Is stenting equivalent to endarterectomy for asymptomatic carotid stenosis?

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4·3 per 100 person-years in patients with high-risk plaque features.[4] Patients with high-risk plaques represent a select population in whom the risk of stroke under best medical therapy might outweigh the procedural hazard of CAS. Unfortunately, few details on plaque composition were available for patients in the ACST-2 trial. We suggest that future trials consider a more comprehensive recording of high-risk plaque features to allow for more granular subgroup analyses.

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The ACST-2 trial[1] is the largest randomised trial to date comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA). The study involved 3625 patients with carotid stenosis and no previous or recent same-sided stroke or transient ischaemic attack. However, we feel it is important to counter the investigators' conclusions that "serious complications are similarly uncommon after competent CAS and CEA, and the long-term effects of these two carotid artery procedures on fatal or disabling stroke are comparable".[1]

First, the peri-procedural period must be experienced by all patients who undergo CEA or CAS. There will always be a rate of serious procedural complications. These complications must be considered when making treatment choices, and not ignored as implied by the terms "competent" or "successful" procedure.[1] Unfortunately, all past randomised trials involving patients with asymptomatic carotid stenosis (including ACST-2) were underpowered; trends suggested more peri-procedural and longer-term rates of stroke and peri-procedural death in asymptomatic or recently asymptomatic patients given CAS than in those given CEA, as indicated by 95% CIs overlapping 1. We have summarised the randomised trials of CAS versus CEA with at least 200 patients and a follow-up of at least 12 months that have investigated peri-procedural and longer-term patient outcomes (appendix).[1–3]

There was a trend towards more peri-procedural stroke or death with CAS in ACST-2 (odds ratio [OR] 1·35, 95% CI 0·91–2·03).[1] The peri-procedural comparison previously reached statistical significance in a meta-analysis of randomised trials involving patients with asymptomatic carotid stenosis, and is consistent with the increased rate of serious CAS complications in symptomatic patients.[4,5] Furthermore, in the ACST-2 trial,[1] the 95% CI for the 5-year rate of stroke or peri-procedural death extended to 1·56 (OR 1·23, 95% CI 0·96–1·59). This finding indicates that it is within the realms of probability that CAS would cause up to 1·59 times as many strokes as CEA with a large sample size, as would be the case if the methods from this study were rolled out into routine practice. Such a finding would be clinically significant. Rates of new strokes after CAS and CEA were similar beyond the peri-procedural period in these randomised trials, meaning that rates of peri-procedural stroke largely determined longer-term rates. Therefore, patients who have a procedural stroke from CAS tend to live with that stroke in the long term, and the excess harm caused by CAS is durable.

Second, no randomised trial has been adequately powered to compare the peri-procedural rate of the most severe strokes (modified Rankin Scale [mRS] score 3–6). This limitation includes the ACST-2 trial, in which only 13 severe strokes occurred with CAS and 12 with CEA (OR 1·09, 95% CI 0·46–2·61; p=0·84, calculated from published data).[1] The 95% CI indicates that, in clinical practice, it is within the realms of probability that CAS would cause up to 2·61 times as many of the most severe strokes as CEA. Again, this finding would be clinically significant.

Third, it is inappropriate to infer that less severe strokes (mRS score <3) are not associated with clinically significant disability and to exclude them from treatment decisions. In fact, ACST-2 provides further evidence that rates of serious complications are higher with CAS than with CEA and that these complications are durable. Serious procedural hazards are avoided by not choosing CAS and by properly considering the value of current best medical intervention alone (eg, lifestyle coaching and medication).[5] Medical intervention was a missing therapeutic option in the ACST-2 trial.

See **Online** for appendix

We declare no competing interests. All authors are members of the Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments (FACTCATs) with a shared goal of optimising stroke prevention. By design, clinicians and scientists of diverse views are encouraged to be FACTCATs. The views of particular FACTCATs do not necessarily reflect the views of other FACTCATs.

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Authors' reply

In the ACST-2 randomised trial[1] we compared carotid endarterectomy (CEA) with carotid artery stenting (CAS). The discussion of its findings drew on two other sources of evidence; first, the procedural hazards seen in large population registries, and second, our meta-analysis of all the properly randomised trials. For in comparing these two procedures, the differences in their immediate hazards and the differences in their long-term effects on stroke incidence are both important. Hence, for both these outcomes the treatment differences should be assessed reliably. To compare procedural hazards, large population registries might well be more reliably informative than trials, partly because of sample size considerations and partly because trial participants are highly selected and may well have procedural hazards that differ substantially from those in the general population.

We therefore interpreted the ACST-2 findings on procedural hazards (which are underpowered) from the ACST-2 trial in light of the procedural hazards recorded in the legally mandated nationwide German registry of carotid procedures. This registry involves vastly larger numbers than any randomised trial and reported similar immediate risks of disabling stroke with CEA and with CAS. Such registries do not allocate patients randomly between CEA and CAS; therefore, some unknown systematic differences must remain between individuals who undergo these procedures. For comparing the short-term procedural hazards of CEA with those of CAS, however, the effects of any such differences can be limited by excluding the few patients known to be at particularly high risk (American Society of Anesthesiologists grade 3 or worse), by adjusting for age and sex (although neither materially affected procedural stroke rates in the German registry), and by concentrating on disabling strokes (given that these are particularly important, and are likely to be reported).

By contrast, to help compare the long-term effects of successful CEA and successful CAS on stroke rates, the effects of systematic differences between the types of patient undergoing the two procedures could well moderately bias non-randomised comparisons in ways that cannot be reliably allowed for. Hence, it is necessary to rely on the magic of randomisation rather than the myth of what gets misleadingly described as real-world evidence.[2] We therefore interpreted the ACST-2 findings on long-term stroke rates (which are also underpowered) in light of our meta-analysis of the ACST-2 findings on long-term stroke incidence and the corresponding findings from all other randomised comparisons of CEA versus CAS, which did not confirm the apparent difference in ipsilateral stroke rates that had been suggested (non-significantly) by ACST-2. Overall, this meta-analysis[1] showed no material difference between successful CEA and successful CAS in their effects on long-term stroke rates. Randomisation into ACST-2 closed on Jan 1, 2021, with a mean follow-up of nearly 5 years; however, follow-up of stroke rates among the many survivors is to continue for a further 5 years, until approximately 2026.

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Department of Error

Ahsan S. Ukrainian health workers respond to war. Lancet *2022;* **399:** *896*—In this World Report, the author's and Dr Bezuhlyy's names were misspelled. These corrections have been made to the online version as of Mar 17, 2022.