Curr Treat Options Cardio Med (2019) 21: 78
DOI 10.1007/s11936-019-0778-4

Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Antithrombotic Management of Ischemic Stroke

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Published online: 3 December 2019

This article is part of the Topical Collection on *Cerebrovascular Disease and Stroke*

Keywords Ischemic stroke · Aspirin · Clopidogrel · Anticoagulation · Warfarin · Direct oral anticoagulants

Abstract

Purpose of review Ischemic stroke describes a condition in which inadequate blood flow leads to lack of oxygenation to the brain tissue and ensuing neuronal death. There are multiple causes of ischemic stroke, each of which may indicate different antithrombotic management strategies. The goal of this review is to provide information about antithrombotic therapies for secondary stroke prevention based on etiology of stroke.
Recent findings New studies of existing antiplatelet and antithrombotic therapies have demonstrated varied efficacies of treatments based on the underlying risk factor of ischemic stroke.
Summary Understanding the optimal therapies for secondary stroke prevention can enhance care of stroke patients and lower the incidence of recurrent cerebrovascular ischemia.

Introduction

Definition of ischemic stroke

Ischemic stroke is the result of lack of blood flow to the brain parenchyma, as opposed to hemorrhagic stroke which is due to bleeding into the brain tissue. The disruption of blood flow in ischemic stroke is usually due to thrombosis (in situ obstruction of the artery), embolism (thrombus originating from another site), hypoperfusion (systemic or focal low blood flow), or a combination thereof. The lack of blood flow to the brain in ischemic stroke culminates with tissue necrosis and subsequent neurological impairment.

Stroke subtypes

The outcome and recurrence of ischemic stroke differ distinctly by stroke subtype [1]. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial criteria categorize ischemic stroke based on etiology into five

categories: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology (Table 1) [2].

"Large-artery atherosclerosis" accounts for 15–20% of ischemic strokes [2, 3]. This refers to occlusion or stenosis of greater than 50% due to atheromatous plaque formation in a large artery intracranially (i.e., middle cerebral, anterior cerebral, vertebral, or basilar arteries) or extracranially (i.e., carotid or vertebral arteries). Risk factors include modifiable (e.g., hypertension, diabetes, dyslipidemia, smoking, alcohol misuse) and non-modifiable causes (e.g., age, sex, race). An often overlooked cause for cerebral ischemia in this category is aortic arch atheroma, especially when there is a complex protruding atherosclerotic plaque > 4 mm [4].

"Cardioembolism" accounts for up to 30% of ischemic strokes [3, 5]. This subtype describes ischemic stroke from an embolus that originates in the heart. The cardiac source can be due to valvular conditions (e.g., mitral stenosis, bioprosthetic or mechanical valve, thrombotic or non-thrombotic endocarditis, or cardiac tumors such as myxoma or fibroelastoma), thrombus formation (e.g., left atrial or ventricular thrombus), arrhythmia (atrial fibrillation, sick sinus syndrome, atrial flutter), or paradoxical embolism through a patent foramen ovale (PFO), with or without atrial septal aneurysm.

"Small-vessel occlusions" are also referred to as lacunar strokes with size of infarct < 20 mm on brain MRI diffusion-weighted imaging. These occlusions occur in the penetrating arteries supplying the deep structures of the brain and account for 25% of ischemic strokes [3, 6, 7]. Arteries become occluded because of chronic microatheroma formation or secondary to lipohyalinosis. Smoking, hypertension, and diabetes all contribute to microatheroma formation [8].

"Stroke of other determined etiology" refers to strokes caused by non-atherosclerotic vasculopathies (e.g., arterial dissections, reversible cerebral vasoconstriction syndromes, inflammatory vasculopathies, drug-induced vasculopathies), hematological disorders, or hypercoagulable states, and account for about 10% of ischemic strokes [2, 3]. Inherited thrombophilias (protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden, prothrombin G20210A mutation, and methylenetetrahydrofolate reductase [MTHFR] C677T mutation) are rare in adults with ischemic stroke. More common hypercoagulable states leading to ischemic strokes in adults are acquired conditions, such as hypercoagulability of malignancy and antiphospholipid antibody syndrome.

"Strokes of undetermined etiology" are otherwise known as cryptogenic strokes and account for about 6–15% of strokes [6, 7]. The work-up of these non-lacunar ischemic strokes demonstrates lack of extracranial or intracranial atherosclerosis causing ≥ 50% luminal stenosis, major-risk cardioembolic source of embolism or other causes of vasculopathy [9]. Embolic stroke of

Table 1. Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of subtypes of ischemic stroke

Subtype	Examples
Large-artery atherosclerosis	Carotid artery stenosis Vertebral artery stenosis Intracranial atherosclerosis of a large artery (e.g., basilar artery, middle cerebral artery)
Cardioembolism	Left ventricular thrombus Atrial fibrillation Prosthetic mechanical valve Mitral stenosis Congestive heart failure (EF < 40%)
Small-vessel occlusions	Microvascular disease Lacunar stroke
Stroke of other determined etiology	Non-atherosclerotic vasculopathies Hypercoagulability
Stroke of undetermined etiology	Two or more causes identified Negative or incomplete work-up Embolic stroke of undetermined source

undetermined source (ESUS) represents a recently defined construct within the category of cryptogenic strokes and is defined as non-lacunar brain infarcts without proximal cardioembolic or thrombotic sources; this type of stroke is the subject of active clinical trials in order to investigate the efficacy of systemic anticoagulation [9].

Antithrombotic strategy by stroke subtype (Table 2)

Large-artery atherosclerosis

Management of large-vessel atherosclerosis depends on whether or not the patient is symptomatic. In patients with asymptomatic extracranial internal carotid artery (ICA) ≥ 50% stenosis, population-based studies have demonstrated exceptionally low risk (< 1% per year) of transient ischemic attack (TIA) or ischemic stroke with optimal medical therapy [10]. These rates approximate the risk of periprocedural stroke seen in carotid interventional procedures [11].

To determine the therapeutic strategy that can best prevent stroke or death, the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study (CREST 2) is a NIH-sponsored study that is currently enrolling asymptomatic patients with 70 to 99% cervical ICA stenosis. This study consists of two parallel trials: carotid artery stenting with intensive medical management, versus intensive medical management alone; or carotid endarterectomy (CEA) with intensive medical management, versus intensive medical management alone [12].

For symptomatic extracranial ICA stenosis, the North American Symptomatic Carotid Endarterectomy trial (NASCET) in 1991 demonstrated that CEA was beneficial for patients with severe (70 to 99%) extracranial ICA stenosis after ipsilateral stroke or ocular and hemispheric TIA compared with medical therapy alone, with rate of stroke 9% versus 26% at 2 years, respectively [13].

Table 2. Suggested antithrombotic therapy based on ischemic stroke etiology

Therapy	Condition treated
Single antiplatelet agent	Lacunar stroke Embolic stroke of undetermined etiology Patent foramen ovale Extracranial carotid stenosis
Dual antiplatelet therapy	Intracranial atherosclerosis (3 months) Minor stroke/TIA (3-4 weeks)
Warfarin	Valvular atrial fibrillation Non-valvular atrial fibrillation Hypercoagulable states Prosthetic mechanical valve Congestive heart failure (EF < 40%)
Direct oral anticoagulants	Non-valvular atrial fibrillation Hypercoagulability (except antiphospholipid antibody syndrome) Congestive heart failure (EF < 40%)

Pooled analyses of clinical trials of management of patients with symptomatic extracranial ICA stenosis of 50 to 99% showed that the number needed to treat (NNT) to prevent one stroke was five for patients operated on within 2 weeks of ischemic stroke or TIA [14].

There is still uncertainty as to the optimal dose and type of antithrombotic to use in the setting of symptomatic extracranial ICA stenosis prior to surgical revascularization. A subsequent analysis of the NASCET trial, which focused on patients with moderate extracranial ICA stenosis (< 70%), showed higher rates of periprocedural stroke and death (8.3%) in patients receiving < 650 mg of aspirin daily, as opposed to 3.7% in those taking > 650 mg daily [15, 16]. In the Aspirin and Carotid Endarterectomy (ACE) trial of patients undergoing CEA with moderate to severe extracranial ICA stenosis (50–99%), doses of aspirin were studied in patients undergoing CEA: low dose (81 or 325 mg daily) and high dose (650 or 1300 mg daily). The combined rate of stroke, myocardial infarction, and death was significantly lower in the low-dose aspirin group than in the high-dose group at 3 months (6.2% vs. 8.4%, $p = 0.03$). Hemorrhagic stroke was more frequent in the high-dose group than in the low-dose group, but the difference was not statistically significant. Additionally, there was a trend towards improved secondary stroke prevention and reduced death with aspirin 325 mg versus 81 mg daily, with identical bleeding rates [16]. Dual antiplatelet therapy (DAPT) with aspirin 75 mg daily and clopidogrel 75 mg daily (after a 300 mg clopidogrel loading dose) has been shown to be beneficial over aspirin 75 mg daily in patients with symptomatic ICA stenosis > 50% for the reduction of microembolic events detected on transcranial doppler ultrasound and recurrent ipsilateral TIA and ischemic stroke over 7 days [17].

Practice patterns differ in terms of choice of antithrombotic therapy while awaiting endovascular intervention. Subgroup analysis of patients in the TOAST study who had hemispheric ischemic stroke secondary to occlusion or > 50% stenosis of the extracranial ICA showed that patients treated with danaparoid within 24 h of ischemic stroke had more favorable 3-month outcomes than those treated with placebo (68.3% vs. 53.2%, $p = 0.02$) [18]. A separate study also suggested that anticoagulation of an extracranial ICA occlusion decreases the incidence of recurrent stroke in the first week (6.7% vs. 38.9%, $p = 0.03$) and of recurrent stroke and death in the first month (13.3% vs. 47.1%, $p = 0.04$). In that study, ICA recanalization was significantly more frequent in patients who were anticoagulated compared with the patients that did not receive anticoagulation [19]. Of note, patients with ICA occlusions are not candidates for carotid endartectomy because of lack of benefit of CEA in this subgroup. It is our practice to initiate a short course of intravenous anticoagulation after complete extracranial ICA occlusion when safe, aiming to avoid intracranial propagation of fresh clot. We usually perform cerebrovascular scanning, either with CT angiography or carotid duplex ultrasound, after 3 months of anticoagulation in order to assess for recanalization. Neurology: Clinical Practice conducted a survey of practice patterns among neurologists regarding preoperative medical management of patients with symptomatic carotid stenosis awaiting intervention and found that antiplatelet monotherapy was used most frequently (44% of time). Survey responders noted that they would use heparin infusion as bridge to surgery if intraluminal thrombus (59%), ulcerated plaque (54%), and microembolic signals on Doppler (48%) were present [20].

Intracranial atherosclerotic disease (ICAD) is a significant contributor to ischemic stroke with marked racial and ethnic differences: the rate of stroke from ICAD is 33–54% in Asians, 9% in Caucasians, 12% in African Americans, and 15% in Hispanics [21, 22]. In patients with ischemic stroke or TIA caused by angiographically verified 50 to 99% stenosis of a major intracranial artery, the Warfarin and Aspirin for Symptomatic Intracranial Disease (WASID) trial compared high-dose aspirin (1300 mg daily) plus risk factor control with therapeutic warfarin for prevention of a combined endpoint of ischemic stroke, hemorrhagic stroke, or vascular death. The study showed no benefit with warfarin compared with aspirin for the primary endpoint; furthermore, the study was stopped early because of more complications in the anticoagulation arm, including death [23]. The Stenting and Aggressive Medical Management for Preventing Stroke in Intracranial Stenosis (SAMMPRIS) trial studied patients who had a TIA or stroke attributed to 70–99% stenosis of a major intracranial artery. The study demonstrated that DAPT (daily aspirin 325 mg plus clopidogrel 75 mg) for 3 months followed by daily aspirin 325 mg, and optimal medical management (systolic blood pressure target <140 mmHg for non-diabetics and < 130 mmHg for diabetics; lipid lowering for goal LDL-C < 70 mg/dL; and lifestyle modifications), was superior to stenting plus the same antiplatelet regimen and optimal medical management for the prevention of stroke or death within 30 days, or stroke in the territory of the diseased artery after 30 days [24]. At 1 year, this regimen of DAPT plus aggressive medical management resulted in significantly lower risk of the SAMMPRIS primary endpoint in SAMMPRIS medical patients (12.6%) compared with WASID patients (21.9%) meeting the same qualifying criteria. After adjustment for confounding baseline characteristics of the medical management groups in WASID and SAMMPRIS, there was still a 1.9-fold higher risk of the SAMMPRIS primary endpoint in the WASID medical arm, supporting the hypothesis that aggressive medical management in SAMMPRIS led to a lower risk of stroke in that study's medical management group [25]. Similarly, the Vertebral Artery Stenting trial found superiority of medical management over arterial stenting for patients with symptomatic posterior circulation ischemia due to > 50% stenosis of an intracranial or extracranial vertebral artery [26, 27].

Cardioembolism

Atrial fibrillation

Atrial fibrillation is a disorder of heart rhythm that affects 33 million people worldwide and can yield an annual stroke risk as high as 12% [28]. The CHA_2DS_2-VASc risk stratification tool aids in determining the benefit of anticoagulation for individual patients with atrial fibrillation [29]. In the absence of other risk factors for embolism such as congestive heart failure, hypertension, diabetes, prior stroke/TIA/systemic embolism, vascular disease, age > 65 years, and female sex, aspirin may be sufficient for the prevention of stroke and systemic embolism. However, the majority of patients with atrial fibrillation will require systemic anticoagulation. In non-valvular atrial fibrillation, direct oral anticoagulants (DOACs) were found to be equivalent to warfarin for reduction of the risk of stroke and systemic embolism and yield fewer hemorrhagic complications than warfarin [30, 31]. Patients with valvular atrial

fibrillation are often excluded from trials of DOACs versus warfarin. Therefore, the American Heart Association (AHA)/American College of Cardiology (ACC) still recommends anticoagulation with warfarin in patients with mitral stenosis and atrial fibrillation [32].

Congestive heart failure

Low ejection fraction and left ventricular dysfunction contribute to slow flow and blood stasis, likely contributing to the risk of intracardiac thrombus formation. The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial enrolled patients with sinus rhythm and cardiac ejection fraction of ≤ 35%. It demonstrated reduction of stroke risk in the warfarin group compared with the aspirin group at the 4th year of the trial. However, this benefit was offset by an increased risk of major hemorrhage in the warfarin arm [33]. More recently, the COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial examined rivaroxaban versus aspirin in patients with sinus rhythm and low cardiac ejection fraction of ≤ 40% and found no benefit of rivaroxaban over aspirin for the primary efficacy endpoint, including all-cause mortality, myocardial infarction, and stroke. However, post hoc analysis demonstrated lower rates of thromboembolic events in those on rivaroxaban [34•].

Prosthetic mechanical valve

The presence of prosthetic material in the heart presents an opportunity for thrombus formation and major cerebral or systemic embolism. Without antithrombotic therapy, the incidence rate of embolism is 8.6 per 100 patient-years [35]. Warfarin reduced this rate to 1.8 per 100 patient-years. The optimal international normalized ratio (INR) goal varies based on the location of the valve replacement: 2.0–3.0 for aortic valve and 2.5–3.5 for mitral valve. The RE-ALIGN trial (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) revealed higher incidence of thromboembolic events and bleeding in patients with mechanical valves receiving dabigatran compared with those receiving warfarin [36]. There is limited data on the use of DOACs in patients with bioprosthetic valves and atrial fibrillation, but the current data suggest similar rates of stroke in edoxaban compared with warfarin [37]. Because of the bleeding risk, antiplatelet therapy in addition to warfarin is not generally recommended by the vascular neurology community, especially if there is atrial fibrillation [38–40]. However, it is still recommended in the American College of Chest Physicians (ACCP) and the ACC/AHA guidelines [41].

Patent foramen ovale

PFO remains a controversial topic in ischemic stroke management. PFO is present in 25% of the population. Although no clear causal relationship has been demonstrated, the presence of PFO is more common in patients with cryptogenic ischemic stroke [42]. Initial trials (CLOSURE I, RESPECT) showed no benefit of closure of PFO over medical therapy for secondary

stroke prevention [43, 44]. In these trials, patients in the procedural arm were given clopidogrel 75 mg daily for 6 months and aspirin, 81 or 325 mg daily for 2 years. Patients in the medical arm were treated with warfarin (with a target INR of 2.0 to 3.0), aspirin (325 mg daily), or both, at the discretion of the principal investigator at each site. Recent studies (CLOSE, REDUCE, DEFENSE-PFO, Long Term Outcomes for RESPECT) have demonstrated lower rates of ischemic stroke in patients with cryptogenic strokes and PFO who undergo percutaneous PFO closure, compared with medical therapy alone. These studies included PFOs with or without high-risk characteristics such as atrial septal aneurysm, atrial septal hypermobility (septal excursion ≥ 10 mm), or PFO size (maximum separation of the septum primum from the secundum) ≥ 2 mm on transesophageal echocardiography [45•, 46, 47, 48]. A meta-analysis of databases of medically treated patients with cryptogenic stroke and PFO comparing antiplatelet and oral anticoagulant therapies demonstrated no difference between the two therapies in the prevention of a composite endpoint of stroke/TIA/death, or of stroke. Thus, unless there is another indication for systemic anticoagulation (e.g., venous thromboembolism, hypercoagulable state), antiplatelet therapy is usually recommended for patients with stroke or TIA and PFO treated medically or surgically [49].

Small-vessel occlusion

Lacunar strokes occur in small perforating (lenticulostriate) arteries supplying deep structures of the brain such as the basal ganglia, thalamus, internal capsule, and pons. Treatment of lacunar strokes is focused on optimization of vascular risk factors in addition to antiplatelet therapies. The Secondary Prevention of Small Subcortical Strokes (SPS3) study compared DAPT (aspirin 325 mg plus clopidogrel 75 mg daily) with aspirin 325 mg daily for secondary stroke prevention after lacunar infarction for the duration of the study (mean follow-up of 3.4 years). DAPT was not superior to aspirin monotherapy for prevention of recurrent stroke. Furthermore, DAPT nearly doubled the risk of major hemorrhage when compared with aspirin alone [50].

Stroke of other determined cause

Malignancy-related stroke

Up to 10% of ischemic stroke patients also have an underlying cancer [51]. Autopsy studies indicate that 15% of individuals with cancer were also found to have pathological evidence of stroke [52]. The most common etiologies of stroke in the cancer patient population are traditional cerebrovascular risk factors, but additional mechanisms of stroke in these patients include angioinvasive, hyperviscosity, tumor embolism, direct compression of tumor, and treatment-related effects [53, 54]. Although anticoagulation is generally used for secondary prevention of stroke, the data is largely based on trials of venous thromboembolism in cancer. Earlier studies have shown the benefit of low molecular weight heparin over vitamin K antagonists with similar rates of bleeding complications [55]. Recent studies of DOACs, including edoxaban and rivaroxaban, have shown non-inferiority and non-superiority, respectively, of these therapies over low molecular weight heparin [56••, 57].

Antiphospholipid antibody syndrome

Among women younger than 50 years of age, lupus anticoagulant antibodies were associated with ischemic stroke, especially in those who were taking oral contraceptives and those who were smokers [58]. To meet criteria for antiphospholipid antibody syndrome, any of the laboratory tests for APLAS (lupus anticoagulant, anticardiolipin IgG or IgM antibodies, or beta-2 glycoprotein IgG or IgM antibodies) must be positive at two time points at least 12 weeks apart in the presence of an arterial or venous thrombotic event and/or pregnancy morbidity, including fetal loss. Given the studies of non-inferiority of DOACs compared with warfarin in the cardioembolic stroke population, rivaroxaban 20 mg daily was compared with warfarin (goal INR 2.5) in high-risk patients with antiphospholipid antibody syndrome; the study was stopped prematurely due to an increased risk of arterial thrombosis and major bleeding in the rivaroxaban group [59].

Arterial dissection

Arterial dissection occurs when there is separation of the layers of an arterial wall and is more common in the cervical arteries. Dissection can occur spontaneously or secondary to minor or major cervical trauma or neck manipulation in 40% of cases [60]. Connective tissue disorders, most commonly fibromuscular dysplasia, have also been associated with increased incidence of arterial dissection of the cervical arteries [61]. In this setting many studies, including the Cervical Artery Dissection in Stroke Study (CADISS), have not shown overall differences in ischemic outcomes for patients treated with antiplatelets versus anticoagulation [61, 62, 63•]. A short course of heparin infusion followed by antiplatelet therapy can be considered for the first 3 to 4 days after an ischemic stroke due to an extradural arterial dissection if the infarct is small to moderate sized. This distinction is because the mean time to enrollment in the CADISS trial was 3.65 days, and patients who suffered an ischemic stroke or TIA before then were not included in the study. In patients with intradural extension of arterial dissection, the safety of anticoagulation is uncertain because a subset of these patients may have a higher risk of dissecting aneurysms with subarachnoid hemorrhage [64, 65]. The duration of antiplatelet use is unclear and provider-dependent. Some advocate discontinuation of antithrombotics after 3–6 months. It is our opinion that in cases of persistent arterial stenosis after dissection, recurrent or multiple dissections, or dissection associated with an underlying vasculopathy (e.g., fibromuscular dysplasia, Ehlers-Danlos syndrome or other connective tissue diseases), indefinite antiplatelet therapy should be considered.

Stroke of other undetermined cause or "cryptogenic"

Embolic stroke of undetermined source

The frequency of embolic stroke of undetermined source is uncertain but estimated to be between 6 and 15% of ischemic stroke cases [6, 7]. Because of the concern for possible cardiac origin of these emboli, anticoagulation with warfarin or DOACs has been postulated as a potential empiric therapy for stroke prevention. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) trial

evaluated aspirin versus warfarin in patients with any etiology of ischemic stroke except those with a known cardioembolic source and found no significant difference between aspirin and warfarin groups in terms of risk of recurrent ischemic stroke, death, or major hemorrhage [66]. However, in subgroup analysis, a benefit of warfarin over aspirin for secondary stroke prevention was noted in patients with elevated pro-B-type natriuretic peptide (> 750 pg/mL) without known atrial fibrillation [67]. The "New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source" (NAVIGATE ESUS) trial and the "Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source" (RE-SPECT ESUS) trial both demonstrated non-superiority of systemic anticoagulation, rivaroxaban, or dabigatran respectively, over aspirin in this patient population for prevention of stroke [68••, 69].

Special considerations in antithrombotic therapy

Several trials of secondary ischemic stroke prevention have demonstrated the efficacy of antiplatelet agents with slight variation in efficacy rates.

Antiplatelet monotherapy

Despite the widespread use of aspirin for prevention of stroke as well as other vascular diseases, there is still uncertainty as to the optimal dose. Meta-analyses of antiplatelet trials have demonstrated that low-dose aspirin (50–150 mg daily) is effective for long-term use in stroke prevention; in acute myocardial infarction or acute ischemic stroke, an initial loading dose may be required to reach the rapid antithrombotic effect [70–72]. The large CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) compared clopidogrel 75 mg daily with aspirin 325 mg daily for the prevention of a composite endpoint of vascular events. While there was an 8.7% relative risk reduction ($p = 0.043$) favoring clopidogrel, most of the benefit of clopidogrel over aspirin was due to its reduction in the risk of peripheral vascular disease [73]. The Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial showed no difference in the risk of stroke, myocardial infarction, or death within 90 days for patients with ischemic stroke or TIA receiving aspirin 100 mg daily, compared with those receiving ticagrelor 90 mg twice daily [74].

Dual antiplatelet therapy

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) compared aspirin plus dipyridamole with aspirin alone in the secondary prevention of minor ischemic stroke and TIA. The study found that combination aspirin/ dipyridamole was associated with an absolute risk reduction of 1% per year for the composite primary outcome of vascular mortality, non-fatal stroke, non-fatal myocardial infarction, or major bleeding (NNT 33) without significantly increasing the risk of hemorrhage, when compared with aspirin monotherapy [75]. Of note, 8.8% of the dipyridamole group discontinued the medication because of severe headaches. The Prevention

Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial found no difference in the primary outcome of any recurrent stroke (9.0% vs. 8.8%) or the composite secondary outcome of stroke, myocardial infarction, or cardiovascular death after ischemic stroke in patients receiving aspirin/extended-release dipyridamole versus clopidogrel, respectively [76].

Recent studies in stroke prevention have altered the landscape of DAPT for acute ischemic stroke. As noted above, a 3-month course of DAPT (aspirin 325 mg and clopidogrel 75 mg) has been described for intracranial atherosclerosis in the SAMMPRIS trial [24]. Additionally, several trials have assessed the value of DAPT immediately after ischemic stroke. The recent international Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial involved a clopidogrel load of 600 mg with aspirin (50–325 mg) followed by clopidogrel 75 mg and aspirin (50–325 mg) daily versus the same daily dose of aspirin. The study demonstrated reduction of stroke, myocardial infarction, or vascular death from 6.5% in the aspirin only group, to 5% in the DAPT group (HR 0.75) with the most benefit seen in the first 21 to 30 days [77••]. In the Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial which also assessed clopidogrel load (300 mg load + aspirin 75–300 mg) followed by aspirin 75 mg plus clopidogrel 75 mg daily for a total of 21 days of therapy versus aspirin 75 mg daily, there was stroke risk reduction with a short course of dual antiplatelet therapy that was not offset by the risk of intracranial hemorrhage in the first 21 days [78]. Additionally, a recent study looked at long-term DAPT for secondary prevention of stroke in patients with over 50% stenosis of a major intracranial or extracranial artery or two or more vascular risk factors. The study found that the combination of cilostazol 100 mg twice daily, plus aspirin (81 or 100 mg daily) or clopidogrel (50–75 mg daily) reduces ischemic stroke recurrence, compared with antiplatelet monotherapy with aspirin or clopidogrel. The risk of severe bleeding was similar in the monotherapy and DAPT groups [79••].

Combined therapies

Patients with atrial fibrillation can also have underlying cardiovascular disease that may require combined antiplatelet and anticoagulant therapies. COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) examined low-dose rivaroxaban (2.5 mg twice daily) plus aspirin 100 mg daily, versus rivaroxaban 5 mg twice daily, versus aspirin 100 mg daily for the secondary prevention of cardiovascular outcomes in patients with stable atherosclerotic disease. This trial found that patients on low-dose rivaroxaban plus aspirin had lower rates of ischemic stroke and other vascular endpoints at 23 months when compared with the other two groups [80•, 81]. PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) had previously demonstrated that in patients with atrial fibrillation undergoing percutaneous coronary intervention, the rates of in-stent thrombosis and stroke were equal among treatment groups with low-dose rivaroxaban plus single antiplatelet or DAPT, but that low-dose rivaroxaban plus monotherapy yielded significantly less hemorrhagic complications than warfarin plus DAPT [82]. WOEST (What is the Optimal

antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing trial) also revealed no benefit in patients on oral anticoagulation undergoing percutaneous coronary intervention treated with triple therapy (aspirin, clopidogrel, and anticoagulation) versus dual therapy (clopidogrel plus anticoagulation) [83].

Conclusion

Understanding ischemic stroke etiology can help guide antiplatelet and antithrombotic therapies in the secondary prevention of ischemic stroke. New studies are emerging to determine the optimal combination of therapies for stroke risk reduction without increased hemorrhagic side effects.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinical subtypes of cerebral infarction. Lancet. 1991;337:1521–6.
2. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.
3. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment Investigators. Stroke: a randomized controlled trial (danaparoid), and outcome after acute ischemic low molecular weight heparinoid, ORG 10172. JAMA. 1998;279(16):1265–72.
4. French Study of Aortic Plaques in Stroke Group, Amarenco P, Cohen A, Hommel M, Moulin T, Leys D, et al. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. N Engl J Med. 1996;334(19):1216–21.
5. Murtagh B, Smalling RW. Cardioembolic stroke. Curr Atheroscler Rep. 2006;8(4):310–6.
6. Schneider AT, Kissela B, Woo D, Kleindorfer D, Alwell K, Miller R, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. Stroke. 2004;35:1552–6.
7. Sudlow CLM, Warlow CP. Comparable studies of the incidence of stroke and its pathological types. Results from an international collaboration. Stroke. 1997;28:491–9.
8. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114(12):1852–66.
9. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429–38.
10. den Hartog AG, Achterberg S, Moll FL, Kappelle LJ, Visseren FL, van der Graaf Y, et al. Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. Stroke. 2013;44(4):1002–7.

11. Brott TG, Calvet D, Howard G, Gregson J, Algra A, Becquemin JP, et al. Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a preplanned pooled analysis of individual patient data. Lancet Neurol. 2019;18(4):348–56.
12. Mott M, Koroshetz W, Wright CB. CREST-2: identifying the best method of stroke prevention for carotid artery stenosis: National Institute of Neurological Disorders and Stroke Organizational Update. Stroke. 2017;48(5):e130–1.
13. North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325(7):445–53.
14. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet. 2004;363:915–24.
15. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med. 1998;339(20):1415–25.
16. Taylor DW, Barnett HJ, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Lancet. 1999;353(9171):2179–84.
17. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005;111(17):2233–40.
18. Adams HP Jr, Bendixen BH, Leira E, Chang KC, Davis PH, Woolson RF, et al. Antithrombotic treatment of ischemic stroke among patients with occlusion or severe stenosis of the internal carotid artery: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology. 1999;53(1):122–5.
19. Damania D, Kung NT, Jain M, Jain AR, Liew JA, Mangla R, et al. Factors associated with recurrent stroke and recanalization in patients presenting with isolated symptomatic carotid occlusion. Eur J Neurol. 2016;23(1):127–32.
20. Ganesh A, Wong JH, Menon BK. Practice current: how do you manage patients with a "hot carotid"? Neurol Clin Pract. 2018;8(6):527–36.
21. Battistella V, Elkind M. Intracranial atherosclerotic disease. Eur J Neurol. 2014;21(7):956–62.
22. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, et al. Ischemic stroke subtype incidence among Whites, Blacks, and Hispanics: the Northern Manhattan Study. Circulation. 2005;111(10):1327–31.
23. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352(13):1305–16.
24. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365(11):993–1003.
25. Chaturvedi S, Turan TN, Lynn MJ, Derdeyn CP, Fiorella D, Janis LS, et al. Do patient characteristics explain the differences in outcome between medically treated patients in SAMMPRIS and WASID? Stroke. 2015;46(9):2562–7.
26. Markus HS, Harshfield EL, Compter A, Kuker W, Kappelle LJ, Clifton A, et al. Stenting for symptomatic vertebral artery stenosis: a preplanned pooled individual patient data analysis. Lancet Neurol. 2019;18(7):666–73.
27. Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. Lancet Neurol. 2015;14(6):606–14.
28. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 Study. Circulation. 2014;129:837–47.
29. Ntaios G, Lip GY, Makaritsis K, Papavasileiou V, Vemmou A, Koroboki E, et al. $CHADS_2$, $CHA_2S_2DS_2$-VASc, and long-term stroke outcome in patients without atrial fibrillation. Neurology. 2013;80(11):1009–17.
30. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500–10.
31. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. Open Heart. 2016;3:e000279.
32. Baumgartner H, Falk V, Bax J, et al. ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017;2017:2939–91.
33. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366:1859–69.
34. • Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med. 2018;379:1332–42 Low ejection fraction has been considered an indication for systemic anticoagulation with warfarin based on the WARCEF

trial; this study demonstrates no benefit of rivaroxaban over aspirin in patients with ejection fraction < 40%.

35. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89(2):635–41.
36. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206–14.
37. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. Circulation. 2017;135(13):1273.
38. Flaker GC, Gruber M, Connolly SJ, Goldman S, Chaparro S, Vabanian A, et al. Risks and benefits of combining aspirin with anticoagulation therapy in patients with atrial fibrillation; an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTF) trials. Am Heart J. 2006;152:967–73.
39. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation; stroke prevention in atrial fibrillation III randomized clinical trial. Lancet. 1996;348:633–8.
40. Gullov AL, Koeford BG, Petersen P, Petersen TS, Andersen ED, Gottifredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs. adjusted-dose warfarin for stroke prevention in atrial fibrillation. Arch Int Med. 1998;158:1513–21.
41. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary: A report of the american college of Cardiology/American heart association task force on practice guidelines. Circulation. 2014;129:2440–92.
42. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med. 1988;318:1148–52.
43. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012;366(11):991–9.
44. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013;368(12):1092–100.
45. • Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377:1011–21

Studies of patent foramen ovale management, including RESPECT and CLOSURE I, previously showed no benefit of PFO closure for secondary stroke prevention. CLOSE, along with REDUCE, DEFENSE-PFO, Long Term Outcomes for RESPECT, have shown that in the right patient population (cryptogenic stroke with PFO), the intervention reduces recurrence of stroke.

46. Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017;377:1033–42.
47. Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, et al. Cryptogenic stroke and high-risk patent foramen ovale: the defense-PFO trial. J Am Coll Cardiol. 2018;71:2335–42.
48. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017;377(11):1022–32.
49. Kent DM, Dahabreh IJ, Ruthazer R, Furlan AJ, Weimar C, Serena J, et al. Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis. Eur Heart J. 2015;36(35):2381–9.
50. The SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012;367:817–25.
51. Navi BB, Reiner AS, Kamel H, Iadecola C, Elkind MS, Panageas KS, et al. Association between incident cancer and subsequent stroke. Ann Neurol. 2015;77(2):291–300.
52. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore). 1985;64:16–35.
53. Zhang YY, Cordato D, Shen Q, Sheng AZ, Hung WT, Chan DK. Risk factor, pattern, etiology and outcome in ischemic stroke patients with cancer: a nested case-control study. Cerebrovasc Dis. 2007;23(2–3):181–7.
54. Navi BB, Iadecola C. Ischemic stroke in cancer patients: a review of an underappreciated pathology. Ann Neurol. 2018;83:873–83.
55. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146–53.
56. •• Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for cancer-associated venous thromboembolism. N Engl J Med. 2018;378(7):615–24

Traditionally, hypercoagulability in malignancy has been treated with enoxaparin. This study demonstrated non-inferiority of edoxaban in this patient population.

57. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36(20):2017–23.
58. Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in

young women in the RATIO study: a case-control study. Lancet Neurol. 2009;8(11):998–1005.
59. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018;132(13):1365–71.
60. Engelter ST, Grond-Ginsbach C, Metso TM, Metso AJ, Kloss M, Debette S, et al. Cervical artery dissection: trauma and other potential mechanical trigger events. Neurology. 2013;80(21):1950–7.
61. Kennedy F, Lanfranconi S, Hicks C, Reid J, Gompertz P, Price C, et al. Antiplatelets vs anticoagulation for dissection: CADISS nonrandomized arm and meta-analysis. Neurology. 2012;79(7):686–9.
62. Chowdhury MM, Sabbagh CN, Jackson D, Coughlin PA, Ghosh J. Antithrombotic treatment for acute extracranial carotid artery dissections: a meta-analysis. Eur J Vasc Endovasc Surg. 2015;50(2):148–56.
63. • Markus HS, Levi C, King A, Madigan J, Norris J, Cervical Artery Dissection in Stroke Study (CADISS) Investigators. Antiplatelet Therapy vs Anticoagulation Therapy in Cervical Artery Dissection: The Cervical Artery Dissection in Stroke Study (CADISS) Randomized Clinical Trial Final Results. JAMA Neurol. 2019;76(6):657–64 Practice patterns have varied regarding therapy for acute cervical arterial dissection, ranging from single antiplatelet to dual antiplatelet to anticoagulation with warfarin. This study found no difference in direct comparison of aspirin and warfarin for prevention of stroke after cervical arterial dissection, potentially sparing patients from unnecessary anticoagulation.
64. Metso TM, Metso AJ, Helenius J, Haapaniemi E, Salonen O, Porras M, et al. Prognosis and safety of anticoagulation in intracranial artery dissections in adults. Stroke. 2007;38(6):1837–42.
65. Ono H, Nakatomi H, Tsutsumi K, Inoue T, Teraoka A, Yoshimoto Y, et al. Symptomatic recurrence of intracranial arterial dissections: follow-up study of 143 consecutive cases and pathological investigation. Stroke. 2013;44(1):126–31.
66. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345(20):1444–51.
67. Longstreth WT Jr, Kronmal RA, Thompson JL, Christenson RH, Levine SR, Gross R, et al. Amino terminal pro-B-type natriuretic peptide, secondary stroke prevention, and choice of antithrombotic therapy. Stroke. 2013;44(3):714–9.
68. •• Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med. 2019;380(20):1906–17
In many patients with embolic stroke of undetermined source, the suspicion for atrial fibrillation is high, but it remains undetected. Given that atrial fibrillation is such a strong indication for anticoagulation, prior to this study (along with NAVIGATE), it was uncertain whether or not patients with suspected cardioembolic source should be placed on systemic anticoagulation. This trial demonstrates non-superiority of anticoagulation over aspirin in the management of patients with cerebral embolism of uncertain etiology.
69. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med. 2018;378(23):2191–201.
70. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71.
71. Hennekens CH, Sechenova O, Hollar D, Serebruany VL. Dose of aspirin in the treatment and prevention of cardiovascular disease: current and future directions. J Cardiovasc Pharmacol Ther. 2006;11(3):170–6.
72. Johnson ES, Lanes SF, Wentworth CE 3rd, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose-response effect of aspirin on stroke. Arch Intern Med. 1999;159(11):1248–53.
73. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348(9038):1329–39.
74. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med. 2016;375(1):35–43.
75. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet. 2006;367(9523):1665–73.
76. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008;359(12):1238–51.
77. •• Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med. 2018;379(3):215–25
While previous studies had suggested that dual antiplatelet therapy conferred a high risk of intracranial hemorrhage for the benefit of stroke risk reduction, this study demonstrated that short-term use of aspirin and clopidogrel in patients with minor stroke or transient ischemic attack can be safe and effective.
78. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11–9.
79. •• Toyoda K, Uchiyama S, Yamaguchi T, Easton JD, Kimura K, Hoshino H, et al. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial. Lancet Neurol. 2019;18(6):539–48
Previous studies of dual antiplatelet therapy have primarily used aspirin, clopidogrel or ticagrelor and have shown high risk of bleeding complications with long-term use. This study

reveals benefit of stroke risk reduction without increased bleeding complications in long-term dual antiplatelet therapy using cilostazol.

80. • Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377(14):1319–30

This study demonstrates that combination of low-dose rivaroxaban plus aspirin conferred a lower ischemic stroke risk than high-dose rivaroxaban plus aspirin or aspirin alone in patients with cardiovascular disease requiring antithrombotic therapy.

81. Sharma M, Hart RG, Connolly SJ, Bosch J, Shestakovska O, Ng KKH, et al. Stroke outcomes in the COMPASS Trial. Circulation. 2019;139(9):1134–45.

82. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med. 2016;375(25):2423–34.

83. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381(9872):1107–15.

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