EDITORIAL

CREST-2: Game Changer or Yet Another Argument for optimised risk stratification?

Spyridon N. Mylonas[1], John D. Kakisis[2]

[1] Vascular Surgery Department, General Hospital of Athens "Georgios Gennimatas", Athens, Greece
[2] 1st Department of Vascular Surgery, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece

Only a limited number of vascular surgical treatment areas are supported by a broad and high-quality evidence base. One of these is the surgical and interventional treatment of extracranial carotid stenosis. Based on randomized controlled trials and meta-analyses including more than 7,000 patients, national, European, and international guidelines recommend carotid endarterectomy (CEA) as the first-line invasive revascularization strategy.[1-5] However, clinical evidence was more robust for symptomatic, rather than asymptomatic, carotid stenosis. The indication for primary preventive revascularization in asymptomatic carotid stenosis remains challenging and requires careful interdisciplinary assessment. The individual long-term stroke risk must be weighed against the perioperative or periprocedural risk. Current guidelines recommend selecting the revascularization strategy based on individual anatomical and clinical factors. Arguments favoring carotid artery stenting (CAS) include high cervical stenosis extending to the skull base, tandem lesions, restenosis after previous open surgery, contralateral cranial nerve injury, and radiation-induced stenosis.

There is broad consensus that outcomes reported in clinical trials are only valid if evidence-based best medical treatment (BMT) is consistently implemented. This includes smoking cessation, optimal blood pressure control, lipid lowering, glycemic control, weight management, and dietary optimization. In routine clinical practice, however, adherence to these measures is often insufficient, resulting in worse outcomes than those reported in randomized trials.[6] This assumption is supported by a recently published longitudinal registry analysis of nearly 47,000 propensity score-matched patients in Germany. Among patients undergoing invasive treatment for carotid stenosis, the 5-year cancer incidence was approximately 17% with a mortality during the same period of 18% in men and 14% in women.[7] This excess non-stroke-related mortality has relevant implications for mortality-related endpoints such as stroke-free survival and may bias trial results if best medical treatment is suboptimal.

At the same time, it has been postulated that best medical treatment has improved substantially over recent decades due to changes in risk factor prevalence and advances in pharmacological therapy. The annual stroke risk in the Asymptomatic Carotid Artery Study was 2% per year and decreased to <1% over time.[8] The assumption that contemporary medical management for extracranial carotid artery stenosis has diminished the clinical utility and net benefit of surgical or endovascular revascularization was a key rationale for the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2).[9]

CREST-2 consisted of two parallel randomized superiority trials comparing either CEA or CAS with strictly defined BMT in patients with asymptomatic high-grade (≥70%) carotid stenosis. Between December 2014 and July 2025, a total of 2,485 patients were randomized in 155 centers, predominantly in the United States, with a mean follow-up of approximately four years. Both trials were conducted using an intention-to-treat design.[10] In the CEA trial (n = 1,240), 18% of patients randomized to best medical treatment crossed over to invasive revascularization. A similar crossover rate (17%) was observed in the CAS trial (n = 1,245). The primary endpoint in both trials was a composite of any stroke or death within 44 days after randomization, or ipsilateral ischemic stroke during follow-up. In the CEA trial, the primary endpoint occurred in 5.3% of patients receiving best medical treatment and in 3.7% of patients undergoing surgery. The absolute risk difference was 1.6% (95% CI: −1.1% to +4.3%; p = 0.240) and the relative risk only 1.43 (95% CI: 0.78 to 2.72). In the CAS trial, the primary endpoint occurred in 6.0% of patients receiving best medical treatment and in 2.8% of patients undergoing stenting, corresponding to an absolute risk difference of 3.2% (95% CI: +0.6% to +5.9%; p = 0.020) and the relative risk 2.13 (95% CI: 1.15 to 4.39).[10] Although CREST-2 was not designed for a direct comparison between CEA and CAS, the authors concluded that carotid stenting provided a statistically significant benefit over best medical treatment, whereas carotid endarterectomy did not.

This interpretation has been the subject of substantial debate regarding the external validity and the extent to which its findings can be extrapolated to broader clinical populations. A

Author for correspondence:

Spyridon N. Mylonas

Vascular Surgery Department, General Hospital of Athens "Georgios Gennimatas", Athens, Greece

E-mail: spyrosmylonas@gmail.com

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closer interrogation of the study data highlights several methodological nuances that warrant rigorous critical appraisal. First, the two trials were conducted independently and differed in patient selection and exclusion criteria. In particular, the CAS trial excluded patients with unfavorable anatomy, including complex aortic arch anatomy, circumferential calcification, severe kinking, lesion length greater than 3 cm, and vulnerable plaque morphology. In contrast, inclusion criteria for CEA were considerably broader. Moreover, primary endpoint rates in the conservative arms differed between the two trials (absolute risk difference of 0.7%), raising concerns regarding comparability of patient populations and follow-up. In this context, differences were also observed in baseline characteristics, including the prevalence of cardiovascular disease, prior coronary revascularization (55% vs 43%), and previous stroke or transient ischemic attack (4.9% vs 8.4%).

Generalizability of the results is further limited by healthcare system differences. In the predominantly North American study centers, CEA was also performed by neurosurgeons and sometimes without adjunctive cross-sectional imaging. Potential interventionalists had to submit 100 CAS operative notes with at least 25 cases performed in the past year; only 50% of applicants were accepted. Potential surgeons had to submit 50 CEA operative notes over any time period; 90% of applicants were accepted. This deviation from the initially required minimum case volume and the relatively low proportion of randomized patients suggest potential selection bias. Moreover, the study protocol allowed local investigators to allocate patients to either trial primarily based on stenosis severity, without applying additional guideline-based criteria. While this reflects real-world practice, it introduces confounding by indication and precludes valid conclusions regarding procedural superiority.

Given the restricted lesion characteristics in the CAS trial (median lesion length 18 mm) and the broader inclusion criteria for CEA, procedural and lesion-related risks were likely not comparable between the two trials. These factors, together with changes in medical therapy during the study period, as discussed also by the authors, may have influenced the results and their statistical robustness as well as the applicability to routine clinical decision-making.

From a clinical perspective, the absolute benefit observed remains modest. Among 100 patients treated with carotid stenting, approximately one ipsilateral stroke is prevented over four years, while this benefit is offset by one periprocedural stroke or death. During a four-year study period, 95 out of 100 patients underwent an unnecessary carotid artery angioplasty. Consequently, the majority of patients undergo invasive treatment without measurable benefit. This underscores the need for improved risk stratification in asymptomatic carotid stenosis, including the evaluation of plaque morphology and other imaging-based predictors.

Inspection of the Kaplan-Meier curves reveals that the benefit observed at the beginning of the follow-up period changes after approximately one year for both the surgical and interventional study arms. The curves then intersect and, after largely overlapping, only diverge in the final year of the follow-up period. The reasons for this pattern remain unclear and require further subgroup and adherence analyses. It is noteworthy that, at the interim analysis, the CEA arm showed more favorable outcomes than CAS. However, there were six late stroke events in the CEA arm 2 to 4 years postoperatively that were unrelated to the procedure or carotid restenosis or reintervention. Because these strokes occurred years after surgery and were not linked to restenosis or reinterventions, it is difficult to understand how they meaningfully reflect the comparative performance of the treatment options.

In summary, interpretation of CREST-2 requires caution. Given the methodological limitations and heterogeneity of the study population, improved risk stratification through interdisciplinary evaluation in neurovascular boards remains essential. Imaging findings, clinical risk profiles, and patient preferences should be integrated into individualized decision-making. Moreover, the role of newer techniques, such as transcarotid artery revascularization (TCAR), and novel stent designs, including dual-layer stents, cannot be assessed based on the CREST-2 data and remains a subject for future studies.

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