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EDITORIAL

In the End, It All Comes Down to the Beginning!

The 2014 American Heart Association (AHA) guidelines on the management of symptomatic carotid disease expanded the indications for carotid artery stenting (CAS), advising that CAS is now an alternative to carotid endarterectomy (CEA) in the treatment of "average risk" patients suffering a transient ischaemic attack (TIA) or minor stroke during the preceding 6 months.[1] This recommendation was based on a review of outcomes from contemporary randomised controlled trials (RCTs), most notably the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST),[2] along with evidence from industry sponsored CAS registries.

The decision to expand CAS indications into average risk symptomatic patients infuriated many surgeons, who were otherwise convinced that this was only possible through the inclusion of peri-operative myocardial infarction (MI) within a composite primary endpoint of 30 day death/stroke/MI. As far as they were concerned, a meta-analysis of pooled European RCT data had clearly shown that CAS was associated with a significantly higher risk of procedural death/stroke (CAS = 8.9% vs 5.8% after CEA, HR 1.53, 95% CI 1.20–1.95; $p = .0006$).[1] Moreover (and not withstanding North American criticisms about interventionist experience and poor outcomes in the European trials), had the traditional "30 day death/stroke" endpoint been retained by the AHA, CREST would also have shown significant benefit favouring CEA in recently symptomatic patients (30 day death/stroke after CAS = 6.0% vs 3.0% after CEA, HR 1.89, 95% CI 1.11–3.21; $p = .019$). Interestingly, in each of the constituent studies, the difference in procedural risk was most marked in older patients and was mainly driven by a higher prevalence of non-disabling stroke.[3]

Following this opening salvo (which led to conflicting guideline recommendations around the world),[1,4] many surgeons probably thought that the war would ultimately be won following publication of late outcome data. Intuitively, surgeons believed that in addition to higher peri-operative risks, CAS would also be handicapped with significantly higher rates of restenosis and, consequently, significantly higher rates of late ipsilateral stroke. Only time would tell.

That time is now upon us and a series of late results from the various RCTs make for interesting reading. The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study surprised the surgical community with a 2008 report showing that while a recurrent stenosis of ≥70% was significantly more common at 2 years after CAS (11.1% CAS vs 4.6% CEA; $p = .0007$), only two patients with a significant recurrent stenosis developed recurrent ipsilateral symptoms.[5] This finding was, thereafter, corroborated in a series of contemporary symptomatic RCTs (EVA-3S, CREST, and ICSS) which showed that severe restenosis/occlusion was rare, with no differences being observed between CAS and CEA. In addition, a meta-analysis of older randomised trials also showed no significant increase in rates of severe restenosis after primary stenting compared with CEA.[6]

Having shown that higher rates of restenosis did not seem to matter, each of the major RCTs has now published late clinical data. Provided any strokes occurring within the first 30 days were excluded, there did not seem to be any difference in the long-term risk of late stroke between CAS and CEA. ICSS is now the latest (and largest RCT in symptomatic patients) to publish long-term data, which in some patients extends out to 10 years.[7] Consistent with previously published findings from CREST, the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), SPACE, and EVA-3S, ICSS has reported that (after excluding peri-operative stroke) the 5 year risk of fatal and/or disabling stroke in patients randomised to CAS was very similar to CEA (3.4% after CAS vs. 4.3% after CEA, HR 0.93, 95% CI 0.53–1.60; $p = .78$). There was also no significant difference in the 5 year rate of ipsilateral stroke (4.7% after CAS vs. 3.4% after CEA, HR 1.29, 95% CI 0.74–2.24; $p = .36$). The key message, therefore, is that six large RCTs have now shown that, after the first 30 days have elapsed, the long-term risk of stroke appears to be virtually the same for both CAS and CEA, and that this appears to be a consistent and statistically robust observation.

Accordingly, the single most important factor in determining whether patients should preferably undergo CAS (as opposed to CEA) remains the magnitude of the initial procedural risk. Put simply, if the procedural risk after CAS can be reduced, it is inevitable that CAS will assume an ever increasing role in everyday clinical practice. Such a reduction might be achieved through better patient selection, the use of simulators, inexperienced interventionists avoiding more challenging cases, and the evolution of better CAS technologies (protection devices, stents, delivery catheters).[8]

However, although it is an indisputable fact that CAS and its associated technologies have advanced considerably over the last decade, there are several "elephants in the room" that must be addressed before CAS can assume a more generalisable role for the majority of symptomatic patients, and by the majority of practitioners. The first relates to developing strategies for overcoming the substantial learning curve associated with CAS (which may require up to 2 years of experience in a high volume centre[9,10]), while the second relates to the perennial issue of how CAS can establish a generalisable and safe role in a world where recently symptomatic patients are now treated as soon as possible after the onset of

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symptoms. Neither of these key issues were addressed in the latest AHA guidelines, but the drive towards treating symptomatic patients as soon as possible after the onset of symptoms has considerable ramifications for expanding the role of CAS in otherwise "average risk" symptomatic patients. The reason for this change in practice is a growing awareness that the highest risk time period for suffering a stroke after the index event is the first few days, with overviews of natural history studies suggesting that the risk of stroke may reach 20% at 7 days.[11] This has led many guideline groups to recommend that carotid interventions be performed within 14 days, whereas some advocate 48 hours.[12] This move towards expedited interventions therefore, poses a considerable challenge to CAS practitioners, especially as a recent meta-analysis suggests that CAS is associated with a threefold excess risk of procedural stroke if performed within 7 days of the index symptom (compared with CEA) and a twofold excess risk when performed between 8 and 14 days.[13] The high procedural stroke risk after CAS (when performed early) is almost certainly secondary to increased rates of intra-procedural embolisation (despite the use of embolic protection devices), because of the higher prevalence of surface thrombus when interventions are undertaken shortly after the index event. More subtly (but of similar importance), surface thrombus and increased intra-procedural embolisation will also have been responsible for the significantly higher rates of new MR-DWI lesions seen after CAS (compared with CEA), which have now been shown to be associated with a higher risk of suffering late neurological events.[14] It remains to be seen whether proximal protection devices can reduce the prevalence of stroke and new DWI lesion when CAS is performed in the hyperacute period after the onset of symptoms.

In conclusion, CAS has witnessed major advances in technology and safety over the last two decades and an important milestone has now been reached in that all of the major RCTs have shown that CAS appears to be as durable as CEA, following the first 30 days. Notwithstanding the important issue of patient preference however, the magnitude of the initial procedural risk will continue to dictate whether CAS or CEA is safer. CREST-2, ACT-1, and ACST-2 will provide valuable information in asymptomatic patients, but the key challenge for CAS practitioners will now be to demonstrate that CAS can be performed safely in the first 7–14 days after onset of symptoms with procedural risks comparable with CEA.

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