Editorial for NEJM on CREST-2 30-10-2025

Title: How should we manage asymptomatic carotid stenosis?

Authors: Martin M Brown FRCP, Emeritus Professor University College London, UK and Leo H Bonati, MD, Professor of Neurology, Department of Clinical Research, Basel University, Switzerland

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The management of carotid artery stenosis that has not caused recent symptoms – asymptomatic carotid stenosis - has been controversial. Clinical trials started over 30 years ago showed a small benefit of carotid endarterectomy compared to medical treatment, but improvements in medical stroke prevention called into question whether endarterectomy is still beneficial.[1] Carotid stenting has emerged as a less invasive but unproven alternative to endarterectomy for treatment of asymptomatic carotid stenosis.

The authors of the article in this week's journal reporting the results of the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trials (CREST-2) have provided us with valuable data to help answer these questions.[2] CREST-2 included two parallel trials in which all patients received intensive medical management. One trial randomizing 1245 patients between stenting and intensive medical therapy alone, showed significant benefit to stenting compared to medical management alone. In contrast, in the parallel trial that randomized 1240 patients between carotid endarterectomy and intensive medical management alone, there was no significant difference between the two arms.

How should we interpret these results? The findings in the CREST-2 endarterectomy trial are in keeping with the results of two other recent trials with similar questions, the Second Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE-2) study[3] and the Second European Carotid Surgery Trial (ECST-2).[4] We can conclude that there is no longer a role for routine carotid endarterectomy in asymptomatic stenosis.

Do the results of CREST-2 mean that stenting should be widely adopted for asymptomatic stenosis? We argue that caution is required. Firstly, the low rate of stroke with stenting reflects careful selection of patients and skilled interventionists, which are not available in all vascular centres. Previous trials comparing stenting versus endarterectomy for asymptomatic carotid stenosis, including the Asymptomatic Carotid Surgery Trial 2 (ACST-2) which included 3625 patients, reported an approximately 1% higher peri-procedural stroke or death rate associated with stenting compared with endarterectomy.[5] Second, the difference between stenting and medical management was based on a small number of events; the authors reported that if only three more events had occurred in the stenting arm, the difference would no longer be statistically significant. In SPACE-2 which only allocated 197 patients to stenting, there was no benefit to stenting compared to best medical therapy alone.[3]

Indeed, looking at the cumulative event rates in all four arms of CREST-2, there are more similarities than differences between endarterectomy and stenting. The benefit from revascularisation of asymptomatic carotid stenosis in preventing stroke has become small with improved medical therapy. Third, medical therapy could be further intensified, as acknowledged by the authors. In CREST-2, only 60–70% of patients had their blood pressure within target (<130 mmHg) during follow up, less than 80% had their LDL within target of <70 mg/dL (<1.8 mmol/L) and only about 50% of the diabetic patients had Hemoglobin A1c within target. Newer lipid-lowering drugs, such as PCSK-9 inhibitors, and lower targets for LDL of <55 mg/dL (<1.4 mmol/L) provide options not available in CREST-2.

An equally important issue is whether the benefit over the 4-year horizon of the trial, justifies the early increase in risk from stenting. In CREST-2, there was a procedural stroke and death rate associated with stenting of 1.3%, whereas there were no early events with medical therapy alone. Subsequently, the rates of ipsilateral stroke were 0.4% per annum in the stenting arm and 1.7% in the medical therapy alone arm. Thus for 100 patients treated with stenting, only about one will benefit by avoiding a stroke per year, at a price of about one suffering an adverse stroke or death from the procedure. Over a 4-year period, 95 of 100 patients will have had an unnecessary procedure. It is also relevant that around two-thirds of the events in the patients treated with intensive medical therapy alone were non-disabling strokes. Such patients make a good or fair recovery and revascularisation is then indicated for symptomatic carotid stenosis.[6]

We therefore consider it reasonable to advise patients with asymptomatic carotid stenosis to start intensive medical therapy immediately, and delay revascularisation until such time as the small proportion become symptomatic. Exceptions would then be made for patients who prefer to take the risk of revascularisation or cannot take medical therapy, when stenting would be the choice for suitable patients at a centre with skilled and experienced interventionists.

The CREST-2 authors are to be congratulated for conducting the first large scale trial investigating the management of asymptomatic carotid stenosis on the background of intensive medical therapy. What we need now are trials focusing on identification of the small proportion of patients with carotid stenosis who develop symptoms despite optimum medical therapy. The most promising approach uses magnetic resonance carotid plaque imaging to identify intraplaque haemorrhage, a strong risk factor for subsequent stroke.[7,8]

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