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Early antithrombotic treatment of acute ischemic stroke and transient ischemic attack

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INTRODUCTION

The management of patients with acute ischemic stroke involves several phases (see "Initial assessment and management of acute stroke"). The goals in the initial phase include:

- Ensuring medical stability
- Determining eligibility for thrombolytic therapy (table 1) and/or mechanical thrombectomy (algorithm 1)
- Determining the pathophysiologic basis of the stroke

Timely restoration of blood flow using thrombolytic therapy is the most effective maneuver for salvaging ischemic brain tissue that is not already infarcted. Intravenous thrombolysis can be administered up to 4.5 hours after symptom onset, and mechanical thrombectomy can be administered up to 24 hours after symptom onset. (See "Approach to reperfusion therapy for acute ischemic stroke" and "Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use" and "Mechanical thrombectomy for acute ischemic stroke".)

In addition to reperfusion therapies for acute treatment, there are two major classes of antithrombotic drugs that can be used to prevent recurrent ischemic stroke:

- Antiplatelets

- Anticoagulants

This topic will review the use of antithrombotic treatments for patients in the first days after acute ischemic stroke onset. Chronic antiplatelet and anticoagulation therapies for secondary stroke prevention are discussed separately. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke" and "Stroke in patients with atrial fibrillation" and "Atrial fibrillation in adults: Use of oral anticoagulants".)

TREATMENT ON PRESENTATION

Evaluate for reperfusion therapy — All patients with acute ischemic stroke should be evaluated to determine eligibility for reperfusion therapy with intravenous thrombolysis using recombinant tissue plasminogen activator (tPA; alteplase or tenecteplase) and/or mechanical thrombectomy (algorithm 1). (See "Approach to reperfusion therapy for acute ischemic stroke".)

Start antiplatelets as soon as possible — Aspirin and other antithrombotic agents should **not** be given alone or in combination for the first 24 hours following treatment with intravenous thrombolysis. Otherwise, in the absence of contraindications (see 'Hemorrhagic transformation and systemic bleeding' below) or a known cardiac source that requires anticoagulation, antiplatelet therapy with aspirin alone or with dual antiplatelet therapy (DAPT) should be started as soon as possible after the diagnosis of transient ischemic attack (TIA) or ischemic stroke is confirmed, even before the evaluation for ischemic mechanism is complete (algorithm 2 and algorithm 3) [1-3].

Note that oral antiplatelets (or any oral medications) should be administered only after a dysphagia screen to evaluate the safety of swallowing. (See "Complications of stroke: An overview", section on 'Dysphagia'.)

Once the ischemic mechanism is determined, antithrombotic therapy can be modified as necessary. (See 'Treatment by ischemic mechanism' below.)

Aspirin alone

Indications for aspirin — For patients with a TIA or acute ischemic stroke who do not have a known cardioembolic source at presentation, early aspirin monotherapy (162 to 325 mg daily) is indicated in the following clinical settings:

- **Low-risk TIA**, as defined by an $ABCD^2$ (for Age, Blood pressure, Clinical features, Duration of symptoms, and Diabetes) score <4 (table 2).

- **Ischemic stroke of moderate or greater severity**, as defined by a National Institutes of Health Stroke Scale (NIHSS) score >5 (table 3). For patients already on antiplatelet therapy with either aspirin or clopidogrel at the time of stroke onset, we continue their existing antiplatelet regimen when the NIHSS score is >5.

Efficacy of aspirin — In large randomized controlled trials, early (within 48 hours) initiation of aspirin was beneficial for the treatment of acute ischemic stroke, as shown in two major trials:

- The International Stroke Trial (IST) enrolled 19,435 patients with suspected acute ischemic stroke [4]. Patients allocated to aspirin (300 mg) within 48 hours of symptom onset experienced significant reductions in the 14-day recurrence of ischemic stroke (2.8 versus 3.9 percent) and in the combined outcome of nonfatal stroke or death (11.3 versus 12.4 percent).

- In the Chinese Acute Stroke Trial (CAST), 21,100 Chinese patients were randomized to 160 mg of aspirin daily or placebo, also within 48 hours of the onset of acute ischemic stroke [5]. Aspirin-allocated patients experienced a 14 percent relative risk reduction in mortality at four weeks (3.3 versus 3.9 percent).

Subsequent studies of pooled data from trials of early aspirin use in acute ischemic stroke (mainly IST and CAST) have made the following additional observations:

- In a combined analysis of the IST and CAST trials, aspirin therapy in acute ischemic stroke led to a reduction of 11 nonfatal strokes or deaths per 1000 patients in the first few weeks but caused approximately two hemorrhagic strokes [6]. Thus, approximately nine nonfatal strokes or deaths were avoided for every 1000 treated patients. These effects were similar in the presence or absence of atrial fibrillation. Using the endpoint of death or residual impairment leaving the patient dependent, the combined data demonstrated a reduction of 13 per 1000 patients after several weeks to six months of follow-up.

- A 2022 systematic review of antiplatelet therapy for acute stroke included 11 trials involving over 42,000 participants, but the IST and CAST trials contributed nearly all of the data [7]. The reviewers concluded that starting aspirin (160 to 300 mg daily) within 48 hours of presumed ischemic stroke onset reduced the risk of early recurrent ischemic stroke without a major risk of early hemorrhagic complications and improved long-term outcomes. The number needed to treat to avoid death or dependency was 79.

- In an analysis of pooled individual patient data from IST and CAST, aspirin reduced the risk of recurrent ischemic stroke for patients with mild and moderate stroke-related neurologic deficits at baseline but not for those with severe deficits [8]. For patients with mild and

moderate deficits, the risk reduction was maximal by the third day after starting aspirin (two- to three-day hazard ratio [HR] 0.37, 95% CI 0.25-0.57).

Short-term dual antiplatelet therapy (DAPT)

Indications for DAPT — For patients with a TIA or acute ischemic stroke who do not have a known cardioembolic source at presentation and who are able to swallow, short-term DAPT using aspirin plus clopidogrel is indicated in the following clinical settings:

- **High-risk TIA**, defined as an $ABCD^2$ score of ≥4. (See 'Efficacy of DAPT' below.)

  For patients on antiplatelet therapy with either aspirin or clopidogrel at the time of TIA onset, we switch to DAPT using aspirin plus clopidogrel for the first 21 days for high-risk TIA (ie, an $ABCD^2$ score of ≥4). For patients on other antiplatelet agents, the decision should be individualized based upon the underlying indication.

- **Minor ischemic stroke**, defined by an NIHSS score ≤5 (table 3). (See 'Efficacy of DAPT' below.)

- **Stroke due to intracranial large artery atherosclerosis**, defined by ischemic stroke attributed to an intracranial large artery atherosclerotic stenosis of 70 to 99 percent. (See "Intracranial large artery atherosclerosis: Treatment and prognosis", section on 'Antiplatelet therapy'.)

Regimen — We use aspirin (160 to 325 mg loading dose, followed by 50 to 100 mg daily) plus clopidogrel (300 to 600 mg loading dose, followed by 75 mg daily) for short-term DAPT. An alternative is aspirin (300 to 325 mg on the first day followed by 75 to 100 mg daily) plus ticagrelor (180 mg loading dose followed by 90 mg twice daily).

- **Duration** – The duration of DAPT is typically limited to 21 days for patients with high-risk TIA or minor ischemic stroke but may be extended to 90 days for patients with stroke due to intracranial large artery atherosclerotic stenosis of 70 to 99 percent. Thereafter, antiplatelet treatment with aspirin alone, clopidogrel alone, or aspirin-extended-release dipyridamole should be continued indefinitely.

- **Benefit is short term** – In the longer term (beyond 90 days after stroke), DAPT using aspirin and clopidogrel is **not** recommended for stroke prevention. As an example, the MATCH trial, with over 7500 patients who were treated and followed for 18 months, found that the combined use of aspirin and clopidogrel did not offer greater benefit for stroke prevention than either agent alone but did substantially increase the risk of bleeding

complications [9]. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke", section on 'Aspirin plus clopidogrel'.)

Efficacy of DAPT

High-risk TIA and minor ischemic stroke — There is high-quality evidence that early initiation and short-term use of DAPT for select patients with acute high-risk TIA or minor ischemic stroke reduces the risk of recurrent ischemic stroke, with a possible small increase in the risk of moderate or major bleeding and no apparent impact on mortality [3,10-15].

The broadly similar results from major randomized trials [16-19] and the findings of the network meta-analysis [20] discussed below suggest that DAPT with aspirin and clopidogrel or DAPT with aspirin and ticagrelor are both reasonable options for patients with high-risk TIA or minor stroke. We favor aspirin and clopidogrel as this combination will generally cost less. There is limited evidence from a subgroup analysis of the csps.com trial from Japan supporting treatment with DAPT using cilostazol in combination with aspirin or clopidogrel and started as early as eight days after stroke onset [21]. However, this study has important limitations, including post hoc design, unblinded treatment, homogeneous population studied, and early stopping of the trial. Higher-quality data are needed to determine the effectiveness of cilostazol in this setting, and for now we do not use cilostazol as a component of early DAPT.

Some randomized trials have defined minor ischemic stroke as those with an NIHSS score ≤3 [16,17], while others have used an NIHSS score ≤5 [18,19]. UpToDate contributors to this topic generally define minor stroke by a NIHSS score of ≤5. However, the volume of infarcted tissue should be accounted for, since the risk of hemorrhagic transformation is likely related more closely to infarct size than to the NIHSS score. Some patients with an NIHSS score ≤5 may have a relatively large volume of infarcted tissue. In such cases, clinical judgment applies, and antiplatelet monotherapy may be preferred over DAPT.

- **Meta-analysis** – A 2018 meta-analysis pooled data from three eligible trials and over 10,400 patients with acute high-risk TIA or acute minor ischemic stroke who were assigned to DAPT using aspirin and clopidogrel or to aspirin alone started within 24 hours of symptom onset [13]. The two largest trials (POINT [16] and CHANCE [17]) in the meta-analysis contributed 96 percent of the patients. High-risk TIA was defined as an $ABCD^2$ score of ≥4 (table 2). Minor stroke was defined as an NIHSS score of ≤3 (table 3). At 90 days, DAPT reduced the risk of nonfatal recurrent stroke compared with aspirin alone (6.3 versus 4.4 percent; relative risk [RR] 0.70, 95% CI 0.61-0.80; absolute risk reduction [ARR] 1.9 percent), possibly increased the risk of moderate or severe extracranial bleeding (RR 1.71, 95% CI 0.92-3.20; absolute risk increase [ARI] 0.2 percent), but had no apparent

effect on mortality (RR 1.27, 95% CI 0.73-2.23). Importantly, most strokes occurred within the first 10 days of randomization; the stroke rates between the treatment groups diverged quickly in the first days of treatment, but there was little or no incremental benefit of DAPT beyond 10 to 20 days.

A similar 2021 meta-analysis pooled data from four trials (including POINT [16], CHANCE [17], and THALES [18]) comparing early treatment with DAPT versus aspirin alone for patients (over 21,000) with acute ischemic stroke or TIA [22]. Compared with aspirin alone, the risk of recurrent stroke was reduced with DAPT (5.8 versus 7.7 percent; RR 0.76, 95% CI 0.68-0.83; ARR 1.9 percent), whereas the risk of major bleeding was increased with DAPT (0.7 versus 0.3 percent; RR 2.22, 95% CI 1.14-4.34; ARI 0.4 percent).

In a 2022 network meta-analysis of short-term DAPT that included five randomized trials with over 22,000 patients, both clopidogrel plus aspirin and ticagrelor plus aspirin were better than aspirin alone for reducing the risk of recurrent stroke and death, while the risk was similar comparing clopidogrel plus aspirin versus ticagrelor plus aspirin (HR 0.94, 95% CI 0.78-1.13) [20].

- **POINT and CHANCE trials** – The international POINT trial randomly assigned 4881 adults within 12 hours of onset of minor ischemic stroke or high-risk TIA to either DAPT using clopidogrel (600 mg loading dose, then 75 mg daily for 90 days) plus aspirin or to placebo plus aspirin for 90 days [16]. The aspirin dose in both groups was 50 to 325 mg daily. At 90 days, the composite outcome of major ischemic events (ischemic stroke, myocardial infarction, or death from an ischemic vascular event) was reduced for the clopidogrel-plus-aspirin group compared with the placebo-plus-aspirin group (5.0 versus 6.5 percent; ARR 1.5 percent; HR 0.75, 95% CI 0.59-0.95), as was the outcome of ischemic or hemorrhagic stroke (4.8 versus 6.4 percent; HR 0.74, 95% CI 0.58-0.94). However, the rate of major hemorrhage was increased for the clopidogrel-plus-aspirin group (0.9 versus 0.4 percent; HR 2.32, 95% CI 1.10-4.87).

  The CHANCE trial randomly assigned 5170 Chinese patients within 24 hours of onset of high-risk TIA or minor ischemic stroke to DAPT using either clopidogrel and aspirin (clopidogrel 300 mg loading dose, then 75 mg daily for 90 days, plus aspirin 75 mg daily for the first 21 days) or placebo and aspirin (75 mg daily for 90 days) [17]. Over one-half of the subjects in CHANCE had intracranial atherosclerosis. At 90 days, there was a significant reduction in all stroke for the clopidogrel-plus-aspirin group compared with the placebo plus aspirin group (8.2 versus 11.7 percent; ARR 3.5 percent; HR 0.68, 95% CI 0.57-0.81). The rate of hemorrhagic stroke was low in both treatment groups (0.3 percent in each).

The results of the CHANCE and POINT trials are not generalizable to all patients with TIA or acute ischemic stroke. Both trials excluded patients with isolated sensory symptoms, isolated visual changes, or isolated dizziness or vertigo. The POINT trial also excluded patients who were candidates for intravenous thrombolysis, endovascular interventions, and carotid endarterectomy. The Chinese population included in the CHANCE trial has higher rates of large artery intracranial atherosclerotic disease and lower rates of vascular risk factor control relative to other populations (see "Intracranial large artery atherosclerosis: Epidemiology, clinical manifestations, and diagnosis", section on 'Epidemiology'). Thus, it is uncertain how to apply the results of these trials to other populations, particularly patients with low-risk TIA, and those with moderate or severe acute ischemic stroke, who may be at higher risk for hemorrhagic transformation with DAPT.

- **THALES trial** – The THALES trial randomly assigned 11,016 patients with mild to moderate noncardioembolic stroke (defined by an NIHSS score of ≤5) or high-risk TIA (defined by an $ABCD^2$ score of 6 or 7) to DAPT with ticagrelor and aspirin or to placebo and aspirin for 30 days [18]. Ticagrelor was given as a 180 mg loading dose followed by 90 mg twice daily; aspirin was given as 300 to 325 mg on the first day followed by 75 to 100 mg daily. The composite outcome of stroke or death within 30 days was lower for the ticagrelor-plus-aspirin group compared with the placebo-plus-aspirin group (5.5 versus 6.6 percent; ARR 1.1 percent; HR 0.83, 95% CI 0.71-0.96). There were 3314 patients in the THALES trial with an NIHSS score of 4 or 5; these patients would have been excluded from CHANCE and POINT because of their NIHSS score. In subgroup analysis, the benefit of DAPT was similar for patients with an NIHSS score of 4 or 5 and those with lower NIHSS score and/or TIA [23]. Severe bleeding was uncommon but was more frequent for the ticagrelor-plus-aspirin group (0.5 versus 0.1 percent; HR 3.99, 95% CI 1.74-9.14). Disability was similar between the two groups.

  Based on the results of the THALES trial, the US Food and Drug Administration (FDA) approved ticagrelor in combination with aspirin for the short-term treatment of acute minor ischemic stroke or high-risk TIA [24].

  The THALES trial results are comparable to the POINT and CHANCE trials in supporting the role of DAPT for minor noncardioembolic stroke or high-risk TIA. Importantly, THALES supports the use of DAPT in subjects with minor stroke and an NIHSS score ≤5; DAPT using aspirin and clopidogrel was not studied in patients with an NIHSS score of 4 or 5 as they were not included in the POINT and CHANCE trials.

- **INSPIRES trial** – The INSPIRES trial from China randomly assigned 6100 adults with noncardioembolic mild to moderate ischemic stroke (NIHSS score ≤5) or high-risk TIA ($ABCD^2$ score ≥4) to receive DAPT (clopidogrel plus aspirin) or matching placebo plus aspirin [19]. Treatment was started within 72 hours of symptom onset and continued for 90 days; patients undergoing thrombolysis or thrombectomy were excluded. The rate of new stroke within 90 days was lower for the DAPT group compared with the aspirin-alone group (7.3 versus 9.2 percent; HR 0.79; 95% CI 0.66-0.94), while the rate of moderate to severe bleeding was low overall but higher for the DAPT group (0.9 versus 0.4 percent; HR 2.08; 95% CI 1.07-4.04).

  While DAPT should be started as soon as possible for minor ischemic stroke or high-risk TIA, results from the INSPIRES trial suggest that DAPT is beneficial when treatment is started as late as 72 hours after symptom onset; earlier trials (POINT, CHANCE, and THALES) started DAPT within 12 to 24 hours of onset.

- ***CYP2C19* variants and clopidogrel metabolism** – Genetic variation in clopidogrel metabolism due to loss-of-function *CYP2C19* variants may affect the efficacy of clopidogrel, but evidence is conflicting. In a subgroup analysis of 2933 subjects in CHANCE who had genotyping for *CYP2C19* genetic variants, the *CYP2C19* *2 or *3 loss-of-function alleles were present in 59 percent [25]. Combined treatment with clopidogrel plus aspirin significantly reduced the risk of new stroke in noncarriers of the *CYP2C19* loss-of-function alleles (6.7 percent, versus 12.4 percent for aspirin alone; HR 0.51, 95% CI 0.35-0.75) but not in carriers of the *2 or *3 loss-of-function alleles (9.4 versus 10.8 percent; HR 0.93, 95% CI 0.69-1.26).

  The CHANCE-2 trial enrolled 6412 Chinese patients with *CYP2C19* loss-of-function alleles and acute minor ischemic stroke or high-risk TIA and randomly assigned them to DAPT for 21 days with either ticagrelor plus aspirin, or clopidogrel plus aspirin [26]. At 90 days, recurrent stroke was reduced in the ticagrelor group (6 versus 7.6 percent; HR 0.77, 95% CI 0.64-0.94). However, in a substudy of the POINT trial with 932 patients genotyped for *CYP2C19* alleles, the rate of stroke or major ischemic events was similar for noncarriers and carriers of *CYP2C19* loss-of-function alleles [27]. Confidence in this result is limited since the number of patients with *CYP2C19* loss-of-function alleles (n = 326) in the POINT substudy was much lower than the cohort evaluated in CHANCE-2, and the event numbers in each group were very low.

  Notably, the POINT trial used a clopidogrel loading dose of 600 mg, compared with a 300 mg loading dose used in both CHANCE and CHANCE-2. It is possible that a higher

clopidogrel loading dose may overcome some of the metabolic differences in patients with and without loss-of-function *CYP2C19* variants.

The possible relationship of loss-of-function *CYP2C19* alleles and clinical outcomes for patients taking clopidogrel is discussed in greater detail separately. (See "Clopidogrel resistance and clopidogrel treatment failure", section on 'Loss of function gene carriers and outcomes'.)

Intracranial large artery atherosclerosis — It is possible (but not established) that treatment with DAPT (aspirin and clopidogrel) for 90 days in patients who had recently symptomatic intracranial large artery atherosclerosis with severe stenosis (70 to 99 percent) may have contributed to the relatively low rate of combined stroke and death that was observed in the aggressive medical treatment arm of the SAMMPRIS trial [28,29]. (See "Intracranial large artery atherosclerosis: Treatment and prognosis", section on 'Stenting'.)

Other antiplatelets — We typically do not use other antiplatelets as monotherapy in the setting of acute ischemic stroke, but exceptions may be made in select clinical scenarios, such as when an allergy to aspirin or clopidogrel is present.

- **Ticagrelor** – Few randomized trials have tested aspirin directly against other antiplatelet agents for the treatment of ischemic stroke or TIA in the acute period. In the SOCRATES trial of over 13,000 subjects with acute ischemic stroke or TIA, ticagrelor monotherapy was not significantly better than aspirin monotherapy (both started within 24 hours of symptom onset) for the 90-day composite endpoint of stroke, myocardial infarction, or death [30]. However, in a prespecified exploratory analysis, ticagrelor was superior to aspirin in the subgroup of patients who had stroke of possible atherosclerotic origin, which was defined by the presence of ipsilateral atherosclerotic stenosis of an extracranial or intracranial artery (including <50 percent stenosis) or mobile thrombus or thick plaque (≥4 mm) in the aortic arch [31]. These data suggest that patients with atherosclerotic stroke may benefit from antiplatelet therapy other than aspirin. However, the optimal definition of "atherosclerotic" stroke and the optimal treatment strategy are uncertain.

- **Clopidogrel** – Clopidogrel has not been well studied as monotherapy in trials that start treatment in the first 24 to 48 hours of acute ischemic stroke. However, clopidogrel is a first-line antiplatelet agent for the secondary prevention of ischemic stroke, as demonstrated in trials that started treatment one week or more after the onset of ischemic stroke. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke", section on 'Clopidogrel'.)

The short-term use of clopidogrel in combination with aspirin for acute ischemic stroke is discussed below.

- **Cilostazol** – Cilostazol monotherapy is a reasonable option for long-term secondary ischemic stroke prevention in East Asian populations, and for all populations if other agents are not available or tolerated. This is reviewed separately. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke", section on 'Cilostazol'.)

- **Tirofiban** – The glycoprotein (GP) IIb/IIIa inhibitor tirofiban may be beneficial for some patients with acute ischemic stroke, but evidence is inconsistent. The SETIS trial of tirofiban versus aspirin was stopped early because there was no trend of benefit [32], the SaTIS trial of tirofiban versus placebo found no benefit in neurologic or functional outcomes at one week or five months [33], and the RESCUE BT trial found no benefit for tirofiban versus placebo given prior to endovascular thrombectomy [34].

  By contrast, tirofiban was efficacious in the RESCUE BT2 trial from China [35]. The trial enrolled 1177 patients with acute ischemic stroke who had no large or medium vessel occlusion (and therefore were ineligible for mechanical thrombectomy), an NIHSS score of ≥5, moderate to severe weakness in at least one limb, and one of several clinical scenarios: ineligible for intravenous thrombolysis (IVT) and within 24 hours since last known to be well; ineligible for IVT with stroke progression from 24 up to 96 hours since last known to be well; or treated with IVT followed by early neurologic deterioration or no improvement within 24 hours after IVT. Patients were randomly assigned to intravenous tirofiban plus oral placebo or oral aspirin plus intravenous placebo for two days, followed by aspirin for the remainder of the trial. At 90 days, more patients in the tirofiban group had an excellent outcome (defined by a modified Rankin scale [mRS] score of 0 to 1) compared with the aspirin group (29.1 versus 22.2 percent, risk difference 6.9 percent, adjusted risk ratio 1.26, 95% CI 1.04-1.53). The risk of symptomatic hemorrhage was low overall but higher in the tirofiban group (1 versus 0 percent).

  Further trials are needed to determine whether tirofiban has a role in the treatment of acute ischemic stroke, in particular which subgroups benefit most from the treatment and whether it provides benefit over oral GP IIb/IIIa inhibitors.

Limited role of early anticoagulation — In agreement with the national guidelines [1,36], we recommend **not** using full-dose parenteral anticoagulation (eg, intravenous heparin) for treatment of unselected patients with acute ischemic stroke because of minimal efficacy and an increased risk of bleeding complications. Instead, we recommend early antiplatelet therapy for

most patients with acute ischemic stroke or TIA. (See 'Treatment on presentation' above and 'Treatment by ischemic mechanism' below.)

Patients already on anticoagulation — For most patients on anticoagulation at the time of acute ischemic stroke onset, anticoagulation should be stopped, at least for the short term, while determining eligibility for acute reperfusion therapies. However, there is no consensus regarding continuation or temporary stopping of anticoagulation at the time of acute ischemic stroke onset in patients using anticoagulation, and evidence related to this question is limited to observational studies [37].

For patients with uncomplicated minor stroke and an appropriate indication, long-term oral anticoagulation can be restarted when the patient is stable, such as at hospital discharge or 24 to 48 hours after stroke onset, depending upon the agent chosen and individual patient factors. Subtherapeutic anticoagulation intensity may be implicated in patients with atrial fibrillation and should be managed accordingly (see 'Anticoagulant failure' below). For patients with large acute infarction, we start aspirin in the interim if there are no significant bleeding complications; oral anticoagulation can be resumed according to indication (and aspirin stopped) after one to two weeks if the patient is stable. (See 'Atrial fibrillation' below and 'Timing of long-term anticoagulation' below and 'Contraindications' below.)

A similar approach, stated by European guidelines, suggests anticoagulation can be started or resumed immediately for patients with a TIA and started or resumed at ≥3 days after onset for patients with minor ischemic stroke and persisting mild neurologic deficit [38]. For patients with ischemic stroke and a moderate neurologic deficit, anticoagulation can be started or resumed at six to eight days, and for those with a severe neurologic deficit, at 12 to 14 days; in both cases, repeat brain imaging should be obtained to exclude significant hemorrhagic transformation within 24 hours prior to starting or resuming anticoagulation.

Indications to start or continue anticoagulation

- **TIA** – For patients with a clear indication for anticoagulation (eg, atrial fibrillation, venous thromboembolism, mechanical heart valve) at onset of TIA, we recommend starting or continuing anticoagulation rather than antiplatelet therapy. In patients who are subtherapeutically or not anticoagulated at presentation, bridging anticoagulation with heparin, low molecular weight heparin, or a direct oral anticoagulant (DOAC) should be considered. In patients who are therapeutically anticoagulated at presentation, management should be individualized based on the underlying mechanism of the TIA. In some instances, such as when the TIA is more likely due to atherosclerosis than to cardioembolism, it may be reasonable to add antiplatelet therapy. Triple therapy (ie,

anticoagulation plus DAPT) is associated with a high risk of hemorrhage and should be avoided. (See 'Anticoagulant failure' below.)

- **Acute ischemic stroke** – Although benefit is unproven, we suggest early parenteral anticoagulation rather than aspirin only for select patients with acute cardioembolic ischemic stroke or TIA due to intracardiac thrombus in the left ventricle or thrombus associated with mechanical or native heart valves who are at high short-term risk for recurrent stroke.

  While many specialists believe it has no role at all in the early acute phase of ischemic stroke, some experts have used early anticoagulation for other ischemic stroke subtypes, including cardioembolic stroke due to atrial fibrillation and stroke due to large artery stenoses or arterial dissection. However, a review of the literature does not support the routine use of anticoagulation in these subgroups [36]. Patients with mechanical heart valves or intracardiac thrombus were either not included or were underrepresented in trials of acute antithrombotic therapy for stroke.

  In the only trial of intravenous unfractionated heparin in hyperacute stroke, a single center in Italy randomly assigned 418 patients with nonlacunar hemispheric infarction (of cardioembolic, atherothrombotic, or unknown/undetermined origin) to receive either intravenous heparin or saline within three hours of stroke onset [39]. Treatment continued for five days. A favorable outcome at 90 days, the primary endpoint, was significantly more frequent in patients assigned to heparin compared with those assigned to saline (39 versus 29 percent). Heparin use was associated with an increased risk of intracranial and extracranial bleeding but no increase in mortality. A majority of patients enrolled in the trial were eligible for intravenous thrombolysis, but none received it since intravenous thrombolysis had not been approved in Italy at the time.

No or uncertain role

- **No benefit for acute stroke due to atrial fibrillation** – Early treatment with heparin for patients who have an acute cardioembolic stroke does not reduce the risk of recurrent ischemic stroke but is associated with an increased risk of symptomatic intracranial hemorrhage, as discussed below. (See 'Atrial fibrillation' below.)

- **No benefit for progressing stroke** – Heparin was once widely used to treat patients who continued to have neurologic deterioration in the first hours or days after ischemic stroke (ie, progressing stroke, also referred to as stroke in evolution). The TOAST trial did not find an improvement in outcomes with danaparoid treatment in such patients [40], nor did a

nonrandomized study of heparin therapy [41]. These findings do not support a role for heparin in halting neurologic worsening after stroke.

- **No benefit for unselected patients** – The largest randomized controlled trial (IST) studied two doses of subcutaneous heparin in 19,435 patients with undefined ischemic stroke and found no significant benefit with heparin [4]. A systematic review updated in 2021 examined the effect of anticoagulant therapy versus control in the early treatment of patients with acute ischemic stroke [42]. This review included 28 trials involving 24,025 subjects; approximately 80 percent of the subjects were from the IST trial. There was considerable variation in the quality of the trials. The anticoagulants tested were standard unfractionated heparin, low molecular weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. The following were the major findings [42]:

  - Anticoagulant therapy did **not** reduce the risk of death from all causes (odds ratio [OR] 0.99, 95% CI 0.90-1.09).

  - Anticoagulants did **not** reduce the risk of being dead or dependent at the end of follow-up (OR 0.98, 95% CI 0.92-1.03).

Anticoagulants **reduced** the odds of recurrent ischemic stroke (OR 0.75, 95% CI 0.65-0.88) but **increased** the risk of symptomatic intracranial hemorrhage (OR 2.99, 95% CI 2.24-3.99).

- **Uncertain benefit for large vessel atherosclerotic disease** – Clinical trials have not adequately evaluated adjusted intravenous anticoagulation in patients with selected stroke subtypes. With this caveat in mind, there are conflicting data regarding the benefit of intravenous unfractionated heparin or low molecular weight heparin in the subgroup of patients with large vessel atherosclerotic disease. Note that these trials included many patients with minor ischemic stroke who would now be treated with short-term DAPT, but the comparator at the time was aspirin monotherapy.

  - The TOAST trial evaluated the efficacy of the low molecular weight heparinoid danaparoid administered as an intravenous bolus within 24 hours of symptom onset and continued for seven days in 1281 patients with acute ischemic stroke [40]. Compared with placebo, danaparoid was associated with no improvement in overall outcome at three months (75 versus 74 percent rates of favorable outcome). However, subgroup analysis suggested a higher rate of favorable outcomes in patients treated with danaparoid who had a large artery atherosclerotic stroke (68 versus 55 percent with placebo).

- The FISS-tris trial evaluated the low molecular weight heparin nadroparin (3800 anti-factor Xa international units, 0.4 mL subcutaneously twice daily) versus aspirin (160 mg once daily) started within 48 hours of acute ischemic stroke onset and continued for 10 days [43]. The main study population was 353 patients with confirmed large artery occlusive disease, consisting of 300 with intracranial, 11 with extracranial, and 42 with both intracranial and extracranial disease. The mean time to treatment was nearly 30 hours. There was no significant difference between treatment with nadroparin or aspirin for the proportion of patients with good outcome at six months, defined by a Barthel Index (table 4) score of ≥85 (73 versus 69 percent). However, there was a significant benefit to low molecular weight heparin in a prespecified secondary outcome measure, good outcome defined by a modified Rankin Scale (table 5) score of 0 to 1 (54 versus 44 percent; OR 1.55, 95% CI 1.02-2.35).

Contraindications — Anticoagulation in the setting of acute stroke may only be considered after a brain imaging study has excluded hemorrhage and estimated the size of the infarct. Early anticoagulation should be avoided when potential contraindications to anticoagulation are present, such as a large infarction (based upon clinical syndrome or brain imaging findings); severe uncontrolled, persistent hypertension (eg, systolic blood pressure ≥185 or diastolic blood pressure ≥110 mmHg); symptomatic hemorrhagic infarction; or other bleeding conditions.

Although there is no standard definition, many stroke experts consider "large" infarcts to be 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 computed tomography (CT) or magnetic resonance imaging (MRI). Infarct size can also be clinically defined, but this process can underestimate the true infarct volume when so-called "silent" areas of association cortex are involved.

Clinical estimation of infarct size may be improved by using validated scales that have been correlated with infarct volume and clinical outcome, such as the NIHSS (table 3). As an example, one study found that an NIHSS score >15 was associated with a median infarct volume of 55.8 cm^3 and worse outcome than NIHSS scores of 1 to 7 (median infarct volume of 7.9 cm^3) or 8 to 15 (median infarct volume of 31.4 cm^3) [44].

Thus, patients with an NIHSS score >15 generally have a large infarct. However, it should be recognized that part of the clinical deficit in the early hours of an acute stroke may be attributed to the penumbra, where the brain is ischemic but not infarcted. Additionally, NIHSS cutoffs may not apply equally well in both hemispheres. It is possible to have a relatively large infarct in the right hemisphere with a low NIHSS [45].

TREATMENT BY ISCHEMIC MECHANISM

Once the evaluation for transient ischemic attack (TIA) or ischemic stroke is complete, antithrombotic therapy can be modified as necessary according to the ischemic mechanism (algorithm 4 and algorithm 5).

Cardioembolic source

Atrial fibrillation — While parenteral anticoagulation (eg, intravenous heparin) is generally **not** recommended for treating ischemic stroke in the acute period, oral anticoagulation with warfarin or a direct oral anticoagulant (DOAC) is recommended for secondary stroke prevention in patients with atrial fibrillation and other high-risk sources of cardiogenic embolism. (See "Stroke in patients with atrial fibrillation" and "Atrial fibrillation in adults: Use of oral anticoagulants".)

The timing of oral anticoagulation initiation for such patients is mainly dependent on the size of the acute infarct and the presence of factors such as symptomatic hemorrhagic transformation and/or poorly controlled hypertension. Oral anticoagulation can be started immediately for patients with TIA due to atrial fibrillation and soon after onset for medically stable patients with a small- or moderate-sized infarct and no bleeding complications. For patients with large infarctions, symptomatic hemorrhagic transformation, or poorly controlled hypertension, withholding oral anticoagulation for one to two weeks is generally recommended [46]. (See 'Timing of long-term anticoagulation' below.)

Although once widely practiced, early treatment with heparin for patients with atrial fibrillation who have an acute cardioembolic stroke causes more harm than good. A 2007 meta-analysis examined seven randomized controlled trials involving 4624 patients and compared heparin or low molecular weight heparins started within 48 hours for acute cardioembolic stroke with other treatments (aspirin or placebo) [47]. The following observations were reported:

- Parenteral anticoagulants led to a nonsignificant reduction in recurrent ischemic stroke within 7 to 14 days (3.0 versus 4.9 percent; OR 0.68, 95% CI 0.44-1.06)
- Parenteral anticoagulants led to an increase in symptomatic intracranial hemorrhage (2.5 versus 0.7 percent; OR 2.89, 95% CI 1.19-7.01)
- Parenteral anticoagulants and other treatments had a similar rate of death or disability at final follow-up (approximately 74 percent)

These results do not support early parenteral anticoagulant treatment of acute cardioembolic stroke [47].

Anticoagulant failure — Subtherapeutic anticoagulation intensity is often implicated when patients with atrial fibrillation present with TIA or ischemic stroke [48]. The first step should be to exclude an alternative ischemic mechanism unrelated to cardiogenic embolism. If ischemia is attributed to atrial fibrillation, an attempt should be made to identify and correct the cause (eg, inadequate compliance with anticoagulant therapy, drug/food interaction). Options include continuing warfarin (after temporary interruption if needed for acute ischemic stroke) with renewed efforts to keep the international normalized ratio (INR) in the 2 to 3 therapeutic range or switching to a DOAC. (See "Stroke in patients with atrial fibrillation", section on 'Anticoagulation failure' and "Atrial fibrillation in adults: Use of oral anticoagulants", section on 'Anticoagulant failure'.)

Intracardiac thrombus — Although benefit is unproven, we suggest early parenteral anticoagulation rather than aspirin only for select patients with acute cardioembolic ischemic stroke who are at high risk for short-term recurrent stroke due to intracardiac thrombus in the left ventricle or thrombus associated with mechanical or native heart valves. This approach is controversial; some experts favor treatment with aspirin rather than anticoagulation in this setting for patients with an acute brain infarction.

Our suggestion to use early parenteral anticoagulation for these selected patients applies only to those with a small- to moderate-sized brain infarct and no evidence of hemorrhage on brain imaging. Anticoagulation should not be given for the first 24 hours following treatment with intravenous alteplase. Full-dose anticoagulation should not be used acutely for patients with a large infarction (based upon clinical syndrome or brain imaging findings), uncontrolled hypertension, or other bleeding conditions. (See 'Contraindications' above.)

In the selected patients who receive heparin in the acute stroke setting, a bolus is not administered. One group has proposed a weight-based nomogram for heparin infusions that, compared with usual heparin therapy, is associated with fewer complications, fewer mistakes in dose adjustment, improved anticoagulation, and decreased nursing and house staff labor (table 6) [49].

Enoxaparin 1 mg/kg dose every 12 hours (or other low molecular weight heparins) may be used as an alternative to intravenous heparin in patients with acute stroke when early anticoagulation is desired to prevent recurrent cerebral embolism; the limited available evidence suggests that low molecular weight heparins have similar efficacy, advantages in administration and monitoring, and reduced rates of thrombocytopenia compared with

heparin. (See "Heparin and LMW heparin: Dosing and adverse effects", section on 'LMW heparin'.)

Generally, patients with TIA or ischemic stroke attributed to an intracardiac thrombus should be transitioned to oral anticoagulation soon after initiation of parenteral anticoagulation. Oral anticoagulation is generally continued at least three months for left ventricular thrombus; concurrent antiplatelet therapy may be indicated for left ventricular thrombus after acute myocardial infarction. Chronic anticoagulation is indicated for patients with mechanical heart valves. (See "Left ventricular thrombus after acute myocardial infarction", section on 'Prevention of embolic events' and "Antithrombotic therapy for mechanical heart valves".)

Noncardioembolic etiologies — Antiplatelet therapy is the mainstay of secondary stroke prevention for patients with a noncardioembolic source of ischemic stroke. For most patients without atrial fibrillation or another indication for long-term oral anticoagulation, the antiplatelet regimen chosen at presentation can be continued:

- For patients with low-risk TIA or moderate to severe stroke, we recommend aspirin monotherapy (160 to 325 mg daily). (See 'Aspirin alone' above.)
- For patients with high-risk TIA or minor ischemic stroke, we recommend short-term dual antiplatelet therapy (DAPT) using aspirin and clopidogrel rather than aspirin alone. (See 'Short-term dual antiplatelet therapy (DAPT)' above.)

After the acute period, treatment should continue with aspirin alone, clopidogrel alone, or aspirin-extended-release dipyridamole. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke".)

However, modifications may apply for select stroke mechanisms:

- **Extracranial internal carotid artery stenosis** – Patients with symptomatic internal carotid artery stenosis as the cause of TIA or ischemic stroke should be treated with early antiplatelet therapy. These patients generally benefit from carotid revascularization to reduce the risk of recurrent ipsilateral ischemic stroke. Aspirin monotherapy is preferred by some experts prior to carotid endarterectomy, while DAPT is preferred by others. DAPT is used prior to and continuing for 30 days after carotid artery stenting. (See "Carotid endarterectomy", section on 'Antiplatelet therapy' and "Overview of carotid artery stenting", section on 'Dual antiplatelet therapy'.)
- **Intracranial large artery atherosclerosis** – For patients with a recent (within 30 days) TIA or ischemic stroke attributed to atherosclerotic intracranial large artery stenosis of 70 to

99 percent, DAPT with aspirin plus clopidogrel is used by some experts for up to 90 days. The use of antiplatelet therapy for patients with acute ischemic stroke due to intracranial large artery atherosclerosis is reviewed in detail separately. (See "Intracranial large artery atherosclerosis: Treatment and prognosis", section on 'Antiplatelet therapy'.)

- **Dissection** – The use of antithrombotic therapy for ischemic stroke and TIA caused by cervical or intracranial artery dissection is discussed elsewhere. (See "Cerebral and cervical artery dissection: Treatment and prognosis", section on 'Choosing between antiplatelet and anticoagulation therapy'.)

- **Other determined etiology** – Several conditions that are uncommon causes of TIA and ischemic stroke are discussed in detail separately:

  - Acute stroke (ischemic and hemorrhagic) in children and adults with sickle cell disease
  - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
  - Moyamoya disease and moyamoya syndrome: Treatment and prognosis
  - Management of antiphospholipid syndrome
  - Nonbacterial thrombotic endocarditis

- **Cryptogenic** – Patients with cryptogenic TIA and ischemic stroke, including those with embolic stroke of undetermined source (ESUS), are generally treated with antiplatelet therapy while awaiting the results of long-term cardiac monitoring to look for atrial fibrillation as a possible cause of stroke. Thus, initial treatment involves aspirin monotherapy for low-risk TIA and moderate to severe ischemic stroke, or short-term DAPT for high-risk TIA and minor stroke. (See 'Indications for DAPT' above.)

  For long-term stroke prevention beyond the acute period, antiplatelet therapy with aspirin alone, clopidogrel alone, or aspirin-extended-release dipyridamole is recommended. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke".)

  Available data have shown no benefit from anticoagulation for secondary stroke prevention in patients with cryptogenic stroke or ESUS. The evaluation and management of cryptogenic stroke and ESUS is discussed in detail separately. (See "Cryptogenic stroke and embolic stroke of undetermined source (ESUS)".)

OTHER TREATMENT ISSUES

Hemorrhagic transformation and systemic bleeding — For patients who develop severe systemic or intracranial bleeding complications, including symptomatic hemorrhagic transformation of the ischemic infarct, we withhold all anticoagulant and antiplatelet therapy for one to two weeks or until the patient is stable, at which time oral antiplatelet or anticoagulant treatment can be started or resumed as indicated.

The development of asymptomatic hemorrhagic transformation of an ischemic infarct does not necessarily preclude the early use of antiplatelets, particularly when the hemorrhage is petechial (ie, scattered and punctate). In this setting, it is likely reasonable to continue aspirin. For asymptomatic parenchymal hematoma (ie, larger confluent bleeding within an infarct), it is not clear that stopping aspirin will have much impact on hematoma progression given the long-lasting effect of aspirin on platelet function, and it may be reasonable to continue aspirin, although management should be individualized. If antiplatelet therapy has not been started, it may be reasonable to delay initiation of antiplatelet therapy in patients with parenchymal hemorrhage until the patient's neurologic condition becomes stable. We avoid dual antiplatelet therapy (DAPT) in patients with hemorrhagic transformation, including those with petechial or parenchymal hemorrhage.

Patients with another indication for chronic anticoagulation — Some patients with acute ischemic stroke have indications other than atrial fibrillation or intracardiac thrombus for prolonged anticoagulation, such as acute coronary syndrome, prosthetic heart valve, or venous thromboembolism. In such cases, and in the absence of significant bleeding, we start aspirin if anticoagulation is delayed because of large infarction, high risk of symptomatic hemorrhagic transformation, and/or poorly controlled hypertension. We then stop aspirin once anticoagulation is started unless there is an indication for the use of concurrent antiplatelet therapy. (See 'Timing of long-term anticoagulation' below and 'Contraindications' above.)

Venous thromboembolism prophylaxis — Aspirin and other antiplatelet agents may be used to treat acute ischemic stroke when subcutaneous heparin or low molecular weight heparin is used for the prevention of venous thromboembolism. The prophylaxis of venous thromboembolism is discussed separately. (See "Prevention and treatment of venous thromboembolism in patients with acute stroke", section on 'Approach to VTE prevention'.)

Swallowing difficulty — Aspirin may be given rectally for patients with acute stroke who are nil per os (NPO) or those who have not had screening for dysphagia. Clopidogrel is available only as a tablet for oral administration.

Timing of long-term anticoagulation — There is no clear consensus about when to start or resume anticoagulation after acute ischemic stroke in patients with atrial fibrillation or another appropriate indication for anticoagulation. Different national guidelines have proposed different recommendations [46]. Based mainly on expert consensus, the timing of anticoagulation initiation for patients with an appropriate indication is mainly dependent on the size of the acute infarct and the presence of factors such as symptomatic hemorrhagic transformation and/or poorly controlled hypertension. The size of the infarction is presumed to correlate with the risk of hemorrhagic transformation.

- **TIA** – For patients with a transient ischemic attack (TIA) and atrial fibrillation, oral anticoagulation can be started immediately.
- **Small- to moderate-sized infarct** – For medically stable patients with a small- or moderate-sized infarct, warfarin can be initiated or restarted soon (eg, 24 hours) after admission with minimal risk of transformation to hemorrhagic stroke. We prefer to wait for 48 hours to start a DOAC, as DOACs have a more rapid anticoagulant effect.
- **Large infarct** – For patients with large infarctions, symptomatic hemorrhagic transformation, or poorly controlled hypertension, withholding oral anticoagulation for one to two weeks is generally recommended [46].

Limited clinical trial data support earlier rather than later initiation of direct oral anticoagulants (DOACs) after ischemic stroke [50,51]. The open-label ELAN trial enrolled 2013 patients with atrial fibrillation and acute ischemic stroke [50]. Patients were randomly assigned in a 1:1 ratio to early anticoagulation (within 48 hours after a minor or moderate stroke or on day six or seven after a major stroke) or later anticoagulation (day three or four after a minor stroke, day six or seven after a moderate stroke, or day 12 through 14 after a major stroke) using a DOAC. Stroke severity was determined by imaging size: an infarct of <1.5 cm was considered minor; an infarct in the distribution of a cortical superficial branch of the anterior, middle, or posterior cerebral artery was considered moderate; a larger infarct in the distributions of those arteries or an infarct >1.5 cm in the brainstem or cerebellum was considered major.

The ELAN trial found a nonsignificant trend towards benefit with earlier anticoagulation [50]. At 30 days, the composite outcome (recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death) occurred in 29 participants in the early anticoagulation group compared with 41 in the later anticoagulant group (2.9 versus 4.1 percent, risk difference -1.18 percent, 95% CI -2.84 to 0.47). Recurrent ischemic stroke in the early and later groups occurred in 14 and 22 participants respectively (1.4 versus 2.5 percent, risk difference -1.14, 95% CI -2.41 to 0.13), while the rate of symptomatic

intracranial hemorrhage was 0.2 percent in both groups. While not definitive, these findings suggest that early DOAC use is safe and may reduce the risk of recurrent ischemic stroke. Limitations to the ELAN trial include small number of events, a low median NIHSS score (3) at randomization, and exclusion of patients on therapeutic anticoagulation at baseline.

For patients with atrial fibrillation in whom the start of anticoagulation will be delayed by more than 48 hours (eg, those with large acute infarction), we start aspirin as soon as possible after the diagnosis of transient ischemic attack (TIA) or ischemic stroke is confirmed if there are no significant bleeding complications; anticoagulation can be resumed according to indication (and aspirin stopped) according to the guidance above if the patient is stable.

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".)

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: Stroke symptoms and diagnosis (Beyond the Basics)" and "Patient education: Ischemic stroke treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Immediate treatment** – All patients with acute ischemic stroke should be evaluated to determine eligibility for reperfusion therapy with intravenous thrombolysis and/or mechanical thrombectomy (algorithm 1), and aspirin and other antithrombotic agents should not be given alone or in combination for the first 24 hours following treatment with intravenous thrombolysis. (See 'Evaluate for reperfusion therapy' above and 'Start antiplatelets as soon as possible' above.)

  Otherwise, antiplatelet agents should be started as soon as possible after the diagnosis of transient ischemic attack (TIA) or ischemic stroke is confirmed, even before the evaluation for ischemic mechanism is complete. For most patients with no indication for long-term oral anticoagulation who have TIA (algorithm 2) or ischemic stroke (algorithm 3), we start antiplatelet therapy as follows (see 'Aspirin alone' above and 'Short-term dual antiplatelet therapy (DAPT)' above):

  - **Aspirin alone for low-risk TIA or moderate to severe ischemic stroke** – For patients with a low-risk TIA, defined by an ABCD^2 (for Age, Blood pressure, Clinical features, Duration of symptoms, and Diabetes) score <4 (table 2), or moderate to major ischemic stroke, defined by a National Institutes of Health Stroke Scale (NIHSS) score >5 (table 3), we start treatment with aspirin (162 to 325 mg daily) alone.

  - **DAPT for high-risk TIA or minor ischemic stroke** – For patients with a high-risk TIA, defined by an ABCD^2 score ≥4 (table 2), or minor ischemic stroke, defined by an NIHSS score ≤5 (table 3), who present within 72 hours of symptom onset, we begin with dual antiplatelet therapy (DAPT) for 21 days using aspirin (160 to 325 mg loading dose, followed by 50 to 100 mg daily) plus clopidogrel (300 to 600 mg loading dose, followed by 75 mg daily) rather than aspirin alone. Aspirin and ticagrelor is an alternative DAPT regimen.

- **Treatment by ischemic mechanism** – Once the evaluation for TIA or stroke is complete, early antithrombotic therapy can be modified if necessary (algorithm 4 and algorithm 5) according to the ischemic mechanism (see 'Treatment by ischemic mechanism' above):

  - **Atrial fibrillation** – For patients with TIA or ischemic stroke who have atrial fibrillation, oral anticoagulation with warfarin or a direct oral anticoagulant (DOAC) is recommended for secondary stroke prevention (see "Stroke in patients with atrial fibrillation"). Oral anticoagulation can be started immediately for patients with TIA and soon after stroke onset for medically stable patients with a small- or moderate-sized infarct and no bleeding complications or uncontrolled hypertension. For patients with

large infarctions, symptomatic hemorrhagic transformation, or poorly controlled hypertension, withholding oral anticoagulation for one to two weeks is generally advised. (See 'Atrial fibrillation' above and 'Timing of long-term anticoagulation' above.)

- **Intracardiac thrombus** – For patients with acute cardioembolic TIA or ischemic stroke who have intracardiac thrombus in the left ventricle or associated with mechanical or native heart valves, we suggest early parenteral anticoagulation rather than aspirin (**Grade 2C**). This approach is controversial. (See 'Limited role of early anticoagulation' above.)

- **Noncardioembolic etiologies** – For most patients without atrial fibrillation or another indication for long-term oral anticoagulation, the antiplatelet regimen chosen at presentation can be continued: for patients with low-risk TIA or moderate to severe stroke, we recommend aspirin monotherapy (160 to 325 mg daily) (**Grade 1A**). For patients with high-risk TIA or minor ischemic stroke, we recommend short-term DAPT using aspirin and clopidogrel rather than aspirin alone (**Grade 1A**). Thereafter, antiplatelet treatment should continue with aspirin alone, clopidogrel alone, or aspirin-extended-release dipyridamole. (See 'Noncardioembolic etiologies' above.)

  However, certain additional modifications may apply:

  - **Carotid revascularization** – Aspirin monotherapy is preferred by some experts prior to carotid endarterectomy, while DAPT is preferred by others. DAPT is used prior to and continuing for 30 days after carotid artery stenting. (See "Carotid endarterectomy", section on 'Antiplatelet therapy' and "Overview of carotid artery stenting", section on 'Dual antiplatelet therapy'.)

  - **Intracranial large artery atherosclerosis** – For patients with TIA or ischemic stroke attributed to intracranial large artery atherosclerosis stenosis of 70 to 99 percent, we suggest DAPT for 90 days. (See "Intracranial large artery atherosclerosis: Treatment and prognosis", section on 'Antiplatelet therapy'.)

  - **Dissection** – The antithrombotic treatment of TIA or ischemic stroke caused by large artery dissection is discussed in detail separately. (See "Cerebral and cervical artery dissection: Treatment and prognosis", section on 'Choosing between antiplatelet and anticoagulation therapy'.)

- **Long-term antiplatelet therapy** – Beyond the acute phase of TIA and ischemic stroke, and in the absence of an indication for oral anticoagulation, long-term antiplatelet therapy for secondary stroke prevention should be continued with aspirin alone, clopidogrel alone,

or aspirin-extended-release dipyridamole. Long-term DAPT with aspirin and clopidogrel is not recommended. (See "Long-term antithrombotic therapy for the secondary prevention of ischemic stroke".)

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Topic 1082 Version 52.0

GRAPHICS

Eligibility criteria for the treatment of acute ischemic stroke with intravenous thrombolysis (recombinant tissue plasminogen activator or tPA)

Inclusion criteria
▪ Clinical diagnosis of ischemic stroke causing measurable neurologic deficit ▪ Onset of symptoms <4.5 hours before beginning treatment; if the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal or at neurologic baseline ▪ Age ≥18 years
Exclusion criteria
Patient history ▪ Ischemic stroke or severe head trauma in the previous three months ▪ Previous intracranial hemorrhage ▪ Intra-axial intracranial neoplasm ▪ Gastrointestinal malignancy ▪ Gastrointestinal hemorrhage in the previous 21 days ▪ Intracranial or intraspinal surgery within the prior three months
Clinical ▪ Symptoms suggestive of subarachnoid hemorrhage ▪ Persistent blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg) ▪ Active internal bleeding ▪ Presentation consistent with infective endocarditis ▪ Stroke known or suspected to be associated with aortic arch dissection ▪ Acute bleeding diathesis, including but not limited to conditions defined under 'Hematologic'
Hematologic ▪ Platelet count <100,000/mm^3* ▪ Current anticoagulant use with an INR >1.7 or PT >15 seconds or aPTT >40 seconds* ▪ Therapeutic doses of low molecular weight heparin received within 24 hours (eg, to treat VTE and ACS); this exclusion does not apply to prophylactic doses (eg, to prevent VTE) ▪ Current use (ie, last dose within 48 hours in a patient with normal renal function) of a direct thrombin inhibitor or direct factor Xa inhibitor with evidence of anticoagulant effect by laboratory tests such as aPTT, INR, ECT, TT, or appropriate factor Xa activity assays
Head CT ▪ Evidence of hemorrhage ▪ Extensive regions of obvious hypodensity consistent with irreversible injury
Warnings¶

- Only minor and isolated neurologic signs or rapidly improving symptoms[Δ]
- Serum glucose <50 mg/dL (<2.8 mmol/L)[◇]
- Serious trauma in the previous 14 days[§]
- Major surgery in the previous 14 days[¥]
- History of gastrointestinal bleeding (remote) or genitourinary bleeding[‡]
- Seizure at the onset of stroke with postictal neurologic impairments[†]
- Pregnancy**
- Arterial puncture at a noncompressible site in the previous seven days[¶¶]
- Large (≥10 mm), untreated, unruptured intracranial aneurysm[¶¶]
- Untreated intracranial vascular malformation[¶¶]

Additional warnings for treatment from 3 to 4.5 hours from symptom onset[ΔΔ]

- Age >80 years
- Oral anticoagulant use regardless of INR
- Severe stroke (NIHSS score >25)
- Combination of both previous ischemic stroke and diabetes mellitus

ACS: acute coronary syndrome; aPTT: activated partial thromboplastin time; ECT: ecarin clotting time; INR: international normalized ratio; PT: prothrombin time; NIHSS: National Institutes of Health Stroke Scale; tPA: tissue plasminogen activator (alteplase or tenecteplase); TT: thrombin time; VTE: venous thromboembolism.

* Although it is desirable to know the results of these tests, thrombolytic therapy should not be delayed while results are pending unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, (2) the patient is currently on or has recently received anticoagulants (eg, heparin, warfarin, a direct thrombin inhibitor, or a direct factor Xa inhibitor), or (3) use of anticoagulants is not known. Otherwise, treatment with intravenous tPA can be started before availability of coagulation test results but should be discontinued if the INR, PT, or aPTT exceed the limits stated in the table, or if platelet count is <100,000 mm^3.

¶ With careful consideration and weighting of risk-to-benefit, patients may receive intravenous thrombolysis despite one or more warnings.

Δ Patients who have a persistent neurologic deficit that is potentially disabling, despite improvement of any degree, should be treated with intravenous thrombolysis in the absence of other contraindications. Any of the following should be considered disabling deficits:

- Complete hemianopia: ≥2 on NIHSS question 3, or
- Severe aphasia: ≥2 on NIHSS question 9, or
- Visual or sensory extinction: ≥1 on NIHSS question 11, or
- Any weakness limiting sustained effort against gravity: ≥2 on NIHSS question 5 or 6, or
- Any deficits that lead to a total NIHSS >5, or
- Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner using clinical judgment

◇ Patients may be treated with intravenous thrombolysis if glucose level is subsequently normalized.

§ The potential risks of bleeding with tPA from injuries related to the trauma should be weighed against the anticipated benefits of reduced stroke-related neurologic deficits.

¥ The increased risk of surgical site bleeding with tPA should be weighed against the anticipated benefits of reduced stroke-related neurologic deficits.

‡ There is a low increased risk of new bleeding with tPA in the setting of past gastrointestinal or genitourinary bleeding. However, tPA administration within 21 days of gastrointestinal bleeding is not recommended.

† Intravenous thrombolysis is reasonable in patients with a seizure at stroke onset if evidence suggests that residual impairments are secondary to acute ischemic stroke and not to a postictal phenomenon.

** tPA can be given in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding.

¶¶ The safety and efficacy of administering tPA is uncertain for these relative exclusions.

ΔΔ Although these were exclusions in the trial showing benefit in the 3 to 4.5 hour window, intravenous tPA appears to be safe and may be beneficial for patients with these criteria, including patients taking oral anticoagulants with an INR <1.7.

Adapted from:

1. *Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359:1317.*
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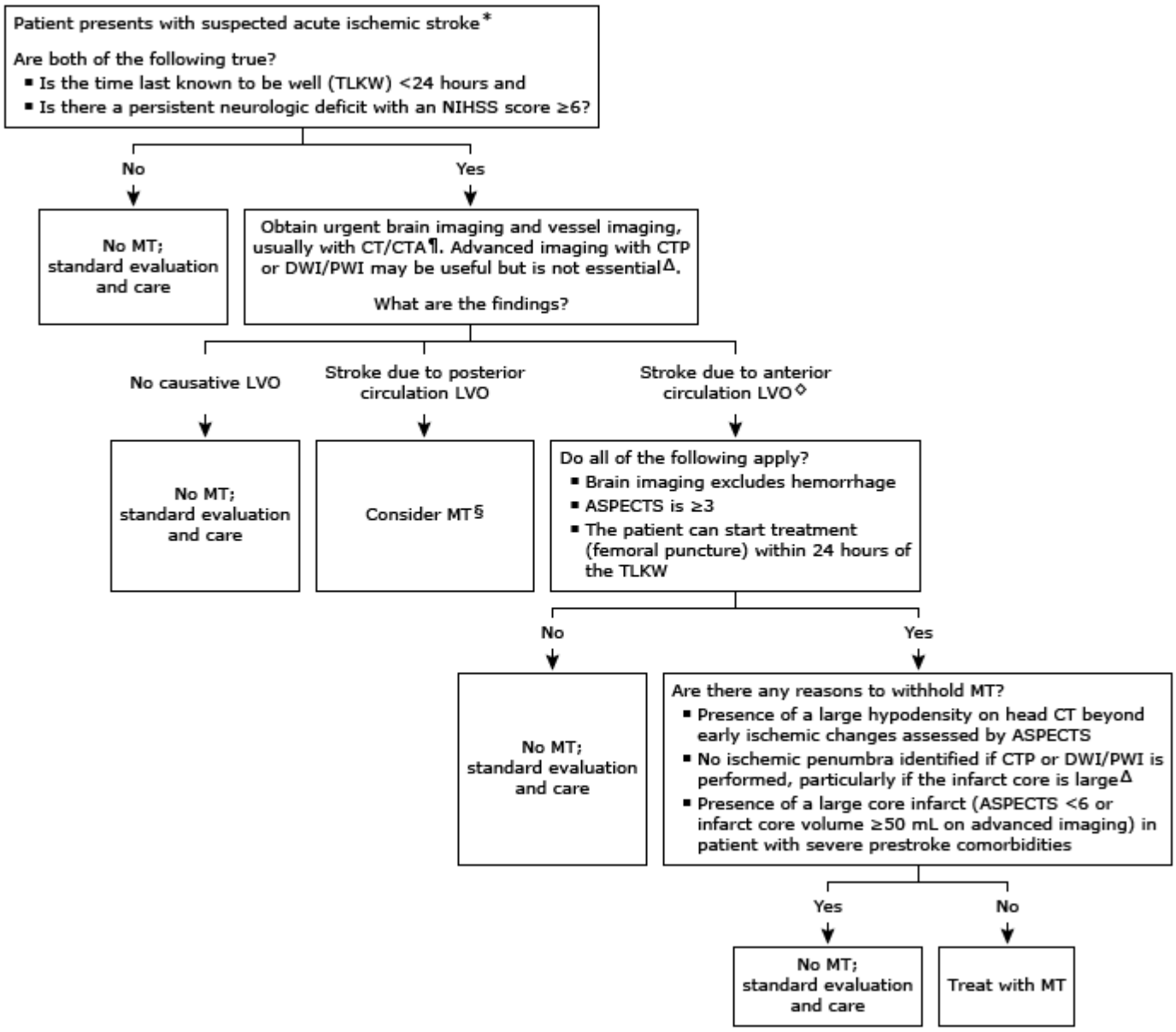
Graphic 71462 Version 27.0

Patient selection for mechanical thrombectomy to treat acute ischemic stroke



MT should be performed at a stroke center with appropriate neurointerventional expertise. The TLKW is judged to be the time of stroke symptom onset (if known), or the time the patient was last seen at their baseline for patients with wake-up stroke or those found down. The ASPECTS method is used to assess the extent of ischemic changes on head CT or DWI. Refer to UpToDate topics for a full discussion of MT, including calculation of ASPECTS, NIHSS, and mRS, and other clinical issues pertaining to MT.

ACA: anterior carotid artery; ASPECTS: Alberta Stroke Program Early CT Score; CT: computed tomography; CTA: computed tomography angiography; CTP: computed tomography perfusion; DSA: digital subtraction angiography; DWI: diffusion-weighted magnetic resonance imaging; ICA: internal carotid artery; LVO: large vessel (artery) occlusion; MCA: middle cerebral artery; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; PWI: perfusion-weighted magnetic resonance imaging.

* All patients with acute ischemic stroke should be simultaneously evaluated for treatment with intravenous thrombolysis; refer to UpToDate topics for details.

¶ Urgent imaging is usually done with CT and CTA, less often with MRI and MRA.

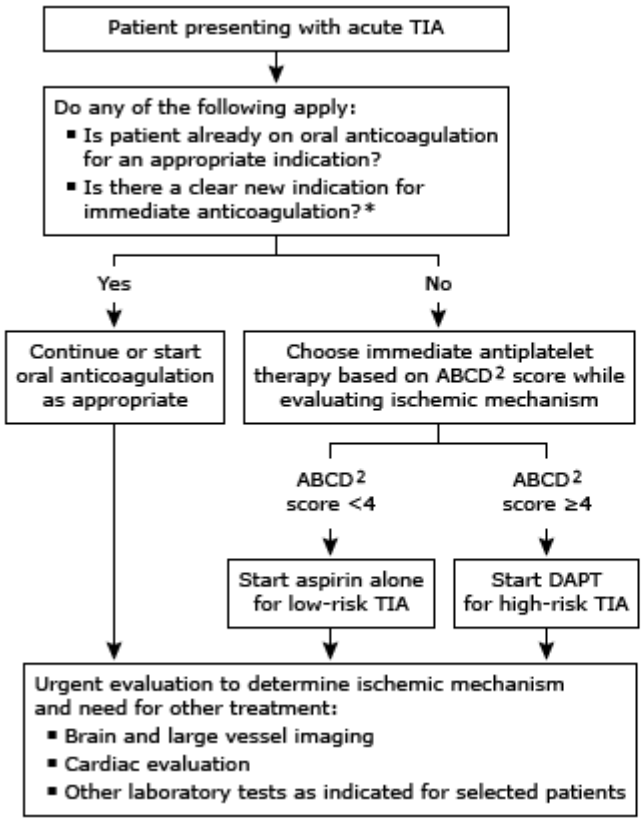
Δ Advanced imaging is not essential but can be used at centers with CTP or DWI/PWI and automated software imaging analysis to determine infarct volume; patients can be selected for MT if they have salvageable brain tissue with a mismatch between a relatively larger area of hypoperfusion (ischemic penumbra) and a smaller area of irreversibly injured brain tissue (infarct core). Refer to UpToDate text for details.

◇ There is intracranial arterial occlusion of the distal ICA, or the M1 or proximal M2 segment of the MCA, as shown by CTA, MRA, or DSA.

§ MT may be a treatment option at expert stroke centers for patients with basilar artery LVO, but benefit is uncertain.

Graphic 141874 Version 2.0

Immediate antithrombotic treatment of transient ischemic attack (TIA)



ABCD^2 score	
Age:	
≥60 years	+1
<60 years	0
BP at TIA presentation:	
SBP ≥140 or DBP ≥90	+1
SBP <140 and SBP <90	0
Clinical features:	
Unilateral weakness	+2
Isolated speech disturbance	+1
Other	0
Duration of TIA symptoms:	
≥60 minutes	+2
10 to 59 minutes	+1
<10 minutes	0
Diabetes:	
Present	+1
Absent	0

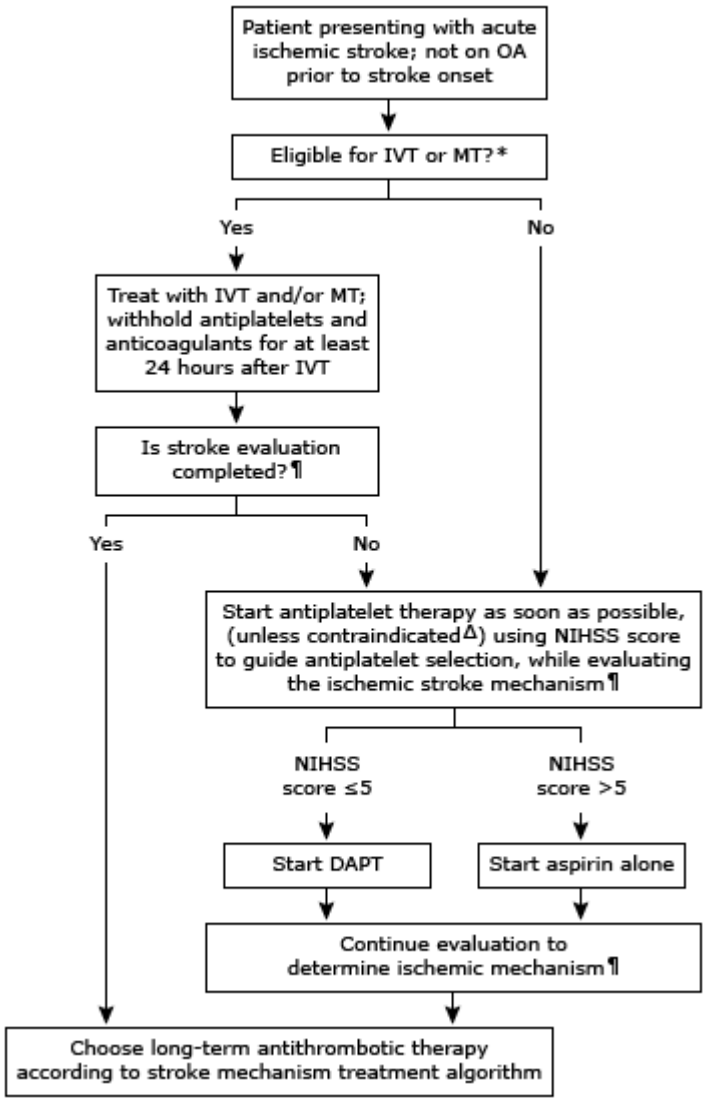
This algorithm is intended to provide basic guidance regarding the use of immediate use of antithrombotic therapy for patients with a TIA. For further details, including suggested dosing regimens of antiplatelet and anticoagulant agents, refer to the relevant UpToDate topic reviews.

ABCD^2: age, blood pressure, clinical features, duration of symptoms, and diabetes; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor); BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

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

Graphic 131692 Version 1.0

Immediate antithrombotic treatment of acute ischemic stroke



This algorithm is intended to provide basic guidance regarding the immediated 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.

OA: oral anticoagulants; IVT: intravenous thrombolysis; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor).

* Refer to text and associated algorithm for details.

¶ Brain and large vessel imaging, cardiac evaluation, and (for select patients) other laboratory tests.

Δ For severe systemic or symptomatic intracranial bleeding, withhold all anticoagulant and antiplatelet therapy for one to two weeks or until the patient is stable.

Graphic 131697 Version 2.0

ABCD^2 score

The ABCD^2 score can be used to estimate the risk of ischemic stroke in the first two days after TIA. The score is tallied as follows:	
Age:	
≥60 years	1 point
<60 years	0 points
Blood pressure elevation when first assessed after TIA:	
Systolic ≥140 mmHg **or** diastolic ≥90 mmHg	1 point
Systolic <140 mmHg **and** diastolic <90 mmHg	0 points
Clinical features:	
Unilateral weakness	2 points
Isolated speech disturbance	1 point
Other	0 points
Duration of TIA symptoms:	
≥60 minutes	2 points
10 to 59 minutes	1 point
<10 minutes	0 points
Diabetes:	
Present	1 point
Absent	0 points

Data from: Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007; 369:283.

Graphic 62381 Version 3.0

National Institutes of Health Stroke Scale (NIHSS)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (ie, repeated requests to patient to make a special effort).

Instructions	Scale definition	Score
1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert;** but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	____
1b. Level of consciousness questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	____
1c. Level of consciousness commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (ie, follows none, one or two commands). Patients with	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	____

trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.		
2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (cranial nerves III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	____
4. Facial palsy: Ask - or use pantomime to encourage - the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	____

5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **5a. Left arm** **5b. Right arm**	____
6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **6a. Left leg** **6b. Right leg**	____
7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN),	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain:_____	____

and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.		
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	____
9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or	0 = **Normal.**	____

repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	
11. Extinction and inattention (formerly neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	____
		____

Adapted from: Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 1997; 28:307.

Graphic 61698 Version 8.0

Barthel Index

Activity	Score
Feeding	
0 = Unable	
5 = Needs help cutting, spreading butter, etc, or requires modified diet	
10 = Independent	
Bathing	
0 = Dependent	
5 = Independent (or in shower)	
Grooming	
0 = Needs to help with personal care	
5 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = Dependent	
5 = Needs help but can do about half unaided	
10 = Independent (including buttons, zips, laces, etc)	
Bowels	
0 = Incontinent (or needs to be given enemas)	
5 = Occasional accident	
10 = Continent	
Bladder	
0 = Incontinent, or catheterized and unable to manage alone	
5 = Occasional accident	
10 = Continent	
Toilet use	
0 = Dependent	
5 = Needs some help, but can do something alone	
10 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	
0 = Unable, no sitting balance	

5 = Major help (one or two people, physical), can sit	
10 = Minor help (verbal or physical)	
15 = Independent	
Mobility (on level surfaces)	
0 = Immobile or <50 yards	
5 = Wheelchair independent, including corners, >50 yards	
10 = Walks with help of one person (verbal or physical) >50 yards	
15 = Independent (but may use any aid; for example, stick) >50 yards	
Stairs	
0 = Unable	
5 = Needs help (verbal, physical, carrying aid)	
10 = Independent	
Total (0-100):	

The Barthel ADL Index: Guidelines

- The index should be used as a record of what a patient does, not as a record of what a patient could do
- The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason
- The need for supervision renders the patient not independent
- Patient performance should be established using the best available evidence provided by the patient, family, friends and caregivers; direct observation and common sense are also important, but direct testing is not needed
- Usually the patient's performance over the preceding 24 to 48 hours is important, but occasionally longer periods will be relevant
- Middle categories imply that the patient supplies over 50 percent of the effort
- Use of aids to be independent is allowed

ADL: activities of daily living.

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1. *Mahoney FI, Barthel D. Functional evaluation: The Barthel Index. Maryland State Medical Journal 1965; 14:56. Used with permission.*
2. *Loewen SC, Anderson BA. Predictors of stroke outcome using objective measurement scales. Stroke 1990; 21:78.*
3. *Gresham GE, Phillips TF, Labi ML. ADL status in stroke: Relative merits of three standard indexes. Arch Phys Med Rehabil 1980; 61:355.*
4. *Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: A reliability study. Int Disability Study 1988; 10:61.*

Graphic 77371 Version 3.0

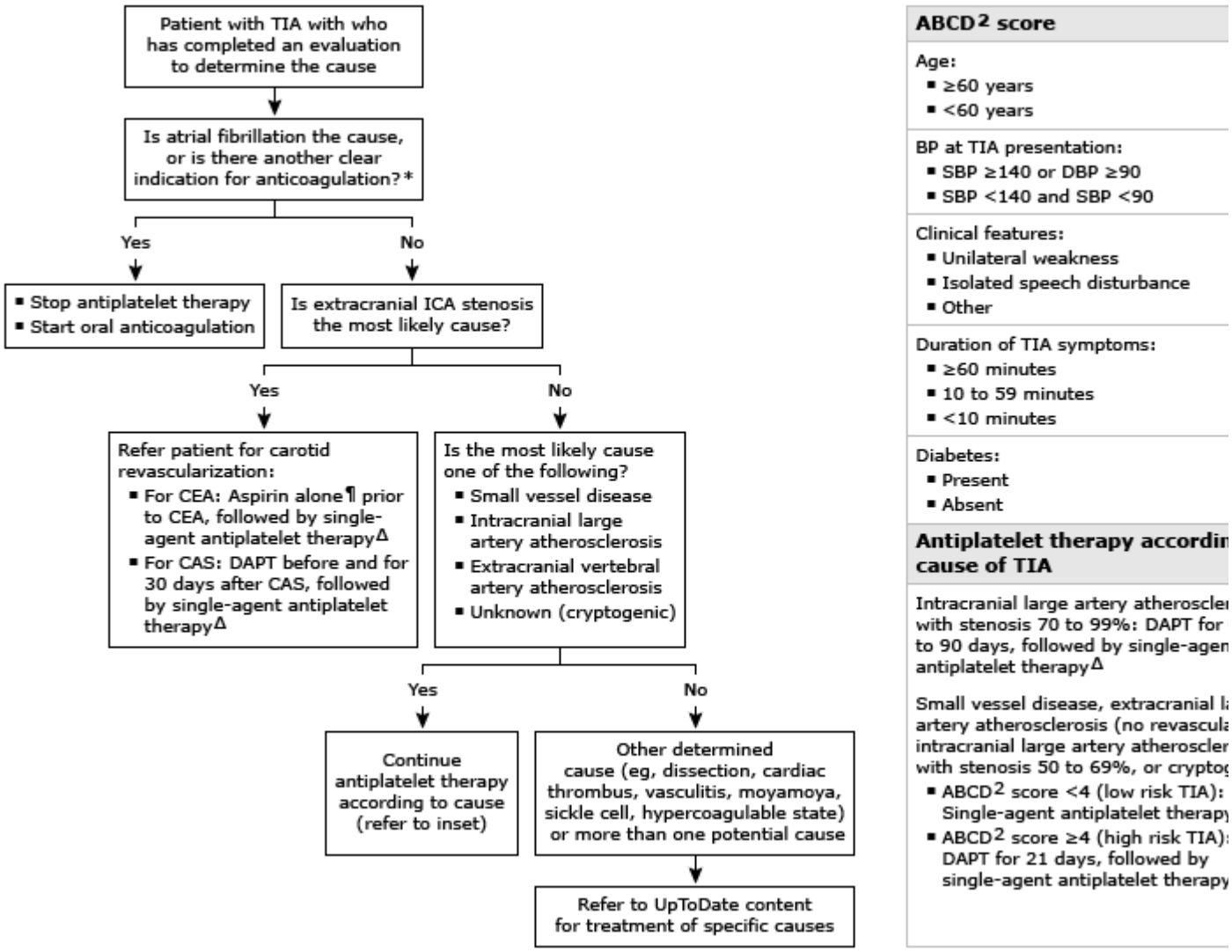
Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Reproduced with permission from: Van Swieten JC, Koudstaa PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19:604. Copyright © 1988 Lippincott Williams & Wilkins.

Graphic 75411 Version 13.0

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.

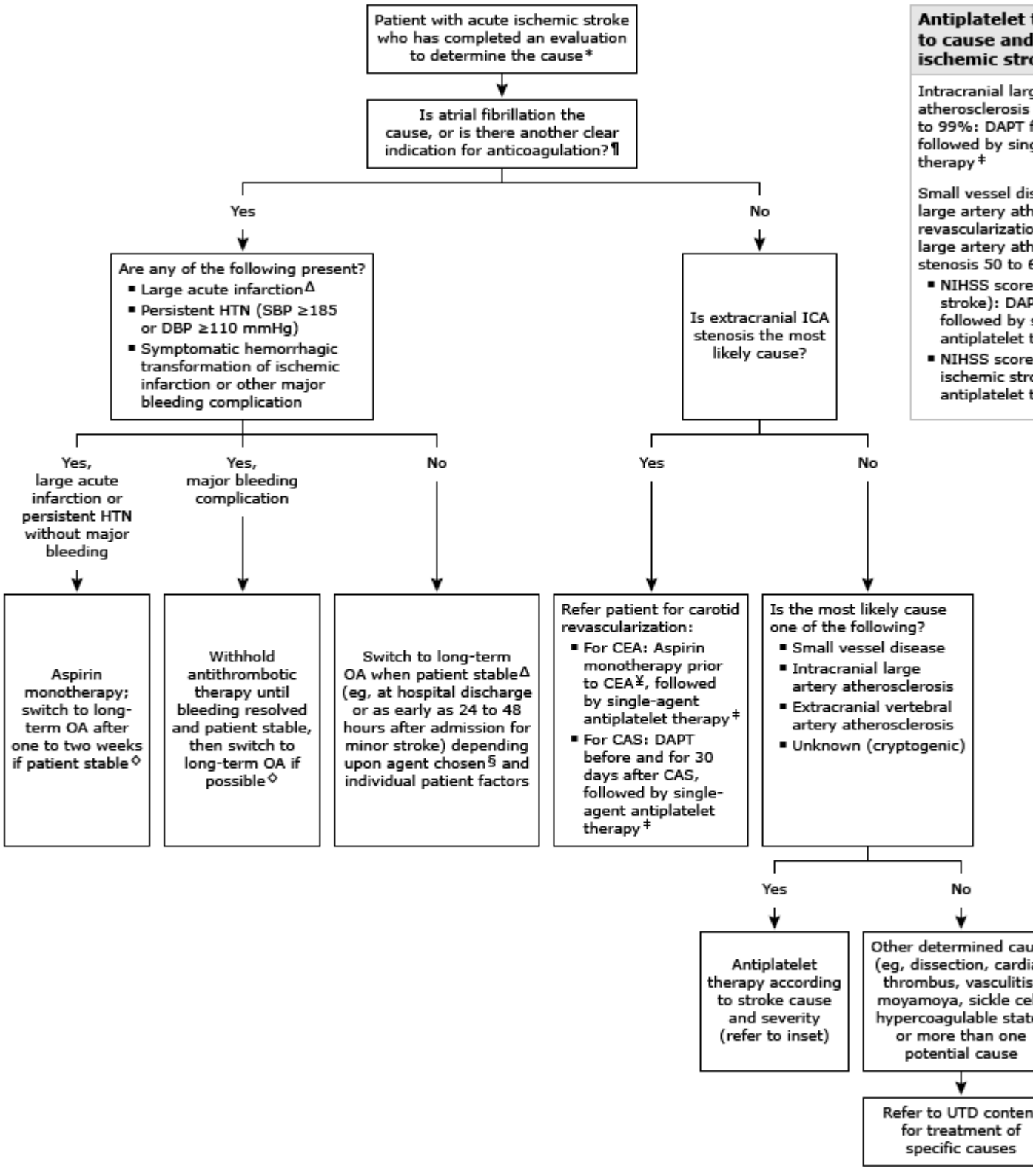
* Indications for long-term oral anticoagulation include atrial fibrillation, ventricular thrombus, mechanical heart valve, and treatment of venous thromboembolism.

¶ 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

Heparin-adjusted nomogram for stroke

Initial dosing for continuous intravenous heparin infusion	
Weight (kg)	**Initial infusion (U/hour)**
<50	500
50 to 59	600
60 to 69	700
70 to 79	800
80 to 89	900
90 to 99	1000
100 to 109	1100
110 to 119	1200
>119	1400

Heparin adjustment based upon aPTT drawn six hours after initiation of therapy			
aPTT (seconds)	**Stop infusion**	**Rate change**	**Repeat aPTT**
<40	No	Increase by 250 U/hour	6 hours
40 to 49	No	Increase by 150 U/hour	6 hours
50 to 59	No	Increase by 100 U/hour	6 hours
60 to 90	No	No change	Next morning
91 to 100	No	Decrease by 100 U/hour	6 hours
101 to 120	No	Decrease by 150 U/hour	6 hours
>120	No	Decrease by 250 U/hour	6 hours

No bolus is administered in patients with acute stroke.

Data from: Toth C, Voll C. Validation of a weight-based nomogram for the use of intravenous heparin in transient ischemic attack or stroke. Stroke 2002; 33:670.

Graphic 53377 Version 2.0