

Carotid Endarterectomy Benefits Patients with CKD and Symptomatic High-Grade Stenosis

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ABSTRACT

Endarterectomy is generally recommended for symptomatic high-grade (70 to 99%) stenosis of the internal carotid artery, but whether this procedure is beneficial among patients with chronic kidney disease (CKD) is unknown. In this re-analysis of data from the North American Symptomatic Carotid Endarterectomy Trial, we included patients with symptomatic stenosis and either stage 3 CKD ($n = 524$) or preserved kidney function ($n = 966$; estimated GFR ≥ 60). For medically treated patients with high-grade stenosis, risk for ipsilateral stroke at 2 yr was significantly higher in patients with CKD than in those with preserved renal function (31.6 versus 19.3%; $P = 0.042$); carotid endarterectomy significantly reduced this risk by 82 and 51%, respectively. To prevent one ipsilateral stroke, the number needed to treat by endarterectomy was four for patients with CKD and 10 for patients with preserved renal function. Compared with patients with preserved renal function, those with CKD had similar rates of perioperative stroke and death but higher rates of cardiac events. In conclusion, patients with stage 3 CKD and symptomatic high-grade carotid stenosis gain a large benefit in stroke risk reduction after endarterectomy.

J Am Soc Nephrol 21: 145–152, 2010. doi: 10.1681/ASN.2009030287

Approximately 795,000 people in North America have a stroke every year, 185,000 of whom have recurrent strokes.¹ As a secondary prevention strategy, current practice guidelines recommend carotid endarterectomy for patients with symptomatic high grade (70 to 99%) carotid stenosis.² Endarterectomy is also offered to patients with moderate-grade (50 to 69%) stenosis, after considering factors such as age, gender, comorbidities, and severity of recent symptoms.²

It is estimated that >15 million Americans have chronic kidney disease (CKD), and the prevalence is increasing.³ Patients with CKD are at high risk for cardiovascular^{4–6} and cerebrovascular disease, including stroke^{7,8}; however, patients with CKD are less likely than others to undergo invasive proce-

dures to reduce this risk,⁹ a phenomenon sometimes called “renalism.”¹⁰ Although patients with CKD are prone to adverse events from procedures and treatments,^{11,12} in some situations patients with CKD derive larger absolute benefits than others because of their high baseline risk.^{13–16}

Received March 15, 2009. Accepted August 28, 2009.

Published online ahead of print. Publication date available at www.jasn.org.

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Little is known about the effectiveness and safety of carotid endarterectomy in patients with CKD. No randomized trial has exclusively focused on endarterectomy in the CKD population, and it remains unlikely that such a trial will ever be conducted. The next best approach is to re-analyze previously conducted trials. Three large randomized trials have examined the benefit of carotid endarterectomy, namely the Asymptomatic Carotid Atherosclerosis Study (ACAS),¹⁷ the European Carotid Surgery Trial (ECST),¹⁸ and the North American Symptomatic Carotid Endarterectomy Trial (NASCET).¹⁹ Of the three trials, only NASCET collected baseline serum creatinine for all trial participants. The aim of this study was to examine the outcomes of patients with and without CKD among those enrolled in NASCET.

RESULTS

Among the 1517 patients who had $\geq 50\%$ internal carotid artery (ICA) stenosis, 25 did not have a baseline serum creatinine recorded and two had implausible values. The remaining 1490 (98.2%) patients were analyzed in this study. Because there were no differences in baseline characteristics between patients assigned to the medical ($n = 740$) and surgical ($n = 750$) arms in both the high-grade and moderate-grade stenosis categories, the baseline characteristics are reported in aggregate (Table 1).

Patients with CKD had a mean age of 69 yr and a mean estimated GFR (eGFR) of 49 ml/min per 1.73 m² compared with 64 yr and 79 ml/min per 1.73 m² among patients without CKD. In addition to being older, patients with CKD were more likely to be female and to have a history of hypertension and myocardial infarction (Table 1).

Of the 750 patients assigned to receive endarterectomy, six did not have surgery. Among the remaining 744 patients, 98.4% had their surgery within 30 d of randomization with a median time of 2 d. Of the 740 patients assigned to the medical arm, 6.9% received endarterectomy during follow-up. The overall median patient follow-up was 2 yr. Log binomial regression was used to calculate risk ratios for treatment group, eGFR category, and the cross-product, before and after adjustment for all baseline characteristics listed in Table 1, except for race, history of congestive heart failure (CHF), and history of arrhythmia. The prevalence of the last three characteristics was too low to include without destabilizing the regression model. The corresponding magnitudes of the unadjusted and adjusted risk ratios all were within 12% of each other, supporting an absence of confounding (Supplemental Tables 1 and 2).²⁰

For medically treated patients with high-grade stenosis, the 2-yr risk for ipsilateral stroke was higher in patients with CKD than those without CKD (31.6 versus 19.3%; $P = 0.042$). With surgery, there was a statistically significant relative risk reduc-

Table 1. Comparison of baseline patient characteristics

Characteristic	eGFR <60 ($n = 524$)	eGFR ≥ 60 ($n = 966$)	P
Age			<0.001
>65 yr (%)	73.3	44.4	
mean (range)	69 (38 to 89)	64 (31 to 85)	
Female gender (%)	37.6	27.1	<0.001
Black race (%)	1.5	3.8	0.01
Qualifying (presenting) ischemic event (%)			
stroke (not TIA)	41.2	38.8	0.37
hemispheric (not retinal)	72.1	71.3	0.74
History of (%)			
TIA or stroke within past 6 mo ^a	54.8	55.7	0.73
hypertension	73.7	54.3	<0.001
diabetes	22.5	21.0	0.50
MI	24.0	18.0	0.006
CHF	3.8	2.0	0.03
arrhythmia	4.2	5.3	0.36
hyperlipidemia	35.7	34.5	0.64
intermittent claudication	17.0	13.8	0.10
Smoking within past 12 mo (%)	34.5	50.2	<0.001
Systolic BP >160 mmHg (%)	23.5	16.7	0.001
Diastolic BP >90 mmHg (%)	13.0	12.0	0.59
Glucose >7 mmol/L (>126 mg/dl) (%)	20.0	21.2	0.59
Degree of ICA stenosis 70 to 99% (%)	41.4	44.5	0.25
eGFR (ml/min per 1.73 m ² ; mean [range])	49 (19 to 60)	79 (60 to 153)	–
Serum creatinine (μ mol/L; mean [range])	127 (86 to 292)	87 (39 to 133)	–
Serum creatinine (mg/dl; mean [range])	1.5 (0.9 to 3.3)	1.0 (0.4 to 1.5)	–

Characteristics were compared using a χ^2 test. TIA, transient ischemic attack; ICA, internal carotid artery stenosis; MI, myocardial infarction.

^aIn addition to the qualifying (presenting) event.

tion of 82.3% (95% confidence interval [CI] 54.5 to 93.1%) in the 2-yr risk for ipsilateral stroke for patients with CKD and 50.8% (95% CI 12.6 to 72.3%) for patients without CKD (Table 2). The number needed to treat by surgery to prevent one ipsilateral stroke within 2 yr was four for patients with CKD and 10 for patients without CKD. The difference in prognosis of patients with and without CKD is graphically illustrated in the left upper and lower panels of Figure 1.

Among patients with moderate-grade stenosis, the 2-yr medical risk of ipsilateral stroke in patients with CKD was approximate half of those with high grade stenosis (Table 3). Among patients with moderate-grade stenosis, the effectiveness of surgery was less and not statistically significant, with less separation between the medical and surgical cumulative outcome curves (Figure 1, right). A similar pattern of results was observed for the composite outcome of any stroke, MI, or vascular death, although they were not statistically significant for patients without CKD. Although the 2-yr risk for death for both the high-grade and moderate-grade stenosis was twice as high among patients with CKD compared with those without CKD, endarterectomy had no effect in reducing overall mortality (Tables 2 and 3). In considering perioperative risk, patients with CKD did not have higher rates of perioperative stroke or death when compared with those without CKD (Table 4). Patients with CKD did, however, have a significantly higher relative risk for perioperative cardiac events (MI, CHF, or arrhythmia; Table 4) even after adjustment for cardiac-related patient characteristics (Table 5).

DISCUSSION

After a comprehensive literature search and communication with carotid endarterectomy trialists, we conclude NASCET is the first and only large randomized trial of carotid endarterectomy in which renal function was assessed in trial participants.

Our results show patients with mild to moderate CKD and symptomatic high-grade carotid stenosis have at least a similar and perhaps a larger absolute benefit in stroke reduction after endarterectomy, compared with those without CKD. The risk for perioperative death was similar between patients with and without CKD; however, rates of perioperative cardiac complications (MI, CHF, and arrhythmias) were higher. This study provides some of the best evidence for physicians and patients to help them make decisions about the appropriateness of endarterectomy.

In those with high-grade carotid stenosis, it is true the benefits of endarterectomy on the prevention of ipsilateral stroke were observed to be greater in those with CKD than in those with preserved kidney function (absolute risk difference $P = 0.018$, relative risk reduction $P = 0.052$). In several large trials, $P < 0.10$ has been interpreted as a significant test for treatment effect modification in subgroup analysis (interaction), despite increasing the chance of type I error,^{21,22} yet cautious interpretation of the interaction terms is required for the NASCET results. The seeming benefit may be in part due to chance variation in the rates of stroke at 2 yr among surgically treated patients with CKD compared with those with preserved renal function (5.6 versus 9.5% respectively; Table 2). Nonetheless, all would agree that patients with mild to moderate CKD benefit at least equally from carotid endarterectomy compared with those without CKD, with no observed increase in the risk for perioperative death or stroke.

For patients with moderate-grade ICA stenosis (50 to 69% stenosis), NASCET results originally demonstrated the 5-yr rate of any ipsilateral stroke was 15.7% among patients who were treated surgically and 22.2% among those who were treated medically (absolute risk reduction of 6.5%; $P = 0.045$). Our results did not capture this modest but significant benefit of surgery in patients with CKD and moderate-grade stenosis. This may be due to the attenuated 2-yr period of patient follow-up used in our analysis. Thus, when considering endarterectomy

Table 2. Two-year risks for outcomes by treatment and CKD status (eGFR, ml/min per 1.73 m²) in patients with high-grade internal carotid artery stenosis (70 to 99%)

Parameter	Medical Risk (%)	Surgical Risk (%)	RRR (%)	Absolute Risk Difference (%)	P	Interaction Test (P)	
	(n = 126) ^a (n = 197) ^b	(n = 91) ^a (n = 233) ^b				Risk Difference	RRR
Ipsilateral stroke ^c							
eGFR <60	31.6	5.6	82.3	26.0 (15.1 to 36.8)	<0.001	0.018	0.051
eGFR ≥60	19.3	9.5	50.8	9.8 (1.9 to 17.7)	0.047		
Death (any cause)							
eGFR <60	9.4	9.7	-3.2	-0.3 (-11.1 to 10.5)	0.94	0.83	0.78
eGFR ≥60	5.9	4.9	16.9	1.0 (-4.4 to 6.4)	0.59		
Any stroke, MI, or vascular death							
eGFR <60	40.7	17.5	57.0	23.2 (9.6 to 36.7)	0.016	0.07	0.26
eGFR ≥60	23.0	15.0	34.8	8.0 (-1.0 to 17.0)	0.13		

Medical and surgical groups were compared using a log-rank test. RRR, relative risk reduction.

^aeGFR <60 ml/min per 1.73 m².

^beGFR ≥60 ml/min per 1.73 m².

^cTo provide a more conservative estimate of the benefits of endarterectomy, the outcome "ipsilateral stroke" includes any stroke and any death within 32 d of randomization (30 d postoperatively; median time from randomization to surgery was 2 d).

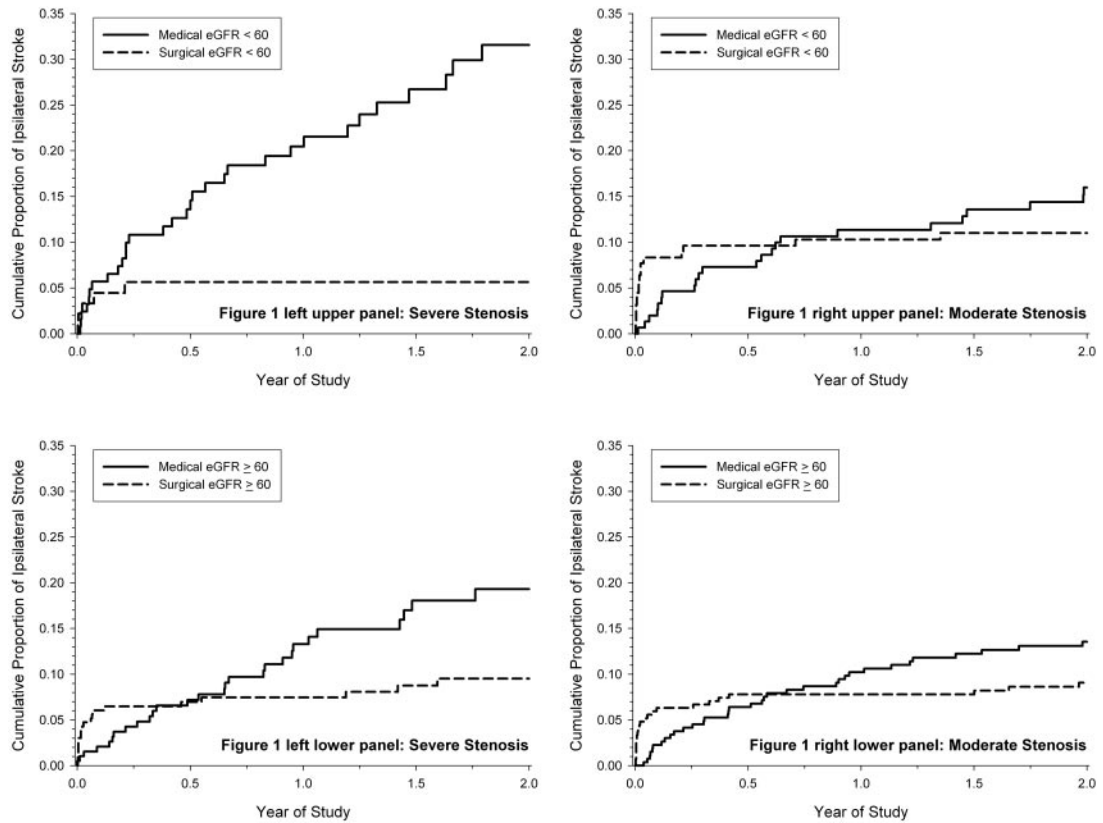


Figure 1. Cumulative proportion of ipsilateral stroke from Kaplan-Meier analyses by degree of ICA stenosis, eGFR level (ml/min per 1.73 m²), and treatment group is shown.

Table 3. Two-year risks of outcomes by treatment and CKD status (eGFR, ml/min per 1.73 m²) in patients with moderate-grade ICA stenosis (50 to 69%)

Parameter	Medical Risk (%)	Surgical Risk (%)	RRR (%)	Absolute Risk Difference (%; 95% CI)	P	Interaction Test (P)	
	(n = 151) ^a (n = 266) ^b	(n = 156) ^a (n = 270) ^b				Risk Difference	RRR
Ipsilateral stroke ^c							
eGFR <60	16.0	11.0	31.2	5.0 (−2.8 to 12.8)	0.34	0.92	0.94
eGFR ≥60	13.6	9.1	33.1	4.5 (−1.0 to 9.9)	0.15		
Death (any cause)							
eGFR <60	10.7	10.4	2.8	0.3 (−6.7 to 7.3)	0.99	0.89	0.88
eGFR ≥60	5.1	5.3	−3.9	−0.2 (−4.1 to 3.6)	0.88		
Any stroke, MI, or vascular death							
eGFR <60	29.9	19.7	34.1	10.2 (−1.3 to 18.4)	0.08	0.26	0.35
eGFR ≥60	21.5	18.2	15.3	3.3 (−2.7 to 11.1)	0.45		

Medical and surgical groups were compared using a log-rank test. RRR, Relative Risk Reduction.

^aeGFR <60 ml/min per 1.73 m².

^beGFR ≥60 ml/min per 1.73 m².

^cTo provide a more conservative estimate of the benefits of endarterectomy, the outcome “ipsilateral stroke” includes any stroke and any death within 32 d of randomization (30 d postoperatively; median time from randomization to surgery was 2 d).

ectomy in a patients with CKD and moderate-grade stenosis, physicians should consider current American Heart Association guidelines: “Recommendation for surgery should be based on clinical judgment, comorbid patient characteristics, and severity of initial cerebrovascular symptoms.”²²

Our study has several strengths. We used an intention-to-treat analysis with patient follow-up of 2 yr. Nearly all patients

in our analysis remained in their randomized arm, with minimal crossover and no loss to follow-up. We adhered to published guidelines for subgroup analysis to guard against spurious results.^{20,23,24} We prespecified the analysis including the statistical test for treatment effect modification, and we reduced false-positive results by avoiding multiple subgroup analyses. We also reported the same primary outcomes as the

Table 4. 30-Day perioperative risks of outcomes by CKD status (eGFR, ml/min per 1.73 m²) for patients assigned to carotid endarterectomy (*n* = 744)

Parameter	eGFR <60 (%; <i>n</i> = 245)	eGFR ≥60 (%; <i>n</i> = 499)	Risk Difference (%; 95% CI)	<i>P</i>
Any stroke or death	6.9	6.4	0.5 (−3.3 to 4.4)	0.79
Any nonfatal stroke	4.9	5.6	−0.7 (−4.1 to 2.7)	0.68
Death (any cause)	2.0	0.8	1.2 (−0.7 to 3.2)	0.15
MI, CHF, or arrhythmia	6.5	1.2	5.3 (2.1 to 8.6)	<0.001
MI	2.0	0.6	1.4 (−0.5 to 3.3)	0.07
CHF	1.6	0.2	1.4 (−0.2 to 3.1)	0.025
Arrhythmia	3.6	0.6	3.0 (0.6 to 5.5)	0.002

Includes patients who had moderate and severe stenoses at time of randomization and actually had surgery. Patients with and without CKD were compared using a χ^2 test.

Table 5. 30-Day perioperative unadjusted and adjusted risk ratios for patients assigned to carotid endarterectomy (*n* = 744) with CKD compared to those without CKD

Parameter	Unadjusted Risk Ratio (95% CI)	<i>P</i>	Adjusted Risk Ratio (95% CI)	<i>P</i>
Any stroke or death	1.08 (0.61 to 1.90)	0.79	1.30 (0.73 to 2.33)	0.37
Any nonfatal stroke	0.87 (0.45 to 1.69)	0.68	1.09 (0.54 to 2.20)	0.81
Death (any cause)	2.55 (0.69 to 9.40)	0.16	2.67 (0.91 to 7.84)	0.07
MI, CHF, or arrhythmia	5.43 (2.15 to 13.71)	<0.001	3.98 (1.60 to 9.90)	0.003
MI	3.39 (0.82 to 14.09)	0.09	3.14 (0.81 to 12.23)	0.10
CHF	8.14 (0.92 to 72.4)	0.06	5.82 (0.77 to 44.07)	0.09
Arrhythmia	6.11 (1.67 to 22.37)	0.006	3.99 (1.17 to 13.65)	0.027

Includes patients who had moderate and severe stenoses at time of randomization and actually had surgery. Patients with and without CKD were compared using log-binomial regression. Patients without CKD served as the referent group. Risk ratios were adjusted for age, gender, and a history of hypertension, MI, or smoking.

original trial; however, several limitations of this study merit consideration. First, serum creatinine was measured in the laboratory of each NASCET participating center and was not standardized for the application of modern eGFR estimating equations.²⁵ Given the historical nature of the study, we were also unable to attain more information about the methods and quality control measures used to assay serum creatinine in each laboratory. Although this could slightly change the number of NASCET patients with CKD, it does not alter the clinical importance of our results. Second, the NASCET trial excluded patients with a serum creatinine greater than twice the upper limit of normal. Among the 524 patients with CKD analyzed in this study, the mean eGFR was 49 ml/min per 1.73 m², with a minimum of 19 ml/min per 1.73 m². Thus, our results apply directly to patients with stage 3 CKD but cannot be generalized to patients with more severe CKD or those who have kidney failure and require dialysis. Finally, NASCET was published before the widespread use of new medical and surgical techniques for secondary stroke prevention. Only 14% of patients were receiving lipid-lowering therapy at time of enrollment, and aspirin was the only recommended antiplatelet agent. Current guidelines for secondary stroke prevention include stringent control of BP and lipids and antiplatelet therapy with clopidogrel or extended-release dipyridole and aspirin.² Compared with risks reported in NASCET, improved medical care has certainly reduced the risk for stroke irrespective of the receipt of endarterectomy.

CKD often coexists with older age, hypertension, and a his-

tory of atherosclerotic disease (Table 1). Each of these conditions is an important risk factor for arterial vascular disease; however, a greater benefit of endarterectomy for high-grade carotid stenosis in patients with CKD was observed even after accounting for baseline differences to those without CKD. Our rationale for studying the subgroup of patients with CKD was to establish the effectiveness and safety of endarterectomy in this “highest risk” group for recurrent vascular events, as highlighted in an American Heart Association scientific statement.²⁵

Our results provide strong evidence for the benefit of carotid endarterectomy in patients with stage 3 CKD; however, a higher risk for perioperative mortality in patients with CKD compared with those without CKD has been described in several previous studies.^{26–28} These studies followed patients with severe CKD, including those who were undergoing dialysis. Our previous meta-analysis confirms a graded increase in the risk for postoperative mortality with declining eGFR.¹¹ Thus, a risk-benefit profile that seems favorable for patients with stage 3 CKD may be less so in those with more advanced kidney failure. A recent review of the literature confirmed the need for additional large-scale, multicenter, prospective trials to identify high-risk patients and quantify their risk better.²⁹

Carotid stenting was recently studied as an alternative therapy to endarterectomy in the patient at high risk for surgical complications.^{30–32} It is not known whether carotid stenting is better than endarterectomy for stroke prevention with less perioperative complications. American Heart Association

guidelines currently describe carotid stenting as “not inferior” to endarterectomy in symptomatic patients with high-grade stenosis and difficult surgical access or medical conditions that greatly increase risk for surgery.² Thus, carotid stenting could be considered in patients who have CKD and symptomatic ICA stenosis and pose a high operative risk.

To generalize our results to individual patient care, physicians must also be aware of local perioperative complication rates. Patient selection and surgical expertise at NASCET study centers resulted in low rates of perioperative complications from carotid endarterectomy. Variability in these rates could alter the benefits of carotid endarterectomy demonstrated in this study.

Finally, in clinical practice, it is common for beneficial invasive therapies to be withheld from patients with CKD because of concern for adverse events.^{10,12} This phenomenon is sometimes called “renalism.”¹⁰ Patients with CKD are frequently excluded from large, randomized trials, and few subgroup analyses for such patients are ever reported.³³ In this broader context, this study is important to help reverse this practice.

CONCISE METHODS

The design of NASCET has been described elsewhere.¹⁹ Briefly, this was a randomized clinical trial to determine the efficacy and safety of carotid endarterectomy in patients with symptomatic ICA stenosis. Patients were eligible for randomization when they had a transient ischemic attack or nondisabling stroke in the preceding 180 d attributable to a carotid artery stenosis on selective angiography. Exclusion criteria were renal impairment defined as greater than twice the normal serum urea nitrogen or serum creatinine value as assessed in the laboratory of each participating center, significant liver disease, diseases likely to cause death within 5 yr, cardiac conditions likely to cause cardioembolism, and intracranial stenosis more significant than the carotid artery lesion. Eligible patients were randomly assigned to endarterectomy plus best medical care or best medical care alone, stratified by center and by degree of stenosis. Neurologists assessed all patients at entry; at 1, 3, 6, 9, and 12 mo; and every 4 mo thereafter. A patient’s serum creatinine was recorded as part of the baseline data collection process. A blinded external committee adjudicated all primary, secondary, and perioperative clinical outcomes.

The timeline of events after the initiation of NASCET is as follows. NASCET began enrollment in December 1987 and stratified patients by degree of ICA stenosis. High-grade stenosis was defined as 70 to 99%, and moderate-grade stenosis was defined as <70%. The measurement of carotid stenosis was strictly defined by the NASCET protocol. Stenosis was calculated using the ratio of the luminal diameter of the narrowest segment of the diseased portion of the artery to the diameter of the artery beyond any poststenotic dilation, determined using angiography.³⁴ By February 1991, 659 patients with high-grade stenosis had been enrolled. Endarterectomy in this group was associated with a significant reduction in ipsilateral stroke (absolute risk reduction of 17%; 95% CI 10 to 24%). Enrollment into this arm of the

study ceased, and these early NASCET results were published.³⁴ Eighteen percent of patients who had high-grade stenosis and were randomly assigned to medical therapy then received an endarterectomy. NASCET continued to enroll patients with moderate-grade stenosis and followed all patients until trial end in December 1997. Final NASCET results were published in 1998.¹⁹ To compare reasonably the treatment groups before the large patient crossover for patients enrolled with high-grade stenosis, we counted in this analysis only outcomes that occurred before February 1991.

Consistent with National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) current recommendations,³⁵ we defined CKD by a GFR <60 ml/min per 1.73 m². We used the Modification of Diet in Renal Disease (MDRD) equation to estimate GFR, where $eGFR$ in ml/min per 1.73 m² = $186 \times (\text{serum creatinine [in mg/dl]}^{-1.154}) \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$.³⁶ In a supportive analysis, we defined a GFR <60 ml/min per 1.73 m² by a serum creatinine >137 $\mu\text{mol/L}$ (1.5 mg/dl) in men and >104 $\mu\text{mol/L}$ (1.2 mg/dl) in women.³⁷

We analyzed the same perioperative and long-term outcomes as in the original NASCET publications.^{19,38} We reported the outcomes of patients with high-grade (70 to 99%) carotid stenosis separately from those with moderate-grade (50 to 69%) carotid stenosis. The two primary outcomes, analyzed separately, were ipsilateral stroke and death (from any cause) within 2 yr of randomization. The ipsilateral stroke outcome included all strokes (at any location) and all deaths (from any cause) during the 30-d postoperative period in the surgical arm and during the 32-d period after randomization in the medical arm, because median time from randomization to surgery was 2 d. Including these early events in the 2-yr outcome of ipsilateral stroke provides a more conservative estimate of the benefits of endarterectomy. The secondary outcome was a composite of any stroke, MI, and vascular death. Thirty-day perioperative outcomes included death, stroke, MI (based on electrocardiogram and cardiac enzyme change), CHF, and arrhythmia requiring treatment with antiarrhythmic medication.

The intention-to-treat principle guided all of our analyses. We compared baseline characteristics for patients with and without CKD using χ^2 tests. We assessed the effect of endarterectomy using a log-rank test from Kaplan-Meier analyses and plotted cumulative outcome curves. From these curves, we derived the risks for outcome within 2 yr of randomization. We calculated SEs for the absolute and relative risk reductions and 95% CIs using Greenwood’s formula.³⁹ We also calculated the number of patients who would need to be treated with endarterectomy to prevent one additional outcome within 2 yr after the procedure. We used recommended methods for subgroup analysis to determine whether the risk differences and relative risk reductions differed among patients with and without CKD.^{23,24,40,41} Because the statistical test of treatment effect modification is known to be underpowered, $P < 0.10$ was considered to be statistically significant.⁴⁰ χ^2 tests were used to compare perioperative risks for outcomes between patients with and without CKD. We repeated these analyses using log binomial regression modeling to assess whether any of the baseline patient characteristics influenced the findings. We avoided Cox proportional hazards modeling because the hazard assumption was not expected to be met because of perioperative adverse events among surgical patients (compared with medical patients). All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC).

ACKNOWLEDGMENTS

This analysis was supported by a research grant from the Physicians Services Incorporated Foundation. The NASCET trial was supported by grant R01-NS-24456 from the National Institute of Neurological Disorders and Stroke. M.E. was supported by the Alberta Heritage Foundation for Medical Research, P.J.D. was supported by a New Investigator Award from the Canadian Institutes of Health Research, and A.X.G. was supported by a Clinician Scientist Award from the Canadian Institutes of Health Research.

We acknowledge Dr. Brian Haynes and the NASCET collaborators for help and support.

DISCLOSURES

None.

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