Special Report

Why Calls for More Routine Carotid Stenting Are Currently Inappropriate

An International, Multispecialty, Expert Review and Position Statement

Anne L. Abbott, MD, PhD, FRACP; Mark A. Adelman, MD; Andrei V. Alexandrov, MD; P. Alan Barber, PhD, MBChB, FRACP; Henry J.M. Barnett, CC, MD; Jonathan Beard, FRCS, ChM, MD; Peter Bell, FRCS, MD, DSC, KBE; Martin Björck, MD, PhD; David Blacker, MD, FRACP; Leo H. Bonati, MD; Martin M. Brown, MD, FRCP; Clifford J. Buckley, MD, FACS; Richard P. Cambria, MD; John E. Castaldo, MD; Anthony J. Comerota, MD, FACS, RVT; E. Sander Connolly, Jr, MD; Ronald L. Dalman, MD, FACS; Alun H. Davies, MA, DM, FRCS, FHEA, FEBVS, FACPh; Hans-Henning Eckstein, MD, PhD; Rishad Faruqi, MD, FRCS (Eng), FRCS (Ed), FACS; Thomas E. Feasby, MD; Gustav Fraidrich, MD; Peter Gloviczki, MD; Graeme J. Hankey, MD, FRACP; Robert E. Harbaugh, MD, FAANS, FACS; Eitan Heldenberg, MD; Michael G. Hennerici, MD; Michael D. Hill, MD, MSc, FRCPC; Timothy J. Kleining, PhD FRACP, MBBS (Hons), BA; Dimitri P. Mikhailidis, BSc, MSc, MD, FRSPH, FCP, FFPM, FRCP, FRCPath; Wesley S. Moore, MD; Ross Naylor, MD, FRCS; Andrew Nicolaides, MS, FRCS, PhD (Hon); Kosmas I. Paraskevas, MD, PhD; David M. Pelz, MD, FRCPC; James W. Prichard, MD; Grant Purdie, MD, FRACP; Jean-Baptiste Ricco, MD, PhD; Peter A. Ringleb, MD, PhD; Thomas Riles, MD; Peter M. Rothwell, MD, PhD, FRCP, FMedSci; Peter Sandercock, MA, DM, FRCPE, FMedSci; Henrik Sillesen, MD, DMSc; J. David Spence, BA, MBA, MD, FRCP, FCAHS; Francesco Spinelli, MD; Jonathon Sturm, MBChB, PhD; Aaron Tan, MD, FRACP; Ankur Thapar, BSc, MBBS, MRCS; Frank J. Veith, MD; Tissa Wijeratne, MD, FRACP; Wei Zhou, MD

Received November 24, 2012; final revision received January 18, 2013; accepted January 28, 2013.

From the School of Public Health and Preventive Medicine, The Alfred Centre, Monash University, Melbourne, Australia (A.L.A.); Baker IDI Heart and Diabetes Institute, Melbourne, Australia (A.L.A.); Florey Institute of Neuroscience and Mental Health, Melbourne, Australia (A.L.A.); Division of Vascular and Endovascular Surgery, New York University Langone Medical Center, New York, NY (M.A.A.); Comprehensive Stroke Center, University of Alabama Hospital, Birmingham, AL (A.V.A.); Department of Medicine, Centre for Brain Research, University of Auckland, Auckland, New Zealand (A.B.); Clinical Neurological Sciences, Division of Neurology, University of Western Ontario, London, Canada (H.J.M.B.); Sheffield Vascular Institute, Northern General Hospital, Sheffield, United Kingdom (J.B.); University of Leicester, University of Leicester Hospitals, Leicester, United Kingdom (P.B.); Department of Surgical Sciences, Vascular Surgery, Uppsala University, Uppsala, Sweden (M.B.); Neurology Department, Sir Charles Gairdner Hospital, Perth, Australia (D.B.); Department of Neurology and Stroke Unit, University Hospital Basel, Basel, Switzerland (L.B.); UCL Institute of Neurology, The National Hospital, Queen Square, London, United Kingdom (M.B.); Texas A&M Health Sciences Center College of Medicine, Scott and White Health Care Systems, Central Texas Veterans Health Care System, Temple, TX (C.J.B.); Division of Vascular and Endovascular Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA (R.P.C.); Neurology Division, USF College of Medicine, Lehigh Valley Health Network, Allentown, PA (J.E.C.); Jobst Vascular Institute, The Toledo Hospital, Toledo, OH (A.J.C.); Department of Neurological Surgery, Columbia University, New York, NY (E.S.C.); Divisions of Vascular Surgery and Cardiovascular Health (Quality and Outcomes), Stanford University, Stanford, CA (R.L.D.); Academic Section of Vascular Surgery, Department of Surgery and Urology, Imperial College School of Medicine, Charing Cross Hospital, London, United Kingdom (A.H.D.); Department for Vascular and Endovascular Surgery/Vascular Center, Klinikum rechts der Isar der Technischen Universität München, München, Germany (H.-E.H.); Stanford University, Stanford, CA (R.F.); University of California, San Francisco, CA (R.F.); Department of Vascular and Endovascular Surgery, Kaiser Permanente Medical Center, Santa Clara, CA (R.F.); Department of Clinical Neurosciences Faculty of Medicine, University of Calgary, Calgary, Canada (T.E.F.); Department of Vascular Surgery, Medical University, Innsbruck, Austria (G.F.); Division of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN (P.G.); Neurology Department, Royal Perth Hospital, University of Western Australia, Perth, Australia (G.J.H.); Penn State Institute of the Neurosciences, Penn State University, Hershey, PA (R.E.H.); Department of Vascular Surgery, Assaf Harofeh Medical Center, Zerifin, Israel (E.H.); Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (E.H.); Neurologische Universitätsklinik, Universitätsmedizin Mannheim, UMM; University of Heidelberg, Mannheim, Germany (M.G.H.); Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada (M.H.D.); Neurology Department, Royal Adelaide and Lyell McEwin Hospitals, Adelaide, Australia (T.J.K.); Department of Medicine, University of Adelaide, Adelaide, Australia (T.J.K.); Department of Clinical Biochemistry (Vascular Disease Prevention Clinics), Royal Free Hospital Campus, University College London Medical School, University College London, London, United Kingdom (D.P.M.); Division of Vascular Surgery, UCLA, Los Angeles, CA (W.S.M.); Vascular Surgery Group, Division of Cardiovascular Sciences, Leicester Royal Infirmary, University of Leicester, Leicester, United Kingdom (R.N.); Department of Vascular Surgery, Imperial College, London, Vascular Non-invasive Diagnostic Centre, London, United Kingdom (A.N.); Red Cross Hospital, Athens, Greece (K.I.P.); Medical Imaging and Clinical Neurological Sciences, University of Western Ontario, London, ON, Canada (D.M.P.); Neurology Department, Yale Medical School, New Haven, CT (J.W.P.); Neurology Department, The Queen Elizabeth (Stroke. 2013;44:1186-1190.)

© 2013 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.000261
To avoid misguidance from calls for more routine practice (nontrial) carotid angioplasty/stenting (CAS), we need to distinguish relevant facts and patients’ best interests from all else (distractions). A recent editorial by White and Jaff is one publication which illustrates this need particularly well. First, these authors are correct in reminding us that the responsibility of physicians is to provide best patient care, putting aside personal interest. This is inherent in any profession. However, misconception, bias, and conflict of interest exist. Therefore, healthcare payment organizations, such as the US Center for Medicare and Medicaid Services are important gatekeepers to facilitate patient access to interventions that are likely to help them, as opposed to all others.

It is also true that CAS and carotid endarterectomy (CEA) result in better outcomes when patients are carefully selected and skilled operators perform the procedures in experienced centers. We would add that key indicators (such as 30-day periprocedural stroke/death rates) must be accurately measured in routine (real-world) practice, particularly as stroke and death rates here may be unacceptably higher than in trials. Therefore, it is most appropriate, as suggested by White and Jaff, that coverage for carotid procedures be dependent on facility accreditation and audited measurement of key standards indicators in all practices performing these procedures. This is a priority issue.

White and Jaff correctly state “a major change in evidence based stroke prevention strategies will require clinical trial data.” These authors are calling for extended US Center for Medicare and Medicaid Services funding for CAS beyond the current indication of high surgical risk symptomatic patients to include asymptomatic and low/average surgical risk symptomatic patients. For CAS, there is a substantial body of data from randomized trials (including the Carotid Revascularization Endarterectomy versus Stenting Trial [CREST]), meta-analyses, and routine practice. Most of these data relate to low/average risk symptomatic patients and demonstrate that, for these patients, even in the best academic centers, CAS is consistently associated with significantly higher rates of stroke or death (during or after the periprocedural period) compared with CEA. It is incorrect that CREST “failed to show a difference in overall stroke rate between CAS and CEA” as stated by White and Jaff. In CREST, for average surgical risk symptomatic patients, the periprocedural stroke and death rates were 6.0% for CAS versus 3.2% for CEA (hazard ratio, 1.89; 95% confidence interval, 1.11–3.21; P=0.02). This indicates that a one-size-fits-all procedural treatment alone. This is about 3× lower than that of asymptomatic CREST CAS-treated patients and about half the rate of asymptomatic CREST CEA-treated patients. This low rate with medical treatment is likely to fall further with improvements in efficacy, definition, and implementation.

The higher periprocedural risk of stroke or death with CAS is particularly evident in the most senior patients (>68–70 years), those undergoing the procedure <7 days of incidental cerebral or retinal ischemic symptoms (when CEA has the highest stroke prevention potential), those undergoing CAS outside clinical trials, and those with certain anatomic features. No study has shown that CAS is more effective than CEA in preventing stroke. Further, most analyses show that CAS costs considerably more, despite calculations derived from CREST results. No randomized trial has been adequately powered to compare the procedural and longer term risk of CAS on stroke or death in low/average risk asymptomatic patients. However, in CREST, the direction of effect was toward nearly twice the risk (periprocedural stroke/death rate was 2.5% for CAS versus 1.4% for CEA; hazard ratio, 1.88; 95% confidence interval, 0.79–4.42; P=0.15). This was consistent with the significantly higher periprocedural stroke rates seen in CREST CAS-treated asymptomatic patients.

Meanwhile, medical treatment for asymptomatic carotid disease has improved significantly since past randomized trials of medical treatment alone versus additional CEA. Medical treatment consists of identification of risk factors for heart and vascular disease and risk reduction using healthy lifestyles and appropriate drugs. Improvement in medical treatment is clear from robust analyses of all published comparable, quality stroke rate calculations (including from, and within, randomized surgical trials) of patients with 50% to 99% asymptomatic carotid stenosis. This knowledge is not, as claimed by White and Jaff, derived from short-cut extrapolation from coronary artery trials. Using the same standardized rate calculations, we are now seeing an average annual rate of ipsilateral stroke of 0.5% with medical treatment alone. This is about 3× lower than that of asymptomatic CREST CAS-treated patients and about half the rate of asymptomatic CREST CEA-treated patients. This low rate with medical treatment is likely to fall further with improvements in efficacy, definition, and implementation.

However, recently published rate calculations indicate that, at most, only 2.5% of low/average CEA risk patients with 50% to 99% asymptomatic carotid stenosis will receive a stroke prevention benefit from CEA or CAS during their remaining average 10-year lifetime if they receive good, current medical treatment (assuming the procedural risk of stroke/death is always zero). This indicates that a one-size-fits-all procedural...
approach for these asymptomatic patients is now unlikely to be beneficial overall. We need to be much more selective. Research is required to determine which asymptomatic subgroups now benefit from carotid procedures in addition to current optimal medical treatment.

We have found no direct information about the influence of current medical treatment in patients with low/average CEA risk symptomatic carotid stenosis. However, improving results for medically treated asymptomatic patients27–32 and procedural trial asymptomatic and symptomatic patients4 indicate that a 6% periprocedural risk of stroke or death (the current standard) is now too high. New randomized and risk stratification studies are required using current optimal medical treatment and procedural methods.36 For example, improved plaque37 and thrombus identification38 or embolic signal detection39 above and below the stenosis may help better identify carotid plaques responsible for carotid territory ischemic symptoms. Further, the best approach for patients with high surgical risk carotid stenosis remains uncertain because risk of stroke or death has not been measured with any standard of medical treatment or adequate procedural trials. However, some registries show significantly higher risks of stroke/death with CAS compared with CEA in asymptomatic and symptomatic high surgical risk patients.40

Calls from other authors for more routine CAS on the grounds of lower periprocedural myocardial infarction (MI) rates compared with CEA are distracting.41 MI is not a measure of stroke prevention efficacy, even though it is an important procedural complication. The inclusion of periprocedural MI with stroke and death in the primary outcome measure in CREST resulted in primary outcome equivalence between CAS and CEA. However, it did not result in efficacy equivalence. In CREST, 1.1% (14/1262) of CAS patients had periprocedural clinical MI (biomarkers plus chest pain/EKG evidence) compared with 2.3% (28/1240) of CEA patients5 (P=0.03). However, periprocedural stroke was nearly as common (81/2502; 3.2%) as periprocedural clinical MI (42/2502; 1.7%) and, as mentioned above, CAS caused almost twice as many of these strokes as CEA. Further, in CREST, the mortality rate up to 4 years was equally poor for CREST patients with periprocedural stroke (20%),42 periprocedural clinical MI (19%),41 or periprocedural biomarker-positive only MI (25%).41 Finally, nonfatal stroke was associated with a poorer quality of life at 1 year than nonfatal MI. Therefore, MI is a measure of carotid procedural risk (not benefit) and must be considered separately from stroke risk. Moreover, in CREST, CAS-associated stroke was more troublesome for patients than CEA-associated MI.

In conclusion, current global evidence shows that, even in the best academic centers, CAS is less effective (causing more strokes) and more expensive than CEA. It is premature that some guidelines have recently added support for routine practice CAS as an alternative to CEA for asymptomatic50,44 and low/average surgical risk symptomatic patients45–47 because CAS may easily be misinterpreted by readers as being equivalent for stroke prevention48 and historical procedural standards were cited. CAS, for these patients, should still only be performed and paid for within well-designed, adequately powered trials. The US Center for Medicare and Medicaid Services is doing its job and setting an excellent global example. It is protecting Medicare beneficiaries from routine practice procedures, which are currently more likely to harm them and waste finite resources47 that could be used for their advantage. Meanwhile, we need to reassess the current routine practice role of CEA and deliver optimal current medical treatment to all who need it.

Sources of Funding
Anne Abbott’s time on this project was partially supported by an Australian National Health and Medical Research Council Fellowship (ID: 472700) and supported in part by the Victorian Government’s OIS Program.

Disclosures
Henry Barnett was PI of the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Jonathan Beard is on the Steering Committee of the International Carotid Stenting Study (ICSS). David Blacker has received sponsorship to scientific meetings from Boehringer Ingelheim. He has previously been a member of the advisory board for NovoNordisk (regarding Factor VII) and receives funding for involvement in the Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin With Terutroban in Patients With a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) Study. Leo Bonati is a member of the ICSS Study Group, a member of the Steering Committee of the European Carotid Surgery Trial 2 (ECST-2) and the coordinating member of the Steering Committee of the Carotid Stenting Trialsists Collaboration (CSTC), Prof Martin Brown is the Chief Investigator of the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS), ICSS, and the ECST-2. Richard Cambria is co-PI for a future transcervical carotid stenting/flow reversal trial (ROADSTER). Anthony Comerota received research funding for the Jobst Vascular Institute to participate in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Ronald Dalman previously served as site PI for the Abbott Industries Protected Carotid Artery Stenting in Patients at High Risk for Carotid Endarterectomy (PROTECT) trial for California and is a co-holder of a provisional patent for a carotid distal protection device. Alun Davies receives funding from the Stroke Association on the evaluation of carotid plaque. Hans-Henning Eckstein is co-PI of the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE-2) Study. He was a member of the Steering Committee of the SPACE-1 Study. Gustav Fradrich is member of the steering committee of the Carotid Stenting Trialsists Collaboration (CSTC) and member of the steering committee of the SPACE-2-Study. He was a member of the Writing Committee of the SPACE-1 Study. Graeme Hankey was a member of the ECST Collaborative Group and the NASCET Collaborators. Michael Hennerici founded the European Stroke Conference: http://www.eurostroke.eu. He is a principal investigator, coordinator, and board member for several international clinical trials including the Clopodogrel versus Aspirin in Patients at Risk of Ischemic Events Trial (CAPRIE), Aspirin and Clopidogrel Compared With Clopidogrel Alone After Recent Ischemic Stroke or Transient Ischemic Attack in High-Risk Patients Trial (MATCH), Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trial (SPARCL), SPACE-1, and SPACE-2. Dimitri Mikhailidis has given talks and attended conferences sponsored by Merck, Sharp and Dohme, Genzyme, and Abbott Industries. Wesley Moore is a co-PI for the CREST and member of the CREST Executive Committee. Peter A. Ringleb is the Clinical coordinator of SPACE-1, a member of the steering committee of SPACE-2 and a member of the guideline-committee of the German Neurological Society, German Stroke Society, and European Stroke Organization. Peter Rothwell is on the Data Monitoring Committee of the SPACE-2 trial. He is Chair of the End point Adjudication Committee of the Asymptomatic Carotid Artery Surgery Trial-2 (ACST-2). He is on the Steering Committee of the ECST-2 and the General Anesthetic versus Local Anesthetic (GALA) for Carotid Surgery Trial. Peter Sandercock is the independent chair of the MRC/
References

1. White CJ, Jaff MR. Catch-22: Carotid stenting is safe and effective (Food and Drug Administration) but it is reasonable and necessary (Centers for Medicare and Medicaid Services)! Am Coll Cardiol Cardiovasc Interv. 2012;5:694–696.


**Key Words:** carotid angioplasty/stenting • carotid endarterectomy • carotid stenosis • health policy • stroke prevention •


*Stroke*. 2013;44:1186-1190; originally published online March 19, 2013;
doi: 10.1161/STROKEAHA.111.000261

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 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/44/4/1186

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/