An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial

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Background: **A large number of patients have hypertension that is resistant to currently available pharmacologic therapy. Electrical stimulation of the carotid sinus baroreflex system has been shown to produce significant chronic blood pressure decreases in animals. The phase II Rheos Feasibility Trial was performed to assess the response of patients with multidrug-resistant hypertension to such stimulation.**

Methods: **The system consists of an implantable pulse generator with bilateral perivascular carotid sinus leads. Implantation is performed bilaterally with patients under narcotic anesthesia (to preserve the reflex for assessment of optimal lead placement). Dose-response testing at 0 to 6 V is assessed before discharge and at monthly intervals thereafter; the device is activated after 1 month's recovery time. This was a Food and Drug Administration–monitored phase II trial performed at five centers in the United States.**

Results: **Ten patients with resistant hypertension (taking a median of six antihypertensive medications) underwent implantation. All 10 were successful, with no significant morbidity. The mean procedure time was 198 minutes. There were no adverse events attributable to the device. Predischarge dose-response testing revealed consistent (r = .88) reductions in systolic blood pressure of 41 mm Hg (mean fall is from 180-139 mm Hg), with a peak response at 4.8 V (P < .001) and without significant bradycardia or bothersome symptoms.**

Conclusions: **A surgically implantable device for electrical stimulation of the carotid baroreflex system can be placed safely and produces a significant acute decrease in blood pressure without significant side effects. (J Vasc Surg 2006;44:1213-8.)**

Hypertension, defined as systolic blood pressure (SBP) more than 140 mm Hg and/or diastolic blood pressure (DBP) more than 90 mm Hg, affects 31% of adults in the United States, a number approaching 65 million people.[1,2] Treatment of hypertension is the second most common reason for physician office visits and is the leading indication for prescribing medications to an adult.[3] Effective treatment reduces the incidence of stroke, myocardial infarction, and congestive heart failure by up to 50%.[1,4] Patients with blood pressures less than 130/80 mm Hg experience a risk reduction for cardiac events twice that of those with blood pressures of only 140/90 mm Hg, and the risk of cardiovascular death has been shown to double with each increment of 20/10 mm Hg that blood pressure exceeds 115/75 mm Hg.[5]

Unfortunately, only 25% to 34% of persons with hypertension have their blood pressure controlled at a level of 140/90 mm Hg.[5] It is estimated that failure to control blood pressure is due to noncompliance with prescribed medication in up to 50% of patients.[6-11] In a large number of patients, however, inadequate control may be due to inadequate therapy and/or true resistance to maximal appropriate antihypertensive therapy. It has been estimated that 30% of hypertension cases cannot be controlled with medications and can be considered resistant to treatment.[12] Of these, a subset have truly dangerous hypertension that places them at significant risk of virulent cardiovascular disease.

Electrical stimulation of the carotid body has successfully decreased blood pressure in acute and chronic normotensive and hypertensive[13-18] animal models and acutely during carotid endarterectomy in humans.[19] On the basis of this work, a device has been developed to electrically activate the carotid baroreflex and decrease blood pressure

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Drs Illig, Levy, Sanchez, Trachiotis, and Shanley are investigators in the Rheos feasibility trial and receive clinical trial reimbursement for enrollment to cover trial expenses. Dr Irwin is a paid consultant of CVRx, Inc, and Drs Pertile, Kieval, and Cody are employees of CVRx. CVRx relinquished editorial control over the manuscript and data analysis, although the employee authors read the manuscript and approved their role as coauthors before submission.

Presented at the Sixtieth Annual Meeting of the Society for Vascular Surgery, Philadelphia, Pa, Jun 1-4, 2006.

Additional material for this article may be found online at www.jvascsurg.org.

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0741-5214/$32.00

doi:10.1016/j.jvs.2006.08.024

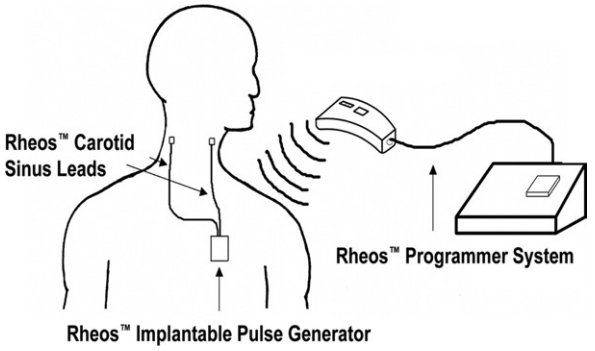

Fig 1. Illustration of the Rheos Baroreflex Hypertension Therapy System.

via intrinsic neurohumoral pathways. As a result of these findings and early European clinical trial results,[20] the Food and Drug Administration (FDA) approved a phase II feasibility trial, which began in March 2005, to explore the utility of the Rheos Baroreflex Hypertension Therapy System (CVRx, Maple Grove, Minn) to produce this effect in humans. The trial consists of 12 months of therapy; this article describes the details of surgical implantation and the early postoperative results of this trial and device in humans with resistant hypertension. The primary objectives are (1) description of technique, (2) documentation of safety, and (c) assessment of peri-implantation immediate hemodynamic effectiveness.

METHODS

The Rheos Baroreflex Hypertension Therapy System currently consists of a programmable pulse generator capable of delivering between 1 and 7.5 V in a temporally variable pattern, along with two electrodes designed to be placed at the carotid bulb. This requires surgical implantation by means of open carotid exposure, but the components are then tunneled subcutaneously, in a fashion similar to pacemaker placement (Fig 1).

This phase II trial was managed by the FDA, and all protocols were approved by each implanting center's institutional review board. All patients were under the care of internists, nephrologists, or cardiologists specializing in the treatment of hypertension, as well as a vascular surgeon interested in this problem. Eligibility was limited to patients with resistant hypertension, defined as SBP greater than 160 mm Hg despite receiving maximal appropriate doses of three or more antihypertensive medications, including a diuretic.[5] Entrance criteria included maximization of antihypertensive treatment, elimination of secondary causes of hypertension (such as renal artery stenosis or adrenal tumors) exclusion of baroreflex dysfunction (absence of dramatic postural pressure changes), and absence of carotid disease (defined as a stenosis, if present, of >50% by duplex ultrasonography and no prior surgery or neck radiation). It is important to note that all patients had to be deemed compliant with their antihypertensive therapy before consideration for enrollment (Tables I and II, online only).

After informed consent and enrollment onto the study, patients underwent 24-hour ambulatory blood pressure monitoring. As described below, patients underwent bilateral lead implantation by using appropriate anesthetic management and perioperative pharmacologic control of their blood pressure. At the time of implantation, while the patient was still under anesthesia and the wounds were open, the blood pressure response to voltages between 1 and 6 V was determined (acute dose-response testing). Dose-response testing was repeated before hospital discharge (postoperative day 1 or 2). Patients will be followed for 13 months after implantation, with all antihypertensive medications continued for the first 4 months (unless modification is deemed necessary for patient safety).

Description of surgical procedure

On the day of surgery, aspirin and β-blockers are administered. Typically, angiotensin-converting enzyme inhibitors and angiotensin receptor–blocking agents are held, and other antihypertensive agents are held at the discretion of the attending surgeon (if needed, blood pressure can be acutely controlled with sodium nitroprusside or nitroglycerin).

Proper anesthetic management is critical, because the baroreceptor reflex is very easily blunted by many anesthetics, including sevoflurane, nitrous oxide, isoflurane, and halothane, and, to a lesser extent, intravenous agents such as propofol.[21-25] If blunting occurs, the optimal location for the carotid sinus electrode may be very difficult to identify.

From the perspective of anesthetic management, the operation can be divided into three phases: phase 1, induction of anesthesia and exposure of the carotid bifurcations; phase 2, carotid sinus mapping, electrode fixation, and testing; and phase 3, tunneling and wound closure. In general, inhalation anesthetics should be minimized or avoided during the first two phases, but conventional anesthesia can be used during phase 3.

Phase 1: anesthetic induction and exposure of the bifurcation. Initial induction and maintenance of anesthesia should primarily be performed with intravenous agents. It is best to avoid sevoflurane, but agents such as isoflurane, at low doses, have been used successfully if the agent is discontinued with sufficient time to allow it to clear from the patient before mapping and dose-response testing are initiated. The carotid bifurcations may be exposed by using oblique or vertical incisions at the discretion of the surgeon; both sides of the neck, as well as the space for the generator pocket, must be draped into the field. In general, the bifurcation should be dissected en masse, with care taken to avoid or minimize any dissection in the area of the bifurcation and distally between the internal and external carotid arteries to avoid trauma to the carotid sinus neurovascular bundle.

Phase 2: carotid sinus mapping and electrode positioning. To identify proper lead positioning, the baroreflex must be fully functional; baroreflex blunting can be minimized by using a combination of short-acting barbiturates and narcotics.[26] After exposure of the carotid bifurca-

tion, the electrode is centered on the carotid sinus, and the lead is temporarily attached to the implantable pulse generator (IPG). The IPG is controlled by a computer-based programming system that communicates with the IPG by using a radiofrequency couple similar to that used for programming cardiac pacemakers. During the mapping procedure, testing is initiated at a low voltage, and the blood pressure–lowering effect is determined (this is generally seen within 30 seconds). The electrode position is adjusted, and testing is repeated to identify the area associated with the optimal hemodynamic response. When the optimal location is identified (defined as the greatest blood pressure drop for a given voltage), the electrode is sutured in place at that location. This mapping procedure is then repeated on the contralateral side with the other electrode. After bilateral implantation, a formal dose-response test is performed to assess the effect of full bilateral activation. Therapy is initiated at 1 V and increased at 1-minute intervals in 1-V increments until a maximal dose of 6 V or a hemodynamic end point is reached (SBP <90 mm Hg, mean arterial blood pressure <60 mm Hg, or heart rate [HR] <50/min).

Phase 3: tunneling and completion of procedure. At this point, preservation of baroreflex function is no longer critical for the conduct of the operation, and conventional anesthetic techniques can be used. A pocket is created in the infraclavicular space for the IPG, in a fashion similar to pacemaker and implantable cardiac defibrillator implantation (the right side has been used preferentially to avoid confusion with the typical left-sided pacemaker placement). Next, tunnels are created between the cervical incisions and the pocket created for the IPG, and the leads from the carotid sinus electrodes are brought to the IPG pocket. Strain-relief loops are created in the cervical incisions, the leads are connected to the IPG, and redundant lead length is coiled in the IPG pocket deep to the IPG. Impedance is tested to ensure the integrity of the electrical connections, and the incisions are closed. After surgery, the patient's usual antihypertensive medical regimen is resumed.

Dose-response testing

Dose-response testing is performed before hospital discharge. Blood pressure is measured by using a cuff appropriately sized for the patient; the same arm is always used. Patients are tested in their hospital beds and remain still and quiet until a stable blood pressure is obtained. Baroreflex activation therapy is then initiated at 1 V and continued for 3 to 5 minutes, at which time blood pressure and HR are recorded manually. Voltage is then increased, and vital signs are recorded at the end of each activation period until a final dose of 6 V is delivered or the patient reaches a prospectively defined hemodynamic end point (SBP <100 mm Hg, mean arterial blood pressure <60 mm Hg, and/or HR <50/min).

Analysis

Data used in this analysis were recorded on case report forms and subsequently entered and stored by using conventional computerized spreadsheet methods. Maximal response, determined for each patient, was compared with the baseline value by using paired *t* testing. Repeated-measures analysis of variance and regression analysis were used to determine the significance of changes over time during dose-response testing, and *t* testing and χ^2 analysis were used, as appropriate, for comparing continuous and categorical variables, respectively. Unless otherwise specified, data are expressed as mean ± SD.

Table III. Patient baseline demographic data (n = 10)

Variable	*Data*
Sex	4 female, 6 male
Race	4 black, 6 white
Age (y)	50 ± 13 (33-71)
BMI (kg/m^2)	34.3 ± 6.7 (29-51)
Office cuff BP (mm Hg)	
Systolic	175 ± 22 (144-204)
Diastolic	101 ± 22 (70-142)
Mean 24-h ambulatory BP (mm Hg)	
Systolic	163 ± 17 (110-222)
Diastolic	96 ± 12 (60-135)
Mean No. antihypertensive medications	6.2 ± 2.3 (3-9)

BMI, Body mass index; *BP,* blood pressure.
All data are expressed as mean ± SD, with ranges following in parentheses.

RESULTS

A total of 10 patients were enrolled in the US Rheos Feasibility Trial, all experiencing resistant hypertension while receiving optimal medical management.[5] An additional 14 patients were screened; 11 did not meet enrollment criteria, and 3 eligible patients declined participation. Patient demographics are presented in Table III. At enrollment, mean office cuff blood pressures were 175 ± 22 mm Hg SBP (range, 204-144 mm Hg) and 101 ± 22 mm Hg DBP (range, 142-70 mm Hg) despite an average of 6.2 ± 2.3 (range, 3-9) antihypertensive medications each. The mean age was 50 years (range, 33-71 years), and mean body mass index was 34.3 kg/m^2 (range, 29-51 kg/m^2). Six of the patients were male, four were black, and six were white.

All patients underwent successful bilateral implantation. There were no unanticipated serious procedure- or device-related adverse events or perioperative deaths. A small number of patients reported subjective awareness of muscle twitching, although no clinically visible effects were seen, a phenomenon previously observed during early experience with this device. Procedure time averaged 198 ± 72 minutes (range, 109-345 minutes).

Intraoperative dose-response data are presented in Table IV. The mean SBP decreased from 170 to 133 mm Hg, a reduction of 37 mm Hg (range, 9-86 mm Hg), at 6 V ($P = .05$). In a similar fashion, DBP decreased from 88 to 64 mm Hg, a decrease of 24 mm Hg ($P = .055$), and pulse pressure decreased from 81 to 68 mm Hg ($P < .05$). HR also decreased from 71/min to 63/min ($P < .05$), and in all cases, consistent dose-response curves were apparent.

The results of the first postimplantation "awake" dose-response test are shown in Table V and Fig 2. The mean

Table IV. Intraoperative dose-response curves

	Dose (V)							
Variable	*0*	*1*	*2*	*3*	*4*	*5*	*6*	P *value*
SBP (mm Hg)	170	158	150	144	137	136	133	.05
Incremental decrease (mm Hg)		12	20	26	33	34	37	
DBP (mm Hg)	88	83	78	79	71	70	64	.055
PP (mm Hg)	81	75	71	65	66	66	68	.05
HR (/min)	71	69	67	71	70	67	63	.05

SBP, Systolic blood pressure; *DBP,* diastolic blood pressure; *HR,* heart rate; *PP,* pulse pressure.
Data are expressed as means, and curves were analyzed for significance by using repeated-measures analysis of variance.

Table V. Predischarge dose-response curves

	Dose (V)							
Variable	*0*	*1*	*2*	*3*	*4*	*5*	*6*	P *value*
No. patients*	10	10	10	10	10	6	5	
SBP (mm Hg)	180	163	150	141	138	140	139	.001
Incremental decrease (mm Hg)		17	30	39	42	40	41	
DBP (mm Hg)	81	76	66	60	63	60	62	.005
PP (mm Hg)	98	87	83	81	75	80	77	.005
HR (/min)	79	79	76	73	72	75	70	

SBP, Systolic blood pressure; *DBP,* diastolic blood pressure; HR, heart rate; *PP,* pulse pressure.
Data are expressed as means, and curves were analyzed for significance by using repeated-measures analysis of variance.
*Note that four patients reached hemodynamic end points (as defined in the text) at 4 v and received no further stimulation.

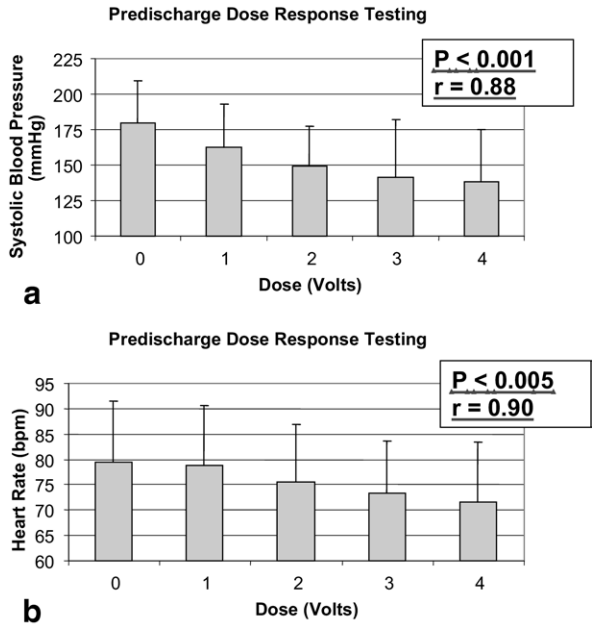

Fig 2. Predischarge dose-response curves (all patients, to 4 V only). **a,** Systolic blood pressure. **b,** Heart rate.

SBP decreased from 180 to 139 mm Hg, a decrease of 41 mm Hg (range, 22-104 mm Hg; $P < .001$). It is interesting to note that the maximum decrease was seen at an average of 4.8 ± 1.5 V (range, 2-6 V). DBP and HR again declined, decreasing 19 mm Hg (range, 11-82 mm Hg; $P < .005$) and 9/min (range, 2/min to 25/min; $P < .005$), respectively. The relationships between dose (voltage) and hemodynamic response were highly linear, with $r = 0.88$ for voltage vs SBP and $r = 0.9$ for voltage vs HR. The hemodynamics of the five patients who achieved the full range of therapy (ie, received the full 6 V without reaching a hemodynamic end point) showed similar results, with relationships between voltage and hemodynamic response also highly linear ($r = 0.93$ for HR and $r = 0.97$ for SBP).

Mean follow-up as of May 2006 is 10 months (range, 4-14 months), and all patients have finished 4 months' follow-up (3 months' stimulation). Two generators have had to be changed for planned battery replacement in patients requiring high voltages for blood pressure control. One infection has occurred in the US trial and one in Europe; the worldwide total infection rate is 5.5% and is expected to decrease with decreasing IPG size. The US infection occurred after the 4-month follow-up visit and was successfully treated by complete excision of the device, with an uneventful recovery. This patient is being followed up in the protocol but did not have another device implanted. No other long-term morbidity has occurred.

DISCUSSION

Perioperative results from the group of the first 10 patients enrolled in this FDA-approved phase II feasibility trial demonstrate that the Rheos Baroreflex Hypertension Therapy System can be safely implanted in patients with severe hypertension and associated cardiovascular risk factors. No acute complication or significant perioperative

morbidity has been seen. Intraoperative effects are impressive, with a mean SBP decrease of 37 mm Hg occurring without troubling bradycardia at easily achievable voltages. Predischarge dose-response tests in the awake state provide similar results, showing a mean SBP reduction of 41 mm Hg (achieved at a mean of 4.7 V), again without significant bradycardia or perceptible side effects. In fact, because several patients did not receive stimulation beyond 4 V, the maximal effect at 6 V might have been even greater if these patients had been further stimulated. Hemodynamic responses correlate highly with applied voltage, thus suggesting that designing strategies for more sophisticated intervention in the future may well be straightforward.

The mechanism of baroreflex activation–induced blood pressure reduction has been intensively investigated in both normotensive and hypertensive (induced by obesity and the infusion of angiotensin II) animals in a large body of work by Thomas Lohmeier at the University of Mississippi. His work has shown that baroreflex activation therapy produces a global reduction in sympathetic nervous system activity, as measured by a decrease in plasma norepinephrine levels and HR. In addition, whereas a reduction in arterial pressure approaching 20 mm Hg is typically associated with activation of the renin-angiotensin system, comparable reductions in blood pressure produced by electrical stimulation of the baroreflex system in this fashion uniquely lead to unaltered plasma renin levels during stimulation. In summary, work from this laboratory supports the hypothesis that electrical baroreflex stimulation decreases blood pressure by reducing sympathetic nervous system activity and preventing activation of the renin-angiotensin-aldosterone system.[13-18,26-28]

The effects of electrical stimulation of the carotid sinus to treat hypertension were first evaluated in the late 1950s in animals and humans with resistant hypertension. These devices were bulky, lacked external dose control, and had significant current leak from the electrodes, thus resulting in extraneous muscle and nerve stimulation, although the concept of an implantable pulse stimulator controlled via external radiofrequency signals was described as early as 1965.[29-33] In a report of eight patients treated, coincidentally, at the University of Rochester, Schwartz et al[34] described a mean sustained reduction in SBP of 48 mm Hg; six of the patients were able to discontinue blood pressure medications altogether.

Interest in this phenomenon resurfaced in the past decade or so, largely through Lohmeier's animal investigations cited previously. In preparation for larger human trials, Schmidli et al[19] studied the acute response to baroreflex activation therapy in patients undergoing elective carotid surgery. After exposure of the carotid sinus, an electrode was placed on the carotid sinus, and the baroreflex was activated. Despite the absence of carotid sinus mapping or specialized anesthetic techniques, a mean SBP reduction of 18 mm Hg was achieved. Results of chronic carotid sinus stimulation were first reported in 2005 in a group of five patients treated at University Hospital, Bern, Switzerland. At 4 months' follow-up, dose-response testing resulted in a 20 to 40 mm Hg decrease in SBP, which seemed to be stable to 4 months.[20] As of May 2006, the Rheos Baroreflex Hypertension Therapy System in its current version has been implanted in 25 patients in Europe (Device-Based Therapy in Hypertension Trial; DEBuT-HT). Finally, very preliminary work in animals suggests that this therapy may be of benefit in heart failure, as well.[35,36]

The current system addresses many of the challenges of the earlier devices. Extraneous nerve and muscle stimulation and pain resulting from current spread have been largely solved by using modern electrode technologies. The technique of placement of the electrode on the carotid sinus reduces the possibility of damage to the carotid sinus nerves and allows the use of established techniques commonly used in the treatment of atherosclerotic disease of the carotid bifurcation for electrode implantation. This facilitates electrode application, makes the operation easier, and shortens the learning curve for the implant procedure. Finally, advances in implantable medical devices allow the system to reliably deliver stable and controlled therapy that can be customized for each patient.

In summary, results in the first group of 10 patients who received implants in the United States suggest that chronic electrical stimulation of the carotid sinus can safely be performed and can, in the short-term, produce significant reductions in blood pressure: SBP reductions of 41 mm Hg were achieved at 4.8 V before discharge. These data parallel emerging results from Europe, which, along with theoretical and animal work, suggest that this effect is durable, although follow-up is as yet extremely limited. Further experience will be required before the role of this therapy in the treatment of hypertension is known, but these data suggest that a promising alternative approach exists for the large group of patients with resistant hypertension.

AUTHOR CONTRIBUTIONS

Conception and design: EI, TP, RK
Analysis and interpretation: KAI, EI
Data collection: KAI, ML, LS, GDT, CS, TP
Writing the article: KAI, EI
Critical revision of the article: KAI, EI, TP
Final approval of the article: KAI, ML, LS, GDT, CS, EI, TP, RK, RC
Statistical analysis: KAI, EI
Obtained funding: TP, RK, RC
Overall responsibility: KAI

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Submitted May 30, 2006; accepted Aug 10, 2006.

Additional material for this article may be found online at www.jvascsurg.org.

Table I, online only. Rheos feasibility trial inclusion criteria

≥21 y of age
Bilateral carotid bifurcations located below C3-4 (determined by duplex ultrasonography)
Office cuff blood pressure >160 mm Hg despite at least 2 mo of stable therapy on ≥3 antihypertensive medications, including a diuretic (JNC-7* definition of resistant hypertension)
Certified by investigator as compliant to taking full doses of medications
Reviewed by Screening/Adjudication Committee to meet study entrance criteria
Have signed an approved informed consent for participation in this study

*Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[5]

Table II, online only. Rheos feasibility trial exclusion criteria

Previously diagnosed baroreflex failure
Cardiac bradyarrhythmias
Chronic atrial fibrillation
Heart transplantation
Carotid stenosis >50% (by ultrasonography or angiographic evaluation)
Grade C ulcerative plaque (plaque with multiple cavities or a cavernous appearance by ultrasonography or angiographic evaluation)
Prior surgery or radiation in either carotid sinus region
Currently have implanted electrical medical device such as a pacemaker, defibrillator, or neurologic stimulation
Pregnant or contemplating pregnancy during the 13-mo follow-up period
Currently undergoing dialysis
Hypertension secondary to a treatable cause (for example, renal artery stenosis or hormonally active tumor)
Clinically significant cardiac valvular disease (defined subjectively by the enrolling cardiologist)
Unable to comply with protocol requirements
Unlikely to survive the protocol follow-up period
Enrolled in another concurrent clinical trial