



Letter to the Editor

Position statement on the CREST-2 clinical trial by the SEACVE Spanish Chapter of Endovascular Surgery (CCEV)

Posicionamiento del Capítulo de Cirugía Endovascular (CCEV) de la SEACVE sobre el ensayo clínico CREST-2

To the Editor,

The CREST-2 clinical trial, recently published in the *New England Journal of Medicine*, represents one of the largest contemporary efforts to provide evidence on the management of significant asymptomatic carotid stenosis ($\geq 70\%$) (1). It is, in fact, the publication of 2 simultaneous and parallel clinical trials evaluating the benefits of adding carotid artery stenting ($n = 1,240$) or endarterectomy ($n = 1,245$) to intensive medical therapy. The included patients came from 155 centers, mostly in North America (94.8 %). Transfemoral carotid artery stenting showed a significant reduction in the 4-year stroke/death rate compared with medical therapy (6.0 % vs 2.8 %; $p = 0.02$), whereas the differences recorded for endarterectomy did not reach statistical significance (5.3 % vs 3.7 %; $p = 0.24$). However, both techniques significantly reduced the annual event rate: stenting, RR, 4.07 (95 %CI, 1.78-9.31), and endarterectomy, RR, 2.38 (95 %CI, 1.13-5.00).

Although these results have in some cases been interpreted as active support for an endovascular strategy in asymptomatic patients, they have also generated considerable discussion within the vascular community (2). After a critical analysis of the study data and clinical implications, the Spanish Chapter of Endovascular Surgery (CCEV) of the SEACVE considers it necessary to issue an official statement analyzing several methodological, clinical, and general applicability aspects that are key:

1. *There are major differences in the characteristics of the population undergoing stenting and endarterectomy.* The former had a strikingly "healthy" profile and received such optimized medical therapy, including telephone coaching and medication funding, that it borders on the unrealistic. It is worth recalling the geographical setting from which most patients came, with health care systems that do not fully fund pharmacological treatments. Very strict targets were set for systolic blood pressure, below 130 mmHg, and LDL cholesterol, below 70 mg/dL, which nevertheless were achieved by 70 % of patients 12 months after inclusion. In addition, the results of medical management differed between the 2 parallel trials, with a stroke/death rate of 6.0 % in the stenting trial compared with 5.2 % in the endarterectomy trial, but they cannot be directly compared because they belong to different studies.
2. *There are also differences in patient selection according to anatomical and lesion-related criteria.* The stenting arm excluded patients with unfavorable anatomy at the surgeon's discretion: type 3 aortic arches, significant angulation of the target vessel, tortuosity, calcification, circumferential internal carotid artery lesions, long lesions (>2 cm), etc. These criteria were not applied to the endarterectomy arm, in which any patient was included except those with hostile necks. This point and the previous one suggest a high degree

of cherry-picking, that is, systematic and deliberate selection of favorable cases for one technique and not for the other.

3. *Differences also existed in the inclusion and exclusion criteria for centers and surgeons.* Participation in the stenting trial required at least 100 procedures, 25 of which had to have been performed in the previous year, and 50 % of candidates were rejected. For endarterectomy, however, the criteria were much more relaxed, 50 operations in any period, and 90 % of candidate centers were accepted. In addition, the same 30-day stroke/death rate threshold, 3 %, was applied to both groups. This figure is excessive for endarterectomy in asymptomatic patients: in large observational studies, such as that by Rothenberg et al. ($n = 1949$), the 30-day stroke/death rate in asymptomatic patients is below 1 % (3). Including centers with rates as high as 3 % indicates excessive leniency, since with these figures the advisability of performing endarterectomies in asymptomatic patients at that center could even be questioned. Along the same lines, it is striking that the carotid-related reintervention rate was 7 % at 1 year, which is also abnormally high.
4. *The final result was biased by patients with fewer comorbidities.* The subgroup analysis shows that the significant differences in favor of stenting occurred at the expense of patients without diabetes, without hypertension, without dyslipidemia, nonsmokers, with a CHA₂DS₂-VASc score of 0 to 3, and completely asymptomatic. This seems to indicate that the benefit of stenting occurs if and only if the patient is falsely optimal from both a clinical and an anatomical standpoint.
5. *The results are strikingly different from those shown in previous trials.* In all previous trials, the stroke/death rate for carotid artery stenting is between 50 % and 90 % higher than that for endarterectomy (4). This difference is more evident in trials involving symptomatic patients, who have a higher baseline event rate, and has not been demonstrated as clearly in asymptomatic patients. Two large

meta-analyses, including more than 3000 and 6000 patients, respectively, confirm beyond doubt that, in the short term, at 30 days and 1 year, stroke/death rates are significantly higher with carotid artery stenting (5,6).

6. *The number of events was low.* The interim analysis of the CREST-2 trial results showed findings favorable to endarterectomy (7). From the time that analysis was performed, in 2023, until the end of the study, 6 additional events were recorded. All were strokes and occurred between 2 and 4 years after the procedure, without any relationship being established with surgery, the presence of restenosis, or reinterventions after evaluation by the relevant committee. Such a low event rate, involving unrelated events, completely distorts the differences between treatments. Moreover, these differences become especially important given that the loss-to-follow-up rate in the stenting trial was 10 %. A single additional recorded event could have had a major influence on the direction and magnitude of the results obtained.
7. *Transcarotid artery revascularization (TCAR) was not included;* according to the authors, it had not been significantly implemented when the study began. The results of TCAR have shown clear superiority over those of transfemoral carotid artery stenting (TF-CAS) in both symptomatic and asymptomatic patients. For the latter, the 3-year stroke/death rate was 22.6 % vs 31.4 %; $p < 0.001$, in the most recent available evidence (8). Note the enormous difference between these percentages and those reported in the CREST-2 trial.
8. *There were differences in postprocedural treatment.* The stenting trial used dual antiplatelet therapy for 1 month before and after the procedure, whereas the endarterectomy trial never used dual antiplatelet therapy.
9. *Design.* These were 2 independent, parallel clinical trials reported in the same study; therefore, this setting was not statistically designed to compare stenting and endarterectomy directly.
10. *There was a high crossover rate in both groups.* Between 15 % and 20 % of patients initially

assigned to the medical therapy arm ultimately underwent either stenting or endarterectomy. The intention-to-treat analysis may be significantly affected by this substantial proportion of patients who crossed over to another arm.

The CCEV recognizes the relevance of CREST-2 as an ambitious trial that provides additional information on the management of asymptomatic carotid stenosis under contemporary standards. However, its results should not be interpreted simplistically and, in light of the limitations discussed, its publication should not lead to a change in routine practice based on guideline recommendations (9-11). It seems reasonable to continue recommending that patients with asymptomatic carotid stenosis start maximum-intensity medical therapy as soon as possible. The best results are always obtained by individualizing management for each patient, considering their risk factors, anatomical and plaque characteristics, expected risk/benefit profile, and the experience and volume of each center. The CCEV reiterates its commitment to clinical excellence, high-quality research, and the capacity for systematic and critical analysis of the evidence to guide all therapeutic decisions in vascular and endovascular surgery.

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