ORIGINAL RESEARCH

Effect of Arteriovenous Anastomosis on Blood Pressure Reduction in Patients With Isolated Systolic Hypertension Compared With Combined Hypertension

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***Background*—**Options for interventional therapy to lower blood pressure (BP) in patients with treatment-resistant hypertension include renal denervation and the creation of an arteriovenous anastomosis using the ROX coupler. It has been shown that BP response after renal denervation is greater in patients with combined hypertension (CH) than in patients with isolated systolic hypertension (ISH). We analyzed the effect of ROX coupler implantation in patients with CH as compared with ISH.

***Methods and Results*—**The randomized, controlled, prospective ROX Control Hypertension Study included patients with true treatment-resistant hypertension (office systolic BP ≥140 mm Hg, average daytime ambulatory BP ≥135/85 mm Hg, and treatment with ≥3 antihypertensive drugs including a diuretic). In a post hoc analysis, we stratified patients with CH (n=31) and ISH (n=11). Baseline office systolic BP (177±18 mm Hg versus 169±17 mm Hg, *P*=0.163) and 24-hour ambulatory systolic BP (159±16 mm Hg versus 154±11 mm Hg, *P*=0.463) did not differ between patients with CH and those with ISH. ROX coupler implementation resulted in a significant reduction in office systolic BP (CH: −29±21 mm Hg versus ISH: −22±31 mm Hg, *P*=0.445) and 24-hour ambulatory systolic BP (CH: −14±20 mm Hg versus ISH: −13±15 mm Hg, *P*=0.672), without significant differences between the two groups. The responder rate (office systolic BP reduction ≥10 mm Hg) after 6 months was not different (CH: 81% versus ISH: 82%, *P*=0.932).

***Conclusions*—**Our data suggest that creation of an arteriovenous anastomosis using the ROX coupler system leads to a similar reduction of office and 24-hour ambulatory systolic BP in patients with combined and isolated systolic hypertension.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01642498. **(*J Am Heart Assoc*. 2016;5: e004234 doi: 10.1161/JAHA.116.004234)**

Key Words: arteriovenous anastomosis • combined hypertension • isolated systolic hypertension • treatment resistant hypertension

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Arterial hypertension is the most prevalent and major modifiable risk factor for cardiovascular morbidity and mortality worldwide.[1] Although several effective and safe antihypertensive drug classes are available, the prevalence rate of treatment-resistant hypertension (TRH) remains ≈8% to 15%.[2,3] Moreover, it has been reported that within a median of 1.5 years after initiation of antihypertensive treatment, 1 of 50 patients develops TRH.[4] This is of crucial importance, since the diagnosis of TRH carries significantly greater cardiovascular risk compared with patients without TRH.[5,6] Therefore, innovative therapeutic strategies are needed to achieve blood pressure (BP) control and reduction of cardiovascular mortality in this population.

Several interventional approaches for lowering BP in patients with TRH have recently been introduced. Most depend on modulation of sympathetic activity, for example through renal denervation (RDN) or baroreflex activation. However, the BP response to RDN is markedly heterogeneous and it is not fully known whether this is due to technical failure or a diminished role of renal sympathetic signaling in nonresponders.[7–9] It has been suggested that the effect of reduced sympathetic activity (due to RDN), and hence the potential to decrease BP in the short term may be limited in patients with advanced vascular remodeling.[10] Furthermore, in patients with isolated systolic hypertension (ISH) (office BP ≥140 mm Hg systolic and <90 mm Hg diastolic), indicative of arterial stiffness, BP reduction due to RDN was attenuated compared with patients with combined hypertension (CH) (office BP ≥140/≥90 mm Hg).[11] This was confirmed in a post hoc analysis of pooled data from the Symplicity HTN-3 trial and the Global SYMPLICITY Registry. Even though patients with ISH had a reduction in systolic BP (SBP) 6 months after RDN, the magnitude of SBP reduction was less pronounced than that seen in patients with CH.[12]

An alternative approach to nonpharmacological BP reduction targeting mechanical aspects of the circulation is the percutaneous creation of a therapeutic arteriovenous anastomosis using the ROX coupler system, thereby increasing arterial compliance and reducing total peripheral resistance.[13] In the randomized controlled ROX Control Hypertension Study (NCT01642498), a central iliac arteriovenous anastomosis resulted in significant reductions in both office and 24-hour ambulatory BP (ABP) compared with medically managed patients.[14]

The aim of the current post hoc analysis was to assess the effects of ROX coupler implantation on office and 24-hour ABP in patients with CH compared with patients with ISH using data from the ROX Control Hypertension Study.

Methods

Study Design and Cohort

The ROX Control Hypertension Study was conducted between October 2012 and April 2014, and its design has been published elsewhere.[14] In brief, the study was a European, open-label, multicenter, prospective, randomized, controlled trial assessing the safety and efficacy of an arteriovenous anastomosis for BP-lowering purposes in patients with TRH. Inclusion criteria were age between 18 and 80 years and presence of TRH (office SBP ≥140 mm Hg and average daytime ABP ≥135/85 mm Hg despite treatment with at least 3 antihypertensive drugs including a diuretic) on a stable drug regimen (without change in dose or medication) for at least 2 weeks. Exclusion criteria were secondary hypertension other than sleep apnea, RDN within the previous 6 months, an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 and type 1 diabetes, current diagnosis of unstable cardiac disease requiring intervention, history of heart failure, recent myocardial infarction, unstable angina, coronary angioplasty or bypass surgery within last 6 months, current severe cerebrovascular disease or stroke within the previous year, and significant peripheral arterial or venous disease. Furthermore, patients in the intervention group with pulmonary arterial hypertension (mean pulmonary artery pressure >25 mm Hg) and/or elevated pulmonary capillary wedge pressure (>15 mm Hg) were excluded.

Patients were randomly (stratified by study site and previous treatment with RDN) assigned to intervention (percutaneous creation of an arteriovenous anastomosis) plus continuation of antihypertensive medication or maintenance of antihypertensive mediation alone in a 1:1 fashion. However, for this post hoc analysis, only patients who were randomized to ROX coupler implementation and were not lost to follow-up were included.

The study was approved by the ethics committees of the participating centers and was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before study entry. The study was registered at www.clinicaltrials.gov (ID: NCT01642498).

Creation of an Arteriovenous Anastomosis

The procedure for creation of an arteriovenous anastomosis is described in detail elsewhere.[14] In brief, the placement of the ROX coupler creates a fixed caliber 4-mm arteriovenous anastomosis between the distal external iliac artery and vein in a standard cardiovascular catheterization laboratory setting under fluoroscopic guidance. The self-expanding nitinol device permits a controlled shunt volume of 800 to 1000 mL/min.[15] Use of anticoagulation was determined on an individual basis by the interventionalist.

Office and 24-Hour ABP Monitoring

Office BP was measured according to standard recommendations in the nondominant arm, and the average of 3

measurements was taken. If BP values were more than 15 mm Hg apart, measurements were repeated and the means of the last 3 consecutive consistent readings were taken. ABP measurements were performed with validated automatic portable devices. Readings were taken every 30 minutes during daytime and every 60 minutes during nighttime. Measurements were deemed acceptable if there were at least 70% successful readings over 24 hours or if 14 successful readings during daytime and 7 during nighttime were recorded. Patients were graded according to their dipping pattern into dippers (nighttime BP fall ≥10%) and nondippers (nighttime BP fall <10%).

A responder was defined as a patient with office SBP reduction ≥10 mm Hg 6 months after intervention.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Following our hypothesis, patients were categorized into CH or ISH groups according to their baseline office BP. Data were compared by paired and unpaired Student *t* tests, Wilcoxon and McNemar tests, and Fisher exact test as appropriate, and were presented as mean±SD in the text and mean±SEM in the figures, respectively. A general linear model was used to assess interaction and adjust for possible influencing factors between the two groups. A 2-sided *P* value of <0.05 was considered statistically significant.

Results

Baseline characteristics of patients stratified according to type of hypertension (CH [n=31] versus ISH [n=11]) are given in Table 1. Office SBP and 24-hour systolic ABP were higher in patients with CH compared with those with ISH, but the difference did not reach statistical significance. Per definition, office diastolic BP (DBP) and 24-hour diastolic ABP were higher in patients with CH compared with those with ISH. There was no difference in the number of patients with prior RDN between the two groups (*P*=0.372).

Office BP

There was a significant reduction of office SBP and DBP after 6 months by −29±21/−24±13 mm Hg (both *P*<0.001) in the CH group and by −22±31/−10±13 mm Hg (both *P*<0.05) in the ISH group. Most importantly, the change in office SBP did not significantly differ between the two groups (*P*=0.445) (Figure 1). The general linear model did not reveal an interaction between baseline office SBP and type of hypertension (*P*=0.226). After adjusting for baseline office SBP, there was no difference in office SBP reduction 6 months after ROX coupler implementation between the two groups (*P*=0.991). Even after full adjustment (sex, age, and office SBP and DBP), no difference in office SBP reduction was detected (*P*=0.669).

Table 1. Clinical Characteristics of Patients Stratified According to Subtype of Hypertension Into CH and ISH

	CH (n=31)	ISH (n=11)	*P* Value
Age, y	58.4±10	63.1±6	0.110
Male/female	22/9	10/1	0.182
Body mass index, kg/m^2	30.0±3.4	31.0±4.8	0.571
Office blood pressure			
Systolic, mm Hg	177±18	169±17	0.163
Diastolic, mm Hg	106±12	87±2	<0.001
Pulse pressure, mm Hg	72±15	82±17	0.092
Ambulatory blood pressure			
Systolic, mm Hg	159±16	154±11	0.463
Diastolic, mm Hg	95±12	86±7	0.019
Pulse pressure, mm Hg	63±11	68±11	0.172
eGFR, mL/min per 1.73 m^2	79.1±20	67.8±19	0.163

CH indicates combined hypertension; eGFR, estimated glomerular filtration rate; ISH, isolated systolic hypertension.

Responder Rate

A total of 25 patients in the CH group (81%) and 9 patients in the ISH group (82%) had an office SBP reduction ≥10 mm Hg (usually defined as a BP responder after an interventional strategy of BP lowering), which was not significantly different (*P*=0.932).

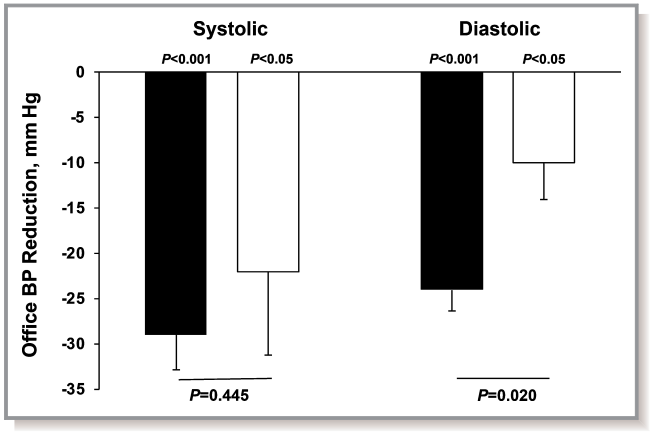

Figure 1. Change in office systolic and diastolic blood pressure (BP) 6 months after ROX coupler implementation in the combined hypertension group (black columns) vs in the isolated systolic hypertension group (white columns).

24-Hour ABP Measurements

ROX coupler implementation resulted in a significant reduction of 24-hour ABP in the CH group by −14±20/−14±10 mm Hg (both $P<0.005$) and in the ISH group by −13±15/−11±9 mm Hg (both $P<0.05$), respectively. In both groups, average daytime (CH: −14±21/−16±10 mm Hg; ISH: −13±16/−11±9 mm Hg [all $P<0.05$]) and nighttime ABP (CH: −11±19/−10±10 mm Hg; ISH: −12±14/−11±8 mm Hg [all $P<0.05$]) were significantly reduced 6 months after ROX coupler implementation. There was no difference in the reduction of 24-hour ($P=0.672/0.412$), daytime ($P=0.592/0.295$), or nighttime ($P=0.632/0.672$) systolic or diastolic ABP between the two groups (Figure 2).

There was also no difference in the change of 24-hour systolic ABP reduction after adjustment for baseline 24-hour systolic ABP ($P=0.695$) as well as after full adjustment (sex, age, 24-hour systolic and diastolic ABP) ($P=0.940$). Similar (nonsignificant) findings were found for daytime systolic ABP reduction (adjustment for baseline daytime systolic ABP: $P=0.765$, and full adjustment [sex, age, and daytime systolic and diastolic ABP]: $P=0.940$) and nighttime systolic ABP reduction (adjustment for baseline nighttime systolic ABP: $P=0.649$, and full adjustment [sex, age, and nighttime systolic and diastolic ABP]: $P=0.786$).

In addition, there was no change in SBP/DBP dipping (baseline: $P=0.501/0.286$; 6 months: $P=0.540/0.665$) as well as dipping status between baseline and 6 months in both subgroups (CH: $P=0.705$; ISH: $P=0.317$).

Antihypertensive Medication

There was no difference in number and type of antihypertensive medication between the two groups at baseline (Table 2).

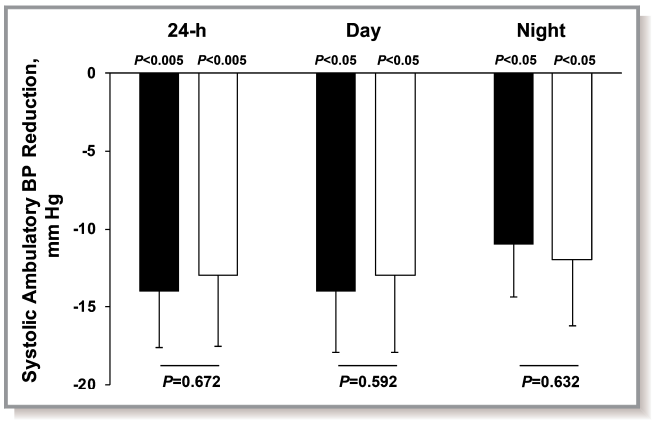

Figure 2. Change in systolic 24-hour, daytime, and nighttime ambulatory blood pressure (BP) 6 months after ROX coupler implementation in the combined hypertension group (black columns) vs in the isolated systolic hypertension group (white columns).

Antihypertensive medication (net effect of change) was decreased/increased in 8/2 patients in the CH subgroup and in 2/2 patients in the ISH group, respectively, while antihypertensive medication remained unchanged in 28 of 42 patients during follow-up. Overall, there was no significant difference in (net effect of change) antihypertensive medication between the subgroups ($P=0.499$).

Renal Function

There was no change in eGFR between baseline and 6-month follow-up in the two groups. eGFR changed from 79.1±20 to 77.6±21 mL/min per 1.73 m^2 ($P=0.420$) in patients with CH and from 67.8±19 to 65.2±16 mL/min per 1.73 m^2 ($P=0.234$) in patients with ISH. Accordingly, no significant mean change in eGFR from baseline was documented between the groups (CH: −1.5±10 versus ISH: −2.6±6 mL/min per 1.73 m^2 [$P=0.906$]).

Table 2. Baseline Antihypertensive Medications of Patients Stratified According to Subtype of Hypertension Into CH and ISH

	CH (n=31)	ISH (n=11)	*P* Value
No. of antihypertensive medications, mean±SD	4.7±1.6	4.4±1.4	0.652
Patients taking ≥5 medications	16 (52%)	5 (45%)	1.0000
Diuretics	28 (90%)	11 (100%)	0.5544
Thiazide	19 (61%)	6 (55%)	0.7327
Loop	7 (23%)	5 (45%)	0.2432
Aldosterone antagonist	13 (42%)	3 (27%)	0.4854
Potassium-sparing	0 (0%)	0 (0%)	1.0000
ACE inhibitors	13 (42%)	5 (45%)	1.0000
Angiotensin receptor blockers	18 (58%)	5 (45%)	0.5038
Direct renin inhibitors	3 (10%)	0 (0%)	0.5544
β-Blockers	23 (74%)	7 (64%)	0.6992
Calcium channel blockers	24 (77%)	7 (64%)	0.4369
Dihydropyridine	20 (65%)	7 (64%)	1.0000
Nondihydropyridine	4 (13%)	0 (0%)	0.5583
α-Blockers	8 (26%)	6 (55%)	0.1358
Centrally acting sympatholytics	5 (16%)	0 (0%)	0.3025
α-Adrenergic agonist	4 (13%)	2 (18%)	0.6437
Vasodilators	1 (3%)	0 (0%)	1.000
Nitroglycerin or nitrates	4 (13%)	0 (0%)	0.5583

Data are expressed as number (percentage) unless otherwise indicated. ACE indicates angiotensin-converting enzyme; CH, combined hypertension; ISH, isolated systolic hypertension.

Discussion

The main finding of our current analysis is that percutaneous creation of a central iliac arteriovenous anastomosis reduced office and ABP to a similar extent in patients with CH and ISH. The magnitude of the BP-lowering effects in patients with CH is similar to results achieved with other interventional techniques such as RDN. However, it was observed that in TRH patients with ISH, BP reduction of both office BP and 24-hour ABP after RDN was clearly reduced in contrast to our observation following creation of an arteriovenous anastomosis.[11,12] This discrepancy may be due to the fact that the underlying treatment mechanism targets different pathophysiologic concepts. In fact, recent expert consensus statements on RDN noted that the failure of RDN to lower BP in some individuals could be the consequence of arterial stiffness with subsequent inability to dilate and decrease vascular resistance, rather than due to technical failure of the procedure itself.[16,17]

From a biophysical standpoint, creating a fixed-caliber central iliac arteriovenous anastomosis adds a low-resistance, high-compliance venous segment to the central arterial tree, resulting in a reduction of systemic vascular resistance.[18] Activation of the Frank-Starling mechanism due to increased venous return increases cardiac output, but not commensurate with the reduction of systemic vascular resistance. Most important, the addition of a highly compliant venous parallel compartment, compared with the chronically hypertrophied and maximally filled arterial tree, reduces the effective arterial blood volume. This small reduction of effective arterial blood volume restores arterial compliance to some extent by modulating the stress-strain curve of the aorta, which shifts to the left with aging and in ISH.[19] Improvement of structural alterations may change the stress-strain relationship back towards the right, resulting in increased arterial compliance for any given BP, thereby restoring the Windkessel effect.

It is worth noting that reduction in effective arterial blood volume is achieved without depleting the intracellular, interstitial, and venous capacitance spaces, and hence without activation of the neurohormonal system. As early as 1937, Hallock and Benson[20] analyzed the relationship between vascular stiffness, aging, and volume expansion and were able to demonstrate that with aging and stiffening of the arteries, a small increase in arterial blood volume is associated with an exaggerated increase in BP. In contrast, diuretics reduce intracellular, interstitial, and venous capacitance volumes before reducing effective arterial blood volume and this is accompanied by activation of the sympathetic nervous system and the renin-angiotensin system.[21,22] In a crossover study comprising patients with TRH, low- versus high-salt diet resulted in a marked decrease in both office and 24-hour ABP, as well as a tendency toward decreased vascular stiffness. Notably, the magnitude of BP reduction induced by sodium restriction is substantially greater in patients with TRH than in normotensive or (stage 1 or 2) hypertensive patients.[23] These findings support the hypothesis that in patients with TRH, increased sodium retention (and hence intravascular volume expansion) is a major contributor to resistance to antihypertensive therapy, particularly when associated with increased arterial stiffness.

Additional analyses strengthened the concept of comparable BP reductions in patients with and without stiffened arteries following ROX coupler implementation. Pulse pressure (PP) is a valid and widely applicable proxy for arterial stiffness.[24] An office PP >60 mm Hg in the elderly is an acknowledged marker of target organ damage that influences prognosis and is used for stratification of total cardiovascular risk.[25] Dichotomization (and full adjustment) of our cohort for PP below versus above this threshold revealed a similar BP reduction in both subgroups (data not shown). Moreover, even after stratifying (and full adjustment) the cohort according to presence of marked ISH (defined as 24-hour ambulatory PP ≥63 mm Hg),[26,27] comparable office BP and 24-hour ABP reduction was evident (data not shown). Notably, only one patient had neither an office PP ≥60 mm Hg nor 24-hour ambulatory PP ≥63 mm Hg, indicating that all patients were at high cardiovascular risk.

We observed that the responder rate to coupler therapy did not significantly differ between patients with CH and ISH. Our findings are also not influenced by changes in antihypertensive medication. Notably, the responder rates were also similar whether patients were stratified according to office PP ≥60 mm Hg or 24-hour ambulatory PP ≥63 mm Hg (data not shown).

From a clinical perspective, ISH is difficult to treat with no formal evidence-based guidance, but it is nonetheless responsible for a substantially increased risk of cardiovascular morbidity and mortality.[28–30] The effectiveness of antihypertensive medication may also be limited by vascular aging and arterial stiffness, both known to contribute to treatment resistance.[31] Indeed, studies have consistently shown lower rates of SBP than DBP control in patients with ISH.[32,33] A central iliac arteriovenous anastomosis may therefore offer a new therapeutic option to treat ISH and may result in an improvement in renal and cardiovascular outcomes.[34–36]

Study Limitations

Several limitations should be discussed. Our findings are based on post hoc analyses with a small sample size, and thus further corroboration by additional studies is required. The ROX Control Hypertension Study was not sham-controlled, but immediate BP reduction after arteriovenous coupler implantation and the resulting palpable thrill in the ipsilateral

groin may limit or even jeopardize any effect to perform a sham-controlled randomized controlled trial. Direct parameters of arterial stiffness (eg, pulse wave velocity) were not measured, but data from a single patient undergoing central arteriovenous anastomosis formation revealed a large reduction in pulse wave velocity (before: 15.2 versus 4 months: 13.7 m/s), which appears (partly) independent of associated BP reduction.[37] Data on cardiovascular outcome are still lacking, but it is well known that the relative risk of cardiovascular mortality is estimated at 2:1 (2% reduction of mortality for each 1-mm Hg BP reduction). Further investigations are necessary, and hence the Global Registry study (www.clinicaltrials.gov: NT1885390) was initiated to further evaluate the ROX coupler. In addition, the consequences of the small shunt were not elusively assessed. In one case report, it was shown that ROX coupler implementation resulted in an immediate as well as long-term (6-month follow-up) reduction of systemic vascular resistance and increment of cardiac output indicating coupler-induced venous filling and hemodynamic unloading of the left ventricle.[38] Moreover, extensive experience in patients with end-stage renal disease and similarly sized shunts for dialysis access suggest that the risk of cardiovascular decompensation is low. In patients with end-stage renal disease, high-output cardiac failure may occur, but volumes exceeding 30% of cardiac output[39] and flow rates of at least 2.0 L/min are necessary.[40] In contrast, the fixed-caliber arteriovenous coupler permits flow of only 0.8 to 1.2 L/min.[15] Moreover, arteriovenous anastomosis can be closed (with a covered stent), if necessary, therefore eliminating its clinical risk. Dipping status was not improved after ROX coupler implementation, which might be related to the poor reproducibility of the classification of patients into dippers and nondippers over time.[41,42]

Conclusions

Our analyses suggest that percutaneous creation of a fixed-caliber arteriovenous anastomosis using the ROX coupler, and therefore modifying the mechanical properties of the arterial vascular tree, reduces office SBP and ambulatory SBP to the same extent in patients with CH and ISH. These data contrast with the results of diminished BP reduction in patients with ISH after RDN. Given the primacy of effective arterial volume as a determinant of BP, this is perhaps not surprising and the >90% response rate to coupler therapy observed in the ROX Control Hypertension Study attests to this. Ongoing studies are examining hemodynamic effects of the coupler in greater detail and future studies should address whether patients with TRH due to ISH would benefit from treatment targeting mechanical properties of the circulation (arteriovenous anastomosis formation) as a first choice rather than RDN.

Appendix

Investigators of the ROX Control Hypertension Study were: Christian Ott, Michael Schmid, Stephan Achenbach, and Roland E. Schmieder, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; Ajay Jain, Charles Knight, Melvin D. Lobo, Anthony Mathur, and Manish Saxena, Barts NIHR Cardiovascular Biomedical Research Institute, Queen Mary University of London, London, UK; Peter Balmforth, Sandra F. Luitjens, and Paul A. Sobotka, ROX Medical Inc, San Clemente, CA, USA; and Gerard Smits, Santa Barbara, CA, USA; Felix Mahfoud, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; Alice Stanton, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland; John R. Cockcroft, Wales Heart Research Institute, Cardiff, UK; Neil Sulke, Eastbourne District General Hospital, East Sussex, UK; Eamon Dolan, Connolly Hospital, Dublin, Ireland; Markus van der Giet, Universitatsmedizin Berlin, Berlin, Germany; Joachim Hoyer, Universitatsklinikum Gießen und Marburg GmbH, Marburg, Germany; Stephen S. Furniss, East Sussex Healthcare NHS Trust, East Sussex, UK; John P. Foran and Dhanraj Mungur, Royal Brompton Hospital, London, UK, and St Helier Hospital, Surrey, UK; Adam Witkowski, Andrzej Januszewicz, Aleksander Prejbisz, Jacek Kadziela, and Elżbieta Florczak, Institute of Cardiology, Warsaw, Poland; Joseph Galvin, Mater Private Hospital, Dublin, Ireland; Danny Schoors, Universitair Ziekenhuis Brussel, Brussels, Belgium; Kyriakos Dimitriadis and Konstantinos Tsioufis, Hippokration General Hospital of Athens, Athens, Greece; Benno J. Rensing, St Antonius Ziekenhuis, Nieuwegein, Netherlands; Benjamin Scott, ZNA-Cardio Middelheim, Antwerp, Belgium; André Ng, University of Leicester Glenfield Hospital/NIHR Leicester Cardiovascular Biomedical Research, Leicester, UK.

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