Original Paper

Evaluation and Treatment of Resistant or Difficult-to-Control Hypertension

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An observational study was conducted in 164 patients with resistant or difficult-to-control hypertension. Treatment was adjusted to achieve blood pressure recommendations from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Patients were mostly male (95.73%) and African American (86.59%) and had an average age of 63.68 years. Comorbidities included diabetes (42.07%) and chronic kidney disease, with an average estimated glomerular filtration rate of 83.55 mL/min/1.73 m^2. At the time of referral, average blood pressure was 160/87 mm Hg. The average number of antihypertensive medications per patient at baseline was 3.43, which increased to 4.06 and 4.18 at 3 and 6 months, respectively (P≤.0008), with about 80% of patients receiving a diuretic prior to intervention. Blood pressure decreased to 135.55/74.55 and 137.62/74.03 mm Hg at 3 and 6 months, respectively (P<.0001). By month 6, the blood pressure goal was reached in 45.10% of patients. At months 3 and 6, 100% of patients were now receiving a diuretic. The average estimated glomerular filtration rate at month 6 was 79.36 mL/min/1.73 m^2 (P=NS). Patients referred for resistant or difficult-to-control hypertension may be controlled by making targeted adjustments to their medical regimen.

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Resistant hypertension (HTN) is defined as a blood pressure (BP) value >140/90 mm Hg or >130/80 mm Hg in patients with diabetes or renal disease despite adherence to a medical regimen that includes at least 3 antihypertensive medications, one of which is a diuretic.[1] Difficult-to-control HTN is somewhat less well defined. It includes patients who do not meet the strict criteria of resistant HTN, but nonetheless their BP is not controlled despite aggressive intervention that may not necessarily include diuretic therapy. The presence of resistant or difficult-to-control HTN imparts significant target end organ damage as well as higher long-term cardiovascular risk compared to patients whose BP is controlled.[2] Added comorbidities such as diabetes, dyslipidemia, and chronic kidney disease contribute to the burden of cardiovascular disease in this patient population.

BP becomes more difficult to control with advancing age; this accounts for the common finding of resistant or difficult-to-control HTN in patients older than 60 years compared with younger patients.[3] In general patient population surveys in 2002 to 2004, results indicated that although awareness of HTN was >70% and >59% of patients were treated, only 34% to 53% of patients had their BP controlled to a target level of <140/90 mm Hg.[4–6] In a recent (2007) national

survey, however, >50% were reported to have controlled BP, and 90% of hypertensive persons were being treated.[7] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), after approximately 5 years of follow-up, 34% of patients' HTN remained uncontrolled on an average of 2 medications,[8] but overall >60% had controlled BP. A specialty HTN clinic reported that only 59% of patients with well-defined resistant HTN had a BP of ≤140/90 mm Hg achieved despite aggressive medication titration.[9] It is important to note that several studies have indicated that BP in about 60% of patients with resistant or difficult-to-control HTN will respond to goal levels with the addition of a diuretic.[10,11]

In this observational study, we evaluated the trend in antihypertensive medication use, BP reduction, secondary causes of HTN, and change in renal function in all new patients referred to a specialty HTN clinic for treatment of resistant or difficult-to-control HTN during an 11-month period.

METHODS

An observational study was conducted in all patients referred to a specialty HTN clinic from July 1, 2006, to May 31, 2007, for the treatment of resistant or difficult-to-treat HTN at the Washington, DC, Veterans Affairs Medical Center. All patients were evaluated by a senior attending physician who was a certified specialist in clinical HTN. Patient follow-up was scheduled at 3 and 6 months after the initial baseline visit. Additional visits were scheduled as needed at the attending physician's discretion between the baseline and 3- and 6-month follow-up visits for medication adjustments. Antihypertensive medications were titrated to their maximally recommended and/or tolerated doses. New medications were added only when the current regimen was maximized. The goal was to achieve a target BP of ≤140/90 mm Hg or ≤130/80 mm Hg for patients with diabetes and/or renal disease.[1] Renal disease was defined as stage III or greater chronic kidney disease as expressed by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 using the 5-variable Modification of Diet in Renal Disease (MDRD) equation.

At each visit, patients were counseled on diet and lifestyle modifications. In addition, patients were screened for the presence of any exogenous and interfering substances that may contribute to BP control, such as sympathomimetic drugs, herbal supplements, and nonsteroidal anti-inflammatory drugs.

BP control was analyzed at baseline and 3 and 6 months after the initial visit. Three BP measurements were obtained 2 minutes apart using an appropriately sized cuff with the patient seated in a quiet room, feet flat on the floor after 5 minutes of rest using a Dynamap automated BP machine (Criticon, Inc, Tampa, FL) by a registered nurse. An additional measurement was obtained by the physician after 5 minutes of rest in the examination room using a calibrated manual cuff. The average of the 4 readings was used in the data analysis.

Antihypertensive medication use was recorded and analyzed at baseline and at months 3 and 6. The patients' eGFR as determined by the 5-variable MDRD[12] equation was calculated at baseline and at month 6. All patients underwent testing of serum chemistries and thyroid function studies at baseline. Testing of serum chemistries were repeated at month 6. Patients were also referred for baseline transthoracic echocardiography. Patient baseline demographic information and medical history were obtained via the initial patient interview as well as by examining the electronic medical records.

Work-up for secondary causes of HTN was carried out following clinical guidelines and as clinically warranted.[13] Screening tests included serum aldosterone levels, plasma renin activity, Doppler ultrasonography or magnetic resonance angiography for renal artery stenosis, overnight sleep studies for sleep apnea, and plasma free metanephrine assessment to exclude pheochromocytoma. Appropriate interventions were carried out if a secondary cause of HTN was discovered.

BP data are presented as a mean ± SD. A paired *t*-test was performed to compare the 3- and 6-month systolic and diastolic BP values with baseline values; eGFR data are also presented as a mean ± SD. A paired *t*-test was performed to compare the baseline eGFR to the eGFR at month 6. The total number of antihypertensive medications used is presented as the average number of medications used per patient. A paired *t*-test was performed to compare the average number of medications used per patient at months 3 and 6 compared with baseline. Antihypertensive medication use is presented as the percentage of patients receiving each class of medication. An unpaired *t*-test was performed to compare specific medication use at baseline to months 3 and 6.

RESULTS

A total of 164 new patients with difficult-to-treat or resistant HTN were seen from July 1, 2006, to May

31, 2007. At 3 and 6 months, 154 and 153 patients had clinic follow-up data available, respectively. No patients were lost due to death. The patients' baseline characteristics and BP values are shown in Table I and Table II. No patients were taking an interfering or exogenous substance that may have contributed to uncontrolled BP, and none were found to have thyroid disease. As expected, the majority of veterans were male (95%), and 86% were black. The patients' average age was 63.68±11.75 years. Average BP was 160.06±15.80/87.45±13.86 mm Hg. None of the patients' BP was at goal at the baseline visit. Slightly more than half (51.83%) had a systolic BP >160 mm Hg at the initial visit. The average duration of HTN was 13.57±11.46 years. The patients had a significant burden of comorbidities, with diabetes (42.07%) and dyslipidemia (65.51%) being the most common. Average eGFR was 83.55±35.30 mL/min/1.73 m^2. Average eGFR in the 43 patients with renal disease was 45.39±12.13 mL/min/1.73 m^2. Baseline transthoracic echocardiography was performed in 90 patients; 65.55% had left ventricular hypertrophy, with an average left ventricular mass index of 199±73.5 g/m^2 and an average ejection fraction of 55.5%±8.07%.

Changes in BP and antihypertensive medication use are shown in Table III and Table IV. Average BP at 3- and 6-month follow-up decreased to 135.60±17.79/74.85±13.14 mm Hg ($P<.0001$ for both) and 137.74±16.05/74.24±11.83 mm Hg ($P<.0001$ for both), respectively (Figure 1). At 6 months, the BP treatment goal had been reached in 45.10% of patients. The treatment goal was achieved in 64.62% of patients without diabetes mellitus and/or renal disease at 6 months. Patients with diabetes mellitus and/or renal disease reached a control rate at 6 months of 30.68%.

At presentation, the average number of antihypertensive medications per patient was 3.43. At 3 and 6 months, the average number of medications per patient increased to 4.06 ($P=.0008$) and 4.18 ($P<.0001$), respectively. However, patients with diabetes mellitus and/or renal disease required significantly more medications at 3 and 6 months compared with the patients without diabetes mellitus or renal disease. Diabetic patients required an average of 4.46 and 4.54 medications per patient at months 3 and 6, respectively. Patients with renal disease required an average of 4.20 and 4.34 medications per patient at months 3 and 6, respectively. The most common medications used at initial presentation (baseline) were the diuretics hydrochlorothiazide or furosemide (79.4%), calcium channel blockers (68.6%), and β-blockers (62.9%). However, when use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers was combined, the combination became the most

Table I. Patient Baseline Characteristics

Characteristic	No. (%) or Mean ± SD
Total patients	164
Male	157 (95.73)
Female	7 (4.27)
Average age, y	63.68±11.75
Ethnicity	
White	20 (12.20)
Black	142 (86.59)
Asian	0 (0)
Pacific Islander	1 (0.57)
Hispanic	1 (0.57)
Average duration of hypertension, y	13.57±11.46
Diabetes	69 (42.07)
Renal disease	43 (26.22)
Diabetes and/or renal disease	87 (53.05)
Average eGFR in total patient population, mL/min/1.73 m^2	83.55±35.30
Average eGFR in patients with DM, mL/min/1.73 m^2	81.24±30.09
Average eGFR in patients with renal disease, mL/min/1.73 m^2	45.39±12.13
Dyslipidemia	114 (65.51)
Coronary artery disease	27 (16.46)
Cerebrovascular disease	20 (12.20)
Peripheral vascular disease	20 (12.20)
Baseline cardiac echo	90 (51.43)
Left ventricular hypertrophy	59 (65.55)
Average left ventricular mass index, g/m^2	199±73.5
Average ejection fraction, %	55.5±8.07

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

Table II. BP at Baseline in Total Patient Population and by Diabetic and Renal Disease Subgroup

BP at Baseline	
Average systolic BP, mm Hg	160.06±15.80
Average diastolic BP, mm Hg	87.45±13.86
Patients without DM and/or renal disease and BP ≤140/90 mm Hg	0
Patients with DM and/or renal disease and BP ≤130/80 mm Hg	0
Patients with systolic BP ≥160 mm Hg	85 (51.83%)

Abbreviations: BP, blood pressure; DM, diabetes mellitus.

Table III. Change in BP at 3 and 6 Months Compared With Baseline

	Baseline	3 Months[a]	6 Months[a]
Average systolic BP, mm Hg	160.06±15.80	135.60±17.79 ($P<.0001$)	137.74±16.05 ($P<.0001$)
Average diastolic BP, mm Hg	87.45±13.86	74.85±13.14 ($P<.0001$)	74.24±11.83 ($P<.0001$)
Total patients with BP at treatment goal	0%	52.60%	45.10%
Total patients with BP ≤140/90 mm Hg	0%	68.18%	63.4%
Patients without DM and/or renal disease and BP ≤140/90 mm Hg	0%	70.15%	64.62%
Patients with DM and/or renal disease and BP ≤130/80 mm Hg	0%	39.08%	30.68%
Patients with renal disease and BP ≤130/80 mm Hg	0%	60%	25%
Patients with DM and BP ≤130/80 mm Hg	0%	22.58%	34.04%
Total patients with systolic BP ≥160 mm Hg	48.57%	6.49%	7.19%

Abbreviations: BP, blood pressure; DM, diabetes mellitus. [a]All *P* values are compared to baseline.

Table IV. Change in Antihypertensive Medication Use at 3 and 6 Months Compared With Baseline

	Baseline	3 Months	6 Months
Average No. of medications/patient	3.43	4.06 ($P=.0008$)[a]	4.18 ($P<.0001$)[a]
Average No. of medications/patient without DM and/or renal disease	3.10	3.67 ($P=.0166$)[a]	3.74 ($P=.0105$)[a]
Average No. of medications/patient with DM	3.85	4.46 ($P=.0689$)[b] ($P=.0018$)[d]	4.54 ($P=.0945$)[c] ($P=.0020$)[e]
Average No. of medications/patient with renal disease	3.61	4.20 ($P=.576$)[b] ($P=.0503$)[d]	4.34 ($P=.5356$)[c] ($P=.0362$)[e]
Patients receiving diuretics	79.4%	108.4% ($P<.0001$)[a,f]	108.5% ($P<.0001$)[a,g]
Patients receiving CCBs	68.6%	76.6% ($P=.1117$)[a]	82.4% ($P=.0045$)[a]
Patients receiving BBs	62.9%	67.5% ($P=.3844$)[a]	66.7% ($P=.4744$)[a]
Patients receiving ACEIs	56.5%	57.8% ($P=.8270$)[a]	60.1% ($P=.5227$)[a]
Patients receiving ARBs	27.4%	32.5% ($P=.3142$)[a]	32.0% ($P=.3637$)[a]
Patients receiving ACEIs and/or ARBs	83.4%	90.2% ($P=.1646$)[a]	91.5% ($P=.1099$)[a]
Patients receiving spironolactone	0.6%	3.2% ($P=.0758$)[a]	4.6% ($P=.0184$)[a]
Patients receiving hydralazine	6.8%	9.2% ($P=.4224$)[a]	11.8% ($P=.1174$)[a]
Patients receiving minoxidil	8.6%	15.6% ($P=.0493$)[a]	16.3% ($P=.0329$)[a]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DM, diabetes mellitus. [a]*P* value compared to baseline; [b]*P* value compared to average number of medications/patient at 3 months; [c]*P* value compared to average number of medications/patient at 6 months; [d]*P* value compared to average number of medications/patient without DM and/or renal disease at 3 months; [e]*P* value compared to average number of medications/patient without DM and/or renal disease at 6 months; [f]8.4% of patients were on 2 diuretics; [g]8.5% of patients were on 2 diuretics.

commonly used medication at the initial visit (83.4%). At 3 and 6 months, the use of diuretics significantly increased to 100%; 8.4% ($P<.0001$) and 8.5% ($P<.0001$) of patients, respectively, were receiving furosemide and hydrochlorothiazide. The use of calcium channel blockers also significantly increased at 6 months to 82.4% ($P=.0045$). The use of minoxidil significantly increased at 3 and 6 months to 15.6% ($P=.0493$) and 16.3% ($P=.0329$), respectively. Spironolactone use also increased significantly by month 6 to 4.6% ($P=.0184$).

Patients suspected of having secondary causes of HTN underwent an appropriate work-up. A total of 23 patients who underwent screening for secondary HTN were found to have a secondary cause (Table V). The most common secondary cause of HTN was obstructive sleep apnea, which occurred in 19 of the screened patients. Hyperaldosteronism was diagnosed in 5 of the screened patients.

As seen in Figure 2, the 6-month eGFRs for the total patient population, diabetes mellitus patients, and patients with renal disease were 79.36±33.95, 77.16±37.71, and 43.55±14.95 mL/min/m^2, respectively. These values were not significantly decreased from baseline ($P>.30$ for the 3 groups). Only 4 of the 43 patients with renal disease demonstrated a decrease in eGFR >5 mL/min/m^2, while the remainder of the renal disease patients' eGFRs remained stable or increased from baseline.

DISCUSSION

The prevalence of true resistant HTN is unknown, but it has been suggested to account for about 2% to 5% of all hypertensive patients.[13] Many of these are older than 60 years and have isolated systolic HTN. In these patients, a BP goal is often difficult to achieve, even under expert guidance.[13,14] Our results, therefore, are encouraging, as we were able to demonstrate that adequate BP control can be achieved in many patients with resistant or difficult-to-treat HTN with close follow-up and careful titration of antihypertensive medications. The average BP in the total patient population decreased from 160.06/87.45 mm Hg at baseline to 135.60/74.85 and 137.74/74.24 mm Hg at 3 and 6 months, respectively. The percentage of patients with BP at treatment goal increased to 52.60% and 45.10% at 3 and 6 months, respectively. It was more difficult to get BP to goal in patients with diabetes mellitus and renal disease. At the 6-month visit, 30.68% of patients with DM and/or renal disease had BP at treatment goal.

Our results are slightly better than those previously reported in the literature. In a general HTN patient population, a systolic BP <140 mm Hg was reported to have been achieved in only 34% to 60% of patients.[4–7,15] In a patient population with resistant HTN referred to a specialty clinic that utilized a "goal-oriented management" strategy adhering to Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) treatment guidelines, BP values ≤140/90 mm Hg were achieved in 59% of the total patient population.[9] We were able to achieve this same BP goal in 63.4% of our total patient population at 6 months. However, when diabetic patients (20% of the study group) were reviewed in this specialty clinic review, the treatment goal of ≤130/80 mm Hg was achieved in only 15% of patients.[9] Our results are slightly better, as the treatment goal was reached in one-third of diabetic patients in our study (42.07% of the study group). This is important to note, as diabetes has been shown to be independently linked to treatment resistance.[16]

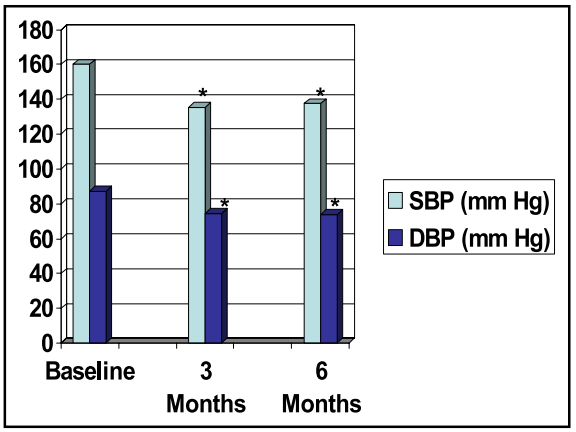

*Figure 1. Change in systolic (SBP) and diastolic blood pressure (DBP) from baseline to 3 and 6 months. *P value compared to baseline <.0001.*

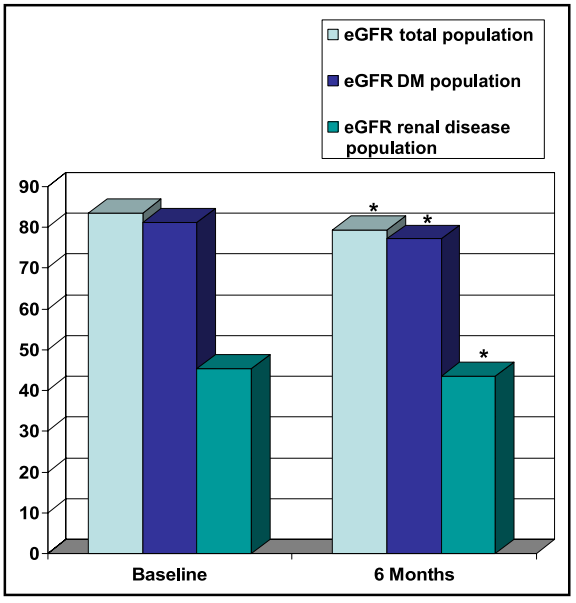

*Figure 2. Change in estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2) from baseline to 6 months in total patient population, diabetic patients (DM), and patients with renal disease using the Modification of Diet in Renal Disease equation. *P value compared to baseline = NS.*

It is clear that the addition of a diuretic has proved to be beneficial in achieving BP control in studies of difficult-to-treat or resistant HTN. About 80% of patients in our study were receiving hydrochlorothiazide or furosemide at the baseline visit. This increased to 100% at the 3- and 6-month follow-up visits, with several patients on 2 different diuretics at follow-up. The importance of utilizing

Table V. Evaluation of Secondary Causes of Hypertension	
Total patients with a secondary cause	23
Single cause	
Obstructive sleep apnea (OSA)	16
Hyperaldosteronism	3
Renal artery stenosis (RAS)	1
Mixed cause	
Hyperaldosteronism and OSA	2
RAS and OSA	1

diuretics has been emphasized repeatedly.[8,17] Volume overload is common among patients with resistant or difficult-to-control HTN, and it is logical to add or increase diuretic therapy in this patient population.[18,19] In ALLHAT, black patients especially assigned to treatment with chlorthalidone-based therapy had significantly lower systolic BP levels over the 5-year study period compared with patients receiving lisinopril-based therapy. A diuretic is generally more effective than an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in black patients who represented a large percentage of our population.[7] Our results reinforce the notion that in order to achieve adequate BP control in a patient population with resistant or difficult-to-treat HTN, a diuretic should be part of the medical regimen. The use of calcium channel blockers also increased significantly from baseline to 6 months. It is likely that the addition of a calcium channel blocker in a predominantly black population provided additional BP-lowering effects in combination with the increased diuretic use. It is well documented that a calcium channel blocker is also more effective in this group of patients than an agent that blocks the renin-angiotensin system.

In general, the patients in this study were receiving a significant number of medications. In another study, the percentages of patients with difficult-to-control HTN requiring 2 and 3 medications reported at a university HTN clinic were 34% and 37%, respectively.[9] The average number of medications per patient in our study at baseline was 3.43. This increased to 4.06 and 4.18 at the 3- and 6-month follow-up visits, respectively. Many studies have confirmed the notion that compliance decreases as the number of medications increases.[20] However, a BP level $\leq$140/90 mm Hg was reached in 63.4% of our patients at month 6. This is an improvement from previously reported data.[4–7,9,10] Compliance can be improved if frequent follow-up can be established and maintained.

It has traditionally been thought that it is more difficult to get BP to goal in black patients, as a group, than in white patients[21]; 86% of our study patients were black. Our results suggest that even in this population of patients with resistant or difficult-to-control HTN, adequate BP control can still be achieved in a fairly high percentage of persons.

Secondary causes are responsible for up to 10% of cases of resistant HTN.[13,22,23] However, it is difficult to make assessments about our actual secondary HTN rate, as not all patients were screened. This practice is in keeping with clinical guidelines that suggest undertaking an evaluation for secondary HTN only if clinical signs or symptoms warrant it.[7,13] It is interesting to note the large number of patients with obstructive sleep apnea in our study. This is an area that we plan to investigate further, in particular, how it may relate to obesity.

Several studies have confirmed that maintaining adequate BP control is essential in preventing the progression of chronic kidney disease.[24,25] This can be a challenging task for clinicians, as it is more difficult to reach BP goals in patients with renal disease compared with a general hypertensive patient population.[26] In our study, the average eGFR remained stable in all patient groups regardless of the presence or absence of diabetes mellitus and/or renal disease. Among patients with renal disease, only 4 of 43 patients demonstrated a decline in eGFR >5 mL/min/1.73 m^2. Given the difficulties in achieving the stringent BP goals set by JNC 7[1] for patients with diabetes mellitus and renal disease, it is encouraging to note that any reduction in BP contributes positively to the preservation of renal function.

One factor that limited our study was the dropout rate. At months 3 and 6, there were 154 and 153 patients available for follow-up. There were no deaths in our study; therefore, we must hypothesize as to the cause of the dropout rate. In conducting the patient interviews, at least 14 patients were found to be noncompliant with the medical treatment regimen (defined by us as missing at least one dose of a medication daily). These noncompliant patients account for a large portion of the dropout rate. In all cases, an attempt was made by phone to contact patients to return to the clinic for their follow-up appointments.

CONCLUSIONS

Our data suggest and confirm that patients with resistant or difficult-to-control HTN have a high burden of comorbidities. These findings have been

noted in other studies. However, a BP goal of ≤140/90 mm Hg in patients without diabetes mellitus and/or renal disease can be achieved in many patients with vigilant follow-up and aggressive BP medication titration. Patients with diabetes mellitus and/or renal disease require tighter control that is more difficult to achieve in the majority of patients. On average, these patients will require at least 3 or 4 antihypertensive medications. In addition, in order to reach goal BP, a diuretic must be part of the treatment program. Thus, these data also confirm findings of other studies. Renal function remained stable over the 6-month follow-up period with the BP reduction achieved.

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