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FOR DEBATE: HOT TOPIC

New Data and the Covid-19 Pandemic Mandate a Rethink of Antiplatelet Strategies in Patients With TIA or Minor Stroke Associated With Atherosclerotic Carotid Stenosis

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INTRODUCTION

The 2017 European Society for Vascular Surgery (ESVS) carotid guidelines, as well as a subsequent literature review, recommend clopidogrel monotherapy or combination aspirin + dipyridamole in recently symptomatic patients not undergoing carotid endarterectomy (CEA).[1,2] In patients scheduled for CEA, antiplatelet therapy was recommended throughout the peri-operative period and in the long-term.[1] It was advised that early treatment with aspirin + clopidogrel or aspirin + dipyridamole 'may be considered' in order to prevent early recurrent events in patients with transient ischaemic attack (TIA) or minor ischaemic stroke and an ipsilateral 50–99% stenosis awaiting expedited CEA (Evidence IIb, Level C).[1] However, the ESVS Writing Group were unable to recommend *routine* aspirin + clopidogrel therapy in patients treated by CEA or medical therapy, because there was no compelling evidence (at the time) that this strategy conferred additional benefit over antiplatelet monotherapy. There were also concerns that aspirin + clopidogrel would increase bleeding complications in patients undergoing urgent CEA.

SO WHAT HAS CHANGED?

New data from recently published randomised controlled trials (RCTs), in conjunction with unforeseen consequences of the evolving Covid-19 pandemic, now mandate an urgent review of antiplatelet strategies in recently symptomatic patients. Prasad *et al*.[3] based on a meta-analysis of three RCTs[4] (CHANCE,[5] POINT[6] & FASTER[7]) in which 10 447 patients were randomised within 24 h of experiencing a minor ischaemic stroke (NIHSS $\leq$3)[5–7] or 'high-risk TIA' (defined as an ABCD[2] score $\geq$4)[5,6] to aspirin monotherapy or short-term aspirin + clopidogrel combination therapy, recommended in a BMJ Rapid Guidelines document that there was now compelling evidence to support short-term treatment with dual antiplatelet therapy (DAPT) in these patient subgroups.[3] This fundamental change in recommendation, towards more routine prescription of short-term DAPT in patients with TIA or minor stroke, assumes even greater relevance due to the consequences of the Covid-19 pandemic, which is currently wreaking havoc on health systems around the world. Health Providers have had to radically reconfigure the way hospitals work, including converting some operating theatres into Intensive Care facilities. This, inevitably, will have a 'knock on' effect on the ability to perform elective and even urgent surgical interventions, including carotid endarterectomy (CEA). The Vascular and Endovascular Research Network (VERN) has established a series of online surveys of vascular surgical practice around the world to gauge the effect of the Covid-19 pandemic on workflow. Between 23rd March and 5th April 2020, 249 centres reported on the impact of the pandemic on carotid surgery practice. Just under half of the centres (42%) were still able to follow national/international guidelines and have not changed practice. However, 45% of centres indicated that they were now treating most recently symptomatic patients with TIA or minor stroke with 'best medical therapy' (after multidisciplinary team review), 12% said they would only offer CEA to patients with 'crescendo' symptoms, while 1% entered 'other strategy' (Thanos Saratzis; personal communication). It is, therefore, essential that these patients really do receive 'best medical therapy'.

SHOULD COMBINATION ANTIPLATELET THERAPY BE THE NEW 'GOLD STANDARD'?

The BMJ Panel[3] was 'confident' that, compared with aspirin monotherapy, aspirin + clopidogrel DAPT started within

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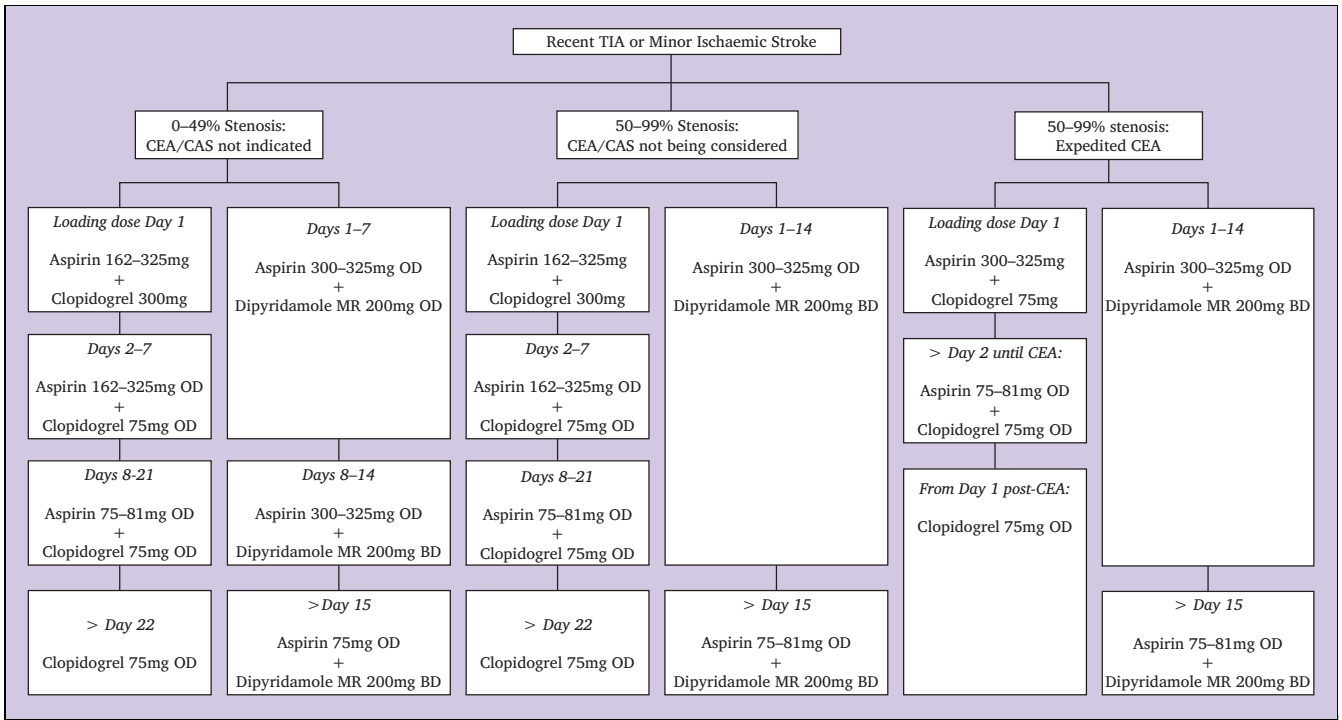

Figure 1. Algorithm detailing suggestions re timing, dose and duration of antiplatelet agents in the early phase after onset of an ischaemic TIA or minor ischaemic stroke. CEA = carotid endarterectomy; CAS = carotid artery stenting; ASAP = 'as soon as possible'; MR = modified release; OD = once daily; BD = twice daily.

24 h of symptom onset reduced the risk of: (i) non-fatal recurrent ischaemic or haemorrhagic stroke in the first 90-days [absolute risk reduction (ARR) 1.9%], (ii) non-fatal ischaemic stroke [ARR 2%], (iii) moderate-severe functional disability [ARR 1.4%] and (iv) a poor quality of life [ARR 1.3%][3]. The BMJ Panel also concluded that DAPT had no significant impact on: (i) all-cause mortality, (ii) myocardial infarction or (iii) TIA. However, there was a small, but important increase in moderate-major extracranial bleeding [absolute risk increase (ARI) 0.2%] and minor extracranial bleeding [ARI 0.7%][4]. These data are consistent with another meta-analysis of the CHANCE and POINT data where the ARR in non-fatal recurrent ischaemic/haemorrhagic stroke was 2.6%, against a 0.2% ARI of major haemorrhage.[8] The BMJ Panel concluded that DAPT should continue for 10—21 days, with most benefit (in terms of recurrent stroke prevention) occurring in the first 10 days after symptom onset.[4] Based on awareness that DAPT reduced recurrent stroke by about 20 per 1 000 population, with a possible increase in moderate to severe bleeding of 2 per 1 000, 'lay-members' of the BMJ Panel concluded that "a non-fatal stroke was 2—3 times worse than a serious gastrointestinal (GI) bleed and that most patients would opt for a 21-day course of DAPT and then change to clopidogrel monotherapy thereafter".[4]

WHAT DO OTHER GUIDELINES NOW ADVISE?

A number of guidelines have adopted the CHANCE and POINT data and now recommend short-term aspirin + clopidogrel DAPT for 21 days in patients with minor non-cardioembolic ischaemic stroke who have not received intravenous tissue plasminogen activator,[9] or for 21 days[10] or 21—30 days in patients with a high-risk TIA or minor ischaemic stroke.[11] The assumption is that the patient should continue clopidogrel or aspirin monotherapy thereafter.

However, no guideline has provided specific advice regarding antiplatelet strategies in recently symptomatic patients with 50—99% stenosis who are under consideration for urgent CEA/CAS. This may be because they were excluded from inclusion in CHANCE/POINT, or through unresolved concerns about the potential heightened risk of perioperative bleeding complications associated with DAPT. This is important, because whilst we now have high-quality evidence supporting a 21-day prescription of DAPT in patients with TIA/ischaemic stroke without 50—99% stenosis, we do not have evidence from RCTs that the balance of benefit *vs*. risk is now in favour of prescribing DAPT in recently symptomatic patients with 50—99% stenosis prior to CEA.

ESVS guidelines recommend that CEA be performed as soon as possible after symptom onset, in order to prevent early recurrent stroke.[1] There is an inevitable delay between being seen in a rapid access TIA clinic and undergoing CEA, during which time patients are vulnerable to recurrent thromboembolic stroke. In an overview of natural-history studies involving TIA patients with 50—99% ipsilateral stenosis, the 7-day risk of early recurrent stroke was 8—20%, with a 14-day risk of 11—25%.[12] However, there is non-randomised evidence that early recurrent stroke might be prevented by early institution of DAPT, which would be consistent with the latest RCT findings. In a

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recent audit, there was a 48–72 h delay between patients being seen in the TIA clinic and undergoing CEA, during which time 13% experienced recurrent stroke/TIA. When a decision was made to start DAPT in the TIA clinic (once parenchymal haemorrhage was excluded on CT/MR), recurrent clinical events prior to CEA fell fivefold from 13% to 3%, in association with a fourfold reduction in rates of spontaneous embolisation from 21% to 5% on transcranial Doppler ultrasound.[13] In addition, performing expedited CEA in patients on DAPT was not associated with a significantly increased risk of peri-operative bleeding complications overall.[13]

PRACTICAL SUGGESTIONS RE OPTIMAL ANTIPLATELET THERAPY FOR SYMPTOMATIC CAROTID STENOSIS

So what practical (empirical) advice might be offered as updated ESVS carotid guidelines are awaited (due in 2022), and especially during the current Covid-19 pandemic, in order to balance the potentially beneficial effects of early DAPT in reducing early recurrent stroke prior to CEA/CAS, with concerns about bleeding complications? Given that patients being treated with CAS are now routinely prescribed aspirin + clopidogrel prior to any intervention, DAPT should be started as soon as possible prior to CAS, as advised in the ESVS guidelines.[1] The debate, therefore, moves to patients being considered for optimal medical therapy (including centres unable to perform CEA due to the Covid-19 pandemic) and in those patients who are still able to undergo expedited CEA.

There are three scenarios where a surgeon/vascular neurologist/stroke physician may be faced with a patient presenting with high-risk TIA/minor ischaemic stroke, where early institution of DAPT (rather than antiplatelet monotherapy) may now be the preferred treatment strategy: (1) 0–49% stenosis with no other mechanism for TIA/stroke on comprehensive neurovascular work-up; (2) recent TIA/stroke plus a 50–99% stenosis, where CEA/CAS is definitely *not* being considered (patient fitness, patient preference or due to the Covid-19 pandemic); and (3) recent TIA/stroke plus a 50–99% stenosis where urgent CEA is planned. One also needs to decide whether it remains appropriate to prescribe DAPT if > 24 h has elapsed after symptom onset?

The first two scenarios are now relatively straightforward (Fig. 1). Extrapolation of evidence from the 'non-carotid stenosis' patient population with high-risk TIA or minor stroke supports a 300 mg loading dose of clopidogrel (in clopidogrel-naïve patients), plus 162–325 mg of aspirin (if not already on aspirin). Patients could then be treated with clopidogrel 75 mg daily and aspirin 162–325 mg daily from days 2–7, followed by clopidogrel 75 mg daily and aspirin 75–81 mg daily during days 8–21. Thereafter, patients revert to long-term monotherapy with clopidogrel 75 mg daily. In patients with 0–49% stenosis, an alternative would be to prescribe aspirin 300–325 mg daily from days 1–14 and then reduce the long-term aspirin dose to 75–81 mg daily, in combination with dipyridamole modified release (MR) 200 mg once daily from days 1–7, increasing to 200 mg BD thereafter. Furthermore, in patients with 50–99% symptomatic stenosis (at much higher risk of recurrent vascular events) in whom a decision has been made *not* to undergo CEA/CAS and in whom clopidogrel is contraindicated, an alternative strategy would be to prescribe aspirin 300–325 mg daily from day 1–14 and then reduce the long-term aspirin dose to 75–81 mg daily, in combination with full-dose dipyridamole MR 200 mg BD from day 1, once tolerated. It is important to note that some physicians have reported recent historical difficulties in accessing and prescribing dipyridamole (personal communication), but this medication is now readily available again in many countries.

The main debate, therefore, relates to group 3 patients who present with a recently symptomatic 50–99% stenosis and who are awaiting expedited CEA (Fig. 1) and who are at a heightened risk of recurrent TIA/stroke pre-operatively. If the surgeon is happy to perform expedited CEA on aspirin + clopidogrel DAPT, parenchymal haemorrhage should first be excluded on CT/MRI and then the patient should be commenced on aspirin 300–325 mg stat (if not already on aspirin), followed by aspirin 75–81 mg daily, in combination with clopidogrel 75 mg daily from day 1 (without a 300 mg loading dose). Expedited CEA, with very careful control of post-operative blood pressure should be performed, because uncontrolled post-CEA hypertension increases the risk of hyperperfusion syndrome, intracranial haemorrhage and neck haematoma formation.[1] Aspirin can then be stopped on day 1 after CEA and clopidogrel 75 mg daily continued indefinitely, unless contraindicated.[8] Whilst CHANCE, POINT and FASTER only included patients within 24 h of symptom onset, if one is certain that the surgeon will perform expedited CEA on aspirin and clopidogrel, it seems reasonable to start DAPT if patients present >24 h after TIA/minor stroke onset, especially within the first 10 days, when the risk of early recurrent stroke is highest. It is also important to prescribe gastric protection with proton pump inhibitors that do not interact with clopidogrel (e.g. pantoprazole) in patients prescribed DAPT, to reduce GI bleeding complications, as per ESVS guidelines.[1]

If the surgeon is *not* happy to perform CEA on aspirin and clopidogrel, an alternative would be to prescribe aspirin 300–325 mg daily from day 1–14 and then reduce the long-term aspirin dose to 75–81 mg daily, in combination with dipyridamole MR 200 mg twice daily from day 1, with advice regarding potential side effects.[2] This regimen was as effective at reducing micro-emboli as aspirin + clopidogrel in patients with a ≥50% recently symptomatic extracranial carotid stenosis with micro-emboli on transcranial Doppler ultrasound.[14] However, one must accept that there are limited data on the risk of peri-CEA bleeding complications with aspirin + dipyridamole therapy.

Some surgeons may still prefer to continue with aspirin monotherapy peri-operatively (75–325 mg daily).[2] However, they must accept that the latest evidence suggests that aspirin monotherapy is less effective than combination therapy and the 2-year risk of recurrent stroke on anti-

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thrombotic therapy ('usually' aspirin 1 300 mg daily) was 9%, even in patients who underwent CEA in NASCET.[15]

Questions have been raised regarding the benefits of testing for 'antiplatelet resistance' or what is now more commonly referred to as 'high on-treatment platelet reactivity (HTPR)' on *ex vivo* platelet function/reactivity testing. Antiplatelet-HTPR is a potential risk factor for vascular events on antiplatelet therapy, but no studies (to date) have been adequately powered to definitively comment on whether *ex vivo* HTPR status predicts the risk of clinical outcome events in asymptomatic or symptomatic carotid stenosis patients in the peri-operative or non-peri-operative phase.[16–19] The prevalence of antiplatelet-HTPR is also positively influenced by the shear stress levels to which platelets are exposed in the *ex vivo* platelet function testing platform in question.[19] Accordingly, further studies are required to determine whether one could optimise secondary prevention with the use of personalised antiplatelet regimens which are tailored to suit individual patients with carotid stenosis based on their antiplatelet-HTPR status.[17–19]

The first 7–14 days after onset of symptoms remains the highest risk period for experiencing a recurrent stroke after the index event Historically, vascular surgeons may not really have considered the prevention of recurrent stroke prior to a final decision regarding the need for CEA as being their primary responsibility, but this needs to change. There is now compelling RCT evidence that early institution of aspirin + clopidogrel significantly reduces early recurrent stroke after a high-risk TIA or minor ischaemic stroke and that aspirin + clopidogrel DAPT only needs to be continued for 21 days. There is also increasing anecdotal evidence that a growing body of surgeons are now more willing to perform expedited CEA on aspirin + clopidogrel DAPT. This should not only reduce rates of early recurrent stroke prior to CEA, but aspirin + clopidogrel DAPT may also reduce early post-operative thrombotic stroke as well.[20]

Whilst the Covid-19 pandemic has led to sometimes radical (and seemingly unthinkable) changes in practice, regarding the ability to perform urgent CEA in many centres, it is now even more important that any patient with a high-risk TIA or minor ischaemic stroke due to a recently symptomatic 50–99% carotid stenosis who is unable to undergo CEA/CAS be started on short-term aspirin-clopidogrel DAPT or long-term aspirin-dipyridamole combination therapy as soon as possible. Once the pandemic subsides, surgeons will still have to face the question as to how to optimise antiplatelet therapy in recently symptomatic patients prior to CEA. Direct and indirect evidence suggests that the strategies outlined above should confer overall benefit to the patient, without significantly increasing haemorrhagic risks associated with carotid intervention.

CONFLICT OF INTEREST

None.

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