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Prevention of stroke in patients with chronic coronary syndromes or peripheral arterial disease

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Stroke is a common and devastating condition caused by atherothrombosis, thromboembolism, or haemorrhage. Patients with chronic coronary syndromes (CCS) or peripheral artery disease (PAD) are at increased risk of stroke because of shared pathophysiological mechanisms and risk-factor profiles. A range of pharmacological and non-pharmacological strategies can help to reduce stroke risk in these groups. Antithrombotic therapy reduces the risk of major adverse cardiovascular events, including ischaemic stroke, but increases the incidence of haemorrhagic stroke. Nevertheless, the net clinical benefits mean antithrombotic therapy is recommended in those with CCS or symptomatic PAD. Whilst single antiplatelet therapy is recommended as chronic treatment, dual antiplatelet therapy should be considered for those with CCS with prior myocardial infarction at high ischaemic but low bleeding risk. Similarly, dual antithrombotic therapy with aspirin and very-low-dose rivaroxaban is an alternative in CCS, as well as in symptomatic PAD. Full-dose anticoagulation should always be considered in those with CCS/PAD and atrial fibrillation. Unless ischaemic risk is particularly high, antiplatelet therapy should not generally be added to full-dose anticoagulation. Optimization of blood pressure, low-density lipoprotein levels, glycaemic control, and lifestyle characteristics may also reduce stroke risk. Overall, a multifaceted approach is essential to best prevent stroke in patients with CCS/PAD.

Introduction

Significant mortality and morbidity arise from complications of either chronic coronary syndromes (CCS), encompassing symptomatic or asymptomatic coronary artery disease (CAD) with or without a history of acute coronary syndrome (ACS),[1] or peripheral artery disease (PAD), including lower extremity arterial disease (LEAD), and carotid artery stenosis.[2] Those with CCS/PAD are at increased risk of acute atherothrombotic events, including ACS,

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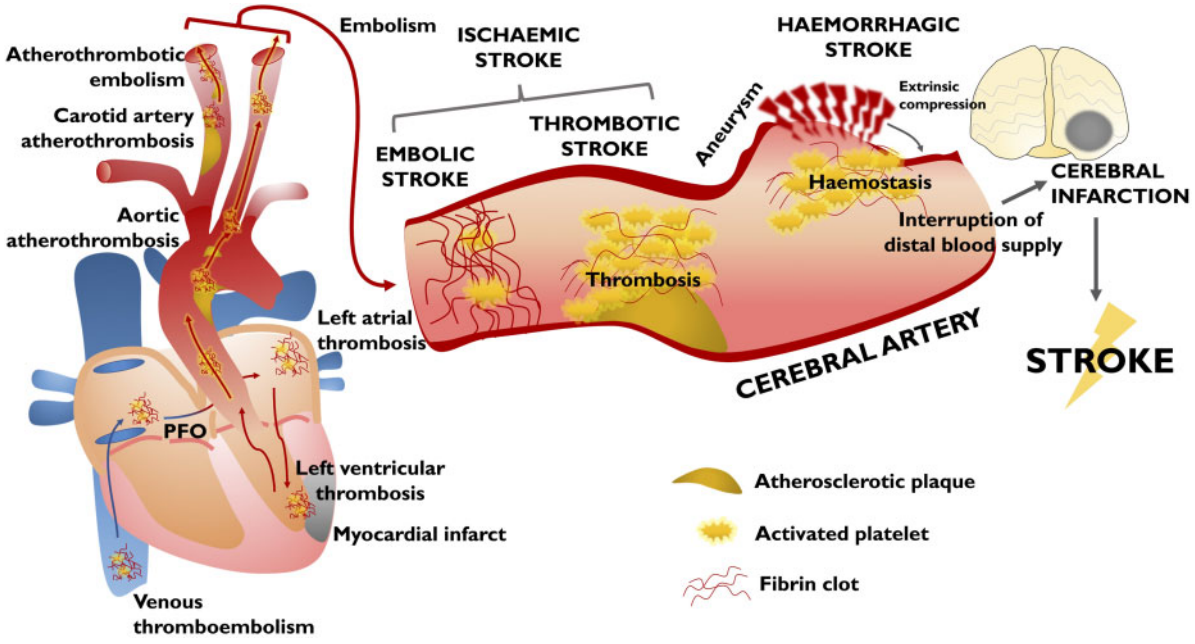

Figure 1 Mechanisms of stroke in patients with CCS/PAD. Stroke is caused by the interruption of blood supply to the brain. Ischaemic stroke may be due to atherothrombosis within a cerebral artery (thrombotic stroke) or from embolism of a thrombus formed at a distant site (embolic stroke), for example the left atrium, aortic arch or carotid arteries. Haemorrhagic stroke results from rupture of a cerebral artery aneurysm. Platelet activation and fibrin clot formation are the central processes in ischaemic stroke, whereas in haemorrhagic stroke these processes may limit its severity. PFO, patent foramen ovale.

[myocardial infarction (MI) or unstable angina (UA)], acute limb ischaemia (ALI), and acute stroke.[1,2]

There are three main mechanisms of stroke (*Figure 1*). Patients with CCS/PAD may be at particular risk of stroke because of shared underlying disease processes and risk-factor profiles (*Figure 2*). Pathological mechanisms of atherothrombotic stroke are shared with most ACS and ALI, involving atheromatous plaque formation, rupture, and/or erosion, triggering thrombosis via activation of platelets and the coagulation cascade.[3] The processes and risk factors leading to cardioembolic stroke, on the other hand, have less in common with CCS and PAD. Compared to atherothrombotic stroke in which platelets and adhesive molecules are central, activation of the coagulation cascade primarily drives cardiac thromboembolism in a setting of stasis and inflammation, most notably from the left atrial appendage in patients with atrial fibrillation (AF), although there are other possible sources (*Figure 1*).[4]

In this review, we present pharmacological strategies to prevent stroke in patients with CCS/PAD. Similarities in pathogenetic mechanisms can provide insights into therapies, and we explore clinical data supporting or refuting these. Whilst focusing on ischaemic stroke, preventing haemorrhagic stroke is also important, particularly since some treatments of CCS, PAD, and acute stroke may increase its incidence.

Antithrombotic therapy

Antiplatelet therapy

As platelet activation is the central process in acute complications of CCS and PAD, there is a clear rationale for the use of antiplatelet therapy (APT) in these groups. Similarly, those treated by coronary or peripheral artery stenting are at risk of platelet-mediated stent thrombosis.[2]

Use of single antiplatelet therapy

Numerous randomized controlled trials (RCTs) have established the benefits of APT in patients with CCS/PAD. Single antiplatelet therapy (SAPT) with aspirin, which inhibits platelet cyclooxygenase-1-mediated TXA_2 synthesis,[5] has proven efficacy in the prevention of major adverse cardiovascular events (MACE, defined as cardiovascular (CV) death, non-fatal MI, or non-fatal stroke) in high-risk patients. A meta-analysis by the Antithrombotic Trialists' Collaboration, including individual data from 135 000 patients with pre-existing CV disease, showed clear benefit, mainly with aspirin alone, in reducing MACE by around 25% [relative risk reduction (RRR): those with prior-MI = 21%, $P < 0.0001$; other-CAD = 37%, $P < 0.0001$; PAD 23%, $P = 0.004$].[6] This included a significant reduction in non-fatal ischaemic stroke (3.5% to 2.6%, RRR = 25%). Increases in haemorrhagic stroke risk were offset by a non-significant reduction in total stroke risk of 21%. Similarly, a more recent meta-analysis has provided further insight, suggesting that aspirin significantly reduces the risk of large-artery atherothrombotic stroke [odds ratio = 0.87, 95% confidence interval (CI) 0.76-1.00; $P = 0.046$], but not small vessel occlusion or cardioembolism.[7]

Platelet $P2Y_{12}$ receptor inhibitors have also been tested in CCS/PAD (*Tables 1 and 2*, *Figure 3*).[16] $P2Y_{12}$, its natural ligand being adenosine diphosphate, plays a central role in the amplification of platelet activation. Three orally-active $P2Y_{12}$ inhibitors have been marketed. The

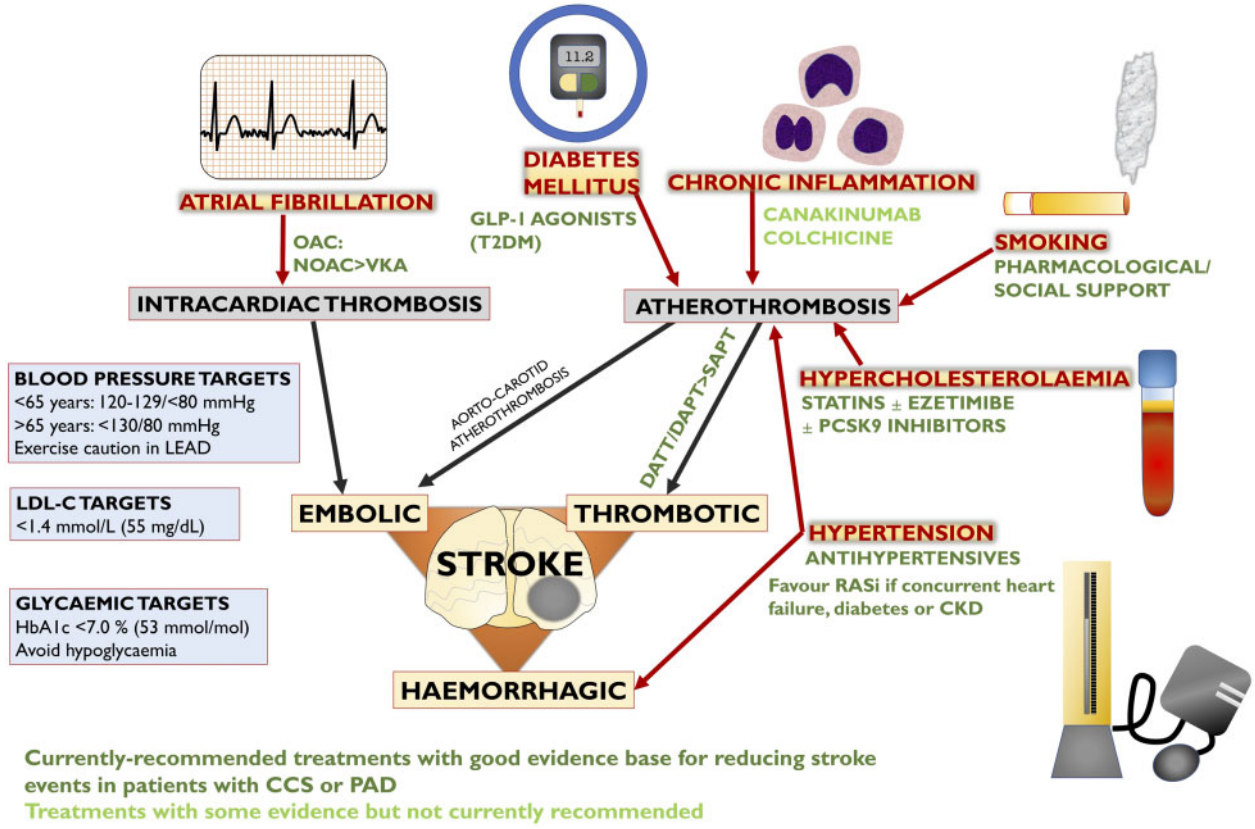

Figure 2 Modifiable risk factors for stroke in patients with CCS/PAD and evidence-based therapies to address these. CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DATT, dual antithrombotic therapy; GLP-1, glucagon-like peptide 1; HbA1c, glycated haemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LEAD, lower-extremity arterial disease; NOAC, non-vitamin K antagonist OAC; OAC, oral anticoagulant; PCSK9, proprotein convertase subtilisin/kexin type 9; RASi, renin-angiotensin-system inhibitor; SAPT, single antiplatelet therapy; T2DM, type 2 diabetes mellitus; VKA, vitamin K antagonist.

thienopyridines clopidogrel and prasugrel are pro-drugs whose active metabolites irreversibly inhibit $P2Y_{12}$.[3] Both require metabolic activation, which is predictably consistent and effective for prasugrel whereas, for clopidogrel, there is significant inter-individual variability and around one-third of the population are poor responders.[3] The cyclopentyl-triazolopyrimidine ticagrelor is a directly-acting, reversibly-binding $P2Y_{12}$ inhibitor and inverse agonist. Ticagrelor and prasugrel are more potent than clopidogrel with less inter-individual variability.[3,17]

In the Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, $P2Y_{12}$ inhibitor SAPT with clopidogrel 75 milligrams (mg) once daily was compared with aspirin 325 mg once daily in patients with CCS and PAD (*Tables 1 and 2*).[8] There was a modest RRR in MACE but a suggestion of greater efficacy in PAD patients, leading to recommendations that, if SAPT is indicated in symptomatic PAD, clopidogrel may be preferred to aspirin.[2] There was no difference in rates between the two treatments for stroke, including in those with PAD. Current ESC guidelines recommend either aspirin or clopidogrel for patients with symptomatic PAD and/or those who have required revascularization.[2] In patients with asymptomatic LEAD, there is no clear evidence that SAPT with aspirin prevents vascular events, including stroke, although studies have been small and underpowered (Supplementary material online).[2]

It has been hypothesized that more potent and consistent $P2Y_{12}$ inhibitors than clopidogrel might offer better protection against MACE. The Examining Use of tiCagreLor In peripheral artery Disease (EUCLID) trial randomized patients with symptomatic PAD to ticagrelor or clopidogrel (*Table 2*).[14] Over a median follow-up of 30 months, there was no significant difference in MACE, although there was a significant reduction in the secondary endpoint of ischaemic stroke with ticagrelor, meaning that, for stroke prevention in PAD, ticagrelor may offer some benefit over clopidogrel, although ticagrelor monotherapy is not approved in PAD.[6]

In The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial, ticagrelor monotherapy was not superior to aspirin monotherapy in 13 199 patients with non-severe ischaemic stroke or high-risk transient ischaemic attack, with similar bleeding profile.[18] Around 12% of the trial population had CAD or previous MI and similarly in these patients there was no superiority of ticagrelor vs. aspirin ($P = 0.89$).

Use of dual antiplatelet therapy

In ACS, aspirin plus a $P2Y_{12}$ inhibitor [dual antiplatelet therapy (DAPT)] has proven benefits over aspirin alone in preventing MACE.[19] When used in DAPT, ticagrelor, in all ACS,

Table 1. Primary and stroke outcomes of total study groups from key RCTs comparing regimens of $P2Y_{12}$ inhibitors or rivaroxaban with aspirin monotherapy in patients with CCS/PAD in sinus rhythm.

Short name (year published)	Population	Experimental group(s)	Comparator	Primary endpoint	Key safety endpoint	Ischaemic stroke	Haemorrhagic stroke	Total stroke
CAPRIE (1996)[8]	19 185 patients with atherosclerotic CV disease (including 6302 with prior MI, 6452 with PAD)	Clopidogrel 75 mg once daily	Aspirin 325 mg once daily	MI, ischaemic stroke, or CV death: 5.32% vs. 5.83%, RRR 8.7% (0.3-16.5), $P = 0.043$. Subgroup analysis: only significant difference in those with PAD	Severe bleeding: 1.38% vs. 1.55% ($P \geq 0.05$)	NR	NR	438 events vs. 432
CHARISMA (2006)[9]	15 603 patients with clinically evident CV disease or multiple risk factors (48% with CCS, 23% with symptomatic PAD)	Clopidogrel 75 mg once daily + aspirin 75-162 mg once daily	Aspirin 75-162 mg once daily	CV death, MI, or stroke: 6.8% vs. 7.3%, HR = 0.93 [0.83-1.05], $P = 0.22$	GUSTO severe bleeding: 1.7% vs. 1.3%, HR = 1.25 [0.97-1.61], $P = 0.09$	1.7% vs. 2.1%, HR = 0.81 [0.64-1.02], $P = 0.07$	NR	1.9% vs. 2.4%, HR = 0.79 [0.64-0.98], $P = 0.03$
PEGASUS TIMI 54 (2015)[10]	21 162 patients aged ≥50 years with a history of spontaneous MI 1-3 years prior to enrolment AND at least one additional atherothrombosis risk factor[b]	Ticagrelor 60-mg or 90-mg twice daily [a] plus aspirin 75-150-mg once daily	Aspirin 75-150-mg once daily	CV death, MI or stroke: 7.77% vs. 9.04%, HR = 0.84 [0.74-0.95], $P = 0.008$	TIMI major bleeding: HR = 2.32 [1.68-3.21], $P < 0.001$	1.28% vs. 1.65%, HR = 0.76 [0.56-1.02], $P = 0.06$	0.19% vs. 0.19%, HR = 0.97 [0.37 to 2.51], $P = 0.94$	1.47% vs. 1.94% HR = 0.75 [0.57-0.98], $P = 0.03$
DAPT (2014)[11]	9961 patients 12 months post-PCI (26% for MI) followed up for a further 18 months	Aspirin 75-162 mg once daily + continued thienopyridine (65% clopidogrel 75 mg once daily, 35% prasugrel 5 or 10 mg once daily adjusted to weight)	Aspirin 75-162 mg once daily	Stent thrombosis: 0.4% vs. 1.4%, HR 0.29 [0.17-0.48], $P < 0.001$; CV death, MI, or stroke: 4.3% vs. 5.9%, HR = 0.71 [0.59-0.85], $P < 0.001$	GUSTO Moderate or severe bleeding: 2.5% vs. 1.6%, HR = 1.61 [1.21 to 2.16], $P = 0.001$	0.5% vs. 0.7%, HR = 0.68 [0.40-1.17], $P = 0.16$	0.3% vs. 0.2%, HR = 1.20 [0.50 to 2.91], $P = 0.68$	0.8% vs. 0.9%, HR = 0.80 [0.51-1.25], $P = 0.32$
THEMIS (2019)[12]	19 220 patients with T2DM and CCS but no history of MI	Aspirin 75-150 mg once daily + ticagrelor 60 mg twice daily (reduced from 90 mg early in the trial)	Aspirin 75-150 mg once daily	CV death, MI, or stroke: 7.7% vs. 8.5%, HR = 0.90 [0.81-0.99], $P = 0.04$	TIMI major bleeding: 2.2% vs. 1.0%, HR = 2.32 [1.82-2.94], $P = 0.005$	1.6% vs. 2.0%, HR = 0.80 [0.64-0.99]	NR	1.9% vs. 2.3%, HR = 0.82 [0.67-0.99]

(continued)

Table 1. Continued

Short name (year published)	Population	Experimental group(s)	Comparator	Primary endpoint	Key safety endpoint	Ischaemic stroke	Haemorrhagic stroke	Total stroke
COMPASS (2017)[13]	27 395 with CCS (91%) + additional risk factors if <65 years old[c]) or symptomatic PAD (27%)	Aspirin 100 mg once daily + rivaroxaban 2.5 mg twice daily; or,	Aspirin 100 mg once daily	CV death, MI, or stroke: 4.1% vs. 5.4%, HR = 0.76 [0.66-0.86], $P < 0.001$;	Modified ISTH major bleeding: 3.1% vs. 1.9%, HR = 1.70 [1.40-2.05], $P < 0.001$;	0.7% vs. 1.4%, HR = 0.51 [0.38-0.68], $P < 0.001$;	0.2% vs. 0.1%, HR = 1.49 [0.67-3.31], $P = 0.33$	0.9% vs. 1.6%, HR = 0.58 [0.44-0.76], $P < 0.001$
		Rivaroxaban 5-mg twice daily		4.9% vs. 5.4%, HR = 0.90 [0.79-1.03], $P = 0.12$	2.8% vs. 1.9%, HR = 1.51 [1.25-1.84], $P < 0.001$	1.0% vs. 1.4%, HR = 0.69 [0.53-0.90], $P = 0.006$	0.3% vs. 0.1%, HR = 2.70 [1.31-5.58], $P = 0.005$	1.3% vs. 1.6%, HR = 0.82 [0.65-1.05], $P = 0.12$

[a]Data shown are for ticagrelor 60-mg twice daily vs. placebo: *P*-value of <0.026 denotes statistical significance.

[b]Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-endstage renal disease.

[c]Documentation of atherosclerosis involving at least two vascular beds or to have at least two additional risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [GFR] <60 mL/min, heart failure, or non-lacunar ischaemic stroke ≥1 month earlier).

Values in square brackets represent 95% confidence intervals.

CCS, chronic coronary syndromes; CV, cardiovascular; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RRR, relative risk reduction; T2DM, type 2 diabetes mellitus, TIMI, thrombolysis in myocardial infarction.

Table 2. Primary and stroke outcomes of key RCTs or subgroup analyses comparing regimens of antithrombotic therapy in patients with PAD in sinus rhythm

Short name (year published)	Population/ subgroup	Experimental group(s)	Comparator	Primary endpoint	Key safety endpoint	Ischaemic stroke	Total stroke
CAPRIE (1996)[8]	Subgroup of 6452 with PAD	Clopidogrel 75-mg once daily	Aspirin 325-mg once daily	MI, ischaemic stroke or CV death: 3.71% vs. 4.86% per year, RRR = 23.8% [8.9-36.2), $P = 0.028$	NR	NR	81 events vs. 82 events
CHARISMA (2006)[9]	Subgroup of 3096 with PAD	Clopidogrel 75-mg once daily + aspirin 75 to 162-mg once daily	Aspirin 75 to 162-mg once daily	CV death, MI or stroke: 8.2% vs. 6.8%, HR = 1.25 [1.08-1.44], $P = 0.002$	GUSTO severe bleeding: 1.7% vs. 1.7%, HR = 0.97 [0.56-1.66], $P = 0.901$	2.3% vs. 2.4%, HR = 0.97 [0.75-1.25], $P = 0.782$	2.6% vs. 2.9%, HR = 0.94 [0.74-1.20], $P = 0.635$
EUCLID (2017)[14]	13 885 patients with symptomatic PAD	Ticagrelor 90-mg twice daily for 36 months	Clopidogrel 75-mg once daily for 36 months	CV death, MI or ischaemic stroke: 10.8% vs. 10.6%, HR = 1.02, [0.92-1.13], $P = 0.65$	TIMI major bleeding: 1.6% vs. 1.6%, HR = 1.10 [0.84-1.43], $P = 0.49$	1.9% vs 2.4%, HR = 0.78 [0.62-0.98]. $P = 0.03$	NR
COMPASS (2017)[13]	Subgroup of 7470 patients with PAD	Aspirin 100-mg once daily + rivaroxaban 2.5-mg twice daily; or,	Aspirin 100-mg once daily	CV death, MI or stroke: 5% vs. 7%, HR = 0.72 [0.57-0.90], $P = 0.0047$	Modified ISTH major bleeding: 3% vs. 2%, HR = 1.61 [1.12-2.31], $P < 0.0089$	NR	1% vs. 2%, HR = 0.54 [0.33-0.87]
		Rivaroxaban 5-mg twice daily		6% vs. 7%, HR = 0.86 [0.69-1.08], $P = 0.19$	3% vs. 2%, HR = 1.68 [1.17-2.40], $P < 0.0043$	NR	2% vs. 2%, HR = 0.93 [0.61-1.40]
VOYAGER PAD (2020)[15]	6564 patients with PAD treated by revascularization	Aspirin 100-mg once daily + rivaroxaban 2.5-mg twice daily	Aspirin 100-mg once daily	ALI, major amputation, MI, ischaemic stroke, CV death: 17.3% vs.19.9%[a], HR = 0.85 [0.76-0.96], $P = 0.009$	TIMI major bleeding: 2.65% vs 1.87%[a], HR = 1.43 [0.97-2.10], $P = 0.07$)	2.7% vs. 3.0%[a], HR = 0.87 (0.63-1.19)	NR

CV, cardiovascular; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; RRR, relative risk reduction; TIMI, Thrombolysis In Myocardial Infarction.

[a]3-year Kaplan-Meier estimation.

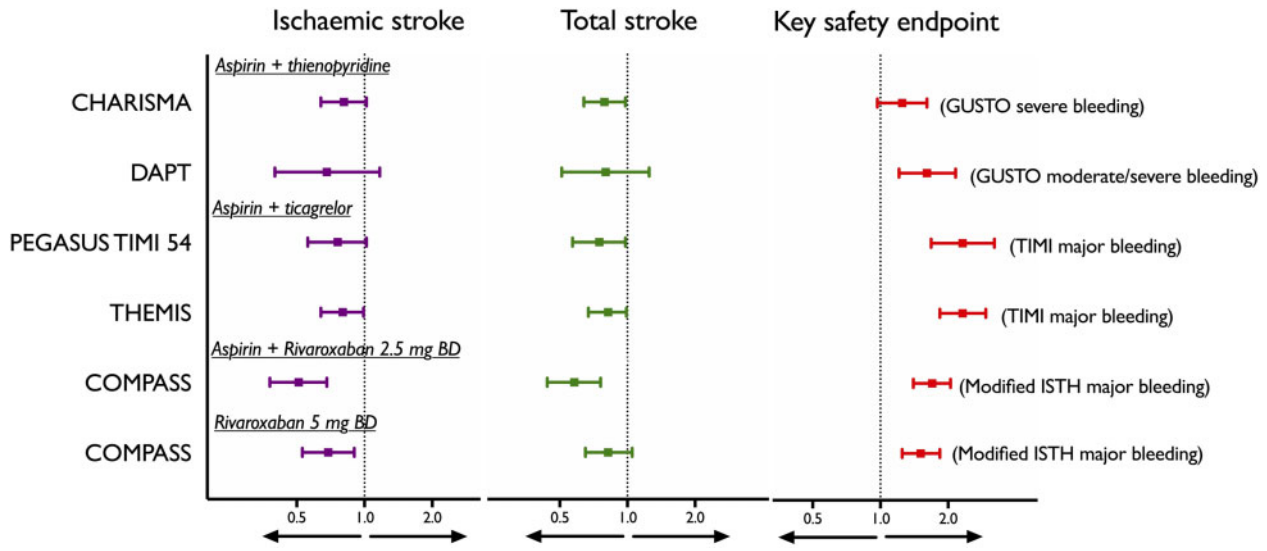

Figure 3 Forest plots showing HR ± 95% CI for ischaemic stroke, total stroke and the key safety endpoint in RCTs of antithrombotic regimens vs. aspirin monotherapy in patients with CCS/PAD (see *Table 1* for trial details). GUSTO, Global Strategies for Opening Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis In Myocardial Infarction.

and prasugrel, in those treated with percutaneous coronary intervention (PCI), are superior to clopidogrel.[6] A recent open-label RCT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5, demonstrated lower MACE rates with aspirin and prasugrel vs. aspirin and ticagrelor in those with ACS scheduled for invasive evaluation.[3] Similarly, in patients with CCS undergoing PCI, DAPT with aspirin, and clopidogrel for ≥6 months reduces stent thrombosis risk vs. aspirin alone.[1] This regimen is also recommended for 1 month in patients undergoing carotid artery stenting and, with weaker evidence, in those undergoing percutaneous revascularization for LEAD.[2]

After a minor stroke or transient ischaemic attack (TIA), a short period of DAPT offers superior protection from major ischaemic events when compared to aspirin alone, including in patients with CCS or PAD, albeit at the expense of more bleeding.[20,21]

Considering the longer-term use of DAPT vs. aspirin alone in patients with CCS/PAD, the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) study provided valuable initial data (*Tables 1 and 2*).[9] There was a non-significant reduction in the primary efficacy endpoint of MACE, although there was slightly greater reduction in the secondary efficacy endpoint (primary endpoint events/hospitalization for UA, TIA, or revascularization) [hazard ratio (HR) = 0.92, 95% CI (0.86–1.00); $P = 0.04$]. Most of the benefit appeared to be stroke-derived [e.g. non-fatal stroke HR = 0.79 (0.64–0.98); $P = 0.03$], with no significant effect on MI or CV death.

Subsequent RCTs have built an evidence base for long-term DAPT post-ACS. For those at high ischaemic but low bleeding risk who have tolerated ≥1 year of DAPT, continuation beyond 1 year after MI is a recommended option.[1] For example, post-MI patients with at least one additional risk-factor benefit from long-term aspirin and reduced-dose ticagrelor (60-mg twice daily) vs. aspirin alone, although underlying bleeding risk should be carefully evaluated. The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-TIMI 54 (PEGASUS-TIMI 54) study showed MACE reduction in those receiving DAPT vs. SAPT (*Table 1*).[10] There was also a reduction in the risk of stroke. Although TIMI-major bleeding was significantly more frequent with ticagrelor, intracranial haemorrhage, haemorrhagic stroke, or fatal bleeding were not.

Evidence for thienopyridines comes from the DAPT study, which showed 30 vs. 12 months of thienopyridine, alongside aspirin, significantly reduced MACE in prior-MI patients (*Table 1*).[22] Stroke was not significantly reduced, although there was a signal of possible benefit in ischaemic stroke. Unlike MI, the stroke did not occur significantly more frequently in those with a prior MI compared to those without (e.g. total stroke = 0.73% vs. 0.85%, $P = 0.51$). Current recommendations suggest long-term thienopyridine in prior-MI patients at moderate/high ischaemic risk.[1] Prasugrel in combination with aspirin in any situation is contraindicated in those with prior stroke, and aspirin with ticagrelor is similarly not recommended for long-term use in this group.

In patients with CCS but without prior MI, there is little evidence for long-term DAPT. THE effect of ticagrelor on health outcomes in diabetes Mellitus patients Intervention Study (THEMIS) randomized 19 220 aspirin-treated patients with T2DM and CCS, but no MI, to ticagrelor (90-mg reduced to 60-mg twice daily during the course of the trial) or placebo, for a median of 40 months (*Table 1*).[12] Whilst there was lower MACE incidence in those receiving ticagrelor vs. placebo, there was a greater increase in TIMI-major bleeding including intracranial haemorrhage. Ischaemic stroke occurred less frequently when receiving DAPT, as did all stroke. Although

meeting its primary endpoint, the net clinical benefit has not supported adoption in practice.

Ticagrelor monotherapy

Ticagrelor monotherapy has been investigated as an alternative to DAPT in CCS patients treated with PCI, though this is not yet endorsed in recommendations (Supplementary material online).

Anticoagulant therapy

Oral anticoagulants (OACs) include vitamin K antagonists (VKAs), e.g., warfarin, and non-VKA oral anticoagulants (NOACs), e.g., the factor Xa (FXa) inhibitors (apixaban, edoxaban, and rivaroxaban) or the thrombin inhibitor dabigatran.[23]

Anticoagulants in coronary syndromes or peripheral artery disease patients with atrial fibrillation

Atrial fibrillation increases the risk of cardioembolism from the left atrium through disruption in flow and inflammation. Anticoagulation reduces stroke risk in AF by around 60%.[1] The CHA_2DS_2-VASc score is recommended for determining whether an OAC is warranted.[1] An OAC is recommended with a score ≥ 2, and should be considered if ≥ 1 (excluding females without other criteria).[1,2]

Non-VKA oral anticoagulants offer superior stroke protection vs. VKA, outside of situations such as moderate/severe mitral stenosis, metallic valve prosthesis, very poor renal function, or non-compliance, groups in whom there are negative data or therapeutic drug monitoring is necessary. A meta-analysis including 71 683 participants of four phase 3 RCTs (15% with prior MI) showed significantly lower rates of stroke or systemic embolism [HR = 0.81 (0.73-0.91), $P < 0.0001$] and haemorrhagic stroke [0.49, (0.38-0.64), $P < 0.0001$] in those receiving a NOAC compared to VKA.[23] There were numerically fewer ischaemic strokes in those receiving a NOAC [0.92 (0.83-1.02), $P = 0.10$]. Different NOACs have never undergone head-to-head clinical outcome-driven RCTs, although observational studies have provided some insight (Supplementary material online). The availability of selective antidotes to both FXa inhibitors (andaxenet alfa) and dabigatran (idarucizumab) has increased the safety of these drugs.

There are limited data regarding long-term use of OAC-APT combinations in patients with CCS/PAD and AF, but current recommendations generally advise OAC alone during long-term maintenance therapy.[1] Recently, evidence from the Atrial Fibrillation and Ischaemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial has largely supported this recommendation (Supplementary material online).

Anticoagulation in patients with coronary syndromes or peripheral artery disease in sinus rhythm

The WArfarin Re-Infarction Study (WARIS) provided the first RCT evidence that an OAC, with or without concurrent aspirin, may offer protection against MACE, including stroke, in CCS/PAD patients without AF, but at the expense of excessive bleeding.[24] In the NOAC-era, an evidence-based option for secondary prevention of MACE in high-risk patients with CCS or symptomatic PAD, but without AF, is very-low-dose rivaroxaban in combination with low-dose aspirin. In the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) study, treatment with aspirin 100-mg once daily plus rivaroxaban 2.5-mg twice daily [low-dose dual antithrombotic therapy (DATT)] led to a significant reduction in the primary endpoint of MACE after a mean follow-up of 23 months, when compared to aspirin 100-mg once daily alone (*Tables 1 and 2*).[13] When compared with aspirin monotherapy, low-dose DATT appeared to have the strongest effect on cardioembolic stroke [HR = 0.40 (0.20-0.78), $P = 0.005$] or embolic stroke of undetermined source [0.30 (0.12-0.74), $P = 0.006$]. Benefits of low-dose DATT on stroke prevention appear present in subgroups with CAD or symptomatic PAD, including carotid disease. These data support use of low-dose DATT over aspirin alone in high-risk patients with CCS and/or symptomatic PAD, both in providing general anti-ischaemic protection but also specifically for stroke prevention. This is reflected in the current ESC CCS guidelines,[1] whereas the current PAD recommendations were last updated before the COMPASS results were known;[2] however, regional bodies such as the European Medicines Agency has approved low-dose DATT in symptomatic PAD as well as high-risk CCS. Recently, the Vascular Outcomes Study of Aspirin Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER-PAD) study has shown similar findings in a PAD population treated by revascularization (*Table 2*).[15]

In patients with PFO and CCS/PAD who have no prior history of stroke, there is no clear evidence that stroke risk is reduced by intensifying antithrombotic therapy beyond that already indicated for the underlying atherothrombotic disease.[4]

Other preventive therapies

Beyond antithrombotic therapy, a wide range of therapies and lifestyle interventions should be incorporated into the routine management of CCS and PAD patients for reducing the risk of stroke (*Figure 2* and Supplementary material online).

Conclusions

Patients with CCS/PAD are at increased risk of a range of ischaemic events, including stroke, with a significant overlap of risk factors and pathological mechanisms (*Figures 1 and 2*). Interventions targeting these factors and mechanisms present common therapeutic targets and have been exploited with good results. Overall, a holistic approach to aggressively manage risk factors (*Figure 2*), including addressing lifestyle aspects, is central to the management of patients with CCS/PAD to prevent the devastating complication of stroke.

Supplementary material

Supplementary material is available at *European Heart Journal Supplements* online.

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