Symptomatic Carotid Artery Stenosis: A Solvable Problem

North American Symptomatic Carotid Endarterectomy Trial

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Last year, the first report appeared from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[1] An editorial in *Stroke* remarked enthusiastically upon the results.[2] Striking benefit could be attributed to surgery. The positive result applied only to symptomatic patients who had a very tight stenosis. In terms of stroke, this subgroup of patients treated without surgery proved to have an extremely grave outlook. Stemming directly from this poor outlook and because of low rates of perioperative complications, the 30-day and the 2-year differences in stroke between the medically treated patients and those in the surgical arm were compelling. This difference exceeded by a factor of three, if not four, that which had been anticipated by contemporary knowledge and opinion.[3] Accordingly, this phase of NASCET was concluded 3 years earlier than had been projected at the onset of the trial. The European Carotid Surgery Trial (ECST), with some differences in design and execution, reached comparable conclusions and also stopped the entry of patients with severe stenosis.[4]

February 1992 marked the first anniversary of the declaration of this dramatic result. The investigators expected that the disclosure of this good news would precipitate a rush, if not a positive stampede, to continue and conclude the final phase of NASCET: the evaluation of endarterectomy in patients with less than very severe degrees of stenosis. This editorial is another "expression of concern" that there has not been such an outburst of activity. The trial for the vital second phase proceeds at a pace no greater than that established between 1988 and 1991. The 50 centers that made up the NASCET team during these first years randomized 701 patients with moderate stenosis, a rate of 19 per month. After the gratifying announcement was made, the number of patients entered into the study with moderate symptomatic disease has not exceeded this monthly number despite an increase to 75 participating centers.

Several factors may contribute to this inertia:

1. The good news about the benefit found in the patients with very severe disease has led some referring communities to assume that the trial is finished. This erroneous impression is being corrected as quickly as possible.

2. In many centers, there has been an understandable, but erroneous, extrapolation of this positive result to patients with less than severe degrees of stenosis. The profession is understandably prone to accord an enthusiastic welcome to proven therapies and readily extends these indications to what are perceived as parallel clinical situations. The conscientious practitioner is keen to apply all knowledge to help his or her patients. It takes time for the restrictions in the applicability of new knowledge to be appreciated and disseminated. Residents are understandably keen to learn the art of endarterectomy. They may persuade themselves and their patients of the benefit to be anticipated at levels lower than are known with certainty.

3. In centers committed to NASCET, a 50% decline has been recorded in the past year in the number of patients randomized into the 60–69% grouping (Figure 1). The measurements for the degrees of stenosis in the arteriograms of patients in the 6th decile are being rounded up to 70% and becoming severe by NASCET categorization.

In a review in one of our centers, it was determined that this upgrading can be overestimated by as much as 25% of the diameter.[5] Many patients with stenosis designated as severe do not come to the attention of the NASCET centers, but yet a number of those undergoing surgery must be less than severe by NASCET criteria.

It has to be assumed also that patients with no more than moderate degrees of stenosis by NASCET criteria are being operated on in their own hospitals without being referred to participating NASCET centers.

Important caveats relative to angiographic data have been stressed in the NASCET reports. The measurement of the degree of stenosis on which the proof of benefit depended was rigid and demanding. To obtain the percent stenosis, the diameter of the normal artery beyond the bulb and beyond the disease involving the bifurcation

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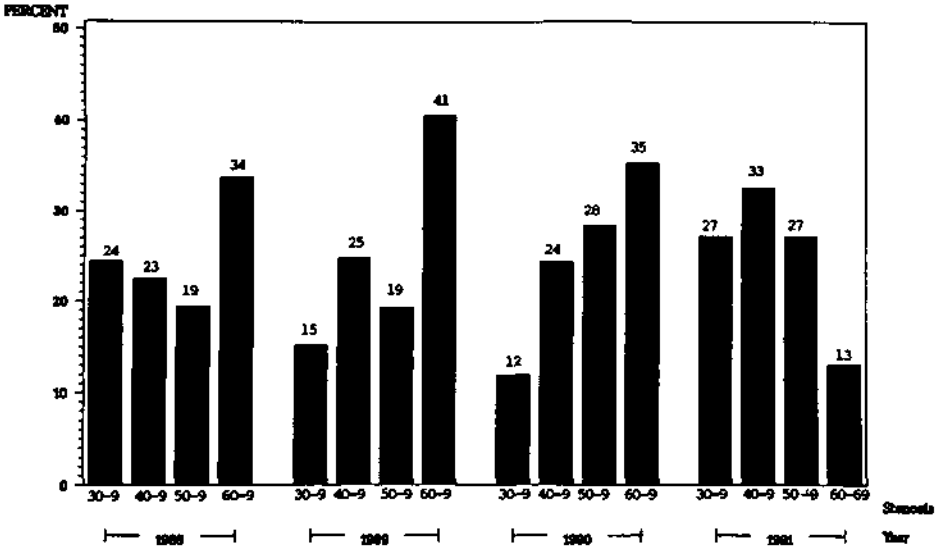

FIGURE 1. *Bar graph depicting distribution of stenosis by year of randomization, showing number of patients in several deciles of stenosis entered into NASCET during 1988–1991. Falloff of those in 6th decile indicates tendency to assume benefit for patients with this degree (60–69%) of stenosis. For this assumption, firm data are nonexistent but will be acquired in continuing NASCET program.*

was the denominator to be compared with the most narrowed segment seen in the arteriogram. No exact information about benefit can be inferred from NASCET analyses if the method of measurement compares instead a dilated or residual carotid bulb to the narrowest segment. Using such a measurement of the bulb as the diameter in the equation adds more patients to the severe category than were included in the NASCET analyses. The putative benefit for these less-severe patients is the prime question being addressed in the ongoing trial.

Ultrasound studies were not used to determine the qualifying degree of stenosis in NASCET. This technique provides a good measure of functional stenosis but will more quickly report a 70% narrowing. Studies have not been conducted to validate ultrasound measurements against those made with the rigid geometric criteria of NASCET. No results of surgical benefit in series dependent on the use of ultrasound measurements have been published except as uncontrolled case studies. Therefore, their use must be regarded as a screening procedure with unproven usefulness in deciding on surgical benefit and, thus, in deciding on appropriateness for surgery. We regard their use in potential NASCET patients as a step along the way in determining the presence or absence of disease in individual patients who merit further study.

4. We are aware that in some quarters, the reporting of a positive benefit for surgery in patients with tight stenosis has led as well to another presumption: that there is no need to investigate any patient whose initial ultrasound studies reveal less than a tight stenosis. This presumes that, because no data exist for patients with symptoms related to less than 70% stenosis (by the rigid methods of angiographic measurements), they will not benefit. The lack of knowledge cannot be used to deny the possibility of benefit. All such patients deserve to know that the profession is determined to acquire accurate evidence about the actual point below which individuals with a given profile of risk factors are not expected to benefit from surgery and above which benefit has been proven by NASCET. The trial for patients in these lesser categories must continue.

NASCET has not enjoyed the enthusiastic endorsement of all who deal medically and surgically with stroke-threatened patients. During 1988 and 1989, 140,000 patients received carotid endarterectomy in the non-Veteran's hospitals in America. In these years, the trial randomized a total of 893 patients, half of whom came from the United States and half from Canada. Thus, in the years for which a figure for total numbers of endarterectomies is available, we enrolled 0.3% of the total number of patients in the United States who had been persuaded to have this operation. It is likely that one third of the 140,000 patients were not eligible for NASCET because they had no symptoms or, at most, had vague (so-called nonhemispheric) symptoms. Others would have been excluded by the demands of our protocol, including the requirement that symptoms had occurred within the past 6 months and that there was no evidence of serious organ failure.

The disappointing lack of involvement in NASCET of many physicians, surgeons, and centers involved in the use of this surgical procedure has a variety of explanations. Some centers may have never been approached to collaborate, and some may not have known of the trial. Other centers and practitioners, for a variety of reasons, have been reluctant to join or support NASCET by referring their patients. These reasons need not be dealt with extensively, but they embrace such motivations as the desire to "do something positive when serious disease threatens," a genuine belief in the anecdotal evidence of benefit from the procedure without reference to severity, and a dislike of clinical trials assigning patients to a treatment by randomization. Some practitioners have told us frankly that their practices include such a major vested interest in the diagnostic and operative procedures associated with this treatment that they are not prepared to alter present practice procedures. The regulatory constraints of managed medical plans discourage referrals from busy practice centers to academic units. Many consulting physicians and surgeons specializing in the field of stroke have reported to us that if they were to join a randomized trial, their referring practitioners would send their patients to another center where their expressed wishes for their own treatment of choice would be followed, rather than

having them submitted to a randomization process that might not result in the treatment of their prejudice. In the opinion of a great many members of the profession, the procedure of carotid endarterectomy is a "standard treatment," and they are not prepared to reverse this thinking and cast it in the category of an experimental treatment modality for any degree of stenosis. If proof obtained by scientific study is the sine quo non to define proof of efficacy, it is the opinion of the NASCET investigators that there is no reason to regard surgery for patients with moderate stenosis as having emerged beyond the hypothetical and, therefore, experimental stage.

The NASCET investigators were at pains to point out, in reporting the first results from this study, that there were, as yet, no data motivating the Monitoring Committee to declare benefit or harm for patients with less than very severe stenosis. The same message was given to the European trialists by their independent Monitoring Committee. In addition, it was pointed out that the differences between the stroke-free survival at 2 years for the medical and the surgical groups declined quite precipitously between the patients in the 9th and those in the 7th decile. The absolute differences for 90–99%, 80–89%, and 70–79% were 26%, 18%, and 12%, respectively. If this decline in benefit continues into the 60% range, as it well may do, the benefit from surgery may not exceed that from nonsurgical management.

The study has evidence that a large number of risk factors add to the poor outlook and reinforces the need for urgent surgery in patients with severe stenosis. By contrast, in the absence of substantial numbers of attendant risk factors, there is a diminishing likelihood of surgical benefit, particularly in the 70% decile of stenosis. Patients with stenosis in the 60–69% range without other risk factors may prove, for all anybody knows, to be no better off with surgery than with only medical care.

Compelling reasons require the completion of NASCET as quickly as is compatible with obtaining an enduring answer. The speculation that has stalked our discussions with patients for nearly 40 years can be replaced by scientific certainty. What a relief this will bring at the bedside and in the clinic! There are some important economic gains to consider as well. Some financial expenditures related to carotid endarterectomy can be claimed, without equivocation, to be eminently justified in health-care budgets. NASCET has demonstrated that, by receiving endarterectomy, many patients with severe stenosis will be spared the devastating and expensive burden of stroke. The same will be true for whatever group of "moderate" patients emerges as benefiting in the final stage of the trial. Just as importantly, we will be able to claim to the public that for those who do not benefit (if such there be) in the moderate group, we will have hard evidence that eliminates the need for placing them at the definite risk of endarterectomy. A large and unnecessary expenditure of health-care dollars may be eliminated.

No civil servant or actuary concerned with health-care financing can deny the great merit of accepting an expense that prevents 17 strokes in 2 years for every 100 patients with very severe carotid stenosis who are submitted to endarterectomy with NASCET levels of perioperative stroke and death. Conversely, bureaucrats and health-care providers are concerned about our lack of awareness of the appropriateness of the procedure in a substantial population of those receiving carotid endarterectomy. The cost to the health-care system of the United States to investigate and submit 100,000 patients per year to endarterectomy in 1984 was $1.2 billion.[6] With rising costs, the same number of these procedures in 1992 would cost something in the neighborhood of $2 billion. Estimating that only one third of these are related to severe disease and at least one third to asymptomatic disease, the conclusion of NASCET and the asymptomatic studies will determine how much of this $2 billion should continue to be committed and how much should be eliminated from the health-care budgets of the United States and Canada.

With a major push from all of those interested in stroke prevention, 2 or 3 years could be cut from the time needed to obtain the answers. The practitioners of North America and, in particular, the readers of *Stroke* are urged to be fully supportive of NASCET. The Editor has agreed to list in the Appendix of this article the North American centers at which the trial is being conducted and the contact person in each center. A toll-free number is available that will direct practitioners to the nearest NASCET center coordinator: 1-800-565-6331.

Appendix

Centers and Coordinators (as of April 23, 1992)

Location	Institution	Coordinator	Telephone number
	United States		
Arizona			
Tucson	University of Arizona	Brenda Vold	(602) 626-4150 792-1450 x5482, 6426
Phoenix	Barrow Neurological Institute	Heidi Jahnke	(602) 285-3000 pg #17-9449 or x3343 (602) 285-3489
Arkansas			
Little Rock	University of Arkansas	Lee Ann Kennedy	(501) 660-2070
Hot Springs	AMI National Park Hospital/St. Joseph's Regional Hospital	Sylvie Frank	(501) 623-0280 623-6216

Centers and Coordinators (as of April 23, 1992) *Continued.*

Location	Institution	Coordinator	Telephone number
California			
San Diego	University of California	Gerry Cali	(619) 294-6170
Los Angeles	University of California School of Medicine	Kathleen G. Walden	(310) 825-6327 825-6301 pg #91327
Los Angeles	Wadsworth VA Hospital	Stanley Cohen, MD	(310) 824-3206 478-3711
Los Angeles	University of Southern California	Sebastian Ameriso, MD	(213) 224-7921 224-7243
San Francisco	California Pacific Medical Center	Patricia Radosevich	(415) 923-3194
Colorado, Englewood	Colorado Neurological Institute	Chris Schumann	(303) 788-4012 788-6911
Florida			
Tampa	University of South Florida	Rachel Varghese	(813) 398-9387 972-2000 pg #269
Miami	University of Miami	Vilma Alfonso	(305) 324-4920
Gainesville	University of Florida	Debbie Brooks	(904) 395-0605 395-0111 pg #2070
Illinois			
Chicago	University of Chicago	Dainis Irbe, MD	(312) 702-1780
Hines	Hines VA/Loyola Medical Center	John Maggio, PhD	(708) 343-7200 x5714
Chicago	University of Illinois	Julie Hoff	(312) 996-9340 996-6780 pg #2489
Chicago	Northwestern University	Linda Chadwick	(312) 908-5834 908-4159
Chicago	Rush Presbyterian–St. Luke's Medical Center	Michael A. Kelly, MD	(312) 563-2030
Indiana, Indianapolis	Indiana University School of Medicine	Kathy Browning	(317) 274-7808 635-7401 pg #437
Iowa			
Iowa City	University of Iowa	Vicki Mitchell	(319) 356-8743 356-2571
Des Moines	Iowa Methodist Medical Center	Mary Beth Craig	(515) 241-8033 280-0301 (beeper)
Kentucky, Lexington	University of Kentucky	Marion McClain	(606) 233-5534
Maryland, Baltimore	Francis Scott Key Medical Center	Brenda Stone	(301) 550-0939
Massachusetts			
Boston	Beth Israel Hospital	Maria Tijerina	(617) 735-4378
Boston	Boston University	Eloise Licata-Gehr	(617) 859-8441
Boston	VA Medical Center	Nancy Allen	(617) 232-9500 x4750
Boston	St. Elizabeth's Hospital	Cindy Yasuda	(617) 789-2364
Minnesota, Minneapolis	University of Minnesota	Nancy Olson	(612) 538-4476 (beeper) 624-8651 or 725-2000 x4260
Mississippi, Jackson	University of Mississippi Medical Center	Robin L. Brown	(601) 984-5700 984-5724 (page)
Missouri			
Columbia	University of Missouri	Anne Bonnett	(314) 882-8040
St. Louis	St. Louis University	Gerry Banet	(314) 577-8738
New Hampshire, Lebanon	Dartmouth–Hitchcock Medical Center	Phyllis Orem	(603) 650-8304
New Mexico, Albuquerque	University of New Mexico	Eda Lyn Johnson	(505) 256-2703

Centers and Coordinators (as of April 23, 1992) *Continued.*

Location	Institution	Coordinator	Telephone number
New York			
Buffalo	Dent Neurologic Institute	Donna Cwudzinski	(716) 887-4555 887-4910
Syracuse	State University of New York	Carole Ficarra	(315) 476-7461 x2512, 2472
New York	New York University	Pat Stewart	(212) 263-6347
Bronx	Montefiore Medical Center	Emelia Klonowski	(212) 920-4232
New York	Neurological Institute/Columbia University	Annette Cruz	(212) 305-7755
Buffalo	DVA Medical Center	Karen Eschberger	(716) 862-3434 834-9200 x2085
New York	Cornell University Medical Center	Helene Abramson	(212) 314-1470 (beeper) 746-4861 or 746-6564
Ohio			
Cincinnati	Good Samaritan Hospital	Rick Helmchen	(513) 872-4009 872-1400 pg #494
Columbus	Ohio State University	Tia Brink	(614) 293-4970
Oregon			
Portland	University of Oregon	Pat de Garmo	(503) 494-7772
Portland	VA Hospital	Prudence Marshall	(503) 273-5172
Pennsylvania			
Pittsburgh	University of Pittsburgh	Sharon DeCesare	(412) 648-1948
Philadelphia	Temple University	Gretel Larese-Ortiz	(215) 221-4350
Allentown	Lehigh Valley Hospital Center	Donna Jenny	(215) 776-8241 776-8999 (overhead page)
Rhode Island, Providence	Rhode Island Hospital	Jo-Ann Sarafin	(401) 277-8795
Tennessee, Memphis	University of Tennessee	Judy Riley	(901) 528-7052
Texas			
Dallas	University of Texas	JoAnne Heller	(214) 688-6841 688-3516
Houston	University of Texas	Patti Bratina/Dora Vital	(713) 792-5777
San Antonio	University of Texas	Diane Rogers	(512) 617-5161
Virginia			
Marshfield	Marshfield Medical Research Foundation	Charmaine Matti	(715) 387-5796
Richmond	Virginia Commonwealth University	Jo Carter	(804) 786-4806 230-1327
Wisconsin			
Madison	University of Wisconsin	Judy Archibald	(608) 256-1901 x7977 (pg) x7976 (mess.)
Eau Claire	Sacred Heart Hospital	Pamela Wold	(715) 839-4180
	Canada		
Alberta			
Calgary	University of Calgary	Maureen Robertson	(403) 268-9666
Edmonton	University of Alberta	Edna Hutchings	(403) 492-8297
British Columbia, Vancouver	University of British Columbia	Jo-Lue Bloomer	(604) 875-4111 x3824
Manitoba, Winnipeg	University of Manitoba	Dan Gladish	(204) 235-3303
Newfoundland, St. John's	Memorial University	Kathy Murphy	(709) 737-6585
Nova Scotia, Halifax	Dalhousie University	Joanne McCormick	(902) 428-7424
Ontario			
Hamilton	McMaster University	Sera Nicosia	(416) 522-7432
Ottawa	University of Ottawa		(613) 761-4377

Centers and Coordinators (as of April 23, 1992) *Continued.*

Location	Institution	Coordinator	Telephone number
Toronto	Toronto Downtown Hospital	Barbara Huth/Sue Slattery	(416) 369-5413
Toronto	Mississauga Hospital	Gillian Barnard	(416) 279-5958
London	Victoria Hospital	Leslie Paddock	(519) 667-6784 667-6714
London	University of Western Ontario	Connie Swan	(519) 663-3500
Toronto	Sunnybrook Health Science Centre	Beverly Bowyer	(416) 480-4287
Quebec			
Quebec City	Hopital St.-Sacrement	Louise Lessard	(481) 682-7622
Chicoutimi	L'Hopital de Chicoutimi	Barbara Leger	(481) 549-2195 x22716
Montreal	Hopital St.-Luc/Charles Lemoyne Hosp.	Marie-Paule Desrochers	(514) 281-2480 281-2444
Montreal	Montreal General Hospital	France Bourque	(514) 934-8057 937-6011 x4233, 4303
Quebec City	Hopital de L'Enfant-Jesus	Alice Lajeunesse	(418) 649-5892 648-2862
Montreal	Jewish General Hospital/Notre Dame	Shirley Entis	(514) 340-8222 x5200
Saskatchewan, Saskatoon	University of Saskatchewan	Carol Regier	(306) 966-8007
	Overseas		
Finland			
Helsinki	University of Helsinki	Riitta Lonnqvist	358-0-4712662
Oulu	University of Oulu	Maarit Nappa	358-81-3154515
Tampere	Tampere University Hospital	Sirpa Antonen	358-31-2475111
Israel			
Haifa	Rambam Medical Center	Prof. A. Schramek	972-4-534887
Jerusalem	Hadassah University	Avinoam Reches, MD	972-2-427427
Tel Aviv	Tel Aviv Elias Sourasky Medical Center	Boris Aronovich, MD	972-3-6973414

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