

# Balloon Angioplasty or Medical Therapy for Hypertensive Patients with Atherosclerotic Renal Artery Stenosis? A Meta-Analysis of Randomized Controlled Trials

Alain J. Nordmann, MD, MSc, Kevin Woo, PhD, Robert Parkes, MSc, Alexander G. Logan, MD

**PURPOSE:** The optimal treatment for hypertensive patients with atherosclerotic renal artery stenosis is controversial. We performed a meta-analysis comparing the effects of balloon angioplasty and medical therapy in these patients.

**METHODS:** We searched MEDLINE, EMBASE, the Science Citation Index, the Cochrane Controlled Trials Registry, and reference lists. Authors of published trials were contacted.

**RESULTS:** We identified three trials involving a total of 210 patients with moderate-to-severe ( $\geq 50\%$ ) unilateral or bilateral atherosclerotic renal artery stenosis and poorly controlled hypertension who were followed for at least 3 months after intervention. Balloon angioplasty was significantly more effective in reducing blood pressure than was medical therapy; the weighted mean difference between the two treatments was  $-7$  mm Hg (95% confidence interval [CI]:  $-12$  to  $-1$  mm Hg) for

systolic blood pressure and  $-3$  mm Hg (95% CI:  $-6$  to  $-1$  mm Hg) for diastolic blood pressure. There was no consistent difference in changes in renal function. Patients treated with balloon angioplasty were more likely to have patent renal arteries after 12 months (52% vs. 19%; odds ratio [OR] = 4.2; 95% CI: 1.8 to 9.8), used fewer antihypertensive medications, and appeared to have fewer major cardiovascular and renovascular complications (OR = 0.27; 95% CI: 0.06 to 1.23;  $P = 0.09$ ).

**CONCLUSION:** Balloon angioplasty has a modest but significant effect on blood pressure and should be considered for patients with atherosclerotic renal artery stenosis and poorly controlled hypertension. There is no evidence supporting its use in improving or preserving renal function, although none of the trials were designed to address this issue. *Am J Med.* 2003;114:44–50. ©2003 by Excerpta Medica Inc.

Atherosclerotic renal artery stenosis is the most common cause of secondary hypertension, accounting for 1% to 5% of all cases (1). It leads to progressive renal ischemia and loss of renal function (2,3), and thus is the underlying cause of end-stage renal disease in up to 20% of older patients starting on dialysis (4). Several invasive procedures have been used to correct the anatomical defect, including balloon angioplasty, stent revascularization, and surgical reconstruction. Comparative trials have shown that stenting and surgery are more effective than balloon angioplasty in restoring

renal artery patency, but neither resulted in better clinical outcomes (5,6).

Early uncontrolled studies of patients with atherosclerotic renovascular hypertension reported a combined rate of cure or improvement of 71% (95% confidence interval [CI]: 58% to 80%), and antihypertensive drug treatment was reduced by at least half a tablet per day in 52% of patients (7). Case series have reported that angioplasty can restore renal function (8,9) and prevent recurrent heart failure (10). Comparative trials with medical therapy, however, failed to confirm the beneficial findings (11), but each trial was small and may have missed important treatment effects. We combined the results of randomized controlled trials that compared the effects of balloon angioplasty with medical therapy in the treatment of atherosclerotic renovascular hypertension to improve statistical power and provide a sounder foundation to guide medical decision making.

From the Department of Medicine (AJN, AGL), University Health Network, Toronto, Ontario, Canada; Department of Medicine (KW, AGL), Mount Sinai Hospital, Toronto, Ontario, Canada; Division of Epidemiology and Biostatistics (RP, AGL), Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada; and Basel Institute for Clinical Epidemiology (AJN), University Hospital Basel, Basel, Switzerland.

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Requests for reprints should be addressed to Alain J. Nordmann, MD, MSc, Basel Institute for Clinical Epidemiology, University Hospital Basel, Hebelstrasse 10, 4031 Basel, Switzerland, or alainnordmann@hotmail.com.

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## METHODS

### *Criteria for Considering Studies for This Review*

To be considered, clinical studies had to be randomized trials comparing balloon angioplasty with medical treat-

ment in hypertensive patients who had atherosclerotic renal artery stenosis with a minimum of 3 months of follow-up after treatment. We included only studies with adult patients (age >18 years) who had uncontrolled hypertension (diastolic blood pressure  $\geq 95$  mm Hg, treated or untreated) and moderate-to-severe ( $\geq 50\%$ ) unilateral or bilateral atherosclerotic renal artery stenosis. Studies analyzing patients with fibromuscular dysplasia, total occlusion of the renal artery, an affected kidney smaller than 8 cm, malignant hypertension, or a serum creatinine level  $>500$   $\mu\text{mol/L}$  were excluded.

Patients had to be assigned randomly to either primary balloon angioplasty or primary antihypertensive drug therapy as the principal intervention. Outcome measures included changes in blood pressure and renal function, number and defined daily doses of antihypertensive drugs used (one defined daily dose is the average maintenance dose per day), renal function as assessed by serum creatinine level or creatinine clearance, patency of the renal artery (defined as stenosis  $<50\%$ ), renovascular and major cardiovascular complications (defined as a  $\geq 50\%$  increase of serum creatinine level, dissection of the renal artery, development of renal failure, myocardial infarction or angina, heart failure, hypotension, death, or need for dialysis), procedural complications, and side effects of antihypertensive drug therapy.

### Search Strategies to Identify Studies

A comprehensive search of MEDLINE from 1966 to June 2000, EMBASE from 1980 to April 2000, the Science Citation Index from 1990 until 2000, the Cochrane Controlled Trials Registry, and personal files was completed. There were no language or other restrictions. The search consisted of the following terms: *random\* control\* trial\** or *clinical trial* or *evidence-based medicine* or *controlled study* and *exp kidney artery stenosis* and *exp angioplasty*.

Reference lists of papers resulting from this search were also hand searched, and authors of published trials were contacted to enquire if they were aware of any eligible unpublished trials. These searches identified three trials: the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) trial (12), the Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) trial (13), and the Essai Multicentrique Medicaments vs Angioplastie (EMMA) trial (14), which fulfilled the eligibility criteria.

### Article Selection and Data Extraction

Two reviewers (AJN, KW) independently assessed all material gathered for relevance and fulfillment of study inclusion criteria. Disagreements in data extracted and assessment of methodological quality were resolved by consensus. Allocation concealment was coded by the method of Schulz (15). The validated method of Jadad (16) was used to rate methodological quality, and the Cochrane

Collaboration criteria were used to score the risk of bias (17).

### Statistical Considerations

All results were combined using Review Manager (RevMan) 4.1 (The Cochrane Collaboration, Oxford, United Kingdom). Analysis was based on the intention-to-treat data from the primary trials, when available. The weighted mean difference and corresponding 95% confidence intervals were calculated to compare differences in blood pressure (18). Mantel-Haenszel odds ratios and corresponding 95% confidence intervals were calculated for dichotomous outcomes. Standard deviations of the change from baseline blood pressure were not provided in two studies (12,13) and could not be obtained on written request from the original authors. Accordingly, they were imputed in the following manner. In one study (12), we used provided data (the *P* value, the group means, and the number of subjects) to determine the standard deviation based on the estimated value from Student *t* distribution for paired data. For the second study (13), in which neither standard deviations nor *P* values were indicated, the largest of the standard deviations obtained in the other studies were used. Heterogeneity among trials was assessed by chi-squared testing, with the significance level set at *P* = 0.1. Because of the low power of the test for heterogeneity, only results of the random-effects model are reported. Available data did not permit subgroup analyses.

## RESULTS

There were 210 patients in the three trials (Table 1). Two studies reported a follow-up of 6 months (13,14), and one (12) reported a follow-up of 12 months. In two studies (12,13), patients had a diastolic blood pressure  $>95$  mm Hg when taking at least two antihypertensive drugs; in the other study (14), subjects had a diastolic blood pressure  $>95$  mm Hg or were taking antihypertensive medication at entry.

Antihypertensive drug therapy was stopped at the time of the intervention in patients assigned to balloon angioplasty in two trials and reintroduced subsequently if necessary (12,14). In the third trial, antihypertensive drug therapy was continued after balloon angioplasty, but clinicians were encouraged to reduce treatment if blood pressure levels permitted (13). In the DRASTIC trial (12), patients assigned to balloon angioplasty received aspirin (300 mg/d) for 6 months. Although the SNRASCG trial presented the results for patients with unilateral and bilateral renal artery stenosis separately (13), they were combined here. Two patients assigned to balloon angioplasty in the DRASTIC trial received a stent, and 20% of patients in the SNRASCG trial who were assigned to the

**Table 1.** Characteristics of Included Studies Comparing the Effects of Medical Therapy with Balloon Angioplasty for the Treatment of Hypertension with Renal Artery Stenosis

Study (Reference)	Number of Patients		Bilateral Stenosis Number (%)	Follow-up (months)	Run-In Period	Primary Outcome	Crossover from Medical Therapy to Angioplasty Number (%)	Comment
	Angioplasty	Medical Therapy						
DRASTIC (12)	56	50	24 (23)	12	—	Office blood pressure	22 (44)	3-month analysis before, 12-month analysis after crossover
EMMA (14)	23	26	0	6	2 to 6 weeks	24-hour ambulatory blood pressure	7 (27)	Endpoints documented before crossover in medical therapy group
SNRASCG (13)	25	30	28 (51)	6	4 weeks	Office blood pressure	0	Results of patients with unilateral and bilateral renal artery stenosis were reported separately

DRASTIC = Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA = Essai Multicentrique Medicaments vs Angioplastie trial; SNRASCG = Scottish and Newcastle Renal Artery Stenosis Collaborative Group trial.

intervention group underwent nephrectomy or surgical revascularization as the primary procedure.

*Methodologic Quality of Included Trials*

The methodologic quality among the trials varied substantially (Table 2). The method to generate allocation sequence was not stated in two trials (13,14). Blinded outcome assessments were achieved in one trial (14) by 24-hour ambulatory blood pressure monitoring and by blinded outcome assessors in another (13). However, unblinded study personnel performed the blood pressure measurements in the largest trial (12). The overall risk of bias was low in one trial (14), but moderate in the

SNRASCG trial and in the 3-month data of the DRASTIC trial. For the 12-month results of the DRASTIC trial, however, the risk was high because of the large number of crossovers to angioplasty after 3 months. Accordingly, we performed separate analyses of the 3-month and 12-month follow-up data.

*Differences in Blood Pressure*

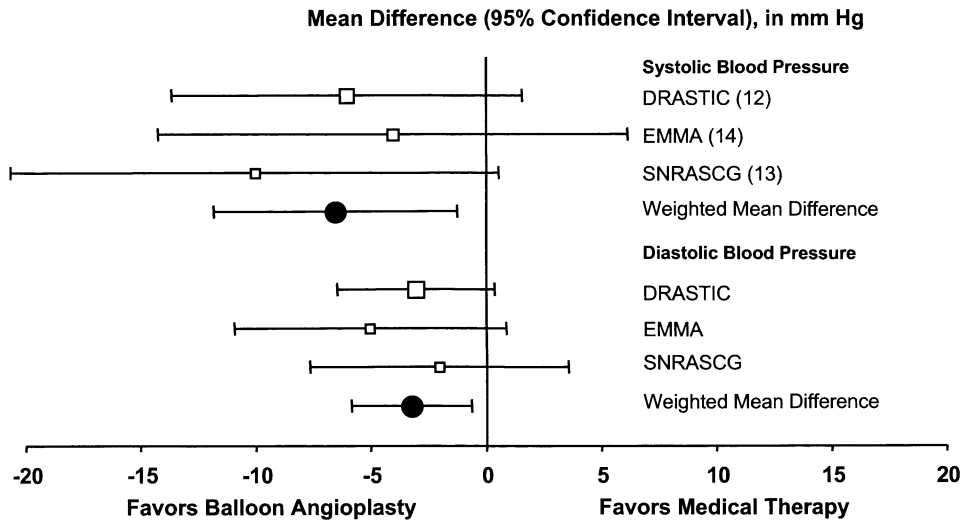
The pooled data using the 3-month follow-up values from the DRASTIC trial and the 6-month data from the two other trials showed a significantly greater decrease in both systolic and diastolic blood pressure from baseline in the angioplasty group as compared with medical ther-

**Table 2.** Methodologic Quality of Included Trials

Study (Reference)	Allocation Concealment	Method of Randomization	Blinding of Main Outcome	Intention-to-Treat Analysis	Number of Patients Withdrawn or Lost to Follow-up	Quality Assessment Score*
DRASTIC (12)	Adequate	Computer-generated	No	Yes	2	3
EMMA (14)	Unclear	Sealed envelopes	No, but objective measurement (24-hour ambulatory blood pressure)	No	1	2
SNRASCG (13)	Unclear	Not mentioned	Yes	No	6	1

\* Range of 0 (low) to 5 (high).

DRASTIC = Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA = Essai Multicentrique Medicaments vs Angioplastie trial; SNRASCG = Scottish and Newcastle Renal Artery Stenosis Collaborative Group trial.



**Figure.** Differences in systolic and diastolic blood pressure. Three-month follow-up data were used from the DRASTIC trial. DRASTIC = Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA = Essai Multicentrique Medicaments vs Angioplastie trial; SNRASCG = Scottish and Newcastle Renal Artery Stenosis Collaborative Group trial.

apy (Figure). The weighted mean difference was  $-7$  mm Hg (95% CI:  $-12$  to  $-1$  mm Hg) for systolic blood pressure and  $-3$  mm Hg (95% CI:  $-6$  to  $-1$  mm Hg) for diastolic blood pressure. The weighted mean differences using the 12-month follow-up data from the DRASTIC trial and the 6-month data from the two other trials were  $-5$  mm Hg (95% CI:  $-10$  to  $1$  mm Hg) for systolic blood pressure and  $-4$  mm Hg (95% CI:  $-7$  to  $-1$  mm Hg) for diastolic blood pressure. At that time, however, 22 (44%) of the 50 patients assigned to medical therapy in the DRASTIC trial had crossed over to undergo angioplasty by 12 months. The chi-squared test of heterogeneity was not significant either at 3 months (Figure) or 12 months, indicating no evidence of discordance among studies.

#### Differences in Number and Defined Daily Doses of Antihypertensive Drugs

Because the method of reporting antihypertensive drug use was not standardized, it was not possible to pool the

results of antihypertensive drug use. The SNRASCG trial did not provide detailed information, but stated that there was no statistically significant group difference in the changes in the number of drugs used at 6 months. In the two trials (12,14) that documented medication use (Table 3), the balloon angioplasty group had a significant decrease in median defined daily doses in the EMMA trial at 6 months ( $P = 0.009$ ) and mean defined daily doses in the DRASTIC trial at 3 months ( $P < 0.001$ ). The number of antihypertensive drugs was also significantly lower in the balloon angioplasty group at both 3 and 12 months in the DRASTIC trial.

#### Changes in Renal Function

It was not possible to pool the results describing the changes in renal function, as the method of measurement was not uniform among the trials. The SNRASCG trial reported the mean serum creatinine level, the EMMA trial reported the mean creatinine clearance, and the

**Table 3.** Differences in the Number and Defined Daily Doses of Antihypertensive Drugs in the DRASTIC and EMMA Trials

Study (Reference)	Period	Number of Antihypertensive Drugs		P Value	Number of Defined Daily Doses		P Value
		Balloon Angioplasty	Medical Therapy		Balloon Angioplasty	Medical Therapy	
		Mean $\pm$ SD		Mean $\pm$ SD or Median (Range)			
DRASTIC (12)	Baseline	2.0 $\pm$ 0.8	2.0 $\pm$ 0.9		3.3 $\pm$ 1.1	3.2 $\pm$ 1.5	
	3 months	1.9 $\pm$ 0.9	2.5 $\pm$ 1.0	0.002	2.1 $\pm$ 1.3	3.2 $\pm$ 1.5	<0.001
	12 months	1.9 $\pm$ 0.9	2.4 $\pm$ 0.9	0.002	2.5 $\pm$ 1.7	3.1 $\pm$ 2.3	0.10
EMMA (14)	Baseline				1.33 (0-3.4)	1.33 (0-3.4)	
	6 months				1.0 (0-6.0)	1.78 (0-4.3)	0.009

DRASTIC = Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA = Essai Multicentrique Medicaments vs Angioplastie trial.

DRASTIC trial reported the median serum creatinine level and creatinine clearance. There was no consistent change in renal function between the angioplasty and medical-therapy groups in any of the studies. Whereas the unadjusted creatinine clearance showed a significant difference at 3 months in the DRASTIC trial ( $70 \pm 25$  mL/min in the angioplasty group vs.  $59 \pm 23$  mL/min in the medical-therapy group,  $P = 0.03$ ), the median serum creatinine level showed no interval change or between-group difference. Moreover, there was no difference in creatinine clearance at 12 months in that trial ( $70 \pm 24$  mL/min in the angioplasty group vs.  $62 \pm 27$  mL/min in the medical-therapy group,  $P = 0.11$ ).

### Patency Rates

The difference in patency rates between the two groups could not be pooled because the SNRASCG trial did not indicate separate patency rates for randomized and non-randomized patients who did not fulfill prespecified trial inclusion criteria, and because the EMMA trial did not provide information on patency rates. In the latter trial, however, none of the stenotic arteries in either of the two groups was totally occluded on the termination angiogram. In the DRASTIC trial, follow-up angiography at 12 months, which was performed in 48 of the 56 patients in the angioplasty group and 43 of the 50 in the medical-therapy group, revealed that 25 patients (52%) assigned to angioplasty had a stenosis  $<50\%$ , compared with 8 patients (19%) allocated to medical therapy (odds ratio [OR] = 4.2; 95% CI: 1.8 to 9.8). None of the patients in the angioplasty group, but 8 patients (9%) in the medical-therapy group, had a total occlusion of the artery.

### Major Cardiovascular and Renovascular Complications

The DRASTIC trial reported complications during a follow-up of 12 months, whereas the two other studies reported complication rates during 6 months of follow-up. The complication rate in the DRASTIC trial was reported erroneously as the number, rather than the percentage, of patients, according to the principal author. Using the correct values in our meta-analysis, there were 10 major cardiovascular or renovascular complications in the balloon angioplasty group, compared with 26 in the medical-therapy group (OR = 0.27; 95% CI: 0.06 to 1.23;  $P = 0.09$ ). There was no substantial change in the odds ratio when the analysis was limited to mutually exclusive events to avoid potential double counting of renovascular events in the SNRASCG trial. The chi-squared test for heterogeneity was not statistically significant.

### Procedural Complications

Of the patients allocated to receive angioplasty, 11 (11%) of 104 were reported to have developed clinically important hematoma at the site of catheter insertion. One patient developed symptomatic hypotension during the

procedure, and there were five technical failures, including one renal artery dissection. No study reported side effects of medical therapy.

## DISCUSSION

In accord with observational data (7), the results of our meta-analysis demonstrate that balloon angioplasty is more effective than antihypertensive drug therapy in reducing blood pressure among hypertensive patients with atherosclerotic renal artery stenosis. The magnitude of the difference, however, is modest, and it remains to be determined whether this benefit will persist in the longer term and improve clinical outcomes. The results were influenced by the DRASTIC trial (12), which contributed 48% weight to the summary values of systolic blood pressure and 58% weight to the summary values of diastolic blood pressure. Although each trial showed a beneficial effect of balloon angioplasty, they were too small to be definitive, and their results did not reach statistical significance. By combining them, we were able to remove some of the uncertainty surrounding the usefulness of this intervention.

In the pooled analysis using the 12-month instead of the 3-month follow-up data for the DRASTIC trial, angioplasty was still favored, although the difference for systolic blood pressure was no longer statistically significant. However, the DRASTIC trial permitted patients in the medical-therapy group who had refractory hypertension or progressive renovascular occlusive disease to undergo balloon angioplasty after 3 months; by 12 months, 44% of the patients in that group had undergone angioplasty, thereby diminishing the between-group differences. By permitting crossovers after 3 months, the purpose of the DRASTIC trial changed from a trial comparing balloon angioplasty with medical therapy to one in which the generalized use of angioplasty was compared with its selective use based on clinical course.

Patients treated with balloon angioplasty used significantly less antihypertensive medication in the two trials in which their use was determined by protocol and administered in the participating centers (12,14). In the trial that showed no change in drug intake (13), treatment decisions after angioplasty were left in the hands of the referring physicians rather than study personnel. The greater reduction in blood pressure and the use of less antihypertensive medications in the angioplasty group emphasize the advantages of this intervention over medical therapy. It also raises the possibility that if the patients in the two groups had been maintained on the same number and defined daily doses of antihypertensive drugs throughout the trials, the magnitude of the blood pressure difference would have been greater.

None of the trials showed a significant improvement in renal function with angioplasty, despite a higher arterial patency rate with balloon angioplasty. It is possible that the duration of the trials was too short to observe the full benefit of this intervention. However, this finding may also reflect intrarenal vascular damage and irreversible glomerular sclerosis. Although there is no evidence to support balloon angioplasty in improving or preserving renal function, none of the trials was designed to address this issue.

There were somewhat fewer major cardiovascular and renovascular complications, but more procedural complications, in the angioplasty group. A major question facing physicians and patients is whether the benefits of angioplasty outweigh its risks. A quantitative approach that takes into account patients' preferences is one way to explore this question (19).

Most atherosclerotic lesions are now treated initially by angioplasty with balloon-expandable stent placement. This procedural shift is based on observational studies suggesting that stenting may be superior technically and comparable clinically to balloon angioplasty (20,21). A randomized trial of treating ostial atherosclerotic renal artery stenosis confirmed these findings (6). In that trial, stenting resulted in a lower acute restenosis rate and higher long-term patency rate than did angioplasty alone. The changes in blood pressure and renal function, however, were similar in the two groups at 6 months (Table 4). Surgical revascularization led to a higher patency rate than balloon angioplasty in another trial (5), but this technical success did not improve clinical outcomes (Table 4). Taken together, these findings suggest that in addition to stenotic lesions, the degree of preexisting renal damage is a major determinant of the clinical response to treatment.

The randomized controlled trials included in this meta-analysis had important methodologic shortcomings, including the failure to mention allocation concealment (13,14) or to undertake blinded outcome assessments (12). Although some might consider these limitations serious enough to threaten internal validity (15,22), the consistency of the blood pressure results between randomized trials and observational studies (7) suggests that the outcomes were not distorted systematically.

The need to impute the standard deviations of the mean difference in blood pressure in the SNRASC trial and to calculate these values indirectly in the DRASTIC trial decreases the precision of our estimates. This emphasizes the importance of reporting clinical study information in sufficient detail to enable investigators to obtain precise estimates of treatment effects when pooling data. We chose a conservative approach in imputing the missing standard deviations to avoid overestimating the effect of balloon angioplasty on blood pressure.

**Table 4.** Randomized Controlled Trials Comparing Balloon Angioplasty with Stenting or Surgery

Comparison (Reference)	Follow-up (Months)	Hypertension Cured		Hypertension Cured or Improved		Renal Function Unchanged or Improved		Patency Rate*	Procedural Complications
		Cured	Cured	Cured or Improved	Cured or Improved	Unchanged or Improved	Unchanged or Improved		
Number (%): Stenting or Surgery vs. Angioplasty									
Stenting (n = 40 patients) vs. balloon angioplasty (n = 41 patients) (6)	6	6 (15) vs. 2 (5)	23 (58) vs. 20 (49)	21/29 (72) vs. 16/22 (73) <sup>†</sup>	30 (75) vs. 12 (29)	21 (50) vs. 18 (43)			
Surgery (n = 28 patients) vs. balloon angioplasty (n = 24 patients) <sup>‡</sup> (5)	24	5 (18) vs. 3 (13)	26 (93) vs. 20 (83)	21 (75) vs. 23 (96)	27 (96) vs. 18 (75)	9 (32) vs. 5 (21)			

\* Defined as stenosis <50

<sup>†</sup> Among patients with impaired renal function at baseline only.

<sup>‡</sup> Includes patients with a technically successful result from intervention only.

In summary, balloon angioplasty was significantly more effective than medical therapy in lowering the blood pressure of hypertensive patients with atherosclerotic renal artery stenosis, and resulted in the use of less antihypertensive medication and perhaps fewer major cardiovascular and renovascular complications. Although it also produced a higher patency rate, this technical success did not improve renal function. Based on clinical trial evidence, balloon angioplasty should be considered for patients with moderate-to-severe atherosclerotic renal artery stenosis and poorly controlled hypertension.

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