

ORIGINAL ARTICLE

Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators*

ABSTRACT

BACKGROUND

Percutaneous revascularization of the renal arteries improves patency in atherosclerotic renovascular disease, yet evidence of a clinical benefit is limited.

METHODS

In a randomized, unblinded trial, we assigned 806 patients with atherosclerotic renovascular disease either to undergo revascularization in addition to receiving medical therapy or to receive medical therapy alone. The primary outcome was renal function, as measured by the reciprocal of the serum creatinine level (a measure that has a linear relationship with creatinine clearance). Secondary outcomes were blood pressure, the time to renal and major cardiovascular events, and mortality. The median follow-up was 34 months.

RESULTS

During a 5-year period, the rate of progression of renal impairment (as shown by the slope of the reciprocal of the serum creatinine level) was -0.07×10^{-3} liters per micromole per year in the revascularization group, as compared with -0.13×10^{-3} liters per micromole per year in the medical-therapy group, a difference favoring revascularization of 0.06×10^{-3} liters per micromole per year (95% confidence interval [CI], -0.002 to 0.13 ; $P=0.06$). Over the same time, the mean serum creatinine level was $1.6 \mu\text{mol}$ per liter (95% CI, -8.4 to 5.2 [0.02 mg per deciliter; 95% CI, -0.10 to 0.06]) lower in the revascularization group than in the medical-therapy group. There was no significant between-group difference in systolic blood pressure; the decrease in diastolic blood pressure was smaller in the revascularization group than in the medical-therapy group. The two study groups had similar rates of renal events (hazard ratio in the revascularization group, 0.97; 95% CI, 0.67 to 1.40; $P=0.88$), major cardiovascular events (hazard ratio, 0.94; 95% CI, 0.75 to 1.19; $P=0.61$), and death (hazard ratio, 0.90; 95% CI, 0.69 to 1.18; $P=0.46$). Serious complications associated with revascularization occurred in 23 patients, including 2 deaths and 3 amputations of toes or limbs.

CONCLUSIONS

We found substantial risks but no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease. (Current Controlled Trials number, ISRCTN59586944.)

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N Engl J Med 2009;361:1953-62.

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ATHEROSCLEROTIC RENOVASCULAR DISEASE is a common condition with a rate of death of about 16% per year, largely from associated cardiovascular disease.¹⁻³ Stenosis of the renal artery is associated with both hypertension and chronic kidney disease, although it is not clear whether these associations are causal.⁴ Treatment has traditionally focused on correcting renal-artery stenosis, with endovascular revascularization having gradually replaced open surgical techniques.

Three small, randomized, controlled trials showed no significant benefits of angioplasty over medical therapy,⁵⁻⁷ but these studies were underpowered, even when their results were combined,⁸ to detect possible moderate but clinically worthwhile improvements in renal function or blood pressure or a reduction in mortality. The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial was designed to determine reliably whether revascularization together with medical therapy improves renal function and other outcomes, as compared with medical therapy alone, in patients with atherosclerotic renal-artery stenosis.

METHODS

STUDY DESIGN

This multicenter, randomized, unblinded clinical trial was designed and conducted by the members of the ASTRAL writing committee and the University of Birmingham Clinical Trials Unit and was supported by the Medical Research Council U.K., Kidney Research U.K., and Medtronic. The trial was approved by the West Midlands United Kingdom Multicenter Research Ethics Committee and the ethics committee at each participating study center. Members of the writing committee assume responsibility for the accuracy and completeness of the data and for the overall content and integrity of the article. Medtronic had no role in the design of the study or in the collection, analysis, and interpretation of the data or the writing of this report.

PATIENTS

Patients were screened for enrollment in the study if clinical findings (e.g., uncontrolled or refractory hypertension or unexplained renal dysfunction) suggested a diagnosis of atherosclerotic renovascular disease. Patients with such findings

underwent renal-artery imaging (with the use of intraarterial, computed tomographic, or magnetic resonance angiography), renal ultrasonography, and other relevant laboratory and clinical assessments.

Patients were eligible to participate if they had substantial anatomical atherosclerotic stenosis in at least one renal artery that was considered potentially suitable for endovascular revascularization and if the patient's doctor was uncertain that the patient would definitely have a worthwhile clinical benefit from revascularization, taking into account the available evidence. Patients were not eligible if they required surgical revascularization or were considered to have a high likelihood of requiring revascularization within 6 months, if they had nonatheromatous cardiovascular disease, or if they had undergone previous revascularization for renal-artery stenosis. All patients provided written informed consent.

RANDOMIZATION

Patients were randomly assigned either to undergo revascularization in addition to receiving medical therapy or to receive medical therapy alone, in a 1:1 ratio with the use of a computerized minimized-randomization procedure. Randomization was stratified according to the serum creatinine level, estimated glomerular filtration rate (as calculated by the Cockcroft-Gault method⁹), severity of renal-artery stenosis, kidney length on renal ultrasonography, and rate of progression of renal impairment in the previous year (with rapid progression defined as an increase in the serum creatinine level of more than 20% or of more than 100 μmol per liter [1.13 mg per deciliter]). Randomization was determined by means of a telephone call to the central trial office or through an online randomization system.

TREATMENT AND FOLLOW-UP

For patients who were assigned to undergo revascularization, the procedure was performed as soon as possible after randomization (ideally, within 4 weeks). The precise revascularization procedure (angioplasty either alone or with stenting) was determined by local practitioners, and renal protection devices were not used.¹⁰ Patients in both study groups received medical therapy, according to local protocols. This therapy typically consisted of statins, antiplatelet agents, and optimal blood-pressure control. Follow-up visits

were scheduled 1 to 3 months, 6 to 8 months, and 1 year after randomization and then annually for 5 years. An independent data and safety monitoring committee reviewed efficacy and safety data every 12 months.

OUTCOME MEASURES

The primary outcome was the change in renal function, which was assessed by measuring the mean slope of the reciprocal of the serum creatinine level over time. This measure was used because it has a linear relationship with creatinine clearance (a surrogate for the glomerular filtration rate), unlike the serum creatinine level, which has a curvilinear relationship. Analyses of absolute serum creatinine levels were also performed. Secondary outcomes included blood pressure, the time to the first renal event, the time to the first major cardiovascular event, and mortality. Renal events were defined as a new onset of acute kidney injury, the initiation of dialysis, renal transplantation, nephrectomy, or death from renal failure. Major cardiovascular events were defined as myocardial infarction, stroke, death from cardiovascular causes, hospitalization for angina, fluid overload or cardiac failure, coronary-artery revascularization, or another peripheral arterial procedure. Treatment complications and serious adverse events were also reported and reviewed by a safety committee.

STATISTICAL ANALYSIS

The trial was designed to detect a reduction of 20% in the mean slope of the reciprocal of the serum creatinine level. Assuming that there would be a mean slope of -1.6×10^{-3} liters per micromole per year (with a standard deviation of 1.5)¹¹ in the medical-therapy group, we determined that achieving a mean slope of -1.28×10^{-3} liters per micromole per year in the revascularization group would require the enrollment of 700 patients, with a power of 80% and a two-tailed P value of 0.05. Target recruitment was initially set at 1000 patients to allow for the crossover of patients from the medical-therapy group to undergo revascularization and for the loss of patients to follow-up. This number was subsequently reduced to a minimum of 750 patients because crossover rates were lower than anticipated. Recruitment continued beyond 750 patients to increase the number of patients in a substudy of cardiac structure and function.¹²

All analyses were performed according to the intention-to-treat principle with the use of all available data through the maximum follow-up of 5 years. For continuous variables, the pattern of change over time was evaluated with the use of repeated-measures analysis,¹³ with differences in slope assessed by testing the significance of a treatment-by-time interaction. If there was no significant treatment-by-time interaction, then a model without the interaction term was fitted to obtain an average treatment difference, with the 95% confidence interval, over time. Between-group differences at each assessment were also compared with the use of t-tests. For time-to-event data, Kaplan–Meier curves were constructed and compared between the groups with the use of the log-rank test, with a hazard ratio of less than 1.0 indicating a benefit of revascularization. All reported P values are two-tailed. All analyses were performed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

PATIENTS

From September 2000 through October 2007, a total of 806 patients were enrolled (403 in each study group) at 57 hospitals (53 in the United Kingdom, 3 in Australia, and 1 in New Zealand). The majority of patients had severe renal-artery stenosis (59% had stenosis of more than 70%) or clinically significant renal impairment (60% had a serum creatinine level of 150 μ mol per liter [1.7 mg per deciliter] or more) or both (Table 1). As of November 1, 2008 (when the database was locked for analysis), the median follow-up was 33.6 months; 38 patients (5%) had withdrawn or been lost to follow-up (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

REVASCULARIZATION

In the revascularization group, the procedure was attempted in 335 of the 403 patients (83%), with the procedure deemed to be a technical success in 317 of the 335 patients (95%). The median time to revascularization was 32 days (range, 0 to 520; interquartile range, 18 to 54) (Fig. 1 in the Supplementary Appendix). The majority of patients who underwent revascularization (95%) received a stent. In the medical-therapy group, 24 patients (6%) crossed over to undergo revascular-

ization after a median of 601 days (range, 7 to 1992; interquartile range, 333 to 1115).

MEDICAL THERAPY

One year after enrollment, the proportions of patients receiving antihypertensive, antiplatelet, and cholesterol-lowering medications were similar to those reported at baseline (Table 1 in the Supple-

mentary Appendix). The average number of anti-hypertensive agents at 1 year was slightly higher for patients in the medical-therapy group (2.97) than in the revascularization group (2.77, $P=0.03$). At baseline, slightly more patients in the revascularization group were receiving renin-angiotensin blockers (47% vs. 38%, $P=0.02$); this difference was maintained at 1 year (50% vs. 43%, $P=0.05$).

Table 1. Baseline Characteristics of the Patients.*

Variable	Revascularization (N=403)	Medical Therapy (N=403)	P Value
Demographic			
Mean age (range) — yr	70 (42–86)	71 (43–88)	0.75
Male sex — no. (%)	254 (63)	253 (63)	0.94
Clinical			
Smoking status — no./total no. (%)			
Current smoker	77/387 (20)	85/391 (22)	0.53
Former smoker	199/387 (51)	216/391 (55)	0.29
Coexisting conditions — no./total no. (%)			
Diabetes	121/387 (31)	115/391 (29)	0.57
Coronary heart disease	192/387 (50)	189/391 (48)	0.22
Peripheral vascular disease	158/387 (41)	157/391 (40)	0.79
Stroke	69/387 (18)	75/391 (19)	0.42
Need for dialysis	0	1/391 (<1)	0.81
Renal function			
Serum creatinine			
Mean (range) — $\mu\text{mol/liter}$	179 (66–551)	178 (64–750)	0.85
Level — no. (%)			
<150 $\mu\text{mol/liter}$	163 (40)	162 (40)	0.99
150–300 $\mu\text{mol/liter}$	212 (53)	212 (53)	
>300 $\mu\text{mol/liter}$	28 (7)	29 (7)	
Rapid increase [†]	48 (12)	49 (12)	0.91
Estimated glomerular filtration rate			
Mean (range) — ml/min	40.3 (5.4–124.5)	39.8 (7.1–121.7)	0.66
Level — no. (%)			
<25 ml/min	89 (22)	89 (22)	1.00
25–50 ml/min	213 (53)	213 (53)	
>50 ml/min	101 (25)	101 (25)	
Urinary protein			
Mean (range) — g/day [‡]	0.55 (0–4.77)	0.72 (0–7.7)	0.18
Related laboratory measures			
Mean blood pressure (range) — mm Hg			
Systolic	149 (87–270)	152 (90–241)	0.07
Diastolic	76 (45–120)	76 (46–130)	0.63
Mean total cholesterol (range) — mmol/liter [§]	4.7 (0.1–14.8)	4.7 (1.9–9.6)	0.79

Table 1. (Continued.)

Variable	Revascularization (N=403)	Medical Therapy (N=403)	P Value
Renal physiology			
Stenosis¶			
Mean (range) — %	76 (40–100)‖	75 (20–99)	0.29
Severity — no. (%)			
<50%	2 (<1)	4 (1)	0.68
50–70%	159 (39)	164 (41)	
>70%	242 (60)	235 (58)	
Mean length of kidney (range) — cm	9.7 (6–14)	9.8 (6–20)**	0.44
Use of concomitant medication			
Antihypertensive drug — no./total no. (%)			
Any	373/384 (97)	383/388 (99)	0.12
Diuretic	261/373 (70)	257/383 (67)	0.40
Calcium-channel blocker	227/373 (61)	259/383 (68)	0.05
Beta-blocker	172/373 (46)	200/383 (52)	0.09
ACE inhibitor or ARB	174/373 (47)	146/383 (38)	0.02
Alpha-blocker	147/373 (39)	141/383 (37)	0.46
Mean no. of antihypertensive drugs in class (range)	2.79 (1–6)	2.80 (1–6)	0.86
Antiplatelet drug — no./total no. (%)			
Any	289/381 (76)	298/383 (78)	0.52
Aspirin	263/289 (91)	277/298 (93)	0.38
Cholesterol-lowering drug — no./total no. (%)			
Any	304/381 (80)	312/389 (80)	0.89
Statin	293/304 (96)	296/312 (95)	0.36
Warfarin — no./total no. (%)	42/380 (11)	42/385 (11)	0.95

* ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586.

† A rapid increase in the serum creatinine level was defined as an increase of more than 100 μmol per liter (1.13 mg per deciliter) or of more than 20% during a 1-year period.

‡ Data regarding urinary protein were not routinely collected at all centers and thus are provided for only 136 patients in the revascularization group and 148 patients in the medical-therapy group.

§ Data regarding cholesterol were not routinely collected at all centers and thus are provided for only 363 patients in the revascularization group and 375 patients in the medical-therapy group.

¶ Data are presented for the more affected kidney for which a surgical plan was provided at the time of randomization.

‖ One patient who underwent randomization had a known occlusion.

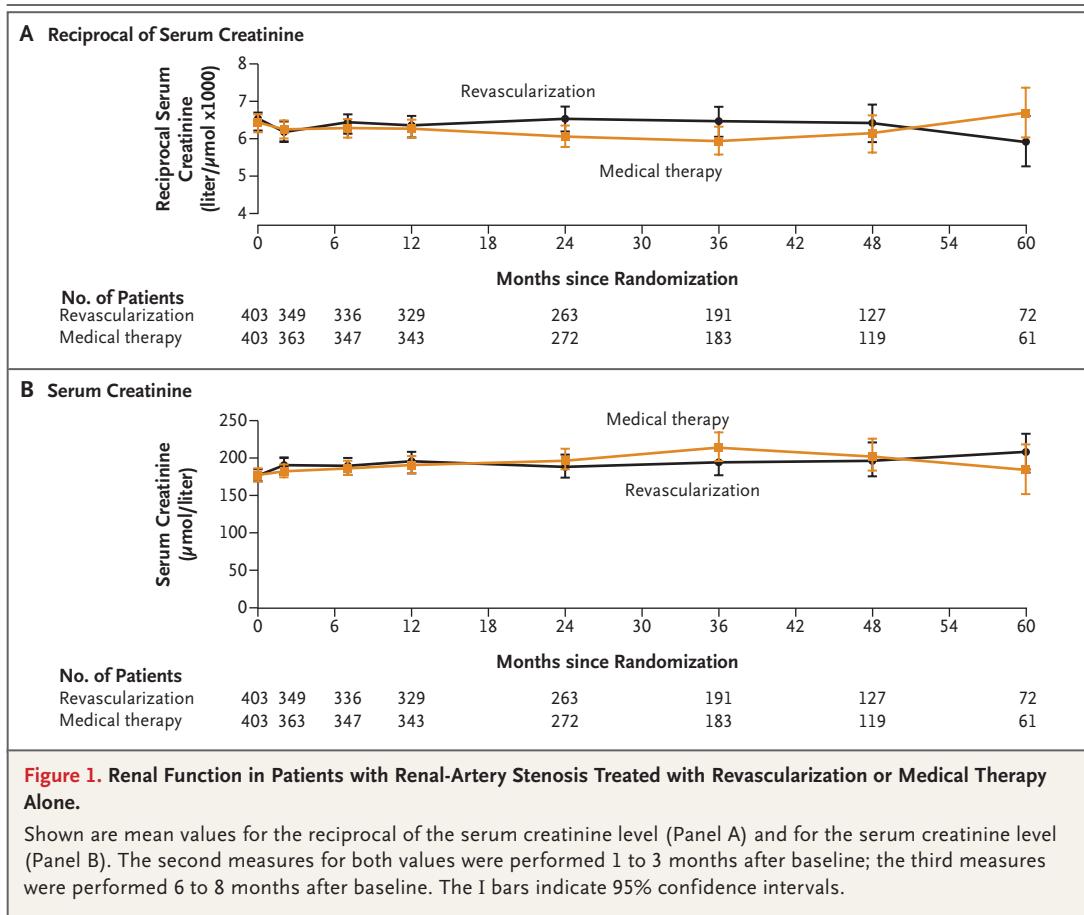
** Two patients had kidney enlargement (length, 16 cm and 20 cm) that was caused by polycystic kidney disease.

RENAL FUNCTION

During the 5-year study period, the overall mean slope of the reciprocal of the serum creatinine concentration was -0.07×10^{-3} liters per micromole per year in the revascularization group, as compared with -0.13×10^{-3} liters per micromole per year in the medical-therapy group, a difference of 0.06×10^{-3} liters per micromole per year (95% confidence interval [CI], -0.002 to 0.13) favoring re-

vascularization ($P=0.06$) (Fig. 1A, and Table 2 in the Supplementary Appendix). During 5 years of follow-up, the mean reciprocal of the creatinine level (the model without the interaction term) was 0.09×10^{-3} liters per micromole (95% CI, -0.02 to 0.20 ; $P=0.10$) higher in the revascularization group than in the medical-therapy group.

During the same period, the mean serum creatinine level was $1.6 \mu\text{mol}$ per liter (95% CI,



–8.4 to 5.2 [0.02 mg per deciliter; 95% CI, –0.10 to 0.06]) lower in the revascularization group than in the medical-therapy group (P=0.64) (Fig. 1B, and Table 2 in the Supplementary Appendix). The proportions of patients with different degrees of improvement or deterioration of renal function at 12 months were similar in the two groups (Fig. 2 in the Supplementary Appendix). In a per-protocol analysis, there was no significant difference in the primary outcome between the 317 patients who underwent successful revascularization and the 379 patients who received medical therapy only (Fig. 3 in the Supplementary Appendix).

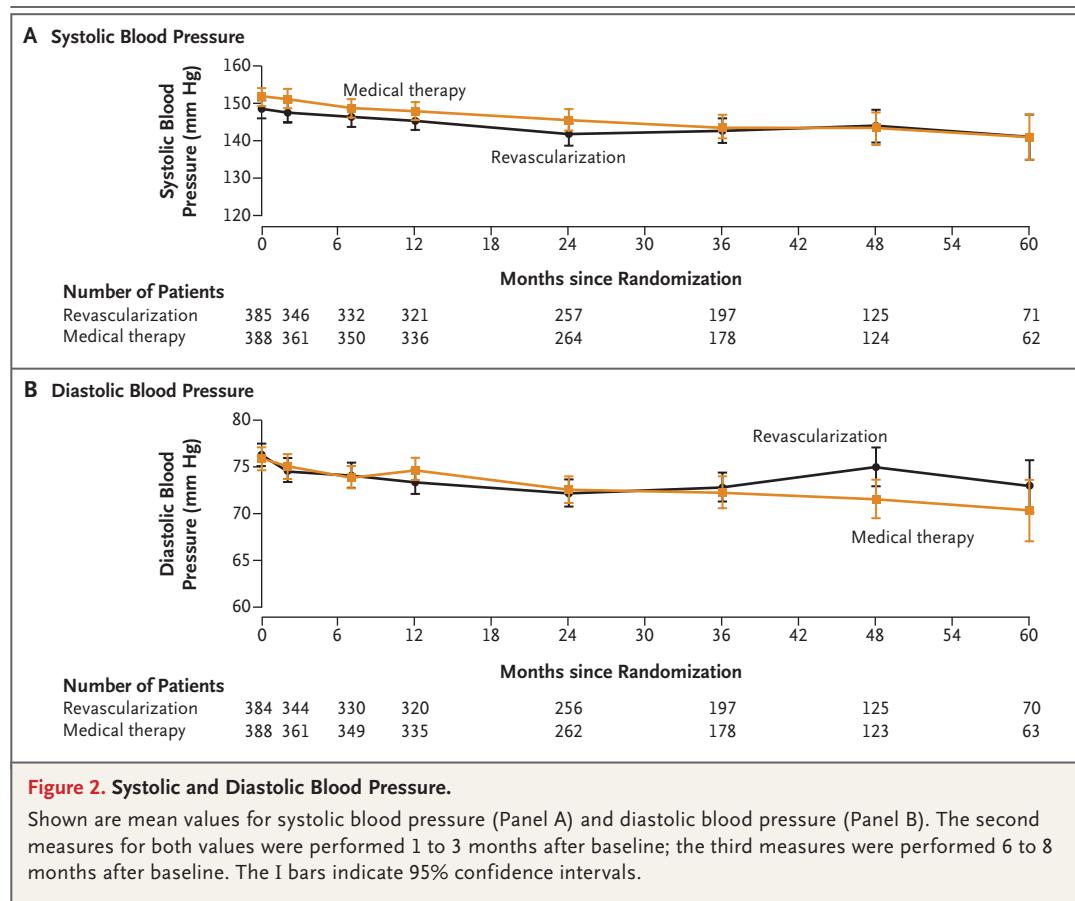
SUBGROUP ANALYSES

There were no significant differences in the primary outcome in any of the protocol-specified subgroups, which were defined according to the serum creatinine level, estimated glomerular filtration rate, severity of renal-artery stenosis, kid-

ney length, and previous rate of progression of renal impairment. In a post hoc subgroup analysis, we also found no significant difference in the primary outcome between the 163 patients with severe anatomical disease (103 patients with bilateral renal-artery stenosis of more than 70% and 60 patients with renal-artery stenosis of more than 70% in a single functioning kidney) and patients without such severe anatomical disease (P=0.23) (Fig. 4 in the Supplementary Appendix).

BLOOD PRESSURE

During the 5-year study period, systolic blood pressure decreased in the two study groups, with no significant difference between the groups (Fig. 2A, and Table 2 in the Supplementary Appendix). The slopes for systolic blood pressure diverged at a rate of 0.27 mm Hg per year (95% CI, –0.83 to 1.38; P=0.63). During 5 years of follow-up, the mean systolic blood pressure (the mod-



el without the interaction term) was 1.6 mm Hg (95% CI, -3.21 to 0.08; $P=0.06$) lower in the revascularization group than in the medical-therapy group. The mean diastolic blood pressure also decreased in both study groups, but conversely, the reduction was greater in the medical-therapy group. The slopes for diastolic blood pressure diverged at a rate of 0.61 mm Hg per year (95% CI, 0.07 to 1.16; $P=0.03$) (Fig. 2B, and Table 2 in the Supplementary Appendix).

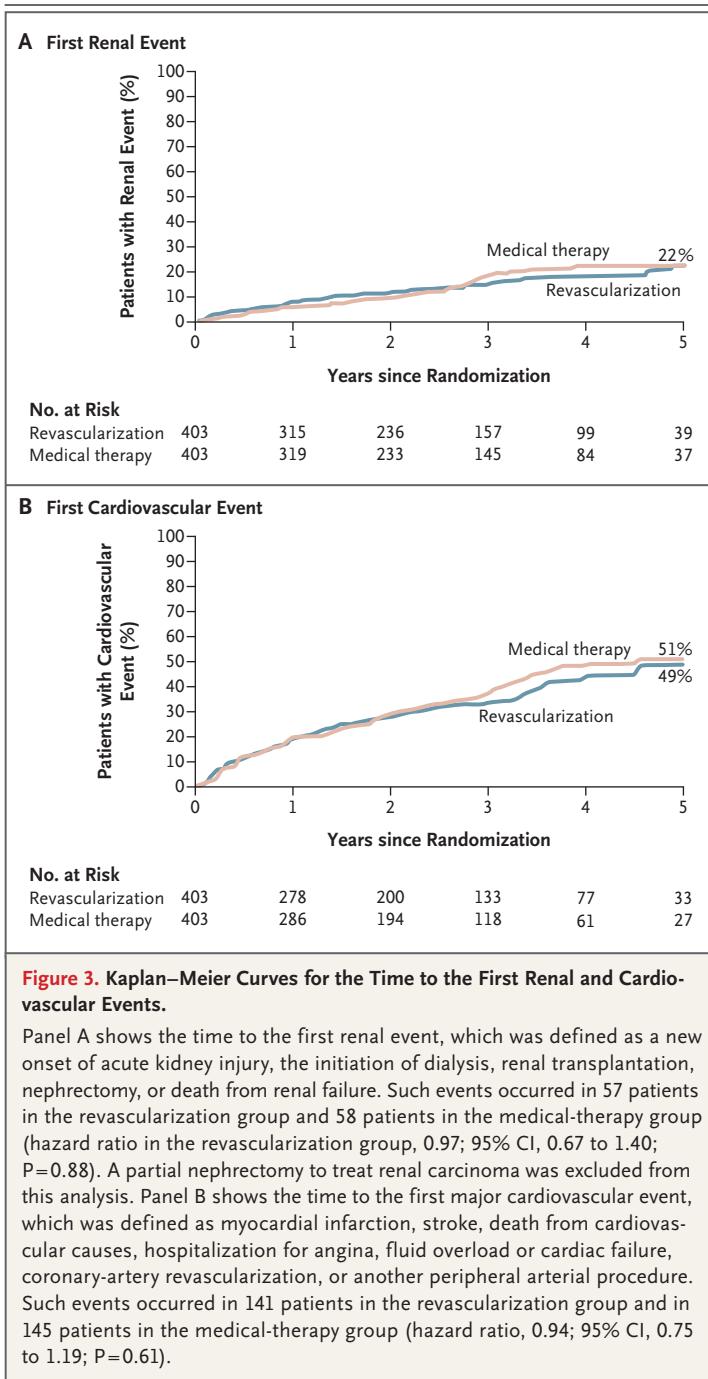
RENAL AND CARDIOVASCULAR EVENTS AND MORTALITY

Among patients who underwent at least one follow-up assessment, 73 renal events occurred in 57 patients in the revascularization group, as compared with 80 events in 58 patients in the medical-therapy group ($P=0.97$) (Table 3 in the Supplementary Appendix). The time to a first renal event did not differ significantly between the two groups (hazard ratio in the revascularization group, 0.97; 95% CI, 0.67 to 1.40; $P=0.88$) (Fig. 3A). Acute kid-

ney injury occurred in 25 of 383 patients (7%) in the revascularization group and in 23 of 392 patients (6%) in the medical-therapy group, and end-stage renal disease developed in 30 patients (8%) in the revascularization group and in 31 patients (8%) in the medical-therapy group.

A total of 238 cardiovascular events were reported in 141 patients in the revascularization group, as compared with 244 events in 145 patients in the medical-therapy group ($P=0.96$) (Table 3 in the Supplementary Appendix). Cardiovascular events occurred at similar rates in the two groups (hazard ratio in the revascularization group, 0.94; 95% CI: 0.75 to 1.19; $P=0.61$) (Fig. 3B).

There was no significant between-group difference in overall survival (hazard ratio in the revascularization group, 0.90; 95% CI, 0.69 to 1.18; $P=0.46$), with 103 deaths in the revascularization group and 106 deaths in the medical-therapy group (Fig. 4, and Table 3 in the Supplementary Appendix).



COMPLICATIONS OF REVASCULARIZATION

A total of 38 periprocedural complications (defined as complications occurring within 24 hours after the procedure) were reported in 31 of the 359 patients (9%) who underwent revascularization (including 1 of the 24 patients in the medical-therapy group who crossed over to revascular-

ization) (Table 4 in the Supplementary Appendix). Nineteen of these events (in 17 patients) were considered to be serious complications, including pulmonary edema in one patient and myocardial infarction in another. In addition, there were five renal embolizations, four renal arterial occlusions, four renal-artery perforations, one femoral-artery aneurysm, and three cases of cholesterol embolism leading to peripheral gangrene and amputation of toes or limbs.

Of the 280 patients in the revascularization group for whom data regarding adverse events were available at 1 month, 55 (20%) had an adverse event between 24 hours and 1 month after the procedure (data were missing for 55 of 335 patients). Of these events, 12 (in 11 patients) were considered to be serious: 2 deaths (both from cardiac causes), 4 cases of groin hematoma or hemorrhage requiring hospitalization, 5 cases of clinically significant acute kidney injury, and 1 renal-artery occlusion (Table 4 in the Supplementary Appendix). Thus, in total, 31 serious complications of revascularization occurred in 23 patients.

DISCUSSION

We found no evidence of a worthwhile clinical benefit in the initial years after revascularization in patients with atherosclerotic renal-artery stenosis. The upper confidence limits for a benefit from revascularization with respect to renal function were below levels that would be considered clinically relevant. No significant improvements in blood pressure or reductions in renal or cardiovascular events or mortality were seen.

A meta-analysis of three previous randomized, controlled trials⁵⁻⁷ suggested that the benefits of angioplasty, as compared with medical management, were at best limited to a slight improvement in blood-pressure control, as manifested by a reduced need for antihypertensive drugs.⁸ These trials had limitations, since they were small (totaling 210 patients); in addition, for most patients undergoing revascularization, only balloon angioplasty was performed, and the crossover rate from the medical-therapy group to the revascularization group was high, averaging 29%.

In contrast to the available data from randomized clinical trials, nonrandomized studies^{14,15} have suggested that revascularization results in improvement in renal function in approximately

25% of patients with atherosclerotic renovascular disease. However, the potential biases in such studies are well known.¹⁶ Indeed, in our study, at 1 year, 27% of patients in the medical-therapy group had an improvement of more than 10 μmol per liter (0.11 mg per deciliter) in the serum creatinine level, which shows how benefits that could erroneously be ascribed to revascularization in an uncontrolled study may actually be due to chance fluctuations or effective medical therapy.

Data from studies in the United States have indicated that revascularization is performed in 16% of patients with newly diagnosed atherosclerotic renovascular disease.¹ Since endovascular interventions are associated with substantial morbidity,¹⁷ inconvenience, and cost, with little apparent benefit, the widespread use of such procedures outside of clinical trials can now be questioned. A related implication is that there seems to be little value in screening asymptomatic patients who have atherosclerosis and chronic renal disease or hypertension for evidence of renovascular disease.

An important limitation of our trial concerns the population that we studied. As noted, patients were enrolled in the trial only if their own physician was uncertain as to whether revascularization would provide a worthwhile clinical benefit. The principle of equipoise requires such uncertainty for the ethical conduct of the trial. However, this enrollment criterion leaves unresolved the question of whether some patients with renovascular disease who did not meet the eligibility criteria might have benefited from revascularization. There is a consensus, which is not evidence-based, that certain groups of patients with severe renal-artery stenosis (e.g., those presenting with acute kidney injury¹⁸ or “flash” pulmonary edema¹⁹) should be treated with revascularization, and such patients were unlikely to have been included in our trial. The trial population was nonetheless intended to be representative of patients undergoing revascularization in clinical practice.

It is noteworthy that the rate of progression of renal impairment in the medical-therapy group (mean slope in the reciprocal of the serum creatinine level, -0.13×10^{-3} liters per micromole per year) was lower by a factor of 10 than that anticipated on the basis of a previous trial¹¹ (in which the corresponding value was -1.6×10^{-3} liters per

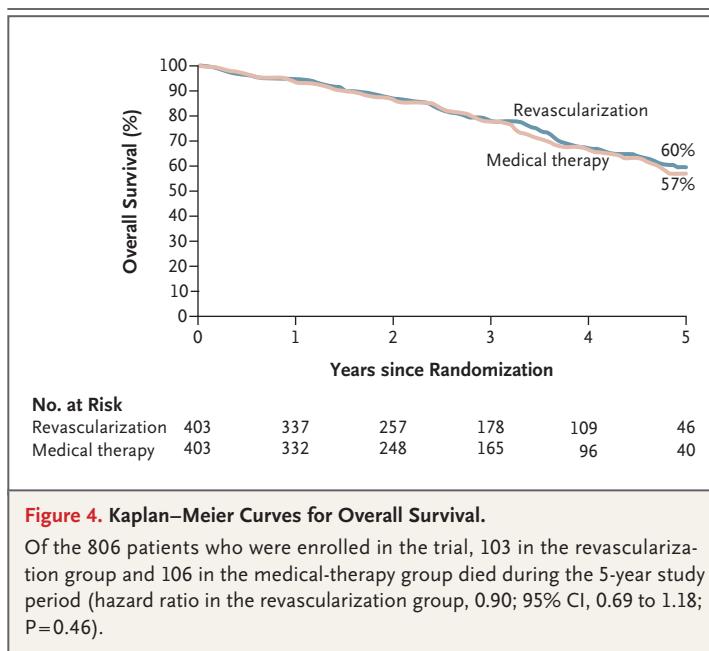


Figure 4. Kaplan–Meier Curves for Overall Survival.

Of the 806 patients who were enrolled in the trial, 103 in the revascularization group and 106 in the medical-therapy group died during the 5-year study period (hazard ratio in the revascularization group, 0.90; 95% CI, 0.69 to 1.18; $P=0.46$).

micromole per year). This finding suggests that the actual enrolled population may have had less rapid loss of renal function than anticipated in the study design. However, since the patients had severe renovascular disease (as shown by their baseline characteristics and the high rate of renal events), the use of more effective antihypertensive and renal protective medical therapies may explain why the patients' renal function deteriorated more slowly than that in similar patients in past studies.

To investigate the issue of patient selection further, we reviewed data on all 508 patients with atherosclerotic renovascular disease who presented to the study center that recruited the largest number of patients. Of 283 patients with renal-artery stenosis of more than 60%, 71 underwent randomization, 24 underwent revascularization outside the trial, and 188 received medical treatment only. Reasons for revascularization outside the trial included poorly controlled hypertension, rapidly declining renal function, and participation in another study. Principal reasons for not undergoing revascularization were a decision by the patient, advanced age, and the presence of coexisting medical conditions. Although this is not a systematic analysis, it provides a possible context for understanding the spectrum of patients to whom the findings of this trial may appropriately apply.

The overall results of a large trial may disguise a worthwhile clinical benefit in smaller subpopulations of patients. However, we found no evidence that the effect of revascularization differed among patients with varying degrees of renal disease, with the serum creatinine level, estimated glomerular filtration rate, severity of stenosis, and renal length used as variables. An important post hoc subgroup analysis of patients for whom many clinicians currently advocate revascularization (those with either bilateral renal-artery stenosis of more than 70% or renal-artery stenosis of more than 70% in a single functioning kidney) also showed no significant difference in outcome between patients with severe renal-artery stenosis and those without such severe disease.

In summary, we compared endovascular revascularization plus medical therapy with medical therapy alone in patients with atherosclerotic renovascular disease. Revascularization carried

substantial risk but was not associated with any benefit with respect to renal function, blood pressure, renal or cardiovascular events, or mortality.

Supported by research grants from Medical Research Council U.K., Kidney Research U.K., and Medtronic. The University of Birmingham Clinical Trials Unit also receives core support from the U.K. Department of Health.

Dr. Wheatley reports receiving consulting fees from Glaxo-SmithKline and grant support from Medtronic; Ms. Ives, grant support from Novartis; Mr. Gray, grant support from Genomic Health and Medtronic; Dr. Kalra, fees for serving on advisory boards for Genzyme, Novartis, Shire, and Takeda, lecture fees from Bristol-Myers Squibb, Daiichi-Sankyo, Genzyme, Merck, Novartis, Pfizer, Roche, and Schering-Plough, and departmental educational grants from Amgen, OrthoBiotech, and Roche; Dr. Baigent, grant support from Merck; Dr. Carr, educational grants from Amgen, Boehringer Ingelheim, and OrthoBiotech; Dr. Chalmers, consulting fees from Medtronic and advisory board fees and grant support from Cordis; Dr. Lipkin, lecture fees from Roche and Wyeth; and Dr. Scoble, consulting fees from Astellas. No other potential conflict of interest relevant to this article was reported.

We thank all the patients who participated in this study to help improve the evidence on the treatment of atherosclerotic renovascular disease.

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