

INVITED COMMENTARY

## The True Risk of Early Recurrent Stroke: Importance of Cohort Composition and Index Event Definition

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Guidelines for the treatment of symptomatic carotid artery disease currently recommend that carotid revascularization should be performed as soon as possible and certainly within 2 weeks of the index symptom. The underlying reason for this is growing evidence that the highest risk period for recurrent stroke is the early time period after onset of symptoms, but this must be balanced against the potential for incurring higher procedural risks. Accordingly, in the current era of better medical therapy, the key question is when exactly should interventions be performed in order to prevent recurrent stroke while not unduly increasing the procedural risk?

In this retrospective study, Strömberg et al.<sup>1</sup> report on the risk of recurrent stroke in a population being worked up for carotid endarterectomy (CEA). The cohort consisted of all patients who were referred for ultrasound imaging and who were found to have a significant ipsilateral carotid artery stenosis. Clinical practice regarding the timing of CEA evolved over time, as is demonstrated by a reduction in the median delay from the “index symptom” to CEA of 36 days in 2005, down to a median 7 days in 2011. The authors concluded that with a 2% rate of recurrent stroke by day 2 (increasing to 4% by day 7), the risk of recurrent stroke was much lower than had been described in earlier studies, suggesting that there was maybe less need to perform emergency carotid interventions than had been previously thought.

However, the reader should be aware that these findings only apply to a subgroup of patients undergoing CEA, as those with “recurrent TIAs, stroke in evolution, or worsening of symptoms” during the first few days after referral were excluded, because the authors were not convinced that these patients would benefit from acute surgery. However, to this observer, any analyses of recurrent stroke rates should include these “emergency cases”, otherwise the reported findings may simply reflect outcomes in a (biased) lower risk cohort. For example, if “stroke in

evolution” patients were included, the risk of recurrent stroke at 48 hours increased from 2% to 3.2%.

The second key question relates to the risk of very early revascularization. Strömberg et al.<sup>2</sup> recommend against performing CEA within the first 48 hours, because of the high risk of procedural stroke observed in an earlier national audit. However, the current study did not assess procedural risk and the methodology was insufficient to draw any conclusions regarding the risks of early surgery. However, also included in the current issue of the Journal (and relevant to this question) is a large series by Rantner et al.,<sup>3</sup> who found no evidence that the procedural risk after CEA increased significantly in patients undergoing surgery within 48 hours of the most recent symptom.

In Strömberg’s current study, the authors based their delay calculations on the time from the event that triggered referral, but this was not necessarily the first neurological event. Although this is accepted practice, in terms of stroke prevention, it is important to remember that the risk for recurrent stroke is especially high in the first few days after the very first event, that is, Strömberg’s data may still be underestimating the actual risk of early recurrent stroke. The exact definition of what is meant by the term “index event” also has a large effect on the calculation of delay and recurrent stroke rates,<sup>4</sup> with delays being significantly longer following the first event than following a subsequent event that led to referral or even the most recent event.

The third question is which choice of intervention will most benefit the patient in the early time period after onset of symptoms, and few studies have specifically reported on outcomes of early carotid artery stenting (CAS). However, a meta-analysis of all three European randomized trials comparing CEA with CAS in symptomatic patients showed that CEA was associated with a 3.2% procedural risk when performed within 7 days of the index symptom, compared with 9.3% when CAS was performed within 7 days of symptom onset.<sup>5</sup> Clearly, there is an urgent need for better-quality data on the respective merits of intervening early to prevent recurrent stroke versus the potential for increased procedural risks. The ongoing Italian SPREAD-STACI trial (which randomizes patients between urgent CEA within 48 hours versus delayed surgery between 48 hours and 14 days; [www.staci.it](http://www.staci.it)) will provide important information to fill this gap in our knowledge.

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