Overview of secondary prevention for specific causes of ischemic stroke and transient ischemic attack

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INTRODUCTION

This topic will review the treatment of specific causes of transient ischemic attack (TIA) and ischemic stroke where the potential cause has been identified, emphasizing secondary prevention of recurrent cerebral ischemia and other vascular events. Risk factor management, which is appropriate for all patients with ischemic stroke or TIA, is reviewed in detail elsewhere. (See "Overview of secondary prevention of ischemic stroke".)

The initial assessment of patients with cerebral ischemia and acute therapy for ischemic stroke are discussed separately. (See "Initial assessment and management of acute stroke" and "Approach to reperfusion therapy for acute ischemic stroke" and "Early antithrombotic treatment of acute ischemic stroke and transient ischemic attack".)

MEDICAL THERAPY

Most patients with an ischemic stroke or TIA should be treated with all available risk reduction strategies, including antithrombotic therapy (algorithm 1 and algorithm 2), blood pressure reduction, low-density lipoprotein lowering therapy, and lifestyle modification. These strategies are reviewed in detail separately:

- Overview of secondary prevention of ischemic stroke
- Early antithrombotic treatment of acute ischemic stroke and transient ischemic attack
- Long-term antithrombotic therapy for the secondary prevention of ischemic stroke
- Antihypertensive therapy for secondary stroke prevention

LARGE ARTERY DISEASE

Options for the secondary prevention of ischemic stroke or TIA caused by large artery disease include revascularization for symptomatic internal carotid artery stenosis due to atherosclerosis, and multifactorial risk reduction including treatment with antiplatelet agents, blood pressure control, and low-density lipoprotein cholesterol (LDL-C) lowering therapy. The role of anticoagulation in this setting is quite limited. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke".)

Some specific situations are discussed below for atheromatous carotid, vertebral, and intracranial disease, and for nonatheromatous causes including carotid web, dissection, fibromuscular dysplasia, and moyamoya.

Symptomatic carotid stenosis — The treatment of symptomatic extracranial carotid atherosclerotic disease requires intensive medical management and may include carotid revascularization with carotid endarterectomy or carotid artery stenting. The importance of medical management, the identification of patients likely to benefit from revascularization, and the choice of revascularization procedure are discussed in detail separately. (See "Management of symptomatic carotid atherosclerotic disease".)

Carotid occlusion — Carotid artery occlusion may occur without clear symptoms, but it can be associated with TIA and stroke. Older data suggest that the subsequent yearly risk of a stroke ipsilateral to the occluded carotid artery is 2 to 5 percent [1,2]; later retrospective data suggest that the rate of early neurologic deterioration or recurrent stroke after symptomatic carotid occlusion ranges from 8 to 30 percent [3].

In most cases, medical management is the only practical option in the setting of chronic carotid occlusion. Data from small observational studies suggest that recanalization can be achieved by stenting of extracranial carotid artery occlusion [4], but clinical benefit is uncertain. Surgical revascularization is a viable option only when residual flow can be demonstrated in the internal carotid artery (ie, near occlusion), but efficacy is likewise unproven. (See "Management of symptomatic carotid atherosclerotic disease", section on 'Patients unlikely to benefit'.)

With acute ischemic stroke related to extracranial internal carotid artery occlusion and a tandem intracranial large artery occlusion, treatment options include acute stenting and/or angioplasty of the extracranial carotid artery combined with mechanical thrombectomy of the intracranial occlusion. (See "Mechanical thrombectomy for acute ischemic stroke", section on 'Approach to tandem lesions'.)

For isolated acute symptomatic internal carotid artery occlusion, the optimal treatment is uncertain. Limited retrospective data from small observational studies suggest that urgent stenting results in a high revascularization rate, but benefit is unproven [5]. More data are needed to determine whether early secondary prevention with endovascular treatment improves outcomes compared with maximal medical therapy [3].

Historically, some experts used short-term (three to six months) anticoagulation for acute symptomatic occlusion; the rationale for this approach is based on limited evidence that emboli may form and propagate from the stump of the occluded artery after acute occlusion [6,7], but the risk and benefit of such an approach, particularly when compared with dual antiplatelet therapy, remains uncertain. An earlier randomized, controlled trial in patients with symptomatic carotid narrowing or occlusion found that surgical treatment using extracranial to intracranial bypass failed to reduce the risk of ischemic stroke [8], and the later Carotid Occlusion Surgery Study (COSS) trial in patients with symptomatic carotid occlusion and hemodynamic cerebral ischemia also found no benefit for extracranial to intracranial bypass surgery compared with medical therapy alone [9].

Carotid web — Carotid web, considered a variant of fibromuscular dysplasia (see 'Fibromuscular dysplasia' below), is a shelf-like projection of intimal fibrous tissue of the internal carotid artery bulb that can be focal or multifocal [10]. It may appear as a filling defect on computed tomographic angiography, magnetic resonance angiography, or conventional contrast angiography (eg, digital subtraction angiography) [11,12].

Carotid web is rarely associated with severe stenosis. However, carotid web may alter hemodynamic flow and increase the risk of platelet aggregation leading to thromboembolism [13].

The optimal management of symptomatic carotid web is uncertain. The 2021 American Heart Association/American Stroke Association guidelines recommend antiplatelet therapy for secondary stroke prevention [14]. The guidelines also note that the risk of recurrent stroke in medically treated patients with symptomatic carotid web is high, and carotid stenting or endarterectomy may be considered to prevent recurrent events, particularly in patients who have a recurrent ischemic stroke despite medical treatment.

Extracranial vertebral artery stenosis — In most cases, prevention of ischemic stroke and TIA due to extracranial vertebral artery stenosis is managed by intensive medical treatment and multifactorial risk reduction, including the use of antiplatelet agents (algorithm 1 and algorithm 2), antihypertensive drugs, and LDL-C lowering therapy [14]. In addition, angioplasty and stenting is a treatment option [15-18], and surgical transposition of the vertebral artery to the common carotid artery is another alternative for vertebral origin stenosis. However, efficacy for these procedures is uncertain [14,18,19]. In an analysis that pooled individual patient data from three trials comparing stenting with medical treatment for the subgroup with symptomatic extracranial vertebral artery stenosis, there was no significant difference in the risk of any stroke in the stenting group compared with the medical treatment group (hazard ratio [HR] 0.63, 95% CI 0.27-1.46) [18]. Thus, extracranial vertebral artery revascularization is generally considered only when maximal medical therapy has failed to prevent embolism or low-flow recurrent ischemic events.

Intracranial large artery atherosclerosis — Atherosclerotic stenosis of the major intracranial arteries (carotid siphon, middle cerebral artery, vertebral artery, and basilar artery) is an important cause of ischemic stroke, particularly in Black, Asian, and Hispanic populations.

Patients with TIA or ischemic stroke attributed to intracranial atherosclerosis should receive intensive medical management with antiplatelet therapy (algorithm 1 and algorithm 2) and strict control of vascular risk factors, including the blood pressure control, LDL-C lowering therapy, and physical activity and other lifestyle modification (eg, smoking cessation, weight control, salt restriction, and a healthy diet). (See "Intracranial large artery atherosclerosis: Treatment and prognosis", section on 'Secondary prevention'.)

Evidence from randomized controlled trials indicates that intensive medical management is superior to stenting for patients with recently symptomatic high-grade intracranial large artery stenosis [20]. (See "Intracranial large artery atherosclerosis: Treatment and prognosis", section on 'Stenting'.)

Dissection — Beyond the hyperacute period, antithrombotic therapy with either anticoagulation or antiplatelet drugs is an accepted treatment for ischemic stroke and TIA caused by dissection, although there is controversy regarding the choice between the two. The management of cerebral and cervical artery dissection is reviewed in detail separately. (See "Cerebral and cervical artery dissection: Treatment and prognosis".)

Fibromuscular dysplasia — Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic disorder that leads to arterial stenosis, occlusion, intraluminal thrombus, aneurysm, dissection, and arterial tortuosity [21]. The most frequently involved arteries are the

renal and internal carotid arteries, followed by the vertebral, visceral, and external iliac arteries. Disease presentation may vary widely, depending upon the arterial segment involved and the severity of disease. TIA and ischemic stroke are potential manifestations of carotid or vertebral artery FMD; hypertension is the most common presenting sign of renal artery FMD. (See "Clinical manifestations and diagnosis of fibromuscular dysplasia".)

In patients with an ischemic stroke or TIA attributed to FMD, secondary prevention measures include antiplatelet therapy, blood pressure control, and lifestyle modification [14]. For patients with recurrent ischemic stroke or TIA attributed to carotid artery FMD, treatment using angioplasty with or without stenting is an option [14].

Moyamoya — Moyamoya disease (MMD) is a unique cerebrovascular disorder characterized by progressive large intracranial artery narrowing and the development of prominent small vessel collaterals in patients who may have genetic susceptibilities but no underlying risk factors. Moyamoya syndrome (MMS) refers to patients with moyamoya angiographic findings who also have an associated medical condition. (See "Moyamoya disease and moyamoya syndrome: Etiology, clinical features, and diagnosis", section on 'Classification and terminology'.)

Ischemic stroke and TIA affecting the anterior circulation are the most common clinical presentations. Hemorrhagic complications of moyamoya, mainly intracerebral hemorrhage, represent a significant clinical burden, particularly in adults. (See "Moyamoya disease and moyamoya syndrome: Etiology, clinical features, and diagnosis", section on 'Clinical presentations'.)

Secondary stroke prevention for patients with symptomatic moyamoya is largely centered on surgical revascularization techniques. Antiplatelet therapy is reasonable [14], but evidence regarding clinical benefit is limited. In adults, hemorrhage may be the predominant manifestation of moyamoya, and anticoagulation is generally not recommended. (See "Moyamoya disease and moyamoya syndrome: Treatment and prognosis".)

For children and adults with asymptomatic or symptomatic ischemic MMD or MMS, some experts use long-term therapy with aspirin or cilostazol. This also applies to patients who undergo surgical revascularization.

Rotational vertebral artery syndrome (bow hunter) — Rotational vertebral artery syndrome is a rare cause of posterior circulation stroke due to vertebral artery compression by bony elements of the cervical spine (usually at C1 to C2) during physiologic head rotation. Antithrombotic therapy is reasonable in patients with ischemic stroke or TIA, and surgical interventions may be considered in patients who have recurrent ischemic symptoms while on antithrombotic treatment. (See "Posterior circulation cerebrovascular syndromes", section on

'Extracranial vertebral arteries' and "Causes of vertigo", section on 'Rotational vertebral artery syndrome'.)

SMALL ARTERY DISEASE

Cerebral small artery disease, often referred to as small vessel disease, may cause a TIA or lacunar infarction due to the occlusion of a small penetrating branch of a large cerebral artery. (See "Lacunar infarcts".)

Early antiplatelet therapy is indicated for most patients with TIA or acute ischemic stroke due to small artery disease who are not receiving oral anticoagulants, as shown in the algorithms (algorithm 1 and algorithm 2). In the acute setting, most patients with a low-risk TIA or moderate to major ischemic stroke are treated with aspirin alone; patients with a high-risk TIA or minor ischemic stroke may benefit from dual antiplatelet therapy using aspirin and clopidogrel for 21 days rather than aspirin alone. (See "Early antithrombotic treatment of acute ischemic stroke and transient ischemic attack", section on 'Efficacy of DAPT'.)

Beyond the acute phase of stroke, long-term antiplatelet therapy for secondary stroke prevention should be continued with either aspirin, clopidogrel, or the combination of aspirin-extended-release dipyridamole, although use of the latter has become increasingly rare in practice. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke".)

In addition to antiplatelet therapy, attention to hypertension, serum lipids, blood glucose, and other modifiable risk factors is important for preventing lacunar strokes in patients with small artery disease. (See "Overview of secondary prevention of ischemic stroke".)

CARDIOGENIC EMBOLISM

Cardiogenic embolism is responsible for 14 to 30 percent of ischemic strokes [22]. In addition to atrial fibrillation, cardiac sources of embolism for which anticoagulation therapy may be indicated include left ventricular thrombus, cardiomyopathy, valvular disease, and congenital heart disease [14].

Minor potential sources of cardiogenic embolism include patent foramen ovale (PFO), left ventricular regional wall motion abnormalities, severe mitral annular calcification, mitral valve prolapse, mitral valve strands, and aortic valve disease (table 1) [23]. The risk of stroke

associated with these sources is low or uncertain, and except for PFO, the efficacy of and need for specific treatment is undefined [24].

Atrial fibrillation — Atrial fibrillation is a major risk factor for ischemic stroke. Anticoagulation with one of the direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, or edoxaban) or warfarin is the most effective treatment to reduce stroke risk [14]. In most patients with atrial fibrillation, DOACs are preferred over warfarin due to convenience and lower risk of intracranial hemorrhage [25]. This subject is reviewed in greater detail elsewhere. (See "Stroke in patients with atrial fibrillation" and "Atrial fibrillation in adults: Use of oral anticoagulants".)

For secondary stroke prevention, virtually all patients with atrial fibrillation who have a history of stroke or TIA of cardioembolic origin should be treated with lifelong anticoagulation in the absence of contraindications. (See "Stroke in patients with atrial fibrillation", section on 'Long-term anticoagulation'.)

Placement of a left atrial appendage occlusion device may be an option for patients with nonvalvular atrial fibrillation who have a contraindication to long-term anticoagulation or strong preference to avoid long-term anticoagulation. (See "Atrial fibrillation: Left atrial appendage occlusion".)

In rare cases when the patient is unwilling or unable to take anticoagulation despite careful consideration of the advantages of oral anticoagulation, or is not a candidate for left atrial appendage occlusion device placement, dual antiplatelet therapy is an alternative to therapy with aspirin alone. This issue is discussed in detail separately. (See "Atrial fibrillation in adults: Selection of candidates for anticoagulation", section on 'Alternatives to anticoagulation'.)

Cardiac tumors — Cardiac tumors, mainly left-sided myxoma and fibroelastoma, are rare causes of cardioembolic TIA or ischemic stroke. Surgical tumor resection via open heart surgery is the main treatment option to prevent recurrent stroke [14]. (See "Cardiac tumors".)

Congenital heart disease — Patients with cyanotic congenital heart disease are at increased risk for thromboembolism. The 2021 American Heart Association (AHA)/American Stroke Association (ASA) guidelines state that it is reasonable to treat patients with cardioembolic ischemic stroke or TIA attributed to congenital heart disease with warfarin anticoagulation [14]. (See "Medical management of cyanotic congenital heart disease in adults", section on 'Thromboembolism'.)

The Fontan procedure is a palliative operation that diverts systemic venous return to the lungs in patients with an anatomic or functional single ventricle. For patients with Fontan circulation

who have a history of thromboembolism, warfarin anticoagulation is advised [14]. (See "Overview of the management and prognosis of patients with Fontan circulation" and "Management of complications in patients with Fontan circulation", section on 'Thrombosis'.)

Cardiomyopathy — For patients in sinus rhythm with prior ischemic stroke or TIA who have either dilated cardiomyopathy (left ventricular ejection fraction ≤35 percent) or restrictive cardiomyopathy, and without evidence of left atrial or left ventricular thrombus, the 2021 AHA/ASA guidelines note that the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized [14]. The role of antithrombotic treatment for individuals with heart failure and prior thromboembolic events is reviewed in greater detail elsewhere. (See "Antithrombotic therapy in patients with heart failure".)

Left ventricular thrombus — Patients with left ventricular thrombus in the specific setting of an acute myocardial infarction have a significantly increased risk of embolic events. The 2021 American Heart Association/American Stroke Association guidelines state that patients with ischemic stroke or TIA in the setting of a left ventricular mural thrombus should be treated with warfarin (target international normalized ratio 2.5; range 2 to 3) for at least three months [14]. Despite very limited supporting evidence, some experts consider using a DOAC rather than warfarin due to convenience, as long as there is no specific indication for warfarin (eg, prosthetic heart valve).

The issue of left ventricular thrombus and acute myocardial infarction is discussed in greater detail separately. (See "Left ventricular thrombus after acute myocardial infarction".)

Patent foramen ovale — Patent foramen ovale (PFO) device closure is more effective than medical therapy alone for select patients with a PFO-associated stroke (ie, a nonlacunar ischemic stroke in the setting of a PFO with a right-to-left interatrial shunt and no other source of stroke despite a comprehensive evaluation). Evaluation and treatment are discussed in detail separately. (See "Stroke associated with patent foramen ovale (PFO): Evaluation".)

Valvular disease

- **With atrial fibrillation** – Patients with atrial fibrillation and valvular heart disease should be treated with oral anticoagulation. The choice between warfarin and DOAC therapy depends upon the type of underlying valvular disease; warfarin is generally preferred for patients with atrial fibrillation and moderate to severe mitral stenosis or a mechanical heart valve, while a DOAC may be preferred for patients with atrial fibrillation and other types of valvular disease (eg, mild mitral stenosis, bioprosthetic valves, or native aortic, pulmonary, or tricuspid valve disease) [14]. (See "Atrial fibrillation in adults: Use of oral

anticoagulants", section on 'Patients with valvular heart disease' and "Rheumatic mitral stenosis: Overview of management", section on 'Prevention of thromboembolism'.)

- **Without atrial fibrillation** – For patients in sinus rhythm with ischemic stroke or TIA and native valvular disease or bioprosthetic heart valves, the 2021 AHA/ASA guidelines recommend antiplatelet therapy [14]. This includes patients with mitral annular calcification or mitral valve prolapse.

  The 2021 AHA/ASA guidelines state that the role of oral anticoagulation has not been adequately studied for patients who have rheumatic mitral valve disease without atrial fibrillation and no other likely cause for ischemic stroke or TIA [14]. However, some experts consider a prior embolic event in patients with moderate to severe mitral stenosis as one of the indications for long-term oral anticoagulation with a vitamin K antagonist. (See "Rheumatic mitral stenosis: Overview of management", section on 'Prevention of thromboembolism'.)

  Note that paroxysmal occult atrial fibrillation and infective endocarditis should be considered as potential causes when embolization occurs in patients with mitral stenosis who are in sinus rhythm.

  Mitral and aortic valvular disease is reviewed in greater detail elsewhere. (See "Clinical manifestations and diagnosis of mitral annular calcification" and "Clinical manifestations and diagnosis of aortic stenosis in adults", section on 'Embolic events' and "Mitral valve prolapse: Overview of complications and their management", section on 'Ischemic neurologic events'.)

- **Mechanical heart valves** – All prosthetic heart valves require antithrombotic prophylaxis [14,26]. Antithrombotic therapy for mechanical and bioprosthetic heart valves is discussed in detail separately. (See "Antithrombotic therapy for mechanical heart valves" and "Overview of the management of patients with prosthetic heart valves", section on 'Antithrombotic therapy'.)

- **Infective endocarditis** – Infective endocarditis is an important cause of embolic stroke and TIA for which anticoagulation is hazardous. Endocarditis must be excluded in any patient with a TIA or stroke and other suggestive findings such as fever and a heart murmur.

  Treatment consists of antibiotic therapy for the infection. Early valve surgery is indicated for patients with left-sided native valve infective endocarditis and one or more additional features, including symptoms or signs of heart failure, complicated infection, persistent

infection, and/or recurrent embolic events. (See "Clinical manifestations and evaluation of adults with suspected left-sided native valve endocarditis" and "Antimicrobial therapy of left-sided native valve endocarditis" and "Antithrombotic therapy in patients with infective endocarditis".).

AORTIC ATHEROSCLEROSIS

There are conflicting data regarding the stroke risk associated with aortic atherosclerosis. However, most reports evaluating secondary stroke risk have found that complex aortic atherosclerosis is a risk factor for recurrent stroke, especially for aortic plaques ≥4 mm and mobile plaques. This issue is discussed separately. (See "Stroke: Etiology, classification, and epidemiology", section on 'Aortic atherosclerosis'.)

The optimal treatment for patients with stroke or TIA attributed to aortic disease is not clear; the 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend antiplatelet therapy (including short-term dual antiplatelet therapy for minor stroke) and intensive lipid management to a low-density lipoprotein cholesterol target <70 mg/dL to prevent recurrent stroke [14].

Medical therapy for secondary prevention of aortic atheromatous disease is discussed in greater detail separately. (See "Thromboembolism from aortic plaque", section on 'Treatment'.)

The open-label ARCH trial was terminated prematurely due to slow recruitment and is therefore inconclusive [27]. The ARCH trial enrolled 349 adults with ischemic stroke, TIA, or peripheral embolism who had thoracic aortic plaque ≥4 mm and no other identified embolic source; patients were randomly assigned to treatment with dual antiplatelet therapy (aspirin 75 to 150 mg daily in combination with clopidogrel 75 mg daily) or warfarin (target international normalized ratio 2.5). At a median follow-up of 3.4 years, the primary endpoint, a composite of cerebral infarction, myocardial infarction, peripheral embolism, vascular death, or intracranial hemorrhage, was lower in the antiplatelet group compared with the warfarin group (7.6 versus 11.3 percent, respectively), but the difference was not statistically significant (adjusted hazard ratio 0.76, 95% CI 0.36-1.61).

SICKLE CELL DISEASE

Stroke is a frequent complication of sickle cell disease (SCD), and the risk of recurrent stroke is high. Stroke risk can be reduced with chronic transfusion therapy. (See "Acute stroke (ischemic

and hemorrhagic) in children and adults with sickle cell disease" and "Prevention of stroke (initial or recurrent) in sickle cell disease".)

For patients with SCD and ischemic stroke or TIA, the 2014 American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend regular blood transfusions to reduce hemoglobin S to <30 percent of total hemoglobin [14]. In addition, the guidelines note that treatment with hydroxyurea is reasonable if transfusion therapy is not available or practical. General measures including traditional stroke risk factor identification and management as well as the use of antiplatelet agents (for prior ischemic stroke) are also reasonable.

The prevention of stroke in patients with SCD is discussed in greater detail separately. (See "Prevention of stroke (initial or recurrent) in sickle cell disease".)

HYPERCOAGULABLE STATES

Antiphospholipid syndrome — The antiphospholipid syndrome (APS) is a hypercoagulable state characterized by recurrent arterial or venous thromboembolism, or pregnancy loss, in association with antibodies directed against plasma proteins that may be bound to anionic phospholipids. The presence of such antibodies may be detected as lupus anticoagulants, anticardiolipin antibodies, or anti-beta2 glycoprotein-I antibodies. (See "Diagnosis of antiphospholipid syndrome".)

This disorder has been referred to as primary antiphospholipid syndrome when it occurs alone; however, it can also be seen in association with systemic lupus erythematosus, other rheumatic disorders, and autoimmune diseases. (See "Clinical manifestations of antiphospholipid syndrome".)

Due to the high rate of recurrent thrombosis, long-term anticoagulation is the mainstay of therapy for patients with thrombotic APS. However, for patients with arterial thromboembolism, including ischemic stroke, data on the optimal therapeutic approach to prevent recurrent thromboembolism are limited. While experts agree that anticoagulation with warfarin (international normalized ratio range, 2 to 3) is the first-line therapy for patients with APS and arterial thromboembolism, some suggest adding low-dose aspirin for most patients with arterial events, particularly those with additional risk factors for atherosclerotic vascular disease. Direct oral anticoagulants (DOACs) may be less effective than warfarin for thrombosis prevention, particularly among patients with known or possible APL who are considered high

risk and/or have a history of arterial thrombosis. (See "Management of antiphospholipid syndrome", section on 'Secondary thrombosis prevention'.)

Inherited thrombophilias — Inherited thrombophilias are hypercoagulable states that include a number of disorders:

- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Activated protein C resistance
- Factor V Leiden as a cause of activated protein C resistance
- Prothrombin G20210A mutation

These conditions are thought to be rare causes of ischemic stroke in adults, but may be more important causes of ischemic stroke in children. (See "Ischemic stroke in children and young adults: Epidemiology, etiology, and risk factors", section on 'Hematologic'.)

The 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines note that it is uncertain whether testing for these hematologic traits is beneficial in the context of secondary stroke prevention [14]. Suspicion for hypercoagulable states as the cause of stroke may be heightened in younger patients with cryptogenic stroke, a history or family history of unprovoked thrombosis, prior spontaneous abortion, or concomitant systemic signs and symptoms suggestive of hypercoagulability. The same guidelines note that for patients with ischemic stroke or TIA of unknown source (despite a thorough diagnostic evaluation) who are found to have an inherited thrombophilia, antiplatelet treatment is reasonable to reduce the risk of recurrent stroke or TIA [14].

The evaluation and management of these conditions is discussed in greater detail separately. (See "Antithrombin deficiency" and "Protein C deficiency" and "Protein S deficiency" and "Factor V Leiden and activated protein C resistance" and "Prothrombin G20210A" and "Overview of homocysteine" and "Cerebral venous thrombosis: Treatment and prognosis".)

Cancer-related hypercoagulable state — Patients with cancer may be at increased risk for stroke due to hypercoagulability and other potential mechanisms, including compression or invasion of blood vessels, marantic endocarditis, infections, paraneoplastic disorders, and complications of cancer therapies [28,29]. (See "Cancer-associated hypercoagulable state: Causes and mechanisms".)

For patients with TIA or ischemic stroke attributed to cancer hypercoagulability, optimal treatment for secondary stroke prevention is unknown, and data are limited [29]. Empiric

treatment with low molecular weight heparin is often used, but the clinical risk and benefit compared with antiplatelets remains uncertain [30]. In patients with venous thromboembolism (VTE) and cancer, anticoagulant therapy is the mainstay of treatment. Low molecular weight heparin or DOACs are preferred in patients without renal insufficiency, whereas warfarin is the preferred treatment in patients with renal insufficiency (eg, creatinine clearance <30 mL/minute). (See "Anticoagulation therapy for venous thromboembolism (lower extremity venous thrombosis and pulmonary embolism) in adult patients with malignancy".)

The 2021 AHA/ASA guidelines note only that in the setting of atrial fibrillation and cancer, it is reasonable to consider anticoagulation with DOACs in preference to warfarin for stroke prevention [14].

CRYPTOGENIC STROKE

Cryptogenic stroke is variably defined and generally designates the category of brain infarction that is not attributed to an established source of cardioembolism, large artery atherosclerosis, small artery disease, or other determined cause of stroke. However, the term cryptogenic stroke has been applied to patients with an incomplete diagnostic evaluation, a complete but unrevealing evaluation, or an evaluation that identifies multiple potential causes of stroke. (See "Cryptogenic stroke and embolic stroke of undetermined source (ESUS)", section on 'Classification'.)

Embolic stroke of undetermined source (ESUS) is a subcategory of cryptogenic stroke defined as a nonlacunar brain infarct without proximal arterial stenosis or cardioembolic sources; ESUS requires a full standardized stroke evaluation to exclude other causes. While the less well-defined term of cryptogenic stroke has been reported to account for approximately 25 to 40 percent of ischemic strokes, the more specific term of ESUS consistently accounts for approximately 20 percent of ischemic strokes. (See "Cryptogenic stroke and embolic stroke of undetermined source (ESUS)", section on 'Embolic stroke of undetermined source'.)

For secondary prevention, most patients with a cryptogenic ischemic stroke or TIA should be treated with blood pressure control, low-density lipoprotein cholesterol lowering therapy, and lifestyle modification. Initial antiplatelet therapy is advised while awaiting the results of long-term cardiac monitoring. For patients initially diagnosed with cryptogenic stroke who have atrial fibrillation of any duration detected on long-term monitoring, even if detected remotely from the incident stroke, anticoagulant therapy with warfarin or a direct oral anticoagulant is advised rather than antiplatelet therapy. (See "Cryptogenic stroke and embolic stroke of undetermined source (ESUS)", section on 'Secondary prevention'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Stroke in adults" and "Society guideline links: Fibromuscular dysplasia".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Stroke (The Basics)")
- Beyond the Basics topics (see "Patient education: Transient ischemic attack (Beyond the Basics)" and "Patient education: Stroke symptoms and diagnosis (Beyond the Basics)" and "Patient education: Ischemic stroke treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Large artery disease** – Secondary prevention for ischemic stroke or transient ischemic attack (TIA) attributed to large artery disease may include the following measures:
    - **Symptomatic internal carotid stenosis** – In addition to medical management, revascularization is generally beneficial for patients with recently symptomatic internal carotid artery atherosclerotic stenosis with 50 to 99 percent luminal narrowing. In the setting of complete carotid occlusion, medical management is the only practical option. (See 'Symptomatic carotid stenosis' above.)

- **Extracranial vertebral artery** – In most cases, ischemic stroke and TIA due to extracranial vertebral artery stenosis is managed by intensive medical treatment with multifactorial risk reduction. (See 'Extracranial vertebral artery stenosis' above.)

- **Intracranial atherosclerosis** – Aggressive medical management is superior to stenting for patients with recently symptomatic high-grade intracranial large artery stenosis. (See 'Intracranial large artery atherosclerosis' above.)

- **Arterial dissection** – Antithrombotic therapy with either antiplatelet or anticoagulant agents is used for the secondary prevention of ischemic stroke and TIA caused by cervical arterial dissection. (See 'Dissection' above.)

- **Small artery disease** – Antiplatelet therapy and treatment of modifiable risk factors is the mainstay for secondary stroke prevention in patients with lacunar stroke or TIA due to small artery disease. (See 'Small artery disease' above.)

- **Cardiogenic embolism** – Virtually all patients with atrial fibrillation who have a history of stroke or TIA should be treated with oral anticoagulation in the absence of contraindications. (See 'Atrial fibrillation' above.)

  Other cardiac sources of embolism for which anticoagulation is often indicated include:

  - Left ventricular thrombus (see 'Left ventricular thrombus' above)
  - Cardiomyopathy (see 'Cardiomyopathy' above)
  - Prosthetic heart valves (see 'Valvular disease' above)
  - Moderate to severe mitral stenosis, even in the absence of atrial fibrillation (see 'Valvular disease' above)
  - Congenital heart disease (see 'Congenital heart disease' above)

  Patent foramen ovale (PFO) device closure is more effective than medical therapy alone for select patients with a PFO-associated stroke. Evaluation and treatment are discussed in detail separately. (See "Stroke associated with patent foramen ovale (PFO): Evaluation".)

- **Aortic atherosclerosis** – The optimal treatment for the prevention of ischemic stroke and TIA attributed to aortic arch atherosclerosis is not clear. Medical management with antiplatelet and low-density lipoprotein cholesterol lowering therapy is reasonable. (See 'Aortic atherosclerosis' above.)

- **Sickle cell disease** – Stroke is a frequent complication of sickle cell disease, and the risk of recurrent stroke is high. Stroke risk can be reduced with chronic transfusion therapy. (See

'Sickle cell disease' above and "Prevention of stroke (initial or recurrent) in sickle cell disease".)

- **Hypercoagulable states** – Anticoagulation with warfarin is the gold standard for patients with antiphospholipid syndrome and arterial thromboembolism; some experts add low-dose aspirin for selected patients with arterial events who also have additional risk factors for atherosclerotic vascular disease.

  With TIA or ischemic stroke attributed to cancer hypercoagulability, the optimal treatment for secondary stroke prevention is unknown.

  Inherited thrombophilias are thought to be rare causes of ischemic stroke in adults. For patients with ischemic stroke or TIA of unknown source (despite a thorough diagnostic evaluation) who are found to have an inherited thrombophilia, antiplatelet treatment is reasonable. (See 'Hypercoagulable states' above.)

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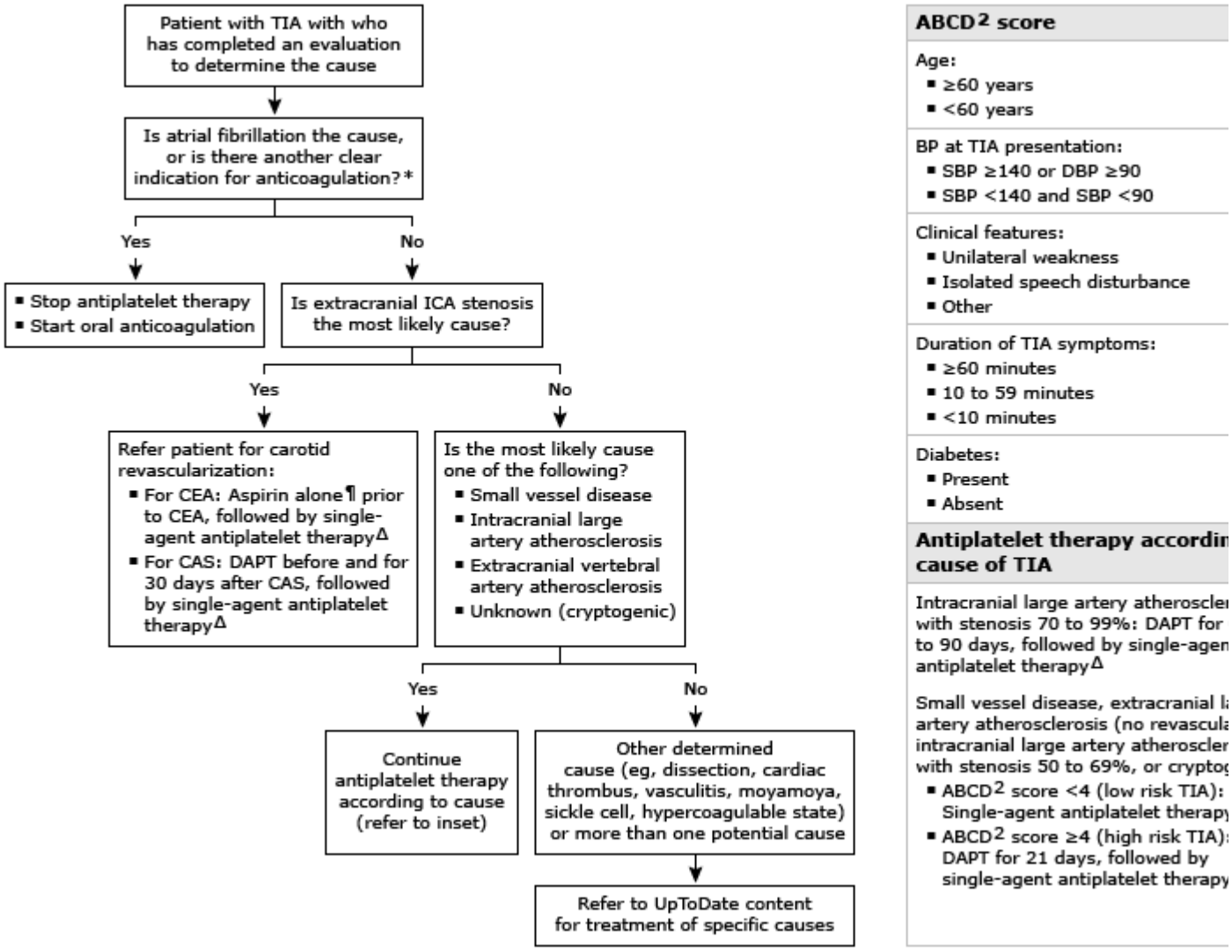
Topic 1119 Version 29.0

GRAPHICS

Antithrombotic therapy according to cause of transient ischemic attack (TIA)



This algorithm is intended to provide basic guidance regarding the use of antithrombotic therapy based on mechanism for patients with a TIA. For further details, including suggested dosing regimens of antithrombotic agents, refer to the relevant UpToDate topic reviews.

ICA: internal carotid artery; CEA: carotid endarterectomy; CAS: carotid artery stenting; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor); $ABCD^2$: age, blood pressure, clinical features, duration of symptoms, and diabetes; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

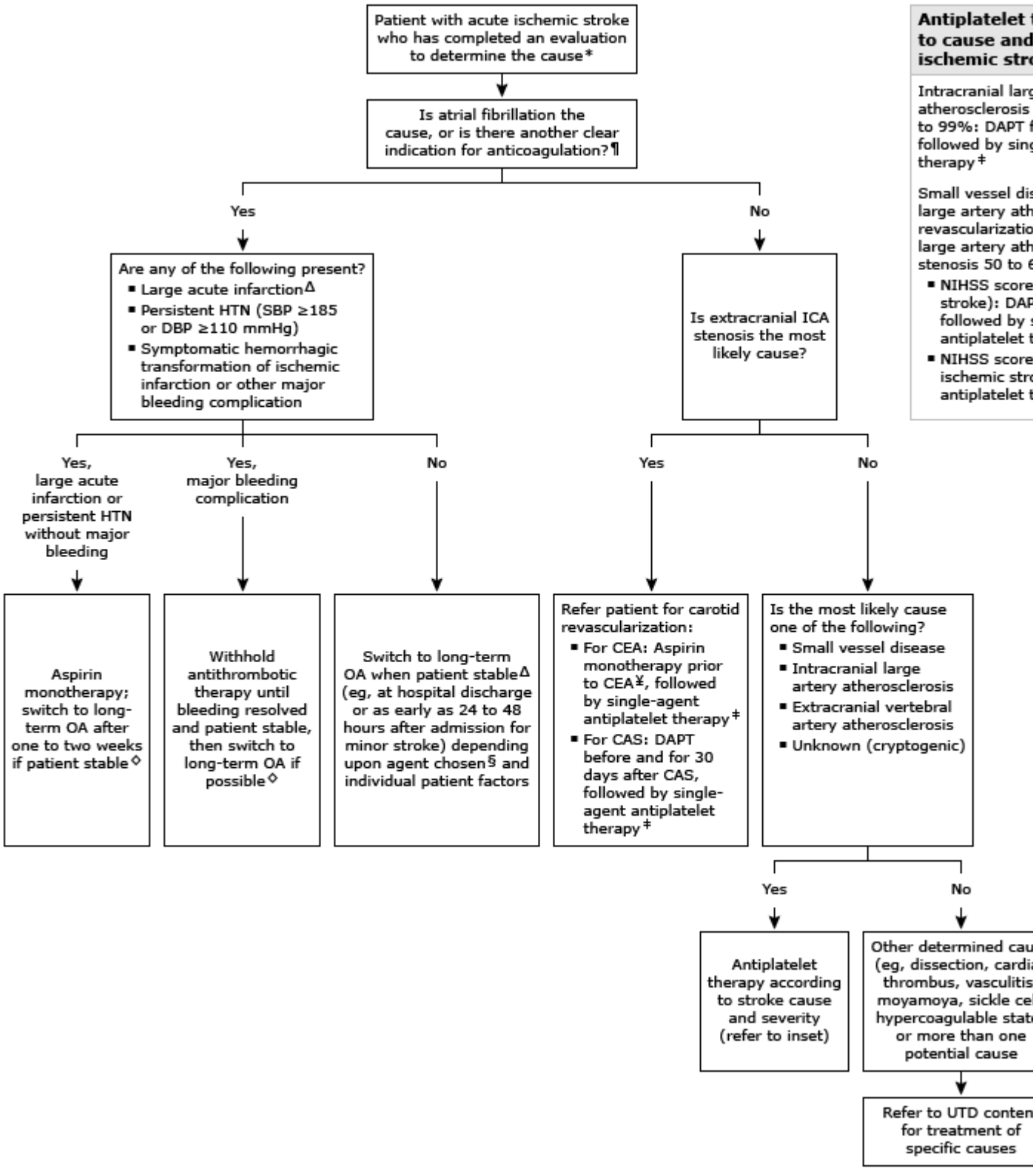
* Indications for long-term oral anticoagulation include atrial fibrillation, ventricular thrombus, mechanical heart valve, and treatment of venous thromboembolism.

¶ Some experts prefer DAPT based upon observational evidence.

Δ Long-term single-agent antiplatelet therapy using aspirin, clopidogrel, or aspirin-extended-release dipyridamole.

Graphic 131695 Version 3.0

Antithrombotic therapy according to cause of acute ischemic stroke



This algorithm is intended to provide basic guidance regarding the immediate use of antithrombotic therapy for patients with an acute ischemic stroke. For further details, including scoring of the NIHSS and suggested dosing regimens of antithrombotic agents, refer to the relevant UpToDate topic reviews.

HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; ICA: internal carotid artery; CEA: carotid endarterectomy; OA: oral anticoagulation; CAS: carotid artery stenting; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor); NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography; MRI: magnetic resonance imaging.

* Brain and neurovascular imaging, cardiac evaluation, and (for select patients) other laboratory tests.

¶ Indications for long-term oral anticoagulation include atrial fibrillation, ventricular thrombus, mechanical heart valve, and treatment of venous thromboembolism.

Δ "Large" infarcts are defined as those that involve more than one-third of the middle cerebral artery territory or more than one-half of the posterior cerebral artery territory based upon neuroimaging with CT or MRI. Though less reliable, large infarct size can also be defined clinically (eg, NIHSS score >15).

◇ Long-term aspirin therapy is alternative (though less effective) if OA contraindicated or refused.

§ Direct oral anticoagulant agents have a more rapid anticoagulant effect than warfarin, a factor that may influence the choice of agent and timing of OA initiation.

¥ Some experts prefer DAPT, based upon observational evidence.

‡ Long-term single-agent antiplatelet therapy for secondary stroke prevention with aspirin, clopidogrel, or aspirin-extended-release dipyridamole.

Graphic 131701 Version 2.0

Cardioaortic sources of cerebral embolism

Sources with high primary risk for ischemic stroke	Sources with low or uncertain primary risk for ischemic stroke
Atrial fibrillation	**Cardiac sources of embolism:**
Paroxysmal atrial fibrillation	Mitral annular calcification
Left atrial thrombus	Patent foramen ovale
Left ventricular thrombus	Atrial septal aneurysm
Sick sinus syndrome	Atrial septal aneurysm and patent foramen ovale
Atrial flutter	Left ventricular aneurysm without thrombus
Recent myocardial infarction (within one month prior to stroke)	Left atrial spontaneous echo contrast ("smoke")
Mitral stenosis or rheumatic valve disease	Congestive heart failure with ejection fraction <30%
Mechanical heart valves	Bioprosthetic heart valves
Chronic myocardial infarction together with low ejection fraction (<28%)	Apical akinesia
Dilated cardiomyopathy (prior established diagnosis or left ventricular dilatation with an ejection fraction of <40% or fractional shortening of <25%)	Wall motion abnormalities (hypokinesia, akinesia, dyskinesia) other than apical akinesia
Nonbacterial thrombotic endocarditis	Hypertrophic cardiomyopathy
Infective endocarditis	Left ventricular hypertrophy
Papillary fibroelastoma	Left ventricular hypertrabeculation/non-compaction
Left atrial myxoma	Recent aortic valve replacement or coronary artery bypass graft surgery
Presence of left ventricular assist device	Paroxysmal supraventricular tachycardia
	Aortic sources of embolism:
	Complex atheroma in the ascending aorta or proximal arch (protruding with >4 mm thickness or mobile debris, or plaque ulceration)

The high- and low-risk cardioaortic sources in this table are separated using an arbitrary 2% annual or one-time primary stroke risk threshold.

Data from:

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Graphic 60843 Version 11.0