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ORIGINAL INVESTIGATIONS

Renal Denervation in High-Risk Patients With Hypertension

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ABSTRACT

BACKGROUND Renal denervation (RDN) is under investigation for treatment of uncontrolled hypertension and might represent an attractive treatment for patients with high cardiovascular (CV) risk. It is important to determine whether baseline CV risk affects the efficacy of RDN.

OBJECTIVES The purpose of this study was to assess blood pressure (BP) reduction and event rates after RDN in patients with various comorbidities, testing the hypothesis that RDN is effective and durable in these high-risk populations.

METHODS BP reduction and adverse events over 3 years were evaluated for several high-risk subgroups in the GSR (Global proSpective registrY for syMPathetic renaL denervatIon in seleCted IndicatIons Through 3 Years Registry), an international registry of RDN in patients with uncontrolled hypertension (n = 2,652). Comparisons were made for patients age ≥65 years versus age <65 years, with versus without isolated systolic hypertension, with versus without atrial fibrillation, and with versus without diabetes mellitus. Baseline cardiovascular risk was estimated using the American Heart Association (AHA)/American College of Cardiology (ACC) atherosclerosis cardiovascular disease (ASCVD) risk score.

RESULTS Reduction in 24-h systolic BP at 3 years was −8.9 ± 20.1 mm Hg for the overall cohort, and for high-risk subgroups, BP reduction was −10.4 ± 21.0 mm Hg for resistant hypertension, −8.7 ± 17.4 mm Hg in patients age ≥65 years, −10.2 ± 17.9 mm Hg in patients with diabetes, −8.6 ± 18.7 mm Hg in isolated systolic hypertension, −10.1 ± 20.3 mm Hg in chronic kidney disease, and −10.0 ± 19.1 mm Hg in atrial fibrillation ($p < 0.0001$ compared with baseline for all). BP reduction in patients with measurements at 6, 12, 24, and 36 months showed similar reductions in office and 24-h BP for patients with varying baseline ASCVD risk scores, which was sustained to 3 years. Adverse event rates at 3 years were higher for patients with higher baseline CV risk.

CONCLUSIONS BP reduction after RDN was similar for patients with varying high-risk comorbidities and across the range of ASCVD risk scores. The impact of baseline risk on clinical event reduction by RDN-induced BP changes could be evaluated in further studies. (Global proSpective registrY for syMPathetic renaL denervatIon in seleCted IndicatIons Through 3 Years Registry; NCT01534299) (J Am Coll Cardiol 2020;75:2879–88) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ASCVD = atherosclerotic cardiovascular disease

BP = blood pressure

CV = cardiovascular

DM = diabetes mellitus

ISH = isolated systolic hypertension

RDN = renal denervation

SBP = systolic blood pressure

Three recent sham-controlled trials verified the short-term (2 to 6 months) safety and efficacy of renal denervation (RDN) in patients with uncontrolled hypertension and relatively few comorbidities (1–3). However, whether patients with comorbidities associated with increased sympathetic activity or with overall higher cardiovascular risk have a differing blood pressure (BP)-lowering response following RDN is unknown. It is also uncertain whether the durability of the BP-lowering effect of RDN could be limited due to disease progression or differences in response in these subpopulations (4). Finally, the rates of clinical events as well as longer-term safety of RDN are not well described.

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The GSR (Global proSpective registrY for syMPathetic renaL denervatIon in seleCted IndicatIons Through 3 Years Registry) is an ongoing, multicenter, international single-arm trial with planned enrollment of 3,000 patients with varying cardiovascular (CV) risk who are followed up to 3 years after RDN. We evaluated short- and long-term BP reduction, clinical events, and adverse event rates after RDN in patients with various comorbidities and baseline CV risk to test the hypothesis of whether RDN is effective and durable in these high-risk populations.

METHODS

TRIAL DESIGN. The design of the GSR (NCT01534299) has been previously published (5). In this international, prospective, single-arm registry, patients are enrolled with uncontrolled hypertension and/or conditions associated with sympathetic nervous system activation. Uncontrolled hypertension was defined as BP above recommended levels (regardless of therapy) according to published local guidelines at the time of enrollment. Sympathetic nervous system activation was defined as conditions associated with increased sympathetic nervous system activity, including diabetes, congestive heart failure, chronic kidney disease, obstructive sleep apnea, or arrhythmias. The study was approved by the institutional review board or ethics committee at each enrolling site, and the trial adhered to the Declaration of Helsinki.

All patients are treated with the Symplicity RDN system (Medtronic, Santa Rosa, California) using either the Symplicity Flex or Symplicity Spyral catheter. The primary objective of the study was to document long-term safety and effectiveness of RDN in a real-world patient population. Follow-up is recommended for 3 years post-RDN. Key endpoints measured in this prospective registry include BP measurements and changes in medications. All protocol-defined safety events were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation, New York, New York).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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TABLE 1 Changes in 24-h and Office SBP at 6, 12, 24, and 36 Months Post-Procedure Compared With Baseline for All Patients

		Change From Baseline at			
	Baseline	6 Months	12 Months	24 Months	36 Months
24-h SBP, mm Hg	154.5 ± 18.2 (n = 1,844)	−7.5 ± 17.9 (−8.5 to −6.4) (n = 1,133)	−8.4 ± 18.6 (−9.6 to −7.3) (n = 1,020)	−9.0 ± 19.6 (−10.4 to −7.5] (n = 690)	−8.9 ± 20.1 (−10.7 to −7.1] (n = 500)
Office SBP, mm Hg	166.1 ± 24.8 (n = 2,576)	−13.1 ± 26.2 (−14.3 to −12.0) (n = 1,986)	−14.1 ± 26.7 (−15.3 to −12.9) (n = 1,887)	−15.4 ± 27.5 (−16.8 to −14.0] (n = 1,459)	−16.5 ± 28.5 (−18.1 to −14.9] (n = 1,183)

Values are mean ± SD (95% confidence interval).
SBP = systolic blood pressure.

Selective monitoring was applied to ensure the quality of the data.

DEFINITIONS. Post hoc analyses were completed for various high-risk subgroups, including: elderly patients (age ≥65 years) and patients with atrial fibrillation (AF), diabetes mellitus (DM) type II, severe treatment resistant hypertension (office systolic blood pressure [SBP] >150 mm Hg despite prescription of ≥3 antihypertensive medications), chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m^2), and isolated systolic hypertension (ISH) (baseline office SBP ≥140 mm Hg and diastolic BP <90 mm Hg). Baseline atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated for patients with available office SBP measurements, antihypertensive medications, and cholesterol measurements, as well as diabetic and smoking status (6). Efficacy was assessed by serial office and, where available, ambulatory BP measurements over the 3 years of follow-up following RDN.

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD. Between-group differences in continuous variables were tested using analysis of covariance (ANCOVA), adjusting for baseline BP. Within-group differences in continuous variables from baseline to follow-up were tested using paired *t*-tests. To account for multiple comparisons over time points, the significance level was determined by the Bonferroni method as indicated in the table and figure footnotes. Categorical variables were presented as counts and percentages and were compared between groups using the Fisher exact test for binary variables and chi-square test for multilevel categorical variables. Some BP measurements at follow-up were adjusted for baseline BP using ANCOVA analyses. These measurements were not adjusted for differences in other baseline covariates. Analyses were performed according to the intention-to-treat principle. BP reduction and adverse events were compared for patients with baseline ASCVD risk scores <10%, ≥10% and <20%,

TABLE 2 24-h and Office SBP Reduction for Patients With BP Measurements at Baseline, 6, 12, 24, and 36 Months, Stratified by Baseline ASCVD Risk Score and Adjusted Using ANCOVA

	ASCVD Risk Score			
	<10% (n = 290)	≥10% to <20% (n = 239)	≥20% (n = 510)	p Value*
24-h SBP, mm Hg	n = 66 matched patients	n = 58 matched patients	n = 125 matched patients	
Baseline	152.3 ± 18.1	148.6 ± 16.7	149.1 ± 14.9	0.39
Change at 6 months	−8.4 ± 22.2 (−13.8 to −2.9)	−6.8 ± 16.7 (−11.1 to −2.4)	−7.1 ± 13.7 (−9.5 to −4.7)	0.93
Change at 12 months	−9.4 ± 21.2 (−14.6 to −4.1)	−6.4 ± 18.3 (−11.2 to −1.6)	−7.3 ± 16.1 (−10.1 to −4.4)	0.97
Change at 24 months	−7.8 ± 22.6 (−13.4 to −2.3)	−6.8 ± 19.8 (−12.0 to −1.6)	−10.5 ± 15.5 (−13.3 to −7.8)	0.08
Change at 36 months	−8.6 ± 24.1 (−14.5 to −2.6)	−6.0 ± 19.2 (−11.0 to −0.9)	−7.6 ± 16.2 (−10.5 to −4.8)	0.72
Office SBP, mm Hg	n = 152 matched patients	n = 116 matched patients	n = 236 matched patients	
Baseline	156.6 ± 21.5	158.4 ± 24.5	166.0 ± 22.7	<0.001
Change at 6 months	−9.5 ± 25.4 (−13.6 to −5.5)	−8.4 ± 25.7 (−13.1 to −3.7)	−15.9 ± 24.8 (−19.1 to −12.8)	0.91
Change at 12 months	−10.4 ± 24.7 (−14.4 to −6.5)	−11.6 ± 24.5 (−16.1 to −7.1)	−15.9 ± 28.1 (−19.5 to −12.3)	0.60
Change at 24 months	−10.2 ± 24.3 (−14.1 to −6.3)	−11.7 ± 25.9 (−16.4 to −6.9)	−16.1 ± 27.4 (−19.6 to −12.5)	0.74
Change at 36 months	−6.3 ± 27.1 (−10.7 to −2.0)	−15.7 ± 25.5 (−20.4 to −11.0)	−17.1 ± 27.1 (−20.6 to −13.6)	0.06

Values are mean ± SD (95% confidence interval). *Statistical significance defined as $p < 0.0125$ by Bonferroni adjustment.
ASCVD = atherosclerotic cardiovascular disease; SBP = systolic blood pressure.

TABLE 3 Changes in 24-h and Office SBP at 6, 12, 24, and 36 Months Post-Procedure From Baseline for Patients in High-Risk Subgroups

		Change From Baseline at			
	Baseline	6 Months	12 Months	24 Months	36 Months
24-h SBP, mm Hg					
Resistant hypertension	157.5 ± 18.2 (n = 1,274)	−8.1 ± 17.9 (−9.3 to −6.8) (n = 751)	−9.5 ± 18.9 (−10.9 to −8.1) (n = 670)	−10.2 ± 20.1 (−12.1 to −8.3) (n = 441)	−10.4 ± 21.0 (−12.7 to −8.0) (n = 302)
Age ≥65 yrs	152.4 ± 17.5 (n = 758)	−6.1 ± 16.1 (−7.6 to −4.6) (n = 460)	−6.9 ± 16.6 (−8.5 to −5.3) (n = 417)	−7.8 ± 18.0 (−10.0 to −5.7) (n = 272)	−8.7 ± 17.4 (−11.1 to −6.2) (n = 197)
Diabetes mellitus type 2	154.6 ± 18.0 (n = 698)	−7.5 ± 17.3 (−9.1 to −5.9) (n = 442)	−7.3 ± 17.8 (−9.1 to −5.6) (n = 406)	−8.2 ± 17.6 (−10.3 to −6.0) (n = 264)	−10.2 ± 17.9 (−12.7 to −7.7) (n = 201)
Isolated systolic hypertension	152.2 ± 16.8 (n = 707)	−6.0 ± 17.3 (−7.7 to −4.4) (n = 435)	−5.9 ± 17.6 (−7.7 to −4.2) (n = 389)	−9.1 ± 17.9 (−11.3 to −6.9) (n = 266)	−8.6 ± 18.7 (−11.2 to −6.0) (n = 199)
Chronic kidney disease	154.3 ± 19.1 (n = 455)	−5.6 ± 19.0 (−7.9 to −3.4) (n = 271)	−6.4 ± 18.5 (−8.8 to −4.0) (n = 229)	−7.0 ± 21.1 (−10.4 to −3.7) (n = 155)	−10.1 ± 20.3 (−13.8 to −6.3) (n = 116)
Atrial fibrillation	153.6 ± 18.0 (n = 232)	−9.2 ± 17.9 (−12.1 to −6.2) (n = 143)	−10.8 ± 19.1 (−14.1 to −7.5) (n = 132)	−11.0 ± 20.6 (−15.3 to −6.8) (n = 93)	−10.0 ± 19.1 (−14.5 to −5.4) (n = 70)
Office SBP, mm Hg					
Resistant hypertension	175.4 ± 19.8 (n = 1,822)	−19.8 ± 24.3 (−21.1 to −18.5) (n = 1,396)	−20.7 ± 25.0 (−22.0 to −19.3) (n = 1,331)	−22.2 ± 25.6 (−23.8 to −20.7) (n = 1,043)	−23.5 ± 27.2 (−25.3 to −21.7) (n = 837)
Age ≥65 yrs	165.6 ± 24.7 (n = 1,059)	−12.7 ± 26.7 (−14.6 to −10.9) (n = 804)	−12.6 ± 27.0 (−14.5 to −10.7) (n = 760)	−14.3 ± 27.7 (−16.6 to −12.1) (n = 596)	−18.4 ± 28.3 (−20.9 to −15.8) (n = 472)
Diabetes mellitus type 2	165.4 ± 22.6 (n = 978)	−13.7 ± 24.5 (−15.4 to −11.9) (n = 766)	−13.4 ± 25.9 (−15.2 to −11.5) (n = 739)	−15.5 ± 26.9 (−17.7 to −13.2) (n = 549)	−16.4 ± 26.8 (−18.8 to −13.9) (n = 465)
Isolated systolic hypertension	163.8 ± 16.8 (n = 995)	−12.3 ± 23.6 (−13.3 to −10.6) (n = 779)	−12.7 ± 23.8 (−14.4 to −10.9) (n = 731)	−14.1 ± 23.6 (−16.0 to −12.1) (n = 553)	−15.9 ± 23.7 (−18.0 to −13.7) (n = 477)
Chronic kidney disease	163.6 ± 25.7 (n = 609)	−12.1 ± 27.3 (−14.6 to −9.6) (n = 463)	−9.8 ± 26.8 (−12.3 to −7.2) (n = 427)	−10.9 ± 27.9 (−14.0 to −7.9) (n = 327)	−11.6 ± 29.6 (−15.2 to −7.9) (n = 254)
Atrial fibrillation	162.6 ± 23.6 (n = 317)	−13.7 ± 25.4 (−16.9 to −10.5) (n = 243)	−15.2 ± 26.2 (−18.6 to −11.9) (n = 235)	−13.9 ± 26.7 (−17.8 to −10.1) (n = 188)	−17.6 ± 27.4 (−22.1 to −13.1) (n = 144)

Values are mean ± SD (95% confidence interval).
SBP = systolic blood pressure.

and ≥20%. Changes in BP over time and adverse event rates were compared for the following subgroups: AF versus no AF, age ≥65 years versus age <65 years, DM versus no DM, and ISH versus non-ISH patients. A 2-tailed p value <0.05 was considered statistically significant, unless otherwise indicated. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

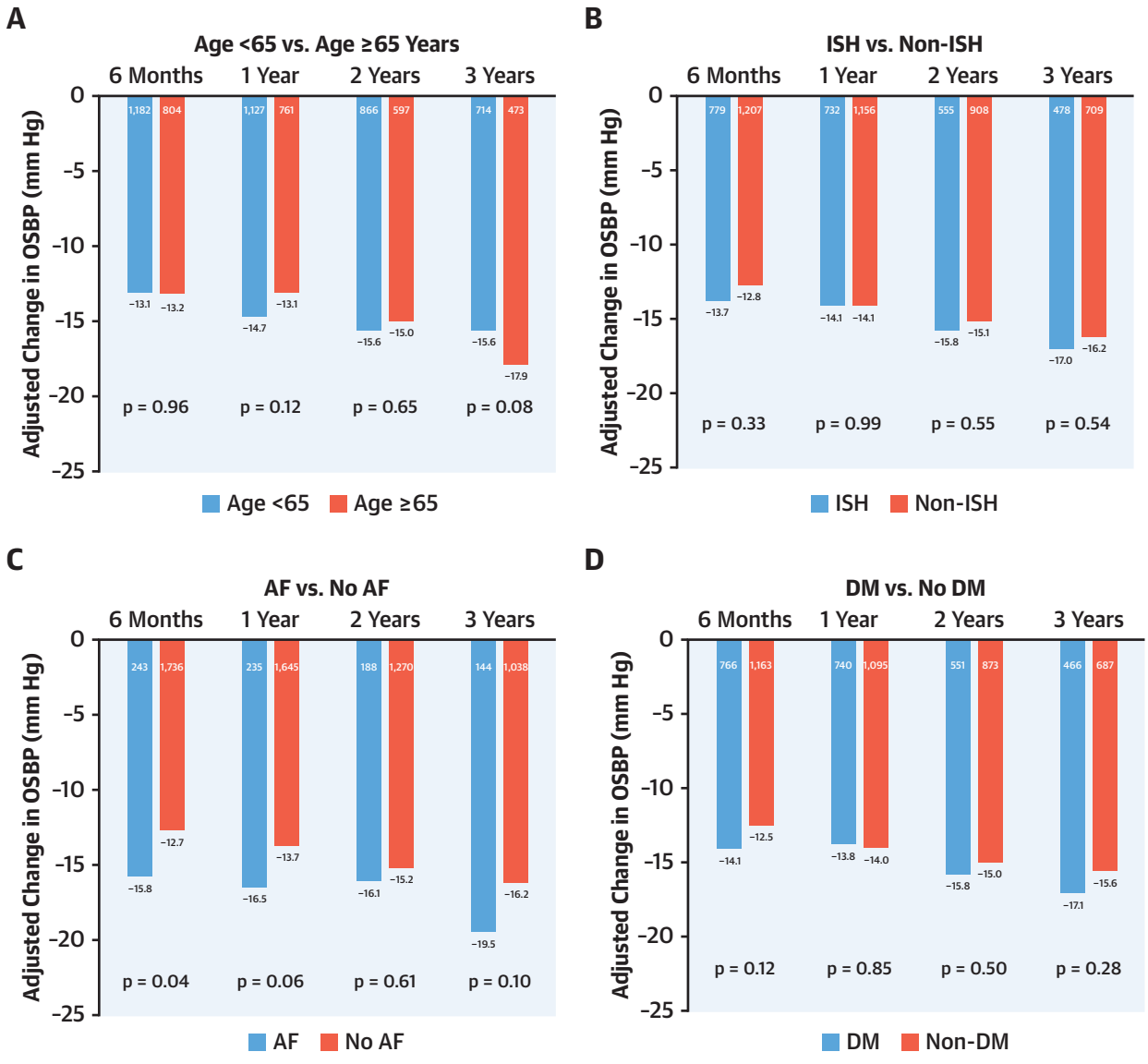
RESULTS

As of March 2019, there were 2,652 patients enrolled at 196 centers in 45 countries, with 2,466 patients reaching 3-year follow-up at the time of this report. A total of 99.8% had a history of hypertension. Median follow-up was close to 3 years. Reductions in office and 24-h SBP for the entire population were sustained from 6 to 36 months post-procedure (Table 1). Baseline ASCVD risk scores were calculated for 1,485 patients (56% of total) primarily due to missing cholesterol measurements. The median ASCVD risk score was 19.8% (Q1, Q3: 9%, 37%). BP reduction in patients with measurements at 6, 12, 24, and 36 months showed similar reductions in office and 24-h SBP for differing baseline ASCVD risk scores (Table 2).

BP reduction in several high-risk cohorts was consistent and sustained across the groups from 6 months to 3 years post-RDN (Table 3). In addition, SBP reduction was compared between subgroups and similar decreases in office (Figure 1) and 24-h SBP (Figure 2) were observed.

Patients with highest baseline ASCVD risk scores (≥20%) had higher 3-year rates of death (8.4%), CV death (4.5%), and hospitalization for new-onset heart failure (5.3%) or AF (6.3%) compared with patients with lower risk scores (Table 4). Adverse events at 3 years were similar between subgroups (Table 5), although several exceptions to this are noted. For patients with versus without DM, there was a higher rate of myocardial infarction (4.0% vs. 1.6%; p = 0.002), end-stage renal disease (2.8% vs. 1.0%; p = 0.005), and elevated creatinine levels (2.4% vs. 0.8%; p = 0.007). Death and CV death rates at 3 years were higher for patients age ≥65 years and patients with DM. Patients with versus without AF had higher rates of death (9.2% vs. 3.1%; p < 0.001). ISH patients

FIGURE 1 **Changes in Office SBP at 6, 12, 24, and 36 Months**



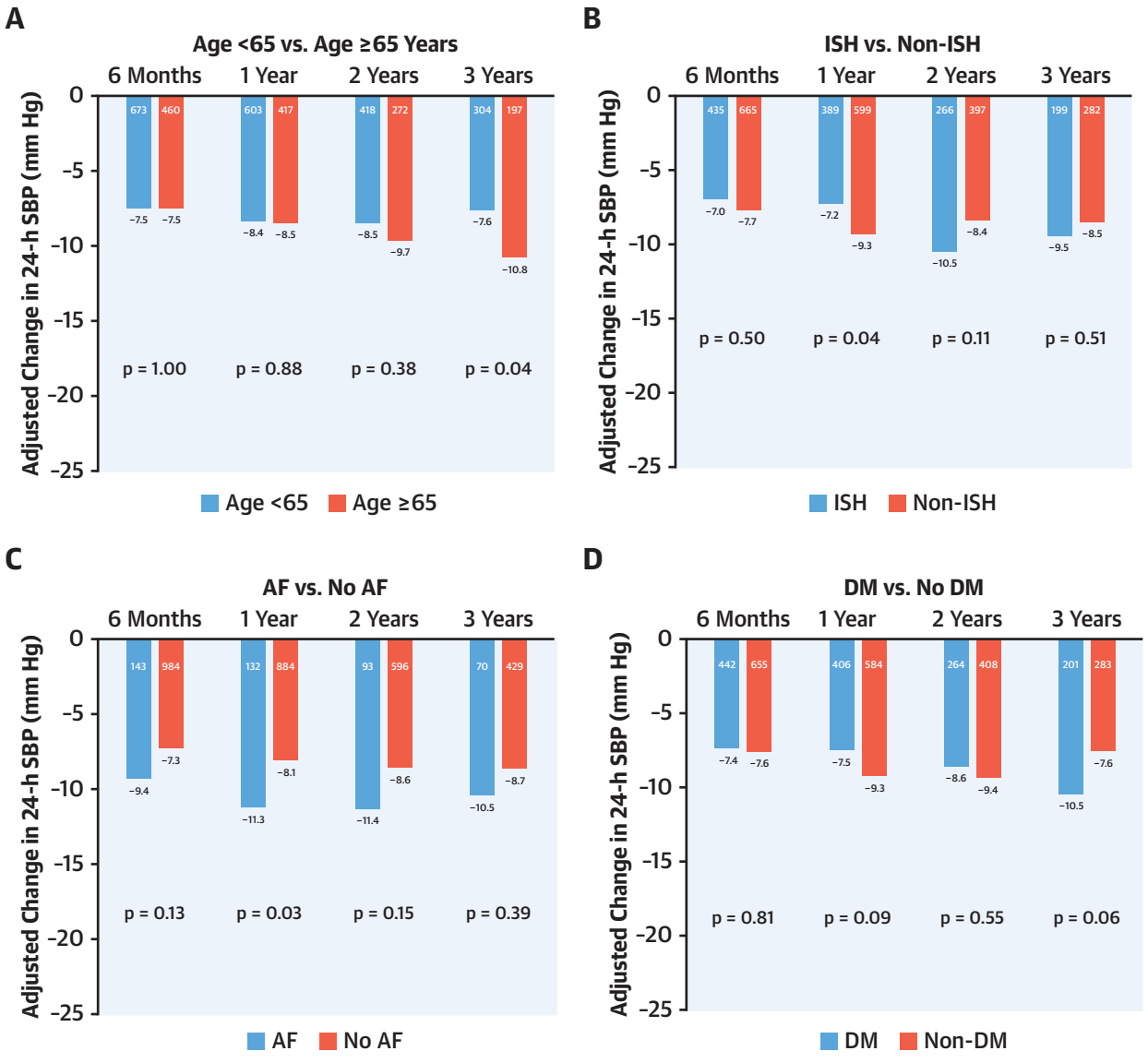
Patients with **(A)** age <65 years vs. ≥65 years; **(B)** ISH vs. non-ISH; **(C)** AF vs. no AF; **(D)** DM vs. no DM. Between-group comparisons and blood pressure (BP) changes are analysis of covariance–adjusted for baseline BP and shown for all patients eligible for 6-month follow-up. All p values are analysis of covariance–adjusted for baseline BP. Statistical significance is defined as $p < 0.0125$ by Bonferroni adjustment. Within each group, $p < 0.001$ at all time points vs. baseline. AF = atrial fibrillation; DM = diabetes mellitus; ISH = isolated systolic hypertension; OSBP = office systolic blood pressure.

had a higher rate of CV death than non-ISH patients (4.0% vs. 2.2%; p = 0.04).

DISCUSSION

Identification of patient cohorts that may derive specific benefit from RDN is important in the context of wider implementation of this therapy in clinical practice and requires balancing of the potential procedural risks against the expected benefits from BP lowering and other RDN-induced effects. Patients at high CV risk represent a potential target cohort. This post hoc analysis from the largest real-world registry of RDN demonstrated clinically and statistically significant reductions in office and 24-h BP in the entire cohort that were

FIGURE 2 **Changes in Mean 24-h SBP at 6, 12, 24, and 36 Months**



Patients with **(A)** age <65 years vs. ≥65 years; **(B)** ISH vs. non-ISH; **(C)** AF vs. no AF; **(D)** DM vs. no DM. Between-group comparisons and BP changes are analysis of covariance–adjusted for baseline BP and shown for all patients eligible for 6-month follow-up. All p values are analysis of covariance–adjusted for baseline BP. Statistical significance is defined as $p < 0.0125$ by Bonferroni adjustment. Within each group, $p < 0.001$ at all time points vs. baseline. SBP = systolic blood pressure; other abbreviations as in Figure 1.

maintained out to at least 3 years following the procedure with low adverse event rates (Central Illustration). The number of prescribed antihypertensive medications for all patients differed slightly from baseline to 3 years (4.56 ± 1.36; n = 2,621 vs. 4.39 ± 1.45; n = 2,449; $p < 0.001$), but changes were not clinically significant, as opposed to what was reported in a smaller RDN registry (7). It is unlikely that changes in medication contributed to the observed decrease in BP, although adherence measurements were not performed routinely. The baseline adjusted BP-lowering effects were similar across subgroups. BP reductions were not dependent on baseline CV risk, although, expectedly, more adverse clinical events occurred in higher CV-risk subgroups. Overall, these results indicate a safe

TABLE 4 Adverse Events at 3 Years for Patients With Different Baseline ASCVD Risk Scores

	ASCVD Risk Score			
	<10% (n = 290)	≥10% to <20% (n = 239)	≥20% (n = 510)	p Value
Follow-up, days	1,095 (788, 1,095)	1,095 (787, 1,095)	1,089 (711, 1,095)	
Death	1.0 (3/290)	2.1 (5/239)	8.4 (43/510)	<0.001
Cardiovascular death	1.0 (3/290)	0.8 (2/239)	4.5 (23/510)	0.002
MI	2.1 (6/290)	2.5 (6/239)	2.2 (11/510)	0.94
Stroke	3.1 (9/290)	3.8 (9/239)	4.7 (24/510)	0.53
New-onset end-stage renal disease	0.7 (2/290)	1.3 (3/239)	2.2 (11/510)	0.29
Serum creatinine elevation >50%	0.7 (2/290)	1.7 (4/239)	2.2 (11/510)	0.31
New renal artery stenosis >70%	0.3 (1/290)	0.0 (0/239)	0.6 (3/510)	0.81
Hospitalization for new-onset heart failure	1.7 (5/290)	2.9 (7/239)	5.3 (27/510)	0.03
Hospitalization for atrial fibrillation	2.1 (6/290)	2.1 (5/239)	6.3 (32/510)	0.003
Hospitalization for hypertensive crisis/ hypertensive emergency	3.4 (10/290)	2.9 (7/239)	2.9 (15/510)	0.91

Values are median (Q1, Q3) or % (n/N).

and durable BP response to RDN in a wide range of patients with uncontrolled BP by conventional drug therapy, including those at high CV risk.

The GSR includes a large population of patients over the age of 65 years (n = 1,059) compared with the recent sham controlled trials of RDN (1–3). We observed office and 24-h SBP reductions in patients age ≥65 years that were sustained to 3 years. Interestingly, the BP reductions were similar for patients above compared with below age 65 years. These results are consistent with a previous report (7) also showing significant BP reductions at 6 months in patients of age ≥75 years.

A post hoc analysis from previous trials and a single-center study both reported less BP reduction for ISH patients after RDN compared with patients with combined systolic-diastolic hypertension (8,9). However, decreases in SBP from our analysis were not different between patients with ISH compared with those without. The present analysis encompasses more patients with longer follow-up and also adjusts for differences in baseline SBP. This is supported by a recent subanalysis of the prospective, randomized, uncontrolled RADIOSOUND (Randomized Comparison of Ultrasound Versus Radiofrequency Denervation in Patients With Therapy Resistant

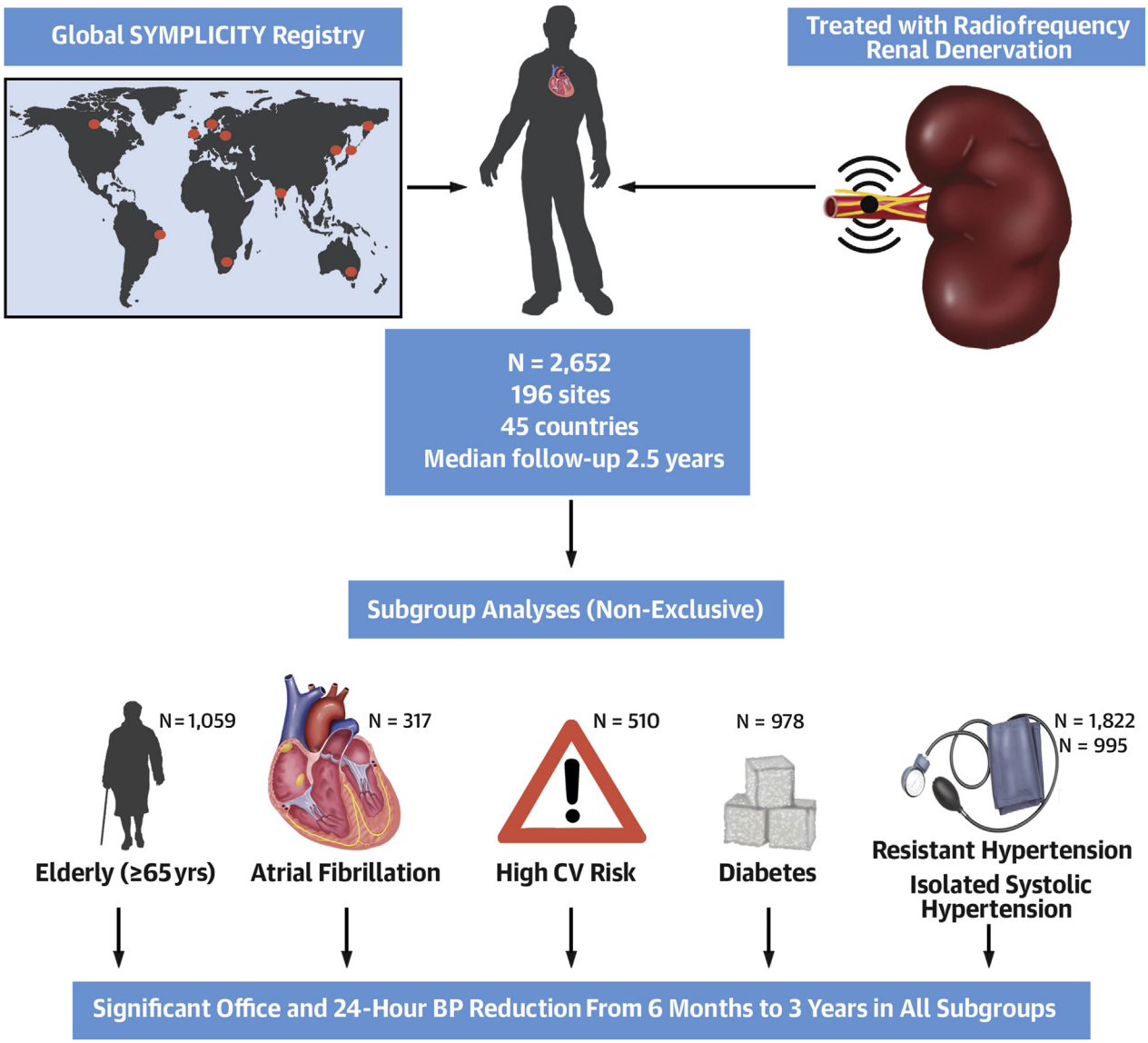
TABLE 5 Rate of Adverse Events at 36 Months for Entire Population and Individual Subgroups

	All Patients (N = 1,749)	Age ≥65 yrs (n = 741)	Age <65 yrs (n = 1,008)	p Value	ISH (n = 676)	Non-ISH (n = 1,028)	p Value	AF (n = 236)	No AF (n = 1,503)	p Value	DM (n = 675)	Non-DM (n = 1,016)	p Value
Death	5.7 (99/1,749)	9.2 (68/741)	3.1 (31/1,008)	<0.001	6.5 (44/676)	5.0 (51/1,028)	0.17	8.5 (20/236)	5.3 (79/1,503)	0.047	7.1 (48/675)	4.5 (46/1,016)	0.02
Cardiovascular death	2.9 (51/1,749)	4.6 (34/741)	1.7 (17/1,008)	<0.001	4.0 (27/676)	2.2 (23/1,028)	0.04	4.7 (11/236)	2.7 (40/1,503)	0.09	4.0 (27/675)	2.0 (20/1,016)	0.01
Myocardial infarction	2.5 (44/1,749)	2.4 (18/741)	2.6 (26/1,008)	0.84	2.8 (19/676)	2.2 (23/1,028)	0.46	2.5 (6/236)	2.4 (36/1,503)	0.89	4.0 (27/675)	1.6 (16/1,016)	0.002
Stroke	4.5 (79/1,749)	5.0 (37/741)	4.2 (42/1,008)	0.41	4.7 (32/676)	4.4 (45/1,028)	0.73	3.8 (9/236)	4.6 (69/1,503)	0.59	4.0 (27/675)	4.6 (47/1,016)	0.54
End-stage renal disease	1.8 (32/1,749)	2.2 (16/741)	1.6 (16/1,008)	0.38	2.7 (18/676)	1.4 (14/1,028)	0.053	1.3 (3/236)	1.9 (29/1,503)	0.61	2.8 (19/675)	1.0 (10/1,016)	0.005
Creatinine elevation >50%	1.4 (25/1,749)	1.5 (11/741)	1.4 (14/1,008)	0.87	1.5 (10/676)	1.5 (15/1,028)	0.97	0.8 (2/236)	1.5 (23/1,503)	0.56	2.4 (16/675)	0.8 (8/1,016)	0.007
New renal artery stenosis >70%	0.3 (6/1,749)	0.3 (2/741)	0.4 (4/1,008)	1.00	0.3 (2/676)	0.3 (3/1,028)	1.00	0.8 (2/236)	0.3 (4/1,503)	0.19	0.3 (2/675)	0.3 (3/1,016)	1.00
Hospitalizations for HTN crisis	3.1 (55/1,749)	3.4 (25/741)	3.0 (30/1,008)	0.64	2.4 (16/676)	3.7 (38/1,028)	0.13	3.0 (7/236)	3.1 (47/1,503)	0.89	3.4 (23/675)	2.8 (28/1,016)	0.44

Values are % (n/N).

AF = atrial fibrillation; DM = diabetes mellitus; HTN = hypertension; ISH = isolated systolic hypertension.

CENTRAL ILLUSTRATION **Effects of Renal Denervation in Patients With and Without Various Comorbidities**



Mahfoud, F. et al. J Am Coll Cardiol. 2020;75(23):2879–88.

CV = cardiovascular.

Hypertension) trial, which showed no difference in the adjusted drop in 24-h mean SBP in ISH patients compared with combined hypertension patients (10). Further randomized controlled trials in patients with ISH are warranted to clarify the response to RDN in this high-risk cohort (8).

Increased sympathetic activity is implicated in both the initiation and maintenance of atrial tachyarrhythmias including AF (11). Most previous trials of RDN, including SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED, included relatively small proportions of patients with AF history (1,3). In the present analysis, office and 24-h SBP reductions were similar for patients with versus without AF. Interestingly, recent reports including prospective randomized trials in patients with hypertensive heart disease and in patients with both AF and uncontrolled hypertension have shown significant reductions in AF burden following RDN alone (12) and in combination with pulmonary vein isolation (PVI) (13). Ongoing

prospective randomized trials are further evaluating the role of RDN in patients indicated for PVI with a history of hypertension (NCT02064764 and NCT02115100).

Patients with higher baseline CV risk, regardless of comorbidity, may derive particular benefit from BP reduction. Indeed, the current American Heart Association/American College of Cardiology guidelines for BP control stratify recommended drug therapy for patients with stage 1 hypertension based on ASCVD risk >10% (14). The GSR subgroups stratified by baseline CV risk score were not associated with a different BP response, including patients with risk above or below 10% (**Table 2**). A previous meta-analysis also found that the estimated number of avoidable CV events increased with higher baseline CV risk and more pronounced BP reduction (15). Therefore, patients with high CV risk might particularly benefit from RDN therapy, which may also extend to cost effectiveness.

Renal nerves have been shown to anatomically recover following ablation in some anatomical models (16). However, functional recovery of nerves following radiofrequency (RF) RDN in animal and humans is uncertain (4). A recent preclinical study in sheep with hypertensive chronic kidney disease showed regrowth of renal nerves and return of function at 30 months following RF-RDN, but levels were only partially restored to levels of intact, suggesting that RDN lowers BP in the long-term and is renoprotective and cardioprotective as a result of lesser nerve regrowth in chronic kidney disease (4). Therefore, clinical evidence of the long-term durability of RDN is vital to determine its potential impact on hypertension control rates (17). Long-term renal function and durability of BP reduction following RDN was previously reported for GSR, the SYMPLICITY HTN-1 and HTN-2 trials, and a smaller registry from Sweden (18–20). To date, GSR is the largest RDN registry with 3-year results corroborating prior evidence of the durability of the RDN procedure.

Long-term safety following the RDN procedure remains of utmost importance for multiple stakeholders, including patients, clinicians, regulators, and payers. Short-term reports of adverse events following RDN with both RF and ultrasound-based devices have been encouraging (1–3). Likewise, a previous report from GSR that focused on patients treated with the first-generation single-electrode RF device showed favorable short- and long-term safety with adverse events proportionate to the basal risk of the population (20). Current results report a low 3-year rate of 0.3% for new renal artery stenosis >70%, and previous work suggests the 3-year rate of natural renal artery disease progression is up to 18% in renal arteries categorized as normal at baseline (21). Moreover, the present results show that clinical event rates following RDN are expectedly related to the baseline comorbidity profile. Results from a meta-analysis suggest that a 10-mm Hg reduction in office SBP leads to a 13% reduction in all-cause mortality (22), and mean office SBP reduction at 3 years in GSR was 16.5 mm Hg. Therefore, because the risks associated with RDN appear to be reasonably low, the potential to reduce clinical events by RDN treatment to lower BP independent of BP drug therapy remains high.

STUDY LIMITATIONS. The current report includes a post hoc analysis from a large, prospective, single-arm, open-label, real-world registry. As often observed in registries, not all patients were available for 3-year follow-up, and no control group was available for comparison. However, the overall large number of patients available and the extended duration of follow-up clearly demonstrated a persistent BP reduction over 3 years. Baseline BP has been reported to be a predictor of BP drop, and several of the comparison subgroups had different baseline SBP (23). However, these differences were appropriately adjusted using ANCOVA (24), and the benefit in BP reduction was consistent. CV risk scores could not be recalculated at follow-up, because serum cholesterol measurement was not mandatory. However, because SBP is a key determinant of risk, one might assume that calculated risk improved in this group.

CONCLUSIONS

BP reduction after RDN was similar in patients with and without baseline conditions associated with increased sympathetic activity and irrespective of ASCVD risk. The reduction in BP was sustained to 3 years, demonstrating the durability of BP reduction by RDN across various subgroups, particularly in patients with high CV risk. Rates of new-onset end-stage renal disease and elevation in serum creatinine levels were very low in patients at high and low CV risk. Clinical events increased with increasing ASCVD risk score, and elevated rates were also seen in patients with AF and diabetes, identifying these subgroups who might derive even greater clinical benefit from improved BP control using RDN.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a large global registry, renal denervation resulted in similar reductions of blood pressure in hypertensive patients across a wide range of cardiovascular risk.

TRANSLATIONAL OUTLOOK: Future studies should assess the efficacy of renal denervation to prevent major adverse cardiovascular events in patients with isolated systolic and other specified forms of hypertension.

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