

Timing of carotid intervention

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In most patients the indication for carotid intervention has been based on neurological symptoms in combination with the degree of stenosis in the ipsilateral carotid artery. Recently, the role of timing of revascularization in the prevention of recurrent stroke in symptomatic patients has gained interest. The evidence to underpin early surgery is principally based on a *post hoc* subgroup analysis performed by the Carotid Endarterectomy Trialists Collaboration (CETC) on pooled data from two RCTs¹. The results of these RCTs were published almost three decades ago, and patient adherence to antiplatelet therapy and statin was low to moderate. The number of patients needed to operate to prevent one ipsilateral stroke in 5 years' time was five for patients randomized within 2 weeks following their last ischaemic event compared with 125 when randomized after more than 12 weeks¹. However, this was not a preplanned analysis and is therefore subject to potential confounding. The 2-week threshold was selected for methodological convenience rather than having any clinical relevance. Some subgroups, such as men with non-ocular events, may benefit fully 14 days or more after the initial event, whereas the benefit for subgroups at low risk of recurrent stroke (such as women with ocular symptoms) remains uncertain and is being investigated in ECST-2 (European Carotid Surgery Trials 2). Nevertheless, based on the CETC analysis, most international guidelines on the treatment of carotid artery disease now recommend that carotid revascularization

is undertaken within 14 days of the index event².

Unfortunately, there are few data on the outcomes of surgery in patients undergoing early carotid revascularization. Of the 12 RCTs^{3–14} that have compared carotid endarterectomy (CEA) with carotid artery stenting (CAS) in patients with significant carotid stenosis, only five^{3,9,10,12,14} provided information on the time from the index event to revascularization. CREST (Carotid Revascularization Endarterectomy *versus* Stenting Trial)¹⁰ reported the shortest median interval; this was still 22 days for CEA and 18 days for CAS. In all except two RCTs, the mean delay from the index event to revascularization was greater than 1 month^{9,12,14}. Even in studies that mostly revascularized sooner after the index event, the mean delay was above the 2-week threshold^{3,10}.

The role of very early carotid intervention, defined as intervention within 48 h of the index event, remains largely unknown. There are limited data on the natural history of the very early phase in patients receiving optimal medical treatment. In patients who had a transient ischaemic attack (TIA) or minor stroke, a recent publication¹⁵ reported a cardiovascular event rate of 6.4 per cent in the first year and a 5-year cumulative event rate of 12.9 per cent, but no data were provided on event rates within the first 48 h or for the first 14 days.

There exists a wide variety of definitions of delay in timing to intervention in the carotid revascularization RCTs. A universal definition is required¹⁶.

In terms of clinical benefit for the individual patient, the time to intervention starting from the initial event is important. The time to intervention measured from the most recent event is more pragmatic, but may overlook patients who have already had a disabling stroke following their initial event. These patients may become a 'lost cohort', being excluded from analysis.

Evidence is emerging that rapid institution of best medical therapy may reduce the risk of early recurrent stroke¹⁷, which might decrease the need for early or very early intervention to prevent early recurrent stroke. In fact, early or very early revascularization might pose an additional risk. The logistics of providing an emergency comprehensive revascularization service are substantial in many health systems. A recent pooled analysis¹⁸ from four RCTs revealed that CAS was associated with a substantially higher periprocedural risk than CEA when revascularization was performed during the first 7 days after the index event (8.3 *versus* 1.3 per cent). No information was provided for the very early phase. National registry data from Sweden suggested that CEA or CAS performed within 48 h was associated with a high stroke/death risk of 11 per cent¹⁹. However, data from the UK²⁰ and Germany²¹ showed only a minor increase in periprocedural risk associated with intervention within 48 h compared with 3–7 days. As a result of the CETC data, the treatment delay has decreased over recent years, from 22 days in 2009 to 12 days in 2013 in

the UK, and from 28 days in 2003 to 8 days in 2014 in Germany.

There is an urgent need to undertake studies dedicated to establishing the true incidence of early recurrent stroke in the era of modern medical management. The outcomes of CEA and CAS in the early and very early phase of TIA/stroke management also need to be determined. The STACI (Surgical Treatment of Acute Cerebral Ischaemia) trial²², which is currently recruiting, is investigating these risks for very early intervention (within 48 h) compared with delayed intervention (between 48 h and 15 days). Trials of this nature should provide answers to the question of whether the risks of early revascularization and best medical therapy outweigh the benefits of best medical therapy alone.

Disclosure

The authors declare no conflict of interest.

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