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Optimal periprocedural antithrombotic treatment in carotid interventions: An international, multispecialty, expert review and position statement

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Abbreviations: 95% CI, 95% confidence interval; AAA, Aspirin for Asymptomatic Atherosclerosis trial; AASER, Acido Acetil Salicilico en la Enfermedad trial; ABCD2, Age, Blood pressure, Clinical features, Duration of TIA and presence or absence of Diabetes; ADP, Adenosine phosphate; AF, Atrial fibrillation; AHA/ASA, American Heart Association/American Stroke Association; ARRIVE, Aspirin to Reduce Risk of Initial Vascular Events trial; ASCEND, A Study of Cardiovascular Events iN Diabetes; AsxCS, Asymptomatic carotid stenosis; ASPREE, ASPirin in Reducing Events in the Elderly trial; BMD, British Medical Doctors trial; BMJ, British Medical Journal; cAMP, cyclic adenosine monophosphate; CAPRIE, Clopidogrel *versus* Aspirin in Patients at Risk of Ischaemic Events; CAS, Carotid artery stenting; CEA, Carotid endarterectomy; CHANCE, Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events; CKD, chronic kidney disease; COX, Cyclooxygenase; CYP2C19, Cytochrome P450 2C19; CVD, Cardiovascular disease; DAPT, Dual antiplatelet treatment; DOACs, Direct oral anticoagulants; DWI, Diffusion weighted MRI; ESC, European Society of Cardiology; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischaemia Trial; ESPS, European Stroke Prevention Study; ESVS, European Society for Vascular Surgery; ETDRS, Early Treatment Diabetic Retinopathy Study; FASTER, Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence; HOT, Hypertension optimal Treatment trial; HR, Hazard ratio; HTPR, High on Treatment Platelet Reactivity; JPAD 2, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; MI, Myocardial infarction; NIHSS, National Institute of Health Stroke Scale; NS, not significant; PHS, Physician's Health Study; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; POPAPAD, Prevention Of Prevention of Arterial Disease And Diabetes trial; PPP, Primary Prevention Project; PRU, P2Y12 reaction unit; RCTs, Randomized controlled trials; ROCKET-AF, Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, Relative risk; RRR, Relative risk reduction; SCS, Symptomatic carotid stenosis; SVS, Society for Vascular Surgery; TCAR, Transcarotid artery revascularization; TIA, Transient ischemic attack; TPT, Thrombosis Prevention Trial; USPSTF, United States Preventive Services Task Force; WHS, Women's Health Study.

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ABSTRACT

Background: The optimal antithrombotic (antiplatelet or anticoagulant) treatment of patients undergoing extracranial carotid artery interventions is a subject of debate. The aim of this multidisciplinary document was to critically review the recommendations of current guidelines, taking into consideration the results of recently published studies.
Methods: The various antithrombotic strategies reported were evaluated for asymptomatic and symptomatic patients undergoing extracranial carotid artery interventions (endarterectomy, transfemoral carotid artery stenting [CAS] or transcarotid artery revascularization [TCAR]). Based on a critical review, a series of recommendations were formulated by an international expert panel.
Results: For asymptomatic patients, we recommend low-dose aspirin (75–100 mg/day) or clopidogrel (75 mg/day) with the primary goal to reduce the risk of myocardial infarction and cardiovascular event rates rather than to reduce the risk of stroke. For symptomatic patients, we recommend dual antiplatelet treatment (DAPT) initiated within 24 h of the index event to reduce the risk of recurrent events. We suggest that following transfemoral CAS or TCAR, patients continue DAPT for 1 month after which a single antiplatelet agent is used. High level of evidence to support anticoagulant treatment for patients with carotid artery disease is lacking.
Conclusions: The antithrombotic treatment offered to carotid patients should be individualized, taking into account the presence of symptoms, the type of intervention and the goal of the treatment. The duration and type of DAPT (ticagrelor instead of clopidogrel) should be evaluated in future trials.

Contents

Introduction

Antithrombotic therapy consists of two main classes of drugs, anticoagulants and antiplatelets.[1–3] The anticoagulants include parenterally administered agents (such as heparin) and oral agents, namely vitamin K antagonists (*e.g.* warfarin) and direct oral anticoagulants (DOACs; such as dabigatran, apixaban, rivaroxaban and edoxaban).[1–3] The antiplatelets include the classical cyclooxygenase (COX)-1 inhibitor acetylsalicylic acid (aspirin), the $P2Y_{12}$ adenosine diphosphate (ADP)-receptor antagonists clopidogrel, ticlopidine, prasugrel and ticagrelor and the cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitor, dipyridamole.[1–3]

The optimal antithrombotic treatment for patients with asymptomatic (AsxCS) or symptomatic (SCS) extracranial carotid artery stenosis is controversial and the subject of extensive debate. The recommendations of recent national and international guidelines regarding the antiplatelet/anticoagulant management of AsxCS/SCS patients often vary considerably (Table 1).[4–8]

The aim of this multidisciplinary document was to critically review the recommendations of current guidelines and the results of recently published studies. Based on this comprehensive review, an international expert panel formulated a series of recommendations to define the best current antithrombotic treatment for patients who undergo extracranial carotid artery interventions.

Methods

PubMed/MedLine, Embase and Scopus were searched up to April 1, 2022, for studies in English evaluating various antiplatelet/antithrombotic strategies for the management of patients with AsxCS/SCS. The search terms used were “asymptomatic carotid stenosis”, “symptomatic carotid stenosis”, “antiplatelet”, “anticoagulant”, “aspirin”, “clopidogrel”, “ticagrelor”, “rivaroxaban”, “prasugrel”, “apixaban”, “edoxaban”, “warfarin” and “dabigatran” in various combinations. The abstracts of all resulting reports were read and when relevant, the full-text article was retrieved. The reference lists of the gathered full-text reports were manually searched. This produced additional articles which were also considered.

Table 1
Recommendations regarding antithrombotic treatment in patients with asymptomatic/symptomatic carotid stenosis undergoing carotid endarterectomy/carotid artery stenting.

Guideline	Recommendation
2017 ESVS. Guidelines[4]	• Aspirin 75–325 mg/day is recommended in AsxCS patients for prevention of late MI and other cardiovascular events (Class I; Level of Evidence: A)
	• Clopidogrel 75 mg daily should be considered in AsxCS patients if aspirin intolerant (Class IIa; Level of Evidence: C)
	• Antiplatelet therapy is recommended in patients with 50–99% SCS not undergoing CEA or CAS. First choice therapy is clopidogrel 75 mg/day or aspirin 75 mg/day plus modified release dipyridamole 200 mg twice daily. If intolerant of dipyridamole or clopidogrel, aspirin monotherapy (75–325 mg) should be used. If aspirin and clopidogrel intolerant, use modified release dipyridamole 200 mg twice daily (Class I; Level of Evidence: A)
	• All patients undergoing CEA should receive antiplatelet therapy throughout the perioperative period and also in the long term. Low-dose aspirin (75–325 mg daily) is recommended rather than higher doses (>625 mg daily) (Class: I; Level of Evidence: B)
	• Early institution of aspirin + clopidogrel (or aspirin + modified release dipyridamole) after TIA or minor stroke may be considered to reduce early recurrent events in patients with a > 50% SCS awaiting CEA (Class: IIb; Level of Evidence: C)
	• Patients undergoing CAS should receive DAPT with aspirin (75–325 mg daily) and clopidogrel (75 mg daily). Clopidogrel should be started at least 3 days prior to CAS or as a single 300 mg loading dose in urgent cases. Aspirin and clopidogrel should be continued for at least 4 weeks after CAS and then optimal long-term secondary preventive antiplatelet therapy should be continued indefinitely (Class: I; Level of Evidence: B)
2017 ESC Guidelines[5]	• In patients with >50% AsxCS, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low (Class: IIa; Level of Evidence: C)
	• In patients with SCS, long-term treatment with aspirin 75–100 mg/day or clopidogrel 75 mg/day is recommended (Class: I; Level of Evidence: A)
	• DAPT with aspirin 75–100 mg/day and clopidogrel 75 mg/day is recommended for at least 1 month after CAS, followed by a single antiplatelet agent lifelong (Class I; Level of Evidence: B)
	• Aspirin 75–100 mg/day or clopidogrel 75 mg/day is recommended for all patients following CEA (Class: I; Level of Evidence: A)
2020 German-Austrian Guidelines[6]	• All patients with a ≥ 50% AsxCS should take 100 mg aspirin/day, provided the risk of bleeding is low (Class: II; Level of Evidence: 2A)
	• All patients with a ≥ 50% SCS should take aspirin 100 mg/day or clopidogrel 75 mg/day (Class: I; Level of Evidence: A)
	• CAS should be preceded by DAPT with aspirin (100 mg) and clopidogrel (75 mg). Treatment with clopidogrel should be initiated at least 3 days before the intervention at 75 mg/day or on the day before the intervention at 300 mg/day. DAPT should continue for at least 1 month (Expert Consensus)
2021 SVS Guidelines[7]	• In patients with a history of stroke or TIAs within 6 months, DAPT with aspirin and dipyridamole is recommended (Expert Consensus)
	• In patients with a history of TIAs or minor stroke within 24 h, DAPT with aspirin and clopidogrel is recommended over aspirin alone as an alternative to aspirin and dipyridamole (Expert Consensus)
	• In patients undergoing CAS, DAPT with aspirin 325 mg and clopidogrel 75 mg is recommended. DAPT should be initiated before the procedure and should be continued for 4 weeks after the procedure (Expert Consensus)
2021 AHA/ASA Guidelines[8]*	• For patients with non-cardioembolic ischemic stroke or TIA, aspirin 50 to 325 mg daily, clopidogrel 75 mg, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated for secondary prevention of ischemic stroke (Class: I; Level of Evidence: A)
	• For patients with recent minor (NIHSS score ≤ 3) non-cardioembolic ischemic stroke or high-risk TIA (ABCD2 score ≥ 4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12–24 h of symptom onset and at least within 7 days of onset) and continued for 21 to 90 days, followed by a single antiplatelet agent, to reduce the risk of recurrent ischemic stroke (Class: I; Level of Evidence: A)
	• For patients with recent (< 24 h) minor to moderate stroke (NIHSS score ≤ 5), high-risk TIA (ABCD2 score ≥ 6), or symptomatic intracranial or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor 90 mg twice a day plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including intracranial hemorrhage (Class: 2b; Level of Evidence: B).
	• For patients with ischemic stroke/TIA, the continuous use of DAPT for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage (Class: 3 [Harm]; Level of Evidence: A)

ESVS.: European Society for Vascular Surgery; AsxCS: asymptomatic carotid stenosis; MI: myocardial infarction; ESC: European Society of Cardiology; SCS: symptomatic carotid stenosis; CEA: carotid endarterectomy; CAS: carotid artery stenting; TIA: Transient ischemic attack; DAPT: Dual antiplatelet treatment; SVS.: Society for Vascular Surgery; AHA/ASA: American Heart Association/American Stroke Association; NIHSS: National Institute of Health Stroke Scale; ABCD2: Age, Blood pressure, Clinical features, Duration of TIA and presence or absence of Diabetes.
* Guidelines for the prevention of stroke in patients with stroke/TIA.

Results

Asymptomatic patients

The efficacy and safety of aspirin for the primary prevention of stroke in asymptomatic patients varies among several randomized controlled trials (RCTs; Table 2).[9–22] Some RCTs were performed exclusively on male patients,[9,10] while one trial randomized only female patients.[14] Furthermore, some RCTs enrolled only diabetic patients.[11,15,18,20] Overall, most RCTs could not demonstrate a significant reduction in the incidence of stroke with aspirin treatment.[12,13,15–22] The Women Health Study[14] was the only RCT which demonstrated a significant reduction in the risk of stroke. This effect was mainly mediated by a significant decrease in the incidence of ischemic stroke, despite a non-significant increase in the risk of hemorrhagic stroke (Table 2). The Women's Health Study was the largest of all RCTs evaluating the effect of aspirin on the incidence of stroke and cardiovascular disease (CVD), with nearly 40,000 apparently healthy female patients aged ≥45 years without history of coronary heart disease, CVD, cancer or other chronic illnesses randomized to aspirin 100 mg/day or placebo.[14]

A meta-analysis investigating the clinical outcomes with aspirin for primary CVD prevention ($n = 15$ RCTs; 165,502 participants; 83,529 patients on aspirin *vs.* 81,973 controls) demonstrated that aspirin use was associated with a > 20% lower risk of transient ischemic attack (TIA; 1.06% *vs.* 1.33%, respectively; relative risk [RR], 0.79; 95% confidence interval [CI], 0.71–0.89; $P < 0.001$) and a 13% lower risk of ischemic stroke (1.29% *vs.* 1.49%, respectively; RR, 0.87; 95% CI, 0.79–0.95; $P = 0.002$) compared with controls.[23] However, its use was also associated with a higher risk of major bleeding (1.47% *vs.* 1.02%, respectively; RR, 1.50; 95% CI, 1.33–1.69; $P < 0.001$), intracranial bleeding (0.42% *vs.* 0.32%, respectively; RR, 1.32; 95% CI, 1.12–1.55; $P = 0.001$) and an increased risk of gastrointestinal ulcers (RR, 1.37; 95% CI, 1.07–1.76; $P = 0.013$) compared with placebo.[23] This meta-analysis concluded that "*these findings suggest that the decision to use aspirin for primary prevention should be tailored to the individual patient based on estimated atherosclerotic CVD risk and perceived bleeding risk, as well as patient preferences regarding types of events prevented versus potential bleeding caused*".[23]

Despite the lack of proven benefit of antiplatelet agents to reduce the risk of stroke in AsxCS patient, current guidelines recognize the fact that patients with advanced AsxCS are at increased risk for myocardial infarction (MI) and CVD deaths.[4–6,24,25] A meta-analysis of 6 primary prevention trials ($n = 95,000$ patients; 660,000 person-years; 3554 serious vascular events) demonstrated that aspirin use was associated with a 12% proportional risk reduction in serious vascular events (0.51% *vs.*

Table 2
Randomized controlled trials evaluating the effect of aspirin *vs.* placebo on the incidence of stroke.

Study (year)	Study design	Study outcome
BMD[9] (1998)	Effect of aspirin 500 mg/day ($n = 3429$) *vs.*. no treatment ($n = 1710$) on CVD outcomes in 5139 apparently healthy male doctors ≤80 years	After a mean follow-up of 6 years, aspirin use reduced the incidence of TIAs (15.9% *vs.* 27.5%; $2P < 0.05$), but was associated with an increase in the incidence of strokes (32.4% *vs.* 28.5%; p = NS), which was mainly disabling strokes (19.1% *vs.* 7.4%; $2P < 0.05$)
PHS[10] (1989)	Effect of aspirin 325 mg every other day (n = 11,037) *vs.* placebo ($n = 11,034$) on CVD outcomes in 22,071 healthy male doctors 40–84 years	After a mean follow-up of 5 years, there was a 44% reduction in the risk of MI in the aspirin group compared with placebo (RR, 0.56; 95% CI, 0.45–0.70; $P < 0.00001$), but an increased risk of stroke among aspirin users which reached borderline significance (RR, 2.14; 95% CI, 0.96–4.77; $P = 0.06$)
ETDRS[11] (1992)	Effect of aspirin 325 mg twice/day ($n = 1856$) *vs.* placebo ($n = 1855$) on CVD outcomes in diabetic patients 18–70 years	After a mean follow-up of 5 years, there were more fatal or non-fatal strokes in patients receiving aspirin compared with those receiving placebo (92 *vs.* 78 strokes, or 5.0% *vs.* 4.2%, respectively; RR, 1.18; 95% CI, 0.88–1.58; P = NS)
HOT[12] (1998)	Effect of aspirin 75 mg/day ($n = 9399$) *vs.* placebo ($n = 9391$) on CVD outcomes in 18,790 patients aged 50–80 years	After a mean follow-up of 3.8 years, aspirin use was not associated with a reduction in the incidence of strokes compared with placebo (146/9399 *vs.* 148/9391 strokes; RR, 0.99; 95% CI, 0.79–1.24; P = NS)
PPP[13] (2001)	Effect of aspirin 100 mg/day ($n = 2226$) *vs.* placebo ($n = 2269$) on CVD outcomes in 4495 patients aged >50 years	After a mean follow-up of 3.6 years, aspirin use was not associated with a reduction in the incidence of stroke compared with placebo (16 *vs.* 24 strokes, or 0.7% *vs.* 1.1%, respectively; HR, 0.67; 95% CI, 0.36–1.27; P = NS)
WHS[14] (2005)	Effect of aspirin 100 mg every other day ($n = 19,934$) *vs.* placebo (n = 19,942) on CVD outcomes in 39,876 healthy females >45 years	After a mean follow-up of 10.1 years, there was a 17% reduction in the risk of stroke in the aspirin group compared with the placebo group (RR, 0.83; 95% CI, 0.69–0.99; $P = 0.04$), consistent with a 24% reduction in the risk of ischemic stroke (RR, 0.76; 95% CI, 0.63–0.93; $P = 0.009$), but a non-significant 24% increase in the risk of hemorrhagic stroke (RR, 1.24; 95% CI, 0.82–1.87; $P = 0.31$)
POPAPAD[15] (2008)	Effect of aspirin 100 mg/day ($n = 638$) *vs.* placebo (n = 638) on CVD outcomes in 1276 diabetic patients ≥40 years	After a median follow-up of 6.7 years, aspirin use was not associated with a significant reduction in the incidence of stroke (37 *vs.* 50, respectively; HR, 0.74; 95% CI, 0.49–1.12; P = NS)
AAA[16] (2010)	Effect of aspirin 100 mg/day ($n = 1675$) *vs.* placebo (n = 1675) on CVD outcomes in 3350 patients aged 50–75 years	After a mean follow-up of 8.2 years, aspirin use was not associated with a significant reduction in the incidence of stroke (44 *vs.* 50, respectively; HR, 0.88; 95% CI, 0.59–1.31; P = NS)
JPPP[17] (2014)	Effect of aspirin 100 mg/day ($n = 7220$) *vs.* placebo ($n = 7244$) on CVD outcomes in 14,444 patients aged 60–85 years	After a median follow-up of 5.02 years, aspirin use was not associated with a significant reduction in the incidence of stroke (166 *vs.* 160, respectively; HR, 0.88; 95% CI, 0.59–1.31; P = NS)
JPAD 2[18] (2017)	Effect of aspirin 81–100 mg/day ($n = 1262$) *vs.* placebo ($n = 1277$) on CVD outcomes in 2539 diabetics 30–85 years	After a median follow-up of 10.3 years, aspirin use was not associated with a significant reduction in the incidence of stroke (56 *vs.* 63, respectively; HR, 0.90; 95% CI, 0.63–1.28; P = NS)
ARRIVE[19] (2018)	Effect of aspirin 100 mg/day ($n = 6270$) *vs.* placebo ($n = 6276$) on CVD outcomes in 12,546 patients aged >55 years	After a median follow-up of 5 years, aspirin use was not associated with a significant reduction in the incidence of stroke (75 *vs.* 67, respectively; HR, 1.12; 95% CI, 0.81–1.55; P = NS)
ASCEND[20] (2018)	Effect of aspirin 100 mg/day (n = 7740) *vs.* placebo ($n = 7740$) on CVD outcomes in 15,480 diabetics >40 years	After a mean follow-up of 7.4 years, aspirin use was not associated with a significant reduction in the incidence of stroke (240 *vs.* 263, respectively; HR, 0.91; 95% CI, 0.77–1.08; P = NS)
ASPREE[21] (2018)	Effect of aspirin 100 mg/day ($n = 9525$) *vs.* placebo ($n = 9589$) on CVD outcomes in 19,114 patients ≥65 years	After a median follow-up of 4.7 years, aspirin use was not associated with a significant reduction in the incidence of stroke (195 *vs.* 203, respectively; HR, 0.97; 95% CI, 0.80–1.17; P = NS)
AASER[22] (2018)	Effect of aspirin 100 mg/day ($n = 50$) *vs.* placebo ($n = 61$) on CVD outcomes in 111 patients with CKD stage 3–4	After a median follow-up of 5.4 years, aspirin use was not associated with a significant reduction in the incidence of stroke (4 *vs.* 2, respectively; HR, 2.44; 95% CI, 0.47–12.78; P = NS)

BMD: British Medical Doctors trial; PHS: Physician's Health Study; ETDRS: Early Treatment Diabetic Retinopathy Study; HOT: Hypertension optimal Treatment trial; TPT: Thrombosis Prevention Trial; PPP: Primary Prevention Project; WHS: Women's Health Study; POPAPAD: Prevention Of Prevention of Arterial Disease And Diabetes trial; AAA: Aspirin for Asymptomatic Atherosclerosis trial; JPPP: Japanese Primary Prevention Project; JPAD 2: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; ARRIVE: Aspirin to Reduce Risk of Initial Vascular Events trial; ASCEND: A Study of Cardiovascular Events iN Diabetes; ASPREE: ASPirin in Reducing Events in the Elderly trial; AASER: Acido Acetil Salicilico en la Enfermedad trial; CVD: cardiovascular diseases; RR: relative risk; 95% CI: 95% confidence interval; TIA: transient ischemic attack; MI: myocardial infarction; NS: not significant; CKD: chronic kidney disease.

0.57% per year, for aspirin *vs.* control, respectively; $P = 0.0001$), due mainly to a reduction of about a fifth in non-fatal MI (0.18% *vs.* 0.23% per year, respectively; $P < 0.0001$).[26] The net effect on stroke was not significant (0.20% *vs.* 0.21% per year, respectively; $P = 0.4$; hemorrhagic stroke: 0.04% *vs.* 0.03% per year, respectively; $P = 0.05$; other stroke: 0.16% *vs.* 0.18% per year; $P = 0.08$).[26]

An RCT randomized 2849 patients scheduled for carotid endarterectomy (CEA) to aspirin 81 mg/day ($n = 709$), 325 mg/day ($n = 708$), 650 mg/day ($n = 715$) and 1300 mg/day ($n = 717$) started before surgery and continued for 3 months.[27] The outcomes of the 2 higher doses were subsequently compared with the 2 lower doses of aspirin. The combined rate of stroke, MI and death was lower in the lower- compared with the higher-dose groups both at 30 days (5.4% *vs.* 7.0% respectively; $P = 0.07$) and at 3 months (6.2% *vs.* 8.4%, respectively; $P = 0.03$). In an efficacy analysis which excluded patients taking ≥650 mg of aspirin before randomization, the combined rates of stroke, MI and death were significantly lower for the lower- compared with the higher-dose groups both at 30 days (3.7% *vs.* 8.2%, respectively; $P = 0.002$) and at 3 months (4.2% *vs.* 10.0%, respectively; $P = 0.0002$).[27] A strong (Class: I; Level of Evidence: A) recommendation was therefore provided for low-dose aspirin use (75–325 mg/day) for prevention of future MI and cardiovascular events in AsxCS patients, rather than for stroke risk reduction, as long as the bleeding risk of the patients is low.[4–6,24] For patients with aspirin intolerance, a weaker (Class: IIa; Level of Evidence: C) recommendation was provided for clopidogrel.[4] There are no data regarding the efficacy of other antiplatelet agents (such as dipyridamole, ticagrelor and prasugrel) or rivaroxaban for AsxCS patients.

Symptomatic patients

In contrast to asymptomatic patients where the net clinical benefit with antiplatelet treatment is small, the evidence supporting antiplatelet treatment in patients with recent cerebrovascular symptoms (TIA or minor stroke) is more robust. In a meta-analysis of 16 secondary prevention trials ($n = 17,000$ patients; 43,000 person-years; 3306 serious vascular events), aspirin use was associated with a reduction in serious

vascular events (6.7% *vs.* 8.2% per year for aspirin use *vs.* non-use, respectively; $P < 0.0001$), with a reduction of about a fifth in total stroke (2.08% *vs.* 2.54% per year, respectively; $P = 0.001$) and in coronary events (4.3% *vs.* 5.3% per year, respectively; $P < 0.0001$).[26]

The results from earlier and recent reports on the topic are presented and discussed.

Antiplatelet treatment and recurrent events

Patients with a recent TIA/minor ischemic stroke ipsilateral to a 50%–99% internal carotid artery stenosis are at increased risk of a recurrent cerebrovascular event in the first few days after the initial episode.[28–30] According to all current guidelines, recently symptomatic patients should be scheduled for an expedited prophylactic CEA, ideally within 2 weeks of the index event, to prevent recurrent events.[4–8]

The antiplatelet/antithrombotic treatment offered to recently symptomatic patients while waiting for their procedure is crucial. There is a delicate balance between preventing recurrent ischemic cerebrovascular events and increasing the risk of periprocedural bleeding, intracerebral hemorrhage or hemorrhagic stroke. Earlier guidelines provided a strong (Class: I; Level of Evidence: A) recommendation for antiplatelet treatment with clopidogrel 75 mg/day or aspirin 75–100 mg/day (Table 1).[4–6] The 2017 European Society for Vascular Surgery (ESVS) guidelines provided an additional weaker (Class: IIb; Level of Evidence: C) recommendation for recently symptomatic patients with aspirin plus clopidogrel or aspirin plus dipyridamole in order to prevent early recurrent events while awaiting an expedited CEA.[4]

The Clopidogrel *versus* Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) RCT demonstrated the superiority of clopidogrel over aspirin in reducing the combined risk of ischemic stroke, MI or vascular death.[31] In CAPRIE, 19,185 patients with documented atherosclerotic vascular disease manifested as either recent ischemic stroke (≥1 week but ≤6 months before randomization), recent MI (≤35 days before randomization) or symptomatic peripheral arterial disease were randomized to clopidogrel 75 mg/day or aspirin 325 mg/day. After a mean follow-up of 1.91 years, patients treated with clopidogrel had a lower annual risk of ischemic stroke, MI or vascular death compared with those treated with aspirin (5.32% *vs.* 5.83%, respectively; relative risk reduction [RRR], 8.7%; 95% CI: 0.3–16.5; $p = 0.043$).[31]

In a double-blind, placebo-controlled RCT from China, the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, 5170 patients were randomized within 24 h after the onset of a minor ischemic stroke or a high-risk TIA (defined as having an ABCD2[5] [Age, Blood pressure, Clinical features, Duration of TIA and presence or absence of Diabetes] score ≥ 4) to a combination of aspirin plus clopidogrel *vs.* aspirin plus placebo for 90 days (Fig. 1).[32] A stroke occurred in fewer patients on dual antiplatelet treatment (DAPT) than on aspirin plus placebo (8.2% *vs.* 11.7%, respectively; $P < 0.001$). There was a significant difference in the occurrence of ischemic strokes between the two groups, while there was no difference with respect to hemorrhagic strokes, MIs, death from cardiovascular/any cause and TIAs (Fig. 1).[32]

The CHANCE[32] results were replicated in a large ($n = 4881$ patients), multicentre ($n = 269$), international RCT, the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (Fig. 2).[33] In POINT, patients with a minor ischemic stroke or high-risk TIA were allocated to either aspirin plus clopidogrel or aspirin plus placebo.[33] The primary efficacy outcome was the composite of ischemic stroke, MI or death from an ischemic vascular event at 90 days. A major ischemic event occurred in fewer patients on aspirin plus clopidogrel *vs.* aspirin alone (5.0% *vs.* 6.5%, respectively; $P = 0.02$), with most of them occurring during the first week after the initial event.[33] However, a major hemorrhage occurred in 23/2434 patients receiving clopidogrel plus aspirin and in 10/2449 patients receiving aspirin alone (hazard ratio [HR], 2.32; 95% CI, 1.10–4.87; $P = 0.02$).[33] Therefore, in POINT,[33] DAPT resulted in a lower incidence of recurrent cerebrovascular events (but a higher incidence of hemorrhage) compared with single antiplatelet therapy in patients with a recent TIA/minor ischemic stroke. A secondary analysis of POINT showed that the benefit of the combination treatment with clopidogrel plus aspirin predominantly occurs within the first 21 days (0–21 days HR, 0.65; 95% CI, 0.50–0.85; $P = 0.0015$; compared with 22–90 days HR, 1.38; 95% CI, 0.81–2.35; $P = 0.24$) and outweighs the low risk of major hemorrhage.[34] When the results of the POINT[33] trial were pooled with those of the CHANCE[32] trial, the benefit of DAPT was confined to the first 21 days after a high-risk TIA or minor stroke.[35]

A meta-analysis of 3 RCTs (CHANCE,[32] POINT[33] and the Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence [FASTER][36] trial), in which 10,447 patients were randomized within 24 h of experiencing a minor ischemic stroke or a high-risk TIA to aspirin monotherapy or aspirin plus clopidogrel combination therapy demonstrated the benefits of DAPT in these patients.[37] Compared with aspirin alone, DAPT with clopidogrel and aspirin started within 24 h of symptom onset reduced the risk of non-fatal recurrent stroke by 30% (RR, 0.70; 95% CI, 0.61–0.80; $I^2 = 0\%$; absolute RRR, 1.9% [high-quality evidence]) with a small increase in the risk of moderate to major extracranial bleeding events (RR, 1.71; 95% CI, 0.92–3.20; $I^2 = 32\%$; absolute risk increase: 0.2% [moderate quality evidence]).[37] Essentially, for every 1000 patients started on DAPT instead of a single antiplatelet agent after a minor stroke/high-risk TIA, 19 recurrent events would be prevented at the cost of 2 patients developing a moderate/major extracranial bleeding.[37]

Based on this meta-analysis, a BMJ Rapid Guidelines document made a strong recommendation for DAPT with clopidogrel and aspirin to be started within 24 h of a minor stroke or high-risk TIA and to be continued for 10–21 days.[38] After that, patients should continue with a single antiplatelet therapy.[38] Importantly, DAPT should not be used for patients with major stroke because of the increased risk of intracranial bleeding in these patients.[38] Subsequently, the 2021 Society for Vascular Surgery Carotid Guidelines[7] and the 2021 American Heart Association/American Stroke Association (AHA/ASA)[8] Guidelines endorsed the recommendation for DAPT in patients with a minor stroke or high-risk TIA (Table 1). Therefore, current evidence indicates that recently symptomatic patients should receive DAPT after their index event and while waiting for their urgent CEA. DAPT should be continued for at least 1 month following transfemoral carotid artery stenting (CAS) or transcarotid artery revascularization (TCAR). After that, a single antiplatelet agent should be continued indefinitely.

The effectiveness of clopidogrel depends on its conversion to an active metabolite by cytochrome P450 2C19 (CYP2C19). Up to 30% of Europeans and 50% of Chinese carry non-functional alleles of the CYP2C19 gene and cannot activate clopidogrel *via* the CYP2C19 pathway.[39–41] High on Treatment Platelet Reactivity (HTPR) to aspirin and clopidogrel (previously called "antiplatelet resistance") is associated with inadequate secondary prevention of TIA/ischemic strokes. Patients on clopidogrel/aspirin with HTPR have an approximately 80% higher risk for recurrent TIA/ischemic stroke episodes than individuals without HTPR (RR, 1.81; 95% CI, 1.30–2.52; $P < 0.001$).[40] Future guidelines may need to consider routine testing for aspirin/clopidogrel resistance in patients undergoing CAS/TCAR.

Several multicentre studies have investigated the efficacy of another antiplatelet agent, dipyridamole, on ischemic stroke outcomes. In the European Stroke Prevention Study (ESPS)-2 RCT, 6602 patients with a recent TIA/stroke episode within the previous 3 months were randomized to 4 groups: i) aspirin 25 mg twice daily alone, ii) modified-release dipyridamole 200 mg twice daily alone, iii) aspirin 25 mg twice daily plus modified-release 200 mg twice daily, or iv) matched placebo.[42] Compared with placebo, stroke risk was reduced by 18.1% with aspirin alone ($P = 0.013$), by 16.3% with dipyridamole alone ($P = 0.039$) and by 37.0% with the combination therapy ($P < 0.001$). The combination therapy reduced stroke risk by 23.1% compared with aspirin alone ($P = 0.006$) and by 24.7% compared with dipyridamole alone ($P = 0.002$).[42]

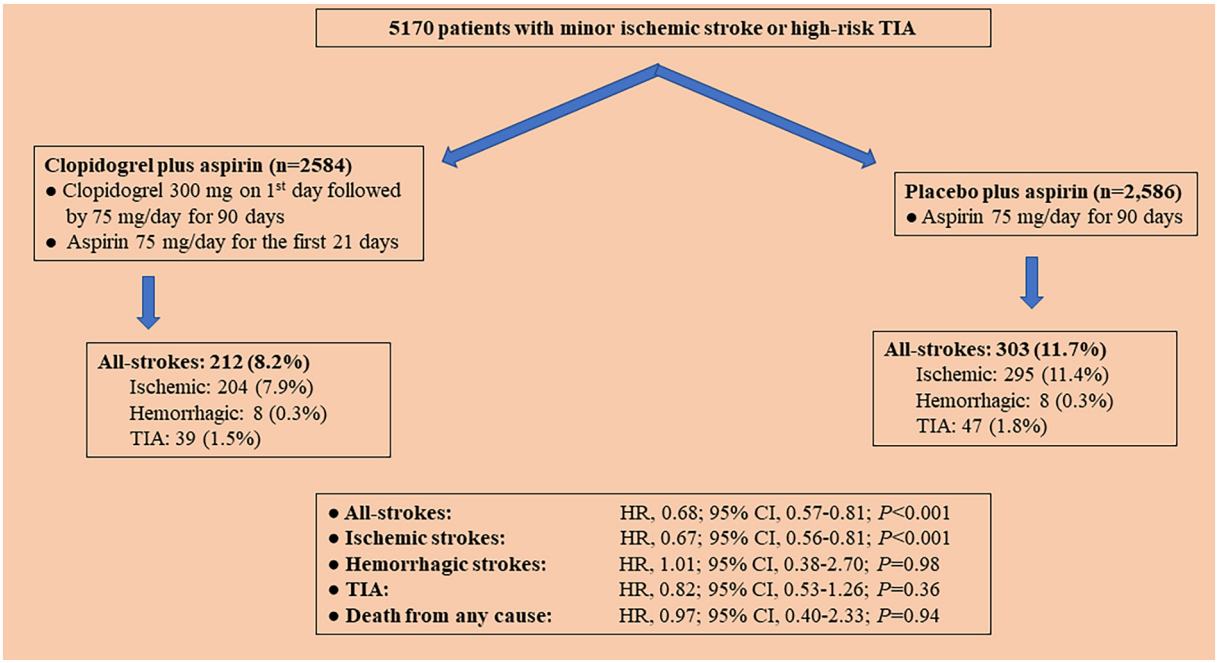

Fig. 1. Design and outcomes in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial.[32]
TIA, Transient ischemic attack; HR, Hazard ratio; CI, Confidence Interval.

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) compared the efficacy and safety of 30–325 mg/day aspirin alone *vs.* 30–325 mg/day aspirin plus 200 mg dipyridamole twice daily in patients within 6 months of a TIA or minor non-disabling ischemic stroke of presumed arterial origin.[43] After a mean follow-up of 3.5 years, the composite of death from all vascular causes, non-fatal stroke, non-fatal MI and major bleeding complication occurred in 20% fewer patients on aspirin plus dipyridamole *vs.* aspirin alone (13 *vs.* 16%, respectively; HR, 0.80; 95% CI, 0.66–0.98; absolute RR, 1.0% per year; 95% CI, 0.1–1.8).[43] Addition of the ESPRIT data[43] to that of 6 previous trials (including ESPS-2)[42] resulted in an overall 3888 patients allocated to aspirin and dipyridamole *vs.* 3907 to aspirin alone. A meta-analysis of these results demonstrated an absolute relative reduction of 18% in the composite outcome of vascular death, non-fatal stroke and non-fatal MI with the combination therapy compared with aspirin alone (RR, 0.82; 95% CI, 0.74–0.91; $P = 0.0003$).[43]

A network meta-analysis including 13 RCTs ($n = 16,771$ patients) compared 7 drug combinations, namely: i) aspirin alone, ii) aspirin plus dipyridamole, iii) aspirin plus clopidogrel, iv) aspirin plus warfarin, v) cilostazol alone, vi) warfarin alone, and vii) ticlopidine alone.[44] Among the 7 drug therapies, aspirin plus dipyridamole was associated with the lowest mortality (OR, 0.46; 95% CI, 0.18–0.99). There was no significant difference among the 7 drug therapies with regards to stroke recurrence, intracerebral hemorrhage, adverse event rate and cerebral infarction.[44]

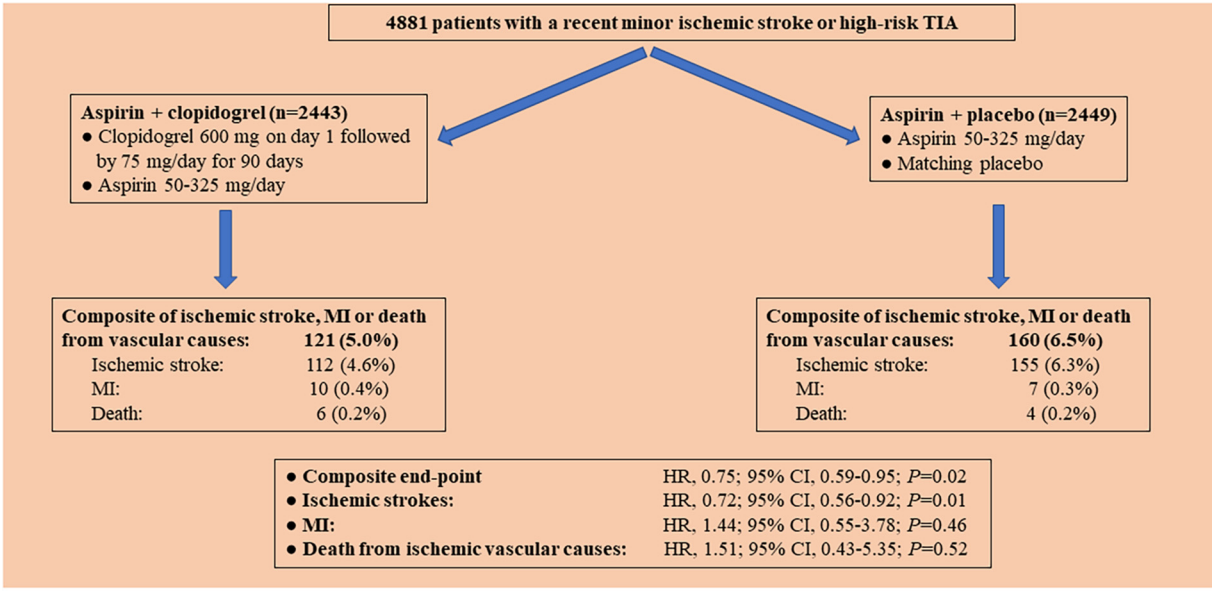

Fig. 2. Design and outcomes in the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial.[33]
TIA, Transient ischemic attack; MI, Myocardial infarction; HR, Hazard ratio; CI, Confidence Interval.

Anticoagulant treatment and recurrent events

The 2021 AHA/ASA Guidelines provided a strong recommendation for anticoagulation (*e.g.* apixaban, dabigatran, edoxaban, rivaroxaban or warfarin) for patients with stroke/TIA and non-valvular atrial fibrillation (AF) to reduce the risk of recurrent stroke (Class: I; Level of Evidence: A).[8] Patients with AF have a 4- to 5-fold higher risk of ischemic stroke. It was supported that carotid artery disease may contribute to the risk of stroke among patients with AF.[45]

A subgroup analysis of the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) aimed to evaluate the frequency of concomitant AF and carotid stenosis, determine the stroke rates in patients with AF and carotid stenosis and assess the safety and efficacy of rivaroxaban *vs.* warfarin in patients with AF with/without carotid stenosis.[46] Of the 14,264 patients randomized in ROCKET-AF, 593 (4.2%) had concomitant carotid stenosis. Patients with AF and concomitant carotid stenosis had a higher frequency of prior stroke, TIA or non-central nervous system embolism compared with those AF individuals without carotid stenosis (72 *vs.* 54%, respectively; $P < 0.0001$). Although the rate of the primary efficacy end-point of stroke or systemic embolism was higher in patients with *vs.* without carotid stenosis (2.95 *vs.* 2.24 events/100 patient-years), the difference was not significant after adjustment for covariates, including age, sex, body mass index, diabetes, prior stroke/TIA, *etc.* (adjusted HR, 0.99; 95% CI, 0.66–1.48; $P = 0.96$). Furthermore, the primary efficacy end-point was higher (but not significantly so) in the rivaroxaban compared with the warfarin group (adjusted HR, 1.32; 95% CI, 0.65–2.29).[46] Consequently, patients with AsxCS/SCS and concurrent AF should receive anticoagulation (rather than an antiplatelet agent) for stroke prevention. Nevertheless, it should be underlined that there is no evidence for/against anticoagulation therapy in patients with AsxCS/SCS undergoing carotid interventions.

Antiplatelet/antithrombotic treatment for patients undergoing CAS/TCAR

Recently symptomatic patients undergoing CAS should be offered DAPT with aspirin plus clopidogrel (or aspirin plus dipyridamole) routinely in the perioperative period.[4–8] According to current guidelines, DAPT should be initiated 3 days before the procedure and continued for at least 30 days after the procedure.[4–8] In contrast, DAPT is associated with an increased risk of neck hematoma and reoperation for bleeding compared with aspirin monotherapy in patients undergoing CEA, with no difference in perioperative stroke rates.[47] Therefore, it was supported that the risks of performing CEA on DAPT outweigh the benefits, even in patients with SCS.[47] Nevertheless, an earlier prospective study had supported that early introduction of DAPT in recently symptomatic patients while awaiting for urgent CEA was associated with a significant reduction in recurrent neurological events and spontaneous embolization prior to CEA, without incurring a significant increase in major perioperative bleeding complications.[48] Therefore, whether DAPT should be stopped before CEA varies according to center and surgeon preference.

Despite the introduction of DAPT, SCS patients undergoing CAS often have a high rate of periprocedural stroke and/or in-stent thrombosis rates. It was hypothesized that antiplatelet resistance/HTPR may play a role in the high stroke rates in CAS patients.[49–51] In a retrospective study from Korea, the results of aspirin/clopidogrel resistance testing were evaluated in 76 patients undergoing CAS.[46] Of these, 45 (59.2%) developed new ischemic lesions on diffusion-weighted MRI (DWI). Clopidogrel resistance was detected more frequently in patients with DWI-positive lesions that in those without (82.2% *vs.* 41.9%, respectively; $P = 0.001$). After adjusting for age, gender and degree of stenosis, clopidogrel resistance was a significant predictor of DWI-positive lesions after CAS (OR, 6.804; 95% CI, 2.225–29.806; $P = 0.001$).[49]

These results were verified in a study from the United States evaluating antiplatelet resistance by mean P2Y12 reaction unit (PRU) values in 449 patients undergoing CAS.[50] Mean PRU values (indicating antiplatelet resistance) were higher in patients with an ipsilateral stroke/TIA at 1 year ($P = 0.008$), stroke at 1 year ($P = 0.029$) and ipsilateral stroke/TIA at 2 years ($P = 0.047$) after CAS compared with patients with no events.[50] It was supported that the possible relationship between clopidogrel resistance and thromboembolic complications in patients undergoing CAS may justify preprocedural testing for clopidogrel resistance in patients undergoing CAS.[51] Recent reports on CAS/TCAR have identified HTPR with clopidogrel as an important drawback and support the use of ticagrelor as an antithrombotic agent instead (Table 3).[52–54] An experimental study comparing the effects of clopidogrel *vs.* ticagrelor on post-balloon injury, in-stent restenosis and in-stent thrombosis in an atherosclerotic rabbit model undergoing carotid balloon injury ± CAS did not demonstrate any differences between the two antiplatelet agents.[55] Nevertheless, a drawback of ticagrelor as part of DAPT is its higher bleeding risk compared with clopidogrel.[53,54]

Antiplatelet/antithrombotic treatment for patients with crescendo TIA/stroke in evolution

A crescendo TIA is defined as repetitive TIA episodes over hours or days followed by return to normal neurologic status.[56] In contrast, in patients with stroke in evolution there is progression of a neurologic deficit without restoration of neurologic status between episodes.[56] Patients with crescendo TIA and unstable neurologic symptoms have a higher risk of stroke or death after CEA compared with patients with a single TIA or a minor stroke.[57,58] A recent systematic review demonstrated that with medical therapy alone, a considerable number of patients with crescendo TIA or stroke in evolution, experience a complete stroke within the first months or year and have a poor prognosis without intervention.[56] No RCT has assessed heparin *vs.* antiplatelet therapy in the prevention of early recurrence in patients with crescendo TIA and high-grade carotid stenosis. In a *post hoc* analysis of an RCT, the Fraxiparin in Stroke Study, the prevalence of neurologic deterioration at 10 days was evaluated with low-molecular weight heparin *vs.* aspirin.[59] Treatment with low-molecular weight heparin was associated with a lower frequency of stroke progression during the first 10 days compared with aspirin (9/180 [5.0%] *vs.* 22/173 [12.7%], respectively; absolute RR, 7.7%; OR, 0.36; 95% CI, 0.16–0.81; adjusted $P = 0.008$).[59] Early introduction of DAPT (aspirin 75 mg/day plus clopidogrel 75 mg/day) in patients with recent onset carotid territory symptoms (TIA: 66%; stroke: 18%; amaurosis fugax: 16%) was associated with a > 4-fold reduction in spontaneous embolization (OR, 4.1; 95% CI, 1.5–10.7; $P = 0.0047$) and recurrent neurological events (OR, 4.9; 95% CI, 1.5–16.6; $P = 0.01$) prior to expedited CEA, without incurring a significant increase in major perioperative bleeding complications.[48] Nevertheless, no RCT has evaluated the optimal antiplatelet/antithrombotic treatment in patients with crescendo TIA or stroke in evolution. Consequently, the 2017 ESVS guidelines concluded that in the absence of quality evidence, it would seem reasonable to offer heparin (plus aspirin) or DAPT in patients with recurrent TIAs or crescendo TIAs prior to urgent CEA.[4]

Discussion

Currently there is no solid evidence to suggest that aspirin reduces the risk of stroke in AsxCS patients. However, aspirin is beneficial to reduce the high risk of MI and CVD events.[4–6,24] The United States Preventive Services Task Force (USPSTF) recommended initiating low-dose (75–100 mg/day) aspirin for the primary prevention of CVD in adults aged 50–59 years who have a 10-year CVD risk of ≥10%, provided these individuals are not at increased risk for bleeding and have a life expectancy of at least 10 years.[24] For individuals aged 60–69 years, the USPSTF recommended that the decision to initiate low-dose aspirin treatment should be individualized after assessment of the benefit *vs.* risk ratio (*i.e.* risk of gastrointestinal bleeding and hemorrhagic stroke) associated with aspirin therapy. Finally, the USPSTF concluded that there is insufficient evidence to recommend aspirin use for the primary

Table 3
Outcomes with ticagrelor in patients undergoing transcarotid artery revascularization (TCAR)/ carotid artery stenting (CAS).

Study (year)	Study design	Outcomes
Ghamraoui and Ricotta (2021)[49]	Investigation of safety and efficacy of ticagrelor 90 mg twice daily as part of DAPT initiated 7 days before TCAR in 67 patients undergoing TCAR	There were 0 major bleeding events, 0 major/minor strokes, 0 MIs, 0 cranial nerve injuries and 0 deaths
Marcaccio et al. (2022)[50]	Comparison of outcomes in 1548 patients who underwent CAS on DAPT with aspirin/clopidogrel *vs.* 517 matched patients undergoing CAS on DAPT with aspirin/ticagrelor	No significant differences were found between aspirin/ticagrelor *vs.* aspirin clopidogrel in the composite end-point of stroke/death (4.1% *vs.* 2.6%; RR, 1.5; 95% CI, 0.87–3.0) or in the individual end-point of stroke (2.9% *vs.* 1.8%; RR, 1.6; 95% CI, 0.87–3.0) or death (1.7% *vs.* 1.1%; RR, 1.6; 95% CI, 0.71–3.5)
Ghamraoui et al. (2022)[51]	Comparison of outcomes in 11,973 TCAR patients who received perioperative DAPT with aspirin + clopidogrel *vs.* 426 TCAR patients who received perioperative DAPT with aspirin + ticagrelor	The occurrence of major bleeding event (2.4% *vs.* 1.4%; $P = 0.175$), stroke (1.3% *vs.* 0.5%; $P = 0.14$), stroke/death (1.4% *vs.* 0.9%; $P = 0.393$), ipsilateral stroke (1.1% *vs.* 0.5%; $P = 0.227$), stroke/TIA (1.7% *vs.* 1.9%; $P = 028$) and stroke/MI/death (1.9% *vs.* 1.6%; $P = 0.706$) did not differ between patients undergoing TCAR with DAPT including clopidogrel *vs.* ticagrelor)

DAPT: Dual antiplatelet treatment; TCAR: transcarotid artery revascularization; MI: myocardial infarction; TIA: transient ischemic attack; CAS: carotid artery stenting; RR: Relative risk; 95% CI: 95% confidence interval.

prevention of CVD and cardiovascular events in patients <50 or ≥ 70 years of age.[24]

In contrast to AsxCS, the evidence supporting antiplatelet treatment in SCS patients is more robust. Patients presenting with a TIA or a minor ischemic stroke ipsilateral to a previously asymptomatic 50–99% internal carotid artery stenosis are at increased risk of a recurrent episode in the first few days after the initial event.[28–30] A pooled meta-analysis of 12 RCTs ($n = 15,778$ patients) evaluating the effects of aspirin *vs.* control in secondary stroke prevention after TIA or ischemic stroke demonstrated that aspirin reduced the 6-week risk of recurrent ischemic stroke by nearly 60% (HR, 0.42; 95% CI, 0.32–0.55; $P < 0.0001$).[60] Furthermore, aspirin reduced the risk of disabling or fatal ischemic stroke by approximately 70% compared with placebo (HR, 0.29; 95% CI, 0.20–0.42; $P < 0.0001$).[60] Importantly, the greatest benefit was noted when aspirin was started early after a TIA or a minor stroke (at 0–2 weeks: HR, 0.07; 95% CI, 0.02–0.31; $P = 0.0004$; at 0–6 weeks: HR, 0.19; 95% CI, 0.11–0.34; $P < 0.0001$).[60] In this analysis, some of the included studies were from the pre-statin era, so it is possible that the benefits of aspirin were magnified.

A novel carotid intervention has been introduced in the last few years, TCAR, which is quickly gaining ground in the interventional management of AsxCS/SCS patients.[61–63] Recent studies have proposed the use of ticagrelor as one of the two antiplatelets agents instead of clopidogrel in DAPT (Table 3).[52–54] These early promising results with ticagrelor need to be verified in larger studies and RCTs. Future guidelines should aim at forming conclusive recommendations regarding the type and duration of antiplatelets/anticoagulants or DAPT in patients undergoing transfemoral CAS/TCAR.

Conclusions

The optimal antiplatelet/antithrombotic treatment of patients undergoing carotid interventions has not yet been conclusively determined. Several factors need to be considered, *e.g.* the presence or absence of symptoms, the type of carotid intervention, the individual resistance to aspirin/clopidogrel and the bleeding risk of each individual patient. For AsxCS patients, we suggest low-dose aspirin (75–100 mg/day) or clopidogrel (75 mg/day), not for the purpose of reducing the risk of stroke, but rather for reducing the risk of MI, cardiovascular events and death. For recently symptomatic patients, we recommend starting DAPT as soon as possible after the index event to reduce recurrent events. According to all international guidelines,[4–8] patients with a recent TIA or minor ischemic stroke should be offered a prophylactic CEA, ideally within 2 weeks of symptoms. If the 2-week target is not met, DAPT should be continued for 21 days following the index event while waiting for the carotid intervention.[34,35] Whether DAPT should be stopped before CEA varies according to center and surgeon preference. Patients with crescendo TIA or stroke-in-evolution should be placed on DAPT and should undergo a carotid revascularization as soon as possible. DAPT should be continued for at least 4 weeks after CAS/TCAR, after which a single antiplatelet agent should be used. Finally, the safety and efficacy of ticagrelor as part of DAPT instead of clopidogrel in patients undergoing TCAR/CAS should be evaluated in future trials.

Declaration of Competing Interest

Dr. Mikhailidis has given talks, acted as a consultant or attended conferences sponsored by Amgen and Novo Nordisk. Dr. Chaturvedi reports consulting for Astra Zeneca and BrainGate and serving as an Associate Editor for *Stroke*, and as an Editorial Board Member of *Neurology* and *Journal of Stroke and Cerebrovascular Diseases*. The other authors report no conflicts.

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