Korean Circ J. 2020 Apr;50(4):343-345
https://doi.org/10.4070/kcj.2020.0023
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

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Reassembling Evidence for Treatment in Asymptomatic Carotid Artery Stenosis

Hyung Oh Kim, MD, and Weon Kim, MD, PhD

Division of Cardiovascular, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University, Seoul, Korea

▸ See the article "Role of Carotid Artery Stenting in Prevention of Stroke for Asymptomatic Carotid Stenosis: Bayesian Cross-Design and Network Meta-Analyses" in volume 50 on page 330.

OPEN ACCESS

Received: Jan 16, 2020
Accepted: Jan 21, 2020

Correspondence to
Weon Kim, MD, PhD
Division of Cardiovascular, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea.
E-mail: mylovekw@hanmail.net

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ORCID iDs
Hyung Oh Kim
https://orcid.org/0000-0003-2157-441X
Weon Kim
https://orcid.org/0000-0003-1264-9870

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Writing - original draft: Kim HO, Kim W; Writing - review & editing: Kim W.

Asymptomatic carotid artery stenosis is an atherosclerotic disease which involves the carotid artery and features no history of ischemic stroke or transient ischemic attack. The prevalence of asymptomatic carotid artery stenosis in the general population is known to range up to 3.1% which is not insignificant.[1] In current clinical practice, medical treatment (MT), carotid endarterectomy (CEA), and carotid artery stenting (CAS) are all available. However, according to 2017 European Society of Cardiology (ESC) guidelines,[2] there is no class I recommendation for treatment modality in asymptomatic carotid artery disease due to weak consistency among the relevant data. More importantly, there is no evidence which compares efficacy between MT and CAS, which are both less invasive, with respect to being included in the guidelines. Therefore, recommendations for asymptomatic carotid stenosis are inevitably indirect at the current time. Ideally, randomized trials are required to compare the efficacy and safety of MT, CEA, and CAS. But considering the ethical and realistic limitations, gathering as much evidence as possible and incorporating it in a large-scale analysis can be a way to overcome the indirectness of previous evidence.

In this issue of *Korean Circulation Journal*, Roh et al.[3] present a study which has 2 strengths. 1) By adopting a Bayesian cross-design, results of randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) were incorporated into a large-scale analysis that compared MT, CEA, and CAS. 2) The Bayesian network meta-analysis enabled indirect comparison between MT and CAS. The authors included 22 studies among which were RCTs and NRCTs. A previous large-scale meta-analysis by Hadar et al.[4] included 41 studies on the MT of asymptomatic carotid artery stenosis. However the meta-analysis did not compare the MTs to other invasive measures such as CEA and CAS. Galyfos et al.[5] recently pooled 10 randomized trials and evaluated 8,711 patients with respect to asymptomatic carotid artery stenosis treatments and compared MT, CEA, and CAS. However, the authors could not compare MT and CAS in head-to-head manner, because there was no study that directly compared those treatment modalities. To the best of our knowledge, the study by Roh et al.[3] is the largest scale study to investigate the efficacy and safety of MT, CEA, and CAS in a head-to-head manner.

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With respect to a comparison of CAS and CEA, Roh et al.[3] demonstrated similar results seen in previous studies. The periprocedural stroke risk increased in CAS compared to CEA and periprocedural myocardial infarction risk increased or was similar in CAS compared to CEA. This result is in line with the 2017 ESC guidelines, which recommends CEA as the first treatment modality to be used in standard patients. The results of the MT and CAS comparison that demonstrated a trend for lower risk in CAS can be interpreted as CAS is better compared to MT in patients with asymptomatic carotid artery stenosis. However, as the authors clarified in their discussion, most analyzed studies regarding MT are mostly outdated. Previous studies which assessed MT for asymptomatic carotid artery stenosis report improved efficacy as the publication date is more recent.[6][7] The efficacy of potent contemporary MT regimens may be clarified to some degree in future studies such as the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)[8] and the Second European Carotid Surgery Trial (ECST-2),[9] which are future randomized trials.

Randomized trials which include a large number of patients will be essential to establish more well-described and updated clinical practices and guidelines for asymptomatic carotid artery stenosis. MTs for the disease include antiplatelet and lipid-modifying agents, and stroke risk factor management. Those drugs and management protocols have dramatically changed from the era of earlier studies on MTs.[7] Single antiplatelet therapy with aspirin has been the classic antiplatelet regimen. Other antiplatelet drugs (i.e., clopidogrel, ticagrelor, or prasugrel) are supported by no data at the current time. At this time, lipid-modifying agents include statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, icosapent ethyl, etc. The 2019 ESC/European Atherosclerosis Society (EAS) dyslipidemia guideline recommended low-density lipoprotein cholesterol level should be targeted below 55 mg/dL in very high risk patients. The accepted blood pressure goal has been changed since the Systolic Blood Pressure Intervention Trial (SPRINT).[10] These recently updated findings should be assessed in future studies. Some of these questions may be answered by the above mentioned CREST-2 and ECST-2, which are underway in North America and Europe, respectively.

There are limitations in the reviewed study that should be noted. The number of RCTs was relatively small with respect to overcoming heterogeneous patient data which included heterogeneous diagnosis modalities and stenosis severity.

Optimal treatment is a problem that has lingered for a long time, along with medical technology advances and paradigm changes with respect to this condition. Future studies may resolve some of the unanswered questions. However, there are pending questions at the moment and precision medicine methods will be necessary for decision making in asymptomatic carotid artery stenosis.

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