Is There a Sex-Related Difference in Response to Renal Denervation?

What do we know, and what questions do we have?

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Renal denervation (RDN) in the treatment of hypertension continues to evolve, with new evidence emerging regarding its safety and efficacy. This evidence is reinforced by the recognition of hypertension as a major contributor to cardiovascular morbidity and mortality and, therefore, the need for adjunct therapy aside from medication to help achieve better blood pressure (BP) control. Hypertensive women have been found to have worse cardiovascular outcomes than their male counterparts. Furthermore, female-specific factors can complicate the management of hypertension and are implicated in the overall increase in cardiovascular risks. As a result, concerns regarding the need for sex-specific consideration in the management of hypertension have been raised previously. With some studies reporting variable BP response to antihypertensives based on sex, an interesting question remains: Does the sex of a patient have an effect on response to RDN? To date, data regarding sex-related differences in response to RDN are limited, and further studies addressing this issue are warranted.

RDN was developed as a treatment option for patients with uncontrolled hypertension despite lifestyle modification and pharmacotherapy.[1] Early randomized trials demonstrated a significant reduction in office BP after RDN.[1-5] However, the first sham-controlled trial, SYMPLICITY HTN-3, showed no difference in BP reduction between the RDN and sham control arms.[6] Nonetheless, more recent studies demonstrated a significant, although less pronounced, reduction in office and 24-hour ambulatory BP.[7-11] Hypertension remains an important risk factor for cardiovascular disease in both men and women. Globally, it affects 30% of the adult population, with an estimated prevalence of resistant hypertension at 14% to 20%.[12-14] A dose-dependent relationship was found between BP and mortality from cardiovascular and cerebrovascular disease.[15] Thus, even a modest reduction in BP can lead to better outcomes with regard to cardiovascular morbidity and mortality.[16] Recently, Mahfoud et al demonstrated that RDN significantly increased time in therapeutic range (TTR), defined as the proportion of time the patient spends within a predetermined BP (< 140 mm Hg for office systolic BP and < 130 mm Hg for ambulatory systolic BP).[17] TTR was shown to be an independent predictor of cardiovascular events in hypertensive patients.[18] In the study reported by Mahfoud et al, a 10% increase in TTR through 6 months post-RDN was associated with a significant reduction in cardiovascular events at 6 through 36 months.[17]

Hypertension in women carries a greater burden on cardiovascular health compared to men.[19] Several sex-specific factors are implicated in the mechanism of hypertension in women, including hormones, pregnancy-related factors, and sympathetic activity. Although some evidence regarding sex-related variation in response to antihypertensives is available, data regarding differences in response to RDN between men and women are limited. In this article, we highlight issues that are specific to hypertension in women. Furthermore, we summarize the available data on sex-related differences in hypertension treatment, including the response to medication as well as RDN.

HYPERTENSION IN WOMEN

Overall, hypertension is more prevalent in men compared to women (52% vs 43% for United States adults aged 20 years or older). However, in adults aged 65 years or older, the prevalence is higher in women.[13] Women are more likely to be aware of their condition, under treatment, or in control of their hypertension.[13] The risk of cardiovascular disease was shown to be higher in women for every 10-mm Hg increase in systolic BP.[19] Moreover, life expectancy was found to be shorter by approximately 5 years in hypertensive compared to normotensive women.[20] Hypertension control resulted in a greater reduction in cardiovascular mortality among women compared to men and was found to have the highest impact on reducing cardiovascular mortality compared to all other risk factors.[16]

Sex-specific factors are implicated in the development and pathogenesis of hypertension in women. Estrogen has a protective effect in premenopausal women. It plays an important role in endothelial function and causes vasodilatation as a result of increased synthesis of nitric oxide and inhibition of sympathetic activity and renin-angiotensin-aldosterone system.[21] Therefore, a sharp reduction in estrogen level after menopause results in activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, which in turn increases risk of hypertension in older women.[21] Moreover, an increase in endothelin level in postmenopausal women due to lack of its inhibition by estrogen can further implicate the development of hypertension by increasing renal vasoconstriction and salt reabsorption. Additionally, sex hormones can influence vascular function and are linked to arterial elasticity,[22] the lack of which during menopause leads to an increase in arterial stiffness and decrease in arterial compliance. Whereas hypertensive women have a lower level of central sympathetic activity than men, there is a more dramatic increase in muscle sympathetic nerve activity (marker for central synthetic activity) in women with age that increases their risk of developing hypertension in older age.[23] Hypertension is one of the most common conditions complicating pregnancy. Gestational hypertension affects 6% to 7%, and preeclampsia affects 10% of pregnancies.[24] Both are associated with an increased risk of developing chronic hypertension.[25] Combined hormonal contraception is associated with a small increase in BP that usually resolves after discontinuation of therapy, the mechanism of which is not fully understood.[26] This risk increases with longer duration of use and in the presence of other cardiovascular risk factors, including smoking and obesity.[27]

Data regarding the effect of hormone replacement therapy on the development of hypertension in postmenopausal women is conflicting and, if present, it only leads to a mild increase in BP.[28-31] Fibromuscular dysplasia as a secondary cause of hypertension is more common in women and should be considered in young hypertensive women.[32]

SEX-RELATED DIFFERENCES IN ANTIHYPERTENSIVES

Sex-related differences in hypertension treatment—including class of medications prescribed, treatment response, side effects, and pharmacokinetics—have been reported across several studies. In a large cross-sectional survey including a hypertensive United States population, women were more likely to be on treatment compared to men (61.4% vs 56.8%, respectively). Furthermore, the use of diuretics and angiotensin receptor blockers (ARBs) was more common in women (31.6% vs 22.3% for diuretic and 11.3% vs 8.7% for ARBs, in women and men, respectively). For those who were receiving antihypertensive medications, men were more likely to use ≥ 3 drugs, especially in the older population (60-69 years, 12.3% vs 19.8%; 70-79 years, 18.6% vs 21.2%; and ≥ 80 years, 18.8% vs 22.8%, in women and men, respectively).[33] In other studies, women were prescribed thiazide more often than men, which could be explained by the added benefit of thiazide on bone density in postmenopausal women as a result of reduced renal calcium excretion and subsequent reduction of fracture risk.[34,35] Furthermore, after adjustment for baseline variables, amlodipine was found to be associated with a better decline in diastolic BP in women with mild to moderate hypertension when compared to men (91.4% vs 83%; $P \leq .001$).[36]

Regarding pharmacokinetics, sex variation in response to β-blockers has been described. It has been shown that men have a quicker absorption rate of metoprolol, whereas women have slower drug clearance and smaller volume of distribution. Thus, a 50% dose reduction of metoprolol was recommended when used in healthy young women compared to men.[37]

Additionally, women were reported to experience more frequent adverse effect to most antihypertensives compared to men, with the exception of mineralocorticoid recepto antagonists.[38,39]

With regard to the BP-lowering effect on clinical outcomes, no significant difference was found between men and women in the occurrence of major adverse cardiovascular events.[40,41]

TABLE 1. SUMMARY OF RDN TRIALS AND REGISTRIES WITH OUTCOMES, INCLUDING SUBGROUP ANALYSIS BY SEX IF AVAILABLE

Study	Year	Population (n)	Intervention and Comparator	Outcomes Assessed	Percentage of Women Enrolled (%), and Subgroup Analysis by Sex (if reported)	Comments
ReSet, Peters et al[49]	2022	Patients with uncontrolled hypertension (RDN = 27, sham = 26)	RF RDN vs sham	Arterial stiffness, central venous pressure, heart rate variability	35% in RDN vs 22% in sham control	No significant effects of RDN on arterial stiffness, central venous pressure or heart rate variability
SYMPLICITY HTN-3 (36-mo follow-up), Bhatt et al[50]	2022	Patients with resistant hypertension (RDN = 364, crossover = 101, noncrossover = 70)	RF RDN vs sham	Difference in BP reduction at 36 mo	41% in RDN, 38% in crossover group, 33% in noncrossover group	At 12 to 36 mo, RDN arm had better decline in BP and better BP control compared to sham
Oslo RDN[51,52]	2014, 2021	Patients with treatment resistant hypertension (RDN group = 9, drug group = 10)	RF RDN vs drug adjustment	Difference in systolic and diastolic BP reduction	22% in RDN vs none in drug group	At 7 y, RDN remains nonsuperior to intensive drug treatment in controlling BP
RADIANCE-HTN TRIO, Azizi et al[44]	2021	Patients with resistant hypertension (RDN = 69, sham = 67)	Ultrasound RDN vs sham	Change in daytime ambulatory systolic BP at 2 mo	19% in RDN vs 21% in sham; subgroup analysis revealed no difference between study groups according to sex	RDN decreased BP at 2 mo when compared to sham
REQUIRE, Kario et al[45]	2021	Patients with resistant hypertension (RDN = 69, sham = 67)	Ultrasound RDN vs sham	Reduction in 24-h ambulatory systolic BP from baseline at 3 mo	30.4% in RDN vs 20.9% in sham; subgroup analysis revealed no difference between sexes 24-h ambulatory systolic BP	Reduction from baseline in 24-h ambulatory systolic BP at 3 mo was not significantly different between two groups
SPYRAL HTN-OFF MED, Böhm et al[8]	2020	Patients with hypertension in the absence of medication (RDN = 166, sham = 165)	RF RDN vs sham	Change in mean 24-h systolic BP from baseline to 3 mo postprocedure (adjusted for baseline 24 hour systolic BP)	36% in RDN vs 32% in sham; subgroup analysis suggested efficacy of RDN regardless sex	The treatment difference between the two groups was −3.9 mm Hg (Bayesian 95% credible interval −6.2 to −1.6) for 24 h systolic BP and −6·5 mm Hg (−9.6 to −3.5) for office systolic BP
RADIANCE-HTN SOLO, Azizi et al[46]	2020	Patients with resistant hypertension (RDN = 65, sham = 67)	RF RDN vs sham	Baseline and covariate-adjusted change in daytime ambulatory systolic BP at 12 mo	33.9% in RDN vs 47.8% in sham; at 12 mo, male sex was a predictor for average real variability in home systolic BP after RDN (P = .0027).	BP control of RDN was maintained at 12 mo with fewer drugs compared with sham

TABLE 1. SUMMARY OF RDN TRIALS AND REGISTRIES WITH OUTCOMES, INCLUDING SUBGROUP ANALYSIS BY SEX IF AVAILABLE (CONT.)

Study	Year	Population (n)	Intervention and Comparator	Outcomes Assessed	Percentage of Women Enrolled (%), and Subgroup Analysis by Sex (if reported)	Comments
ACHIEVE study, Daemen et al[53]	2019	Single arm, nonrandomized cohort, patients with resistant hypertension (n = 96)	Ultrasound RDN	Change in office and 24-h ambulatory BP at 12 mo compared to baseline	41%	RDN resulted in sustained decline in office and 24-h ambulatory BP through 12-mo follow-up
SPYRAL HTN-ON MED[9,10]	2018	Patients with uncontrolled hypertension on medical therapy (RDN = 38, sham = 42)	RF RDN vs sham	BP change from baseline at 6 mo	13% in RDN vs 9% in sham control	Office and 24-h ambulatory BP declined significantly at 6 mo in RDN group
WAVE IV trial, Schmieder et al[54]	2018	Patients with uncontrolled hypertension (RDN = 42, sham = 39)	RF RDN vs sham	BP change from baseline at 6 mo	18.6% in RDN vs 35.9% in sham	No significant differences in changes in office or ambulatory BP at 6 mo
Zeng et al[47]	2017	Prospective, nonrandomized study; Chinese patients with refractory hypertension (RDN = 42, control = 10)	RDN vs control	Mean systolic and diastolic BP at 3 mo	54.76% in RDN vs 70% in control; women had larger systolic BP reduction after RDN (CI, 9.222-3.068; *P* = .005) whereas sex had no impact on diastolic BP response to RDN (CI, −5.197 to 2.566; *P* = .05)	Mean BP significantly declined in RDN group (153.0/99.8 ± 16.8/12.2 vs 166.5/90.5 ± 12.6/11.5 mm Hg; *P* < .001) vs no significant decline in control group
DENERVHTA trial, Oliveras et al[55]	2016	Patients with resistant hypertension (RDN = 13, spironolactone = 11)	RDN vs spironolactone	Mean change in ambulatory 24-h systolic BP from baseline to 6 mo	45% in RDN vs 31% in spironolactone group	Spironolactone was better than RDN to reduce both systolic and diastolic BP
Global SIMPLICITY registry, Böhm et al[56]	2015	Prospective cohort recruited patients with uncontrolled hypertension (n = 998)	RF RDN	Change in ambulatory systolic BP at 6 mo	39.1% subgroup analysis (extended GSR DEFINE registry, 42% women) showed decline in office and 24-h ambulatory systolic BP up to 3 y was similar regardless of sex[48]	At 6 mo, changes in office and 24-h systolic BP were −11.6 ± 25.3 and −6.6 ± 18.0 mm Hg for all patients (*P* < .001)
INSPiRED study, Jacobs et al[57]	2014	Pilot randomized study including patients with resistant hypertension (RDN = 6, control = 9)	RF RDN vs control	Baseline-adjusted differences in 24-h systolic BP	50% in RDN vs 55.6% control	Change in 24-h systolic 22.4/13.1 mm Hg (−21.7/−12.8 in RDN vs +0.7/+0.3 in control; *P* =.049)

TABLE 1. SUMMARY OF RDN TRIALS AND REGISTRIES WITH OUTCOMES, INCLUDING SUBGROUP ANALYSIS BY SEX IF AVAILABLE (CONT.)

Study	Year	Population (n)	Intervention and Comparator	Outcomes Assessed	Percentage of Women Enrolled (%), and Subgroup Analysis by Sex (if reported)	Comments
SYMPLICITY HTN-3 trial, Bhatt D et al[6]	2014	Patients with resistant hypertension (RDN = 364, sham = 171)	RF RDN vs sham	Changes in BP between the two groups at 6 mo	Subgroup analysis revealed no difference between study groups according to sex; women constitute 40.9% of RDN, 35.7% of crossover group	No significant differences between both groups in change in BP
SYMPLICITY HTN-1, Krum et al[3]	2014	Open label study recruited 150 patients with resistant hypertension; 88 completed 36-mo follow-up	RF RDN	Change in office systolic and diastolic BP	38%, 42% completed follow-up	Change in systolic BP (–32 mm Hg; 95% CI, –35.7 to –28.2) and diastolic BP (–14.4 mm Hg; 95% CI, –16.9 to –11.9); a decline of ≥ 10 mm Hg in systolic BP was seen in 93% at 36-mo follow-up
SYMPLICITY HTN-2 trial, Esler et al[5]	2014	Patients with treatment resistance hypertension (n = 52 in RDN, medical therapy alone n = 54)	RF RDN vs medical therapy	Changes in BP at 36 mo	30% in RDN vs 63% in cross over group	Systolic and diastolic BP drop at 36 months for RDN group was 23.3 mm Hg (95% CI, 24.0-22.5; $P < .01$) vs 21.4 mm Hg (95% CI, 21.7-21.0; $P < .01$) in medical treatment group
Ukena et al[58]	2013	Prospective, patients with resistant hypertension (n = 136, 6-mo follow-up, n = 88)	RF RDN	Heart rate and systolic BP at 3 and 6 mo	42%, no impact of sex on degree of heart rate reduction	Decline in systolic BP was 25.5 ± 2.4 mm Hg ($P < .001$) and 28.1 ± 3 mm Hg ($P < .001$); reduction in heart rate was 2.6 ± 0.8 bpm at 3 mo ($P = .001$) and 2.1 ± 1.1 bpm at 6 mo ($P = .046$)
Ott et al[59]	2013	Prospective, patients with moderate treatment-resistant hypertension, n = 54	RF RDN	Change in office systolic and diastolic BP at 6 mo	30%	Office BP and heart rate significantly reduced at 6 mo after RDN

Abbreviations: BP, blood pressure; RF, radiofrequency; RDN, renal denervation.

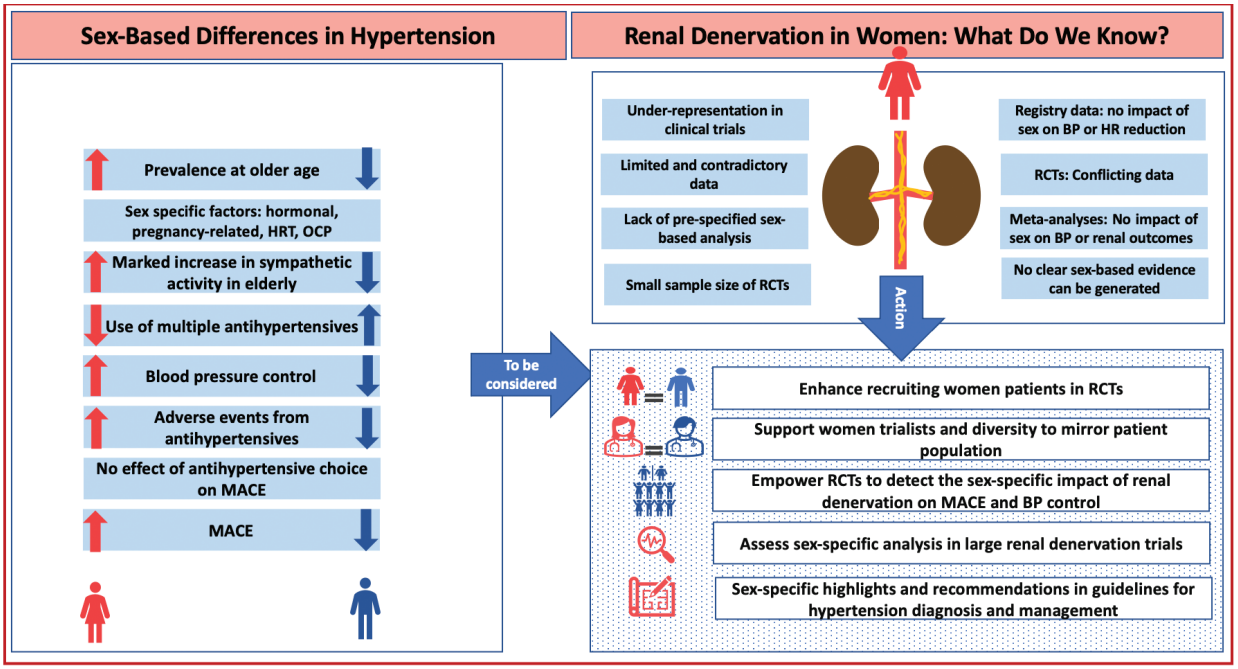

Figure 1. An illustration that summarizes sex-related differences in hypertension and currently available information regarding RDN in women, with suggestions made for future clinical trials. HR, heart rate; HRT, hormone replacement therapy; MACE, major adverse cardiovascular events; OCP, oral contraceptive pills; RCT, randomized controlled trial.

SEX-RELATED DIFFERENCES IN RESPONSE TO RDN

Data regarding sex-related difference in response to RDN are limited. A meta-analysis including 15 studies evaluated the efficacy of RDN in 857 patients with resistant hypertension at 6 months compared to medical therapy and/or sham procedure; it revealed that patient sex does not impact either 24-hour systolic blood pressure (meta-regression coefficient, −0.0119; 95% CI, −0.0481 to 0.0242; *P* = .5174) or 24-hour diastolic blood pressure (meta-regression coefficient, −0.0061; 95% CI, −0.0421 to 0.0299; *P* = .7407) after RDN.[42]

In another meta-analysis assessing the impact of RDN on renal outcomes, a univariable mixed effects meta-regression analysis performed on 48 cohorts showed that female sex was not a predictor for change in estimated glomerular filtration rate (coefficient of 0.57; CI, 0.40-1.54; *P* = .25).[43]

RADIANCE-HTN TRIO, a randomized single-blinded trial that assessed the impact of ultrasound RDN on daytime ambulatory systolic BP at 2 months in patients with resistant hypertension, demonstrated no difference in change in daytime ambulatory systolic BP according to patient sex (*P* = .69).[44] Similar results were found in the REQUIRE and SYMPLICITY HTN-3 trials.[6,45]

SPYRAL-HTN OFF MED, a single-blinded randomized sham-controlled trial, recruited patients with mild to moderate hypertension on no medical therapy to evaluate the impact of RDN on baseline-adjusted difference in 24-hour systolic BP. In the prespecified subgroup analysis, the change in 24-hour systolic BP at 3 months for RDN and the sham group were similar for women and men (−2.5[−6.8 to 1.8] versus −4.8 [−7.4 to −2.2]; *P* = .35, respectively).[8]

RADIANCE-HTN SOLO, another United States RDN study, recruited patients with resistant hypertension and had a primary outcome of change in daytime ambulatory systolic BP at 12 months. A multivariate model analysis showed that male sex was a predictor for average real variability in home systolic BP after RDN (*P* = .003).[46]

In a prospective cohort involving a Chinese population with resistant hypertension and assessing the effect of RDN on mean systolic and diastolic BP reduction at 3 months, women had a better response in systolic BP reduction after RDN (β −0.31; *P* = .005), whereas sex had no impact on diastolic BP response to RDN (β −0.243; *P* = .051).[47]

Analysis from the extended GLOBAL SIMPLICITY DEFINE registry (n = 2,872 patients, 42% women), showed no difference in office systolic or ambulatory 24-hour systolic BP reduction in women versus men (−18.4 vs −15.5, *P* = .13 for systolic BP for women and

men, respectively; and −8.8 vs −9.3, P = .14 for ambulatory 24-hour systolic BP, respectively).[48] Table 1[3,5,6,8-10,44-59] summarizes the outcomes from RDN studies, including subgroup analysis by patient sex when included.

PERSPECTIVE

Hypertension is a major contributor to cardiovascular health in women, especially in the older population. Therefore, using all available resources to adequately control BP in hypertensive women is of paramount importance. RDN is a potential option for hypertension treatment, with new studies showing positive results. Although current guidelines have no sex-specific recommendation for hypertension treatment, awareness and understanding of factors that impact hypertension and its management in women are important to improve outcomes. The currently available data on sex-related differences in response to hypertension treatment (medication or RDN) have limitations, the reasons for which include underrepresentation of women in hypertension trials, small sample size, inclusion of heterogeneous population in meta-analyses, and differences in clinical trials designs and protocols (Figure 1). Therefore, little evidence can be generated from the existent literature, and addressing these limitations in future studies trials will help to derive a patient-centered therapeutic approach (Figure 1). ■

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