Effect of Nonoptimal Imaging on the Relationship Between the Measured Degree of Symptomatic Carotid Stenosis and Risk of Ischemic Stroke

R.L. Cuffe, MSc; P.M. Rothwell, MD, PhD, FRCP

Background and Purpose—Some recent studies of noninvasive carotid imaging have identified high rates of inappropriate decision-making about endarterectomy compared with conventional arterial angiography (CAA), but there is substantial inconsistency across the published literature. CAA is usually regarded as the gold standard for carotid imaging, partly because the degree of angiographic stenosis is a powerful predictor of ischemic stroke and hence of benefit from endarterectomy. However, there are very few published data on the extent to which predictive power varies with type of CAA or the number and quality of views of the stenosis obtained.

Methods—We analyzed measurements of stenosis made by 2 independent observers on 967 consecutive patients randomized to medial treatment alone in the European Carotid Surgery Trial (ECST). We determined prediction of 3-year risk of ipsilateral ischemic stroke (as a hazard ratio from a Cox model and as the area under a receiver operating characteristic curve [AUC]) in relation to the technique of angiography, the number and quality of views of the stenosis, and the use of 2 independent measurements.

Results—Using 2 independent measurements of stenosis increased predictive power slightly, but the effect was much smaller than that attributable to the type of CAA and the number of views of the stenosis. Prognostic value was greater in patients who had selective carotid injection CAA and at least biplane views (AUC, 0.75; 0.68 to 0.82) than in patients with only a single view or aortic arch injection CAA (AUC, 0.65; 0.56 to 0.73; P=0.03).

Conclusions—The dependence of the prognostic value of CAA on the type of angiography and the number of views of the stenosis obtained has implications for the future development and validation of noninvasive methods of carotid imaging. (Stroke. 2006;37:1785-1791.)

Key Words: angiography ■ carotid stenosis ■ carotid endarterectomy ■ risk

In patients with symptomatic carotid stenosis, the degree of stenosis is the most important independent predictor of ipsilateral ischemic stroke over the next few years. Randomized controlled trials (RCTs) have demonstrated that endarterectomy reduces the risk of stroke in patients with recently symptomatic 70% to 99% carotid stenosis. Benefit is more modest for 50% to 69% stenosis, and surgery is harmful in patients with <50% stenosis. There is no reason to suspect that the degree of stenosis will be any less important in selection of patients for angioplasty/stenting.

Screening of patients for inclusion in the RCTs was usually performed with Doppler ultrasound, but conventional arterial angiography (CAA) was required before randomization in the RCTs of surgery for symptomatic stenosis. However, CAA is costly, time-consuming, and can cause stroke. A systematic review of prospective studies of the risks of CAA in patients with cerebrovascular disease reported a 0.1% risk of death and a 1.0% risk of permanent neurological sequelae. More recent studies have reported lower risks in both academic centers and community hospitals, but most centers have already adopted a policy of operating on the basis of Doppler ultrasound alone or in combination with another noninvasive method of imaging.

In recent years, several studies and reviews have questioned the wisdom of selecting patients for surgery on the basis of noninvasive imaging alone. In particular, high rates of inappropriate decision-making about surgery have been demonstrated for noninvasive imaging versus CAA. For example, a recent comparison of CAA with Doppler ultrasound in 569 consecutive patients in “accredited” laboratories with experienced radiologists found that 28% of decisions about endarterectomy based on Doppler ultrasound alone were inappropriate. However, the published literature on the agreement between noninvasive imaging and CAA in determining clinically important thresholds of severity of carotid stenosis is inconsistent, with variable sensitivities (60% to 90%) and specificities (70% to 90%) for detection of stenosis that would be appropriate for surgery when compared with...
angiography, even when recent technological advances in imaging are taken into account.\textsuperscript{11,13,14} Some of the apparent variation in findings is attributable to poor study design, inadequate sample size,\textsuperscript{15} and inappropriate analysis and presentation of data,\textsuperscript{16} but some will be attributable to differences between studies in imaging technique. It tends to be assumed that such differences between studies will be attributable almost entirely to differences in the performance and interpretation of the noninvasive methods of imaging,\textsuperscript{13} but it is possible that differences in the type and quality of CAA also contribute. CAA is generally regarded as the gold standard for carotid lumen imaging, but there is still clinically significant interobserver and intraobserver variation in measurement of degree of stenosis on angiograms,\textsuperscript{5} which varies depending on angiographic technique used and the quality of views obtained.\textsuperscript{17} However, there are no published data on how any differences in the type or quality of CAA might affect the predictive value of measured stenosis for subsequent stroke. Major differences in predictive value would have important clinical implications for both the use of CAA itself to select patients for surgery and its consideration as a uniform standard for comparisons with noninvasive carotid lumen imaging. We therefore determined to what extent the relationship between the degree of symptomatic stenosis and risk of ipsilateral ischemic stroke is affected by interobserver error in measurement of degree of stenosis on CAA, by the identification of near-occlusions,\textsuperscript{3,18} by type of angiography, and by availability of biplane views.

Methods

The European Carotid Surgery Trial (ECST)\textsuperscript{2} was an RCT of carotid endarterectomy versus best medical treatment alone in patients with recently symptomatic carotid stenosis. All patients underwent CAA (usually selective or aortic arterial injection) before randomization, and a selection of the films were subsequently sent to the trial office. All patients were followed up ~4 months and 12 months after randomization and annually thereafter. Details of any strokes or deaths occurring during follow-up were obtained at clinical review. Clinical details, results of any investigations, and any postmortem information were sent to the main trial office for classification by a trial neurologist. An independent blinded audit committee reviewed the classification of all strokes and deaths.

As reported previously,\textsuperscript{4,19} in 1001 consecutive patients randomized to medical treatment, 2 independent and experienced observers measured the degree of stenosis of the symptomatic carotid artery using a jeweler’s eyepiece graduated in 0.1-mm units. Measurements were made using ECST, North American Symptomatic Carotid Endarterectomy Trial (NASCET), and common carotid methods of measurement.\textsuperscript{4,19} Both observers made measurements on the single angiographic image that provided (in the opinion of the first observer) the clearest view of the stenosis. The view showing the tightest stenosis was selected if the clarity of 2 different views was comparable. A record was made of whether the angiogram was aortic arch or selective injection, whether at least biplane views of the stenosis had been taken, and near-occlusions were identified as reported previously.\textsuperscript{2,3} One of the observers also measured the degree of stenosis on the other angiographic view(s) of the stenosis if available (not all images taken in the centers were sent to the trial office). In the majority of cases, only 2 views were available (usually anterior–posterior and lateral).

Previous work has shown that the predictive value of symptomatic carotid stenosis for ipsilateral ischemic stroke is very much reduced >3 years after a transient ischemic attack or stroke.\textsuperscript{1,20} We therefore calculated a Cox proportional hazards model for the 3-year risk of ipsilateral ischemic stroke against the measured degree of symptomatic stenosis assessed in 3 ways: (1) a single measurement by 1 observer, (2) a single measurement by 1 observer adjusted for the identification of near-occlusions, and (3) the mean of measurements by 2 independent observers adjusted for the identification of near-occlusions.\textsuperscript{3,16} In each case, the model also adjusted for age, sex, time since presenting event, and type of presenting event. We also quantified the predictive value as the area (95% CI) under a receiver operating characteristic (ROC) curve.

In view of the fact that selective carotid injection CAA with at least biplane views of the stenosis was the stated ideal for carotid imaging in each of the large RCTs of endarterectomy that required CAA,\textsuperscript{1,2} we compared the predictive value of the measurements of the degree of carotid stenosis described above in patients who had at least biplane views on selective carotid injection CAA (optimal imaging) with patients who did not (ie, selective carotid injection CAA with only a single view or arch injection CAA; nonoptimal imaging). We did not distinguish between conventional and digitally subtracted images because these have been shown previously to have similar interobserver and intraobserver variability in measured stenosis.\textsuperscript{17}

Results

Data on all parameters included in the analysis were complete for 967 (96.7%) patients, of whom 692 (71.9%) were male, 116 (12.0%) diabetic, 397 (41.1%) treated hypertensives, and 497 (51.4%) smokers. Thirty-eight (3.9%) patients had near-occlusion of the symptomatic carotid artery. Presenting events were as follows: 209 (21.6%) monocular ischemic events, 347 (35.9%) cerebral transient ischemic attacks, and 411 (42.5%) nondisabling ischemic strokes. The mean (SD) age was 62.1 (7.8), mean time since presenting event was 61 days (interquartile range 20 to 89), mean baseline systolic blood pressure, diastolic blood pressure, and pulse pressure were 150.0 (21.3), 86.3 (10.8), and 64.0 (16.7) mm Hg, respectively. During the first 3 years of follow-up, 94 (9.7%) patients experienced an ipsilateral ischemic stroke.

Biplane views of selective carotid injection CAA (optimal imaging) were available for 422 (43.6%) patients. The remainder comprised 350 selective injection CAA with a single view and 195 aortic arch injection CAA. Table 1 shows that patients with optimal imaging were more likely to be male and to have been randomized sooner after their presenting event. These associations primarily reflect differences in recruitment practices and angiographic techniques between trial centers. However, all analyses of stroke risk were adjusted for these potentially confounding factors, although Cox models of risk of ipsilateral ischemic stroke actually found no evidence of an interaction between either factor and the predictive value of stenosis ($P = 0.47$ and 0.56, respectively). There were no differences in the mean (SD) degree of stenosis between the 2 groups of patients (Table 1) or in the overall risks of ipsilateral ischemic stroke at 3 years (8.8%; 95% CI, 5.9 to 11.6% in patients with optimal imaging versus 8.2%, 95% CI, 5.6 to 10.1% in patients with nonoptimal imaging). For the sake of brevity, all analyses below are based on the ECST method of measurement of stenosis. However, results were qualitatively very similar for all 3 methods of measurement of stenosis.

Figure 1 shows the interobserver agreement for measurement of the degree of carotid stenosis on the single preselected view that showed the stenosis most clearly in the 422 patients with optimal imaging. Interobserver agreement was
significantly less than perfect (intraclass correlation coefficient [ICC], 0.90; 95% CI, 0.88 to 0.92). Interobserver agreement was slightly less good in patients with nonoptimal imaging (ICC, 0.88; 95% CI, 0.86 to 0.90), but this difference was not statistically significant (P=0.21), and agreement was similar for selective carotid injection CAA with a single view (ICC, 0.87; 95% CI, 0.84 to 0.90) and for aortic arch injection CAA (ICC, 0.89; 95% CI, 0.86 to 0.91).

Figure 2 shows the measurements of stenosis from the 422 patients with biplane views from selective carotid injection CAA comparing the most severe measurement of stenosis with the less severe measurement. Although the measure-
ments were highly correlated ($r^2=0.75$; 95% CI, 0.67 to 0.83), there was a substantial spread of values. The median (interquartile range) difference between the views was 13.7% (5.0 to 19.4) stenosis. The predictive value of a single measurement of the most severe linear stenosis was greater than that of the less severe stenosis (log hazard ratio per 10% stenosis, 0.53; 95% CI, 0.32 to 0.74 versus 0.43; 0.27 to 0.59). The predictive value of the product of the 2 measurements (ie, a crude surrogate for area stenosis) was intermediate.

Table 2 shows both log hazard ratios for the risk of ipsilateral ischemic stroke for a 10% increase in degree of stenosis and the overall area under the ROC curves separately for patients with and without optimal imaging. In both imaging subgroups, using 1 measurement of stenosis rather than the mean of 2 reduced the relative predictive value of stenosis slightly, although the difference was not statistically significant. Failing to account for near-occlusions in the analysis of stroke risk also reduced the predictive value by a small amount in both groups, although again, the difference in predictive value was not statistically significant.

However, more striking was the difference in predictive value of stenosis measurements derived from patients with optimal versus nonoptimal imaging (Table 2; Figure 3). The predictive values for stroke risk of each of the 3 analyses of

**Figure 2.** Relationship between the degree of stenosis measured on the angiographic view showing the most severe stenosis vs the view showing the least severe stenosis in patients with selective carotid injection CAAs with at least biplane views.

**TABLE 2.** The Predictive Value of Stenosis in Patients With Selective Carotid Injection CAAs With Biplane Views (optimal imaging) Vs Patients With Arch Injection CAAs or Selective Carotid Injection CAAs With Single Views (nonoptimal imaging)

| Predictive value of stenosis | Optimal Imaging | | | | Nonoptimal Imaging | | | |
|----------------------------|-----------------|---|---|-------------------|---|---|---|---|---|---|---|---|
|                             | LnHR            | 95% CI   | $P$  | LnHR              | 95% CI   | $P$  | $P$ (difference) |
| Mean of 2 readings (+)      | 0.49            | (0.29–0.68) | <0.0001 | 0.27         | (0.11–0.43) | 0.0008 | 0.056 |
| Single reading (+)          | 0.44            | (0.26–0.63) | <0.0001 | 0.24         | (0.09–0.39) | 0.0022 | 0.065 |
| Single reading (−)          | 0.43            | (0.25–0.61) | <0.0001 | 0.22         | (0.08–0.36) | 0.0024 | 0.071 |
| AUC                         | 0.75            | (0.68–0.82) | <0.0001 | 0.64         | (0.56–0.73) | 0.0010 | 0.032 |
| Mean of 2 readings (+)      | 0.73            | (0.66–0.81) | <0.0001 | 0.63         | (0.54–0.71) | 0.0030 | 0.034 |
| Single reading (+)          | 0.73            | (0.66–0.80) | <0.0001 | 0.63         | (0.54–0.71) | 0.0020 | 0.036 |

LnHR indicates the log of the hazard ratio.

(+) indicates adjustment made for near-occlusions; (−), no adjustment made for near-occlusions.
degree of stenosis, as estimated either by the log hazard ratios per 10% stenosis or the ROC curves, were approximately double in patients with optimal versus nonoptimal imaging (for the ROC curves, an area of 0.5 represents no predictive value and an area of 1.0 represents perfect prediction, and so an area of 0.7 represents approximately double the predictive value of an area of 0.6). There were no significant differences between the predictive values in patients with selective carotid injection CAs without biplane views (log hazard ratio/10% stenosis, 0.25; 95% CI, 0.07 to 0.43; area under ROC curve, 0.64; 95% CI, 0.53 to 0.74) and those in patients with aortic arch injection CAA (log hazard ratio/10% stenosis, 0.23; 95% CI, –0.06 to 0.51; area under ROC curve, 0.64; 95% CI, 0.51 to 0.77).

From a more clinical perspective, the absolute risks (95% CI) of ipsilateral ischemic stroke at 3 years in patients with <50% stenosis, 50% to 69% stenosis, and ≥70% stenosis were 2.8% (0.4 to 5.2), 10.4% (4.1 to 16.3), and 18.4%, respectively, based on the mean of measurements by 2 independent observers in patients with optimal imaging and 5.7% (2.4 to 8.9), 9.1% (4.2 to 13.7), and 15.3% (10.0 to 20.3), respectively, based on the mean of measurements by 2 independent observers in patients with nonoptimal angiographic investigation.

Figure 4 compares the ROC curves from the most highly predictive measurements (the mean of measurements made by 2 independent observers on optimal imaging with adjustment for near-occlusion) and the least predictive measurements (1 measurement by a single observer made on a nonoptimal angiographic investigation without adjustment for near-occlusion). The areas under each curve and associated CIs are given in Table 2. The difference in areas under the respective ROC curves was statistically significant (0.12; SE=0.057; P=0.016).

Discussion

We attempted to quantify the range of prognostic information provided by different levels of reliability of measurement of the degree of symptomatic carotid stenosis on CAA. Arterial angiography is regarded as a gold standard, but there can be a considerable range in the quality of views obtained. Selective carotid injection CAA is widely regarded as providing the best view of the bifurcation, free from overlap with other vessels and with optimal lateral views of the posterior wall of the vessel. Given that the residual lumen at the point of maximum stenosis is frequently noncircular in cross-section, it is generally accepted that at least biplane views (usually a lateral and anterior–posterior view) are required for optimal visualization of stenosis. A good lateral view is particularly important because the tendency of plaque to form on the posterior wall of the carotid bifurcations means that measurements of stenosis on lateral views are systematically more severe than measurements made on anterior–posterior or oblique views.

However, despite the general view that selective carotid injection CAA with biplane views is the optimal angiographic approach to visualization of the degree of carotid stenosis, many previous comparative studies with noninvasive imaging have pooled data derived from different angiographic techniques. We have shown previously that the quality of...
visualization of the stenosis does affect the interobserver agreement in measurement of the degree of stenosis, but there have been no previous studies of any differences in predictive value for ipsilateral ischemic stroke in relation to type of angiography or availability of biplane views. Future studies are, of course, no longer possible because of the need for intervention in patients with severe carotid stenosis.

We made several clinically useful observations. First, we confirmed that there is clinically significant interobserver variability in measurement of the degree of carotid stenosis even in the most optimal situation: 2 experienced observers making measurements with a jeweler’s eyepiece on the single preselected clearest view of the stenosis on selective carotid injection CAA. This level of variability in measurement of degree of stenosis will approximately represent the least possible variability that can be expected between a noninvasive method of imaging and selective carotid injection CAA. In other words, even a perfect noninvasive method of imaging would always have less than perfect agreement with selective carotid injection CAA.

Second, we showed that there are significant differences between the degree of stenosis measured on different views of the same stenosis on selective carotid injection CAA and that the predictive value for ipsilateral ischemic stroke tended to be greater for the tighter measurement of stenosis. Interestingly, the approximation of area stenosis that we derived from the product of both measurements was no more predictive than maximum linear stenosis measurement, although we did not have the statistical power to exclude a small difference reliably. However, these results underline the importance of obtaining at least biplane views on the stenosis.

Third, we showed a statistically and clinically significant difference in predictive value for ipsilateral ischemic stroke between patients with selective carotid injection CAA and biplane views and patients with nonoptimal CAA. Of course, we were not able to compare the predictive value of the 2 techniques in the same group of patients, but we were unable to identify any difference between the 2 subgroups of the ECST cohort that accounted for the difference in predictive value. There was no difference in overall absolute risk of stroke between the 2 groups or in the mean degree of measured stenosis, making it likely that our findings were attributable to genuine differences in prognostic value between the 2 techniques. However, even assuming that the 2 groups of patients were comparable, the trial did not have the statistical power to look at the impact of angiographic technique on the apparent relationship between degree of stenosis and benefit from surgery.

The reasons for the superior predictive value of selective carotid injection CAA with biplane views are probably multiple. First, quality of visualization of stenosis tends to be greater than that with aortic arch angiography, although this does not translate into a major difference in interobserver agreement in the measurement of the degree of stenosis. Paradoxically, observer agreement can sometimes be greater on poor quality imaging because observers tend to select a more limited number of stenosis values (e.g., 25%, 50%, 75%, etc). Second, as detailed above, the availability of biplane views...
views, and particularly lateral views, allows more reliable estimation of the tightest degree of linear stenosis. Given the nonlinearity of the relationship between stenosis and stroke risk, even a relatively small improvement in accuracy of measurement, particularly at the upper end of the stenosis range, would be expected on the basis of similar work in other areas of medicine be expected to have a significant impact on the observed risk relationships.29,30

We have shown previously that the predictive values of the different methods of measurement of stenosis on angiographic films (eg, ECST, NASCET, and common carotid methods) are identical,4 and we found no differences between the methods in this study in respect of the greater predictive value of stenosis measured in patients with selective carotid injection CAA and biplane views. This observation suggests that the greater predictive value is derived from more accurate measurement of the minimum residual lumen, measurement of which is common to all 3 methods rather than the denominator measurement.

In conclusion, the prognostic value of CAA for ipsilateral ischemic stroke is dependent on the angiographic technique used and the availability of biplane views of the stenosis. The improvement in prognostic value gained by more accurate measurement of the degree of stenosis (eg, mean of 2 independent observers) within a particular angiographic technique is small in comparison. These findings have implications for the future development and validation of noninvasive methods of carotid imaging.

Acknowledgments

We are indebted to Professor Charles Warlow and the European Carotid Surgery Trials’ Collaborative Groups for allowing us to report data from the ECST.2

Disclosures

None.

References

12. Rothwell PM. For severe carotid stenosis found on ultrasound, further arterial evaluation prior to carotid endarterectomy is unnecessary: the argument against. Stroke. 2003;34:1817–1819.
Effect of Nonoptimal Imaging on the Relationship Between the Measured Degree of Symptomatic Carotid Stenosis and Risk of Ischemic Stroke

R.L. Cuffe and P.M. Rothwell

Stroke. 2006;37:1785-1791; originally published online June 15, 2006; doi: 10.1161/01.STR.0000227231.85653.ea

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/37/7/1785

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/