Timing of carotid endarterectomy and clinical outcomes

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Abstract: The timing of carotid endarterectomy (CEA) for symptomatic ipsilateral carotid artery stenosis has evolved in practice over time. Key landmark trials outlined the benefit of performing CEA in the recently symptomatic carotid artery stenosis, defined as revascularisation within 6 months of the index neurological event. Further evidence and sub-analysis demonstrate that performing CEA within 2 weeks of symptoms has the maximal benefit in reducing stroke free survival and is associated with a safe perioperative complication profile. This has translated into guideline recommendations and widespread clinical practice. The case for performing urgent CEA (within 48 hours of index neurological event) over early CEA (within 2 weeks) has been put forward and studied. Data examining perioperative complications for urgent CEA are mostly derived from retrospective single series studies. A moderate balance exists in the literature for the safety and risk of urgent CEA. Although many studies present acceptable perioperative stroke and mortality rates associated with urgent CEA, evidence still exists that the perioperative complications may not be insignificant. This is particularly the case if the presenting neurology is a stroke, rather than a transient ischaemic attack (TIA) or amaurosis fugax. This should be contextualised in the practice of modern aggressive medical therapy with dual antiplatelets and statins, with evidence suggesting a reduction in recurrent ischaemic events prior to surgical intervention. Careful patient selection, presenting neurology and medical therapy is likely to be a key feature in considering urgent CEA versus early CEA.

Keywords: Carotid endarterectomy (CEA); stroke; transient ischaemic attack (TIA); carotid artery stenosis

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The disease burden arising from stroke remains a global epidemiologically important problem. One in eight strokes are fatal within 30 days and one in four are fatal within a year. It stands as the second largest cause of death globally. Thromboembolism arising from an ipsilateral carotid artery stenosis is an important aetiological process accounting for 20% of all strokes (1,2).

Surgical management of the carotid artery stenosis introduced in the 1950’s has evolved into an effective treatment in preventing stroke. The two landmark randomized controlled trials, the European Carotid Surgery Trial (ECST) (3) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (4), have demonstrated the relative benefit of carotid endarterectomy (CEA) in the recently (within 6 months) symptomatic ipsilateral carotid artery stenosis. The findings from these trials translated into grade A recommendations from the American Heart Association guidelines for performing CEA for symptomatic 70–99% carotid artery stenosis within 6 months of an ipsilateral non-disabling carotid artery ischaemic event (5). Delaying operative intervention for 6–8 weeks after a cerebral event was thought to be beneficial at that time due to the perceived increased risk of haemorrhagic transformation and increased peri-procedural risk together with the belief that delaying CEA would allow the carotid plaque to stabilise (6,7). Further evidence from
pooled analysis of NASCET and ECST demonstrated contrary evidence (8). The maximal benefit in preventing future transient ischaemic attack (TIA) and stroke was shown to be in the first 2 weeks after the initial ischaemic event in these trials. Beyond 2 weeks, the benefit of CEA fell dramatically for men with >69% stenosis. The 5-year absolute risk reduction was 30.2% with a number needed to treat (NNT) of 3 to prevent 1 ipsilateral stroke if CEA was performed within 2 weeks (7). The NNT doubles to 6 if CEA is delayed between 2–4 weeks (7). In females, benefit was only seen by performing CEA for >69% stenosis within 2 weeks (8). Studying the natural history of symptomatic carotid artery stenosis, the recurrent neurological event rate is highest in the earlier period following an ischaemic event. Stroke rate after a TIA is 6.7% at 2 days and 11.7% at 7 days (9). In a study of 163 patients with symptomatic carotid artery stenosis, the recurrent stroke rate was found to be 20.9% within 3 days, 6.7% between 3 and 7 days and 3.7% between 7 and 14 days (10). Early (<30 days) vs. delayed (>30 days) CEA did not differ in the peri-procedural stroke or death rate [relative risk: 0.92; 95% confidence interval (CI): 0.16–5.27; P=1.00] in further NASCET analyses (11), providing further support in performing CEA within 2 weeks. Naylor contextualised the argument for early (within 2 weeks) CEA with insights from a re-analysis of NASCET (12), ECST (13) and the Veteran Affairs trial (14). This analysis suggests that if CEAs are performed within 2 weeks even with a 10% perioperative stroke risk, at 5 years more strokes will have been prevented than by delaying CEA beyond 4 weeks with an associated 0% perioperative stroke risk (7,15).

European and North American guidelines provided recommendations favouring early CEA (<2 weeks) for symptomatic ipsilateral stenoses (16,17). The UK National Stroke Strategy advocated performing CEA within 48 hours (urgent) in patients with stable neurology (18). Surveying practice within the United Kingdom reflected this guidance when analysing the UK National Vascular Registry (NVR). CEA was performed in only 10% of patients within 2 weeks of the index event in 2008, rising to 37% in 2009 and 58% in 2014 (19). The median delay from index symptom to CEA decreased from 22 days (IQR 10–56 days) in 2009 to 12 days (IQR 7–26 days) in 2014. In examining real-world practice over time, the earlier concerns regarding increased peri-operative complication rates with early CEA were not found in this study. As the median time to CEA decreased over 6 years in the UK, no corresponding trend towards increasing peri-operative complications was observed. The overall postoperative 30-day stroke rate and death rates after CEA were 1.85% (95% CI: 1.67–2.02) and 0.83% (95% CI: 0.71–0.94). The combined 30-day stroke and death rate post CEA was 2.31% (95% CI: 2.11–2.50). These rates were stable over time. Despite clear guidelines of a 2-week target, several studies have demonstrated that this target is not met. Up to 40% of patients do not have their CEA performed within 2 weeks of symptom onset (19). The reason for this has been multifactorial. They include a delay in access to carotid imaging, long waiting times to theatre, delay in referral to a vascular surgeon, delays resulting from co-morbidities and a delay in patients seeking medical help (20-27). Studying trends reported in the UK National Vascular Registry from 2009–2014 found the most common delays to be referral to a vascular surgeon, followed by delay in the patient seeking medical attention after symptom onset and a delay in access to carotid imaging (19). The delay times and rank order of delay reasons had not changed in the last 3 years of the study period. The most recent NVR 2019 report outlined the median time from symptom onset to CEA was 12 days (IQR 7–23 days) (28). Only 60% of patients were treated within 2 weeks. The median delay times were 4 days (IQR 1–9 days) from symptom to referral; 1 day (IQR 0–5 days) from referral to vascular surgeon review; 5 days (IQR 2–10 days) from vascular surgeon review to CEA (28).

The specific question of timing of intervention and safety of early CEA has now been investigated in several studies beyond the two seminal RCTs and their sub-analyses. No statistical difference in peri-procedural stroke rates were found in an international multicentre study analysing 145 CEAs performed urgently or early. Groups divided into urgent (CEA <48 hours from index cerebral event) and early (3–14 days to CEA from index cerebral event) were similar in their stroke rate (10.0% vs. 4.1%; P=0.260) (29). CEAs performed across 4 different time periods from symptom onset (0–2 days, 3–7 days, 8–14 days and >14 days) did not influence peri-operative outcome in a multivariate analysis of 761 symptomatic patients [odds ratio (OR) 0.93 (0.63–1.36), P=0.71] (30). The majority of patients in this study had initial non-disabling events (admission Rankin score <2 in over 90% of patients). The same finding was observed in patients with severe neurological disability from the index event (Rankin score >1), with a composite stroke and death rate of 4.4%, 1.8%, 4.4% and 2.5% in patients undergoing CEA at 0–2 days, 3–7 days, 8–14 days and >14 days respectively (30). The National Norwegian Carotid Study examined almost all (99.2%) patients undergoing CEA in...
Norway between April 2014 and March 2015 (31). The composite outcome of 30-day stroke/death rates for CEA within 48 hours, 3–7 days, 8–14 days and >14 days from index event to operation were 0%, 3.4%, 5.4% and 2.8% respectively (31). No statistical difference was observed in the complication rate in urgent versus early CEA groups in this prospective population study. Ferrero et al. also found relatively acceptable perioperative stroke rates for CEAs performed within 48 hours. The study investigated 285 patients in 5 treatment groups (CEA within <48 hours, 48 hours–2 weeks, 2–4 weeks, 4–8 weeks, 8–24 weeks). The stroke rate amongst <48 hour group was 4.2% which did not differ statistically from the other groups (48 h–2 weeks =3.2%; 2–4 weeks =0%; 4–8 weeks =3.4%; 8–24 weeks =3.8%) (32). In this study, patients were not eligible for CEA if they presented with a disabling neurological event (modified Rankin score >5), cerebral lesion greater than 3 cm, suspected or confirmed parenchymal haemorrhage associated with infarct, occlusion of the middle cerebral artery or considered unfit for surgery (American Society of Anaesthesia classification grade V). The authors concluded that performing CEA within 48 hours is safe in appropriately selected patients with non-disabling stroke.

Ferrero et al. also reported on a series of 176 patients in 2014 investigating the perioperative risk of urgent CEA differentiated by presenting neurological feature—TIA, crescendo TIA (cTIA) and stroke in evolution (SIE). The stroke/MI death rates at 30 days were 1.8% (TIA), 0% (cTIA) and 7.6% (SIE). The higher complication rate in SIE was not statistically significant in comparison to TIA and cTIA in this study (33).

The argument that performing CEA within 2 weeks is both safe and beneficial has now been well established. Although favourable results have been published for urgent CEA, concerns have been reported in the perioperative risk associated with urgent CEA (<48 hours) compared to early CEA (within 2 weeks). The Swedish Vascular Registry reported 2,596 CEAs performed for asymptomatic carotid artery stenosis between May 2008 and May 2011. According to time to CEA from the neurological event, patients were investigated across 4 groups (0–2, 3–7, 8–14 and 15–180 days). The corresponding combined stroke/death rate was found to be 11.5% (0–2 days), 3.6% (3–7 days), 4.0% (8–14 days) and 5.4% (15–180 days). Over a 4-fold increase risk of stroke/death was seen between the 0–2 day group and 3–7 day group (OR: 4.24; 95% CI: 2.07–8.70; P<0.001) (34). Further reports from Sweden on the Carotid Alarm Study published in 2017 highlighted similar concerns regarding urgent CEA. Prospective studying 418 patients, multivariate regression analysis identified urgent CEA (<48 hours) as an independent risk factor for death and stroke within 30 days of CEA (35). Urgent CEA conferred an 8.0% risk of death or stroke versus 2.9% for the 2–14-day group. The Vascular Study Group of New England (VSGNE) studied outcomes from 989 patients identified in their database undergoing symptomatic CEA. Four groups according to timing of surgery were identified—group 1, <2 days; group 2, 2–5 days; group 3, ≥6 days; group 4, same day CEA. Stroke rates after CEA were highest in group 1 (7.3%; P=0.016) (36). Other adverse outcomes were comparable amongst groups. Rango et al. published a systematic review and meta-analysis in 2015 of 47 studies investigating carotid revascularisation and timing of intervention (37). Of the included studies, 35 were CEA, 7 on carotid artery stenting and 5 included both. The pooled estimate periprocedural stroke risk for TIA subgroup of patients was 2.7% for CEA within 48 hours, 1.5% for CEA between 0–7 days and 1.6% for CEA <15 days (37). However, when analysing patients presenting initially with stroke as the index neurological event, the CEA periprocedural stroke risk is much higher, particularly for the urgent group (<48 hours): 8.0% (<48 hours), 5.3% (0–7 days), 5.0% (0–15 days) (37). Villwock et al. studied the National Inpatient Sample database between 2002 and 2011, including 59,327 patients having a CEA (38). Rates of stroke/TIA were analysed for CEA performed within 48 hours or deferred (48 hours–14 days) and according to the presence or absence of cerebral infarction. Within 48 hours, the death and stroke rates were 1.3% and 1.7% respectively for infarction, versus 0.4% and 1.1% without infarction. The death and stroke rates for CEA between 48 hours and 14 days were 0.9% and 1.3% respectively with infarction, versus 0.8% and 1.8% without infarction. The death and perioperative stroke rates were very favourable in this study, however the authors do note that performing urgent (<48 hours) CEA for patients with infarction is associated with a small increase in mortality and stroke perioperatively (39).

The risks of perioperative complications with urgent CEA has to be contextualised further with the state of modern medical therapy. Earlier studies quantifying the risk of recurrent stroke in symptomatic carotid artery stenosis may have been overestimated in comparison to the contemporary strategy of intensive medical therapy with dual antiplatelets and statins. Aggressive medical therapy with dual antiplatelets and statins reduces the recurrent risk of an
early ischaemic event prior to undergoing a CEA (40-42). A 5-fold reduction in recurrent neurological events prior to CEA has been shown with aggressive medical therapy (42). Recent data demonstrated the risk of recurrent early neurological event with dual antiplatelet therapy and statin pharmacotherapy is reduced to 2.0% within 2 days, 4% within 7 days and 7.5% within 30 days (41). The role medical therapy in the timing of CEA is still debated, particularly given that the Management of A Thrombosis with Clopidogrel in High-risk Patients (MATCH) trial failed to demonstrate the superiority of dual antiplatelets versus clopidogrel monotherapy (43).

The National Institute of Clinical Excellence (NICE) recommends time from symptom to intervention within 14 days (44). The United Kingdom National Vascular Registry reported the median time to intervention was 12 days (IQR 7–23 days) in 2018 (45). Between 2016 and 2018, The UK national operative (within 30 days) death and/or stroke rate was 2% (45). The evidence has now been well established in performing early CEA (within 2 weeks) maximising stroke free survival from recurrent ischaemic events and has an established safety profile in terms of peri-procedural complications. Although there is a relative balance of evidence in the literature for urgent CEA (within 48 hours), the periprocedural risks still remain a concern, with complications exceeding 2% for urgent CEA in studies reporting the effect of timing on surgical complications. This seems to be particularly the case when performing CEAs on patients with significant neurology and stroke as the index event. Careful patient selection, presenting neurology and medical therapy is likely to be a key feature in considering urgent CEA versus early CEA.

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Footnote

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