Clinical Outcomes of Renal Denervation for Resistant Hypertension: The Tel Aviv Renal Denervation Prospective Registry

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ABSTRACT **Background:** Apparent treatment-resistant hypertension (aTRH) is a high-risk phenotype associated with increased cardiovascular and renal morbidity. Renal denervation (RDN) has emerged as a promising intervention for patients with refractory blood pressure (BP) despite maximal medical therapy.

Objectives: To present the first Israeli prospective cohort evaluating RDN outcomes in aTRH patients.

Methods: The Tel Aviv Renal Denervation registry is a single-center, prospective cohort of 19 patients with aTRH who underwent RDN between 2021 and 2024. Baseline data included demographics, co-morbidities, medication burden, ambulatory BP monitoring (ABPM), and renal function. Outcomes were assessed at 3 and 12 months post-procedure, with repeated measures analyses used to evaluate longitudinal trends.

Results: The cohort (median age 62 years, 42% female) exhibited a high burden of co-morbidities including ischemic heart disease (37%), diabetes (26%), and chronic kidney disease (21%). Baseline ABPM showed a median 24-hour systolic BP of 152 mmHg. Following RDN, mean systolic BP decreased to 143 mmHg at 3 months and 138 mmHg at 12 months ($P = 0.097$), with a significant reduction in nighttime systolic BP ($P = 0.033$). Pill burden decreased from a median of 7 to 4 pills daily ($P = 0.037$). The number of antihypertensive drug classes declined from 6 to 4 ($P = 0.052$). Renal function remained stable throughout follow-up.

Conclusions: In this Israeli RDN cohort, patients with aTRH experienced clinically meaningful reductions in BP and medication burden, with preserved renal function and minimal complications. These findings support further expansion of national RDN registries to better guide patient selection and optimize long-term outcomes.

IMAJ 2026; 28: 110–115

KEY WORDS: ambulatory blood pressure monitoring (ABPM), hypertension, preventive medicine, renal denervation, denervation, denervation, resistant hypertension

Arterial hypertension is a main risk factor for cardiovascular morbidity and mortality in adult patients [1]. Since the prevalence of hypertension is on the rise, the search for specific patient characteristics is growing [2]. Of these characteristics, patients with clinically defined apparent treatment-resistant hypertension (aTRH) are considered both highly challenging to manage and at a high risk for future related complications. aTRH is defined as uncontrolled blood pressure despite adherence to at least three antihypertensive agents, including a diuretic if tolerated, or requiring four or more medications to achieve target blood pressure (BP) levels [3]. The prevalence of aTRH is estimated in 10–20% of hypertension patients according to recent surveys [3].

When compared to patients with well controlled hypertension, patients with aTRH are at greater risk for numerous adverse outcomes. Patients with aTRH exhibit a 47% higher risk of cardiovascular disease (CVD) mortality [4]. Rates of composite major adverse cardiovascular events and end-stage renal disease (ESRD) are also significantly elevated in this population [5]. In addition, patients with aTRH face a greater incidence of cognitive decline and dementia [6].

Over the past decade, studies have proven the efficacy of renal denervation (RDN) in improving blood pressure control, likely due to the lowering of sympathetic nervous stimulants. High-risk patient populations, including those with elevated CVD risk, ESRD, and type 2 diabetes mellitus with refractory hypertension, have shown significant reductions in systolic blood pressure (ranging from 8.9 to 20 mmHg) following RDN, alongside evidence suggesting a protective effect on renal vascular health [6-9]. A systematic review by Salehin et al. [10], which analyzed seven randomized sham-controlled clinical trials, concluded that RDN is a reasonable treatment option for resistant hypertension. This conclusion was

validated by the 2024 ESH guidelines, following FDA approval of two RDN devices [3,11,12]. Patient registries have played an important role in advancing the field. The global SYMPLICITY registry [13] has provided critical insights into the long-term efficacy and safety of RDN in high-risk hypertensive patients, demonstrating long-term, stable, blood pressure reductions.

As with all interventional medical procedures, renal denervation (RDN) has been closely scrutinized for potential adverse events such as access-site complications, renal artery injury, and contrast-induced nephropathy. Contemporary randomized trials and registries have demonstrated a low incidence of these complications, with long-term data confirming stable renal function and minimal late vascular sequelae [9,13,14]. These reassuring findings, supported by recent regulatory approvals and international guideline endorsements [2,3,11,12], underscore the procedural and long-term safety of RDN when performed in experienced centers.

As RDN procedures rise in popularity, Israeli patients have yet to be thoroughly studied or included in robust prospective trials. We believe that due to Israel diverse ethnic and socioeconomic demographics, a similar registry would help shed more in light into the specific patient characteristics that will benefit from the procedure. In this article we provide the first prospective cohort of patients with severely unresponsive hypertension and co-morbidities who underwent RDN at our center.

PATIENTS AND METHODS

STUDY POPULATION AND DESIGN

This prospective, single-center registry study was conducted at Tel Aviv Sourasky Medical Center. We evaluated patients referred for RDN due to drug-resistant hypertension. Secondary causes of hypertension were ruled out prior to inclusion. All patients were referred by a hypertension specialist after exhausting multitude treatment regimens. The study protocol was approved by the institutional review board at the Tel Aviv Medical Center, and all participants provided informed consent prior to enrollment. Inclusion criteria were patients that were defined as aTRH (BP > 140/90 under at least 3 types of hypertension medications), a computed tomography angiography or magnetic resonance angiography examinations of the renal arterial anatomy demonstrating anatomy suitability and no evidence of renal artery stenosis was completed in all patients. Patients with chronic kidney disease (CKD) were eligible for enrollment provided that renal function was preserved, defined as an estimated glomerular filtration rate (eGFR) greater than 30 ml/min/1.73 m^2. All patients included in the study underwent the same RDN procedure. Some degree of variability during the procedure was accepted due to distinctive anatomy of renal vasculature.

Arterial access was obtained under ultrasound and landmark guidance according to standard protocols. Renal denervation was performed using the Symplicity Spyral multielectrode catheter and Symplicity G3 RF generator (Medtronic, Minneapolis, MN, USA) to deliver circumferential radiofrequency ablations to the main renal arteries and all accessible branch vessels measuring 3–8 mm in diameter. Any accessory renal artery ≥ 3 mm was also ablated. All procedures were performed by the same experienced interventionalist.

STUDY MEASUREMENTS AND OUTCOMES

Baseline assessments included detailed medical history, current medications, 24-hour ambulatory ABPM, office blood pressure, number of antihypertensive drugs, and daily medications taken. Laboratory evaluations comprised complete blood count and comprehensive chemistry panels. Procedural data, including procedure duration, renal angiography findings, and the number and location of ablations, were recorded. Prior co-morbidities, including ischemic heart disease, congestive heart failure, type 2 diabetes mellitus, chronic renal failure, coronary artery bypass grafting, hypertension, hyperlipidemia, smoking, chronic obstructive pulmonary disease, obstructive sleep apnea, atrial fibrillation or flutter, peripheral vascular disease, cerebrovascular accident, and anxiety or depression, were documented using ICD-10 codes.

Follow-up assessments were conducted at predefined intervals: one month before RDN, at 3 months and 12 months post-procedure. The primary study endpoints included changes in 24-hour ABPM at 3 months and 12 months. Secondary outcomes included mean office blood pressure, number of antihypertensive medications, daily pills taken, and laboratory findings. Adverse events related to RDN, including acute or chronic renal injury, access site complications, 30-day survival or any readmission or post-procedural adverse event were monitored through routine measurements of serum creatinine, blood urea nitrogen (BUN), and eGFR calculations using CKD-EPI creatinine equation [15] and postoperative follow-up visits. Health-related quality of life and mental well-being were assessed using the EuroQol five-dimension scale (EQ-5D) [16] and the Mental Health Inventory-5 (MHI-5) [17], re-

spectively at baseline and at 12 months follow-up. Other adverse events monitored were major or minor bleeding or re-hospitalization due to hypertensive or hypotensive episodes or bleeding requiring urgent care.

STATISTICAL ANALYSIS

Categorical variables were presented as sum (percentage from total) and continuous variables as median (interquartile range [IQR]). All outcomes were assessed at baseline, 3 months, and 12 months. To account for the three assessment points, we performed repeated measure analyses using linear mixed-effect models, which consider each time point and can accommodate missing data between different patients at each time point. For paired baseline as well as follow-up EQ-5D and MHI-5 scores, comparisons were performed using the Wilcoxon signed-rank test. Results were presented as median (IQR). Incidence of adverse events was reported using descriptive statistics. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 28.0 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 19 patients were enrolled in the Tel Aviv Renal Denervation registry between 2021 and 2024. The median age was 62 years (IQR 55–69), with 42% female representation. Follow-up duration varied due to consecutive enrollment, with 12-month data presented [Table 1].

The cohort exhibited substantial cardiovascular co-morbidities typical of aTRH patients, including hyperlipidemia (68%), diabetes (26%), ischemic heart disease (37%), obstructive sleep apnea (21%), stroke history (26%), chronic renal failure (21%), and anxiety or depression (26%). Baseline antihypertensive therapy included calcium channel blockers (90%), alpha blockers (90%), beta blockers (84%), angiotensin receptor blockers (79%), mineralocorticoid receptor antagonists (79%), and diuretics (63%). Median antihypertensive drug classes were 6 (IQR 4–6), corresponding to 7 daily pills (IQR 5–11). RDN procedures were technically successful in all patients. Median ablations were 19 (IQR 15–22.5) left and 19 (IQR 15.5–22) right renal arteries, totaling 39 per patient (IQR 34–

Table 1. Baseline characteristics: demographic, medical history, drug therapy, baseline ambulatory blood pressure monitoring measurement, baseline laboratory results

Variable	Total (N=19)	Variable	Total (N=19)
Age, years, median (IQR)	62 (55–69)	**Medications**	
Female sex	8 (42%)	ACE inhibitors	4 (21%)
Hyperlipidemia	13 (68%)	Angiotensin receptor blockers	15 (79%)
Hypertension	19 (100%)	Beta blockers	16 (84%)
Diabetes	5 (26%)	Alpha blockers	17 (90%)
Ever smoker	5 (26%)	Calcium channel blockers	17 (90%)
Obstructive sleep apnea	4 (21%)	Hydralazine	2 (11%)
Stroke	5 (26%)	Vasodilators	4 (21%)
Ischemic heart disease	7 (37%)	Mineralocorticoid receptor antagonists	15 (79%)
Prior CABG	1 (5%)	Diuretics	12 (63%)
Heart failure	0 (0%)	**Baseline laboratory, median (IQR)**	
Chronic renal failure	4 (21%)	Creatinine, mg/dl	1.01 (0.9–1.17)
Psychiatric co-morbidity	5 (26%)	Estimated eGFR	79 (60-86)
Baseline 24-holter blood pressure		BUN, mg/dl	21 (13–28)
Systolic BP, IQR	152 (147–163)	Hemoglobin, g/dl	14.1 (13–15)
Diastolic BP, IQR	86 (77–94)	WBC, g/dl	8.5 (7.1–9.3)
Baseline mental health questionnaires, median (IQR)		Platelets, 10^3/μL	222 (187–291)
EQ5D	52 (50–71)		
MHI5	60 (48–72)		

ABPM = ambulatory blood pressure monitoring, ACE = angiotensin-converting enzyme, BP = blood pressure, BUN = blood urea nitrogen, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, IQR = interquartile range, WBC = white blood cell count

Figure 1. 24-hour mean systolic ambulatory blood pressure monitoring measurements at baseline, 3 months and 12 months

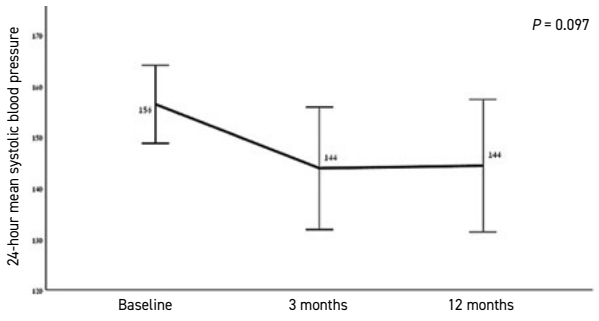

Figure 2. Mean daily drug groups and mean daily pills taken

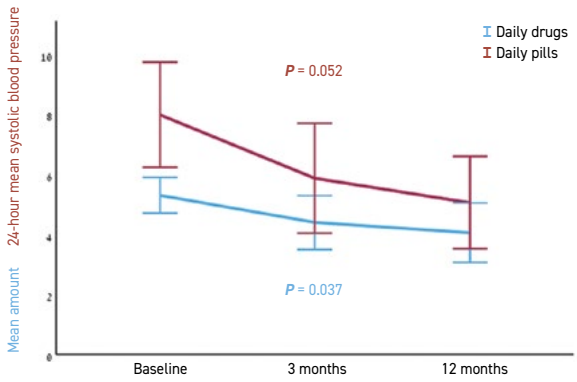

Table 2. Comparison of ambulatory blood pressure monitoring, creatinine, blood pressure medications and pills daily at baseline, 3 months, 12 months

Variable	Baseline	3 months	12 months	*P*-value
24h mean systolic BP, mmHg	152 (147–163)	143 (127–153)	138 (129–161)	0.097
24h mean diastolic BP, mmHg	86 (77–94)	80 (67–89)	76 (69–88)	0.634
ABPM systolic day, mmHg	159 (151–169)	148 (133–159)	140 (132–165)	0.106
ABPM diastolic day, mmHg	87 (81–97)	83 (76–91)	79 (74–90)	0.356
ABPM systolic night, mmHg	149 (131–154)	137 (116–150)	126 (121–139)	0.033
ABPM diastolic night, mmHg	79 (70–90)	76 (58–86)	67 (61–81)	0.212
Creatinine, (mg/dl)	1.01 (0.90–1.17)	1.00 (0.91–1.1)	1.02 (0.94–1.2)	0.842
eGFR (ml/min/1.73 m²)	79 (60–86)	82 (65–89)	74 (62–85)	0.698
Blood pressure meds, number	6 (4–6)	5 (4–6)	4 (4–5)	0.052
Blood pressure pills, number	7 (5–11)	5 (4–8)	4 (3–7)	0.037
24h mean pulse	72 (64–83)	70 (64–83)	65 (60–77)	0.394
ABPM heart rate day	74 (62–83)	69 (61–84)	68 (63–78)	0.570
ABPM heart rate night	66 (56–79)	62 (53–74)	60 (54–69)	0.313
EQ5D	52 (50–71)	–	72 (49–86)	0.098
MHI5	60 (48–72)	–	72 (48–76)	0.371
Subgroup analysis: CKD patients, n=4				
Creatinine, (mg/dl)	1.95 ± 0.56	1.82 ± 0.36	1.91 ± 0.09	0.78
eGFR, (ml/min/1.73 m²)	40.8 ± 8.3	42.5 ± 14.1	40.5 ± 4.5	0.82
24h mean systolic BP, mmHg	139.8 ± 22.7	150.7 ± 17.6	143.7 ± 14.8	0.22
24h mean diastolic BP, mmHg	73.0 ± 16.9	87.3 ± 12.0	76.3 ± 6.4	0.61

Data are presented as median (interquartile range). Overall change across time points was assessed using the Friedman test for repeated measures, with $P < 0.05$ considered statistically significant

ABPM = ambulatory blood pressure monitoring, BP = blood pressure, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate

43.5). Accessory renal arteries were present in 26.3% (left) and 21.1% (right), with bilateral in 10.5%.

Laboratory evaluation revealed median serum creatinine 1.01 mg/dl (IQR 0.90–1.17), eGFR 79 ml/min/1.73m² (IQR 60–86), and BUN 21 mg/dl (IQR 13–28). Baseline ABPM showed 24-hour systolic/diastolic BP of 152/86 mmHg (IQR 147–163/77–94), daytime pressures 159/87 mmHg (IQR 151–169/81–97), and nighttime values 149/79 mmHg (IQR 131–154/70–90) [Table 2].

Following RDN, 24-hour systolic BP decreased from 152 mmHg to 143 mmHg at 3 months and 138 mmHg at 12 months (14 mmHg reduction; $P = 0.097$). Nighttime

systolic BP significantly reduced from 149 mmHg to 126 mmHg (IQR 121–139) at 12 months ($P = 0.033$). Diastolic pressures showed favorable trends, declining from 86 mmHg to 76 mmHg (IQR 69–88) at one year [Figure 1].

Medication burden improved meaningfully: antihypertensive drug classes decreased from 6 to 4 (IQR 4–5; $P = 0.052$), while daily pills dropped significantly from 7 to 4 (IQR 3–7; $P = 0.037$). Renal function remained stable with unchanged creatinine (1.02 mg/dl; $P = 0.842$) and eGFR (74 ml/min/1.73m²; $P = 0.698$) at 12 months [Figure 2].

Quality of life showed modest improvements: EQ-5D scores increased from 52 (IQR 50–71) to 72 (IQR 49–86), median change +2 (IQR 0–16; $P = 0.099$). MHI-5 scores rose from 60 (IQR 48–72) to 72 (IQR 48–76), median change 0 (IQR 0–8; $P = 0.371$).

Safety outcomes were favorable, with only one conservatively managed access-site bleed and one stroke 35 days post-procedure without a confirmed temporal association. No acute or chronic renal injury occurred. In the four patients with CKD (21%), renal function remained stable across follow-up, with creatinine of 1.95, 1.82, and 1.91 mg/dl and eGFR of 40.8, 42.5, and 40.5 ml/min/1.73 m² at baseline, 3 months, and 12 months, respectively ($P = 0.78$ and 0.82).

DISCUSSION

To the best of our knowledge, this study represents the first prospective Israeli registry evaluating renal denervation outcomes in patients with apparent treatment-resistant hypertension. Our findings demonstrate clinically meaningful blood pressure reductions and decreased medication burden following RDN, with preserved renal function and excellent safety profile over 12 months.

While the primary endpoint of 24-hour systolic BP reduction did not reach statistical significance ($P = 0.097$), the 14-mmHg absolute decline represents clinically meaningful improvement in this refractory population. This magnitude aligns with established cardiovascular benefit thresholds, particularly given limited therapeutic options for aTRH patients. Importantly, we observed a statistically significant nighttime systolic BP reduction ($P = 0.033$), which deserves particular attention as nocturnal hypertension is a stronger predictor of cardiovascular outcomes than daytime pressures [18].

We demonstrated a statistically significant reduction in daily pill burden from 7 to 4 pills ($P = 0.037$), representing important clinical benefit beyond blood pressure control. Medication complexity correlates with non-adherence, particularly in elderly patients with multiple co-morbidities. This polypharmacy reduction may create positive feedback, where improved adherence contributes to sustained blood pressure control. Concurrent medication reduction during follow-up may have attenuated observable RDN blood pressure effects.

Both EQ-5D and MHI-5 scores showed modest improvements following RDN, with EQ-5D suggesting improved self-perceived health status and MHI-5 indicating stable mental health. These findings underscore the importance of tracking patient-reported outcomes, as modest quality-of-life shifts may be clinically meaningful in select individuals.

Renal denervation has demonstrated a consistent and favorable safety profile across randomized trials and large registries, with a very low incidence of vascular or renal complications [9,13,14]. Corresponding with these reports, a single case of access-site bleeding was observed during our follow-up period. Renal function remained stable (creatinine $P = 0.842$; eGFR $P = 0.698$), further supporting the renal safety of contemporary RDN techniques, even among patients with pre-existing chronic kidney disease (21% of the cohort). The overall complication rate compares favorably with previously published registry data [13,14].

Study limitations include the modest sample size, which may limit statistical power, and the single-center design, which could restrict the generalizability of our findings. The absence of a control group also precludes definitive causal inference. In addition, potential confounding effects related to post-procedural medication adjustments and intensified follow-up cannot be excluded. Nevertheless, our results are consistent with international registry data from SYMPLICITY and SPYRAL HTN-ON MED [13,14], suggesting that Israeli patients demonstrate comparable responses to those observed in global populations.

These findings support integrating RDN into clinical management for aTRH patients in Israel, given favorable safety profile and medication complexity reduction potential. Registry expansion to multiple centers would enhance statistical power and enable identification of patient subgroups most likely to benefit from the procedure.

In this first Israeli aTRH cohort undergoing RDN, we observed clinically meaningful reductions in blood pressure and medication burden with preserved renal function. While the primary endpoint did not achieve statistical significance, our statistically significant findings in nighttime blood pressure reduction and medication burden decrease support RDN's therapeutic potential in carefully selected patients.

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Capsule

Oral Transmission of Classical Bovine Spongiform Encephalopathy in ARR/ARR Sheep

Selection for the $A_{136}R_{154}R_{171}$ *PRNP* allele is known to curb classical scrapie in sheep, and **Huor** et al. expected it to minimize the risk for classical bovine spongiform encephalopathy (c-BSE) propagation. The authors challenged newborn ARR/ARR and ARQ/ARQ lambs with ovine-passaged c-BSE. Contrary to their expectations, prion disease developed in all ARR/ARR lambs after markedly longer incubation times (approximately 50 months) than ARQ/ARQ controls (approximately 20 months). Tissue distribution of the abnormal isoform of prion protein (PrP) in clinically affected ARR/ARR sheep largely mirrored tissue distribution seen in ARQ/ARQ animals. Bioassays in bovine- and human-PrP transgenic mice showed that passage through ARR/ARR sheep did not increase the agent's zoonotic potential. Transmission efficiency in human normal cellular isoform PrP-expressing mice remained similar to cattle c-BSE and lower than ARQ-passaged c-BSE. The data revealed the limitations of breeding exclusively for ARR when the objective is to mitigate c-BSE risk, and underscored the need to maintain specific-risk-material removal and surveillance programs.

Emerg Infect Dis 2025; 31: 2243
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