Time is brain: An update

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Time is brain: an update

A Ross Naylor

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The ‘6-month’ threshold for treating symptomatic patients is obsolete. There is compelling evidence that the highest-risk period for stroke (after suffering a transient ischemic attack) is the first 2 weeks, especially the first few days, and that carotid endarterectomy (CEA) confers maximal benefit when performed early. Despite well-documented anxieties, there is increasing evidence that CEA can be performed safely within the first 7 days after onset of symptoms, although risks may be higher when performed within 48 h. The role for carotid artery stenting in the hyperacute period remains uncertain. Centers performing carotid artery stenting within 14 days of symptom onset with risks equivalent to CEA should be encouraged to continue and help others to achieve similar outcomes. For the majority, however, CEA will probably remain the safer option.

**KEYWORDS:** carotid artery stenting • carotid endarterectomy • carotid stenosis • medical therapy • stroke • transient ischemic attack

The 1998 American Heart Association (AHA) Guidelines [1] advised that carotid endarterectomy (CEA) was recommended in patients suffering a transient ischemic attack (TIA) or minor stroke within the preceding 6 months and who had a 50–99% ipsilateral internal carotid artery (ICA) stenosis, provided operative risks were <6%. This recommendation was, however, frequently simplified to mean that “provided CEA was performed within 6 months in symptomatic patients with a 50–99% stenosis, optimal care was being delivered”.

Over the next decade, however, publications began to question the appropriateness of uncritically retaining this ‘6-month’ threshold [2,3] proposing, instead, that CEA should be performed as soon as possible after onset of symptoms. This advice raised concerns within the surgical community, where it was intuitively believed that early interventions would equate to increased procedural risks. As a consequence, a ‘comfort zone’ evolved, based on the following assumptions. First, was the belief that the early risk of stroke after a TIA was low; that is, there was really no need to treat TIA patients akin to acute coronary syndromes. Second, because the AHA still retained its ‘6-month’ treatment threshold, surely this meant there was no real need to intervene much earlier. Third, was the ingrained belief that operating early would increase the procedural risk, possibly to the extent of negating any potential benefit from intervening early. These three factors, together with a realization that it would also be very difficult to overcome the learning curve of carotid artery stenting (CAS) if this had to be performed early after onset of symptoms, meant that there was little or no incentive towards intervening early.

In 2008; NICE and the European Society of Vascular Surgery (ESVS) Guidelines included a caveat that symptomatic patients should undergo CEA within 14 days of symptom onset [4,5]. Interestingly, 1 year earlier, the UK Department of Health [6] had published its ‘Strategy for Stroke’ document, which advised that “interventions for recently symptomatic severe carotid stenosis should be regarded as emergency procedures in patients who were neurologically stable and should ideally be performed within 48 hours of a TIA or minor stroke”.

What evidence precipitated these changes in attitude towards expedited interventions and why did it take another 3 years for the AHA to adopt a similar (if not watered down) recommendation?

**Why perform CEA within 14 days?**

In 2005, Rothwell et al. published a subgroup analysis of patients randomized in the...
European Carotid Surgery Trial (ECST). This focused on the time interval before undergoing CEA amongst randomizing centers. It was reported that ‘fast centres’ (defined as a median delay from symptom to CEA of <50 days) delivered a highly significant absolute risk reduction (ARR) in ipsilateral stroke (including perioperative stroke/death) of 23.6% at 5 years (95%CI 13.7–33.5), compared with a statistically non-significant ARR of 6.2% (95%CI 4.3–16.6) in centers where the median delay to CEA exceeded 50 days [7]. Put simply, had ‘slow’ centers dominated ECST, CEA would not have conferred any statistical benefit.

The ‘14-day’ NICE/ESVS treatment threshold was derived from an individual patient meta-analysis of 6000+ patients randomized within ECST, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Veteran’s Affairs (VA) trials [8,9]. Figure 1 shows the number of strokes prevented at 5 years per 1000 CEAs, stratified for delay from randomization to CEA. In practice, an average of 7 days elapsed between symptom and randomization (PM Rothwell, personal communication). Figure 1 shows that the benefit conferred by CEA diminished rapidly as the interval between randomization and CEA increased, especially in patients with 50–69% stenoses. The benefit conferred by CEA in males with 70–99% stenoses was generally maintained, even if 12 weeks had elapsed (Figure 2), although the benefit in moderate stenoses diminished more rapidly. By contrast, the benefit conferred by CEA in females (Figure 3) diminished very rapidly with delay (across all degrees of stenosis), to the extent that there was actually little evidence that symptomatic females with 50–69% (or even 70–99% stenoses) benefited from CEA after > 4 weeks had elapsed from symptom onset.

Why perform CEA within 48 hours?
The 2007 UK ‘Strategy for Stroke’ document advised that CEA should be performed within 48 h of symptom onset [6]. At the time, this was considered a very radical recommendation and only Denmark has since adopted this time threshold. No randomized controlled trial (RCT) supported a 48-h threshold and, for some time, it was unclear why the committee had made this recommendation. However, it subsequently transpired that it was the lay member of the committee who pushed for the 48-h threshold, on the basis that the quicker one intervened, the greater the benefit conferred to the patient (M Brown, personal communication). But was the layperson correct?

What is the early risk of stroke after a TIA?
An individual patient meta-analysis from ECST, NASCET and the VA study showed that medically treated patients with 50–99% stenoses faced a 21% stroke risk at 5 years from the time of randomization [8]. However, some began...
to question whether the landmark RCTs reflected ‘real world’ practice. One of the first studies to question the external validity of ECST/NASCET involved 2416 stroke patients, where 549 (23%) suffered a TIA prior to their stroke. Overall, 43% of strokes occurred within 7 days of the herald TIA, with the majority occurring either on the same day, or within the preceding 24 h [2].

Since 2005, eight natural history studies have documented the very early risk of stroke after a TIA in patients with 50–99% carotid stenoses (Table 1) [10–18]. The early risk of stroke was very much higher than previously thought, with prevalences ranging from 5–8% at 48 h [11–13], 4–17% at 72 h [13–15], 8–22% at 7 days [12–14,16,17] and 11–25% at 14 days [12–14,18]. The glaring discrepancy in Table 1 is that the 21% 5-year risk of stroke in medically treated patients in the RCTs is at complete odds with the 11–25% risk of stroke at 14 days in contemporary natural history studies. Notwithstanding the proven benefit of CEA in the RCTs, Table 1 suggests that patients who were randomized within ECST, NASCET and the VA trials were unlikely to have been recruited within the first few days/weeks after the onset of symptoms, that is by default, the trials excluded the very highest risk (for stroke) cohort of patients.

The available information, therefore, suggests that even though RCTs showed that CEA conferred significant benefit in patients reporting symptoms within the preceding 6 months, there was another cohort of much higher-risk patients who were rarely randomized and who suffered their stroke without having a chance to benefit from CEA. When faced with the natural history data in Table 1, surgeons frequently comment that they never see such high rates of recurrent stroke in patients awaiting CEA. The simple explanation for this apparent discrepancy is that (historically) patients were rarely referred within days of symptom onset and because they were seen some considerable time later, the highest-risk period (for stroke) had passed and fewer then suffered a recurrent stroke whilst awaiting CEA.

**Why are these patients at so high-risk?**

In 1977, Harrison and Marshall reported that when CEA was performed within 4 weeks of symptom onset, carotid stenoses were significantly more likely to have macroscopic thrombus overlying an acutely disrupted plaque (Figure 4), than when surgery was performed at a later date (66 vs 21%) [19]. This explains why TIA patients are more likely to suffer early embolic strokes, while the overlying thrombus is fresh and unstable.

This observation is supported by a number of clinical, imaging and pathological studies. In a series of symptomatic patients undergoing expedited CEA, Salem et al. observed that 43% of patients undergoing CEA <7 days of their TIA/minor stroke had evidence of spontaneous embolization on transcranial Doppler (TCD) prior to surgery, compared with 22% undergoing CEA between 8 and 14 days and 16% where surgery was performed >14 days after the index event [20]. Almost a quarter of patients with TCD diagnosed embolization suffered

![Figure 3. Number of ipsilateral strokes prevented at 5 years by performing 1000 CEAs in symptomatic female patients with 50–69% and 70–99% carotid stenoses, relative to interval from randomization to undergoing surgery.](image)


**Table 1. Early risk of stroke after suffering a TIA or minor stroke in patients with a 50–99% ICA stenosis.**

<table>
<thead>
<tr>
<th></th>
<th>48 h</th>
<th>72 h</th>
<th>7 days</th>
<th>14 days</th>
<th>5 years</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST + NASCET + VA medical therapy</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[5]</td>
</tr>
<tr>
<td>Fairhead (2005)</td>
<td></td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Purroy (2007)</td>
<td></td>
<td></td>
<td>10%</td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Ois (2009)</td>
<td></td>
<td>17%</td>
<td>22%</td>
<td>25%</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Bonifati (2011)</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[11]</td>
</tr>
<tr>
<td>Johansson (2013)</td>
<td></td>
<td>5%</td>
<td>8%</td>
<td>11%</td>
<td></td>
<td>[12]</td>
</tr>
<tr>
<td>Mono (2013)</td>
<td></td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td>[15]</td>
</tr>
<tr>
<td>Merwick (2013)</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Marnane (2014)</td>
<td>5%†</td>
<td>9%†</td>
<td>9%†</td>
<td>16%†</td>
<td></td>
<td>[13]</td>
</tr>
</tbody>
</table>

†Additional data provided by authors (personal communication).

ECST: European carotid surgery trial; ICA: Internal carotid artery; NASCET: North American Symptomatic Carotid Endarterectomy Trial; TIA: Transient ischemic attack.
recurrent neurological events in the 48–72 h prior to expedited CEA [28]. Altaf et al. have also shown that an MRI diagnosis of intraplaque hemorrhage (detected within a median of 19 days after the index TIA/minor stroke) was associated with a significantly increased prevalence of acute and subacute Diffusion Weighted Imaging (DWI) lesions in the brain (odds ratio [OR] 5.8 (95%CI 1.0–32.8)), as well as a significantly higher prevalence of spontaneous embolization [21].

Salem et al. have also reported that ultrasound markers of carotid plaque instability (in this case a large lipid core and a Gray Scale Median <25) were highly predictive of a significantly increased risk of recurrent neurological events in the 48–72 h period prior to expedited CEA [22]. In a subsequent study, two ultrasound-based plaque features were associated with a high probability of there being a histologically unstable carotid plaque: i) plaque area >95 mm² and ii) a juxta-luminal black area >6 mm². When both features were present, there was a 90% probability of finding an unstable plaque on blinded histology [23]. Finally, in a group of patients undergoing MRI <48 h of symptom onset, Lindsay et al. observed that 78% had (on average) seven embolic lesions on DWI imaging. There was no association between AHA plaque type and the prevalence of acute DWI lesions, but an MRI diagnosis of fibrous cap rupture was associated with a higher burden of acute DWI lesions [24].

**What can be done to change practice?**

Box 1 summarizes political, logistical and professional barriers towards changing practice. Some are historical, reflecting a continued unwillingness to accept that the early risk of stroke after a TIA is higher than previously thought, or that performing CEA in the hyperacute period will unnecessarily increase procedural risks. Some represent antiquated management pathways (e.g., limited access to non-invasive imaging, no investment in rapid access TIA Clinics), while others are either logistical (e.g., a reluctance to identify dedicated carotid operating lists) or suggest a reluctance (on the part of surgeons) to work up a patient so that another colleague can perform expedited surgery within health systems that function on a ‘fee per case’ basis.

The Leicester group has previously observed that simply asking highly motivated surgeons to change the way they practice in an *ad hoc* manner (e.g., phoned/faxed referrals rather than written, overbooking outpatient clinics, cancelling non-urgent cases, utilizing vacated elective theatre lists or using the emergency theatre) made little practical difference to the time interval between referral and CEA [25]. What was required was a total reconfiguration of the entire patient pathway. Data highlighting the high, early risks of stroke after symptom onset, as well as the benefit of expedited CEA, were the foundations for reconfiguring TIA services in Leicester [26]. However, crucial to the viability of the proposed ‘rapid access’ TIA service was the need to also deliver a robust, financial case. This was aided by the EXPRESS study [27,28], which was singularly influential in securing funding for the project.

During Phase 1 of the EXPRESS study (April 2002–September 2004), weekday TIA clinics enabled family doctors to book appointments. Imaging was either undertaken or booked and a treatment plan faxed to the family doctor within 24 h. The patient was then asked to visit their family doctor to be prescribed antiplatelet/statin therapy as well as to co-ordinate risk factor control. To many, this seemed a much improved service, but there were persistent delays in undergoing carotid imaging and patients took (on average) 19 days to visit their doctor and start their medications, during which time they were exposed to a heightened risk of suffering a stroke [27,28] (i.e., although they had been seen earlier than before, nothing was actually done to prevent their stroke). In Phase 2 (October 2004 to March 2007), a 7-day TIA clinic was introduced. Investigations (including carotid and MR/CT imaging) were undertaken in a single-visit environment and patients were started on their antiplatelet/statin therapy in the clinic, as well as being given lifestyle advice and risk factor control.
Changes implemented during the second phase of EXPRESS (7-day clinics, early imaging, early medical therapy) were associated with an 80% decrease in the 90-day risk of stroke, a reduction in fatal stroke, significantly fewer readmissions for recurrent stroke, reduced in-patient stay and an average hospital saving of £624 per patient [27,28]. For a hospital serving a population of 1 million, this equated to 165 strokes prevented per year, a saving of 4790 in-patient hospital beds per year and an estimated saving of £1.2 million per year [27,28]; that is, much more than the costs of introducing and running the new rapid access TIA service.

In October 2008, a ‘rapid access’ TIA clinic was established in Leicester [26] and the referral/treatment protocol is summarized in the left hand panel of Figure 5. In summary, the referring family or emergency room doctor started 300 mg Aspirin and 40 mg Simvastatin in anyone suspected of having suffered a TIA or minor stroke. An electronic referral was made to the TIA clinic and triaged according to the ABCD [2] score [29]. Patients whose ABCD [2] score was 0–3 were seen within 7 days, while those with an ABCD [2] score of 4–7 were seen within 24 h, as their 7-day predicted stroke risk was 7%. Interestingly, a high ABCD [2] score did not predict a greater likelihood of identifying patients with significant carotid stenoses [30]. Within the clinic, patients underwent assessment including baseline bloods, CT/MRI imaging and a carotid Duplex ultrasound scan. The supervising stroke physician advised on lifestyle changes and risk factor modifications and was responsible for implementing ‘best medical therapy’. In addition, patients with an ipsilateral 50–99% stenosis were transferred directly to the vascular unit for expedited CEA. In accordance with existing vascular unit policy to prevent early postoperative thromboembolic stroke, patients received a single 75 mg dose of Clopidogrel (in addition to their regular aspirin) the night before surgery [31].

Figure 5. Referral and management protocol for the Leicester ‘Rapid Access’ TIA Clinic. Left hand panel shows protocol from October 2008 to July 2013. Right hand panel shows revised protocol from August 2013, where dual antiplatelet therapy starts as soon as parenchymal hemorrhage had been excluded in the TIA Clinic on CT/MR. TIA: Transient ischemic attack.

Figure 6. Cumulative delay (days) from date of referral to undergoing Carotid Endarterectomy in three sequential audits.

Reproduced with permission from Salem et al. Rapid access carotid endarterectomy can be performed without a significant increase in the procedural risk. Eur J Vasc Endovasc Surg 2011;41:222-8.
The move towards expedited carotid interventions in symptomatic patients is now being embraced around the world (although not everywhere). Table 2 summarizes delays from index symptom to undergoing CEA in three recently published series. SwedVasc, the national vascular registry of Sweden, reported in 2012 that 6% of their 2596 CEAs were performed within 48 h of the index event, increasing to 37% by 7 days and 63% by 14 days [32]. The Leicester series reported that 9% of 475 patients underwent CEA within 48 h, 44% within 7 days and 72% by 14 days [33]. More recently, Rantner et al. have reported that they were able to perform 27% of 761 CEA procedures within 48 h of the index symptom, increasing to 56% within 7 days and 74% by 14 days [34].

In 1997, an audit by the Vascular Society of Great Britain and Ireland (VSGBI) reported a median delay from symptom onset to undergoing CEA of 183 days [35], reflecting the ‘non-urgent’ and rather casual approach to performing CEA at that time. These delays were justified (at the time) by a belief that provided CEA was performed within 6 months of symptom onset, units were adhering to AHA guidance and delivering optimal practice. However, as a consequence of the 2008 NICE/ESVS recommendation that CEA should be performed <14 days, the UK CEA Audit (a collaboration between the VSGBI, the UK Health Quality Improvement Program, the Royal College of Physicians and the Royal College of Surgeons) undertook serial audits of practice to drive up standards throughout the UK. In 2008, the median delay between index symptom and undergoing CEA was 42 days, which fell to 15 days by 2012 and 11 days by 2014 [36]. The German CEA Registry has reported (for the first time) that the median delay from symptom to surgery was 8 days [37]. In Sweden, the median delay from symptom to undergoing CEA in three recently published series.

Table 3. Reasons for patients not undergoing CEA within 14 days in the UK CEA Audit [36].

<table>
<thead>
<tr>
<th>Reasons for delay &gt;14 days to CEA</th>
<th>2010 n = 1782</th>
<th>2011 n = 2123</th>
<th>2012 n = 2122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in referral to Vascular Surgeons</td>
<td>40%</td>
<td>41%</td>
<td>41%</td>
</tr>
<tr>
<td>Delay in patient presenting</td>
<td>18%</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>Delay in carotid imaging</td>
<td>9%</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Limited availability of surgeon</td>
<td>9%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Patient choice (canceled or delayed)</td>
<td>8%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Lack of operating time</td>
<td>8%</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Patient canceled/delayed (medical reasons)</td>
<td>7%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Other case took priority</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Limited availability of anesthetist</td>
<td>1%</td>
<td>1%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

CEA: Carotid endarterectomy.
in making surgeons more cautious about undertaking expedited interventions [41]. In an increasingly litigious world of uncrirical public and medico-legal censure, this is perfectly understandable. The UK government currently publishes 30-day mortality rates after elective AAA repair, as well as 30-day death/stroke rates after CEA for individual surgeons in the UK. The aim of surgeon specific outcomes was to promote openness, improve quality and to enable patients/professionals to be informed about how local hospitals and surgeons performed [42]. The upshot, however, was that sections of the UK media [43] primarily focused on vascular surgeons they perceived to be ‘poorly performing’, even though none were statistical outliers. One unfortunate consequence, therefore, of surgeon specific reporting has been the emergence of ‘risk averse’ behavior [44,45], where some ‘higher-risk’ patients may be declined expedited CEA in order for surgeons not to appear ‘bad’ in published league tables.

The potential for ‘risk averse’ behavior (e.g., deferring CEA in ‘higher risk’ symptomatic patients in order to achieve lower procedural risks) should not be underestimated. Moreover, in some parts of the world (especially the US), there are little or no data regarding hospital CEA volumes or institutional outcome data, never mind knowledge about delays to CEA or how delays might impact on preventing stroke in high-risk individuals [46].

Given this background, it was perhaps inevitable that concerns acutely heightened when SwedVasc reported that patients undergoing CEA within 48 h of their index symptom faced an 11% risk of perioperative stroke/death [32], compared with only 3–5% if surgery was performed after 48 h had elapsed (Table 4). The message from SwedVasc was that CEA should be deferred for 48 h, but many surgeons simply interpreted the SwedVasc data as further justification for deferring CEA by several weeks.

Since publication of the SwedVasc data, two large, single-centre series have published procedural risks, stratified for delays to surgery (Table 4). Sharpe et al., reporting on a series of 475 CEA patients, observed no increase in procedural risk in patients undergoing CEA within 48 h [33]. This finding was corroborated by a larger, Austrian series, where 27% of 761 patients underwent CEA <48 h of their index symptom without any excess procedural risk [34]. To date, the UK CEA Audit has not stratified 30-day death/stroke rates according to whether surgery was performed within 48 h or not, but 1611 CEAs were performed within 7 days of the index symptom in the 2013 audit with a 30-day death/stroke rate of 2.7% [35].

But even if the procedural risk was 10% when CEA was performed in the early time period after onset of symptoms, would this adversely impact on late stroke prevention, as is assumed by so many surgeons? In fact, a re-analysis of pooled NASCET/ECST/VA data (Figure 7) suggests that the surgeon who operates within 2 weeks with a 10% risk will actually prevent more strokes at 5 years than the surgeon who waits 4 weeks and who then operates with a zero percent risk [3]. Future guidelines must recognize that it may be reasonable to increase the threshold of acceptable risk when CEA is performed in the first 2 weeks after onset of symptoms, so as to lessen the likelihood of surgeons exhibiting ‘risk averse’ behavior.

In conclusion, the available evidence suggests that most patients can safely undergo CEA within 7 days of onset of symptoms with more than acceptable procedural risks. Only a relative minority currently undergoes CEA within 48 h and the

| Table 4. 30-Day death stroke after CEA stratified for delay from index symptom to surgery. |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 30-day death/stroke      | 0–48 h                   | 3–7 days                 | 8–14 days                | >14 days                 | Ref.                     |
| SwedVasc                 | 17/148                   | 29/804                   | 26/677                   | 52/967                   | [32]                     |
|                          | 11.5%                    | 3.6%                     | 4.0%                     | 5.4%                     |                          |
| Sharpe                   | 1/41                     | 3/167                    | 1/133                    | 1/134                    | [33]                     |
|                          | 2.4%                     | 1.8%                     | 0.8%                     | 0.7%                     |                          |
| Rantner                  | 9/206                    | 4/219                    | 6/136                    | 5/200                    | [34]                     |
|                          | 4.4%                     | 1.8%                     | 4.4%                     | 2.5%                     |                          |

CEA: Carotid endarterectomy.

![Figure 7. Strokes prevented per 1000 CEAs at 5 years stratified for: (i) delay from last event to surgery and (ii) 30-day death/stroke risk.](image-url)


CEA: Carotid endarterectomy.
goal should be to ensure that the majority undergo CEA within 14 days, with a view to reducing this to < 7 days thereafter.

Current uncertainties?

What is the role of CAS?

The 2011 AHA guidelines [1] were unique for two reasons. First, the AHA finally acknowledged the potential benefits of early carotid intervention, including a somewhat ‘watered down’ caveat that “it was reasonable to perform CEA within 14 days (rather than delaying), provided there were no contraindications to early revascularization”. Second, the AHA now advised that CAS was an alternative to CEA in ‘average risk’ symptomatic patients.

The decision to liberalize CAS indications was based on CREST [47], in conjunction with industry-sponsored registries (predominantly in asymptomatic patients), which reported a progressive decline in procedural risks to levels recommended by the AHA [48]. It was also supported by the fact that no fewer than six large, randomized trials had shown that (following the perioperative period) there was no long-term difference in late ipsilateral stroke following CAS or CEA [48].

As a consequence, the key issue that will determine whether recently symptomatic patients should undergo CEA or CAS will be the magnitude of the initial procedural risk. If (compared to CEA) the procedural risk after CAS is similar, then most patients will probably opt for CAS. Alternatively, if procedural risks after CAS remain significantly higher than after CEA, most patients will probably benefit from CEA. The AHA never considered the impact of expedited carotid interventions (especially relating to CAS) and this was an important omission. The ‘learning curve’ associated with CAS is already challenging and will assume even greater importance as a greater proportion of symptomatic patients are referred within the first 14 days after onset of symptoms. Previous evidence suggested that trainees required at least 2 years experience in a high-volume CAS unit and to have performed a minimum of 72 CAS procedures before procedural risks were likely to fall within AHA risk thresholds [49,50]. However, these data were based upon intervening using the traditional ‘6-month’ timeline in symptomatic patients and not for intervening within 14 days.

Interpretation of the CREST trial, which reported that death/stroke and myocardial infarction were not significantly different between CEA and CAS, was confounded by the decision to combine data for both symptomatic and asymptomatic patients [47]. CREST was originally a ‘symptomatic trial’, but asymptomatic patients were subsequently included when recruitment rates began to falter. However, a subgroup analysis of symptomatic CREST patients [51] reported that the 30-day death/stroke rate after CAS was twice that seen after CEA (6 vs 3.4%). These outcome data were very similar to those observed in a meta-analysis of procedural risks in symptomatic patients randomized within the three European RCTs [52], which also reported a significantly higher 30-day death/stroke rate after CAS (8.9%) compared with CEA (5.8%).

CAS advocates have argued that the main reason that the procedural risks after CAS were so high in the European RCTs was because of inadequate interventionist experience. On closer inspection, however, this is a little inappropriate, as the most experienced stenters in the French EVA-3S trial incurred the highest rates of perioperative stroke/death (10.5%) [53], while the most experienced CAS centers in the ICSS trial reported higher procedural risks (8.7%) than their less experienced counterparts (6.9%) [54]. Given the volume of criticism relating to interventionist experience in the European RCTs, it is perhaps appropriate to document that the 8.9% death/stroke rate in the three European RCTs (where CAS was performed within 14 days of the index symptom) was no different to the 8.8% 30-day death/stroke rate reported by the US Cordis Carotid Stent Registry, when patients underwent protected CAS within 14 days of suffering their TIA or minor stroke [55].

Table 5. 30-Day death/stroke after carotid artery stenting stratified for delay from index symptom.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>0–7 days versus &gt;8 days</th>
<th>0–14 days versus &gt;14 days</th>
<th>0–28 days versus &gt;28 days</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–7 days</td>
<td>&gt;8 days</td>
<td>0–14 days</td>
<td>&gt;14 days</td>
</tr>
<tr>
<td>SwedVasc (2015)</td>
<td>4/98 (4.1%)</td>
<td>11/225 (4.9%)</td>
<td>9/178 (5.1%)</td>
<td>6/145 (4.1%)</td>
</tr>
<tr>
<td>Setacci (2010)</td>
<td>1/17 (5.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wach et al. (2014)</td>
<td>9/158 (5.7%)</td>
<td>5/151 (3.3%)</td>
<td>10/194 (5.2%)</td>
<td>0/27 (0.0%)</td>
</tr>
<tr>
<td>ICSS/EVA-3S/SPACE (2013)</td>
<td>13/138 (9.4%)</td>
<td></td>
<td>19/234 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>Groschel et al. (2011)</td>
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<td>10/142 (7.0%)</td>
<td>17/178 (9.6%)</td>
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<td>Topakian et al. (2007)</td>
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<td>6/23 (26.1%)</td>
<td>1/54 (1.9%)</td>
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<td>Cordis Stent Collaboration (2010)</td>
<td>6/68 (8.9%)</td>
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<td>Lin (2010)</td>
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There is, unfortunately, a paucity of good quality published data regarding the risks of CAS, stratified for timing after onset of symptoms (Tables 5 & 6). Table 5 summarizes published procedural risk data according to whether CAS was performed within 7 days, 14 days or >14 days. Overall, it is clear that some centers are reporting outcomes that are broadly comparable to CEA (Table 4), but it is difficult to be certain whether this represents the well-documented tendency towards preferentially publishing ‘positive’ outcomes in the literature.

One of the largest comparative studies was a meta-analysis of the three largest European CAS versus CEA symptomatic RCTs (Table 5), which observed a 26% 30-day death/stroke rate when CAS was performed within 7 days of symptom onset (9.4 vs 2.8% OR 3.4 (95% CI: 1.01–11.8)) and a twofold excess risk, where CAS was performed between 8 and 14 days after onset of symptoms (8.1 vs 3.4% OR 2.4 (95% CI: 1.0–5.7)) [52]. By contrast, three smaller studies (including one national registry) have reported procedural risks that were <6% when CAS was performed within 7 days of symptom onset (56–58) (i.e., within the AHA risk threshold) [1]. The main exception in Table 5 was the series by Topakian et al. who observed a 26% 30-day death/stroke rate when CAS was performed within 14 days [62], compared to <2% when CAS was performed thereafter. The CAPTURE registry has also reported that performing CAS within 14 days of the most recent symptom was associated with a two to threefold excess risk of procedural stroke compared to where CAS was performed at a later time (OR 2.5 (95% CI: 1.3–4.8)) [66].

The only national registry data come from SwedVasc (i.e., the same registry that reported an 11% stroke risk after CEA when performed within 48 h [58]). In their latest report, involving 323 recently symptomatic patients undergoing CAS, the procedural risk was 0% in 13 patients who underwent CAS within 48 h of the index event, increasing to 4.7% in 85 patients undergoing CAS between 3 and 7 days, 6.3% in 80 patients undergoing CAS between 8 and 14 days and 4.1% in 145 patients undergoing CAS after >14 days had elapsed since the index event [58].

Whilst many of the published series in Tables 5 and 6 suggest that CAS can be performed within accepted risk thresholds in recently symptomatic patients, a recent systematic review suggests that this may not be indicative of ‘real world’ practice [67]. Paraskevas et al. performed a systematic review of administrative dataset registries (> 1,500,000 procedures), which reported 30-day stroke/death rates after both CEA and CAS in ‘average risk for CEA’ patients who reported symptoms within the preceding 6 months. This study observed that 30-day stroke/death rates after CAS were significantly higher than after CEA in 11/18 registries (61%). In five registries, CAS was associated with higher stroke/death rates, but formal statistical comparison was not reported. Most importantly, however, CAS was associated with 30-day stroke/death rates that exceeded the 6% AHA risk threshold in 13/18 registries (72%). In 5/18 registries (28%), the procedural risk after CAS in ‘average-risk’ symptomatic patients exceeded 10% [67]. This would suggest that the majority of patients undergoing CAS within 6 months of symptom onset (in the ‘real world’) face procedural risks well in excess of the 6% AHA threshold, suggesting that they would probably face even higher risks of CAS to be performed within 7 or 14 days.

The available data, therefore, suggest that CEA can be performed safely within 7–14 days after onset of symptoms in the majority of patients, with supporting evidence from national registries. It is also clear that selected centers are able to perform CAS within 7–14 days of symptom onset with results comparable to CEA. In the latter situation, it is therefore perfectly reasonable to offer CAS and these interventionists should be encouraged to train their peers and trainees as to how this can be achieved. However, given the data from the systematic review regarding outcomes in ‘real world’ practice, the available data would also suggest that (for the time being) CEA can probably be performed more safely in the majority of patients within the first 7–14 days after onset of symptoms. This may, of course, change with improvements in CAS technology.

How soon after thrombolysis should CEA (CAS) be performed?
This question is increasingly being asked of surgeons and interventionists, who have little high-quality evidence with which to answer it. The reality is that only a small minority of acute stroke patients (perhaps 5–7%) currently undergo thrombolysis and are then found to have a severe ipsilateral stenosis, thereby making them candidates for expedited CEA or CAS [68]. The
general consensus is that indications for an expedited carotid intervention after thrombolysis include: i) the patient who has made a good neurological recovery and scores a Rankin 0–2; ii) the area of cerebral infarction is < 33% of the overall MCA territory; iii) a previously occluded middle cerebral artery mainstem is now patent; iv) non-invasive imaging after thrombolysis reveals an ipsilateral 50–99% stenosis and v) there is no evidence of parenchymal hemorrhage or significant brain edema on CT/MR imaging [69,70]. Contraindications to expedited CEA/CAS after thrombolysis include: i) a severe persisting neurological deficit; ii) high anticipated surgical risk because of co-morbidities (where CAS may be considered) and iii) the presence of parenchymal hemorrhage.

There was no consensus on the optimal timing of CEA/CAS after thrombolysis in 13 published series involving 361 patients [68], although the majority were undertaken within 14 days. One small study reported a higher risk of intracranial hemorrhage when CEA was performed within 72 h of lysis completion [71], although this has not been corroborated elsewhere. Any decision regarding the timing of CEA/CAS must take account of patient co-morbidities and whether the patient is still embolizing on TCD. It should also be remembered that there is a complex hematological ‘milieu’ shortly after thrombolysis ceases. Markers of coagulation activation and fibrin formation increase and may not return to normal for 72 h [72] and this can predispose the patient to an increased risk of rethrombosis. Paradoxically, there is also a parallel increase in blood–brain barrier permeability and an increase in fibrin degradation products and it has been suggested that an increase in fibrin degradation products >200 mg/l is predictive of a five-fold increased risk of intracerebral hemorrhage [73].

In practical terms, it is generally advised that antiplatelet therapy should be withheld for 24 h after lysis completion. Thereafter, provided the patient is neurologically stable, most surgeons would be happy to proceed with CEA once antiplatelet therapy has been restarted. In the 13 published series involving 361 patients (dominated by the Scandinavian Registry which contributed 202 patients [74]), the pooled 30-day rate of death/stroke was 3.6%, which includes a 2.5% rate of intracranial hemorrhage [68]. From a practical point of view, surgeons/cardiologists considering expedited interventions in patients who have undergone recent thrombolysis will benefit from having access to written guidance for managing post-CEA/CAS hypertension [75]. Uncontrolled hypertension following expedited CEA after thrombolysis will almost certainly increase the risk of parenchymal hemorrhage.

With regard to the need for pragmatic preoperative imaging, the aim should be to ensure that the patient has access to non-invasive imaging as soon as possible after the index event. For many, this will involve Duplex ultrasound, while others may prefer MR or CT angiography. The former is more accessible and ‘purists’ should not insist on corroborative CTA/MRA if it is going to introduce significant delays in the patient pathway. In reality, patients are probably more likely to suffer a recurrent stroke secondary to embolization of thrombus overlying an unstable plaque in the first few days after symptom onset, rather than suffering a perioperative stroke following CEA/CAS in someone with a <50% stenosis.

Second, is to not accept a diagnosis of ‘near occlusion’ following Duplex ultrasound assessment in the hyperacute period after onset of symptoms. These patients must undergo corroborative CT/MR angiography before this diagnosis is made. In chronic subocclusion, there is a tiny residual flow channel extending towards the skull base, usually with no antegrade diastolic flow and very low systolic flow velocities throughout the tiny flow channel (often with a reverberant systolic ‘spike’ waveform). These patients will not benefit from revascularization and can be managed conservatively [8]. However, in the first few days after onset of symptoms, it is not uncommon for the vascular sonographer to report an unusual phenomenon where the patient has very high peak systolic velocities within a very narrow residual lumen, in the presence of what appears to be a collapsed distal ICA which is then difficult to image into the upper reaches of the neck. To the untrained, this might be misdiagnosed as a ‘near occlusion’, but the key observation is that the peak systolic velocities within the narrowed channel are very high, indicating that there must be an adequate distal ICA. In the presence of high peak systolic velocities, CT/MR angiography will almost always reveal a normal calibre distal lumen and these patients can safely undergo expedited CEA [76].

A third practical issue includes ‘lessons from the operating theatre’. Patients undergoing CEA (CAS) in the first few days after onset of symptoms are highly likely to have disrupted carotid plaques with overlying thrombus, which is prone to spontaneous embolization. It is, therefore, important to ensure that the anesthetist is particularly careful with regard to the position of his/her hand holding the oxygen mask over the patient’s face during induction of anesthesia. Gripping the mandible with fingers that compress the underlying carotid bifurcation can lead to significant embolization. Second is the need to be very careful with aseptic skin preparation as careless (clumsy) prepping can also precipitate embolization before the procedure has begun. Third, intraoperative TCD is invaluable in warning the vascular sonographer to report an unusual phenomenon where the patient has very high peak systolic velocities within an upper reaches of the neck. To the unwary, this might be a collapsed distal ICA which is then difficult to image into the upper reaches of the neck. To the untrained, this might be misdiagnosed as a ‘near occlusion’, but the key observation is that the peak systolic velocities within the narrowed channel are very high, indicating that there must be an adequate distal ICA. In the presence of high peak systolic velocities, CT/MR angiography will almost always reveal a normal calibre distal lumen and these patients can safely undergo expedited CEA [76].

Finally, it is important to warn theatre recovery staff that patients undergoing CEA with a pre-existing acute, neurological deficit will almost certainly have a transient worsening of their deficit immediately following the procedure, especially if this
has been done under general anesthesia. This is probably secondary to a period of transient hypoperfusion within the ischemic penumbra surrounding the area of recent acute infarction. The key issue (in determining whether the endarterectomy zone needs to be immediately re-explored) is the speed with which the patient recovers from anesthesia. Rapid awakening is a reassuring (and key) observation, as it invariably means that any worsening of the pre-existing neurological deficit will disappear within an hour or so and there is no need for urgent re-exploration. If, however, there was delayed awakening from anesthesia in conjunction with a worsening neurological deficit, this is a sign that a more extensive intraoperative brain injury has occurred and the endarterectomy zone should be re-explored [76].

**Does aggressive medical therapy reduce early stroke risk?**

Following the introduction of the rapid access TIA clinic in Leicester in 2008 (Figure 5, left hand panel), patients with an ipsilateral 50–99% carotid stenosis were transferred directly to the vascular unit for expedited CEA [26]. The median interval between the index symptom and undergoing CEA fell to 8 days, which included a median 3-day period between transfer from the TIA clinic to undergoing CEA. During this 3-day period, two prospective audits (involving 212 patients) revealed that 13% suffered recurrent neurological events prior to CEA [26,77], emphasizing the unstable nature of the underlying carotid plaques.

Previously, the Leicester unit had only rarely encountered in-patient recurrent events prior to CEA, reflecting historical delays in getting patients through surgery. However, with the move towards performing CEA as soon as possible after onset of symptoms, others have also reported an increased prevalence of recurrent events. In Blaser’s series, the median delay from index symptom to investigation was 19 days. However, in the 10 days (median) between investigation and CEA, 15 patients (10%) suffered recurrent events [78]. In a similar series, where patients were seen about 14 days after symptom onset, Kastrup observed that over the next 7 days, 3% suffered a recurrent TIA, while 12% developed new DWI lesions on MRI [79]. In Mono’s series, where 94 patients were admitted within 48 h of onset of symptoms and where CEA was performed a median of 5 days after onset of symptoms, 13% suffered in patient recurrent neurological events before undergoing CEA [15]. The highest rates of recurrent stroke (prior to expedited CEA) were reported by Johansson, who found that the rate of recurrent ipsilateral stroke was 5% at 48 h after onset of symptoms, increasing to 8% at 7 days and 11% at 14 days [12].

Given the relatively high rate of recurrent symptoms prior to expedited CEA, the Leicester group hypothesized that if it were possible to start dual antiplatelet therapy earlier in the patient pathway, it might be possible to reduce the prevalence of in-patient recurrent thromboembolic events prior to CEA.

In August 2013, a revision was made to the rapid access TIA Clinic protocol (Figure 5, right hand panel). The main difference was that when the patient attended the TIA Clinic and was found to have a 50–99% ipsilateral stenosis, provided there was no evidence of parenchymal hemorrhage on CT/MRI imaging, 75 mg Clopidogrel was added to regular aspirin and dual antiplatelet therapy was then continued throughout the 2–3 day preoperative period. In a subsequent prospective audit of 100 recently symptomatic patients undergoing CEA with early commencement of dual antiplatelet therapy [80] (where there was no difference in patient demographics, median delay between symptom and CEA and median delay between transfer to undergoing CEA compared to the two previous audits), 2–3 days of dual antiplatelet therapy were associated with a fivefold reduction in the prevalence of recurrent, inpatient TIA/stroke prior to surgery (3 vs 13%; OR 4.9 (95% CI 1.5–16.6) p = 0.01) as well as a four-fold reduction in the prevalence of spontaneous embolization immediately prior to surgery (5 vs 21%, OR 4.1 (95% CI: 1.5–10.7); p = 0.0047). The 30-day death/stroke rate was 1% in patients where dual antiplatelet therapy was started as soon as parenchymal hemorrhage was excluded (hemorrhagic transformation of an ischemic infarct) and dual antiplatelet therapy was not associated with a significant increase in perioperative bleeding complications (3%) [80].

Few other studies have evaluated the effect of early implementation of statin therapy and dual antiplatelet therapy on preventing recurrent events prior to expedited CEA, but Shahidi et al. [81] have reported a similar finding, where recurrent events were reduced following the early introduction of dual antiplatelet therapy, compared to historical controls. In addition, Stromberg et al. [82] have reported that a policy towards implementing ‘best medical therapy’ as soon as possible prior to CEA was associated with a 2% rate of recurrent stroke at 48 h, increasing to 4% at 7 days in patients awaiting CEA, which was considerably lower than historical controls. Finally, a multi-centre registry has reported that in patients suffering a TIA/minor stroke who were found to have an ipsilateral 50–99% stenosis, the overall rate of recurrent stroke at 7 days was 8.3% [83]. However, patients who were not administered statin therapy after symptom onset had a 13.2% rate of recurrent stroke at 7 days, compared with only 3.8% in patients who were either taking statins at the time of their TIA/stroke, or who were commenced on statins immediately after onset of symptoms [83].

These data are from observational, non-randomized trials, but they do suggest that early implementation of ‘best medical therapy’ (especially dual antiplatelet and statin therapy) may reduce early recurrent stroke in patients with 50–99% stenoses who are awaiting CEA. Whether this means that carotid interventions can then be delayed (in order to reduce procedural risk) requires further evaluation. For the moment, it would seem reasonable to start aspirin and a statin in the community as soon as a diagnosis of TIA/minor stroke is suspected, pending urgent referral to the TIA clinic. Once parenchymal hemorrhage has been excluded in the clinic, clopidogrel can be added to the antiplatelet regimen pending transfer and urgent
work-up for expedited CEA. One might also speculate whether it might be reasonable to start dual antiplatelet therapy in the community in patients whose symptoms resolve within 1–2 h, as they are highly unlikely to have parenchymal hemorrhage and they will be at higher risk of suffering a further ischemic event than suffering a neurological deterioration secondary to hemorrhage.

**Expert commentary**

The ‘6-month’ threshold for treating symptomatic patients should now be considered obsolete. This was introduced as an inclusion criterion for randomizing patients within ECST and NASCET and was not evidence-based. There is now compelling evidence that the highest risk period for suffering a stroke after a TIA is the first 2 weeks, especially the first few days. This type of patient was rarely randomized within the trials and represent a ‘lost tribe’ who were destined to suffer their stroke before having any chance of being started on optimal medical therapy and undergoing CEA.

Notwithstanding the undeniable fact that RCTs showed CEA to confer significant benefit, the benefit (in terms of late strokes prevention) is maximal when CEA is performed early. A number of studies and registries have shown that CEA can be performed safely within the first few days after onset of symptoms, although risks may be higher when CEA is performed within 48 h. The role for CAS in the hyperacute period remains uncertain. Those centers who can perform CAS in the hyperacute period with risks equivalent to CEA should be encouraged to continue and they should help others to achieve similar outcomes. For the majority of patients, however, CEA will probably remain the safer option. ‘Best medical therapy’ (which should include lifestyle advice and risk factor control) should be implemented as soon as a TIA is suspected and there is evidence from two studies that dual antiplatelet therapy started early in the patient pathway may reduce recurrent events prior to expedited CEA without increasing perioperative bleeding complications. It is also important to ensure that lifestyle modifications, risk factor control and antiplatelet and statin therapy are continued in the long term.

**Five-year view**

It is inevitable that there will be important advances in the concept of ‘best medical therapy’ and, in particular, when dual antiplatelet therapy should be commenced. This may mean that the need to intervene within the first few days will lessen, thereby enabling patients to undergo deferred interventions that may carry lower procedural risks. Such a decision would be made much easier if it were possible to develop an imaging algorithm for identifying patients at highest risk of suffering a stroke in the first 48 h. These patients could then be triaged for emergency CEA, leaving the remainder to undergo expedited CEA or CAS some time later.

It is inevitable that CAS technology will also improve and make CAS a potentially safer intervention in the hyperacute period; for example, improvements in proximal protection technologies and membranous or biological stents. The ‘learning curve’ will, however, remain an important issue for expanding CAS indications. At present, it is difficult to see how CAS practitioners can learn how to perform CAS in the early time period after onset of symptoms, without incurring higher procedural risks. In that situation, it would be unacceptable to introduce delays into the treatment pathway in order to be able to ‘practice’ on lower risk patients.

Finally, future improvements in ‘best medical therapy’ will inevitably raise the question as to whether the historical RCTs retain any relevance in the modern era, raising the question as to whether these should be repeated. Guideline groups (like the AHA and NICE) prioritize multi-centre RCTs as being the highest level of evidence in their guideline recommendations. Accordingly, if the only RCTs available become too historical, it is then very much more difficult to develop clinically relevant guidelines of practice that are applicable to contemporary practice. It is likely that performing CEA early will still be highly beneficial, but the merits of intervening after 1 month (in females) and after 3 months (in males) may be much reduced. At these latter time periods, it would also be inappropriate to retain a 6% procedural risk threshold as being acceptable.

**Financial & competing interests disclosure**

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No writing assistance was utilized in the production of this manuscript.
Key issues

- The highest risk period for suffering a stroke after a transient ischemic attack is the first few days.
- The landmark randomized controlled trials did not randomize and treat many patients in the first few days after onset of symptoms, leaving a ‘lost tribe’ of high-risk patients who have most to gain from carotid interventions.
- Carotid surgery confers maximum benefit if performed as soon as possible after onset of symptoms.
- The best way to minimize delays to medical and surgical treatment is for patients to be seen in a daily, transient ischemic attack clinic which offers single-visit access to imaging and for commencing ‘best medical therapy’.
- Carotid endarterectomy can be performed safely in the first 7–14 days after onset of symptoms.
- Provided carotid stenting can be performed with equivalent risks to surgery in the first 7–14 days after onset of symptoms, there is no reason why it should not be offered to patients.
- It is inappropriate to delay treatment simply to allow carotid artery stenting practitioners or surgeons to be able to intervene in a ‘lower risk’ patient in order to look good on ‘league tables’.
- Early implementation of ‘best medical therapy’, especially dual antiplatelet and statin therapy may reduce the risk of early recurrent events without increasing perioperative bleeding risks.
- Surgeons who operate in the first 7–14 days need to modify their surgical strategy in order to minimize the risk of intraoperative embolization from highly unstable carotid plaques with overlying thrombus.
- Carotid endarterectomy or carotid stenting can be performed safely after thrombolysis, although it may be better to defer this for 48–72 h after lysis completion. Antiplatelet therapy should be withheld for the first 24 h and then restarted.

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- of interest
- of considerable interest

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This prospective audit showed that starting dual antiplatelet therapy earlier in the patient pathway (after onset of symptoms) reduced the risk of recurrent neurological events whilst awaiting expedited CEA, without increasing the risk of perioperative hemorrhagic complications.

