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Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial

Michael Böhm[1]*, Felix Mahfoud[1], Raymond R. Townsend[2], David E. Kandzari[3], Stuart Pocock[4], Christian Ukena[1], Michael A. Weber[5], Satoshi Hoshide[6], Manesh Patel[7], Crystal C. Tyson[8], Joachim Weil[9], Tolga Agdirlioglu[9], Martin Fahy[10], and Kazuomo Kario[6]

[1]Department of Internal Medicine III, University Hospital of Saarland, Saarland University, Kirrberger Street 1, 66421 Homburg/Saar, Germany; [2]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA; [3]Department of Interventional Cardiology, Piedmont Heart Institute, 275 Collier Rd NW #500, Atlanta, GA 30309, USA; [4]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, Keppel St, Bloomsbury, London, WC1E 7HT, UK; [5]Department of Medicine, SUNY Downstate College of Medicine, 450 Clarkson Ave, Brooklyn, NY 11203, USA; [6]Department of Cardiovascular Medicine, Jichi Medical University School of Medicine, Tochigi, Tochigi-ken 329-0498, Japan; [7]Department of Cardiology, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27710, USA; [8]Department of Internal Medicine, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27710, USA; [9]Department of Cardiology, Sana Cardiomed Heart Center, Kronsforder Allee 71, 23560 Lübeck, Germany; and [10]Medtronic PLC, Santa Rosa, CA, USA

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Aims The randomized sham-controlled SPYRAL HTN-OFF MED trial demonstrated that renal denervation (RDN) using a multi-electrode catheter lowers ambulatory blood pressure (BP) in non-medicated hypertensive patients. The current report describes the effects of RDN on heart rate (HR) in this population.

Methods and results Patients were enrolled with an office systolic BP (SBP) of ≥150 mmHg and <180 mmHg, office diastolic BP (DBP) of ≥90 mmHg, and a mean ambulatory SBP of ≥140 mmHg and <170 mmHg. Patients were drug naïve or removed from their anti-hypertensive medications. Eighty patients were randomized 1:1 to RDN or sham procedure. This *post hoc* analysis examines the effect at 3 months of RDN on HR and of high baseline 24-h HR on BP and HR changes. There was a significant reduction in 24-h HR at 3 months for the RDN group (-2.5 b.p.m.) compared with sham (-0.2 b.p.m.), $P = 0.003$ (analysis of covariance). Mean baseline-adjusted treatment differences were significantly different between groups at 3 months for average morning HR (-4.4 b.p.m., $P = 0.046$) and minimum morning HR (-3.0 b.p.m., $P = 0.026$). RDN patients with baseline 24-h HR above the median (73.5 b.p.m.) had significant reductions in average ambulatory SBP (-10.7 mmHg difference, $P = 0.001$) and DBP (-7.5 mmHg, $P < 0.001$), whereas BP changes in RDN patients with below-median HRs were not significant.

Conclusion Average and minimum morning HR were significantly reduced at 3 months for RDN compared with sham patients. A baseline 24-h HR above the median predicted greater BP reductions and may allow physicians to select patients likely to respond to the procedure.

Keywords Heart rate • Renal denervation • Hypertension

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

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Introduction

Heart rate (HR) is regulated by the interaction of the sympathetic and parasympathetic nervous system.[1] High resting HR is associated with cardiovascular morbidity and mortality in the general population,[2] as well as increased incidence of hypertension,[3,4] elevated risk status[5] and worsened renal outcomes.[6] In a high-risk population where 75% had hypertension, elevated HR is predictive of incident heart failure[7] and it indicates an elevated risk for heart failure hospitalization and cardiovascular death in heart failure patients.[8] Renal denervation (RDN) has revealed promising results in uncontrolled studies[9,10] and in comparative, controlled studies with antihypertensive drugs plus RDN.[11] After one randomized, blinded trial with some methodological uncertainties,[12] the recently published SPYRAL HTN-OFF MED study provided evidence for a significant reduction of blood pressure (BP) in patients without medications in a randomized sham-controlled study design.[13] In patients with resistant hypertension, a reduction of HR after RDN has been observed in a single-centre study[14] and in the large Global Symplicity Registry.[15] More than 50% of patients in the latter trial received beta blockers and many other anti-hypertensive drugs, which might have confounded the effect of RDN on HR.[14,15] In this analysis, we re-evaluated the effect of RDN on the 24-h ambulatory HR in the RDN group compared with the blinded sham group from the SPYRAL HTN-OFF MED study in order to avoid confounding by antihypertensive medication, in particular beta blockers. This study therefore investigated the effect on HR detected by ambulatory BP monitors (ABPM) and day- and night-time average HRs as well as day- and night-time surges in HRs. Furthermore, the BP response was studied at time points where sympathetic activities according to HRs were particularly high (HR above and below the median 73.5 b.p.m.).

Methods

Study design in patients

The rationale and study design of SPYRAL HTN-OFF MED (clinicaltrials.gov: NCT02439749) has been described elsewhere.[16] In brief, SPYRAL HTN-OFF MED was a multicentre, international, single-blinded, randomized, sham-controlled proof-of-concept trial enrolling patients aged 20–80 years with mild to moderate hypertension. Inclusion criteria were an office systolic BP (SBP) ≥150 mmHg and <180 mmHg, office diastolic BP (DBP) ≥90 mmHg and a mean 24-h ambulatory SBP ≥140 mmHg and <170 mmHg. Patients were enrolled in the USA (10 centres), Germany (four centres), Japan (two centres), UK (two centres), and Australia, Austria, and Greece (one centre each). The trial complies with the Declaration of Helsinki, local ethics committees of all centres approved the research protocol and written informed consent was obtained from all patients.

Blinding and randomization

Patients were assigned either to RDN or sham procedure by a 1:1 randomization. Randomization was done by Icon PLC by use of SAS based software to generate lists of randomization codes. Before randomization, patients were required to be off all anti-hypertensive medication. An initial screening visit was done to verify eligibility criteria and initiate medication washout if needed. After a 3–4-week washout period, BP levels were confirmed to determine patient eligibility for randomization. All patients' urine and plasma were evaluated for the absence of anti-hypertensive medication by use of tandem high performance liquid chromatography and mass spectrography by an independent laboratory.[17] Office BP and HR measurements were obtained with an automated BP monitor (Omron, Omron Health Care, Inc., Lake Forest, IL, USA). The 24-h ABPM (Mobil-O-Graph I.E.M. GmbH, Stolberg, Germany) was applied to evaluate BP and HR over 24 h. Blood pressure and HR was taken every 30 min and only patients with at least 21 daytime and 12 night-time measurements were included in the final analysis.

Intervention

Patients were not informed of their randomization and were scheduled for eligibility by renal angiogram. If anatomically suitable, patients were randomized to RDN or the sham procedure. During this procedure patients were blinded by a combination of sensory isolation (blindfolding and music) and conscious sedation. Patients were not familiar with procedural details and duration of the angiogram. Physicians and designated staff were blinded during the angiogram until randomization and assignment to the respective treatment arm. All follow-up visits were performed by blinded staff and referring physicians were not informed of the treatment allocation. The blinding score was determined by asking patients to guess which randomization group they were allocated to at discharge and at 3 months.

Radiofrequency ablation treatments were performed using the Symplicity Spyral multi-electrode catheter (Medtronic, Galway, Ireland) and the Symplicity G3 (Medtronic, Minneapolis, MN, USA) generator. This catheter allows circumferential ablation treatments in a spiral pattern in all four quadrants of vessels greater than 3 mm and less than 8 mm. All interventionalists had previous experience with RDN and completed a structured proctoring programme. With this approach, all accessible renal arteries including branch vessels and accessory arteries were targeted. A renal angiogram was performed in the control group and patients remained on the table for at least 20 min to prevent unblinding.

Blood pressure and heart rate effects

The primary efficacy outcome was BP reduction based on ABPM measurements at 3 months, which was not a pre-specified endpoint but an important physiological measure. In this *post hoc* analysis, we examine the effects of RDN on HR at different daytime and night-time periods. Daytime and night-time periods in this analysis were defined as 9:00 a.m. to 8:59 p.m. and 1:00 a.m. to 5:59 a.m., respectively.[18] Specific parameters were defined as follows[19]: average morning HR as average HR measured between 7:00 a.m. and 8:59 a.m., moving peak morning HR as highest 1 h moving average of ≥3 consecutive HR measurements between 6:00 a.m. and 9:59 a.m., average morning HR surge as average morning HR minus average night-time HR, average peak night-time HR as average of three highest HR measurements during the night-time, moving lowest night HR as lowest 1-h moving average of ≥3 consecutive night-time HR measurements, and average night-time HR surge as average peak night-time HR minus average night-time HR. Then, groups were separated by average 24-h HR above and below the median (median = 73.5 b.p.m.) and the BP responses for average 24-h, average daytime, average night-time SBP and DBP were evaluated. In addition, morning average, maximum, and minimum SBP were evaluated in the two HR groups.

Night-time HR fall (%) was calculated as $100*[1 - HR_{PM}/HR_{AM}]$, where HR_{PM} is mean night-time HR and HR_{AM} is mean daytime HR. Patients were classified as extreme dippers if night-time HR fall was >20%, dippers had a drop ≥10% and <20%, non-dippers had a drop ≥0% and <10%, and reverse dippers had a drop <0%.

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Statistical analysis

Statistical analysis was performed according to the intention to treat principle. Means and standard deviations of continuous variables are presented per treatment group. Analysis of covariance was employed to adjust for baseline BP measurements. Between group differences were tested with unpaired *t*-tests and differences between baseline and a 3-month follow-up assessment test with paired *t*-tests. Comparison of treatment groups for categorical variables was tested with the exact test for binary variables and the χ^2 test for multilevel categorical variables. Interaction testing between baseline 24-h HR and treatment effect on 3-month outcomes was also conducted. SAS (version 9.2) was used for all statistical analyses and the sponsor (Medtronic) performed the statistical analyses. All authors had full access to the data.

Table 1 Baseline demographics

	RDN (*N* = 38)	Sham control (*N* = 42)
Age (years), mean ± SD	55.8 ± 10.1	52.8 ± 11.5
Male, % (*N*)	68.4 (26)	73.8 (31)
BMI (kg/m^2), mean ± SD	29.8 ± 5.1	30.2 ± 5.1
Body weight (kg), mean ± SD	88.8 ± 16.6	90.9 ± 19.1
Diabetes Type 2, % (*N*)	2.6 (1)	7.1 (3)
Current smoker, % (*N*)	10.5 (4)	23.8 (10)
Obstructive sleep apnoea, % (*N*)	7.9 (3)	7.1 (3)
Peripheral artery disease, % (*N*)	2.6 (1)	0.0 (0)
Coronary artery disease[a], % (*N*)	0.0 (0)	4.8 (2)
Stroke and transient ischaemic attack[a], % (*N*)	2.6 (1)	0.0 (0)
Myocardial infarction/acute coronary syndrome[a], % (*N*)	0.0 (0)	2.4 (1)

P = NS for differences in all baseline characteristics.
BMI, body mass index; RDN, renal denervation; SD, standard deviation.
[a]These events occurred >3 months before randomization.

Results

The first results of SPYRAL HTN-OFF MED were generated in 38 patients after RDN and 42 patients after sham procedure. *Table 1* summarizes the baseline patient characteristics. There were no statistical differences according to baseline characteristics. Patients were overweight and had low prevalence of comorbidities like diabetes Type 2, obstructive sleep apnoea, peripheral artery disease, coronary disease, history of stroke and transient ischaemic attack, or acute coronary syndrome. Blinding was successfully achieved, and the majority of patients adhered to the protocol and had no evidence of antihypertensive medication used in the toxicological analysis at baseline and after 3 months as previously reported.[13]

Mean 24-h HR, SBP, and DBP measurements were similar at baseline (*Table 2*). Changes in 24-h HR and DBP at 3 months were significantly different for the RDN group compared with sham and trended towards greater reduction for SBP (*Table 2*).

There was a nominal decrease in average daytime HR and maximum morning HR, while average morning HR was significantly reduced compared with sham (*Figure 1A*). Average night-time and maximum night-time HR were not significantly reduced, but a significant difference between groups was observed for average peak night-time HR (*Figure 1B*). *Figure 1C* shows a significant reduction and intergroup difference in the minimum morning HR and moving peak morning HR. The difference between groups for the average HR surge was not statistically significant (*Figure 1C*). Likewise, moving lowest and minimum night-time HR and average night-time surge were numerically but not significantly different.

Given that increased sympathetic tone impacts HR and RDN is hypothesized to impact systemic and sympathetic tone, an analysis was done to see if baseline HR predicts the response of RDN to both HR and BP. We separated the populations into those with a 24-h baseline HR above and below the median (≥ or <73.5 b.p.m.). *Figure 2A* shows that for a HR above the median, there was a significant reduction of average 24-h SBP, average 24-h DBP, and average

Table 2 24-h heart rate and blood pressure measurements at baseline and 3 months, and changes at 3 months

	Baseline		3 months		Change at 3 months		
	RDN (*N* = 35)	Sham (*N* = 36)	RDN (*N* = 35)	Sham (*N* = 36)	RDN (*N* = 35)	Sham (*N* = 36)	Mean difference: RDN vs. sham[a]
24-h HR (b.p.m.)	72.9 ± 11.0	74.4 ± 11.7	70.4 ± 8.5	74.2 ± 9.6	-2.5 ± 5.3 (-4.3 to -0.7)	-0.2 ± 4.1 (-1.5 to 1.2)	-2.7 (-4.5 to -1.0) *P* = 0.003
24-h SBP (mmHg)	153.5 ± 9.2	152.3 ± 7.6	148.0 ± 10.8	151.8 ± 11.1	-5.5 ± 10.3 (-9.1 to -2.0)	-0.5 ± 10.1 (-3.9 to 2.9)	-4.6 (-9.2 to 0.1) *P* = 0.053
24-h DBP (mmHg)	99.6 ± 7.4	98.9 ± 8.3	94.8 ± 8.3	98.5 ± 9.9	-4.8 ± 6.4 (-7.0 to -2.6)	-0.4 ± 5.4 (-2.2 to 1.4)	-4.3 (-7.1 to -1.5) *P* = 0.003

Data are presented as mean ± standard deviation.
b.p.m., beats per minute; DBP, diastolic blood pressure; HR, heart rate; RDN, renal denervation; SBP, systolic blood pressure.
[a]*P*-value from analysis of covariance model, adjusting for baseline heart rate or blood pressure.

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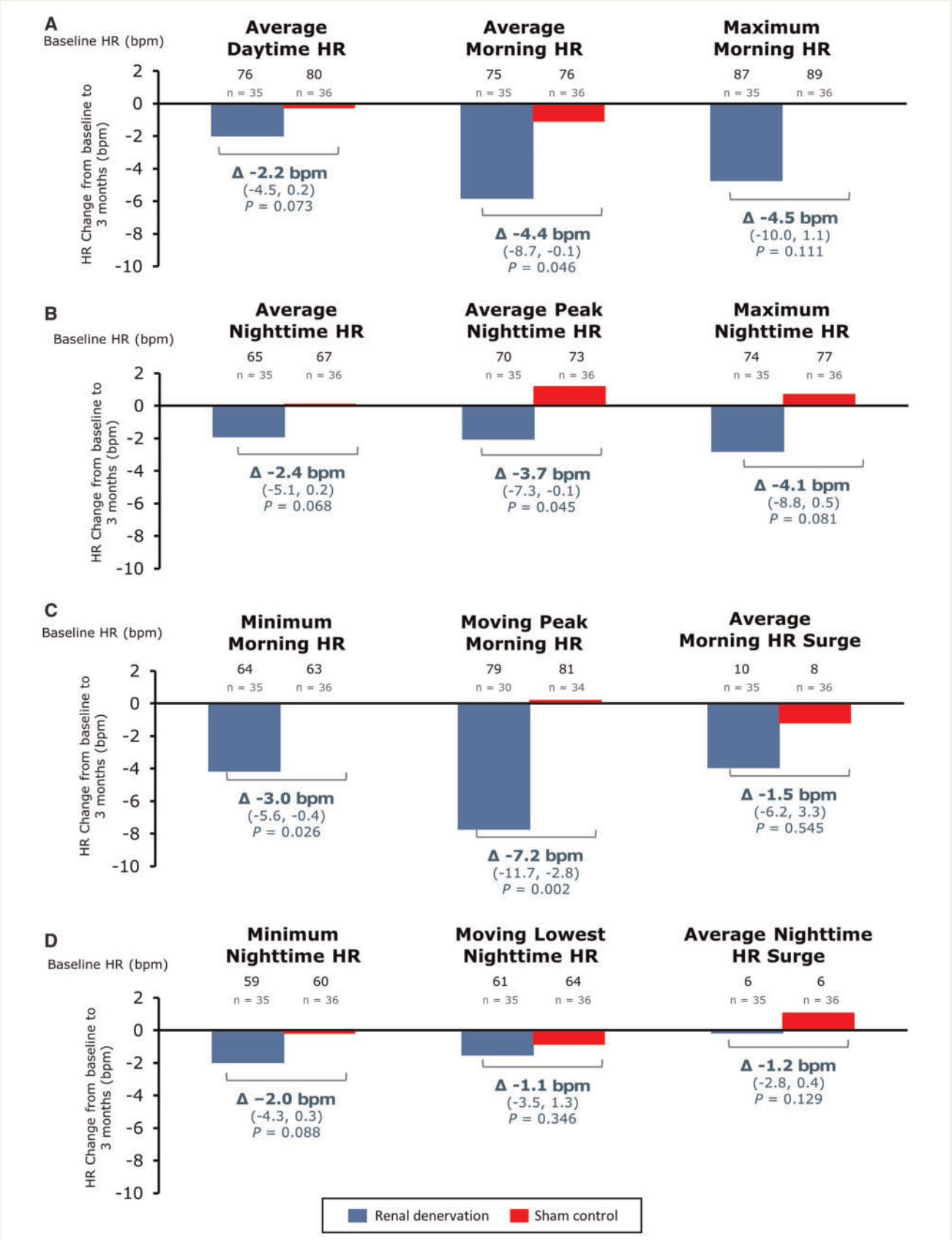

Figure 1 Changes in 24-h heart rate after renal denervation (blue) or sham treatment (red) on average daytime heart rate, average morning heart rate, and maximum morning heart rate (*A*); average night-time heart rate, average peak night-time heart rate, and maximum night-time heart rate (*B*); minimum morning heart rate, moving peak morning heart rate, and average morning heart rate surge (*C*); and minimum night-time heart rate, moving peak night-time heart rate, and average night-time heart rate surge (*D*). Treatment differences, 95% confidence intervals and *P*-values were calculated from analysis of covariance model, adjusting for baseline blood pressure.

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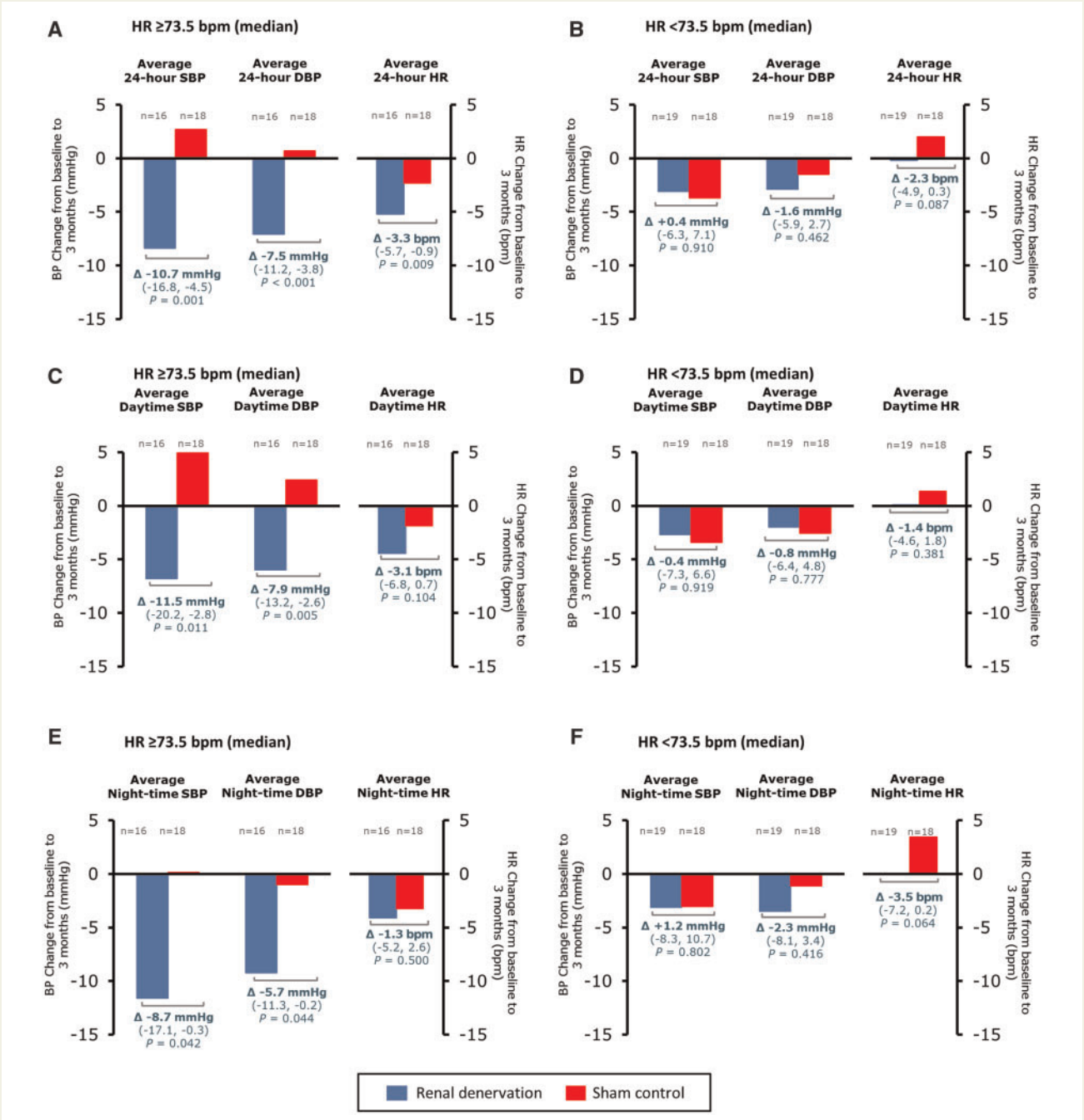

Figure 2 Changes in heart rate and blood pressure from baseline to 3 months comparing patients with baseline 24-h heart rate above and below the median (73.5 b.p.m.). Treatment differences, 95% confidence intervals and *P*-values were calculated from analysis of covariance model, adjusting for baseline blood pressure. *P*-values calculated from interaction testing (*P*int) between baseline 24-h heart rate and treatment effect for each 3-month outcome are included. (*A* and *B*) Compare average 24-h systolic blood pressure (*P*int = 0.028), diastolic blood pressure (*P*int = 0.044), and heart rate (*P*int = 0.306). (*C* and *D*) Compare average daytime systolic blood pressure (*P*int = 0.029), diastolic blood pressure (*P*int = 0.015), and heart rate (*P*int = 0.398). (*E* and *F*) Compare average night-time systolic blood pressure (*P*int = 0.049), diastolic blood pressure (*P*int = 0.205), and heart rate (*P*int = 0.842).

24-h HR for the RDN group compared with sham. These reductions were greater compared with the subgroups with a HR below the median (<73.5 b.p.m.), where no statistical intergroup differences were observed (*Figure 2B*). Similar results were obtained for average daytime SBP and DBP (*Figure 2C*) and average night-time SBP and DBP (*Figure 2E*) with significant reductions after RDN in the group with baseline 24-h HR above the median. Compared with the group with lower 24-h baseline HRs (<73.5 b.p.m. median), no differences in average daytime SBP, DBP, or HR (*Figure 2D*) or night-time SBP, DBP, or HR (*Figure 2F*) were observed. Finally, the average morning SBP was significantly reduced only at a HR above the median, but not below (see Supplementary material online, *Figure S1A and B*).

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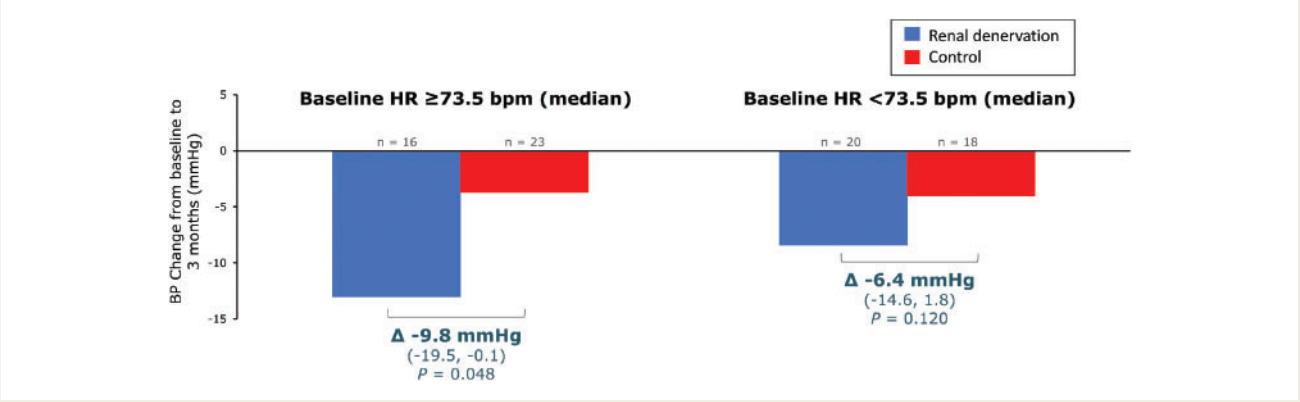

Figure 3 Changes in average office systolic blood pressure in patients with a 24-h baseline heart rate above the median (≥73.5 b.p.m.) (left) and below the median (<73.5 b.p.m.) (right) after renal denervation (blue) or sham procedure (red). Treatment differences, 95% confidence intervals and *P*-values were calculated from analysis of covariance model, adjusting for baseline blood pressure. *P*-value calculated from interaction testing between baseline 24-h heart rate and treatment effect for average office systolic blood pressure was 0.330.

In order to explore whether the average office BP response was different according to average 24-h baseline HR, we investigated the average office SBP changes from baseline to 3 months. There was a significant difference between RDN and sham groups at HRs above the median (≥73.5 b.p.m.), but not for patients with HRs below the median (*Figure 3*). Changes in 24-h, morning, daytime, and night-time HR at 3 months for individual patients in RDN and sham groups are shown in *Figure 4*. Overall, the dipping patterns of HR did not change after RDN (see Supplementary material online, *Table S1*).

Discussion

Renal denervation therapy has been shown to reduce BP in open studies,[9,10] two randomized studies[11,20] and one randomized sham-controlled trial[21] as well as one real-world registry involving more than 2000 patients.[22] The recently published randomized, sham-controlled SPYRAL HTN-OFF MED trial provided the biological proof of principle that catheter-based RDN can reduce BP in hypertensives without any anti-hypertensive medications.[13] Therefore, neither the effect of BP reduction nor the effect of other physiological parameters of sympathetic activation like HR is confounded by the effects of drugs. Herein, we report that RDN reduces HR measured during ABPM with a different effect at various times of the day. Significant reduction of HR was observed in the morning with significant reductions of the peak morning HR and average morning HR surge. Importantly, patients with baseline 24-h HR above the median had greater reductions in 24-h mean, daytime, and night-time BP after RDN. Higher baseline HR could be a surrogate test for neurogenic hypertension, potentially providing a method of identifying patients likely to respond to RDN.

This investigation confirms and extends previous studies[14,15] that reported a decrease in HR after RDN. However, in the previous studies, including a large single-centre registry[14] and the Global Symplicity Registry[15], HR was not predictive of BP reduction by RDN. However, 88% and 77% of these patients were treated with beta blockers, respectively.[14,15] Therefore, pharmacological treatments might have confounded the association between HR and BP reduction. The SPYRAL HTN-OFF MED study provides a unique opportunity to examine the association of HR to BP responses in the absence of medications. Herein, we report that in patients with a HR above the median as a potential sign of sympathetic activation, higher HR was predictive of reduction in average daytime SBP, daytime DBP, and office SBP.

Only limited data are available on HR from 24-h ambulatory recordings, so we performed an in-depth analysis employing parameters previously characterized for ambulatory BP recordings. Interestingly, the analysis of 24-h HR sheds light on the differential effects of sympathetic modulation on HR profiles. While there was a significant reduction of HR in the morning hours and during daytime, there was no significant effect on HR at night. Furthermore, the lowest HRs in the morning were more reduced than higher HRs at daytime. This study suggests the hypothesis that RDN may act in part by decreasing basal sympathetic activity, while still maintaining the capacity to activate the sympathetic nervous system during activity or in response to stimulus. This is in agreement with exercise studies[23,24] showing that BP and HR are reduced, not only on exercise but also at rest. However, the increase of HR and BP during exercise is not affected by catheter-based RDN treatment for hypertension.[23,24] Nevertheless, the complex interaction of HR, sympathetic drive and parasympathetic activity, potentially also affected by RDN has to remain open presently.

Heart rate is a predictor of cardiovascular outcomes in various cardiovascular and non-cardiovascular conditions,[23,25] including in the general population,[3] in hypertension,[4,5] in high-risk vascular patients after stroke or myocardial infarction[7] and in heart failure.[8] Diagnostic data from implantable cardiac devices such as high night-time HR have been associated with a higher risk of heart failure re-admission.[26] Also, night-time and morning BPs are more significantly associated with cardiovascular outcomes compared with average 24-h SBP or average daytime SBP.[25] Therefore, 24-h HR profiles and their association to cardiovascular outcomes need to be studied in

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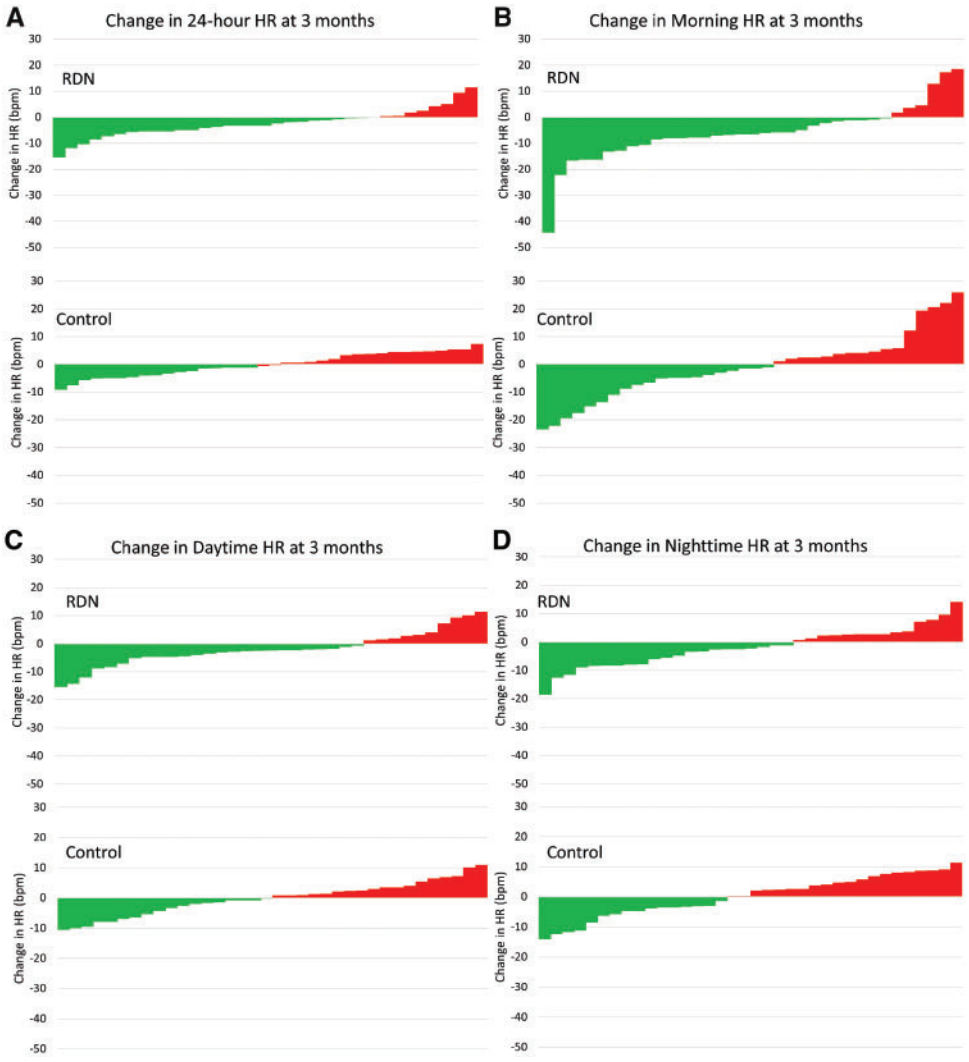

Figure 4 Changes at 3 months for individual patients in renal denervation and sham control groups for (*A*) 24-h heart rate; (*B*) morning heart rate; (*C*) daytime heart rate; and (*D*) night-time heart rate. b.p.m.: beats per minute; RDN: renal denervation.

the future. Herein, we observed that a particular reduction in morning HRs after RDN. The same association exists for BP. Further study is needed to determine whether reduction in BP or HR is more closely associated with a reduction in adverse outcomes.

Limitations

Several limitations should be considered. This was a proof-of-concept trial with a small sample size, and HR was not pre-specified as a secondary endpoint. Nevertheless, the strict and rigorous inclusion criteria, rigorous blinding of investigators and patients as well as toxicological drug testing resulted in low variability of these data. The advancement of RDN technology compared with previous studies[9–12] resulted in a significant and clinically meaningful BP and HR reduction, reported herein. The SPYRAL Pivotal trial has identical inclusion and exclusion criteria to the OFF MED trial with a larger sample size powered to demonstrate the safety and efficacy of RDN. Finally, HR is also affected by vagal activation potentially altered in hypertension with different degrees of sympathetic activity or different comorbidities like obesity or diabetes. Thus, mechanistic conclusions about regulation of HR by central or peripheral sympatho-parasympathetic interactions remain behind the horizon of these clinical observations. The concept of RDN to reduce sympathetic activation in disease states is summarized in the *Take home figure*.

Conclusion

In conclusion, catheter-based RDN reduced BP, particularly in the morning hours. These findings indicate that sympathetic modulation with RDN also involves HR reduction, which has been associated with cardiovascular outcomes.[2–8,23,24] If confirmed in a larger, more definitive trial, identification of high average 24-h HRs could allow physicians to select patients responding to RDN.

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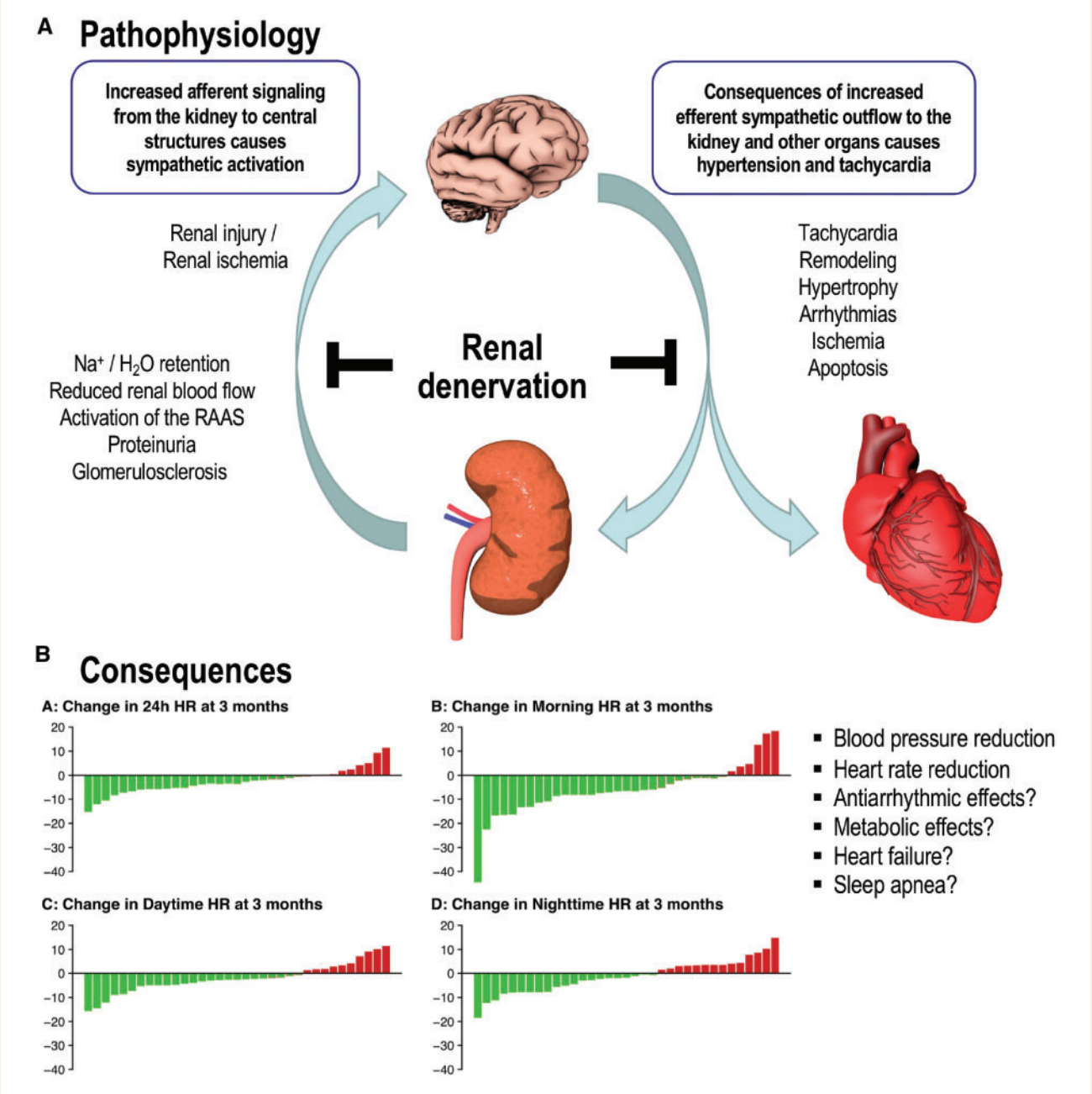

Take home figure Physiology of sympathetic activation by the interaction of the brain with the kidneys involved in hypertension and high heart rate as well as other sympathetically driven disturbances like arrhythmias, metabolic disease, heart failure, and sleep apnoea. Renal denervation, by using contemporary approaches allowing renal artery main-stem and branch treatments, exerts effects not only on blood pressure but also on ambulatory circadian heart rate parameters. (*A*) Sympathetic activation is generated in the brain and stimulates the heart, the vessels and the kidney by efferent nerves, which mediate the physiological and pathophysiological effects. In turn, afferent nerve stimulation from the kidney to the sympathetic nervous system increase central sympathetic outflow producing a vicious cycle effect on whole body sympathetic activity. Renal denervation interrupts afferent and efferent signalling to the brain reducing sympathetic activity. The contemporary technique using the SPYRAL catheter system allowing reliable circumferential as well as branch plus main-stem treatments has been used. (*B*) The consequences are a reduction of 24-h heart rate, morning heart rate, daytime- and night-time heart at 3 months, which was significantly different compared with placebo in particular at a higher baseline heart rate. While the blood pressure reducing effects have been reported previously and the heart rate effects are reported herein, the significance of experimental findings like antiarrhythmic effects, metabolic effects, effects on heart failure models, and sleep apnoea need to be scrutinized in clinical studies.

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Supplementary material

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

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