial)[22] incorporated an ED substudy, which has been previously published.[6,23] In these trials no statistically significant differences between randomized treatment groups were seen regarding the primary composite outcome and its individual components,[21,22] or with respect to ED.[6] Since HR and SBP are associated with cardiovascular outcomes, we hypothesized that an interaction with these competing risk factors might influence the development of ED in this high-risk population. The primary objective of the study was to evaluate the role of HR and SBP on the development of ED in high-risk cardiovascular patients by analysing the relationship between SBP and HR on the development of ED in 1015 patients at high cardiovascular risk enrolled in this ED substudy.[6,23]

Methods

Study design

In the ED substudy of ONTARGET and TRANSCEND, 1594 patients were enrolled from the 22,168 male patients participating in the main trial of high-risk patients with proven atherosclerotic disease (after a stroke, myocardial infarction, or with diabetes mellitus plus two additional risk factors). These patients shared similar eligibility criteria and baseline characteristics as those in the main trials[21,22] as published in the earlier report of the ED substudy.[23] In this new analysis of the ED substudy, we used the evaluation of ED score (Kölner (Cologne) Evaluation of Erectile Dysfunction Score, KEED)[24], consisting of six questions on a five-point Likert scale as reported previously.[23,24] A score with a cut off $\geq$18 points defined definite ED. After consenting to participate, patients completed the questionnaire at baseline (run in visit), at 24 months, and at the penultimate visit (approximately 48 months follow up). Patients withdrawing from the study were also asked to complete the questionnaire.

The questionnaire was in two parts; part one consisted of questions on medical history and was completed at the study visit (with support from the study coordinator, physician or nurse if required): part two consisted of sensitive questions on ED which were completed by the patients in the privacy of their home. Questionnaires were sent back in sealed envelopes for processing at the Population Health Research Institute Project Office in Canada.

This substudy protocol was approved by the Ethics Committees of all local participating institutions. A detailed description of the procedure and the baseline characteristics of the ED substudy patients was reported earlier.[23] The cardiovascular outcomes and treatment effects on ED were also reported elsewhere.[6] In this analysis 1015 patients had questionnaires available at both baseline and penultimate visit with complete data necessary for this analysis. At each of the visits, resting HR and SBP was measured in duplicate in sitting position after 3 minutes of rest. Blood pressure was taken using an automated validated device (model HEM 757; Omron, Japan).

Statistical analysis

All statistical analyses were done using SAS version 9.2 (SAS Institute, NC, USA). Mean HR and SBP were calculated using the measurements taken at all available visits before the final KEED questionnaire. Baseline demographic and clinical characteristics were obtained for all included patients, and for patients below and above the median of the mean (of all visits) HR ($<$69.8 vs. $\geq$69.8 bpm), and for those below and above the median mean (of all visits) SBP ($<$132.4 vs. $\geq$132.4 mmHg), where the mean in the average value of all visit values of individual patients. The chi-squared test was used to test for differences between patients below and above the median (mean HR, mean SBP, and combined) regarding demographics and clinical characteristics. Logistic regression analysis was used to assess the impact of mean HR and mean SBP (individually and combined) on the presence of ED at study termination, adjusting for age ($<$65 vs. $\geq$65 years) and presence of ED at baseline and allowing for interaction between mean HR/SBP and ED at baseline. In addition, we developed multivariate logistic models that included other potential predictors for ED; all characteristics displayed in Table 1 were candidates in the model selection procedure, but only covariates with a p-value $<$0.1 were taken into consideration. Results are presented as odds ratios (OR) with 95% confidence intervals. In respective sensitivity analyses, KEED values at baseline were included as a continuous

Table 1. Demographics of patients according to heart rate and systolic blood pressure

								Heart rate			
								Below median		Above median	
		Heart rate			Systolic blood pressure			Systolic blood pressure		Systolic blood pressure	
	Total	Below median	Above median	*p*	Below median	Above median	*p*	Below median	Above median	Below median	Above median	*p*
No. of patients	1015	507	508		507	508		268	239	239	269	
Pulse rate sitting, baseline [beats/min]	69.1 ± 12.8	62.3 ± 10	76 ± 11.6	<0.0001	68.1 ± 12.2	70.2 ± 13.3	0.0099	62.4 ± 10.8	62.2 ± 9	74.5 ± 10.5	77.3 ± 12.4	<0.0001
Number of visits	10.9 ± 1.4	10.9 ± 1.5	11 ± 1.3		11 ± 1.2	10.9 ± 1.5		10.9 ± 1.3	10.8 ± 1.6	11 ± 1.1	10.9 ± 1.4	
Age (years)	64.2 ± 6.1	64.4 ± 6.1	64 ± 6	0.23	63.7 ± 6.1	64.7 ± 5.9	0.0097	63.4 ± 5.9	65.5 ± 6.1	64 ± 6.4	63.9 ± 5.7	0.0008
Age group (years)												
<65	53.2	52.5	53.9	0.64	55.8	50.6	0.095	59.7	44.4	51.5	56.1	0.0041
≥65	46.8	47.5	46.1		44.2	49.4		40.3	55.6	48.5	43.9	
Race												
Asian	28.5	15.4	41.5	<0.0001	29.6	27.4	0.43	17.5	13	43.1	40.1	<0.0001
Other	18.4	16.8	20.1		19.3	17.5		18.7	14.6	20.1	20.1	
White	53.1	67.9	38.4		51.1	55.1		63.8	72.4	36.8	39.8	
Body mass index (kg/m^2)	27.6 ± 4.2	27.8 ± 4.2	27.5 ± 4.3	0.17	27.4 ± 4.4	27.9 ± 4.1	0.087	27.8 ± 4.4	27.8 ± 4	26.9 ± 4.3	27.9 ± 4.2	0.029
Alcohol consumption	51.3	57	45.7	0.0003	47.9	54.7	0.030	54.5	59.8	40.6	50.2	0.0003
Tobacco use												
Current	12.7	10.1	15.4	0.032	12.8	12.6	0.99	10.8	9.2	15.1	15.6	0.29
Formerly	59.5	60.4	58.7		59.6	59.4		60.4	60.3	58.6	58.7	
Never	27.8	29.6	26		27.6	28		28.7	30.5	26.4	25.7	
Physical activity												
2–4 times/week	24.1	27	21.3	0.0036	22.5	25.8	0.53	25.4	28.9	19.2	23	0.064
5–6 times/week	6.6	8.3	4.9		7.1	6.1		9	7.5	5	4.8	
<Once/week	8.3	8.7	7.9		8.5	8.1		9	8.4	7.9	7.8	
Every day	43.9	42.4	45.5		46	41.9		42.9	41.8	49.4	42	
Mainly sedentary	17	13.6	20.5		16	18.1		13.8	13.4	18.4	22.3	
SBP sitting, baseline (mmHg)	139.6 ± 16.7	138.8 ± 17.8	140.5 ± 15.5	0.11 ±	132.7 ± 15.2	146.5 ± 15.3	<0.0001	130.8 ± 15	147.8 ± 16.4	135 ± 15.1	145.4 ± 14.2	<0.0001
DBP sitting, baseline (mmHg)	82.1 ± 10.4	81.3 ± 10.7	83 ± 10	0.013	79.6 ± 9.8	84.7 ± 10.3	<0.0001	79.1 ± 10.5	83.8 ± 10.3	80.2 ± 9	85.4 ± 10.3	<0.0001
eGFR MDRD (ml/min/1.73 m^2)	75.5 ± 19.8	75.4 ± 17.6	75.7 ± 21.8	0.85	77.2 ± 18.9	73.9 ± 20.5	0.0077	77.7 ± 17.8	72.9 ± 17.1	76.7 ± 20.1	74.8 ± 23.2	0.037
Diabetes	33.1	27.2	39	0.0001	27	39.2	<0.0001	20.5	34.7	34.3	43.1	<0.0001
Hypertension	70.6	68.4	72.8	0.12	57.2	84.1	<0.0001	53.7	84.9	61.1	83.3	<0.0001
Myocardial infarction	51.1	60	42.3	<0.0001	57.6	44.7	<0.0001	65.7	53.6	48.5	36.8	<0.0001
Angina	41.7	51.7	31.7	<0.0001	46	37.4	0.0057	56.7	46	33.9	29.7	<0.0001

(continued)

Table 1. Continued

	Total	Heart rate			Systolic blood pressure			Heart rate					
								Below median		Above median			
		Below median	Above median	p	Below median	Above median	p	Systolic blood pressure		Systolic blood pressure			
								Below median	Above median	Below median	Above median	p
Stroke/TIA	26.7	17.6	35.8	<0.0001	23.3	30.1	0.014	14.9	20.5	32.6	38.7	<0.0001
Beta-blockers	57.2	68.6	45.9	<0.0001	56.8	57.7	0.78	68.3	69	43.9	47.6	<0.0001
Diuretics	23.2	23.5	22.8	0.81	18.9	27.4	0.0015	19	28.5	18.8	26.4	0.015
CCBs	30.5	25.2	35.8	0.0003	27	34.1	0.015	22	28.9	32.6	38.7	0.0004
Statins	52.5	67.3	37.8	<0.0001	55	50	0.11	65.7	69	43.1	33.1	<0.0001
Nitrates	25.6	28.2	23	0.059	30.6	20.7	0.0003	32.5	23.4	28.5	18.2	0.0012
Oral hypoglycaemic agents	19.7	13.8	25.6	<0.0001	17	22.4	0.028	11.2	16.7	23.4	27.5	<0.0001
Viagra/sildenafil	0.8	1.4	0.2	0.033	0.8	0.8	0.99	1.5	1.3		0.4	0.18

Values are mean±SD or %.; CCB, calcium-channel blocker; DBP, diastolic blood pressure; eGFR MDRD, estimated glomerular filtration rate by Modification of Diet in Renal Disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

variable rather than using the cut-off value of 18 points. Statistical significance was assumed at a p-value <0.05.

Results

Questionnaires on ED at baseline and follow up were obtained from 1015 patients. HR and BP measurements were available from 10.9 ± 1.4 visits. The demographic data and clinical characteristics of these patients are summarized in Table 1. Mean age was 64.2 years with 53.2% being younger than 65 years. Patients with low HR (<69.8 bpm) were predominately white, more frequently drank alcohol, were less frequently smokers, were more frequently physically active, and had lower DBP at baseline compared to patients with high HR. Diabetes and history of stroke/transient ischaemic attack was less frequent in the patients with HR below median whereas history of myocardial infarction and angina was more frequent. Beta-blockers, statins, and viagra were more frequently taken as concomitant medications whereas calcium-channel blockers and oral hypoglycaemics were taken less frequently in patients with lower HR.

Patients with lower SBP (<132.4 mmHg) were younger, less frequently drank alcohol, and had lower BP at baseline (as expected) and kidney function was better compared to patients with higher SBP. Diabetes, hypertension, and history of stroke/transient ischaemic attack was less frequent in the patients with mean SBP below median whereas history of myocardial infarction and angina was more frequent, and nitrates were more frequently taken, whereas diuretics, calcium-channel blockers, and oral hypoglycaemics were taken less frequently.

ED related to HR, but not SBP

Presence of ED was determined at the penultimate visit. Figure 1 shows the prevalence of ED above and below median of mean HR obtained over all study visits in all patients as well as in patients <65 years or ≥65 years. Patients were further separated into no ED (KEED <18) or pre-existing ED (KEED ≥18) at baseline. In patients without pre-existing ED, new onset ED was detected in 29.4% of patients below and 41.1% above the median HR; in patients with pre-existing ED the percentages of patients with ED were 81.3 and 78.7%, respectively. Logistic regression analysis revealed that baseline KEED and age were significantly associated with ED ($p < 0.0001$ for both). There was a significant interaction ($p = 0.023$) between baseline ED and mean HR. For patients without ED at baseline, an adverse effect of higher HR on the development of ED was seen (OR 1.72, 95% CI 1.18–2.50, $p = 0.0047$). For patients with pre-existing ED, the effect of higher HR on

the prevalence of ED at study termination was neutral (OR 0.88, 95% CI 0.56–1.36, $p = 0.56$, Figure 2, left).

In patients without pre-existing ED, new ED was detected in 32.2% of patients below and in 38.2% above the median SBP. The respective percentages in patients with pre-existing ED were 83.0 and 77.4%. These effects of mean SBP on ED were not significant. For patients without ED at baseline, the OR for mean SBP above vs. below median was 1.03 (95% CI 0.66–1.59, $p = 0.91$), whereas for patients with pre-existing ED, the OR was 0.65 (95% CI 0.39–1.06, $p = 0.083$; Figure 2, right).

Cumulative risk of ED according to age, ED status, HR, and SBP

The additive effects of the combined risk factors age, ED status at baseline, HR, or SBP above the median are demonstrated in Table 2, where the patients at lowest risk (i.e. <65 years, no ED at baseline, low HR, low SBP) are used as the reference group and odds ratios for the other risk combinations then calculated.

The cumulative risk of developing ED was influenced by age and ED at baseline. Higher HR and higher SBP had additional effects on developing ED amounting to an OR of 20 or higher in the unadjusted and adjusted model, when HR or SBP were higher in elderly patients with pre-existing ED. Table 2 also shows the (additional) impact of the other factors which were included in the model due to $p < 60;0.1$.

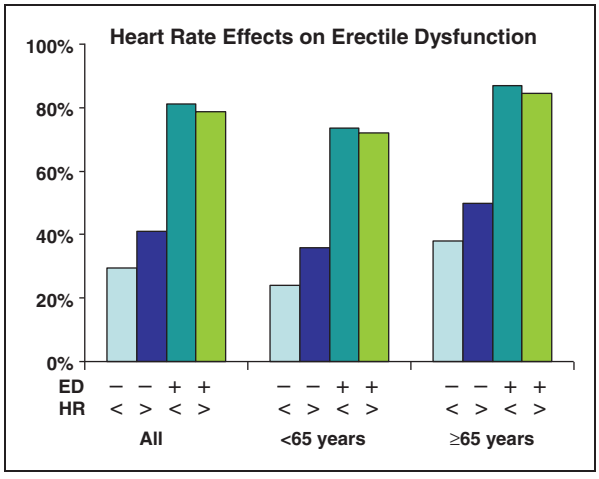

Figure 1. Procedure of erectile dysfunction (ED) in the total population (all) and in individuals <65 years or ≥65 years with (+) or without (−) preexisting erectile dysfunction (ED) above (>) or below (<) the median of heart rate (HR).

Risk associated to baseline ED

When baseline KEED was entered into the models as a continuous variable rather than using a cut-off value of 18 points for diagnosis of ED, the results above were confirmed. Figure 3A shows the impact of HR above the median vs. HR below the median depending on the baseline KEED, adjusted for age. It clearly shows that the effect of higher mean HR was detrimental when the KEED baseline values are low (i.e. below 18). For SBP above the median, there was no significant effect (Figure 3B). Figure 3C–E show that the risk for developing ED was especially increased in patients with higher HR or SBP (compared to patients with low HR and low SBP) when KEED values at baseline were low.

Discussion

The present study showed that HR, but not SBP, is significantly associated with the development of ED in individuals at high cardiovascular risk. This effect was observed in individuals with no pre-existing ED at baseline.

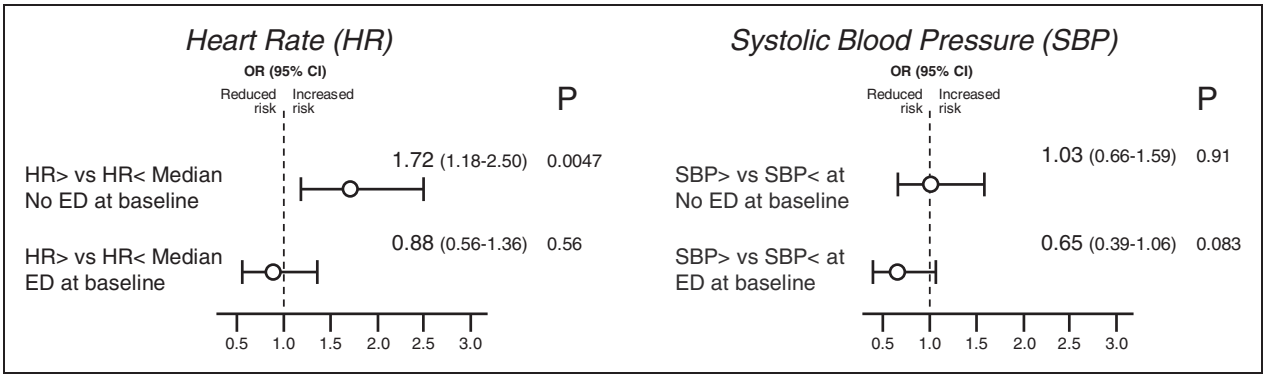

Figure 2. Heart rate (HR) or systolic blood pressure (SBP) above (>) or below (<) the median (left) with no erectile dysfunction (ED) at baseline or with ED at baseline.

Table 2. Odds ratios of erectile dysfunction (KEED ≥18) depending on age, erectile dysfunction status at baseline, HR mean, and SBP mean

	HR mean below median		HR mean above median	
	SBP mean below median	SBP mean above median	SBP mean below median	SBP mean above median
Unadjusted				
<65 years				
KEED at baseline <18	1 reference	1.01 (0.59–1.74)	1.40 (0.84–2.33)	2.14 (1.28–3.56)
KEED at baseline ≥18	8.30 (4.65–14.8)	11.2 (6.28–20.1)	16.0 (8.42–30.5)	5.95 (3.64–9.72)
≥65 years				
KEED at baseline <18	2.01 (1.50–2.68)	2.72 (1.34–5.53)	2.81 (1.58–5.02)	4.29 (2.36–7.80)
KEED at baseline ≥18	16.7 (8.71–31.9)	22.6 (12.0–42.6)	32.2 (15.9–65.0)	11.9 (6.8–21.0)
Adjusted for race, presence of angina, and use of diuretics				
<65 years				
KEED at baseline <18	1 reference	0.92 (0.72–1.17)	1.05 (0.57–1.96)	1.25 (0.75–2.10)
KEED at baseline ≥18	5.54 (2.78–11.0)	6.99 (4.05–12.1)	13.2 (6.10–28.5)	8.77 (4.91–15.7)
≥65 years				
KEED at baseline <18	1.88 (1.39–2.53)	2.37 (1.56–3.59)	1.98 (1.00–3.90)	2.36 (1.31–4.25)
KEED at baseline ≥18	10.4 (4.95–21.8)	13.1 (7.15–24.1)	24.8 (10.9–56.4)	16.4 (8.6–31.4)
Other factors				
Asian vs. White	1.26 (0.86–1.83)			
Other vs. White	0.69 (0.46–1.04)			
History of angina	0.74 (0.54–1.02)			
Use of diuretics	1.48 (1.04–2.12)			

HR is well recognized as a marker of cardiovascular outcomes in hypertension, coronary artery disease, or heart failure.[11–14] Higher HR is linked to endothelial dysfunction – which is reversible after pharmacological reduction of HR.[16,17] ED is linked to endothelial function in humans.[25,26] Higher BP is associated with coronary artery disease, heart failure, and stroke,[9] but also with ED.[27] Some antihypertensive treatments are associated with improvement of ED,[27,28] while others worsen ED.[29,30] Since ED is also associated with cardiovascular events,[6] we evaluated the effects of HR and SBP on ED.

Since ED is strongly associated with age,[31] we separated the population into those aged <65 and ≥65 years. There was a consistently higher prevalence of ED in the older population independent of higher SBP and higher HR, and similar results were seen in those who already had ED at baseline, with only minor spontaneous improvement (3–5%). We also evaluated the development of ED in relationship to baseline erectile function according to KEED scores. In the overall population, higher HR was significantly associated with presence of ED, if baseline KEED was below 18, while there was no significant effect of SBP. However, the effects of HR were accentuated at higher SBP, while lower SBP attenuated this. Overall, the negative impact of higher HR or higher SBP on ED was attenuated when either of these parameters was below the median. Our data also suggest that HR, unlike SBP, is predictive for ED development.

Higher heart rates have been associated with other microvascular damage,[16,17] which can be modified by interventions like diet.[32] Higher HR in higher-risk hypertensive subjects is associated with microalbuminuria in patients with sinus rhythm[33] and even more so with atrial fibrillation,[34] which can be modified by exercise.[35] In the PROFESS trial, patients after a first stroke experienced higher cognitive decline at higher HR (corrected for SBP), with a cut off of 77 bpm, without any change in the number of recurrent strokes or other cardiovascular outcomes.[36] This is supported by experimental results, where the increase of stroke size in a stress model is attenuated by HR reduction, resulting in less cerebral inflammation and smaller infarct size.[18] Therefore, high HR might induce microvascular disease leading to adverse cardiovascular outcomes,[6] cognitive decline,[36] and microalbuminuria.[33,34]

There are some potential limitations in this study. This analysis is a retrospective ad hoc analysis of a randomized trial with neutral outcomes. Therefore,

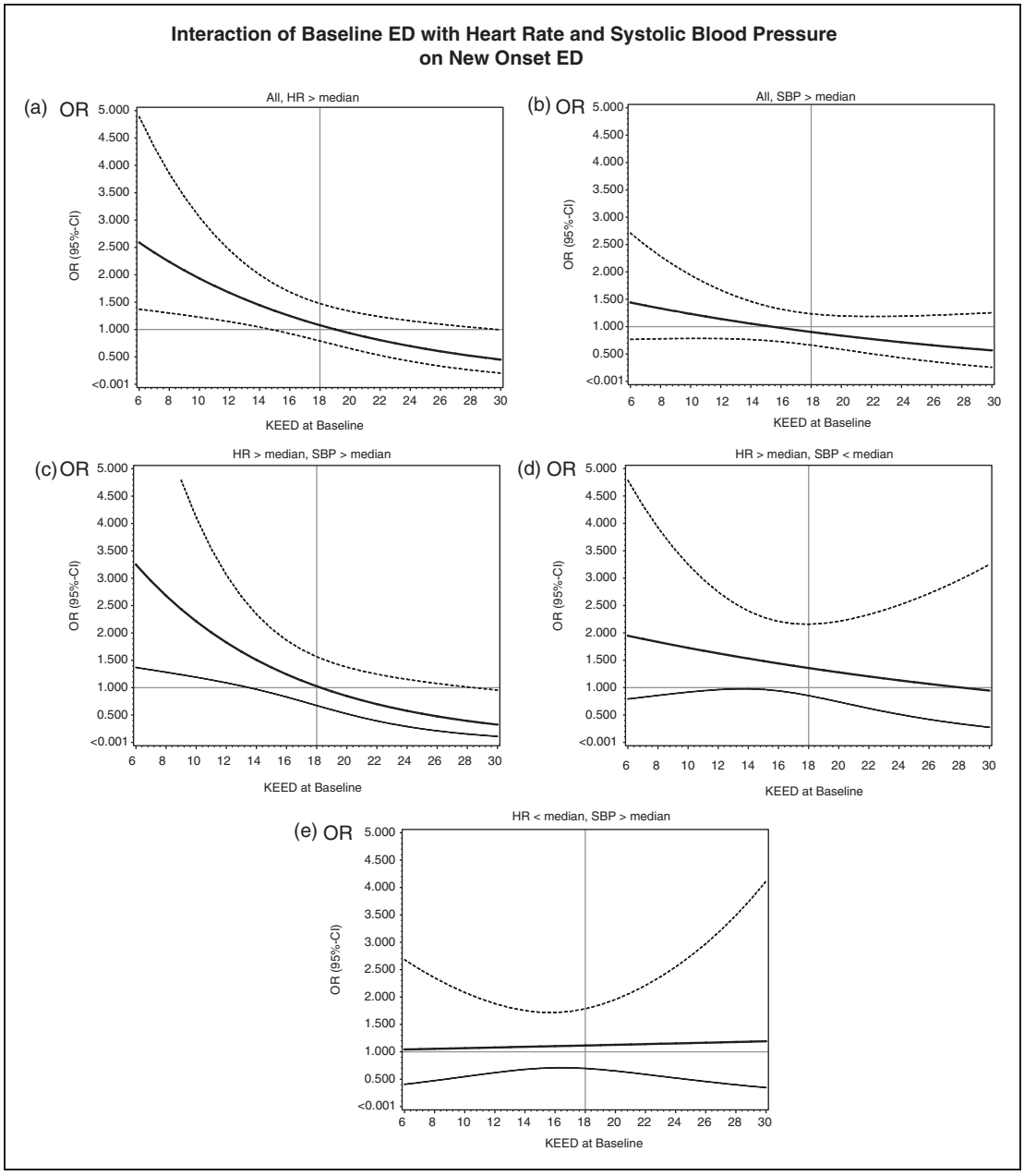

Figure 3. Odds ratio (OR) of new onset ED according to preexisting erectile status (KEED at baseline) in individuals with heart rate above the median (all, HR > median, a), systolic blood pressure above the median (all, SBP > median, b) or individuals with HR > median and SBP > median (c) or HR > median and SBP < median (d) or HR < median and SBP > median (e).

the grouping of HR above/below the median is non-random and we could only analyse for captured confounders. However, it is the largest database on ED with follow up of patients at high cardiovascular risk. Furthermore, it is the first study evaluating directly the interaction of HR and SBP in this type of microvascular damage. Another strength is that HR and SBP were available and measured over the whole study period at >10 visits. Therefore, the reliability of HR and SBP data provides important information about the interaction of these vital signs with the development of ED. Finally, it has to be pointed out that, in the ONTARGET/TRANSCEND population, BP was unusually well controlled, so our findings might be different from uncontrolled hypertension.

In conclusion, HR, but not SBP, is a risk marker for the development of ED in patients at high cardiovascular risk. The effect of HR appeared to be modified by SBP, which on its own did not show a significant effect. This hypotheses generating analysis puts forward the

not yet proven hypothesis that higher resting HR could be a potential therapeutic target to reduce new onset ED (in addition to achieving SBP control) in order to improve quality of life and subsequently improve cardiovascular outcomes, but this has to be investigated in prospective intervention trials in the future.

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Conflict of interest

All authors except MTK, FM, and JP were involved in the TRANSCEND and ONTARGET trial and received trial support from Boehringer-Ingelheim. MTK, FM, JP, and MB are supported by the Ministry of Economy and Science of the Saarland, Germany, the Deutsche Forschungsgemeinschaft (DFG, KFO 196), Deutsche Hochdrucklige (DHL, FM) and the Deutsche Gesellschaft für Kardiologie (DGK, FM, MB).

Clinical Trial Registration

www.clinialtrials.gov unique identifier: NCT 00153101.

References

1. NIH Consensus Development Panel on Impotence NIH Consensus Conference. Impotence. *JAMA* 1993; 270: 83–90.
2. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005; 294: 2996–3002.
3. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 2004; 291: 2978–2984.
4. Kloner RA and Speakman M. Erectile dysfunction and atherosclerosis. *Curr Atheroscler Rep* 2002; 4: 397–401.
5. Gazzaruso C, Solerte S, Pujia A, et al. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease. *J Am Coll Cardiol* 2008; 51: 2040–2044.
6. Böhm M, Baumhäkel M, Teo K, et al. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril or both. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular disease (ONTARGET/TRANSCEND) trials. *Circulation* 2010; 121: 1439–1446.
7. Ching-Wan R, So WY, Yang X, et al. Erectile dysfunction predicts coronary heart disease in type 2 diabetes. *J Am Coll Cardiol* 2008; 51: 2045–2050.
8. Kloner R. Erectile dysfunction. *J Am Coll Cardiol* 2008; 51: 2051–2052.
9. Chobanian AV, Bakris GL, Black HR, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42: 1206–1252.
10. Lewington S, Whitlock G, Clarke R, et al. Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths. *Lancet* 2007; 370: 1829–1839.
11. Reil JC, Custodis F, Swedberg K, et al. Heart rate reduction in cardiovascular disease and therapy. *Clin Res Cardiol* 2011; 100: 11–19.
12. Kolloch R, Legler UF, Champion A, et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the International Verapamil-SR/trandolapril Study (INVEST). *Eur Heart J* 2008; 29: 1327–1334.
13. Diaz A, Bourassa MG, Guertin MC, et al. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005; 26: 967–974.
14. Böhm M, Swedberg K, Komajda M, et al. SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomized placebo-controlled trial. *Lancet* 2010; 376: 886–894.
15. Solomon H, Man JW and Jackson G. Erectile dysfunction and the cardiovascular patients: endothelial dysfunction is the common denominator. *Heart* 2003; 89: 251–253.
16. Custodis F, Schirmer S, Baumhäkel M, et al. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol* 2010; 56: 1973–1983.
17. Custodis F, Baumhäkel M, Schlimmer N, et al. Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function and prevents atherosclerosis in apolipoprotein E deficient mice. *Circulation* 2008; 117: 2377–2387.
18. Custodis F, Gertz K, Balkaya M, et al. Heart rate contributes to the vascular effects of chronic mental stress: effects on endothelial function and ischemic brain injury in mice. *Stroke* 2011; 42: 1742–1749.
19. Baumhäkel M, Schlimmer N, Büyükafsar K, et al. Nebivolol, but not metroprolol, improves endothelial function of the corpus cavernosum in apolipoprotein E-knockout mice. *J Pharmacol Exp Ther* 2008; 325: 818–823.
20. Baumhäkel M, Custodis F, Schlimmer N, et al. Heart rate reduction with ivabradine improves erectile dysfunction in parallel to decrease in atherosclerosis plaque load in ApoE-knockout mice. *Atherosclerosis* 2010; 212: 55–62.
21. ONTARGET Investigators. Telmisartan, ramipril or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–1559.

22. TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. *Lancet* 2008; 372: 1174–1183.
23. Böhm M, Baumhäkel M, Probstfield J, et al. ONTARGET/TRANSCEND ED-Investigators. Sexual function, satisfaction and association of erectile dysfunction with cardiovascular disease and risk factors in cardiovascular high-risk patients: substudy of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNT Study in ACE-Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND). *Am Heart J* 2007; 154: 94–101.
24. Braun M, Wassmer G, Klotz T, et al. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res* 2000; 12: 305–311.
25. Solomon H, Man JW and Jackson G. Erectile dysfunction and the cardiovascular patients: endothelial dysfunction is the common denominator. *Heart* 2003; 89: 251–253.
26. Billups KL. Endothelial dysfunction as a common link between erectile dysfunction and cardiovascular disease. *Current Sexual Health Reports* 2004; 1: 137–141.
27. Düsing R. Sexual dysfunction in male patients with hypertension. Influence of antihypertensive drugs. *Drugs* 2005; 66: 772–786.
28. Baumhäkel M, Schlimmer N and Böhm M. Effect of irbesartan on erectile function in patients with hypertension and metabolic syndrome. *Int J Impot Res* 2008; 20: 493–500.
29. Baumhäkel M, Schlimmer N, Kratz M, et al. Cardiovascular risk, drugs and erectile function – a systematic analysis. *Int J Clin Pract* 2011; 65: 289–298.
30. Grimm RH Jr, Granditis GA, Prineas RJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: treatment of mild hypertension study (TOMHS). *Hypertension* 1997; 28: 8–14.
31. Blanker MH, Bosch JL, Groeneveld FP, et al. Erectile and ejaculatory dysfunction in a community-based sample of men 50–78 years old: prevalence, concern, and relation to sexual activity. *Urology* 2001; 57: 763–768.
32. García-López M, Martínez-González M, Basterra-Gortari F, et al. Adherence to the Mediterranean dietary pattern and heart rate in the SUN project. *Eur J Prev Cardiol* 2012; Epub ahead of print.
33. Böhm M, Reil J-R, Danchin N, et al. Association of heart rate with microalbuminuria in cardiovascular risk patients: data from I-SEARCH. *J Hypertens* 2008; 26: 18–25.
34. Böhm M, Thoenes M, Neuberger H–R, et al. Atrial fibrillation and heart rate independently correlate to microalbuminuria in hypertensive patients. *Eur Heart J* 2009; 30: 1364–1371.
35. Pöss J, Ukena C, Mahfoud F, et al. Physical activity is inversely associated with microalbuminuria in hypertensive patients at high cardiovascular risk: data from I-SEARCH. *Eur J Prev Cardiol* 2012; 19: 1066–1073.
36. Böhm M, Cotton D, Foster L, et al. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *Eur Heart J* 2012; 33: 2804–2812.

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In the above paper the affiliation for Guiseppe Mancia was incorrect, the correct details are published below.

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