Blood Pressure Outcome of Angioplasty in Atherosclerotic Renal Artery Stenosis
A Randomized Trial

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Abstract—Data for the effects on blood pressure of renal artery balloon angioplasty are mostly from uncontrolled studies. The aim of this study was to document the efficacy and safety of angioplasty for lowering blood pressure in patients with atherosclerotic renal artery stenosis. Patients were randomly assigned antihypertensive drug treatment (control group, n=26) or angioplasty (n=23). Twenty-four-hour ambulatory blood pressure, the primary end point, was measured at baseline and at termination. Termination took place 6 months after randomization or earlier in patients who developed refractory hypertension. In those allocated angioplasty, antihypertensive treatment was discontinued after the procedure but was subsequently resumed if hypertension persisted. Secondary end points were the treatment score and the incidence of complications. Two patients in the control group and 6 in the angioplasty group suffered procedural complications (relative risk, 3.4; 95% confidence interval, 0.8 to 15.1). Early termination was required for refractory hypertension in 7 patients in the control group. Antihypertensive treatment was resumed in 17 patients in the angioplasty group. Mean ambulatory blood pressure at termination did not differ between control (141±15/84±11 mm Hg) and angioplasty (140±15/81±9 mm Hg) groups. Angioplasty reduced by 60% the probability of having a treatment score of 2 or more at termination (relative risk, 0.4; 95% confidence interval, 0.2 to 0.7). There was 1 case of dissection with segmental renal infarction and 3 of restenosis in the angioplasty group. No patient suffered renal artery thrombosis. In unilateral atherosclerotic renal artery stenosis, angioplasty is a drug-sparing procedure that involves some morbidity. Previous uncontrolled and unblinded assessments of angioplasty overestimated its potential for lowering blood pressure.

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Key Words: renal artery obstruction ■ atherosclerosis ■ randomized controlled trials ■ angioplasty, balloon

Renal artery stenosis, mostly caused by atherosclerosis, can cause both renovascular hypertension, a form of hypertension reversible with renal revascularization, and renal insufficiency. Treatment of RAS by surgery or balloon angioplasty aims at avoiding lifelong antihypertensive treatment and progressive renal ischemia. The frequency of documented RAS varies from 0.5% to 2%, according to age and the thoroughness of investigation, and will probably increase with increasing population age and the widespread use of noninvasive screening tests. Attempts at revascularization will also increase because angioplasty, reported to be as effective as surgery and recently improved by the availability of renal artery stents, allows treatment of older and more fragile patients. The efficacy and safety of angioplasty should be objectively evaluated. With the exception of a randomized trial reported in abstract form, however, only information based on retrospective analyses is available.

We compared the 6-month BP outcome and the incidence of complications after diagnostic angiography plus antihypertensive drug treatment (control group) or angiography plus angioplasty (angioplasty group) in patients with hypertension and unilateral atherosclerotic RAS. The number of antihypertensive agents required to obtain target BP was determined, and BP outcome was documented with the use of 24-hour ABP monitoring, an observer-independent assessment that improves the repeatability of BP measurement.

Methods

Patient Selection
Patients were referred to the participating centers for hypertension and unilateral atherosclerotic RAS documented with intravenous subtraction angiography or a previous arteriography. Eligible patients were men and women younger than 75 years, with diastolic OBP readings >95 mm Hg on at least three occasions and/or receiving antihypertensive treatment, and with a creatinine clearance of ≥0.83 mL/s (50 mL/min). Patients with malignant hypertension or a history of stroke, pulmonary edema, or myocardial infarction in the previous 6 months were not included. Anatomic inclusion criteria were determined from the qualifying angiography immediately before randomization (see below). They comprised (1) the atherosclerotic nature of the RAS, as

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Selected Abbreviations and Acronyms

- ABP = ambulatory blood pressure
- BP = blood pressure
- DDD = defined daily dose
- OBP = office blood pressure
- RAS = renal artery stenosis

inferred from renal artery and aortic views; (2) a reduction in arterial diameter of either \( \geq 75\% \) without thrombosis or of \( \geq 60\% \) with a positive lateralization test (lateralized intravenous pyelography, renal scintigraphy, or renal vein renin determination, performed according to the usual practice of each center); (3) a stenosis affecting the main renal artery, which had not been previously dilated; and (4) a functional kidney on the opposite side exhibiting a normal main artery or an arterial diameter reduction \(<50\%\). The protocol was approved by the Broussais Hospital Ethics Committee and patients gave written informed consent before the qualifying angiography.

Clinical Evaluation

Patients who met clinical inclusion criteria entered a 2- to 6-week run-in period to standardize the antihypertensive regimen. Previous treatments were discontinued or adapted to maintain sitting diastolic BP \(<110\) mm Hg. When deemed necessary, antihypertensive agents were prescribed in the following sequence: slow-release nifedipine, 20 mg BID; idem plus clonidine, 0.15 mg BID; idem plus prazosin, 2.5 mg daily. These drugs were chosen because of their minimal interference with the glomerular filtration rate and renal vein renin determinations. Patients with diastolic BP levels \(>109\) mm Hg despite triple therapy were not included. At the end of the run-in period, the treatment score and the number of DDD units were determined (see below), \(^{16}\) the creatinine clearance was estimated from serum creatinine concentration with the Cockcroft formula, \(^{17}\) and ABP was monitored over the 24 hours before hospitalization. Patients were hospitalized for lateralization tests and the qualifying catheter angiography. Renal arteries on each side were classified into five grades on the basis of the ratio of the narrowest artery diameter to the distal diameter measured just before renal artery bifurcation (no lesion, stenosis \(<60\%, 60\%\) to 75\%, >75\%, thrombosis). \(^{18}\)

Randomization and Treatment

Patients meeting the anatomic inclusion criteria were randomized during angiography. Randomization was stratified by center, and sealed, numbered envelopes opened in sequential order were used. All envelopes (sealed or opened) were checked at the end of the trial. According to treatment allocation, either angioplasty was not performed and antihypertensive treatment adapted as necessary (control group), or angioplasty was immediately performed with or without stent placement, and antihypertensive treatment was stopped (angioplasty group). All patients were administered aspirin, 100 mg daily, from the day after angiography to termination.

Therapeutic decisions were based on the average of three oscillometric determinations of BP (see below). BP was determined 15 days after discharge and monthly thereafter. The target BP for both groups was a diastolic pressure \(<95\) mm Hg in the sitting position. If diastolic BP exceeded 109 mm Hg on first outpatient visit or 95 mm Hg on two successive visits, atenolol 50 mg/d, furosemide 40 mg/d, or enalapril 10 mg/d was added to the prerandomization regimen in the control group, and drug treatment was started or resumed in the angioplasty group. After a 6-month follow-up, ABP levels were measured, treatment score and glomerular filtration rate were determined, and the patency of the stenosed renal artery was assessed by intra-arterial or intravenous subtraction angiography. Premature termination of the trial was permitted in cases of refractory hypertension defined as diastolic BP \(>104\) mm Hg despite a maximal tolerated antihypertensive regimen. In such cases, ABP, treatment score, and plasma creatinine concentration were determined before renal angiography and, if deemed necessary, angioplasty with or without stent placement.

During the run-in and the follow-up periods, BP was measured with the patient in the sitting position after a 5-minute rest, using an A&D UA-751 semiautomated cuff-oscillometric sphygmomanometer \(^{19}\) (A&D Engineering). The average of three determinations obtained in the presence of the physician was used for treatment adaptation. Before randomization and at termination, 24-hour ABP was measured with Space Labs 5300 or 90207 (Space Labs, Inc) or Colin ABPM 630 (Colin Medical Instruments) monitoring devices programmed to record BP every 15 minutes during the day and every 30 minutes during the night. The same monitor was used on the same arm of each patient before randomization and at termination. Sitting BP was also measured with a mercury sphygmomanometer during each visit to compare OBP readings with oscillometric and ambulatory determinations.

End Points

The primary outcome measure was ABP at termination. Secondary end points were the treatment score and the incidence of complications. \(^{20}\) The treatment score was defined as the number of antihypertensive agents administered. Treatment was also quantified in DDD units \(^{12}\) at randomization and termination, using the following DDD: nifedipine 30 mg, clonidine 0.45 mg, prazosin 5 mg, furosemide 40 mg, enalapril 10 mg, and atenolol 75 mg. Immediate complications of angiography with or without angioplasty were defined as events requiring additional days in the hospital and classified into renovascular complications (dissection requiring surgical intervention and/or segmental renal infarction) or other complications (hematoma at puncture site and indirect \(^{21}\) complications). At termination, adverse renal events were defined as occlusion of the stenosed artery, renal infarction, an increase of \(\geq 50\%\) in the plasma creatinine concentration, and, in the angioplasty group, restenosis (residual stenosis one grade higher on the follow-up angiogram than on the immediate postangioplasty angiogram \(^{18}\)).

Data Analysis

We intended to enroll 52 patients. This sample size would have allowed 90% power to detect a 10 mm Hg difference in diastolic ABP at termination between the two groups, with a type I error of 5%. Previous experience in the participating centers suggested that this number would be attained in 2 years. SAS software was used for statistical analysis. Proportions were compared by use of the Proc Freq procedure and quantitative variables by use of the Proc Ttest procedure, or, in the case of nonnormal distribution, the Mann-Whitney test was used.

Results

Screening, Randomization, and Baseline Characteristics

Recruitment in the trial started in January 1992 and ended in June 1995, when 76 eligible patients had been screened (Fig 1). Twenty-seven declined inclusion on the basis of physician or patient refusal or because they were unable to return monthly. The 27 nonincluded patients and the 49 included did not differ in the percentage of men (70.4% versus 73.5%) and smokers (54.5% versus 63.3%); in mean \(\pm SD\) age (60.2 \(\pm\) 9.8 years) or in OBP (169/96 \(\pm\) 17/12 versus 170/100 \(\pm\) 20/11 mm Hg); in the proportion given two or more antihypertensive agents (66.6% versus 57.1%); and plasma creatinine levels (103 \(\pm\) 23 versus 103 \(\pm\) 21 \(\mu\) mol/L [1.16 \(\pm\) 0.26 versus 1.16 \(\pm\) 0.24 mg/dL]) at referral. Of the 49 enrolled, 26 were allocated medical treatment and 23 angioplasty. Patient characteristics at the end of the run-in period were evenly distributed between the two treatment groups (Table 1). Five patients in the control group and three in the angioplasty group were receiving no antihypertensive treatment, whereas all others were taking one to three antihypertensive agents.
Sixteen patients in the control group and 11 in the angioplasty group had positive lateralizing test results; such tests were not performed in patients in whom previous angiography suggested a luminal diameter reduction >74%. There were four minor protocol violations in patients whose calculated creatinine clearance was 0.83 mL/s (50 mL/min): two in the control group (0.47 and 0.62 mL/s [28 and 37 mL/min], respectively) and two in the angioplasty group (0.37 and 0.52 mL/s [22 and 31 mL/min], respectively). Of the 23 patients in the angioplasty group, 21 underwent angioplasty alone and 2 angioplasty plus stent placement.

Outcomes
In the control group, a 71-year-old patient with a history of angina was hospitalized 4 months after randomization for symptomatic hypotension and was therefore withdrawn from the study because of a major event. ABP was not determined in this patient and she did not undergo follow-up angiography. She had an OBP of 160/80 mm Hg under bitherapy 1 year after randomization with stable creatinine levels. In another 7 control patients, early termination 1 to 5 months after randomization was decided according to the protocol for refractory hypertension, all of whom underwent angioplasty before the 6th month (Table 2). End points were therefore determined on early termination or after a 6-month follow-up in 25 of 26 patients in the control group and all patients in the angioplasty group (Fig 1).

Mean ABP at termination and the average reduction in ABP between groups (Table 2 and Fig 2), nor did final oscillometric BP levels or the reduction in oscillometric BP (Fig 2).

However, unblinded assessment of OBP, using sphygmomanometric determinations, showed a larger BP reduction in the angioplasty group than in the control group (systolic/diastolic: 14±20/8±11 versus 7±23/1±12 mm Hg, P=.24/0.04) (Fig 1).

![Figure 1. Trial profile. End points were documented before angioplasty in patients randomized to medical treatment who subsequently underwent renal artery angioplasty within 6 months of inclusion.](http://hyper.ahajournals.org/)

**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical Treatment  n=26</th>
<th>Angioplasty  n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>59.5 (10.8)</td>
<td>59.2 (8.4)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>18 (69)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Median (range) duration of hypertension, y</td>
<td>5 (32)</td>
<td>6 (37)</td>
</tr>
<tr>
<td>Patients with diabetes, No. (%)</td>
<td>4 (15)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Patients with hypercholesterolemia, No. (%)</td>
<td>12 (46)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Past/current smokers, No. (%)</td>
<td>8/8 (31/31)</td>
<td>12/3 (52/13)</td>
</tr>
<tr>
<td>Mean (SD) body height, cm</td>
<td>170 (8)</td>
<td>166 (9)</td>
</tr>
<tr>
<td>Mean (SD) body weight, kg</td>
<td>76.1 (11.1)</td>
<td>73.5 (16.1)</td>
</tr>
<tr>
<td>Mean (SD) body mass index, kg/m²</td>
<td>26.4 (3.4)</td>
<td>26.4 (4.5)</td>
</tr>
<tr>
<td>Mean (SD) BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With sphygmomanometer (OBP)</td>
<td>165/96 (22/13)</td>
<td>165/98 (24/11)</td>
</tr>
<tr>
<td>With oscillometric device*</td>
<td>158/93 (25/14)</td>
<td>162/92 (24/11)</td>
</tr>
<tr>
<td>24-Hour ABP</td>
<td>149/89 (14/12)</td>
<td>151/91 (17/9)</td>
</tr>
<tr>
<td>No. given &lt;2 or ≥2 antihypertensive agents</td>
<td>12/14</td>
<td>15/8</td>
</tr>
<tr>
<td>Median number of DDD units (range)</td>
<td>1.33 (0–3.4)</td>
<td>1.33 (0–4.5)</td>
</tr>
<tr>
<td>Plasma creatinine (SD), µmol/L</td>
<td>105 (24)</td>
<td>101 (18)</td>
</tr>
<tr>
<td>Calculated creatinine clearance (SD), mL/s</td>
<td>1.22 (0.40)</td>
<td>1.22 (0.42)</td>
</tr>
<tr>
<td>Angiographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with stenosis grade 60%–74%, No. (%)</td>
<td>13 (50)</td>
<td>15 (65)</td>
</tr>
<tr>
<td>Patients with stenosis grade ≥75%, No. (%)</td>
<td>13 (50)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Patients with ostial stenosis, No. (%)</td>
<td>12 (46)</td>
<td>7 (30)</td>
</tr>
</tbody>
</table>

*Mean of three consecutive determinations.
2). Six patients in the angioplasty group and none in the control group were free of treatment at termination. Angioplasty reduced by 60% the probability of having a treatment score of $2$ at termination (relative risk, $0.4$; 95% confidence interval [CI], $0.2$ to $0.7$). The median numbers of DDD units given to patients in the medical treatment and in the angioplasty group were $1.78$ (range, $0$ to $4.3$) and $1.0$ (0 to $6.0$) respectively, at termination ($P = .009$ by the Mann-Whitney U test) (Table 2).

Two patients in the control group and 6 in the angioplasty group had procedural complications (Table 2). Therefore, the risk of complication was 3 times higher in the angioplasty group than in the control group (relative risk, $3.4$; 95% CI, $0.8$ to $15.1$). One patient undergoing angioplasty had a branch dissection that resulted in segmental infarction affecting one third of the kidney. All stenotic renal arteries were patent on termination angiogram. There was one adverse renal event in the control group (an increase of $51\%$ in the plasma creatinine level to $133 \text{ mol/L} \ [1.5 \text{ mg/dL}]$) and four in the angioplasty group, including the above-mentioned segmental renal infarction and three restenoses.

### Subsequent Follow-up

Patients were managed freely after trial termination. Another 14 patients in the control group underwent angioplasty, with 6 complications. Two of the 3 patients in the angioplasty group who exhibited restenosis had repeat angioplasty with 1 complication. OBP was determined 10 to 14 months after randomization in 24 patients of the control group and all those in the angioplasty group: For those previously allocated medical treatment, OBP averaged $145 \pm 12/88 \pm 7 \text{ mm Hg}$, and $21 (88\%)$ were receiving antihypertensive drugs. The corresponding figures in those previously allocated angioplasty were $150 \pm 23/86 \pm 10 \text{ mm Hg}$ and $16 (70\%)$.

### Discussion

We found that renal artery angioplasty and adaptation of antihypertensive regimen led to similar ABP levels in patients with hypertension and unilateral atherosclerotic RAS. Compared with medical treatment alone, angioplasty was more

### Table 2. Treatment Outcomes

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Medical Treatment</th>
<th>Angioplasty</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal artery angioplasty &lt;6 months after randomization</td>
<td>7</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Endoprosthesis placement/bypass surgery</td>
<td>0/0</td>
<td>2/0</td>
<td></td>
</tr>
<tr>
<td>Adverse outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (% with complications after initial procedure,</td>
<td>2 (8)</td>
<td>6 (26)</td>
<td>0.13</td>
</tr>
<tr>
<td>including:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renovascular complication*</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hematoma at puncture site and others</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No. with a major event</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>End points at termination†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) systolic ABP, mm Hg</td>
<td>141 (15)</td>
<td>140 (15)</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean (SD) diastolic ABP, mm Hg</td>
<td>84 (11)</td>
<td>81 (9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Mean (SD) change in systolic ABP, mm Hg</td>
<td>$-8$ (16)</td>
<td>$-12$ (20)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean (SD) change in ABP, mm Hg</td>
<td>$-5$ (10)</td>
<td>$-10$ (11)</td>
<td>0.12</td>
</tr>
<tr>
<td>No. given $&lt;2$ or $\geq2$ antihypertensive agents</td>
<td>3/22</td>
<td>15/8</td>
<td>0.001</td>
</tr>
<tr>
<td>Median No. of DDD units (range)</td>
<td>1.78 (0–4.3)</td>
<td>1.0 (0–6.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Calculated creatinine clearance (SD), mL/s</td>
<td>1.23 (0.33)</td>
<td>1.28 (0.45)</td>
<td>0.73</td>
</tr>
<tr>
<td>No. (% with renal adverse event, including:</td>
<td>1</td>
<td>4</td>
<td>0.17</td>
</tr>
<tr>
<td>No. with occlusion of the stenosed artery</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. with a $50%$ increase in plasma creatinine</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. with dilatation failure‡</td>
<td>...</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Dissection with segmental renal infarction.
†End points were documented before angioplasty in patients randomized to medical treatment who subsequently underwent renal artery angioplasty within 6 months of inclusion.
‡Dissection with renal segmental infarction, 1; restenosis, 3.

![Figure 2. Difference in blood pressure reduction (mean and 95% confidence interval) between patients allocated to medical treatment and those allocated to angioplasty by the method of blood pressure assessment.](image-url)
frequently associated with complications but allowed BP control with a smaller number of antihypertensive agents.

In patients with hypertension and RAS, renal artery angioplasty should ideally provide a cure for hypertension, that is, normal BP without treatment. Angioplasty allows hypertension cure in ≈50% of patients with fibromuscular RAS, and complications are not frequent in this group. However, the cure rate is lower and the incidence of complications higher among patients with atherosclerotic RAS.13,20 Atherosclerotic patients more frequently suffer technical failures or subsequent restenosis than those with fibromuscular RAS.14,18 They frequently have preexisting primary hypertension, structural changes in large arteries, or impaired renal function that limits the efficacy and safety of angioplasty.2,3,7,14,20 Retrospective series report that the usual BP outcome after angioplasty for atherosclerotic RAS is improvement, that is, a reduction in BP levels and/or in the required number of antihypertensive agents.14 There are no uniform criteria for assessing improvement, however, and it may be spontaneous or a consequence of alterations in drug choice and dosage.3,12,14 There is therefore a need for randomized controlled trials to assess risks and benefits associated with angioplasty in atherosclerotic RAS.

The Scottish and Newcastle Renovascular Collaborative Group reported in abstract form a trial of angioplasty versus medical therapy in patients with bilateral or unilateral atherosclerotic RAS. The main outcome variable used was OBP, and no detail was provided concerning treatment standardization.

The present trial was targeted toward patients with unilateral RAS because such cases are more frequent and revascularization is easier, safer, and more likely to result in a favorable BP outcome than in cases with bilateral RAS or RAS affecting a solitary kidney.21 Patients with fibromuscular RAS were not included because good evidence is already available that the benefits of angioplasty outweigh the risks in such patients.11 It is difficult to differentiate patients with primary hypertension associated with RAS from those having hypertension secondary to RAS, that is, renovascular hypertension.1,3 To increase the likelihood of our patients having renovascular hypertension, they were selected on the basis of high-grade stenosis (renal artery diameter reduction ≥75%) or a stenosis of ≥60% plus a positive lateralizing test. Patients had been screened for RAS on the basis of poor efficacy and/or tolerance of previous antihypertensive regimen and referred to the participating centers because a unilateral atherosclerotic RAS was present. Although those with refractory hypertension were not included for safety reasons, patients in this trial are representative of the population of cases with unilateral atherosclerotic RAS in whom renal revascularization may be considered.1,3

To avoid a biased evaluation of BP outcome, patients in both groups were treated according to a standardized stepwise antihypertensive regimen. In real life, the early use of a combination of diuretics and angiotensin-converting enzyme inhibitors might have resulted in adequate BP in a larger number of patients. Furosemide and/or enalapril were used in this study only if a combination of nifedipine, clonidine, prazosin, and/or atenolol was poorly tolerated or did not decrease diastolic BP to <105 mm Hg. The reasons for this choice were that before randomization, furosemide and enalapril might have altered glomerular filtration rate, and, after randomization, that long-term exposure to enalapril with or without furosemide might have compromised the function of the stenotic kidney.3,22 To avoid the biases, poor repeatability, and lack of precision associated with OBP determination, therapeutic decisions were based on the average of three measurements, using a semiautomatic device, and outcome was assessed by 24-hour ABP monitoring. Mean ABP levels, including sleep time BP readings, were lower than mean OBP levels, as expected. The difference between ABP and OBP levels was 15/7 mm Hg (systolic/diastolic) at randomization in our patients, a difference comparable to that reported at the first visit (12/9 mm Hg) in the 50 hypertensive patients analyzed by Bottini et al.15 The mean ABP levels in the two groups were similar at termination, although the drop in diastolic OBP levels was higher in the control group than in the angioplasty group. These results emphasize the need for an outcome assessment made independent of investigators when blinding is not possible.

Although mean ABP levels were very similar in both groups at termination, angioplasty allowed easier BP control than medication alone. Treatment scores were higher in the control group than in the angioplasty group, antihypertensive agents being required at termination for all control patients but not for 6 of the 23 allocated to angioplasty (26%). Moreover, 7 of 25 patients in the control group (28%) developed refractory hypertension leading to secondary angioplasty within 6 months. The high BP levels and treatment scores that these 7 patients exhibited immediately before secondary angioplasty were included in the analysis. Guidelines for early interruption were established at the design stage of the study and stated that patients should be withdrawn for safety reasons if hypertension were refractory or there were intolerable drug-induced side effects. These guidelines necessitated an on-treatment analysis, with 7 patients in the control group having a follow-up of <6 months. We did not perform an intention-to-treat analysis at 6 months because this would have overestimated the drop in BP in the control group, the BP effects of angioplasty being added to those of medication in the 7 patients developing refractory hypertension and switched to angioplasty. It is possible that their 6-month ABP levels and treatment score would have been even higher if early termination had not been allowed, raising the possibility that the BP difference between control and angioplasty groups was underestimated because of safety dispositions. The BP effects of randomized therapeutic regimen, medication, and angioplasty were only compared in the short term, the experimental period lasting for 6 months or less. However, mean OBP levels and the proportion of patients given antihypertensive treatment were similar 1 year after randomization in the control and angioplasty groups, confirming that the BP-lowering effect of angioplasty in the short and medium terms is limited in atherosclerotic RAS. Although they were selected on the basis of high-grade stenosis (>75%) and/or a positive lateralizing test, only a minority of our
patients had true renovascular hypertension, that is, a form of hypertension fully reversible after revascularization.\textsuperscript{1,3} In addition to frequently associated primary hypertension and impaired renal function, individuals with atherosclerotic RAS lose the ability, with increasing age, to reverse the structural vascular changes associated with secondary hypertension.\textsuperscript{21} This underlines the need for early detection of RAS to allow angioplasty in patients with a short duration of hypertension.\textsuperscript{3,4,23}

The complication rate in our group of patients undergoing angioplasty was substantial (6 of 23, or 26\%) and higher than in many retrospective series.\textsuperscript{14,20} Clinicians involved in the present trial may have used a lower threshold to define the presence of a complication. However, they probably applied the same criteria to patients in both treatment groups, and angioplasty was more frequently associated with complications than diagnostic angiography alone. It is also possible that complication rates have been underestimated in some series because they were not documented prospectively in a standardized clinical report form. In the largest retrospective series of angioplasty for atherosclerotic RAS, mechanical complications and acute renal failure (generally reversible) occurred in 26\% and 14\% of procedures, respectively.\textsuperscript{21} In a prospective randomized trial comparing angioplasty with surgery in atherosclerotic RAS,\textsuperscript{9} there were major and minor complications in 5 and 11 of the 29 patients in the angioplasty group (17\% and 48\%), respectively. In the present trial, most immediate complications were mild and transient. However, renal events present at termination are likely to require additional therapeutic procedures and/or to compromise long-term BP and renal outcome. Such events occurred in 1 control patient (a rise of 51\% in the plasma creatinine concentration) and in 4 undergoing angioplasty (3 restenoses requiring repeat angioplasty and 1 segmental renal infarction).

The external validity of this study is debatable. First, 1 in 3 eligible patients declined inclusion, mostly because of the patient’s (or referring physician’s) preference for angioplasty. We were unable to document subsequent outcome in patients eligible but not included. Included and nonincluded eligible patients did not differ, however, in terms of age, sex distribution, severity of hypertension, and renal function. Second, the total number of randomized patients was small. Third, efficacy and safety results could have been different in other hands or if renin-angiotensin inhibitors (in the control group) and intravascular stents (in the angioplasty group) had been used more frequently. The present trial was designed to assess the BP outcome of angioplasty and did not address long-term renal and cardiovascular outcomes in patients with atherosclerotic RAS. Considering renal outcome, angioplasty seems attractive because it might prevent ischemic nephropathy and progression to renal artery thrombosis. Angioplasty with or without renal artery stenting in patients with progressive renal failure has limited BP-lowering potential, however, and it is associated with some mortality and a substantial morbidity.\textsuperscript{5,11,24} The efficacy and safety of angioplasty for stabilizing renal function in patients with atherosclerotic renovascular disease should therefore be assessed by specifically designed trials.\textsuperscript{2}

In summary, previous uncontrolled and unblinded assessments of angioplasty overestimated its potential for lowering BP. Using a PROBE (Prospective Randomized Open Blinded Outcome) design, we found that angioplasty made BP control easier in the short term but was more frequently associated with complications than conservative management in patients with unilateral atherosclerotic RAS. Most patients undergoing angioplasty still needed antihypertensive agents 6 or 12 months after the procedure. The reduction in treatment required by patients undergoing angioplasty should therefore be weighed against the risks of complications and restenosis. Previously reported data and this evidence suggest that patients with RAS and little or no renal insufficiency should be offered angioplasty if the underlying disease is fibromuscular dysplasia,\textsuperscript{14} in cases with recurrent pulmonary edema,\textsuperscript{25} and in those with refractory hypertension. Patients with atherosclerotic RAS also have or develop atherosclerotic plaques or stenoses on extrarenal arteries. In such patients with stable renal function and controllable hypertension, the effects of angioplasty on long-term cardiovascular outcome should be compared with those of conservative treatment by using antihypertensive and lipid-lowering agents. Until such a comparison becomes available, the immediate risks and the potential long-term benefits of angioplasty should be weighed for each individual patient, possibly by including patient preference.

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Appendix

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References


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