

common time point where patients are identified, the referral event.

This leads us to a second problem with definitions. As indicated by de Borst, Rantner et al.³ recently reported that acute carotid endarterectomy does not confer increased procedural risk, in contrast to our earlier prospective analysis showing that very early carotid endarterectomy is associated with increased risk.³ However, Rantner et al.³ defined the index event as the latest event rather than the event that resulted in referral, and we argue that this difference could explain part of the discrepancy.⁴ Guidelines state that patients seeking medical care for a neurological event should receive immediate treatment with statins and antiplatelet agents. A recent study showed that the risk of recurrent stroke is lower in patients pre-treated with statins, and it is thus likely that the procedural risk is reduced by medical treatment received in hospital.⁵ Thus, defining the index event as the most recent event may result in a bias towards lower complication rates.

We agree that the benefit with early (within 14 days) carotid endarterectomy is proven. However, the advantage of surgery within 2 days of a referring event is not clear and could even be associated with higher risk than medical treatment alone.

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K. Österberg

Department of Vascular Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

G.M.L. Bergström

The Sahlgrenska Centre for Cardiovascular and Metabolic Research, Wallenberg Laboratory, Institute of Medicine, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

S. Strömberg*

Department of Vascular Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

The Sahlgrenska Centre for Cardiovascular and Metabolic Research, Wallenberg Laboratory, Institute of Medicine, The

Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

*Corresponding author. Department of Vascular Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

Email-addresses: sofia.stromberg@vgregion.se, sofia.stromberg81@gmail.com (S. Strömberg)

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

In the individual patient with symptomatic significant carotid artery stenosis there are two means of reducing the overall risk of recurrent stroke: (i) by early recognition of the presenting symptom and fast work up to perform expedited carotid revascularization thus preventing recurrent events in the waiting time to surgery; and (ii) by performing safe carotid revascularization.^{1,2}

In recent years, in symptomatic patients with carotid artery disease (CAD), the focus has been on early intervention, to be performed as soon as possible but at least within 2 weeks of presentation. To reach this 2 week threshold and in order to score the effectiveness of the center and specialist involved, the referral event is the easiest and most practical starting point. However, in using the referral event to assess the rate of recurrent events, patients that suffered a recurrent stroke as secondary event before referral may be missed, and as a consequence may no longer be candidates for revascularization. These patients, with a second severe cerebral event prior to referral, have been named "the lost cohort" as these patients are often not included in studies on patients undergoing carotid revascularization. By counting the very first event as the index event in patients with symptomatic CAD, it will be possible to analyze the true risk of early recurrent stroke and also include those that had their recurrent event prior to referral. In doing so, the true impact of recurrent events can become identifiable, and this has more relevance to the overall prevention of stroke instead of reporting only the events in patients scheduled for intervention.

The definitions "latest event", "referral event", or "most recent event" all distract from what is most relevant to the patient: recognition of the symptoms as being related to severe CAD, needing urgent work up and expedited revascularization. In order to protect as many patients as possible it is therefore necessary to keep in mind that most recurrent events can be prevented when using the very first event as the index event for intervention. The clinical

importance here is that if a person has a minor stroke or transient ischemic attack, it is a major indicator that this patient is at high risk of further stroke in the early days following the event.³ For the future guidelines should apply a universally agreed definition of the index event to make reports of delay to carotid endarterectomy more comparable.

Medication is able to stabilize the vulnerable plaque, especially by reducing macrophage content and increasing smooth muscle cells, but its relative contribution depends on the type of index symptom and may take weeks to become effective.^{4,5} It is not expected that statins can play a major role when performing carotid revascularization within days of first contact. As the effect of medication on plaque stabilization may take weeks there is no reason to expect bias towards lower complication rates, especially as dedicated medication is often started only after the first specialist contact initiating full therapy. Clearly, there is no need to wait longer for the effect of medication to stabilize the plaque as there is already an effective intervention to reduce the risk of recurrent stroke, namely expedited carotid revascularization.⁶

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G.J. de Borst

*Department of Vascular Surgery, University Medical Center
Utrecht, G04.129, PO Box 85500, 3508GA, Utrecht,
The Netherlands*

Email-address: g.j.deborst-2@umcutrecht.nl

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