Myocardial Infarction After CAS and CEA: Why Does It Matter?

Clinical or subclinical MI predicts mortality after carotid intervention and should be included in the primary endpoint composite of carotid trials.

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Recent results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) showed no statistically significant difference between carotid endarterectomy (CEA) and carotid artery stenting (CAS) in the primary endpoints of periprocedural stroke, myocardial infarction (MI), or death, as well as the postprocedural rate of ipsilateral stroke at up to 4 years.[1] However, the risk of periprocedural stroke was found to be higher with CAS versus CEA (4.1% vs 2.3%), and the risk of periprocedural MI was higher with CEA than with CAS (2.3% vs 1.1%). In CREST, periprocedural strokes translated into a significant impact on patients' quality of life (QOL) based on SF-36 scores, and the impact was found to be much worse than that of periprocedural MI. At 1 year, the affect on physical health from a periprocedural stroke was −15.8 points on the physical component of SF-36, whereas the affect of periprocedural MI was only −3. The study investigators found that even minor periprocedural strokes had a significant affect on mental health at 1 year, which measured −3.4 on the mental component of SF-36.[1]

On the basis of these QOL analyses among survivors at 1 year, the investigators concluded that stroke had a greater adverse effect on a broader range of health domains than MI and that MI in the postprocedural setting is perhaps less of an adverse event than periprocedural stroke. Nevertheless, this view is controversial and frequently challenged because several studies have shown an association between MI and biomarkers for myocardial injury and future mortality in a variety of vascular and nonvascular procedures.[2-5]

MI/CARDIAC BIOMARKER ELEVATION AND MORTALITY IN CARDIAC, VASCULAR, AND NONVASCULAR INTERVENTIONS

In a meta-analysis of 20 studies with 15,581 patients who underwent percutaneous coronary interventions, troponin elevation was associated with increased mortality.[4] Oscarsson et al[5] showed a 15-fold increase in mortality at 1 year with a postoperative cardiac troponin elevation in 546 elderly patients who underwent noncardiac surgical procedures. In a study of 393 patients who underwent major vascular procedures, troponin elevation was also associated with a twofold increase in all-cause mortality.[2] In a study of 447 patients who underwent major vascular procedures, Landesberg et al[3] showed that both creatinine kinase-MB fraction (CK-MB) levels > 10% and cardiac troponin-I levels > 1.5 ng/mL and/or cardiac troponin-T levels > 0.1 ng/mL independently predicted fourfold and twofold increases in long-term mortality, respectively. However, these studies were not conducted in the setting of carotid interventions; it is unclear whether such findings can be extrapolated to patients undergoing CEA or CAS.

SIGNIFICANCE OF PERIPROCEDURAL MI IN CAROTID INTERVENTION

To address the impact of periprocedural MI on the mortality of patients undergoing carotid intervention, the CREST investigators performed a post hoc analysis to explore the prognostic significance of MI among patients undergoing either CAS or CEA.[6] In CREST, elec-

trocardiogram (ECG) and cardiac biomarker (a mixture of troponin-I or -T, CK, and CK-MB) measurements were routinely obtained before and after the carotid revascularization procedure. MI was defined as biomarker elevation plus either chest pain or ECG evidence of ischemia. An additional category of biomarker elevation only without symptoms or ECG changes was prespecified. Crude and risk-adjusted mortality rates were obtained and compared for patients with and without MI or biomarker elevation only. Among 2,502 patients, 14 MIs occurred in the CAS group and 28 MIs in the CEA group (hazard ratio [HR], 0.5; *P* = .032). An additional eight CAS and 12 CEA patients had biomarker elevation only; however, the difference between the two groups was not significant (*P* = .36). Compared to patients without biomarker elevation only or MI, mortality was higher over 4 years for those with MI (HR, 3.4; *P* < .001) or biomarker elevation only (HR, 3.57; *P* = .005). After adjustment for baseline risk factors, the mortality of patients with perioperative MI or biomarker elevation only remained significantly higher (HR, 3.67; *P* = .001 and HR, 2.87; *P* = .023, respectively).

In other words, patients with MI or biomarker elevation only were three to four times more likely to die during the follow-up period than those with no evidence of MI (clinical or subclinical), even after adjustment for important baseline characteristics (including age, diabetes, and history of cardiovascular disease).

On the other hand, unlike MI and biomarker-only elevation, per-protocol analysis of CREST showed a lack of association between minor strokes and long-term mortality (*P* = .34). Compared with a minor stroke, MI was associated with a 5.2-fold higher risk of long-term mortality (*P* = .02).[7] Thus, a patient who had a postprocedural MI has a 4-year survival rate of only 75% compared with a 95% 4-year survival rate after a minor stroke. On the basis of the previously mentioned analyses of MI-associated mortality, the impact of MI after carotid intervention clearly needs to be given strong consideration.

INCORPORATION OF MI AS A PRIMARY ENDPOINT IN CAROTID TRIALS

In the past, MI was not included in the primary endpoint composite of several large randomized controlled trials comparing CAS and CEA, such as Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis (EVA-3S)[8] and Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE).[9] On the contrary, studies that included MI as a primary outcome, such as the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial,[10] received heavy criticism because MI had never been included in any large carotid trials as a primary endpoint up to that point.

Even in trials when MI was included as part of the primary endpoint, cardiac biomarkers were not routinely obtained; consequently, the incidence of MI was underreported. For example, the documented rates of MI were 0.4% for CAS and 0.8% for CEA in EVA-3S, 0.4% for CAS and 0.6% for CEA in the International Carotid Stenting Study (ICSS),[11] and 0% for both in SPACE. By comparison, the CREST investigators[1] reported a 2.5% rate of MI or positive biomarkers, and in SAPPHIRE, the rate of MI was 5.9% for CEA patients and 2.4% for CAS patients. As the impact of MI on long-term mortality becomes increasingly evident, all future trials of carotid intervention must not only incorporate MI into their primary outcome composite but also include a protocol-driven routine collection of cardiac biomarkers to capture all patients with perioperative MIs and biomarker positivity without symptoms or ECG changes.

Emphasis of MI in carotid disease management can certainly be observed in ongoing large randomized controlled trials. The Asymptomatic Carotid Surgery Trial-2 (ACST-2),[12] the Carotid Stenting Versus Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I),[13] and the Transatlantic Asymptomatic Carotid Intervention Trial (TACIT)[14] all include periprocedural MI, in addition to stroke and death, as a primary outcome measure. Moreover, each trial has a precise but unique definition of MI (Table 1).

Standardization of the definition of MI (eg, by use of the universal definition of MI[15]) in future trials would enhance uniformity and comparison of different trials with respect to the incidence of MI after carotid intervention. Regarding the cardiac biomarkers collected, measurement of the less-specific CK and CK-MB levels (without cardiac troponin levels), as in SAPPHIRE,[10] should be discouraged to minimize false-positive results in the CEA group from CK and CK-MB released from skeletal muscle during surgery. In future trials, the timing of postprocedural cardiac biomarker assessment should also be extended to 48 hours (as opposed to 6–8 hours) for both CEA and CAS, as peak detection rate of postsurgical cardiac biomarkers for major surgical procedures is reported to be between 24 and 48 hours after surgery.[16]

Although CREST is the largest carotid trial to date, it still only represents one set of data on the incidence of stroke and MI after carotid interventions. For a consensus to be reached by the medical community on the importance of periprocedural MI, especially in relation

TABLE 1. DEFINITION OF MI IN VARIOUS ONGOING LARGE RANDOMIZED CONTROLLED CAROTID TRIALS

Trial	MI Definition
ACST-2[12]	Any two of the following: • symptoms consistent with MI • positive cardiac enzyme or biomarker changes consistent with MI • ECG changes consistent with MI
ACT I[13]	Rise and fall of biochemical markers of myocardial necrosis plus at least one of the following: • ischemic symptoms • development of Q waves • ST-segment elevation or depression
TACIT[14]	Inclusive of: • development of Q waves • cardiac enzymes twice normal values
Universal definition of MI[15]	Detection of the rise and/or fall or cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit plus at least one of the following: • symptoms of ischemia • ECG changes indicative of new ischemia • development of Q waves • imaging evidence of new loss of viable myocardium

to strokes, future trials should continue to define the true incidence of MI after carotid interventions and the degree of association between MI or positive cardiac biomarkers to mortality, as shown in the CREST post hoc analysis.[6]

Perhaps similar post hoc analyses with MI and mortality can be performed for other large carotid trials with long-term follow-up, such as SAPPHIRE, ICSS, EVA-3S, and SPACE. Moreover, the impact of both perioperative MI and stroke on QOL should be restudied in future trials with longer follow-up (as opposed to 1 year in CREST), as patients with minor strokes often make a complete recovery. Certainly, the QOL of such patients at 1 year after a minor stroke would not be the same at 4 years. Finally, future studies should consider collecting additional demographic and outcome data directed at the study of perioperative MI. Indices of perioperative MI risk, such as those proposed by Lee et al[17] and Detsky et al,[18] may be of value in post hoc analysis to elucidate the relative value of endarterectomy by comparison with stenting in patients at high risk for periprocedural MI.

CONCLUSION

Carotid artery disease and coronary artery disease are inherently intertwined conditions. With medical advances, patients with coronary artery disease will continue to live longer. Thus, periprocedural MI is likely to become a more frequent concern for patients undergoing carotid revascularization procedures.[19] Although the relative importance of periprocedural stroke versus MI is still a point of contention, the CREST data presented by Blackshear et al[6] have proven that periprocedural MI is a relevant issue in carotid revascularization trials. ■

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