In this issue of Stroke, Marnane et al\(^1\) reports that 12/44 patients (27%) with 50% to 99% stenoses had recurrent, ipsilateral strokes within 28 days of symptom onset, with 17% occurring <48 hours, 33% <7 days, and 58% <14 days of the index event. A 27% stroke risk at 28 days contrasts markedly with the 21% risk of ipsilateral stroke at 5 years reported in a meta-analysis of medically treated patients with 50% to 99% stenoses in the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the Veteran’s Affairs (VA) Study.\(^2\)

In the study of Marnane et al\(^1\), recurrent stroke was associated with histological features of plaque instability. After multivariate analysis; the only independent predictor was heavy macrophage inflammation, and this is consistent with evidence that inflammation diminishes after symptom onset after plaque stabilization,\(^3\) and that heavy macrophage infiltration is associated with higher rates of spontaneous embolization.\(^4\) Marnane et al\(^1\) concluded that their findings might influence imaging technologies for identifying patients at highest risk of early, recurrent stroke and for monitoring the effectiveness of medical treatments.

Studies like Marnane’s invariably attract differing interpretations. The realist will argue that although the results seem to support investment in technologies for imaging macrophage inflammation (eg, positron emission tomography-computed tomography), history suggests that small, hypothesis-generating studies frequently publish highly positive associations (exemplified by their high hazard ratios and wide confidence intervals), but then rarely complete the dual hurdles of external validation and translation into clinical practice. Therefore, realists will acknowledge the advance in knowledge, but conclude that (in the light of previous false dawns) it is unlikely to influence patient selection for carotid endarterectomy (CEA) or carotid artery stenting for the foreseeable future.

However, idealists will agree with Marnane. To them, it is vital that patients at highest risk of having a stroke in the hours/days after onset of symptoms are rapidly identified. In a study highlighting just how brief the window of intervention really is, Rothwell et al\(^5\) showed that in 500 patients who had a stroke preceded by a transient ischemic attack (TIA), 17% of strokes occurred on the same day as the TIA, whereas 43% occurred <7 days. In a recent audit from Leicester, symptomatic patients with 50% to 99% stenoses were admitted from the rapid-access TIA Clinic for urgent CEA, but 11% still had recurrent symptoms between admission and surgery, reflecting the underlying, unstable carotid plaque.\(^6\) If it were possible to develop accessible and reliable imaging strategies for identifying patients at highest risk of early recurrent stroke, only a small number would actually require emergency CEA/carotid artery stenting.

However, the pragmatist will observe that <10% of strokes follow thromboembolism from a previously asymptomatic 50% to 99% stenosis,\(^7\) and that a greater proportion of strokes would be prevented by improving patient awareness about seeking urgent medical advice after symptom onset. It is salutary to observe that, in the study of Marnane, all 12 recurrent strokes occurred after the index event, but before seeking medical advice,\(^1\) that is, no amount of imaging investment would have prevented them. The pragmatist will also observe that, however, attractive it might be to invest in technologies for imaging macrophage inflammation using positron emission tomography-computed tomography,\(^8\) this genre of imaging modality will never become accessible for everyday clinical use.

Accordingly, if the goal is to develop imaging strategies for identifying the highest risk patient for early recurrent stroke, this will only become effective if the research translates into clinical practice using imaging modalities that are immediately accessible to the supervising physician (ie, magnetic resonance/CT or more probably ultrasound). In a series of 179 symptomatic patients (<6 months) with 50% to 99% stenoses, 114 (64%) had evidence of intraplaque hemorrhage on high-resolution MRI. Sixty-two patients (35%) had recurrent events before CEA, death, or during follow-up on medical therapy, and 57 of these (92%) had MRI evidence of intraplaque hemorrhage.\(^9\) Although this represents a strong causal association, the fact that two thirds of all the symptomatic patients had an MRI diagnosis of intraplaque hemorrhage suggests that this parameter (alone) might be too insensitive to identify the small cohort of highest risk patients for emergency CEA/carotid artery stenting (ie, within 24–48 hours of symptom onset). In the study of Marnane, intraplaque hemorrhage was not predictive of an increased risk of early recurrent stroke.\(^1\)

Duplex ultrasound remains the most accessible imaging modality, but it must deliver reproducible and objective data. In studies similar to Marnane, Salem et al\(^10\) showed that a Gray Scale Median <25 was associated with a significantly increased risk of recurrent events in the hyperacute period between admission and CEA, whereas 2 ultrasound features were associated with histological plaque instability. On the basis of a multivariate analysis, if plaque area >95 mm\(^2\), and a juxta-luminal black area >6 mm\(^2\) was present, we found that 90% had an unstable plaque on blinded histological analysis.\(^11\)
This algorithm has not been independently validated or correlated with transcranial Doppler ultrasound diagnosed embolization, another well-recognized marker of plaque instability and increased stroke risk. However, these ultrasound-based technologies might prove to be a more accessible means of identifying the higher risk patient.

By contrast, the Nihilist will argue that they never see such high rates of recurrent stroke while their patients await CEA/carotid artery stenting. Most Nihilists remain unconvinced about the need to deliver expedited interventions; they think that a little delay is welcome (to reduce procedural risk), and they are generally dismissive about the validity and generalizability of small studies such as the study of Marnane. However, although the scientific message of Marnane may have been the prognostic importance of macrophage inflammation, perhaps its most important role has been to corroborate 6 other contemporary, natural history studies that found that the early risk of stroke after a TIA in patients with 50% to 99% stenoses was significantly higher than previously thought (5%–8% at 48 hours,12,13 17% at 72 hours,14 8%–22% at 7 days,13,14 and 11%–25% at 14 days).13,14,17

The obvious discrepancy between a 27% stroke risk at 28 days1 versus a 21% risk at 5 years2 is explained by there being 2 distinct cohorts of symptomatic patient in this debate. The former includes contemporary patients with 50% to 99% stenoses who were recruited into natural history studies shortly after onset of symptoms. These patients have a much higher incidence of early, recurrent stroke that was previously, grossly underestimated. The latter group comprises patients who were randomized to medical therapy within the historical ECST/NASCET/VA studies. Few were recruited within the hyperacute period after symptom onset and most underwent surgery sometime after the highest risk 14-day period had elapsed (never mind the first 24–72 hours).

The title of this Editorial is taken from a quotation by Benjamin Franklin (1706–1790) and refers to mankind’s tendency towards procrastination (“to postpone or delay needlessly”). It is particularly appropriate about the benefits of delivering best medical therapy and expedited interventions to patients with TIA with a priority similar to that afforded to acute coronary syndromes. Although there is emerging evidence that rapid implementation of statin and dual antiplatelet therapy might reduce the overall risk of recurrent stroke,16,18 the evidence from the study of Marnane is that this probably cannot confer enough protection in patients with grossly unstable carotid plaques. The Nihilistic approach is obsolete. The future clearly mandates a balance of idealism, realism, and pragmatism, but it is inescapable that developing accessible imaging strategies for identifying patients at highest risk of early recurrent stroke would be a major advance in optimizing the management of patients in the hyperacute period after onset of symptoms.

Disclosures

None.

References


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You May Delay, but Time Will Not!

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