Hypertension

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Outcomes Following Radiofrequency Renal Denervation According to Antihypertensive Medications: Subgroup Analysis of the Global SYMPLICITY Registry DEFINE

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BACKGROUND: The Global SYMPLICITY Registry DEFINE investigates radiofrequency renal denervation (RDN) in a broad range of patients with hypertension. We evaluated whether the number or type of antihypertensive medications were associated with increased long-term blood pressure (BP) reductions and cardiovascular outcomes following radiofrequency RDN.

METHODS: Patients underwent radiofrequency RDN and were categorized by baseline number (0–3 and ≥4) and different combinations of medication classes. BP changes were compared between groups through 36 months. Individual and composite major adverse cardiovascular events were analyzed.

RESULTS: Of 2746 evaluable patients, 18% were prescribed 0 to 3 and 82% prescribed ≥4 classes. At 36 months, office systolic BP significantly decreased ($P<0.0001$) by −19.0±28.3 and −16.2±28.6 mm Hg in the 0 to 3 and ≥4 class groups, respectively. Twenty-four–hour mean systolic BP significantly decreased ($P<0.0001$) by −10.7±19.7 and −8.9±20.5 mm Hg, respectively. BP reduction was similar between the medication subgroups. Antihypertensive medication classes decreased from 4.6±1.4 to 4.3±1.5 ($P<0.0001$). Most decreased (31%) or had no changes (47%) to the number of medications, while 22% increased. The number of baseline antihypertensive medication classes was inversely related to the change in prescribed classes at 36 months ($P<0.001$). Cardiovascular event rates were generally low. More patients in the ≥4 compared with 0 to 3 medication classes had myocardial infarction at 36 months (2.8% versus 0.3%; $P=0.009$).

CONCLUSIONS: Radiofrequency RDN reduced BP safely through 36 months, independent of the number and type of baseline antihypertensive medication classes. More patients decreased than increased their number of medications. Radiofrequency RDN is a safe and effective adjunctive therapy regardless of antihypertensive medication regimen.

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Key Words: humans ■ hypertension ■ myocardial infarction ■ risk reduction behavior ■ stroke

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NOVELTY AND RELEVANCE

What Is New?

Radiofrequency renal denervation was effective at lowering blood pressure in all patients regardless of their number and type of antihypertensive medication classes.

Radiofrequency renal denervation was also effective in patients taking less common, reserve antihypertensive medications, such as α-adrenergic blockers, centrally acting sympatholytics, direct renin inhibitors, and direct-acting vasodilators.

Following radiofrequency renal denervation, more patients decreased than increased their medication regimen through 36 months. Each unit increase in the number of baseline prescribed antihypertensive medication class was associated with a reduction by 0.31 antihypertensive medication classes at 36 months.

There was a higher risk of myocardial infarction in patients taking ≥4 antihypertensive medication classes than in patients taking 0 to 3 medication classes, but patients taking ≥4 medication classes had significantly higher cardiovascular comorbidities. Adequate blood pressure control and reduction of cardiovascular risk factors in the latter group may be particularly important.

What Is Relevant?

This Global SYMPLICITY Registry DEFINE study reflects on the real-world challenge of patients with multiple comorbidities, uncontrolled hypertension despite taking average 5 different classes of antihypertensive medications.

Clinical/Pathophysiological Implications?

High burden of antihypertensive medications is associated with nonadherence. Radiofrequency renal denervation may offer an effective, adjunctive hypertension therapy, while reducing the burden of long-term antihypertensive medications.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
BP	blood pressure
CAS	centrally acting sympatholytics
CCB	calcium channel blocker
GSR	Global SYMPLICITY Registry
MI	myocardial infarction
RDN	renal denervation

Hypertension remains a global health burden with 1 in 3 adults; equivalent to 1.6 billion people worldwide will have hypertension by 2025.[1] Lowering systolic blood pressure (BP) by 10 mm Hg reduces the relative risk of major adverse cardiovascular events by 20%, irrespective of baseline BP or previous diagnoses of cardiovascular disease.[2,3] Moreover, there is a continuous relationship of absolute BP reduction from baseline with cardiovascular outcomes. However, controlling BP to target values can be challenging despite the availability of multiple classes and combinations of pharmacotherapy. Increasing the number of prescribed medications is associated with greater risk of intolerance, side effects, and nonadherence,[4] particularly in the elderly.[5] Therefore, a clinical need exists for adjunctive procedural treatment options for hypertension that do not depend on pharmacotherapy and daily patient adherence.

Multiple trials have demonstrated that renal denervation (RDN) is a safe, effective, and durable approach to reduce BP in patients with uncontrolled hypertension in both the absence and presence of antihypertensive medications.[6–13] The Global SYMPLICITY Registry (GSR) DEFINE is an ongoing all-comers study designed to assess the safety and efficacy of radiofrequency RDN in a real-world setting, including a large proportion of patients prescribed multiple antihypertensive medications and meeting clinical criteria for resistant hypertension.[14–16] The latter is defined as BP above goal despite concurrent use of 3 antihypertensive drugs, 1 being a diuretic in appropriate doses and combinations. Recently, we reported that BP reduction after radiofrequency RDN was similar for patients with varying high-risk comorbidities.[14] This analysis aimed to determine whether the number or type of prescribed antihypertensive medications was associated with increased long-term BP reductions and cardiovascular outcomes following radiofrequency RDN in real-world patients with uncontrolled hypertension.

METHODS

The authors declare that all supporting data are available within the article and its Supplemental Material.

Study Design

The study design of GSR DEFINE was described previously (https://www.clinicaltrials.gov; unique identifier: NCT01534299).[17] GSR DEFINE is a prospective, multicenter,

single-arm, open-label, observational, international registry in an all-comer population undergoing radiofrequency RDN, including patients with uncontrolled hypertension. All patients provided written informed consent. The study was approved by the institutional review board or ethics committee at each enrolling center, and the study adhered to the Declaration of Helsinki.

Study Procedures

Radiofrequency RDN was performed using either the first-generation single-electrode Symplicity Flex or the current-generation 4-electrode Symplicity Spyral catheter (Medtronic plc, Santa Rosa, CA). The procedural technique has been described elsewhere.[9,10,18] Patients were followed at 6, 12, 24, and 36 months after the procedure per standard of care. Office and 24-hour ambulatory BP was measured at baseline before the RDN procedure and at each follow-up visit.[19] Prescribed antihypertensive medication classes were catalogued although dosages were not reported. Adverse events included myocardial infarction (MI), stroke, hospitalization for heart failure, cardiovascular death, all-cause death, and composite events comprising of all of the above were recorded through 36 months. Adverse events were independently adjudicated by the Clinical Events Committee (Cardiovascular Research Foundation, New York, NY).

Statistical Analyses

Subjects were divided into 2 main groups according to the baseline distinct antihypertensive medication classes (ie, 2 antihypertensive medications of the same class counted as 1 class) prescribed including 0 to 3 medications and ≥4 medications. Baseline demographics, BP changes from baseline, and adverse event rates were compared between the 2 groups. Further subgroup analyses included changes to the number of medication classes, categorization of different combinations of medication classes as recommended by the ESC/ESH guideline[20] (Table S1) and their corresponding BP changes, specific combination of medication classes in resistant hypertension (uncontrolled BP despite ≥3 medications not including an aldosterone antagonist versus ≥3 medications including an aldosterone antagonist), and specific reserve hypertension medication classes (ie, α-adrenergic blockers, centrally acting sympatholytics, direct renin inhibitors, and direct-acting vasodilators) and their effects following radiofrequency RDN on BP through 36 months.

SAS for Windows, version 9.4 (SAS Institute, Cary, NC), was used for all statistical analyses. Continuous variables are presented as mean±SD. Categorical variables are presented as n (%), and data were compared across groups with Pearson χ^2 tests. Paired *t* tests were used to compare changes in BP from baseline within medication groups. Comparisons in baseline demographics and changes in BP from baseline among different groups used a Pearson χ^2 test or Mann-Whitney-Wilcoxon test, unless stated otherwise. A linear regression analysis was performed to look for any significant correlation between the number of baseline antihypertensive medication classes and changes in the number of medication classes at 36 months. ANCOVA test was used to adjust for baseline BP when comparing 36-month BP change from baseline between groups: 0 to 3 versus ≥4 medication classes and ≥3 medications including aldosterone antagonist versus ≥3 medications without aldosterone antagonist. Cardiovascular outcomes were compared between different groups using the Pearson χ^2 test.

RESULTS

Baseline Demographics

As of March 2023, 3332 patients were enrolled into GSR DEFINE. The present cohort consisted of 2872 patients with available data on both the number and type of prescribed antihypertensive medication classes. Of these, 2746 also had sequential BP data available to correlate with prescribed medication. The detailed baseline characteristics of the full present GSR DEFINE cohort are summarized in Table 1. The mean age was 61±12 years, and 42.2% were women. The baseline office systolic BP was 166.0±24.8 mm Hg and the baseline 24-hour systolic BP was 154.5±18.6 mm Hg. Of patients, 22.3% were treated with the multielectrode Symplicity Spyral catheter and 77.7% with the first-generation single-electrode Symplicity Flex catheter. Overall, patients were prescribed an average of 4.6±1.4 antihypertensive medication classes. The full breakdown of proportion of patients taking different number of medication classes is depicted in Figure S1A. The most commonly prescribed classes were diuretics (78.9%), calcium channel blockers (CCBs; 78.2%), β-blockers (77.8%), and angiotensin receptor blockers (ARBs; 63.9%). Less commonly prescribed were centrally acting sympatholytics (37.9%), α-adrenergic blockers (36.7%), ACE (angiotensin-converting enzyme) inhibitors (34.6%), aldosterone antagonists (27.9%), direct-acting vasodilators (13.8%), and direct renin inhibitors (5.3%; Figure S1B).

Of patients, 18% were prescribed 0 to 3 antihypertensive medication classes (average of 2.5±0.8), and 82% patients were prescribed ≥4 antihypertensive medication classes (average of 5.2±1.1). Patients prescribed ≥4 medication classes, as compared with 0 to 3 medication classes, were more likely to be younger, male, have higher body mass index and higher rate of diabetes, cardiac disease including history of heart failure, sleep apnea, chronic kidney disease, and lower estimated glomerular filtration rate. The baseline office (0–3 meds, 167.3±23.8 mm Hg versus ≥4 meds, 165.7±25.1 mm Hg) and 24-hour systolic BP (0–3 meds, 154.2±19.7 mm Hg versus ≥4 meds, 154.8±18.5 mm Hg) was similar between groups, as well as the baseline diastolic BP between groups (Table 1). The office and the 24-hour heart rates were significantly higher in patients taking 0 to 3 medication classes, compared with patients taking ≥4 medication classes (72.2±14.3 versus 69.7±12.9 bpm, P=0.0011; 71.2±11.5 versus 68.1±11.4 bpm, P<0.0001), and a significantly higher proportion of patients were prescribed β-blockers in the ≥4 medication classes group (≥4 meds, 85.2% versus 0–3 meds, 43.6%; P<0.0001).

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Table 1. Demographics of Patients by Number of Antihypertensive Medication Classes

Demographics	All (N=2872)	0–3 meds* (n=495)	≥4 meds* (n=2251)	*P* value†
Age, y	60.7±12.0	61.6±12.0	60.4±12.0	0.038
Female	42.2%	48.5%	41.3%	0.0035
BMI, kg/m²	31.0±5.7	29.7±5.3	31.3±5.7	<0.0001
Diabetes	40.8%	32.7%	42.6%	<0.0001
Cardiac disease	47.0%	43.3%	48.2%	0.050
Atrial fibrillation	12.4%	10.5%	12.9%	0.15
Hypercholesterolemia	36.0%	34.4%	35.9%	0.52
eGFR, mL/min per 1.73m²	75.9±25.0	78.3±22.5	75.4±25.5	0.010
Chronic kidney disease (eGFR <60 mL/min per 1.73 m²	20.5%	13.6%	21.8%	<0.0001
Sleep apnea	19.4%	14.5%	20.5%	0.0032
Office systolic BP	166.0±24.8	167.3±23.8	165.7±25.1	0.15
Office diastolic BP	90.2±16.8	91.2±15.1	89.8±17.1	0.023
Office heart rate	70.2±13.2	72.2±14.3	69.7±12.9	0.0011
24-h ambulatory systolic BP	154.5±18.6	154.2±19.7	154.8±18.5	0.36
24-h ambulatory diastolic BP	86.8±14.5	87.3±14.3	86.9±14.5	0.70
24-h ambulatory heart rate	68.6±11.4	71.2±11.5	68.1±11.4	<0.0001
Medications				
No. of antihypertensive medication classes	4.6±1.4	2.5±0.8	5.2±1.1	<0.0001
ACE inhibitors	34.6%	24.4%	37.0%	<0.0001
ARBs	63.9%	48.9%	67.5%	<0.0001
Calcium channel blockers	78.2%	50.7%	84.4%	<0.0001
Diuretics	78.9%	44.8%	86.6%	<0.0001
Aldosterone antagonists	27.9%	5.9%	32.7%	<0.0001
β-Blockers	77.8%	43.6%	85.2%	<0.0001
α-Adrenergic blockers	36.7%	13.7%	41.7%	<0.0001
Centrally acting sympatholytics	37.9%	11.7%	43.6%	<0.0001
Direct renin inhibitors	5.3%	2.2%	6.0%	0.0006
Direct-acting vasodilators	13.8%	2.6%	16.1%	<0.0001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; and eGFR, estimated glomerular filtration rate.

*These subgroups of patients had evaluable office systolic BP at baseline, as well as number and type of antihypertensive medication class information.

†0–3 vs ≥4 medications comparison.

Change in BP by the Number of Antihypertensive Medication Classes

Overall, at 36 months, the office and 24-hour systolic BP reductions from baseline were −16.7±28.6 and −9.1±20.2 mm Hg, respectively (*P*<0.0001). The office and 24-hour diastolic BP reductions were −6.3±16.2 and −4.6±12.1 mm Hg, respectively (*P*<0.0001). In the 0 to 3 and ≥4 antihypertensive medication class groups, there was a progressive reduction in systolic (Figure 1) and diastolic BP (Figure S2) throughout 36 months, with significant changes compared with baseline at each follow-up time point (*P*<0.0001). At 36 months, office systolic BP in patients taking 0 to 3 and ≥4 medication classes decreased from baseline by −19.0±28.3 and −16.2±28.6 mm Hg, respectively. There was no significant difference between the groups (adjusted difference, −0.7 mm Hg [95% CI, −4.0 to 2.6]; *P*=0.69; Figure 1A). The 24-hour systolic BP decreased from baseline by −10.7±19.7 and −8.9±20.5 mm Hg, respectively, without group differences (adjusted difference, −2.8 mm Hg [95% CI, −7.2 to 1.6]; *P*=0.21; Figure 1B). There was also no significant difference in diastolic BP, both in office (Figure S2A) and 24-hour BP between groups (Figure S2B).

Change in Number of Antihypertensive Medication Classes

The average number of prescribed antihypertensive medication classes decreased at 36 months from baseline, in the full cohort (4.6±1.4 to 4.3±1.5; *P*<0.0001). Prescriptions for all medication classes reduced by 36 months, but there was a slight increase in the prescription of aldosterone antagonists (Table S2). Overall, there was a significant inverse relationship between the number of baseline prescribed antihypertensive medication classes and its change at 36 months (regression coefficient, −0.31; *P*<0.001). Each unit increase in the number of baseline prescribed antihypertensive medication class was associated with a reduction by 0.31 antihypertensive medication classes at 36 months.

Through 36 months, most patients did not change their number of medication classes (46.8%), followed by patients who decreased (31.2%), and the least proportion increased their number of medication classes (22.0%). At 36 months, the office systolic BP significantly decreased from baseline (*P*<0.0001) by −17.5, −17.2, and −15.7 mm Hg in increased, no change, and decreased medication groups, respectively. There was no significant difference between these groups (*P*=0.51; Figure 2A). Similar results were observed in 24-hour systolic BP changes at 36 months (Table S3).

Also, a significantly greater proportion of patients taking 0 to 3 medication classes had increased their

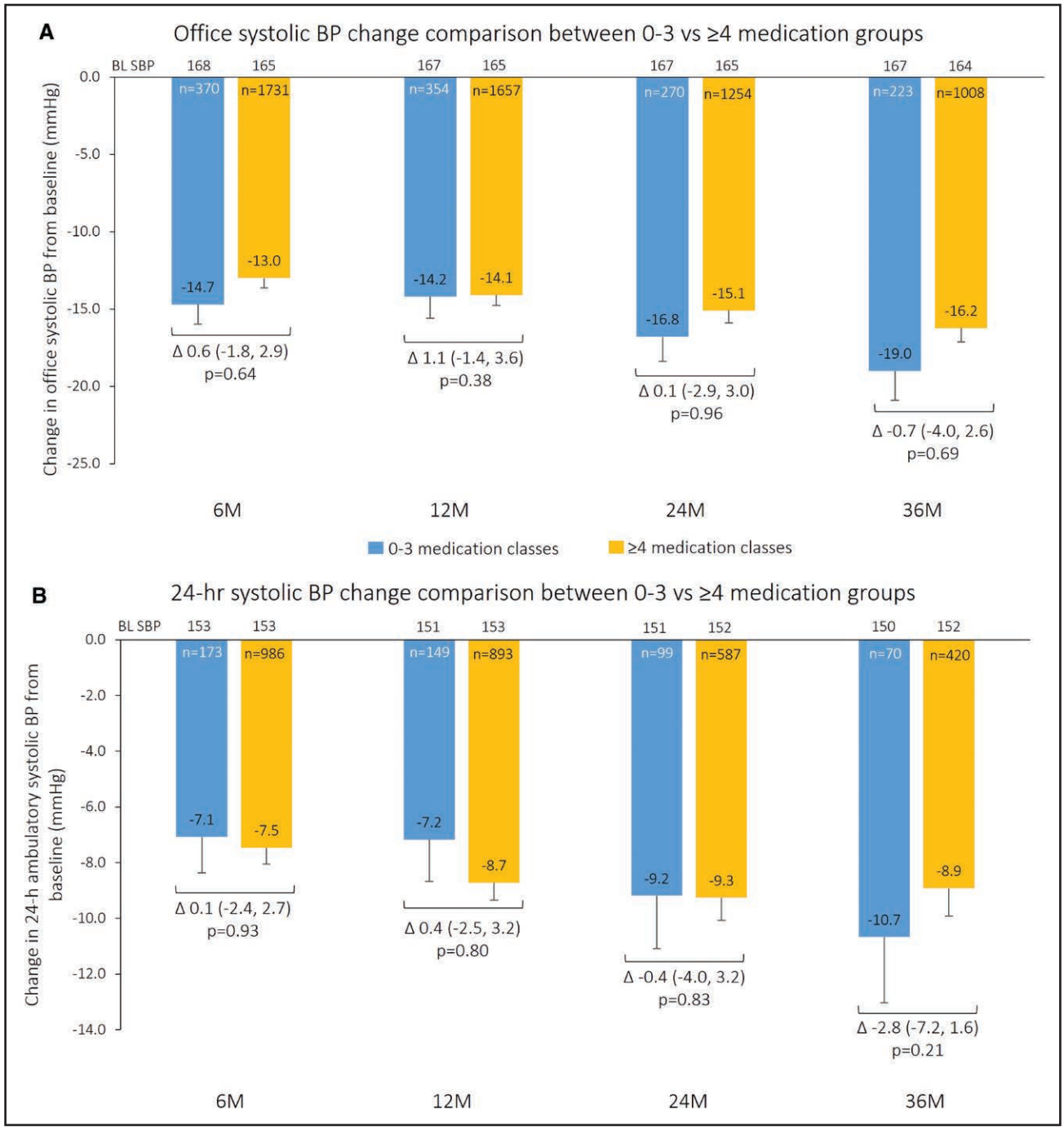

Figure 1. Bar graph showing systolic blood pressure (SBP) changes from baseline (BL) and comparisons between 0 to 3 and ≥4 medication classes.

A, Office SBP changes from BL and blood pressure (BP) change comparison between 0 to 3 and ≥4 medication classes. **B**, Twenty-four–hour ambulatory SBP changes from BL and BP change comparison between 0 to 3 and ≥4 medication classes. Error bars represent SE. All BP changes compared with BL in both groups had *t* test *P* value <0.0001. *P* values for between-group comparisons were adjusted for each BL SBP displayed on top of the bars, using ANCOVA test.

number of medications from baseline, compared with patients taking ≥4 medication classes (23.2% versus 10.6%; *P*<0.0001; Figure 2B). In contrast, a significantly greater proportion of patients taking ≥4 medication classes had decreased their number of medications compared with patients taking 0 to 3 medication classes (20.9% versus 7.3%; *P*<0.0001). There was a similar proportion of patients who did not change the number of medication classes (0–3 meds, 27.9% versus ≥4 meds, 27.8%; *P*=0.98). At 36 months, the patients taking 0 to 3 medication classes were on average 3.1±1.4 medication classes, which had increased from baseline

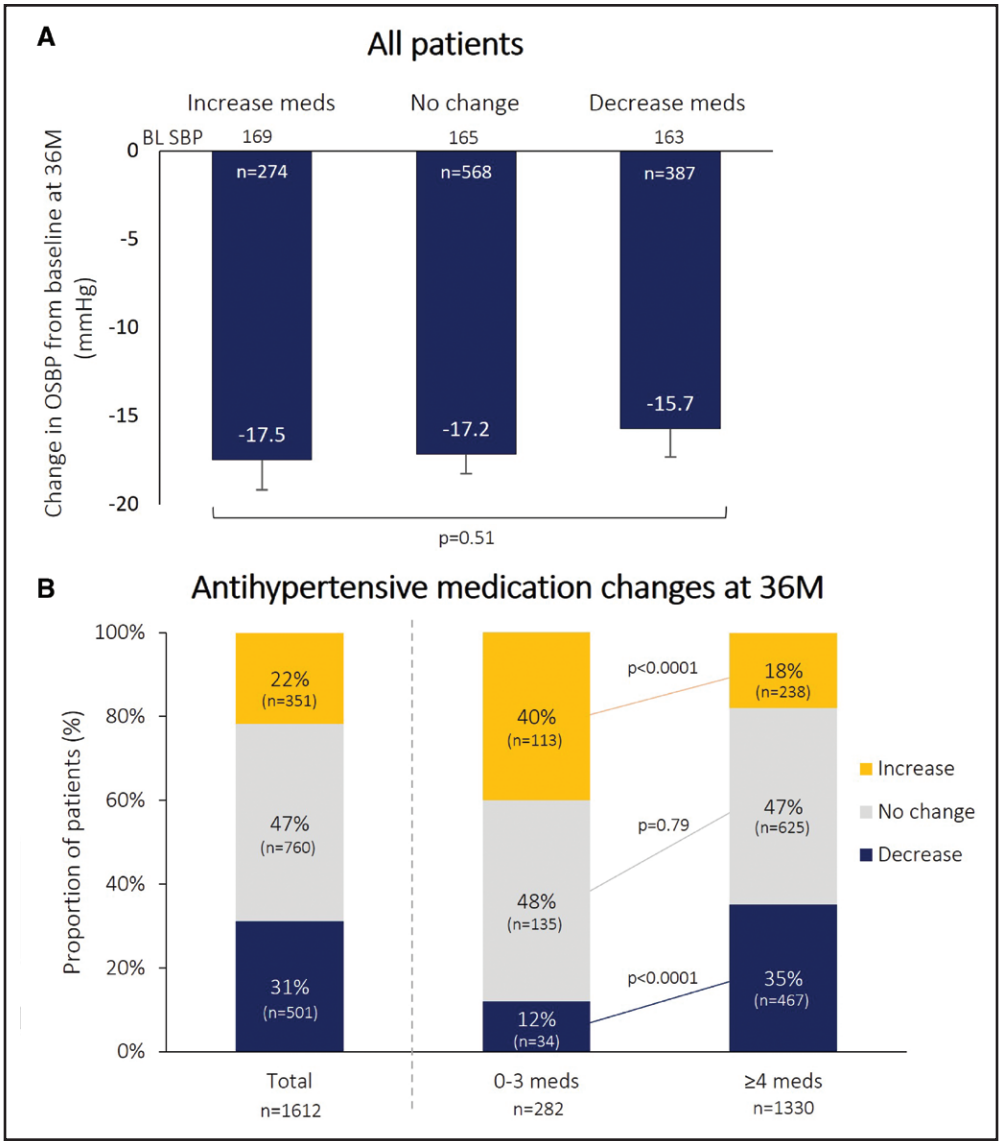

Figure 2. Office systolic blood pressure (SBP) and medication changes at 36 months after radiofrequency renal denervation. **A**, Bar graphs with office SBP changes at 36 months from baseline in patients who decreased, had no change or increased medications. All blood pressure (BP) changes compared with baseline in these groups had *t* test *P* value <0.0001. **B**, Left-hand bar graph representing the overall population with changes in systolic BP from baseline at 36 months corresponding with increase, decrease, and no change in medication classes at 36 months. The right-hand bar graphs show a comparison in medication changes between 0 to 3 and ≥4 antihypertensive medication classes. Error bars represent SE.

(2.5±0.8). Patients taking ≥4 medication classes were on average 4.9±1.5, which had decreased from baseline (5.2±1.1). There was no significant difference in systolic BP changes between patients on 0 to 3 and ≥4 medication classes at 36 months after radiofrequency RDN (Figure 1).

Different Combinations of Antihypertensive Medication Classes and BP Changes

Patients were categorized into nonmutually exclusive groups of commonly prescribed antihypertensive medication classes at baseline that followed a stepwise pharmacological approach for hypertension management as per the ESC/ESH guideline for the management of hypertension[20] (Table S1). Patients on less common, reserve classes of antihypertensive medications were also evaluated. In category 1, 10.9% of patients were prescribed 1 to 3 antihypertensive medication classes including ACE inhibitor or ARB, CCB, diuretic, and β-blocker, which represented 64.7% of all patients prescribed 1 to 3 medications. Of patients, 47.1% took 1 to 3 of these classes without β-blocker (Table S4) and 17.6% patients were prescribed ≥3 classes without β-blocker. In category 2, 22.1% of patients were prescribed 4 to 6 classes of antihypertensive medications including ACE inhibitor or ARB, CCB, diuretic, β-blocker, aldosterone antagonist, or α-blocker, which represented 32.4% of all patients prescribed 4 to

6 medications. In category 3, 10.3% of patients were prescribed 1 to 4 reserve antihypertensive medication classes including any of the following: centrally acting sympatholytics, direct-acting vasodilators, and direct renin inhibitors, which represented 24.2% of all patients prescribed 1 to 4 medications. A majority of patients (55.5%) were in category 4, which included any class combination of ≥5 antihypertensive medications. Finally, 8.7% of patients were simultaneously prescribed both an ACE inhibitor and an ARB within their medication regimen (category 5), which is not guideline recommended.[20]

The baseline demographics were similar across all 5 categories based on baseline prescribed medications (Table S5). In all 5 categories, office systolic BP decreased significantly ($P<0.0001$) through 36 months (Figure 3). Mean 24-hour systolic BP also decreased significantly in all groups at 36 months except for category 5 (Table S6).

Resistant Hypertension Cohort and BP Changes

In the resistant hypertension cohort (uncontrolled BP on ≥3 antihypertensive medication classes), there was a progressive and significant BP reduction from baseline in both office and 24-hour BP through 36 months after RDN ($P<0.0001$; Figure 4). Of this cohort, 54.2% were on ≥3 antihypertensive medication classes including ACE inhibitor or ARB, CCB, and a diuretic.

At 36 months, patients with resistant hypertension on ≥3 antihypertensive medication classes including an aldosterone antagonist at baseline had office and 24-hour systolic BP decreased by −15.3 and −8.6 mm Hg, respectively. Patients with resistant hypertension without an aldosterone antagonist at baseline had office and 24-hour systolic BP decreased by −16.8 and −9.5 mm Hg, respectively (Figure 4). There was a significant difference in the office systolic BP change between the groups at 12 months (adjusted difference, 2.8 mm Hg [95% CI, 0.6–4.9]; $P=0.013$) and at 24 months (adjusted difference, 3.6 mm Hg [95% CI, 1.0–6.2]; $P=0.006$) in favor of patients without aldosterone antagonist, but no significant difference was observed at 6 (adjusted difference, 0.3 mm Hg [95% CI, −1.7 to 2.4]; $P=0.76$) or 36 months (adjusted difference, 1.3 mm Hg [95% CI, −1.7 to 4.2]; $P=0.39$; Figure 4A). There was no significant difference between the groups with 24-hour systolic BP change at any time point (Figure 4B). The office and 24-hour diastolic BP changes are depicted in Figure S5. Furthermore, at 36 months after radiofrequency RDN, 23.8% of the patients with resistant hypertension and aldosterone antagonist treatment at baseline were no longer prescribed an aldosterone antagonist.

Adverse event rates 36 months after RDN

At 36 months, adverse event information was available in 1832 patients. A breakdown of adverse events was previously reported for the pooled cohort[16]; 2.4% had spontaneous MI, 4.6% stroke, 3.9% hospitalizations for new-onset heart failure, 2.9% cardiovascular death, and 5.7% all-cause death. The composite event rate through 36 months was 11.1%. Comparison between patients on 0 to 3 and ≥4 medication classes showed that significantly more patients taking ≥4 medication classes had MI at 24 months (1.8% versus 0.3%; $P=0.023$), with a greater difference at 36 months (2.8% versus 0.3%; $P=0.009$; Table 2). There were no other significant differences in adverse events between the groups.

DISCUSSION

Radiofrequency RDN has been shown to be safe and effective in randomized, sham-controlled trials and real-world patients, including a broad range of patients with difficult-to-control hypertension and varying comorbidities.[14–16] However, the efficacy of RDN against the background of different number and type of antihypertensive medication classes has not been investigated in detail. Such analysis is particularly relevant since recently published consensus statements on RDN have recommended application in patients with uncontrolled resistant hypertension on ≥3 antihypertensive drugs.[21,22] In this international study, there was a widely variable number and class combination of antihypertensive medications, reflective of the difficult-to-control patient population considered for radiofrequency RDN. Most GSR DEFINE patients (94%) also met criteria for resistant hypertension. Of these resistant hypertension patients, 54.2% were prescribed ≥3 guideline-directed first-line antihypertensive drugs (ie, ACE inhibitor or ARB, CCB, and diuretics). Furthermore, a relatively large proportion of patients was prescribed reserve antihypertensive medications, such as α-adrenergic blockers, centrally acting sympatholytics, direct-acting vasodilators, and direct renin inhibitors. To our knowledge, the effect of RDN in combination with these reserve antihypertensive medications has not been previously investigated in detail.

The present analysis shows that radiofrequency RDN significantly lowered BP independently of the number and type of antihypertensive medication classes at baseline. Furthermore, more patients decreased their number of antihypertensive classes than increased, particularly when prescribed higher number of medication classes at baseline (≥4 versus 0–3 medication classes). Indeed, the number of baseline prescribed antihypertensive medications was related to the long-term change in prescribed medications, with each additional baseline medication predicting a decrease by 0.31 in prescribed medications at 36 months. The greater the number of baseline antihypertensive medications prescribed, the greater the reduction in medication burden after radiofrequency RDN in this population. Notably, radiofrequency RDN

Categories	Description	N=2836	%
1	Patients taking 1-3 antihypertensive meds ONLY from the following: 1. ACE-i or ARB but not both 2. CCB 3. Diuretic 4. Beta blocker	310	10.9
2	Patients taking 4-6 antihypertensive meds ONLY from the following: 1. ACE-i or ARB but not both 2. CCB 3. Diuretic 4. Beta blocker 5. Aldosterone antagonist or spironolactone but not both 6. Alpha blocker	628	22.1
3	Patients taking 1-4 antihypertensive meds including any of the following 3 classes: 1. Centrally-acting sympatholytics 2. Direct-acting vasodilators 3. Direct renin inhibitors	291	10.3
4	Patients on ANY combination of ≥5 antihypertensive meds	1574	55.5
5	Patients on both ACE-i and ARB	247	8.7

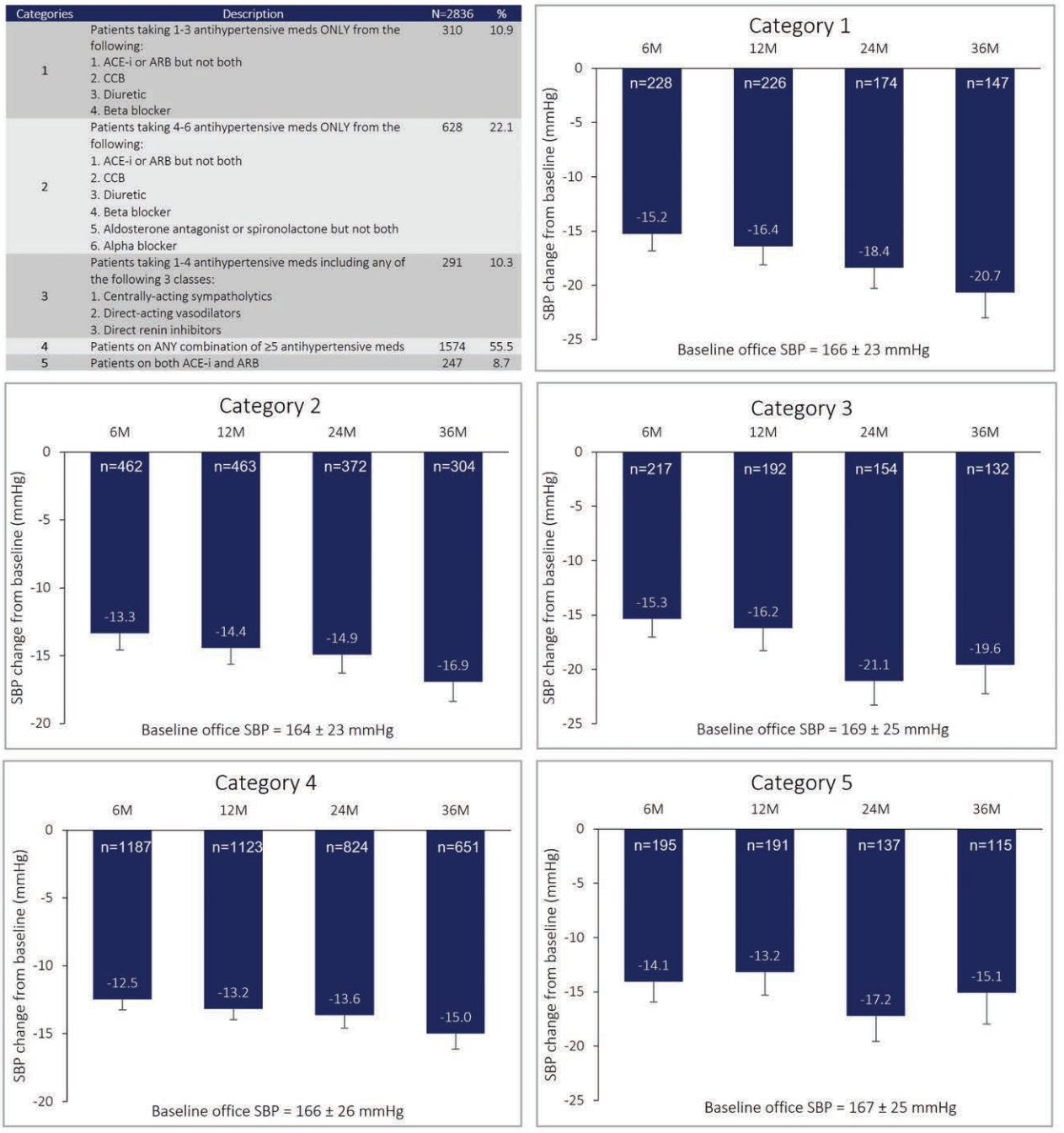

Figure 3. Different categories of baseline antihypertensive medication class combos and their office systolic blood pressure (SBP) change through 36 months.

Category 1: 1 to 3 antihypertensive medication classes including ACE (angiotensin-converting enzyme) inhibitor or angiotensin receptor blocker (ARB), calcium channel blocker, diuretic, and β-blocker. Category 2: 4 to 6 classes of antihypertensive medications including ACE inhibitor or ARB, calcium channel blocker, diuretic, β-blocker, aldosterone antagonist, or α-adrenergic blocker. Category 3: 1 to 4 medications including any of the following reserve antihypertensive medication classes: centrally acting sympatholytics, direct-acting vasodilators, and direct renin inhibitors. Category 4: any class combination of ≥5 antihypertensive medications. Category 5: any class combination including ACE inhibitor and ARB. The bar graphs show office SBP change from baseline for each category of medication class combos. Error bars represent SE. RDN indicates renal denervation.

achieved significant BP reductions from baseline, independent of changes to the number of medication classes at 36 months.

GSR DEFINE is the first study showing no meaningful difference in either short- or long-term BP reductions between substantially large subgroups of patients treated

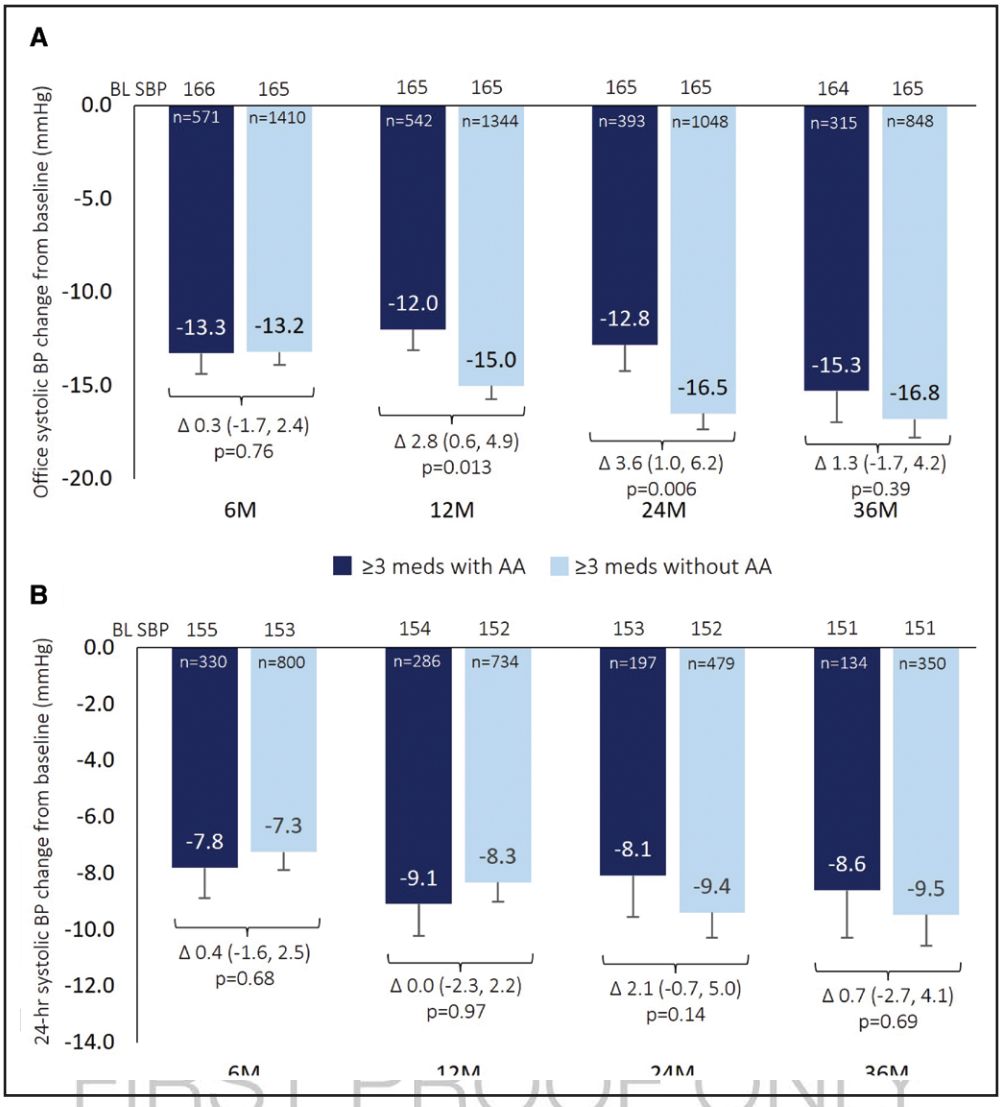

Figure 4. Bar graph showing systolic blood pressure (SBP) changes from baseline (BL) in resistant hypertension patients on ≥3 antihypertensive medications with or without aldosterone antagonist (AA).
A, Office SBP changes from BL. **B**, Twenty-four-hour ambulatory SBP changes from BL. All blood pressure (BP) changes compared with BL in these groups had *t* test *P* value <0.0001. *P* values were ANCOVA adjusted for each BL SBP as displayed below the bars.

with various prescribed medication classes. Similarly, no difference was observed between patients with resistant hypertension on ≥3 medications with and without aldosterone antagonist. A previous post hoc subanalysis of the randomized sham-controlled SYMPLICITY HTN-3 trial showed that baseline prescription of aldosterone antagonists, but not vasodilators, β-blockers, or calcium channel blockers, was associated with BP response at 6 months following radiofrequency RDN.[24] However, that trial was not designed to power post hoc analyses of associations or predictors of response. RDN has also previously been shown to lower plasma renin activity and aldosterone concentrations in patients not receiving any antihypertensive medications.[25] Notably, 23.8% of patients with resistant hypertension prescribed an aldosterone antagonist at baseline were no longer prescribed that at 36 months after radiofrequency RDN. Overall, these data suggest that radiofrequency RDN is a safe and effective option for patients on complex antihypertensive medication regimens that include aldosterone antagonists.

Objective analysis of antihypertensive medication adherence by toxicological assessments was beyond the scope of this global, real-world study. Therefore, whether patients prescribed ≥3 antihypertensive drugs met the more stringent criteria for true resistant hypertension is unknown.[20] Previous reports have indicated that about half of all patients with apparent resistant hypertension are actually pseudoresistant[26] and that levels of adherence to prescribed medications is low in the uncontrolled hypertension population and proportionate to the number of prescribed medications.[4] It is reasonable to assume that patient nonadherence in this real-world population is similar to clinical practice and that radiofrequency RDN may offer particular benefits to nonadherent patients.

Table 2. Adverse Events by Number of Baseline Antihypertensive Medication Classes at Each Time Point

Adverse events	All	0–3 medications	≥4 medications	*P* value*
6 mo	n=2737	n=471	n=2154	
Composite events	2.2%	1.9%	2.2%	0.67
MI	0.6%	0.2%	0.7%	0.22
Stroke	0.9%	0.6%	0.9%	0.54
Hospitalization with HF	0.8%	0.4%	0.7%	0.51
CV death	0.2%	0%	0.3%	0.25
All-cause death	0.4%	0.4%	0.5%	0.91
12 mo	n=2593	n=446	n=2040	
Composite events	3.8%	4.0%	3.8%	0.79
MI	0.9%	0.2%	1.0%	0.10
Stroke	1.5%	2.2%	1.4%	0.18
Hospitalization with HF	1.2%	0.4%	1.2%	0.17
CV death	0.7%	0.2%	0.9%	0.15
All-cause death	1.3%	1.6%	1.3%	0.69
24 mo	n=2230	n=390	n=1757	
Composite events	7.3%	6.7%	7.4%	0.61
MI	1.5%	0.3%	1.8%	0.023
Stroke	2.8%	3.6%	2.7%	0.36
Hospitalization with HF	2.4%	1.3%	2.4%	0.18
CV death	1.8%	0.8%	2.0%	0.09
All-cause death	3.5%	3.6%	3.5%	0.95
36 mo	n=1832	n=310	n=1465	
Composite events	11.1%	10.6%	11.1%	0.83
MI	2.4%	0.3%	2.8%	0.0089
Stroke	4.6%	5.5%	4.5%	0.44
Hospitalization with HF	3.9%	1.9%	4.1%	0.066
CV death	2.9%	2.3%	3.1%	0.43
All-cause death	5.7%	6.8%	5.4%	0.35

CV indicates cardiovascular; HF, heart failure; and MI, myocardial infarction.
*0 to 3 vs ≥4 medications comparison.

We previously demonstrated reduced incidence of major adverse cardiovascular events, including stroke, in the GSR DEFINE population using a modeled comparator based on published meta regression of hypertension induced outcome risk.[27] The present analysis showed that the risk of stroke was similar between the 0 to 3 and ≥4 antihypertensive medication class groups. However, MI was observed more frequently in the ≥4 medication class group, at both 24 and 36 months. This might have been due, in part, to the higher rate of baseline comorbidities including diabetes, cardiac disease (including coronary artery disease), obesity, and chronic kidney disease in the ≥4 medication class group. Hospitalization with new-onset heart failure, with pathognomonic factors including both hypertension and MI, also trended higher in the ≥4 medication class group. Changes in other cardiovascular outcomes were similar between groups. Both groups had similar baseline office and 24-hour BP and similar reductions in office and 24-hour BP, despite different demographics and more common baseline comorbidities in the ≥4 medication class group. Overall, there was a relatively low incidence of any single major cardiovascular event in this study, compared with 12.3% of the equivalent reported by the large meta-analysis of 344 716 patients from BP-lowering pharmacological RCTs at median 4 years of follow-up.[2]

Perspectives

RDN is recommended as a potential adjunctive therapy for uncontrolled resistant hypertension.[21,22] This GSR DEFINE study evaluated real-world patients treated with an average of 5 different classes of antihypertensive medications, with multiple comorbidities. A relatively large proportion of the patients were prescribed reserve antihypertensive medications, such as α-adrenergic blockers, centrally acting sympatholytics, direct-acting vasodilators, and direct renin inhibitors. GSR DEFINE showed that radiofrequency RDN significantly lowered BP independently of the number and type of antihypertensive medication classes at baseline. In addition to this, each unit increase in the number of baseline prescribed antihypertensive medication class was associated with a reduction by 0.31 antihypertensive medication classes at 36 months. More patients decreased their medications than increased through 36 months. Although no objective medication adherence evaluation was performed in this study, it is reasonable to assume that patient nonadherence in this real-world population is similar to clinical practice. There was a relatively low incidence of any single major cardiovascular event in this study, compared with previous large meta-analyses data on BP-lowering pharmacological RCTs. Further investigations are needed to address the efficacy of radiofrequency RDN for reducing cardiovascular events.

Limitations

GSR DEFINE is a large real-world global observational registry with no comparative control group. However, the reductions in BP observed to 3 years are similar in magnitude to long-term reports from randomized, sham-controlled trials.[10,11] This is an observational registry based on routine clinical practice, and not all patients in the GSR DEFINE have data collected or available at all follow-up time points. Objective adherence testing was not performed. We did not collect the overall number or dose of medications, regardless of class. Therefore, we could not analyze medication burden or discern what proportion of patients were

on duplicate classes of medications. The majority of patients in the registry were treated with the first-generation single-electrode catheter, and the number of applied lesions also varied.[15] However, it is unlikely that procedural details influenced the interaction between radiofrequency RDN response and prescribed medication therapy.

Conclusions

In this real-world registry of patients with uncontrolled hypertension and comorbidities, radiofrequency RDN reduced BP safely and consistently through 36 months independent of the number (including 0–3 and ≥4 antihypertensive medications) and type of baseline antihypertensive medication classes. Most patients decreased or did not change their number of antihypertensive medication classes after radiofrequency RDN. Radiofrequency RDN may be a safe and effective adjunctive therapy in patients with a widely variable background antihypertensive medication regime.

ARTICLE INFORMATION

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