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# Effect of Contralateral Occlusion on Long-Term Efficacy of Endarterectomy in the Asymptomatic Carotid Atherosclerosis Study (ACAS)

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**Background and Purpose**—The Asymptomatic Carotid Atherosclerosis Study (ACAS) established the effectiveness of prophylactic carotid endarterectomy, for patients in good health who had stenosis  $\geq 60\%$ , if conducted by surgeons with a surgical morbidity and mortality of  $< 3\%$ . This secondary analysis was performed to determine whether the presence of contralateral cervical carotid occlusion alters the efficacy of asymptomatic ipsilateral carotid endarterectomy.

**Methods**—One hundred sixty-three participants who had a baseline contralateral occlusion documented by Doppler ultrasound (77 medical, 86 surgical) were compared with 1485 participants with a patent contralateral carotid artery (748 medical, 737 surgical) for the risk of a combined end point of perioperative (30-day) death or stroke or long-term (5-year) ipsilateral stroke.

**Results**—For those without contralateral occlusion, surgery was associated with a 6.7% absolute reduction in the 5-year risk (95% CI, 2.1% to 11.4%), while for those with a contralateral occlusion, surgery was associated with a 2.0% absolute increase in risk (95% CI,  $-9.3\%$  to 5.2%), which was a statistically significant difference in the effect of surgery ( $P=0.047$ ). This difference is primarily attributable to low long-term risk for medically managed patients with contralateral occlusion.

**Conclusions**—While this post hoc analysis should be interpreted with caution, the findings suggest that endarterectomy in asymptomatic subjects with contralateral occlusion provides no long-term benefit (and may be harmful) in preventing stroke and death. These findings were a result of the benign course of medically treated subjects. (*Stroke*. 2000;31:2330-2334.)

**Key Words:** carotid artery diseases ■ carotid artery occlusion ■ carotid endarterectomy

The Asymptomatic Carotid Atherosclerosis Study (ACAS) established that the long-term risk of ipsilateral stroke in neurologically asymptomatic patients with a  $\geq 60\%$  carotid stenosis was reduced by carotid endarterectomy. The 5-year estimated risk for ipsilateral stroke was 11.0% and 5.1% for the medical and surgical groups, respectively, ie, a 53% relative risk reduction in favor of surgery.<sup>1</sup>

Cervical atherosclerosis produces stroke by 1 of 2 methods. Arterial thrombosis or particulate atherosclerotic matter may embolize from the neck lesion to an artery in the brain, producing an ischemic stroke. Second, the atherosclerosis/thrombosis may progress beyond a critical point, which leads to hypoperfusion of distal vessels, resulting in ischemic stroke. Under these circumstances, survival of the ipsilateral cerebral hemisphere would depend on adequate collateral circulation.

We hypothesized that patients with a contralateral carotid occlusion would be at an increased risk for stroke. Theoret-

ically, these patients would have decreased collateral flow and pressure, and thus embolic and thrombotic events would be more apt to lead to cerebral infarction. In an effort to test this hypothesis, we compared the outcomes of ACAS patients who did and did not have a contralateral internal carotid artery occlusion at baseline.

## Subjects and Methods

ACAS randomized 1662 participants with hemodynamically significant carotid stenosis to receive either aspirin 325 mg daily plus risk factor reduction management or this regimen plus carotid endarterectomy. The presence of the study lesion was documented by either arteriogram or noninvasive techniques (Doppler and/or ocular pneumoplethysmographic examination). The outcome of interest (for ACAS as well as the present analysis) is a combined end point of either (1) any death or stroke during the 30-day perioperative period or (2) ipsilateral stroke during the postoperative period. Details of the design of the study are published elsewhere.<sup>2</sup>

Three in the surgery group were lost to follow-up and, as was done in the primary analysis, are excluded from this secondary analysis.

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Of the 1659 patients in this analysis, only 647 (39%) had carotid atherosclerosis established by an arteriogram performed before randomization. The presence of the study lesion in the remaining 1008 (61%) was established by noninvasive techniques (4 patients have incomplete data). By study design, a preoperative arteriogram was required for patients randomized to surgery, but because of ethical considerations it was not required for those randomized to medical management. Arteriograms (performed either before or after randomization) are available for 741 of the 825 surgically managed participants (90%) but for only 314 of the 834 medically managed participants (38%). Therefore, an angiographic definition of contralateral occlusion could not be used for this analysis.

Baseline Doppler assessment of stenosis was required on all ACAS participants and was available on 1648 of the 1659 participants (99.3%). The ability of the noninvasive assessment to establish contralateral occlusion against the “gold standard” of angiography was established in the 384 patients eligible by noninvasive criteria and randomized to surgery who subsequently received an angiogram. Among these participants, 344 were categorized as not having a contralateral occlusion on the basis of Doppler, and this was verified by arteriogram in all patients. Conversely, 40 participants were categorized as having a contralateral occlusion by Doppler. Of these 40 participants, 38 were shown by angiography to be occluded. Therefore, in this data set Doppler has a 100% sensitivity (38/38), a 99% specificity (344/346), a 95% positive predictive value (38/40), a 100% negative predictive value (344/344), and a 99.5% overall accuracy (382/384) to establish contralateral occlusion as defined by angiogram. This high level of performance supports the validity of Doppler to establish the presence of contralateral occlusion for this analysis. Baseline Doppler results were therefore used to classify patients into groups.

This report focuses on the primary end point from the ACAS trial: stroke or death during the 30-day perioperative period or ipsilateral stroke during the post-30-day follow-up period. Throughout the article, references to “proportion event free” or the “proportion of the population with events” are referring to this primary end point for the ACAS trial.

**Statistical Methods**

Overall, ACAS demonstrated that endarterectomy was associated with a 5.9% decrease in the 5-year event rate for patients with asymptomatic lesions  $\geq 60\%$  (5-year event rate in the medically managed group of 11.0%, event rate in the surgically managed group of 5.1%).<sup>1</sup> The focus of the current analysis is to assess whether the relative benefit produced by surgery is affected by the presence or absence of a contralateral occlusion, ie, is the benefit for surgery, estimated to be 5.9% overall, the same for patients who have contralateral occlusion as for those who do not have contralateral occlusion?

In ACAS, the perioperative (30-day) risk of events was greater in surgically managed patients than in the medically managed patients. However, postoperatively, the risk was lower for the surgically managed participants, resulting in the overall benefit for surgery. These changes in the relationship of the risk of events over the follow-up period (ie, nonproportional hazards) makes the use of many “standard” survival techniques questionable.<sup>3</sup> As such, the role of contralateral occlusion as a potential modifier of the benefit of surgery is assessed by contrasting the differences in 5-year cumulative event rates for those with and without such a contralateral occlusion. Specifically, the Kaplan-Meier estimates of event rates were calculated (with Greenwood’s formula for variance estimates)<sup>4</sup> for 4 strata of patients: medically managed without contralateral occlusion ( $M_N$ ), surgically managed without contralateral occlusion ( $S_N$ ), medically managed with contralateral occlusion ( $M_O$ ), and surgically managed with contralateral occlusion ( $S_O$ ). The efficacy of endarterectomy can then be assessed by the difference in these survival estimates for those without contralateral occlusion ( $M_N - S_N$ ) and for those with contralateral occlusion ( $M_O - S_O$ ). In addition, the hypothesis that contralateral occlusion affects the relative efficacy of surgery can be directly tested by assessing whether the surgical versus medical difference in the presence/absence of a contralateral

**TABLE 1. Study Groups, by Treatment Group and by Presence/Absence of Contralateral Occlusion by Doppler**

	No Contralateral Occlusion		Contralateral Occlusion	
	Medical	Surgical	Medical	Surgical
n	748	737	77	86
Age, mean $\pm$ SD, y	67 $\pm$ 7	67 $\pm$ 7	66 $\pm$ 7	68 $\pm$ 7
% White	95	94	97	98
% Male	64	64	83	80
% Hypertensive	64	64	68	65
% Diabetic	22	25	20	16
% History of coronary artery disease	68	68	70	73
% Previous contralateral stroke or TIA	24	19	57	51
% Current smoker	24	28	27	28

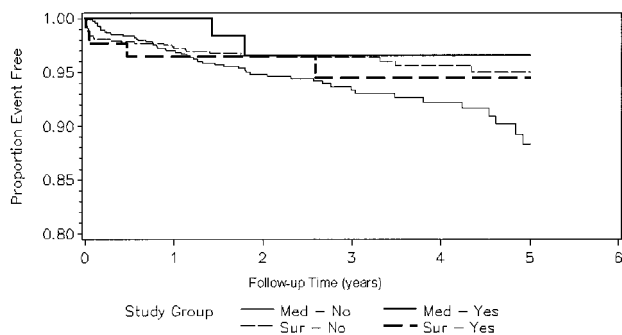
TIA indicates transient ischemic attack.

occlusion is equal to zero, ie,  $H_0: (M_N - S_N) - (M_O - S_O) = 0$ . The statistical significance of each of these relationships can be assessed by forming the ratio of the estimate to its standard error and testing the resulting ratio against the standard normal distribution. There is 80% power to detect a significant difference in the efficacy of endarterectomy between those with and without contralateral occlusion if the magnitude of that difference exceeds approximately 8.1%.

**Results**

Of the 1648 ACAS participants with a baseline Doppler evaluation, there were 1485 (90%) without a contralateral occlusion, of which 748 (50%) were randomized to medical management and 737 (50%) to surgical management. There were 163 participants (10%) with contralateral occlusion by Doppler, of which 77 (47%) were randomized to medical management and 86 (53%) to surgical management. A description of these participant groups is provided in Table 1. While there was not a substantial difference in the age of the participants, those with contralateral occlusion were more likely to be white and male. With the exception of a previous history of contralateral stroke or transient ischemic attack (which was more likely among those with a contralateral occlusion), there were also no substantial differences in the prevalence of coexisting diseases and risk factors.

The Figure provides the Kaplan-Meier estimates of the proportion event free as a function of years of follow-up. Not surprisingly, since the vast majority of the study population did not have a contralateral occlusion, the estimated proportions event free in the groups without contralateral occlusion are nearly identical to the overall ACAS results. Specifically, Table 2 shows the estimates of the 5-year event rate [(1 - proportion event free)  $\times$  100] among the group without contralateral occlusion to be 11.7% for medical management and 5.0% for surgical management, for a 6.7% reduction in risk associated with surgical management ( $P = 0.0047$ ). However, among those with a contralateral occlusion, the estimate of the 5-year event rate was 3.5% for medical management and 5.5% for surgical management, for a 2.0% increase in risk associated with surgical management ( $P = 0.58$ ). There was a significant difference ( $P = 0.047$ ) in efficacy of surgery versus



Kaplan-Meier survival estimates for those patients medically managed without contralateral occlusion (Med - No), surgically managed without contralateral occlusion (Sur - No), medically managed with contralateral occlusion (Med - Yes), and surgically managed with contralateral occlusion (Sur - Yes).

medical management between those with and without contralateral occlusion: 8.7% [6.7% - (-2.0%) = 8.7%]. This statistically significant interaction suggests that the efficacy of the treatments should be assessed conditional on the patency of the contralateral artery. The perioperative (30-day) event rate in the surgical arm was equivalent (2.3% versus 2.2%) in patients with and without contralateral occlusion. This significant effect modification was largely the product of differences in the medically managed group, in which those with a contralateral occlusion had roughly a third of the event proportion of those without a contralateral occlusion (3.5% compared with 11.7%;  $P=0.011$ ). In contrast, the long-term outcome of surgically managed patients was very similar among those without a contralateral occlusion (5.0% event rate) compared with those with a contralateral occlusion (5.5% event rate;  $P=0.86$ ).

## Discussion

ACAS randomly allocated large numbers of asymptomatic patients with  $\geq 60\%$  internal carotid artery stenosis (established by angiographic and ultrasound criteria) into medical and surgical treatment arms. All patients were cleared for surgery before randomization, and thus there should be little selection bias between the medical and surgical groups vis-à-vis survival. All patients were prescribed one 325-mg aspirin daily and received counseling regarding management of cardiovascular risk factors. The surgeons participating in

ACAS were selected on the basis of their past excellent surgical results, and surgeons who had high ( $>3\%$  for asymptomatic or  $>5\%$  for all indications) stroke and death rates after carotid endarterectomy were excluded from participation.<sup>5</sup> All patients were evaluated by the study neurologist to ensure that every adverse effect was recorded.

Part of the impetus for this study was the report by Gasecki et al<sup>6</sup> representing the North American Symptomatic Carotid Endarterectomy Trial (NASCET), in which 43 patients with a contralateral internal carotid artery occlusion were followed and compared with 559 patients with contralateral mild-to-moderate stenosis ( $<70\%$  diameter stenosis) and with 57 patients with a contralateral severe stenosis (70% to 99% diameter stenosis). In both the medically and surgically treated groups, patients with an occluded contralateral artery were more than twice as likely to have had an ipsilateral stroke by 2 years than either of the groups with patent contralateral arteries. In the surgically treated group, the perioperative risk of stroke or death was higher in patients with a contralateral occlusion (14.3%) than in patients with either a contralateral severe stenosis (4.0%) or a contralateral mild-to-moderate stenosis (5.1%). However, the authors suggest that despite this higher perioperative morbidity, endarterectomy was indicated because of the more dismal long-term outlook for these patients under medical management.

In our report, medically treated asymptomatic patients with  $\geq 60\%$  internal carotid stenosis who in addition had a contralateral internal carotid artery occlusion were actually protected from events (any stroke or death during the first 30 days, ipsilateral stroke thereafter) over time compared with those patients with a patent contralateral internal carotid artery. Overall, the cumulative 5-year event rate was 11.7% for medical patients with a patent contralateral carotid but only 3.5% for those medical patients with a contralateral internal carotid occlusion. This finding is in contrast to our original hypothesis as well as the NASCET conclusions and is difficult to explain. Regardless, we speculate that collateral circulation may be a potential cause for this difference. Consider 2 patients with a carotid stenosis opposite a carotid total occlusion who differ only in their extent of collateral circulation. Let one assume that a patient with symptoms, due to either emboli or low flow, has poorer collateral circulation. The one patient who is symptomatic and has poorer collateral circulation is enrolled in NASCET, whereas the other patient

**TABLE 2. Cumulative 5-Year Kaplan-Meier Estimates of Event Rates**

	ACAS Treatment Group		Difference Between Medical and Surgical Management
	Medical	Surgical	
<b>Contralateral artery status</b>			
Patent	11.7 $\pm$ 2.1	5.0 $\pm$ 1.1	6.7 $\pm$ 2.4 ( $P=0.0047$ )
Occluded	3.5 $\pm$ 2.4	5.5 $\pm$ 2.8	-2.0 $\pm$ 3.7 ( $P=0.58$ )
Difference between individuals with patent vs occluded contralateral artery	8.2 $\pm$ 3.2 ( $P=0.011$ )	-0.5 $\pm$ 3.0 ( $P=0.86$ )	

Values are percentages  $\pm$  Greenwood Standard errors.

who is asymptomatic with better collateral circulation is enrolled in ACAS. Thus, NASCET would have been burdened with patients who have poor collateral flow, whereas ACAS would have been enriched by patients with good collateral flow. One must further assume that good collateral flow protects patients from stroke over time, hence the advantage to the ACAS patients with a contralateral occlusion.

The perioperative event rate was 2.2% (16/737) in patients without a contralateral occlusion and 2.3% (2/86) in patients with a contralateral occlusion. Although the number of patients with contralateral occlusion is relatively small, these results suggest that endarterectomy can be safely performed in the presence of such an occlusion in asymptomatic patients. That the presence of a contralateral occlusion did not influence the surgical outcome is in contrast to that reported in the symptomatic trials.<sup>6,7</sup> The initial joint study of extracranial arterial occlusion, in 1969, reported a 45% mortality rate in patients with contralateral occlusion but rightly pointed out that many patients had an acute, severe neurological deficit and that some operations were on the occluded carotid.<sup>8</sup> A perusal of the current surgical literature indicates that good surgical results in patients with a contralateral internal carotid artery occlusion are not unique. New York University Medical Center reported a modern series with a stroke/death rate of 0.7%,<sup>9</sup> John Hopkins a perioperative stroke rate of 2.8%,<sup>10</sup> Northwestern University 4.9% (2 of the 4 strokes were due to intercerebral hemorrhage),<sup>11</sup> Emory University a combined morbidity/mortality rate of 4.3%,<sup>12</sup> and Julia et al from Paris, France, a combined morbidity/mortality of 1.7% (however, they excluded a 6.9% incidence of transient morbidity).<sup>13</sup> Da Silva et al,<sup>14</sup> representing the audit committee of the Vascular Surgical Society of Great Britain, reported that the combined death and stroke rate for patients with a contralateral internal carotid artery occlusion was 5.6% compared with 2.4% in those patients with a patent contralateral carotid artery ( $P=NS$ ). In contrast, Rothwell et al<sup>7</sup> reviewed a variety of studies, including the European Carotid Stenosis Trial (ECST), and found that patients with contralateral internal carotid artery occlusion undergoing carotid endarterectomy had an intraoperative stroke rate that was twice that of the other patients. These studies, however, by and large, represent symptomatic or combined symptomatic and asymptomatic patient populations, used a variety of methods and designs, and did not always report comparable information. However, under the assumption that asymptomatic patients with an occluded contralateral artery are likely to have good collateral flow, the presence of this collateral flow could contribute to the lower mortality and morbidity associated with surgery in our patients with occluded contralateral arteries. Symptomatic studies, such as NASCET and ECST, observed higher surgical morbidity and mortality among surgically treated patients with contralateral occlusion, perhaps because patients with occluded contralateral arteries in these studies are less likely to have good collateral circulation. Moreover, and perhaps more importantly, we are not privy to the incidence of ipsilateral infarcts, the criteria for shunt usage, and the comparative frequency of shunt usage. Thus, good surgeons, as selected by the ACAS method, using

a variety of surgical techniques, can achieve good perioperative results in asymptomatic patients regardless of the status of the contralateral internal carotid artery.

The hypothesis that medically treated asymptomatic patients with contralateral occlusion have a benign outcome, while symptomatic patients do not, has some support in the literature. The neurology group from London, Ontario, reported a stroke rate distal to an occluded carotid artery of 5% per year in a mixed population of symptomatic and asymptomatic patients.<sup>15</sup> However, Bornstein and Norris<sup>16</sup> from Toronto suggested that patients who were asymptomatic with an internal carotid artery occlusion had a benign course. They observed 40 asymptomatic patients with carotid occlusion for up to 7 years. No stroke occurred after detection of the occlusion. Of those patients with an already occluded internal carotid artery on study entry, 4 suffered transient ischemic attacks (3 were ipsilateral to the occlusion) and there were no strokes. At randomization, more than half of the ACAS patients with contralateral occlusion reported neurological symptoms attributed to the side of the occlusion; thus, their course would not be expected to be entirely benign. Although a National Institutes of Health Stroke Scale severity score was not available on ACAS patients at baseline, it is reasonable to assume that their neurological deficit must have been mild or they would not have been candidates for a surgical study.

Our study has several shortcomings. It is well known in clinical trial methodology that subgroup analysis such as this may lead to spurious findings. We have made attempts to protect against this, however, by using the principles for subgroup analysis as set forth by Yusuf et al.<sup>17</sup> Specifically, this analysis was guided by an a priori hypothesis, the subgroup was defined by baseline characteristics, the number of subgroup analyses within the ACAS data set has been limited, and the statistical methods were specified in advance. Confirmation of results from these and other subgroup analyses should be sought from similar subgroups from ongoing, prospective trials. In addition, the small number of patients and particularly the few adverse events should caution practicing physicians to continue to examine this clinical situation before implementing these findings into patient care algorithms. In addition, this analysis relies on the use of ultrasound (rather than the gold standard of angiography) to establish the presence of contralateral occlusion. However, the ability of ultrasound to demonstrate the presence of a contralateral occlusion has been clearly documented since it has a positive and negative predictive value, a sensitivity and specificity, and an overall accuracy all >95%.

In conclusion, we have shown that there is a significant difference in the efficacy of endarterectomy to prevent events among asymptomatic patients with and without contralateral occlusion, with endarterectomy showing little benefit in those with contralateral occlusion. Unlike the symptomatic trials that demonstrated a high complication rate among symptomatic patients with contralateral occlusion, our data in an asymptomatic population showed no difference in surgical outcome of those with and without contralateral occlusion. The lack of a benefit of endarterectomy in the group with a contralateral occlusion was the result of an unanticipated good outcome of medically managed asymptomatic patients with a contralateral occlusion.

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