Is stenting equivalent to endarterectomy for asymptomatic carotid stenosis?

Abbott, Anne L.; Wijeratne, Tissa; Zeebregts, Clark J.; Ricco, Jean-Baptiste; Svetlikov, Alexei

Published in:
LANCET

DOI:
10.1016/S0140-6736(21)02498-3

Publication date:
2022

through sociobehavioural factors (eg indoor crowding in response to the cold). The unpublished example in the appendix of Vicedo-Cabrera and colleagues' Correspondence that simultaneously accounts for lagged effects, trends, and season from a single mid-latitude location is insufficient to show that seasonal effects are globally generalisable or that seasonal adjustments are epidemiologically sound.

Probably more important than the effect of lags and seasonality, our estimates only included causes of death that were significantly associated with temperature, whereas the previous studies cited by Vicedo-Cabrera and colleagues are either based on all-cause mortality[2,3] or exclude non-accidental causes.[4]

See Online for appendix

Further, our study showed that the shape of the exposure–response relationship varies across different causes, highlighting the importance of the underlying mortality composition. Our focus on cause-specific mortality is relevant for the design of interventions and necessary for accurate global applications, such as our new method framework to estimate the heat-attributable and cold-attributable burden for 204 countries and territories.[5]

The strength of our study lies in estimating the exposure–response relationships along different temperature zones and for a multitude of different mortality causes. Together, these features allow for the estimation of the attributable burden by applying our risk curves to data-sparse regions. Although global applications come with limitations and uncertainties, we consider our study to be an important step towards establishing much-needed estimates for areas without data availability.

We are well aware of the method developments in climate epidemiology over the past 20 years but suggest that future research can also build on our work, especially the importance of cause-specific analyses when developing reliable estimates for regions where daily mortality data are not available. We and others are undertaking ongoing work to estimate future mortality effects for different climate scenarios. Ignoring spatiotemporal changes in cause-specific mortality and exposure–response relationships will probably lead to erroneous projections. In an era of climate change, reliable estimates are needed to inform effective, evidence-based interventions.

We declare no competing interests.

*Katrin G Burkart, Michael Brauer, Aleksandr Y Aravkin, William W Godwin, Simon I Hay, Jaiwei He, Vincent C Iannucci, Samantha L Larson, Stephen S Lim, Jiangmei Liu, Christopher J L Murray, Peng Zheng, Maigeng Zhou, Jeffrey D Stanaway
katburk@uw.edu

Institute for Health Metrics and Evaluation (KGB, MB, AYA, WWG, SIH, JH, VCI, SLL, SSL, CJLM, PZ, JDS) and Department of Health Metrics Sciences (KGB, MB, AYA, SIH, SSL, CJLM, PZ, JDS), School of Medicine, University of Washington, Seattle, WA 98105, USA; School of Population and Public Health, The University of British Columbia, Vancouver, BC, Canada (MB); Non-Communicable Disease Centre, Chinese Centre for Disease Control and Prevention, Beijing, China (JL, MZ)

1 Burkart K, Brauer M, Aravkin AY, et al. Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: a two-part modelling approach applied to the Global Burden of Disease Study. *Lancet* 2021; **398:** 685–97.
2 Zhao Q, Guo Y, Ye T, et al. Global, regional, and national burden of mortality associated with non-optimal ambient temperatures from 2000 to 2019: a three-stage modelling study. *Lancet Planet Health* 2021; **5:** e415–25.
3 Martínez-Solanas È, Quijal-Zamorano M, Achebak H, et al. Projections of temperature-attributable mortality in Europe: a time series analysis of 147 contiguous regions in 16 countries. *Lancet Planet Health* 2021; **5:** e446–54.
4 Chen R, Yin P, Wang L, et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. *BMJ* 2018; **363:** k4306.
5 GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1223–49.

Is stenting equivalent to endarterectomy for asymptomatic carotid stenosis?

We read with interest the findings of the ACST-2 trial.[1] However, some of the observations made us wonder whether it was accurate to conclude that carotid artery stenting (CAS) and carotid endarterectomy (CEA) were comparable.

First, in both the intention-to-treat and per-protocol analyses, the rate of procedural strokes in patients receiving CAS was above 3% and significantly higher than in those randomly assigned to CEA (appendix). Second, the trial was probably underpowered to detect a difference between CAS and CEA for disabling or fatal strokes, non-disabling strokes, and the composite endpoints. CEA was superior to CAS for all comparisons, with a power above 45% (appendix). Additionally, evidence suggests that the safety profile of CEA could be further improved by decreasing serum concentrations of lipoprotein(a).[2,3] Third, as shown in the appendix to the Article,[1] the rates of death or any ipsilateral stroke was significantly higher in the CAS group (5·5%) than in the CEA group (3·6%; p=0·005 in intention-to-treat analysis). This finding is important because strokes occurring later during follow-up are less likely to be related to the intervention or to the index carotid stenosis than are strokes occurring within 30 days of the intervention. Furthermore, the first carotid intervention is not expected to prevent strokes due to other causes identified during follow-up (eg, contralateral carotid stenosis, atrial fibrillation, aortic plaques, infections, uncontrolled hypertension, or subsequent carotid surgery).

We have previously reported that the incidence of stroke in patients with asymptomatic carotid stenosis was 3·2 per 100 person-years overall and

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.

JK-T is supported by the Faculty of Medicine and Dentistry Motyl Graduate Studentship in Cardiac Sciences, an Alberta Innovates Graduate Student Scholarship, the Department of Medicine Ballermann Translational Research Fellowship, the Izaak Walton Killam Memorial Scholarship, and the University of Alberta Andrew Stewart Memorial Graduate Prize from the University of Alberta. GCJ receives research grant support from the Canadian Institutes of Health Research, Heart and Stroke Foundation, University of Alberta Hospital Foundation, Canada Foundation for Innovation, and National Institutes of Health.

*Joseph Kamtchum-Tatuene, Glen C Jickling
kamtchum@ualberta.ca

Neuroscience and Mental Health Institute (JK-T) and Department of Medicine (GCJ), Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G 2E1, Canada

1 Halliday A, Bulbulia R, Bonati LH, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet* 2021; **398:** 1065–73.
2 Kamtchum-Tatuene J, Jickling GC. Letter by Kamtchum-Tatuene and Jickling regarding article, "Elevated Lp(a) (lipoprotein[a]) levels increase risk of 30-day major adverse cardiovascular events in patients following carotid endarterectomy". *Stroke* 2021; **52:** e64–65.
3 Waissi F, Dekker M, Timmerman N, et al. Elevated Lp(a) (lipoprotein[a]) levels increase risk of 30-day major adverse cardiovascular events in patients following carotid endarterectomy. *Stroke* 2020; **51:** 2972–82.
4 Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, Saqqur M, Shuaib A, Jickling GC. Prevalence of high-risk plaques and risk of stroke in patients with asymptomatic carotid stenosis: a meta-analysis. *JAMA Neurol* 2020; **77:** 1524–35.

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.