Editorial

Carotid Endarterectomy and the Measurement of Stenosis

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Three randomized clinical trials have been published that assign treatment consisting of either best medical care alone or best medical care combined with carotid endarterectomy to patients with recent symptoms judged to be due to severe degrees of carotid artery stenosis as shown by carotid arteriography.1-3

The two larger trials1,2 established without equivocation that stroke-free survival was improved by surgery. The smaller Veterans Administration (VA) Symptomatic Trial was stopped prematurely when the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) established so clearly the benefit of surgery.3 None of these trials based the eligibility for entry into the trials on ultrasound studies; records were kept of the ultrasound observations in the NASCET and VA patients.1,3 All trials required that there be demonstrated expertise in the performance of arteriography in the collaborating centers. Intracranial studies were mandated by the NASCET and VA protocols; invasive arteriography was requested in all of them. The trials were not in a position to equip each center with state-of-the-art equipment for noninvasive studies, nor to perform strict quality control measures, including the assurance that expert technologists performed all the studies in all the patients to be randomized. Duplex was in its infancy when the ECST was launched in 1981.

NASCET and the Veterans Administration Symptomatic Trial have reported the disappointing correlation found between the measurement of the percentage of stenosis in the arteriograms and in the ultrasound studies.3,4 These observations were based on Central Office review of the x-ray films and ultrasound tracings submitted by the respective participating centers. Other large studies have been published in which these discrepancies between arteriograms and ultrasound measurements have been observed.5,6 Neither NASCET, ECST, nor the Veterans Administration Symptomatic Trial pretended to evaluate CE based on a measure of area stenosis.

Without doubt, the discrepant correlation between arteriography and ultrasound will narrow when all institutions performing endarterectomy are employing state-of-the-art color-flow duplex sonographic equip-

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Preliminary analysis of angiograms of patients randomized to no-surgery in ECST suggests that 70% stenosis measured using the ECST method is approximately equivalent to 82% stenosis measured using the NASCET method. ECST results have been reanalyzed for ECST patients with >82% stenosis by the ECST method. The survival curves for ECST (top panel) and those previously published by NASCET (bottom panel) look remarkably similar. Stroke risk at 2 years in the medical groups range from 20% to 25%, and a "cross-over" point in both studies occurs at about 3 months.

Specimens. Not surprisingly, in view of the fact that a "mature plaque" sheds out more readily at surgery, all of the reported and intact specimens revealed a high degree of stenosis. Their pathological observations were not extended to plaques from patients with moderate stenosis, and yet their conclusions embrace the gamut of lesions from mild to most severe. Their observations must be regarded as inconclusive without validation being accorded to a larger number of patients and a full range of stenosing lesions.

By their own admission, the measurement of area stenosis by their own scrupulous use of ultrasound instrumentation in this small series was not discrepant from their own method of calculation applied to their arteriograms. If all ultrasound laboratories were as well equipped and meticulous and all the reported large series could claim such an exact correlation, there would be less of a problem in utilizing this methodology to decide on surgery, at least for the extracranial part of the cerebral circulation. Being much safer than conventional arteriography, improved ultrasound coupled with MRA could become eventually the best combination of preoperative investigations.

There is a serious flaw in the paper by Alexandrov et al that has been drawn to the editorialists' attention by the Editors of Stroke. This flaw invalidates some of the
conclusions: The analyses of the data in the article by Alexandrov et al are based on linear correlations of the percent stenoses calculated in various ways. This approach is fine when linear values are compared with linear values. However, when area measurements are related to linear variables, this is an improper or less-than-ideal technique that would not be expected to yield very high correlations. This is because linear variables and the areas derived from them are related to each other by a quadratic relationship. For example, the area of a circle is proportional to the square of the radius. If one fits a linear relationship to the integers 1, 2, 3, 4, etc., over a broad range of values on one hand and their squares on the other, one would not ordinarily expect a very high correlation. This is seen in Fig 2 of the Alexandrov paper: as the linear variable increases, the relationship curves off and progressively deviates more markedly from a straight line. Only if the range of linear variables is limited would one expect a high correlation, because over a limited range of values a straight line can approximate a higher order relationship, such as a quadratic relationship. Accordingly, Alexandrov et al should have used a relation of the type \( y=ax+bx^2+c \) (where \( y \) is the area and \( x \) the linear variable, and \( a, b, \) and \( c \) are coefficients determined statistically) when they compared area measurements to linear measurements. Their failure to do so misled them into erroneous interpretations.

Contrary to what is stated in the article by Alexandrov et al, the results they present show clearly that the methods used in the NASCET and possibly in the ECST studies for measuring the percent stenoses represent excellent techniques that measure the percent stenoses very accurately. This is shown in the in vivo data, in which the area calculated from the linear measurements as done in the NASCET study (N\(^2\)) gives a mean value for the percent stenoses numerically exactly equal to the so-called “true” value calculated from the duplex data and a correlation coefficient that is exceedingly high (0.917). This is an almost perfect correlation. The correlation with the area calculated by the ECST techniques (E\(^2\)) does not have as high a correlation, probably because of a different choice of the normal vessel to compare with and possibly as a result of deviations from a circular shape of cross-sectional area. Similar relationships are seen in the data from the 15 patients from whom the plaque was removed. In this case, both the areas calculated by the NASCET and the ECST methods show excellent agreement with the data from the duplex method as well as from the planimetry of the angiographic data. Evidently, the authors expect the linear measurements to have numerically equal values to the areas. This, of course, cannot be so because of the quadratic relationship between the linear values and the areas. This is an elementary and serious misinterpretation that skews the conclusions.

We are aware that the formulae used by NASCET and ECST give different measures of the degrees of stenosis in the same arteriogram. In their preliminary report of benefit for surgery, the ECST used a larger denominator in the equation (the carotid bulb) than did NASCET (the artery beyond the bulb and the disease). We have reported that 48% of ECST patients previously designated as “severe” (ie, greater than 70% stenosis) became “moderate” (ie, less than 70% stenosis) when remeasured by the NASCET formula.\(^6\) The survival curves in both trials when the ECST arteriogram measurements were adjusted to correspond with the NASCET measurements and calculations are remarkably similar (Figure). Both trials have conducted interobserver and intraobserver studies that validate the reproducibility by blinded observers of the respective arteriographic measurements used in NASCET and ECST. Final resolution of the benefit of surgery for the high-moderate patient (50% to 69% stenosis by NASCET measurements and less than 82% stenosis as NASCET measures apply to ECST patients) awaits the completion of the ongoing phases of NASCET and ECST. When these two trials are completed, it will be simple to resolve the question of whether to use the NASCET method or a modified ECST method as the ideal measure of arteriographic stenosis. It will serve no useful purpose to drop both at this time and adopt an ultrasonographic measurement against which treatment benefit has never been validated.

The confirmation that the NASCET and ECST measurements of stenosis are equally good predictors of ipsilateral stroke is reassuring because the yardstick against which decisions are made about surgery depend for the immediate future upon the degree of stenosis found in an arteriogram. No other group of patients save those with symptoms due to a linear stenosis at and above 70% by arteriography can be claimed to have been shown to benefit from endarterectomy.

Therapeutic decisions and the reproducible index of the degree of narrowing are independent of any discussion of the search for a definition of “true” stenosis. The compelling quest is for a method of measurement that during life predicts ipsilateral ischemic stroke, not what will be seen at surgery or after death. It would be unnecessary, indeed absurd, to recommend that the surgical trials be repeated using noninvasive technology. The search must be for a reproducible method of converting the percentage measurements of NASCET and ECST taken from arteriograms to the newest and best noninvasive method, whatever it proves to be. If this conversion is found to be reliably correlated with the diameter arteriographic measurements, it will be possible then to predict without arteriography which patients will benefit from carotid endarterectomy. That is what we really want. At the present time, this benefit applies to a symptomatic patient with a stenosis of 70% or greater. The accurate identification of a variety of cut-off points may become equally important when the ongoing phase of NASCET and ECST for patients with less than 70% stenosis is completed, and it certainly will be a major requirement if the ongoing asymptomatic studies identify a specific group of patients above a certain level of stenosis who benefit from surgery.

Two vital caveats must be extended to the application of ECST and NASCET results to clinical practice. First and possibly foremost, the surgical procedure must be performed with the skill of the trial surgeons. Otherwise, the benefit of surgery compared to medical care alone will slip away. Second, extreme care will be demanded of those who interpret the images which at this point in time will have to be selective arteriograms.

Finally, skepticism must be accorded to the confidence which Alexandrov and his colleagues have extended to the “eyeballing” method of recording the
degree of stenosis. Surely it cannot be claimed to be good science to advocate a method of measurement which cannot be objectively taught? The patients being selected for a surgical procedure which even in the most skilled hands carries a real (albeit small) risk of complicating stroke deserve evaluation that is as free from guesswork as modern radiology departments can provide. Our experience in these trials that have involved thousands of patients has shown us that estimates without careful measurement can be remarkably variable. Overestimation puts patients into the “severe” category when they are not and underestimation denies patients surgery or entry into the “moderate” arm of NASCET and ECST.

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