

Management of Patients with Asymptomatic and Symptomatic Carotid Artery Disease: Update on Anti-Thrombotic Therapy

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Abstract

The most common causes of ischaemic stroke are represented by carotid artery atherosclerotic disease (CAAD) and atrial fibrillation. While oral anticoagulants substantially reduce the incidence of thromboembolic stroke (< 1%/year), the rate of ischaemic stroke and other cardiovascular disease events in patients with CAAD remains high, ranging from 8.4 to 18.1 events per 100 patient-years. Similar to any other atherosclerotic disease, anti-thrombotic therapies are proposed for CAAD to reduce stroke and other cardiovascular events. The 2017 European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) guidelines recommend for patients with asymptomatic CAAD $\geq 60\%$ the use of aspirin 75 to 100 mg once daily or clopidogrel 75 mg once daily at the exception of patient at very high bleeding risk. For patients with symptomatic CAAD $\geq 50\%$, the use of aspirin 75 to 100 mg once daily or clopidogrel 75 mg once daily is recommended. New perspectives for anti-thrombotic therapy for the treatment of patients with CAAD come from the novel dual pathway strategy combining a low-dose anticoagulant (i.e. rivaroxaban) and aspirin that may help reduce long-term ischaemic complications in patients with CAAD. This review summarizes current evidence and recommendations for the anti-thrombotic management of patients with symptomatic or asymptomatic CAAD or those undergoing carotid revascularization.

Keywords

- ▶ carotid artery disease
- ▶ anti-thrombotic therapy
- ▶ anti-platelet
- ▶ anticoagulant
- ▶ rivaroxaban
- ▶ aspirin

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Introduction

Cardiovascular (CV) disease is one of the most important causes of morbidity and mortality worldwide, with a substantial burden on quality of life, particularly in patients who are left with disabilities after a disabling myocardial infarction (MI) or stroke.¹ About one-quarter of all ischaemic strokes are cardioembolic in origin, mostly occurring in patients with atrial fibrillation (AF),² and three-fourths are atherothrombotic, including carotid artery atherosclerotic disease (CAAD).³

Vitamin K antagonists (VKAs) reduce stroke by approximately 70% in patients with AF.⁴ The difficulties in managing VKA treatment, and their high associated bleeding risk, prompted the development of the non-VKA oral anticoagulants (NOACs), either thrombin or factor Xa inhibitors, which are at least as effective and safer than VKAs.⁵

Ischaemic stroke in patients with CAAD may result from arterial occlusion or embolization of a thrombus from an unstable carotid plaque to the cerebral vessels.⁶

Anti-thrombotic therapy is the primary treatment for patients with carotid stenosis to reduce the risk of peri-procedural and long-term complications. This includes anti-platelet drugs such as aspirin, which irreversibly acetylates COX-1, thereby preventing production of platelet thromboxane A₂, or P2Y₁₂ receptor antagonists, which inhibit interaction of adenosine diphosphate with the receptor.⁷ Recent studies evaluated NOAC-based anti-thrombotic regimens combined with anti-platelet therapy. For example, the combination of the factor Xa inhibitor rivaroxaban with aspirin in patients with stable vascular disease, thereby targeting two different anti-thrombotic pathways.⁸

In addition to anti-thrombotic drugs, optimal medical therapy of patients with clinically apparent atherosclerosis should include smoking cessation, and use of anti-hypertensive agents and lipid-lowering drugs,⁹ as burden and progression of CAAD is strictly dependent on concomitant atherosclerotic risk factors such as smoking, hypertension, diabetes or dyslipidaemia.¹⁰

In this narrative review, we summarize the management of CAAD with a focus on anti-thrombotic therapy in patients with asymptomatic and symptomatic disease.

Epidemiology and Screening of CAAD

The prevalence of CAAD depends greatly on the population studied and the stenosis threshold used for inclusion.¹¹ In the Tromsø Study, which included subjects from the general population > 50 years, the prevalence of carotid stenosis of $\geq 35\%$ was 3.8% among men and 2.7% among women.¹² In the Offspring Cohort of the Framingham Heart Study, which included 3,173 subjects (mean age: 55 years), the prevalence of carotid stenosis of $\geq 25\%$ was 24% in men and 14% in women.¹³ The prevalence of CAAD was shown to greatly increase in patients 65 years and older in the Cardiovascular Health Study, with carotid plaques observed in 75% of men and 62% of women in this age group.¹⁴

Screening for asymptomatic CAAD in the general population is not recommended by the U.S. Preventive Services Task

Force, given the lack of randomized trials showing the value of the screening.¹⁵ An evidence-based guideline recommended to screen for asymptomatic CAAD patients with symptomatic peripheral artery disease (PAD), coronary artery disease or atherosclerotic aortic aneurysm.¹⁶ Furthermore, patients with two or more of the following CV risk factors, including arterial hypertension, hyperlipidaemia, smoking, a family history of early-onset atherosclerotic disease in a first-degree relative or a family history of ischaemic stroke, could be screened for the presence of asymptomatic CAAD.¹⁶

Given the very slow rate of intima-media thickness (IMT) growing (> 0.01 mm/year) in the general population,¹¹ it is not reasonable to repeat carotid Doppler ultrasound in patients with a first normal/mildly increased IMT. Conversely, it is reasonable to repeat duplex ultrasonography annually to assess the progression or regression of CAAD and response to therapeutic interventions in patients with carotid stenosis of $> 50\%$.¹⁷

Patients with CAAD are usually classified as 'asymptomatic' and 'symptomatic' (i.e. acute signs or symptoms of cerebral or ocular ischaemia in the previous 6 months). In the general population, the prevalence of asymptomatic moderate CAAD (stenosis $\geq 50\%$) in subjects aged ≥ 70 years was 12.5% in men and 6.9% in women, and the overall prevalence of severe CAAD (stenosis $\geq 70\%$) was 1.7%.¹⁸ A pooled analysis of 23,706 individuals from four population-based cohort studies showed that factors associated with CAAD ($> 50\%$ or $> 70\%$ stenosis) were age, sex, prior vascular disease, systolic and diastolic blood pressure, total cholesterol/high-density lipoprotein ratio, diabetes mellitus and smoking status.¹⁹

Risk of Cardiovascular and Cerebrovascular Events in Patients with CAAD

When a significant carotid plaque is detected, as defined by a focal narrowing of the carotid artery of $\geq 50\%$ or an increased carotid IMT of ≥ 1.5 mm, a patient is categorized as 'high risk' for CV disease.²⁰

The risk of ischaemic stroke is dependent on clinical presentation and is higher in patients with symptomatic carotid artery stenosis compared with asymptomatic patients. In patients with asymptomatic CAAD (stenosis $> 50\%$), the annual rate of stroke is 2% and the rate of coronary events is 7%.^{21,22} In patients with symptomatic carotid stenosis who are treated with medical therapy only, the risk of CV events is higher, ranging from 8.4 to 18.1 events per 100 patient-years.^{9,23} Moreover, in a registry of patients with near occlusion carotid artery stenosis treated medically after a first ischaemic stroke, the incidence of recurrent ipsilateral stroke/transient ischaemic attack is 10.6% at 90 days.²⁴ This high risk of further events in the 14 days after the initial event was demonstrated in a study of 377 patients with symptomatic carotid stenosis of 50 to 99% awaiting elective revascularization.²⁵ Current guidelines recommend that, when revascularization is considered appropriate in symptomatic patients with $> 50\%$ stenosis, this should be performed as soon as possible, preferably within 14 days of symptom onset.²⁶

This risk is even higher in patients with CAAD who have clinically overt atherosclerosis in other vascular beds, such as coronary artery disease or PAD in the lower limbs.²⁷

Finally, in patients undergoing carotid surgery, the 4-year rates of stroke and death were 8.0 and 6.4% for symptomatic patients and 4.5 and 2.7% for asymptomatic patients, respectively.²⁸

However, when evaluating the risk of CV and cerebrovascular events in a patient with CAAD, it should be taken into consideration not only the degree of carotid stenosis, but also the presence of cardiometabolic risk factors frequently associated with CAAD.²⁹ Patients with asymptomatic CAAD and additional uncontrolled CV risk factors are at increased risk for CV events. For instance, patients with cardiometabolic diseases, such as AF, diabetes mellitus, metabolic syndrome and co-existence of CAAD, are at higher risk of ischaemic events as compared with patients without CAAD (►Table 1).²⁰

Carotid Revascularization

Determining whether patients with CAAD are eligible for carotid revascularization has been a clinical challenge for many years. The 2017 European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) guidelines indicate that asymptomatic patients with carotid stenosis of > 60% (if life expectancy is > 5 years, favourable anatomy

and high risk of stroke) or symptomatic patients with carotid stenosis of > 50% are potential candidates for vascular surgery (►Fig. 1).²⁶

Invasive treatments for CAAD include carotid endarterectomy (CEA) and carotid artery stenting (CAS). In a retrospective single-centre study of consecutive patients eligible for CEA ($n = 1,118$) or CAS ($n = 1,084$), there was no difference between the CAS and CEA groups in their 5-year combined risk of stroke or death within 30 days or ipsilateral stroke after the procedure (CAS, 3.7%; CEA, 4.7%).³⁰ The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) randomized 2,502 asymptomatic and symptomatic patients to undergo CEA or CAS.³¹ The 4-year rate of stroke or death was 6.4% with CAS and 4.7% with CEA (hazard ratio [HR], 1.50; $p = 0.03$). However, this difference was mainly driven by the rate of ipsilateral stroke in the peri-procedural period.³¹ Furthermore, an increased risk of peri-procedural MI was found in patients treated with CEA (2.3% vs. 1.1% of CAS, $p = 0.03$).²⁸ Based on these findings, the decision for CEA or CAS should be individualized, taking into consideration each patient's characteristics and surgery risk.³² Moreover, CEA should be considered for patients with a life-expectancy of more than 3 to 5 years and with the following characteristics: (1) asymptomatic men < 80 years with stenosis > 60%; (2) symptomatic women with stenosis of 70 to 99% within 2 weeks of their last ischaemic event; (3) symptomatic men with stenosis of 50 to

Table 1 Risk of cardiovascular and cerebrovascular events associated with the presence of CAAD

Disease/condition	Endpoint	Study sample size	Measure of association	Ref.
Atrial fibrillation	Ischaemic stroke	724	cIMT continuous per 1 SD: HR 1.23, 95% CI, 1.04–1.46, $p = 0.02$ Carotid plaque: HR 1.56, 95% CI, 1.00–2.45, $p = 0.100$	52
Elderly (≥ 65 y)	CHD	5,895	Plaques at 1 site: HR, 1.5, 95% CI, 1.0–2.2; Plaques at ≥ 2 sites: HR, 2.2, 95% CI 1.6–3.1; $p < 0.001$	66
Diabetes	MACE	259	Carotid plaque: HR, 5.10, 95% CI, 1.37–19.0; $p = 0.02$	67
	CVD	3,263	Common carotid max IMT (per 0.1 mm): HR, 1.08, 95% CI 1.06–1.11; $p < 0.001$	68
	MACE	581	Heterogeneous plaque: HR, 3.10, 95% CI, 2.09–4.23 Echogenic plaque: HR, 3.71, 95% CI 2.09–5.59	69
Hypertension	Stroke	356	Plaque relative risk, 3.86; $p = 0.002$	70
Peripheral artery disease	Coronary events	3,561	Carotid atherosclerosis ^a : HR, 1.37 (95% CI, 1.17–1.60), $p < 0.0001$	71
Coronary artery disease	Coronary events	12,982	Carotid atherosclerosis ^a : HR, 1.25 (95% CI, 1.16–1.35), $p < 0.0001$	71
Cardiovascular surgery	Peri-operative stroke	1,059	Carotid stenosis: OR, 4.68 (95% CI, 1.62–13.47, $p = 0.001$)	72
SAVR	Peri-operative stroke	50,979	Carotid stenosis: OR, 1.8, 95% CI, 1.1–2.8, $p = 0.009$	73

Abbreviations: CAAD, carotid atherosclerotic artery disease; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IMT, intima-media thickness; MACE, major adverse cardiovascular events; OR, odds ratio; SAVR, surgical aortic valve replacement; SD, standard deviation.

^aEvidence of ≥ 1 carotid plaque, asymptomatic carotid stenosis $\geq 70\%$ and history of carotid revascularization.

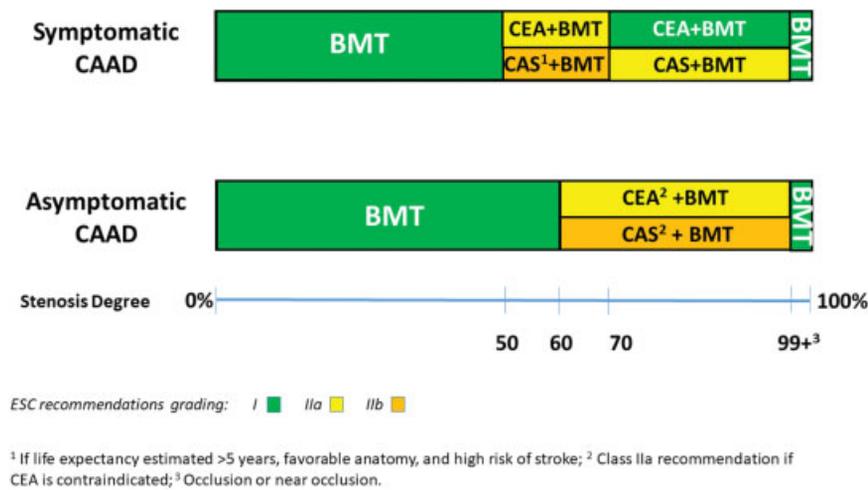


Fig. 1 Summary of recommendations for the management of patients with carotid atherosclerotic artery disease (CAAD). BMT, best medical therapy; CAAD, carotid artery atherosclerotic disease; CAS, carotid artery stenting; CEA, carotid endarterectomy.

69% within 2 weeks of their last ischaemic event; and (4) symptomatic men with stenosis of 70 to 99% and without near-occlusion within 12 weeks from their last ischaemic event.³³ Conversely, CAS should be considered in patients with restenosis after prior CEA, or with high risk of peri-operative complications, such as in patients with previous neck surgery or cranial nerve injury.²⁹ Furthermore, a recent meta-analysis suggested that for patients with asymptomatic CAAD, CEA is preferred over CAS, owing to the increased risk for periprocedural stroke or death associated with CAS.³⁴

According to the 2017 ESC/ESVS guidelines, patients with asymptomatic CAAD and stenosis of < 60%, or symptomatic patients with carotid stenosis of < 50%, gain no benefit from revascularization compared with medical therapy (►Fig. 1).²⁶ This recommendation is confirmed in a recent Cochrane review reporting that in symptomatic patients with < 30% stenosis, CEA increased the 5-year risk of ipsilateral ischaemic stroke and had no effect in those with 30 to 49% stenosis.³⁵

Therefore, all these asymptomatic patients' categories should be considered for medical therapy to manage atherosclerotic risk factors and reduce atherosclerotic burden and its complications. Lifestyle interventions are the first-line approach including smoking cessation, regular physical activity, weight loss to achieve a normal body mass index and healthy diet (i.e. Mediterranean diet).^{9,36} Moreover, tight glycaemic control, regular blood pressure monitoring and low levels of low-density lipoprotein cholesterol and triglycerides should always be a goal for these patients.⁹

The Carotid Revascularization Endarterectomy versus Stent Trial (CREST-2) is on-going and will randomize patients with asymptomatic carotid stenosis to medical therapy alone or with the addition of CEA or CAS.³⁷

Treatment

The first medical approach to a patient with CAAD relies on the management of associated CV risk factors. Lifestyle interventions including weight loss, healthy diet, smoking

cessation, physical activity, adequate blood pressure monitoring and tight glycaemic control should always be obtained in patients with CAAD (►Table 2). In particular, lipid-lowering therapy with statins should always be considered in these patients.²⁹

In addition to lifestyle interventions and management of atherosclerotic risk factors, anti-platelet and anticoagulant drugs represent the mainstay of anti-thrombotic therapy in patients with CAAD.

Anti-Platelet Drugs

The rationale for the use of anti-platelet drugs in patients with carotid stenosis is based on the key role of platelets in the onset of acute thrombotic occlusion.³⁸ Interventional trials with aspirin or thienopyridines showed a significant reduction in CV events in patients with or at risk for CV disease. In particular, a 12% reduction of serious adverse events in primary prevention trials (HR, 0.88; 95% confidence interval [CI], 0.82–0.94; $p = 0.0001$) versus controls and a 19% in secondary prevention trials (HR, 0.81; 95% CI, 0.75–0.87; $p < 0.00001$) versus controls was reported.³⁹ A summary of different guidelines recommendations on the use of anti-platelet drugs in patients with CAAD is provided in ►Table 2.

Asymptomatic CAAD: In patients with asymptomatic carotid artery stenosis, there is only weak evidence for the use of anti-platelet agents in primary prevention of CV events. In 372 patients with asymptomatic carotid stenosis of $\geq 50\%$ followed up for 2 years and randomized to receive placebo or aspirin 325 mg/day, there was no significant difference in the rate of ischaemic events between the two groups (11.0% vs. 12.3%).⁴⁰ Current guidelines generally recommend single anti-platelet therapy (commonly low-dose aspirin) in patients with asymptomatic CAAD, especially when the bleeding risk is low (►Table 2).²⁶

Symptomatic CAAD: A recent meta-analysis including 15,778 participants from 12 trials of aspirin versus control for the secondary prevention of stroke, showed that aspirin reduced the 6-week risk of recurrent ischaemic stroke by 60%

Table 2 Management of patients with symptomatic and asymptomatic CAAD

Intervention/drug	Asymptomatic CAAD ($\geq 60\%$ stenosis)	Symptomatic CAAD ($\geq 50\%$ stenosis)/Vascular surgery (CEA/CAS)
Lifestyle interventions ³⁶		
Weight loss (to BMI < 24 kg/m ²) Healthy diet (i.e. Med-Diet) Smoking cessation Physical activity (150 min/wk of moderate aerobic or 75 min/wk of vigorous aerobic activity)	Always	Always
Control of atherosclerotic risk factors		
Blood pressure < 140/85 mm Hg Tight glycaemic control LDL cholesterol target according to cardiovascular risk	Always	Always
Anti-thrombotic therapy		
Anti-platelet		
2017 ESC/ESVS ²⁶	ASA 75–100 mg once daily or clopidogrel 75 mg once daily at the exception of patient at very high bleeding risk (IIaC)	ASA 75–100 mg once daily or clopidogrel 75 mg once daily (IA) DAPT for at least 1 month after CAS (IA)
2012 ACCP ⁷⁴	ASA 75–100 mg once daily (IIB)	Clopidogrel 75 mg once daily or ASA-ERD 25/200 mg twice daily or ASA 75–100 mg once daily (IA)
2011 AHA ⁷⁵	ASA 75–325 mg once daily ^a	ASA 75–325 mg once daily or clopidogrel 75 mg once daily, or the ASA-ERD 25/200 mg twice daily (IB) ^b ASA-ERD (25/200 mg twice daily) preferred over ASA+ clopidogrel (IB) ^b
Anticoagulants		
Anticoagulant alone	Not recommended ^c	
ASA + rivaroxaban 2.5 mg twice daily	Selected patients ^d	
Anti-platelet + standard dose oral anticoagulant	No evidence	No evidence

Abbreviations: ACCP, American College of Clinical Pharmacy; AHA, American Heart Association; ASA, aspirin; BMI, body mass index; CAAD, carotid atherosclerotic artery disease; CAS, carotid artery stenting; CEA, carotid endarterectomy; DAPT, dual anti-platelet therapy; ERD, extended-release dipyridamole; ESC, European Society of Cardiology; ESVS, European Society for Vascular Surgery; LDL, low-density lipoprotein; PAD, peripheral artery disease.

^aObstructive or non-obstructive atherosclerosis involving extracranial carotid and/or vertebral arteries for prevention of myocardial infarction. No establish benefit for stroke prevention.

^bObstructive or non-obstructive extracranial carotid or vertebral atherosclerosis who have sustained an ischaemic stroke.

^cIn absence of other indications for anticoagulation (i.e. atrial fibrillation, mechanical prosthetic valves, recurrent venous thromboembolism).

^dIn the COMPASS trial, carotid disease included both asymptomatic CAAD and patients with previous revascularization. Low-dose rivaroxaban + ASA were maximally effective in patients with 'symptomatic PAD' defined as the co-existence of symptomatic peripheral artery disease of lower extremities and carotid artery disease.

and the risk of disabling or fatal ischaemic stroke by 70%.⁴¹ The use of aspirin was also associated with less severe cerebrovascular events.⁴¹ Thus, in symptomatic carotid stenosis, the current European guidelines recommend long-term single anti-platelet therapy (grade IA).²⁶

Also, the use of dual anti-platelet therapy (DAPT) has been investigated in symptomatic CAAD in the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis trial showing that, in subjects with recently symptomatic $\geq 50\%$ carotid stenosis, combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization (relative risk reduction,

39.8%; 95% CI, 13.8–58.0; $p = 0.0046$).⁴² Similar results were observed in the clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and micro-embolic signals (CLAIR) study (relative risk reduction, 42.4%; 95% CI, 4.6–65.2; $p = 0.025$).⁴³

However, current guidelines do not support the use of DAPT in patients with symptomatic CAAD, indicating long-term monotherapy with aspirin or clopidogrel or aspirin extended-release dipyridamole as the most appropriate treatment for these patients (**► Table 2**).

CAAD patients undergoing revascularization: In patients undergoing invasive carotid treatment (CEA/CAS), DAPT with

aspirin and clopidogrel is currently recommended for ≥ 1 month after CAS (grade IB), to avoid early complications after the procedure.²⁶ A recent study including 28,683 CEA procedures, showed that the use of pre-operative DAPT was associated with a 39% risk reduction in neurologic events compared with aspirin alone (odds ratio [OR], 0.61; 95% CI, 0.43–0.87; $p = 0.007$), but also incurred a significantly increased risk of re-operation for bleeding after CEA (OR, 1.71; 95% CI, 1.20–2.42; $p = 0.003$).⁴⁴

By contrast, DAPT was related to increased all-cause mortality in 471 patients with asymptomatic CAAD undergoing carotid intervention (47% vs. 40%; $p = 0.05$ compared with aspirin alone), especially in patients aged ≥ 75 years (82% vs. 56%; $p = 0.001$ compared with aspirin alone).⁴⁵ Conversely, no effect was noted in patients with symptomatic CAAD (38% vs. 39%; $p = 0.53$).⁴⁵

Furthermore, there is no firm evidence on the optimal duration of DAPT after carotid revascularization. In Asymptomatic Carotid Surgery Trial-2, 86% of centres prescribed DAPT post-operatively after CAS with a mean duration of 3 months (range, 1–12), compared with 9% of centres prescribing long-term DAPT. Moreover, in patients who underwent CEA, 24% of centres prescribed DAPT post-operatively with a mean duration of 3 months (range, 1–5) and 10% prescribed long-term DAPT.⁴⁶

Another strategy was tested in the ARMYDA-9 CAROTID (Clopidogrel and Atorvastatin Treatment During Carotid Artery Stenting) study, which showed that 600 mg clopidogrel load and a short-term reload with high-dose atorvastatin (80 + 40 mg) reduced 30-day ischaemic cerebral events as compared with clopidogrel 300 mg in 156 patients undergoing carotid stenting (18% vs. 35.9% in the 300-mg group; $p = 0.019$).⁴⁷

The use of DAPT is currently recommended only by ESC/ESVS for at least 1 month after CAS procedure (► **Table 2**).

Anticoagulants

The value of anticoagulants in patients with CAAD and no other indication for anticoagulation is unclear. Several trials are evaluating the efficacy and safety of NOACs in combination with anti-platelet therapy in patients with vascular disease, including CAAD.^{48,49} The⁵⁰ Cardiovascular Outcomes for

People Using Anticoagulation Strategies (COMPASS) trial investigated a new therapeutic approach combining low-dose rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily) in patients with stable artery disease ($n = 27,395$) showing a beneficial effects in terms of reduction of CV events in patients with coronary artery disease⁵¹ ($n = 24,824$, HR, 0.74; 95% CI, 0.65–0.86; $p < 0.0001$) or PAD⁸ ($n = 7,470$, HR, 0.72; 95% CI, 0.57–0.90, $p = 0.0047$). The latter category included patients with previous carotid revascularization as well as those with asymptomatic CAAD stenosis of $\geq 50\%$.⁸ Patients with CAAD were randomized to low-dose rivaroxaban 2.5 mg twice daily plus aspirin ($n = 617$), rivaroxaban alone 5 mg twice daily ($n = 622$) or aspirin 100 mg once daily ($n = 680$).⁸ The results in this sub-group of patients were consistent with the overall results of the COMPASS trial and those with PAD. Specifically, patients with CAAD had a lower incidence of major adverse cardiovascular events (MACEs) treated with rivaroxaban 2.5 mg twice daily plus aspirin compared with those treated with aspirin alone (3.9% vs. 6.0%, $p = 0.07$), with a similar rate of bleeding events between the two groups.⁸ Furthermore, combination therapy reduced major adverse CV and limb events compared with aspirin alone in patients with CAAD (some of whom had concomitant PAD), with an increase in non-serious major bleeding (► **Table 3**).

Also in patients with AF, in whom CAAD is detected in up to 38% of cases,^{52–54} a post hoc analysis from the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation showed that patients with AF had a similar risk of thromboembolism whether or not they had carotid disease, and that rivaroxaban had similar safety and efficacy compared with warfarin in this sub-group of patients.⁵⁵

Another issue is the impact of low-dose rivaroxaban plus aspirin in patients presenting with multi-bed vascular disease, such as PAD in combination with CAAD and/or coronary artery disease. A recent study including 155,647 patients showed that CAAD and PAD may frequently co-exist ($> 60\%$ of patients), increasing the risk of death and limb amputation.⁵⁶ Thus, the effect of low-dose rivaroxaban in this very high-risk sub-group of patients with PAD and CAAD (including both prior carotid revascularization or existent asymptomatic carotid artery stenosis) seems to be of particular

Table 3 High-risk peripheral artery disease sub-groups in the COMPASS trial

	All patients	Hazard ratio (95% confidence interval) for low-dose rivaroxaban + aspirin (vs. aspirin alone)		
	N	MACE	MACE/MALE ^b	Major bleeding
LEAD ^a by eligibility	5,551	0.74 (0.57–0.96)	0.70 (0.55–0.88)	1.75 (1.16–2.65)
Carotid disease by eligibility ^c	1,919	0.63 (0.38–1.04)	0.64 (0.41–1.01)	1.18 (0.55–2.50)
Total with carotid and concomitant LEAD	840	0.43 (0.20–0.92)	0.58 (0.31–1.08)	0.78 (0.25–2.48)

Abbreviations: ABI, ankle–brachial index; LEAD, lower-extremity artery disease; MACE, major adverse cardiovascular event; MALE, major adverse limb event.

^aDefined as intermittent claudication with ABI < 0.90 or stenosis of $\geq 50\%$; or previous aorta-femoral or lower extremity bypass surgery, percutaneous transluminal angioplasty of iliac or infra-inguinal arteries or limb or foot amputation for arterial vascular disease.

^bCombined outcome of MACEs and MALEs including major amputation.

^cDefined as previous carotid endarterectomy or stent or asymptomatic carotid artery stenosis of $\geq 50\%$.

interest as this combination reduced by 32% the risk of CV events including MACEs and major adverse limb events including major amputation in the recent COMPASS trial (►Table 3).

A still open issue is the combination of standard dose anticoagulant with single antiplatelet therapy or DAPT in patients with CAAD. This association has been tested in different populations of patients with CV disease with divergent results. A previous meta-analysis showed that the addition of a VKA oral anticoagulant (international normalized ratio range, 1.4–3.0) to aspirin (325 mg) increased major bleeding (OR, 2.13; 95% CI, 1.27–3.57) and mortality (OR, 1.57; 95% CI, 1.16–2.12) in patients with PAD.⁵⁷

In patients with recent coronary artery disease, the addition of aspirin to a NOAC reduced the incidence of MACEs (HR, 0.70; 95% CI, 0.59–0.84), but increased clinically significant bleeding (HR, 1.79; 95% CI, 1.54–2.09).⁵⁸ Furthermore, the addition of a NOAC to DAPT only modestly decreased the incidence of MACE (HR, 0.87; 95% CI, 0.80–0.95), but the risk of bleeding was at least doubled (HR, 2.34; 95% CI, 2.06–2.66).⁵⁸

►Table 2 summarizes medical and anti-thrombotic treatment for patients with CAAD.

For patients with PAD/CAAD and an indication to receive long-term anticoagulation, such as those with AF, mechanical prosthetic heart valves or recurrent venous thromboembolism, evidence for adding an anti-platelet therapy should be wisely considered for the risk of bleeding. After an endovascular revascularization procedure, aspirin or clopidogrel should be considered in addition to oral anticoagulant for the shortest needed time (i.e. 1 month), especially if the bleeding risk is high.²⁶ In this regard, particular attention should be paid on Asian AF patients treated with VKAs, for whom the risk of intracranial haemorrhage is increased compared with non-Asian patients.⁵⁹ Conversely, anticoagulant therapy with standard-dose NOACs was more effective and safer in Asians than in non-Asians when compared with warfarin.⁶⁰

However, no specific data on the risk of bleeding in Asian patients with CAAD treated with anticoagulant therapy (with or without anti-platelet drugs) are available.

Future Perspectives

The data detailed in this review indicate that some areas of medical and anti-thrombotic therapy in the carotid stenosis setting are still undefined and should continue to be explored in future. A summary of the levels of evidence for surgical or medical intervention for patients with CAAD is reported in ►Fig. 1.

Peri-procedural and long-term CV risks are both elevated despite current anti-thrombotic therapy. The duration of anti-platelet therapy in patients undergoing vascular surgery is also unclear, but single anti-platelet therapy generally is administered lifelong. The effect of combination therapy of aspirin plus low-dose rivaroxaban in this group of patients should be investigated given their different risk profile.

An important still open issue is the mechanism accounting for the beneficial ‘vascular effect’ of low-dose rivarox-

aban in atherosclerotic patients. Rivaroxaban reduces thrombin generation and eventually platelet activation, but a direct factor Xa-mediated anti-platelet effect cannot be excluded. Thus, there is evidence that glycoprotein (GP) VI is crucial for platelet activation by collagen as documented by impaired platelet responsiveness in case of platelet GPVI depletion.⁶¹ Similarly, factor Xa directly activates GPVI and rivaroxaban (1 µg/mL) inhibits GPVI-mediated platelet activation.^{61,62} Recent data supported and extended this report showing that, upon interaction with GPVI, factor Xa activates platelets by up-regulating nicotinamide adenine dinucleotide phosphate oxidase (Nox2), an enzyme which plays a crucial role not only in the immune system but also in the thrombotic process.^{63–65} Furthermore, concentrations of rivaroxaban (25–100 ng/mL) amplified the aspirin’s anti-platelet effect by inhibiting Nox2-mediated platelet oxidative stress and eventually formation of the eicosanoids thromboxane A2 and isoprostanes.⁶³ Future investigations are required to determine if this effect occurs in vivo.

Conclusion

Patients with CAAD have an increased risk of ischaemic stroke and other CV events. The combination of aspirin plus low-dose rivaroxaban appears superior to aspirin alone in reducing CV death, MI and stroke. There is a need for further research in patients with CAAD to optimize CV outcomes with anti-thrombotic therapy.

Conflict of Interest

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