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REVIEW

Clinical and Imaging Features Associated with an Increased Risk of Early and Late Stroke in Patients with Symptomatic Carotid Disease

A.R. Naylor [a,*], **H. Sillesen** [b], **T.V. Schroeder** [c]

[a] Department of Vascular Surgery at Leicester Royal Infirmary, Leicester, UK
[b] Department of Vascular Surgery at Rigshospitalet, Copenhagen, Denmark
[c] Centre for Clinical Education at Rigshospitalet and University of Copenhagen, Denmark

WHAT THIS PAPER ADDS

This is a contemporary review of clinical features, clinical scoring systems, and imaging parameters that have been associated with an increased (or decreased) risk of early/late stroke in patients with symptomatic carotid disease. Most, however, require independent validation before they can be applied to clinical practice.

Objective: The aim of this review was to identify clinical and/or imaging parameters that are associated with an increased (decreased) risk of early/late stroke in patients with symptomatic carotid disease.

In the first 14 days: Natural history studies suggest that 8–15% of patients with 50–99% stenoses will suffer a stroke within 72 hours of their index symptom. Currently, there are insufficient validated data to identify highest-risk patients for emergency carotid endarterectomy (CEA), but an increased risk of stroke appears to be predicted by (i) an $ABCD^2$ score of 4–7; (ii) the presence of acute cerebral injury on CT/MRI; (iii) Gray Scale Median (GSM) <15, (iv) spontaneous embolisation on Transcranial Doppler (TCD); and (v) increased fluorodeoxyglucose (FDG) uptake in the carotid plaque on positron emission tomography (PET). A future goal must be to develop predictive algorithms (based on accessible imaging strategies) for identifying acutely symptomatic patients with highly unstable plaques for emergency CEA.

Medium to long term: In the randomised trials, about 70% of patients with symptomatic 70–99% stenoses were stroke-free on "best medical therapy" at 5 years. Clinical predictors of increased stroke risk include (i) male gender; (ii) age >75; (iii) hemispheric symptoms; and (iv) increasing comorbidity. Imaging features associated with increased stroke risk include (i) irregular stenoses; (ii) contralateral occlusion; (iii) increasing stenosis severity, but not subocclusion; (iv) tandem intracranial disease; (v) a failure to recruit intracranial collaterals; (vi) low GSM; (vii) MR diagnosis of intra-plaque haemorrhage; (vii) spontaneous embolisation on TCD; and (viii) increased FDG uptake in the carotid plaque on PET. Clinical/imaging parameters associated with a lower risk of stroke include (i) female gender, especially those with 50–99% stenoses; (ii) ocular symptoms/lacunar stroke; (iii) smooth stenoses; and (iv) chronic subocclusion.

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INTRODUCTION

In 1991, the European Carotid Surgery Trial (ECST) and the North American Carotid Endarterectomy Trial (NASCET) reported that carotid endarterectomy (CEA) reduced the 5-year risk of stroke (compared with best medical therapy [BMT] alone) in patients with 50–99% stenoses who had suffered carotid territory symptoms within the preceding 6 months.[1,2] Since that time, a large amount of research has been published in a wide range of scientific journals, across a broad spectrum of medical disciplines, making it difficult for surgeons to remain appraised of potentially important developments and innovations.

Two areas of clinical practice are currently of particular interest in recently symptomatic patients. First, the risk of stroke in the early period after onset of symptoms appears

* Corresponding author. Vascular Research Group, Division of Cardiovascular Sciences, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE27LX, UK.
E-mail address: ross.naylor@uhl-tr.nhs.uk (A.R. Naylor).

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to be much higher than was previously thought, with contemporary natural history studies suggesting that 8—15% of patients with a 50—99% stenosis may suffer a stroke within 72 hours of their index presenting symptom.[3,4] This type of patient was rarely (if ever) randomised within ECST/NASCET and management strategies need to change to deliver interventions as soon as possible after onset of symptoms, accepting that benefit must always be balanced against the potential for increased procedural risk in some patients. It would clearly be advantageous if it were possible to develop and then validate accessible imaging strategies that were capable of identifying a small proportion of patients who would benefit most from emergency CEA or carotid artery stenting (CAS) within 72 hours of onset of symptoms, as opposed to those with a lower immediate stroke risk who could then undergo a delayed intervention.

Second, despite showing significant benefit favouring CEA, pooled data from ECST and NASCET[5] (Table 1) reveal that only 78 strokes would be prevented at 5 years per 1000 CEAs in patients with 50—69% stenoses (i.e. 922 [92%] were ultimately unnecessary), compared with 156 strokes prevented at 5 years in patients with 70—99% stenoses (i.e. 844 [84%] were ultimately unnecessary). Even if the procedural risk could be reduced to zero, the number of strokes prevented at 5 years per 1000 CEAs in patients with 50—69% stenoses would only increase to 162 (i.e. 838 [84%] were still ultimately unnecessary), while only 218 strokes would be prevented at 5 years in patients with 70—99% stenoses if they underwent CEA with a 0% risk (i.e. 782 [78%]) ultimately unnecessary). In short, although any strategy that reduces the procedural risk is to be welcomed, this will have relatively little impact on increasing the overall effectiveness of CEA in terms of late stroke prevention. It would clearly optimise decision-making and minimise exposure to avoidable risk, if clinical and/or imaging algorithms could identify a "high-risk for stroke" cohort in whom to target CEA/CAS. This is particularly important, as the concept of BMT has changed considerably since the 1990s. It is worth remembering that BMT (at the time of ECST/NASCET) was (at best) aspirin and smoking cessation advice. High-dose statins were not available and treatment goals for diabetes and hypertension were very much different to what is considered normal practice today.

The aim of this topical review is to deliver an overview of published data from the randomised trials (RCTs), as well as contemporary, non-randomised studies to inform the reader of clinical features, clinical scoring systems, and imaging strategies that have been shown to predict a greater (or lesser) risk of stroke, both in the hyperacute period after onset of symptoms and in the medium to long term.

THE RANDOMISED TRIALS

Table 1 summarises 5-year stroke rates (including perioperative stroke/death) in a meta-analysis of 6000+ patients randomised to CEA or BMT within ECST, NASCET, and the Veteran's Affairs (VA) Study.[5] While these trials are now somewhat historical and aspects of management have changed considerably (better medical therapy, emergence of carotid artery stenting as an alternative to CEA, declining procedural risks after CEA), there are still important findings from the trials that are worthy of inclusion in this review.

Surgery conferred significant benefit in recently symptomatic patients who had a 50—69% or a 70—99% stenosis, measured using the NASCET method.[5] Surgery conferred no benefit in patients with 0—49% stenoses, or in those with "near-occlusion". Near occlusion was defined as a 90—95% stenosis in the presence of collapse of the distal ICA lumen on angiography.

Patients with 70—99% stenoses gained maximum benefit from CEA, but nearly 70% remained stroke-free on BMT at 5 years. Because >6000 patients were randomised within ECST, NASCET, and the VA trials, it was possible to undertake meaningful subgroup analyses.[5—13] Although these subgroup analyses are historical (i.e. the actual benefits accrued using modern BMT may have lessened the 5-year stroke risks or benefits from CEA), it is likely that the messages (relating to age, gender, plaque irregularity, rapid treatment, etc.) remain relevant in the current era.

Predictive clinical parameters from the RCTs

Table 2 details clinical/imaging parameters that were associated with a significant increase in late stroke in the randomised trials. Surgery conferred incremental benefit with increasing age.[5—7] The highest absolute risk reduction (ARR) was observed in patients aged >75 years (Table 2). The benefit conferred by CEA in patients aged <65 years with 50—99% stenoses was relatively modest (ARR 5.6% at 5 years), compared with 8.6% for patients aged 65—74 years and 19.2% in patients aged >75 years. There was a similar relationship between age and more severe carotid disease. Carotid endarterectomy prevented 74 strokes at 5 years per 1000 CEAs in recently symptomatic patients aged <65 years who had 70—99% stenoses, increasing to 173

Table 1. Pooled individual patient meta-analysis of outcomes from the European Carotid Surgery Trial, the North American Symptomatic Carotid Endarterectomy Trial, and the Veteran's Affairs Study (data derived from Rothwell et al.[5]).

Stenosis severity	5-year stroke risk (%)		ARR in stroke (%)	Stroke prevented per 1000 CEAs
	CEA	BMT		
<30%	18.36	15.71	−2.6	0 @ 5 years
30—49%	22.80	25.45	+2.6	26 @ 5 years
50—69%	20.00	27.77	+7.8	78 @ 5 years
70—99%	17.13	32.71	+15.6	156 @ 5 years
Near-occlusion	22.40	22.30	−0.1	0 @ 5 years