EDITORIAL

Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis

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A recently published systematic review and meta-analysis[1], focused on the debate regarding the optimal timing for "early" carotid intervention after transient ischemic attack (TIA) or minor stroke. The underlying concern was the challenge in balancing the natural history risk for a second (recurrent) event against the potential higher procedural risk of carotid intervention when performed very early (i.e. within 48-72 hours) after the onset of symptoms.[2]

Of relevance, this debate is even more complex when we realize something as elementary as the definition of "index event" has been applied in a highly heterogeneous manner within scientific literature. The definition has occasionally been applied ambiguously within randomized controlled trials (RCTs) developed specifically to study the outcome of carotid endarterectomy (CEA) or carotid artery stenting (CAS) in symptomatic patients. A commonly applied definition is "the most recent neurologic event" before randomization[3] and/or before revascularization[4]. Alternatively, the index neurologic event has also been defined as the very first ischemic event or as the event that lead the patient to seek medical attention[5]. From a pathophysiological point of view the latter definition seems the most relevant while the risk for a recurrent event has been shown to be highest in the early days after the initial event. Not surprisingly, these different definitions of index event can have a significant impact on the reporting of delay times.

The European Society for Vascular Surgery (ESVS) guidelines (and most other international guidelines) recommend that CEA should be performed within 14 days of the "index event" not providing, however, any guidance or reporting standard for the definition of index event. Furthermore, RCT´s and large international registry analysis revealed that (only) a minority of patients was treated within this 14-day time range (independent of the applied definition).[6] This means that RCTs can only contribute to the debate on safety of expedited CEA in small part.

It seems needless to say that ideally studies reporting delay after carotid revascularization should apply a universally accepted definition of the index event and debate to reach conformity in reporting should be encouraged.[7] In our previous review, we focused on the optimal timing for carotid intervention within the 14-day time frame. However, scrutinizing RCTs and real world data, we cannot help but wonder: are we setting up unrealistic standards?

The results of our review suggested that (at present) and considering absolute rates of 30-day stroke, mortality, and death/stroke, CEA performed within two days of the index event complies with the accepted thresholds in international guidelines. Also, at present CEA is safer than CAS when performed within 2 and 7 days of the index event.[1] In other words, we have no doubt that when a patient requires early carotid revascularization, CEA should be considered first-line therapy. The real questions are: Do these patients benefit from an early (<2 days) intervention? How can we (timely) identify patients eligible for this early intervention? And can (most) national health systems logistically provide such an expedited clinical response?

To make the interpretation more complicated, it must be highlighted that in our analysis the balance with the risk for recurrent events was not assessed due to lack of data. Best medical treatment (BMT) has been revolutionized in recent years: (1) generalization in the use of antiplatelet and statin therapy for all patients with carotid atherosclerotic disease; (2) higher rates of smoking cessation, (3) higher rates of achievement of target values for systolic and diastolic pressure and (4) stricter targets for low-density lipoproteins (LDL).[6] Also, dual antiplatelet therapy (DAPT) within 24 hours of experiencing a minor ischemic stroke or "high risk TIA" showed now compelling evidence of benefit (versus aspirin monotherapy), even though in most studies patients scheduled for carotid intervention were excluded.[8]

Overall, with BMT optimization the balance between recurrent and peri-operative events has been once more disturbed, with a potential reduction in recurrent events while awaiting for intervention. The impact of BMT may go further than reducing the risk of recurrent events while awaiting for CEA as it may actually replace carotid revascularization in a

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selected group of patients with symptomatic carotid stenosis having a low risk for recurrent events. The European Carotid Surgery Trial 2 (ECST-2) is an international RCT investigating the optimal treatment of patients with symptomatic or asymptomatic moderate or severe carotid stenosis at low or intermediate risk of future stroke (estimated 5-year risk of stroke of <20%, as calculated using the Carotid Artery Risk score). The ECST-2 trial will compare the risks and benefits of treatment by modern optimized medical management alone versus the addition of immediate carotid surgery (or stenting). The underlying hypothesis is that patients with carotid stenosis ≥50% associated with a low to intermediate risk of stroke will not benefit from additional carotid revascularization when treated with optimized BMT.[9]

While answering questions regarding the capacity of different national health systems goes beyond the scope of this editorial, the questions on "who" and "when" to intervene still remain. Patients with "crescendo TIA" or "stroke in evolution" are particularly at risk for a recurrent event and are recommended to be submitted to CEA within 24 hours.[6] Other subgroups that may benefit from a (very) early intervention may be identified from further cohort studies. Several factors have been already identified that have been associated to a higher risk of recurrence, such as hemispheric (versus ocular) symptoms, demographic patient data (co-morbidities) and plaque characteristics.[6] However, the true future challenges for the next five year will be a) to identify additional (and more specific) plaque and brain specific imaging based criteria to identify those that benefit from early carotid intervention; and b) to validate these parameters in prospective studies. Only then the question of national health systems capacity to provide treatment would become the next focus by limiting the need for invasive treatment to a specific group.

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