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EDITORIAL

Words of Caution Regarding Safety Comparisons Between Transcarotid Artery Revascularization, Carotid Endarterectomy, and Carotid Stenting

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Columbo et al[1] are to be congratulated for this analysis of 118 566 patients who underwent carotid endarterectomy (CEA), transfemoral carotid artery stenting (CAS) or trans-carotid arterial revascularisation (TCAR) in association with the VQI (Vascular Quality Initiative) registry between September 2016 and June 2021 in this issue of the *Journal of the American Heart Association* (*JAHA*). According to the authors, this is the first large-scale, real-world comparison of these procedures using a 2-stage residual inclusion instrumental variable (IV) methodology to account for selection bias and unmeasured or unmeasurable confounding, as well as for known confounding variables.

See Article by Columbo et al.

The authors acknowledge that their analysis does not address the efficacy of carotid artery procedures in reducing stroke risk.[1] Procedural efficacy can be assessed using only studies of patient outcomes with carotid artery procedures compared with noninvasive medical intervention alone (ie, encouragement of healthy lifestyle practices and appropriate use of medication). This analysis by Columbo et al is about the relative safety of carotid artery procedures with respect to the in-hospital and 1-year rate of patient stroke or death within the environment of the VQI registry.

Using the IV methodology, the overall in-hospital stroke or death rate was higher with TCAR compared with CEA. Again using the IV methodology, at 1 year after the procedure, there was no statistically significant difference in the rate of stroke or death for individuals who had TCAR compared with CEA. Further, using the IV methodology, the subgroup of patients classified as symptomatic had the lowest likelihood of stroke or death at 1 year after the procedure with TCAR.[1] However, in all other statistical comparisons of in-hospital stroke and death rates, TCAR was more hazardous than CEA, and 1-year postprocedural stroke or death rates with TCAR were inferior, or not significantly different, compared with CEA. In addition, both TCAR and CEA appeared to be less hazardous than CAS at both time points, consistent with the existing evidence base demonstrating excess hazards of CAS compared with CEA.[2–4]

Using their results, Columbo et al[1] acknowledged that CEA remains the gold-standard procedure for patients with carotid stenosis. Any apparently favorable results with TCAR using the IV methodology are, at best, hypothesis generating, and readers should not interpret them as encouragement for ongoing use of TCAR in routine clinical practice. There are several reasons for this:

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1. Favorable results with TCAR compared with CEA were limited and seen only using the IV method. This method takes into account unknown and unmeasured and therefore perhaps clinically inappropriate confounders. The authors correctly stated that they cannot conclude that the unmeasured confounding accounted for in their analysis, and that may have been related to treatment decisions, was appropriate with respect to selecting patients likely to benefit from a carotid artery procedure compared with noninvasive medical intervention alone.[1]

   Indeed, the only established indicators of an overall stroke risk reduction benefit from a carotid artery procedure (specifically only from CEA) compared with noninvasive measures alone, are few and relatively simple. They relate to patient symptomatic status, age, and general fitness to undergo CEA; degree of carotid stenosis and how this is measured; point-of-care procedural hazard; and standard of noninvasive interventions used. These indicators are extractible from the previous randomized trials of CEA plus noninvasive medical intervention versus noninvasive medical intervention alone.[5–9] Of note, the overall average annual stroke risk reduction benefit from CEA in these randomized trials was small: ≈1% for asymptomatic carotid stenosis patients and up to ≈3.2% for symptomatic patients with ipsilateral carotid stenosis.[2]

   The patient subgroups with carotid stenosis with an overall benefit from CEA in the above-mentioned randomized trials (or with an overall benefit from early versus deferred CEA[10]) had to satisfy all trial selection criteria, have a life expectancy of at least 3 to 5 years, and fit into 1 of the 4 following groups[1,2]:

(i) Men aged <75 to 80 years with 60% to 99% asymptomatic (or recently asymptomatic) carotid stenosis (by way of conventional intra-rterial angiography or ultrasound and NASCET [North American Symptomatic Carotid Endarterectomy Trial] criteria)[5,7,10]
(ii) Symptomatic women with 70% to 99% stenosis (by way of conventional intra-arterial angiography and NASCET criteria) having CEA within 2–3 weeks of their last same-sided nonsevere stroke or transient ischemic attack.[7–9]
(iii) Symptomatic men with 50% to 69% stenosis (by way of conventional intra-arterial angiography and NASCET criteria) having CEA within 2 to 3 weeks of their last same-sided nonsevere stroke or transient ischemic attack.[6–9]
(iv) Symptomatic men with 70% to 99% stenosis (by way of conventional intra-arterial angiography and NASCET criteria) having CEA within 3 months of their last same-sided nonsevere stroke or transient ischemic attack. However, the benefit fell rapidly over this time and was highest within 2 to 3 weeks of their last same-sided nonsevere stroke or transient ischemic attack.[6–9]

   Although proceduralists may have access to a variety of other factors regarding their patients,[1] these factors have not been shown in trials to identify individuals likely to benefit from a carotid artery procedure compared with noninvasive measures alone. Moreover, past randomized trials of CEA versus noninvasive medical intervention alone have been increasingly outdated since they were started because of continuing improvement in the stroke prevention effectiveness of noninvasive medical intervention.[2] This means that there is no current trial evidence of benefit from any form of carotid artery procedure in any subgroup of patients with carotid stenosis.

2. The IV analysis methodology is not the same as a randomized trial of appropriate patients, and reasons why proceduralists chose or preferred TCAR, CEA, or CAS were not provided.[1]
3. The VQI registry methods, and therefore its results, are not generalizable given the unknown nature of possible confounding factors, incomplete knowledge about the categorization of asymptomatic and symptomatic patients, and incomplete knowledge about the nature of the noninvasive medical intervention received by the registry patients and how appropriate and effective it was in terms of reaching treatment goals.[1]
4. Although results of the analysis by Columbo et al[1] indicate that TCAR is safer than CAS, it is already well established that CEA is safer than CAS with respect to short- and long-term stroke, plus or minus rates of periprocedural death or myocardial infarction.[2–4] Why use a new, alternative procedure, such as TCAR, with its necessary learning curves, when it is not proven to be as safe as or safer than CEA, and TCAR has no proven superior stroke risk reduction benefit compared with current noninvasive medical intervention alone?
5. Guidelines worldwide already encourage use of carotid artery procedures in subgroups not shown to benefit compared with noninvasive medical intervention alone.[2,3,11] This should be recognized and resisted, including for new procedural approaches, such as TCAR.
6. In this analysis by Columbo et al, there was no measurement of the stroke prevention efficacy of TCAR, CEA, or CAS against current standards of noninvasive medical intervention alone.[1] Studies to characterize current best practice, noninvasive medical intervention and measure its impact, independently of carotid procedures, are top priority.[2]

The fact that TCAR has become so popular in parts of the United States is very concerning. This analysis by Columbo et al is documentation of new, inappropriate use of carotid artery procedures, building on continued use of CEA and CAS in asymptomatic and symptomatic individuals without current (and sometimes any) evidence of patient benefit but with ongoing clinically significant procedural risks.[2,12] We can only hope that this inappropriate procedural intervention recedes and that, instead, patients are diverted into the studies that are so critically needed to establish what can now be achieved with current best practice, noninvasive medical intervention alone, and if any subgroups of carotid stenosis patients now benefit from the addition of a carotid artery procedure.[2]

ARTICLE INFORMATION

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Disclosures

A/Prof Abbott is a neurologist. She is the founding member of the Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments (FACTCATS, see https://factcats.org/). FACTCATs have a shared goal of optimizing stroke prevention. By design, clinicians and scientists of diverse views are encouraged to be FACTCATs in this online environment which encourages substantiation of opinion with scientific evidence. The views of particular FACTCATs do not necessarily reflect the views of other FACTCATs. A/Prof Abbott has received several grants for independent research on the topic of stroke prevention. She was partially funded by a National Health and Medical Research Council grant (APP1168295) at the time of creating this article. The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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