

CAROTID MASTERCLASS

Delay May Reduce Procedural Risk, But at What Price to the Patient?

A.R. Naylor*

The Department of Vascular Surgery at Leicester Royal Infirmary, Leicester, UK

The renewed strategy towards performing carotid endarterectomy (CEA) within 1–2 weeks of a patient presenting with a TIA or minor stroke is based on a large body of evidence showing that the highest risk period for the patient is the first seven days after the index event. Unfortunately, most stroke/vascular services are inadequately resourced to achieve this target and many are more likely to be pre-occupied with treating large numbers of asymptomatic individuals. This paper reviews the evidence underlying the current drive towards expedited intervention in patients presenting with TIA and minor stroke. It will also try to provide reassurance to the surgeon as to how such a strategy can be reconciled with understandable concerns that early CEA in symptomatic patients is associated with poorer perioperative outcomes.

© 2008 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.

Keywords: Stroke; Carotid; Endarterectomy; Angioplasty.

Introduction

“Carotid intervention for recently symptomatic, severe carotid stenosis should be regarded as an emergency procedure in patients who are neurologically stable, and should ideally be performed within 48 hours of a transient ischaemic attack or minor stroke.”

The National Stroke Strategy.¹

The UK Department of Health, 5th December 2007.

The American Academy of Neurology (AAN) and the American Heart Association (AHA) recommend that carotid endarterectomy (CEA) be performed within two weeks in patients presenting with a transient ischaemic attack (TIA) or a non-disabling stroke.^{2,3} The available evidence, however, suggests that very few centres achieve this threshold.⁴ In a 2006 survey of practice in eleven centres in Holland, only 24% of patients presenting with a TIA/minor stroke and a 70–99% stenosis underwent endarterectomy within 6 months.⁵ In the recently completed GALA trial, the

median delay to surgery was 80 days.⁴ In 1997, an audit of UK practice found that the median delay from index event to surgery was 189 days,⁶ falling to 45 days when repeated in 2007.⁷ While the latter example represents a considerable improvement in practice, it is nowhere near the AAN and AHA ‘two week’ recommendation and ‘light years’ from achieving the ‘48 hour’ aspiration of the United Kingdom Government.

So, why is there such a discrepancy between national/international recommendations and ‘real world’ practice? The answer is multifactorial but requires governments and health providers to consider cerebral vascular disease on a par (in terms of political and fiscal priority) with cancer and heart disease. More controversially, it requires surgeons/interventionists to recognise that the current pre-occupation with treating vast numbers of asymptomatic patients will do little to reduce the overall burden of stroke. It is an uncomfortable fact that even if one could identify every patient with an asymptomatic 60–99% stenosis and perform CEA/CAS with a 2.3% procedural risk, 97% of strokes destined to occur in the community will still happen.^{4,8}

This paper reviews the evidence underlying the current drive towards expedited intervention in patients presenting with TIA and minor stroke. It will also try to provide reassurance to the surgeon as to how such a strategy can also be reconciled with a recent report⁹ suggesting that “early CEA in

*Corresponding author. Professor A. R. Naylor, Dept of Vascular Surgery, Clinical Sciences Building, PO Box 65, Leicester Royal Infirmary, Leicester LE2 7LX, UK.
E-mail address: ross.naylor@uhl-tr.nhs.uk

symptomatic patients is associated with poorer peri-operative outcomes.”

Level I, Grade a Evidence...

Most interventionists and surgeons cite data from the international, randomised trials as being the level I, Grade A evidence base upon which their clinical practice is founded (Table 1). In effect, ECST, VA and NASCET showed that ‘recently symptomatic’ patients (defined as events occurring within the preceding 6 months) with 50–99% NASCET stenoses benefited from ‘intervention’, whilst ACAS and ACST found that surgery was of significant benefit in asymptomatic patients with 60–99% stenoses.^{10–14} Armed with such high quality data from more than 10,000 randomised patients, the only remaining issue is usually whether that ‘intervention’ should still be surgery or carotid angioplasty with stenting (CAS).

Not surprisingly, attempts to divert contemporary debate away from whether CEA or CAS is preferable and back towards identifying who benefits most from intervention is not always welcomed. For many, the rationale is simple. If, for whatever, reason, CEA/CAS cannot be performed within six months of the index event, then surely the results from ACAS and ACST justify any intervention thereafter? Why make it any more complicated?

At first sight, this interpretation of the trials seems logical, reasonable and difficult to counter. However, anyone who does read beyond the ‘headlines’ will realise that this is far too simplistic an interpretation. It is an uncomfortable fact that the system currently allows most practitioners of CEA and CAS to treat

myriads of relatively ‘low risk for stroke’ patients within nationally accepted guidelines, while the really ‘high risk’ patients suffer strokes with little chance of undergoing any intervention. Just look again at Table 1 to see just how few strokes are prevented at five years by operating on 1000 patients with symptomatic 50–69% or 60–99% asymptomatic stenoses.

To this observer, the ongoing debate should not just be about whether ACAS/ACST justifies intervention should the 6 month ‘symptomatic’ threshold elapse (they probably do), nor whether CEA or CAS is ‘king’ (just do the randomised trials properly), but can health providers, physicians, surgeons and interventionists change attitudes and practice and then prioritise resources towards those who really need our help. Contrary to political and professional preferences, this does not mean expending resources on asymptomatic carotid screening programmes as the number one priority. As will be shown, this money would be far better being used to expedite the investigation and treatment of symptomatic patients within one/two weeks of presentation. Once that has been achieved, it is then reasonable to treat as many asymptomatic patients as you like!

Something Old...

In common with many of you, I was taught that; (i) CEA should be delayed for 6–8 weeks after a stroke because of the increased risk of haemorrhagic transformation of the infarct, i.e. emergency surgery was dangerous, (ii) early/expedited surgery (in general) was probably associated with an increased rate of complications, so why expose yourself to unnecessary

Table 1. Principle outcomes from the randomised trials

(a) Carotid Endarterectomy Trialists Collaboration*: Five year risk of ‘any stroke’ (including 30-day stroke/death) from the VA, ECST and NASCET trials^{10–12}

Trial	Stenosis	n	30-day CEA risk	Five Year Risk		ARR	RRR	NNT	Strokes prevented per 1000 CEAs
				Surgery	Medical				
CETC	<30%	1746		18.36%	15.71%	-2.6%	n/b	n/b	none at 5 years
CETC	30–49%	1429	6.7%	22.80%	25.45%	+2.6%	10%	38	26 at 5 years
CETC	50–69%	1549	8.4%	20.00%	27.77%	+7.8%	28%	13	78 at 5 years
CETC	70–99%	1095	6.2%	17.13%	32.71%	+15.6%	48%	6	156 at 5 years
CETC	String	262	5.4%	22.40%	22.30%	-0.1%	n/b	n/b	none at 5 years

(b) ACST & ACAS^{13,14}: Five year outcomes (including 30-day death/stroke)

Trial	Endpoint	30-day CEA risk	Five Year Risk		ARR	RRR	NNT	Strokes prevented per 1000 CEAs
			Surgery	Medical				
ACAS	ipsilateral stroke	2.3%	11.0%	5.1%	+5.9%	54%	17	59 at 5 years
ACST	‘any stroke’	2.8%	11.8%	6.4%	+5.4%	46%	19	53 at 5 years

n/b = no benefit conferred by CEA, ARR = Absolute Risk Reduction, RRR = Relative Risk Reduction, strokes prevented per 1000 CEAs = number of strokes prevented at five years by performing 1000 CEAs at the risk quoted.

* data derived from the CETC^{10–12} with all pre-randomisation angiograms remeasured using NASCET method.

medico-legal risk, especially as (iii), the risk of suffering a stroke in the first few weeks after presentation was probably not really that high and (iv) early symptom resolution was generally taken to be a sign that urgent investigation/treatment was unnecessary.¹⁵ *Interpretation:* A little bit of delay in the system probably does no real harm and might, actually, be beneficial to the patient (and possibly to the surgeon regarding published risks). *Outcome:* No professional impetus to change the way the system works.

This nihilistic attitude persists into the modern era, is rarely mentioned in debates about developing the roles of CEA and CAS and was completely ignored in a recent survey of doctor's attitudes towards "treating stroke as a medical emergency". In this study, Wang¹⁶ ascertained that there was; (i) room for improvement in recognising symptoms due to stroke/TIA (that in itself is a damning indictment of attitude and practice), (ii) scepticism regarding the role of CEA in asymptomatic individuals, which varied according to the doctor's specialty (no surprise there then) and (iii) 28% of physicians would not administer tissue plasminogen activator in acute stroke (but at least the majority knew it was beneficial if administered quickly). However not one single question was directed towards ascertaining whether doctors knew that rapid access to surgery was highly beneficial to the very recently symptomatic patient.

Something New...

The recent drive towards promoting expedited investigation and intervention has not generally been led by surgeons (with a few notable exceptions)^{17,18} but rather by Neurologists and Stroke Physicians. In a series of surprisingly 'basic' methodological studies and provocative editorials, they have challenged accepted dogma and thrown down a very large gauntlet for their surgical colleagues to respond to.¹⁹⁻³¹

The first myth to be challenged by the Neurologists was the conventional teaching that the early risk of stroke after TIA/minor stroke was only about 1-2% at 7 days and 2-4% at 30 days. These data were primarily derived from a collection of 'cohort' studies,^{19,22-24} which had largely stood the test of time and which generally reassured surgeons that there was no real need to change existing practice and intervene urgently. However, these cohort studies tended to recruit their patients some time after the index event, patients suffering a stroke in the intervening period were excluded, as were those who suffered a stroke on the same day as their TIA. More importantly, most patients were recruited following attendance at

the outpatient clinic or accident and emergency department and few were derived from prospective community/population based environments.^{19,22-24} In short, these cohort studies were heavily biased in their design and they influenced practice in a manner more than was justified.

In a systematic review of 18 independent cohort studies which reported the early risk of stroke in 10,216 patients presenting with a TIA, Giles observed that the pooled risk of stroke was 5.2% at seven days, *i.e.* about three to four times greater than is traditionally quoted.³¹ However, this study encountered some of the limitations alluded to earlier (e.g. many of the constituent trials recruited from outpatient clinics or the accident and emergency department etc). A separate meta-analysis of three population based studies (which used 'face to face follow-up') observed that the risk of stroke at 2 days was 6.7% and was 10.4% at seven days.³¹ Population based studies are more likely to represent 'real world' practice and these figures suggest that the highest risk period for the TIA patient is the first seven days after the index event. How many medical and surgical units are 'geared up' to deal with TIA/minor stroke patients this quickly?

One of the three population based studies²³ was particularly informative as it also reported early stroke risks for patients presenting with a minor stroke as well as TIA (Fig. 1). Note that there was no significant difference in the early risk of recurrent stroke at 7, 30 and 90 days relative to mode of presentation. 'Conventional teaching', however, dictates that patients suffering a minor stroke should wait 6-8 weeks for CEA. As was actually observed in Coull's study, by that time, most of those destined to suffer a stroke will have already done so.²³ The surgeon is,

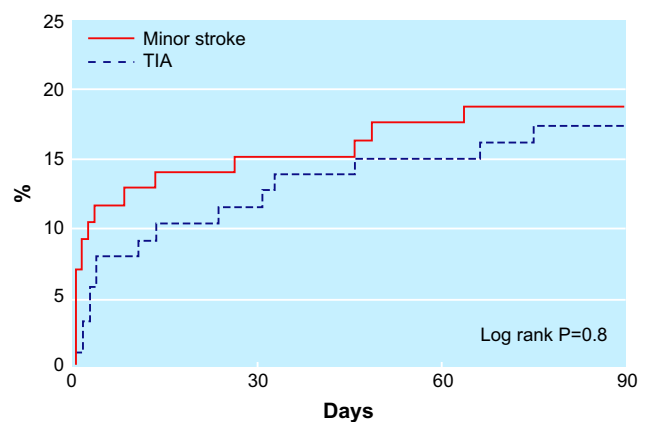


Fig. 1. Cumulative risk of stroke after transient ischaemic attack (TIA) or minor stroke. Reproduced with permission from Coull and the British Medical Journal.²³

in effect, left with a 'safer' cohort of patients whose long term risk of stroke is probably much less.

In an alternative approach to evaluating 'early stroke risk', Rothwell combined four independent patient databases comprising 2416 patients who had presented with an ischaemic stroke.²⁶ Approximately one quarter of these stroke victims (549 patients) reported a preceding TIA. Almost one fifth (17%) of the preceding TIAs occurred on the *same day* as the stroke, 9% happened on the day prior to the stroke, while 43% of TIAs (overall) occurred within the seven days prior to stroke onset.

Of course, not all strokes are secondary to thromboembolic disease from the carotid artery and this could confound meaningful interpretation of the data. Approximately 25% of strokes are due to small vessel intracranial disease, while 15% are cardioembolic. In order to correct for the effect of the underlying aetiology on the risk of recurrent stroke, Lovett *et al.* performed a meta-analysis of four studies which stratified for underlying aetiology.²⁴ Table 2 summarises the principle findings. Early recurrent stroke was extremely rare after small vessel (lacunar) stroke. However, stroke due to 'large artery' disease (*i.e.* predominantly involving the carotid artery) was associated with the highest rate of early recurrent stroke (4% at 7 days, 12.6% at 30 days and 19.2% at 3 months).

The studies detailed so far clearly suggest that the early risk of stroke after TIA/minor stroke is much greater than previously thought and most centres will logistically be unable to immediately change practice in order to investigate and treat these patients more quickly. It would, therefore, be helpful (in the interim) if 'higher risk' subgroups of patients could be identified for 'fast-tracking'. A number of studies have tried to identify clinical/imaging parameters that are predictive of an increased risk of early recurrent stroke. These include presentation with; (i) motor deficit,^{19,32} (ii) dysphasia or dysarthria,^{19,32} (iii) contralateral occlusion, (iv) exhausted cerebral vascular reserve,²¹ (v) age >60 years¹⁹ and (vi) diabetes mellitus.¹⁹ This theme was developed further by Rothwell in the form of the 'ABCD' scoring system (Table 3),

Table 2. Cumulative recurrent stroke risk stratified for underlying aetiology*

	7 days	1 month	3 months
'large vessel disease'	4.0% (95%CI 0.2–7.8)	12.6% (95%CI 5.9–19.3)	19.2% (95%CI 11.2–27.2)
cardioembolic	2.5% (95%CI 0.1–4.9)	4.6% (95%CI 1.3–7.9)	11.9% (95%CI 6.4–17.4)
'small vessel disease'	0.0%	2.0% (95%CI 0.0–4.2)	3.4% (95%CI 0.5–6.3)

* data derived from meta-analysis by Lovett.²⁴

Table 3. ABCD criteria for predicting very early stroke risk*

	Score
A Age ≥60 years	1
Age <60 years	0
B BP: systolic ≥140 mmHg or diastolic ≥90 mmHg	1
BP: neither of the above	0
C Clinical features:	
Unilateral weakness	2
Speech disturbance, no weakness	1
Other	0
D Duration of symptoms	
≥60 minutes	2
10–59 minutes	1
<10 minutes	0
Maximum Score	6

* details derived from Rothwell.²⁷

superseded by the ABCD2 version.^{27,33} The origins and validation of this predictive scoring system has been discussed in greater detail in the March Carotid Masterclass.³⁴ In summary, TIA patients with an ABCD score of 0–3 incurred a 0% seven day risk of stroke, increasing to 2.2% for a score of 4, 16.3% for a score of 5 and 35% for patients with a maximum score of 6.²⁷ In the future, such scoring systems could become invaluable in identifying patients meriting emergency admission after suffering their TIA/minor stroke (eg those with an ABCD score of 5+).

Something Borrowed...

Table 1 summarises the principle findings from the randomised trials that have influenced practice most of all. It will be noted that no attempt has been made to separate NASCET, ECST and VA outcomes in the symptomatic cohort of patients. This is because the Carotid Endarterectomy Trialists Collaboration (CETC) provided an invaluable service by combining all of these data together, having remeasured all of the pre-randomisation angiograms using the NASCET measurement method.^{10–12} This database of >6000 patients is now the largest and most comprehensive set of outcome data in symptomatic patients with carotid disease (despite being somewhat historical). More importantly, it's very large size has enabled a number of important subgroup analyses to be performed that would go on to challenge many preconceived notions about what really constitutes being 'recently symptomatic'.

Table 4 details some of the CETC findings in a format slightly different to that used in Table 1. The absolute risk reduction conferred by surgery (ARR), the number needed to treat to prevent one stroke at 5 years (NNT) and the number of strokes prevented per 1000 CEAs at 5 years (CVA/1000) are detailed for three NASCET stenosis subgroups (50–69%, 70–99%

Table 4. Absolute risk reduction conferred by CEA in the 5 year cumulative risk of ipsilateral carotid territory ischaemic stroke (including the peri-operative risk) in patients with a NASCET 50–99% stenosis, stratified for delay from index event to randomisation*

Time since randomisation	50–69% stenoses			70–99% stenoses			ALL 50–99% stenoses		
	ARR	NNT	CVA/1000	ARR	NNT	CVA/1000	ARR	NNT	CVA/1000
< 2 weeks	14.8	7	148	23.0	4	230	18.5	5	185
2–4 weeks	3.3	30	33	15.9	6	159	9.8	10	98
4–12 weeks	4.0	25	40	7.9	13	79	5.5	18	55
>12 weeks	–2.9	nil	nil	7.4	14	74	0.8	125	8

nil = no benefit conferred by CEA, ARR = Absolute Risk Reduction (%) conferred by surgery over best medical therapy, NNT = number of CEAs needed to be performed to prevent one stroke at 5 years, CVA/1000 = number of strokes prevented at five years by performing 1000 CEAs.

* data derived from the CETC^{10–12} with all pre-randomisation angiograms remeasured using NASCET method.

and 50–99%) and stratified according to the delay between onset of symptoms and randomisation. In the trials, CEA was performed (on average) within 7 days of randomisation (*P Rothwell, personal communication*). As can clearly be seen, the benefit conferred by CEA was maximum if the delay between symptom onset and randomisation was <2 weeks. In symptomatic patients with 50–69% stenoses, the ARR conferred by surgery fell rapidly with time with no benefit being apparent after 12 weeks had elapsed (how many of you even consider this fact when discussing the rationales of surgery with some of your patients?).

In symptomatic patients with 70–99% stenoses, the benefit conferred by surgery again diminishes with increasing delays to surgery (< 2 weeks, ARR = 23% versus > 12 weeks, ARR = 7.4%), although the cumulative benefit was greater than that observed in similar time delayed patients with 50–69% stenoses. One important caveat to be borne in mind, however, is that the ‘70–99%’ and ‘50–99%’ outcome data in Table 4 does include patients with angiographic evidence of ‘near occlusion’. The CETC have shown that CEA does not confer significant benefit in patients with this pattern of disease.¹⁰ If these patients are excluded, the ARR conferred by CEA at 5 years increases to 30.2% for patients randomised <2 weeks with 70–99% stenoses and to 17.6% (2–4 weeks), 11.4% (4–12 weeks) and 8.9% (>12 weeks).

These data were some of the first to really challenge surgeons to question how their own practice influenced long term patient benefit. Put quite simply, surgeons who performed CEA very rapidly prevented far more strokes than those whose practice allowed excessive delays to occur. But there was more...

One further very important issue emerged from the CETC secondary analyses; gender.¹² Interestingly, not one national guideline includes any recommendation that gender might be an issue when discussing the rationales of intervention with symptomatic patients. Fig. 2 details the number of strokes prevented at five

years by performing 1000 CEAs in patients with 50–69% and 70–99% stenoses, having now stratified for gender. As can be seen, males appear to gain continuing benefit from CEA (albeit cumulatively reduced with time) for both moderate (50–69%) and severe (70–99%) stenosis subgroups.⁴ Contrast this with what appears to be happening in females. Notwithstanding methodological criticisms regarding the validity of subgroup analyses and whether the trials were adequately powered, the CETC data suggest

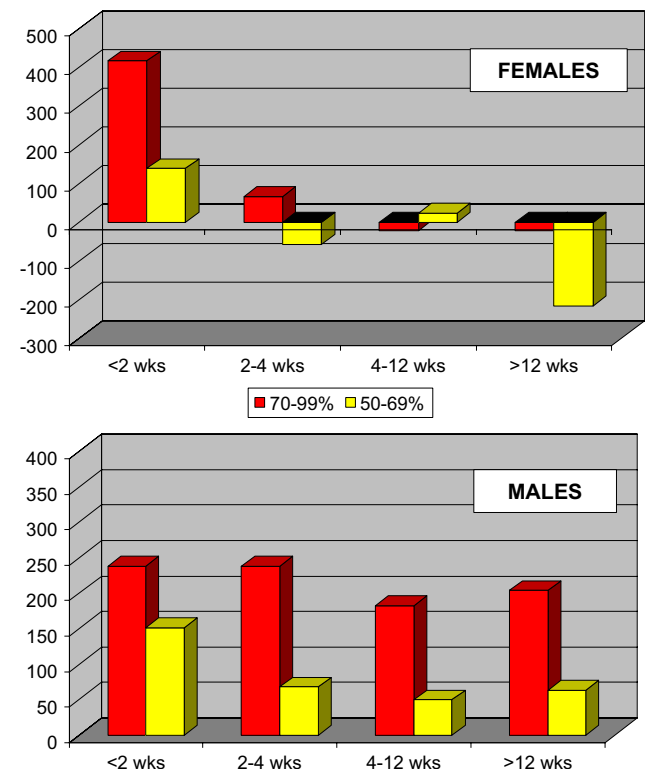


Fig. 2. Number of strokes prevented at 5 years by performing 1000 CEAs. Effect of gender and timing from event to CEA on prevention of late stroke relative to degree of stenosis (recalculated from CETC data^{10–12} and reproduced with permission from AR Naylor).⁴

a very clear trend towards little benefit accruing to the female patient if surgery is deferred beyond four weeks, even if severe carotid disease was present. This author does not suggest that we should now stop operating on all symptomatic female patients should 4+ weeks elapse, but can anyone *really* look at the data in Table 4 and Fig. 2 and still say that 'delay to surgery' does not matter?

Something Blue...

The rationale underlying early surgery in patients presenting with TIA and minor stroke includes; improving overall cerebral perfusion, reducing cumulative neuronal loss by restoring blood flow to the ischaemic penumbra, preventing early progression towards thrombosis and, of course, removing a source of ongoing embolism.

But doesn't early surgery increase the procedural risk and so negate any long term benefit to the patient? This is another very important and often confounding issue. There have been a number of publications citing 30-day outcomes in patients undergoing early/urgent carotid surgery, but very few centres have published median delay data for *all* of their symptomatic patients. In a recent review of the available literature,⁴ only Vancouver has published a median delay of 14 days from onset of symptoms to surgery for all patients.³⁵ *Interpretation:* surgeons are aware of the AAN and AHA 'two week' recommendations, but most will say that they do not have the infra-structure to achieve it...

Or is there, perhaps, another important factor to be considered in this debate? I suspect that while most surgeons do accept that rapid intervention will capture some of the patients who would previously have suffered a stroke before any intervention could be offered, they remain concerned that any increased procedural risks incurred by implementing such a strategy might lead to unwarranted professional censure and criticism. After all, who wants to be publicly labelled as one of the worst performing carotid surgeons if a little bit of delay in the system conveniently avoided this? Anyone who doubts the ability/intention of the media to criticise individual surgeon's performances might like to read the July 12th edition of the San Diego Union Tribune³⁶ which lists the 'best' and 'worst' performing cardiac surgeons in the state of California. League tables are fine provided they stratify for case-mix. To-date, no national guideline has ever considered 'very early surgery' within its 'accepted' risk recommendations.

The paradox of early intervention equating to increased risk was amply highlighted by a very

important paper from New York which showed that symptomatic patients undergoing CEA within 4 weeks of the index event incurred a threefold increase in the 30-day death/stroke risk from 1.6% to 5.1%.⁹ The authors concluded (in their manuscript title) that "early endarterectomy was associated with poorer peri-operative outcomes", thereafter recommending that it might be better to delay surgery in order to get better procedural results. Given the style of reporting in the San Diego Union Tribune, it might be hard not to agree with them!

So how can this paradox be reconciled, especially as the first half of this paper has provided compelling evidence that the highest risk period for a patient suffering a TIA or minor stroke is the first seven days? Two further sets of evidence and an alternative way of interpreting the literature may provide a solution, *provided* future 'Guideline Makers' recognise that a slight increase in the accepted early procedural risk is acceptable in selected patients.

Is Rockman's experience of increased procedural risk consistent with other published studies? Bond *et al.*³⁷ performed a systematic review of the published data (11 trials, 4278 patients) and compared the 30-day risk of stroke/death in patients presenting with a minor stroke who underwent either early CEA (<3 to 6 weeks) versus late CEA (>3 to 6 weeks). The findings were consistent across all of the studies in the review and no excess risk was associated with early versus late CEA, provided the patient presented with stable neurological symptoms (Pooled Odds Ratio = 1.13, 95% CI 0.79–1.62). This suggests that surgery within the previously accepted 6 week threshold was not associated with *excess* risk.

Few studies have, however, published outcomes when CEA was performed within the 'two week' recommendation laid down by the AAN and the AHA. Table 5 details 30-day outcomes and conversion rates to intracranial haemorrhage in 8 studies published since 2000 where the median delay from onset of events to surgery was <14 days.^{38–45} In seven studies, the median delay to surgery was <7 days. There was no standardisation within studies regarding scoring the severity of a 'stroke' and only four studies documented that there was independent neurological assessment.

The first key message from reviewing these studies was that the overall 30-day death/stroke rates probably were higher than that cited in the 'popular' literature. However, the highest 30-day risk (16.4%) was probably not typical of the type of patient normally being considered for early intervention. Huber's study included patients with a high proportion of residual severe neurological deficits (48%) and some

Table 5. 30-Day Death/Stroke rates following CEA when performed within a median of 14 days since onset of symptoms

Reference	Year	n	Symptom	Median days from event to CEA	Stroke score	30-day death/stroke	ICH ^a
Ricco ³⁸	2000	72	CVA	5.5 (range 2–15)	NESS=3 ^e	2.8%	0.0% ^h
Paty ³⁹	2004	72	CVA	<7	'non-disabling'	2.8%	not stated
Paty ³⁹	2004	131	CVA	<14	'non-disabling'	3.1%	not stated
Dorigo ⁴⁰	2007	70	CVA/TIA	2.0	'non-disabling'	5.4% ^g	not stated
Aleksic ⁴¹	2006	50	CVA/TIA	4.5 (range 1–21)	Rankin <4	6.0%	4.0% ⁱ
Karkos ⁴²	2007	42	TIA ^c	3.0 (range 1–7)	Rankin <4	7.0%	0.0% ^h
Sbarigia ⁴³	2006	96	CVA	1.5 (range 1–11)	NIHSS <22 ^f	7.3% ^g	0.0% ^h
Rantner ⁴⁴	2006	226 ^b	CVA	12 (IQR 8–19)	66% Rankin ≤2	8.4% ^g	0.4% ^h
Huber ⁴⁵	2003	67	CVA/TIA ^d	2.0 (range 0–18)	48% Rankin 3–5	16.4% ^g	1.5% ^h

^a prevalence of intracranial haemorrhage.
^b Rantner's paper combined data from Eckstein¹⁷, Woelfle⁴⁶ and Rantner.⁴⁷
^c cohort had suffered ≥3 TIAs in preceding 7 days.
^d mixed cohort including completed strokes, crescendo TIAs and patients with carotid occlusion and severe (Rankin 3–5) neurological deficits.
^e Neurological Event Severity Score.
^f NIHSS = National Institute of Health Stroke Scale.
^g independent neurological verification of outcomes.
^h post-op CT scans only done in patients with worsening/new neurological deficit. None of these had CT evidence of new haemorrhage.
ⁱ new haemorrhage present on CT scan, but not associated with symptoms.

with carotid occlusion.⁴⁵ The second key message was that the rate of conversion to intracranial haemorrhage was reassuringly low, although there was no real consistency regarding the performance of routine post-operative CT scans unless there were complications.

Rantner's study⁴⁴ (226 stroke patients) combined patients from three contributory databases^{17,46,47} and represents the largest published series to-date. Two thirds of Rantner's stroke patients were classified as 'minor' on the modified Rankin system (0–2) and the 30-day death/stroke rate of 8.4% probably represents 'real world' practice, especially as it included independent neurologist assessment.

Many of the constituent studies listed in Table 5 were too small to provide reliable guidance regarding which patients with stroke benefited most (and least) from early intervention, but a number of common themes emerged. The literature suggests that patient subgroups in whom one should 'avoid' early surgery include; (i) evidence of recent carotid occlusion,⁴¹ (ii) Rankin score ≥3^{41,44} (Table 6), (iii) ischaemic infarct >two thirds of the middle cerebral artery territory⁴³ (iv) no neurological plateau⁴⁴ (v) fluctuating conscious levels and (vi) evidence of intracranial

haemorrhage on CT scan. The worst outcomes after early CEA (23% death/stroke rate at 30-days) were seen in stroke patients presenting with the combination of a Rankin score ≥3 + an ASA score >2 + CEA within 12 days.⁴⁴ This excessively high procedural risk compares with a 30-day death/stroke rate of 6.4% in patients presenting without this combination.

If one accepts that Rantner's data from a large cohort of independently monitored patients undergoing surgery within 14 days of a stroke reflects 'real world' practice, is there any evidence to suggest that their 8.4% procedural risk represents poor surgical practice? I suspect that many surgeons will, intuitively, say yes. However, the data from Fig. 3 might convince them otherwise! Fig. 3 presents an alternative way of interpreting the CETC database. Because the CETC provided the 'raw' 5 year medical and surgical stroke risks as well as the procedural risks stratified for the

Table 6. The modified Rankin scoring system⁴⁸

0	no deficit
1	minimal deficit without any functional impairment
2	minor deficit, slight functional impairment, patient independent
3	moderate deficit, patient can walk alone, needs some assistance in daily life
4	severe deficit, patient can walk only with assistance
5	disabling stroke, patient confined to bed or wheelchair
6	dead

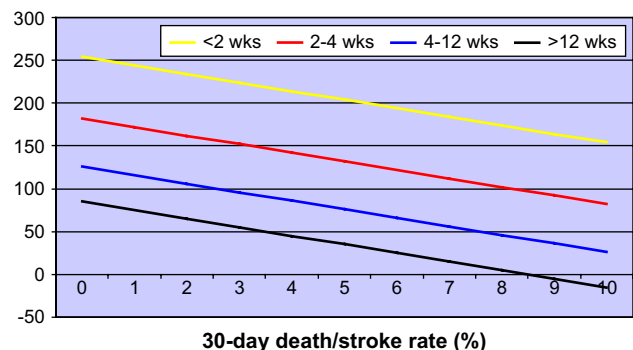


Fig. 3. Strokes prevented per 1000 CEAs at 5 years stratified for; (i) delay from last event to surgery and (ii) 30-day death/stroke risk (recalculated from CETC^{10–12} and reproduced with permission from AR Naylor).⁴

effect of 'delay to surgery', it is possible to model the benefit conferred by CEA depending on different delays to surgery and procedural risks.⁴ For example, a surgeon operating within 2 weeks of the index event with a 10% procedural risk (which most of you I suspect will think unacceptable) will still prevent 150 strokes at 5 years per 1000 CEAs performed. Despite the very high initial risk used in this example, the CETC data suggest that this surgeon will still prevent more strokes in the long term than if he/she waited for >4 weeks and then operated with zero risk! Bear that in mind the next time you are asked to interpret published outcomes in the literature or are tempted to criticise surgeons/interventionists who operate very early!

In Conclusion

To this observer, the natural history data documenting the high early risk of stroke after suffering a TIA/minor stroke are quite compelling. The system currently ignores the very highest risk patients and commits far too many resources towards treating relatively low risk patients. The '48 hour' aspirations of the UK Government are almost certainly beyond the reach of most centres, but a seven day target to treatment would be an absolutely massive improvement in practice and will prevent far more strokes in the long term than by treating large numbers of asymptomatic individuals. However, 'Guideline Makers' must recognise that a drive towards rapid intervention will probably come at the expense of a slightly increased procedural risk. Unless this is recognised, few surgeons will change their practice for fear of being labelled as 'poorly performing'. As a (personal) suggestion, what about considering that a 30-day death/stroke risk of 8% is acceptable if CEA is performed within 2 weeks of the index event, reducing this threshold of acceptable risk to 6% if surgery is performed between 2–4 weeks and down to 4% if CEA is delayed beyond 4 weeks. If you are still moved to disagree with this suggestion, look again at Fig. 3 and see for your self which threshold is preventing the most strokes in the long term!

Conflict of interest

None.

References

- 1 The National Stroke Strategy, www.dh.gov.uk/stroke
- 2 CHATURVEDI S, FEASBY T, HOLLOWAY R, BENAVENTE O, COHEN SN, KOTE R *et al.* Carotid endarterectomy- an evidence based review: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology* 2005;**65**:794–801.
- 3 SACCO RL, ADAMS R, ALBERS G, ALBERTS MJ, BENAVENTE O, FURIE K *et al.* Guidelines for the prevention of stroke in patients with ischaemic stroke or transient ischaemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;**37**:577–617.
- 4 NAYLOR AR. Time is brain!. *The Surgeon* 2007;**5**:23–30.
- 5 SCHOLTE OP, REIMER WJM, DIPPEL DWJ, FRANKE CL, OOSTENBRUGGE RJ, DE JONG G, HOEKS S, SIMOONS ML *et al.* Quality of hospital and outpatient care after stroke or transient ischaemic attack. *Stroke* 2006;**37**:1844–1849.
- 6 MCCOLLUM PT, DA SILVA A, RIDLER BDM, DE COSSART L, the Audit Committee for the Vascular Surgery Society. *Eur J Vasc Endovasc Surg* 1997;**14**:386–391.
- 7 Carotid Endarterectomy Audit of Great Britain and Ireland: clinical audit interim progress report. Copies can be obtained by emailing: ceaaudit@rcplondon.ac.uk.
- 8 HANKEY GJ. Asymptomatic carotid stenosis: how should it be managed? *Med J Aust* 1995;**163**:197–200.
- 9 ROCKMAN CB, MALDONADO T, JACOBOWITZ GR, CAYNE NS, GAGNE PJ, RILES T. Early endarterectomy in symptomatic patients is associated with poorer perioperative outcomes. *J Vasc Surg* 2006;**44**:480–487.
- 10 ROTHWELL PM, ELIASZIW M, GUTNIKOV SA, FOX AJ, TAYLOR DW, MAYBERG MR *et al.* for the Carotid Endarterectomy Trialists Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**:107–116.
- 11 ROTHWELL PM, ELIASZIW M, GUTNIKOV SA, WARLOW CP, BARNETT HJM. for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;**363**:915–924.
- 12 ROTHWELL PM, ELIASZIW M, GUTNIKOV SA, WARLOW CP, BARNETT HJM. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischaemic attack and minor stroke. *Stroke* 2004;**35**:2855–2861.
- 13 Asymptomatic Carotid Surgery Trial Collaborators. The MRC Asymptomatic Carotid Surgery Trial (ACST): carotid endarterectomy prevents disabling and fatal carotid territory strokes. *Lancet* 2004;**363**:1491–1502.
- 14 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;**273**:1421–1428.
- 15 JOHNSTON SC, FAYAD PB, GORELICK PB, HANLEY DF, SCHWAYDER P, VAN HUSEN D *et al.* Prevalence and knowledge of transient ischaemic attack among US adults. *Neurology* 2003;**60**:1429–1434.
- 16 WANG MY, LAVINE SD, SOUKASIAN H, TABRIZI R, LEVY ML, GIANNOTTA SL. Treating stroke as a medical emergency: a survey of resident physicians attitudes towards 'brain attack' and carotid endarterectomy. *Neurosurgery* 2001;**48**:1109–1117.
- 17 ECKSTEIN HH, RINGLEB P, DORFLER A, KLEMM K, MULLER BT, ZEGELMAN M *et al.* The carotid surgery for ischaemic stroke trial: a prospective observational study on carotid endarterectomy in the early period after ischaemic stroke. *J Vasc Surg* 2002;**36**:997–1004.
- 18 WELSH S, MEAD G, CHANT H, PICTON A, O'NEILL PA, MCCOLLUM CN. Early carotid surgery in acute stroke: a multicentre randomised pilot study. *Cerebrovasc Dis* 2004;**18**:200–205.
- 19 JOHNSTON SC, GRESS DR, BROWNER WS, SIDNEY S. Short term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;**284**:2901–2906.
- 20 NGUYEN-HUYNH MN, FAYAD P, GORELICK PB, CLAIBORNE-JOHNSTONE S. Knowledge and management of transient ischaemic attacks among US primary care physicians. *Neurology* 2003;**61**:1455–1456.

- 21 BLASER T, HOFMANN K, BUERGER T, EFFENBERGER O, WALLSCH C-W, GOERTLER M. Risk of stroke, transient ischaemic attack and vessel occlusion before endarterectomy in patients with symptomatic severe carotid stenosis. *Stroke* 2003;**33**:1057–1062.
- 22 LOVETT JK, DENNIS MS, SANDERCOCK PAG, BAMFORD J, WARLOW CP, ROTHWELL PM. Very early risk of stroke after a first transient ischaemic attack. *Stroke* 2003;**34**:e138–e142.
- 23 COULL A, LOVETT JK, ROTHWELL PM, on behalf of the Oxford Vascular Study. Early risk of stroke after a TIA or minor stroke in a population-based incidence study. *BMJ* 2004;**328**:326–328.
- 24 LOVETT JK, COULL AJ, ROTHWELL PM. Early risk of recurrence by subtype of ischaemic stroke in population based incidence studies. *Neurology* 2004;**62**:569–573.
- 25 FAIRHEAD JF, MEHTA Z, ROTHWELL PM. Population based study of delays in carotid imaging and surgery and the risk of recurrent stroke. *Neurology* 2005;**65**:371–375.
- 26 ROTHWELL PM, WARLOW CP. Timing of TIAs preceding stroke: the time window for prevention is very short. *Neurology* 2005;**64**:817–820.
- 27 ROTHWELL PM, GILES MF, FLOSSMAN E, LOVELOCK CE, REDGRAVE JN, WARLOW CP *et al.* A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005;**366**:29–36.
- 28 GILES MF, ROTHWELL PM. The need for emergency treatment of transient ischaemic attack and minor stroke. *Expert Rev Neurother* 2005;**5**:203–210.
- 29 KASTRUP A, ERNEMANN U, NAGELE T, GROSCHEL K. Risk factors for early recurrent cerebral ischaemia before treatment of symptomatic carotid stenosis. *Stroke* 2006;**37**:3032–3034.
- 30 ROTHWELL PM. Transient ischaemic attacks: time to wake up. *Heart* 2007;**93**:893–894.
- 31 GILES MF, ROTHWELL PM. Risk of stroke after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2007;**6**:1063–1072.
- 32 GLADSTONE DJ, KAPRAL MK, FANG J, LAUPACIS A, TU JV. Management and outcomes of transient ischaemic attack in Ontario. *CMAJ* 2004;**170**:1099–1103.
- 33 KOTON S, ROTHWELL PM. Performance of the ABCD and ABCD2 scores in TIA patients with carotid stenosis and atrial fibrillation. *Cerebrovasc Dis* 2007;**24**:231–235.
- 34 ROTHWELL PM. Prediction and prevention of stroke in patients with symptomatic carotid stenosis: the high-risk period and the high-risk patient. *Eur J Vasc Endovasc Surg* 2008;**35**:255–263.
- 35 TURNBULL RG, TAYLOR DC, HSIANG YN, SALVIAN AJ, NANJI S, O'HANLEY G *et al.* Assessment of patient waiting times for vascular surgery. *Can J Surg* 2000;**43**:105–111.
- 36 www.signonsandiego.com/news/state/20070712-9999-1n12cardiac.html
- 37 BOND R, RERKASEM K, ROTHWELL PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 2003;**34**:2290–2303.
- 38 RICCO JB, ILLUMINATI G, BOUIN-PINEAU MH, DEMARQUE C, CAMIADE C, BLECHA L *et al.* Early carotid endarterectomy after a non-disabling stroke: a prospective study. *Ann Vasc Surg* 2000;**14**:89–94.
- 39 PATY PSK, DARLING RC, FEUSTEL PJ, BERNARDINI GL, MEHTA M, OZSVATH KJ *et al.* Early carotid endarterectomy after acute stroke. *J Vasc Surg* 2004;**39**:148–154.
- 40 DORIGO W, PULLI R, BARBANTI E, AZAS L, TROISI N, PRATESI G *et al.* Carotid endarterectomy in patients with acute neurological symptoms: a case control study. *Interact Cardiovasc Thor Surg* 2007;**6**:369–373.
- 41 ALEKSIC M, RUEGER MA, LEHNHARDT FG, SOBESKY J, MATOUSSEVITCH V *et al.* Primary stroke unit treatment followed by very early carotid endarterectomy for carotid artery stenosis after acute stroke. *Cerebrovasc Dis* 2006;**22**:276–281.
- 42 KARKOS CD, McMAHON G, MCCARTHY MJ, DENNIS MJ, SAYERS RD, LONDON NJM *et al.* Urgent carotid surgery for crescendo transient ischemic attacks. *J Vasc Surg* 2007;**45**:1148–1154.
- 43 SBARIGIA E, TONI D, SPEZIALE F, ACCONCIA MC, FIORANI P. Early carotid endarterectomy after ischaemic stroke: the results of a prospective multicentre Italian Study. *Eur J Vasc Endovasc Surg* 2006;**32**:229–235.
- 44 RANTNER B, ECKSTEIN HH, RINGLEB P, WOELFLE KD, BRUIJNEN H, SCHMIDAUER C *et al.* American Society of Anesthesiology and Rankin as predictive parameters for the outcome of carotid endarterectomy within 28 days after an ischaemic stroke. *J Stroke Cerebrovasc Dis* 2006;**15**:114–120.
- 45 HUBER R, MULLER BT, SEITZ RJ, SIEBLER M, MODDER U, SANDMANN W. Carotid surgery in acute symptomatic patients. *Eur J Vasc Endovasc Surg* 2003;**25**:60–67.
- 46 WOELFLE KD, PFADENHAUER K, BRUIJNEN H, BECKER T, ENGELHARDT M, WACHENFELD-WAHL C *et al.* Early carotid endarterectomy in patients with a non-disabling ischaemic stroke: results of a retrospective analysis. *Vasa* 2004;**33**:30–35.
- 47 RANTNER B, PAVELKA M, POSCH L, SCHMIDAUER C, FRAEDRICH G. Carotid endarterectomy after ischaemic stroke: is there a justification for delayed surgery? *Eur J Vasc Endovasc Surg* 2005;**30**:36–40.
- 48 DE HAAN R, LIMBURG M, BOSSUYT P, VAN DER MEULEN J, AARONSON N. The clinical meaning of 'Rankin' handicap grades after stroke. *Stroke* 1995;**26**:2027–2030.

Accepted 9 January 2008

Available online 7 February 2008