CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic and Thrombolytic Therapy for Ischemic Stroke

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Objectives: **This article provides recommendations on the use of antithrombotic therapy in patients with stroke or transient ischemic attack (TIA).**

Methods: **We generated treatment recommendations (Grade 1) and suggestions (Grade 2) based on high (A), moderate (B), and low (C) quality evidence.**

Results: **In patients with acute ischemic stroke, we recommend IV recombinant tissue plasminogen activator (r-tPA) if treatment can be initiated within 3 h (Grade 1A) or 4.5 h (Grade 2C) of symptom onset; we suggest intraarterial r-tPA in patients ineligible for IV tPA if treatment can be initiated within 6 h (Grade 2C); we suggest against the use of mechanical thrombectomy (Grade 2C) although carefully selected patients may choose this intervention; and we recommend early aspirin therapy at a dose of 160 to 325 mg (Grade 1A). In patients with acute stroke and restricted mobility, we suggest the use of prophylactic-dose heparin or intermittent pneumatic compression devices (Grade 2B) and suggest against the use of elastic compression stockings (Grade 2B). In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), the combination of clopidogrel plus aspirin (Grade 1B), or triflusal (Grade 2B). Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin (Grade 2B) or cilostazol (Grade 2C). In patients with a history of stroke or TIA and atrial fibrillation we recommend oral anticoagulation over no antithrombotic therapy, aspirin, and combination therapy with aspirin and clopidogrel (Grade 1B).**

Conclusion: **These recommendations can help clinicians make evidence-based treatment decisions with their patients who have had strokes.** ***CHEST 2012; 141(2)(Suppl):e601S–e636S***

Abbreviations: AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke or transient ischemic attack; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; HR = hazard ratio; IA = intraarterial; ICH = intracerebral hemorrhage; INR = international normalized ratio; IST = International Stroke Trial; LMWH = low- molecular-weight heparin; MCA = middle cerebral artery; MI = myocardial infarction; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; PE = pulmonary embolism; PFO = patent foramen ovale; PICO = patient, intervention, comparison, outcome; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RR = relative risk; r-tPA = recombinant tissue plasminogen activator; TIA = transient ischemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.1.1. In patients with acute ischemic stroke in whom treatment can be initiated within 3 h of symptom onset, we recommend IV recombinant tissue plasminogen activator (r-tPA) over no IV r-tPA (Grade 1A)**.**

2.1.2. In patients with acute ischemic stroke in whom treatment can be initiated within 4.5 h but not within 3 h of symptom onset, we suggest IV r-tPA over no IV r-tPA (Grade 2C)**.**

2.1.3. In patients with acute ischemic stroke in whom treatment cannot be initiated within 4.5 h of symptom onset, we recommend against IV r-tPA (Grade 1B)**.**

2.2.1. In patients with acute ischemic stroke due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV r-tPA, we suggest intraarterial (IA) r-tPA initiated within 6 h of symptom onset over no IA r-tPA (Grade 2C)**.**

2.2.2. In patients with acute ischemic stroke we suggest IV r-tPA over the combination IV/IA r-tPA (Grade 2C)**.**

Remarks: Carefully selected patients who value the uncertain benefits of combination IV/IA thrombolysis higher than the associated risks may choose this intervention. Patients who prefer to avoid risk in the setting of uncertain benefits are more likely to choose IV r-tPA alone.

2.3. In patients with acute ischemic stroke, we suggest against the use of mechanical thrombectomy (Grade 2C)**.**

Remarks: Carefully selected patients who value the uncertain benefits of mechanical thrombectomy higher than the associated risks may choose this intervention.

2.4. In patients with acute ischemic stroke or transient ischemic attack (TIA), we recommend early (within 48 h) aspirin therapy at a dose of 160 to 325 mg over no aspirin therapy (Grade 1A)**.**

2.5. In patients with acute ischemic stroke or TIA, we recommend early (within 48 h) aspirin therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation (Grade 1A)**.**

3.1.1. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) or intermittent pneumatic compression devices over no prophylaxis (Grade 2B)**.**

3.1.2. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B)**.**

3.1.3. In patients with acute stroke and restricted mobility, we suggest against elastic compression stockings (Grade 2B)**.**

Remarks: Pharmacologic and mechanical prophylaxis should be initiated as early as possible and should be continued throughout the hospital stay or until the patient has regained mobility. Mechanical devices should be temporarily removed as often as needed to

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allow for early mobilization and screening for skin complications.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

3.2.1. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose subcutaneous heparin (UFH or LMWH) started between days 2 and 4 or intermittent pneumatic compression devices over no prophylaxis (Grade 2C)**.**

3.2.2. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B)**.**

3.2.3. In patients with primary intracerebral hemorrhage and restricted mobility, we suggest against elastic compression stockings (Grade 2B)**.**

Remarks: Patients who prefer to avoid a theoretically increased risk of rebleeding with heparin would favor mechanical prophylaxis with intermittent pneumatic compression devices over pharmacologic prophylaxis.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

4.1.1. In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended-release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A)**, oral anticoagulants** (Grade 1B)**, the combination of clopidogrel plus aspirin** (Grade 1B)**, or triflusal** (Grade 2B)**.**

4.1.2. Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin (Grade 2B) **or cilostazol** (Grade 2C)**.**

Remarks: With long-term use (>5 y), the benefit of clopidogrel over aspirin in preventing major vascular events may be offset by a reduction in cancer-related mortality with regimens that contain aspirin.

4.2.1. In patients with a history of ischemic stroke or TIA and atrial fibrillation (AF), including paroxysmal AF, we recommend oral anticoagulation over no antithrombotic therapy (Grade 1A)**, aspirin** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)**.**

4.2.2. In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, we suggest oral anticoagulation with dabigatran 150 mg bid over adjusted-dose VKA therapy (target International Normalized Ratio range, 2.0-3.0) (Grade 2B)**.**

4.2.3. In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel over aspirin (Grade 1B)**.**

Remarks: Patients should be treated (ie, bridged) with aspirin until anticoagulation has reached a therapeutic level.

Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset. Earlier anticoagulation can be considered for patients at low risk of bleeding complications (eg, those with a small infarct burden and no evidence of hemorrhage on brain imaging). Delaying anticoagulation should be considered for patients at high risk of hemorrhagic complications (eg, those with extensive infarct burden or evidence of significant hemorrhagic transformation on brain imaging).

Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less).

4.3. In patients with a history of a symptomatic primary intracerebral hemorrhage (ICH), we suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke (Grade 2C)**.**

Remarks: Patients who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep hemorrhages) and relatively high risk ($>7\%$ per year) of thromboembolic events (eg, with mechanical heart valves or $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke or TIA) score ≥ 4 points).

5.1. In patients with cerebral venous sinus thrombosis, we suggest anticoagulation over no anticoagulant therapy during the acute and chronic phases (Grade 2C)**.**

This article provides guidance for clinicians managing patients with stroke. The article covers three different stroke subpopulations: (1) patients with

ischemic stroke or transient ischemic attacks (TIA), (2) patients with intracerebral hemorrhage (ICH), and (3) patients with cerebral venous sinus thrombosis.

The interventions of interest include both drug-based and device-based interventions. The drugs covered include antiplatelet agents, oral anticoagulants, parenteral anticoagulants, and thrombolytic agents. The devices covered include embolectomy devices used for the removal of blood clots from the cerebral circulation and devices used to prevent DVT formation in patients hospitalized for stroke.

Table 1 lists the clinical questions in PICO (population, intervention, comparator, and outcome) format. Recommendations for the primary prevention of stroke are addressed in the articles by Vandvik et al[1] (coronary artery disease), Alonso-Coello et al[2] (peripheral arterial disease), You et al[3] (atrial fibrillation [AF]), and Whitlock et al[4] (valvular disease) in this supplement. Recommendations on antithrombotic use for patients undergoing carotid endarterectomy are discussed in the article on peripheral artery disease by Alonso-Coello et al.[2]

1.0 Methods

Guideline development for this article followed the procedures set forward in the article by Guyatt et al[5] in this supplement. A systematic review of the literature was conducted in November 2009. A systematic approach developed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group was used as the foundation to judge the quality of evidence and to determine the strength of our recommendations.[6] Meta-analyses were performed using RevMan 5.1 (v5.1.1; The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). A random effects model was used for all meta-analyses, with the exception of analyses that included only two studies or analyses that included a single dominant study with a markedly different result from the other studies.

For almost all interventions discussed in this article we included all-cause mortality as a critical outcome. For additional outcomes (eg, stroke, myocardial infarction [MI]), to avoid double counting, we report nonfatal events as opposed to total events. When available, we used observational studies to determine baseline risks (control group risks). When observational data were absent or of low quality, we used data from randomized trials.

Patients have varying levels of bleeding risk. The risk of bleeding is increased in patients who have experienced a previous major bleeding event, severe renal failure, concomitant antiplatelet/thrombolytic use, or are >80 years old. We, do not provide bleeding risk-specific recommendations, however, because validated risk-stratification tools for patients with stroke do not exist. Clinicians and patients need to consider the risk of bleeding when making treatment decisions, specifically for interventions for which the recommendation is weak. In situations of uncertain benefit of a treatment and an appreciable probability of harm, we took a "*primum non nocere*" approach and recommended against such treatment.

We summarize our results in the text in the form of succinct summary of findings tables. The Supplemental Tables include the more detailed evidence profiles. The evidence profiles and summary of findings tables were generated with GRADEpro, a computer program designed for guideline development according to GRADE criteria.[7]

1.1 Values and Preferences

In developing the recommendations, we explicitly accounted for patients' values for the different outcomes of interest. For that purpose, and as described in the article by Guyatt et al,[5] we used ratings from participating guideline panelists informed by a systematic review of the literature.[8] We considered that values vary appreciably between individuals and that there is considerable uncertainty about average patient values. We assumed that, on average, patients would find a stroke (ischemic or hemorrhagic) three times as aversive as a major extracranial bleeding event (typically GI bleeding). We attributed a similar disutility (negative value) to DVT, pulmonary embolism (PE), DVT with PE, and major GI bleeding. We assumed that vitamin K antagonist (VKA) therapy does not have an important negative impact on quality of life.[8]

2.0 Acute Ischemic Stroke Treatment

Therapies aimed at restoring perfusion are the mainstay of acute stroke therapy. The goal of early reperfusion therapy is to minimize neurologic impairment, long-term disability, and stroke-related mortality. Reperfusion can be achieved through administration of thrombolytic agents such as recombinant tissue plasminogen activator (r-tPA) (sections 2.1 and 2.2) or by mechanical removal of blood clots (section 2.3). A second focus of acute stroke therapy is to prevent early recurrence of cerebrovascular events. This includes treatment with antiplatelet agents (section 2.4) and anticoagulants (section 2.5). Prevention of VTE in patients hospitalized for acute stroke is discussed in section 3.

In developing recommendations for the acute management of stroke, we considered the following patient-important outcomes: mortality at 90 days and good functional outcome among survivors at 90 days. For recommendations related to IV thrombolytic therapy, we defined favorable functional outcome as a score of ≤ 1 out of a maximum of 5 on the modified Rankin Scale (mRS); this indicates full functional recovery with no symptoms or only minor symptoms that do not cause functional impairment. For recommendations dealing with endovascular stroke therapy, a favorable outcome was defined as an mRS score ≤ 2, indicating functional independence for activities of daily living. Different definitions of favorable outcome were chosen because patients eligible for endovascular treatment, on average, have more severe strokes than the population of patients who are eligible for IV thrombolysis. Consequently, "functional independence" reflects a marked improvement from presenting symptoms for the average patient who is eligible for endovascular therapy, whereas "full functional recovery" reflects a marked improvement for the average patient who is eligible

Table 1—*Structured Clinical Questions*

Rec.	Table	S-Table[a]	Population	Intervention(s)	Comparator	Outcome	Method
			Ischemic stroke: acute management				
2.1.1 2.1.2 2.1.3	2, 3, 4	1, 2, 3, 4	Patients with acute ischemic stroke	IV r-tPA	No IV r-tPA	Mortality, good functional outcome	R
2.2.1	5	5, 6	Patients with acute ischemic stroke	Intraarterial r-tPA	No IA r-tPA	Same as above	R
2.2.2	6	5, 7	Patients with acute ischemic stroke	Intraarterial + IV r-tPA	IV r-tPA	Same as above	C
2.3		8, 9, 10	Patients with acute ischemic stroke	Mechanical thrombectomy	No mechanical thrombectomy	Same as above	C
2.4	7	11, 12	Patients with acute ischemic stroke or TIA	Aspirin	No aspirin	Mortality, good functional outcome, nonfatal major extracranial bleed	R
2.5	8	13, 14	Patients with acute ischemic stroke or TIA	Therapeutic anticoagulation	Aspirin	Same as above	R
			VTE prevention in stroke patients				
3.1.1	9	15, 16	Patients with acute ischemic stroke and restricted mobility	Prophylactic-dose heparin	No prophylactic-dose heparin	Mortality, PE, symptomatic DVT, symptomatic intracranial hemorrhage, major extracranial hemorrhage	R
3.1.2 3.2.2	10	15, 17	Patients with acute stroke (ischemic or hemorrhagic) and restricted mobility	Prophylactic-dose unfractionated heparin	Prophylactic-dose LMWH	Same as above	R
3.1.1 3.2.1	11	15, 18	Patients with acute stroke (ischemic or hemorrhagic) and restricted mobility	Intermittent pneumatic compression stockings	No intermittent pneumatic compression stockings	Mortality, PE, symptomatic DVT	R
3.1.3 3.2.3	12	15, 19	Patients with acute stroke (ischemic or hemorrhagic) and restricted mobility	Elastic compression stockings	No elastic compression stockings	Mortality, PE, symptomatic DVT, skin complications	R
3.2.1	13	15, 20	Patients with primary ICH and restricted mobility	Prophylactic-dose heparin	No prophylactic-dose heparin	Mortality, PE, symptomatic DVT, rebleeding	R
3.2.1	14	15, 21	Patients with primary ICH and restricted mobility	Early (day 2) prophylactic-dose heparin	Late (day 4) prophylactic-dose heparin	Same as above	R
			Secondary stroke prevention				
4.1.1	15	22, 23	Patients with a history of noncardioembolic ischemic stroke or TIA	Aspirin	No aspirin	Mortality, nonfatal recurrent stroke, nonfatal MI, nonfatal major extracranial bleeding	R
4.1.1 4.1.2	16	22, 24	Patients with a history of noncardioembolic ischemic stroke or TIA	Clopidogrel	Aspirin	Same as above	R
4.1.1 4.1.2	17	22, 25	Patients with a history of noncardioembolic ischemic stroke or TIA	Aspirin plus dipyridamole	Aspirin	Same as above	R
4.1.1 4.1.2	18	22, 26	Patients with a history of noncardioembolic ischemic stroke or TIA	Aspirin plus dipyridamole	Clopidogrel	Same as above	R
4.1.1	19	22, 27	Patients with a history of noncardioembolic ischemic stroke or TIA	Aspirin plus clopidogrel	Clopidogrel	Same as above	R
4.1.1 4.1.2	20	22, 28	Patients with a history of noncardioembolic ischemic stroke or TIA	Cilostazol	Aspirin	Same as above	R

(Continued)

Table 1—*Continued*

Rec.	Table	S-Table[a]	Population	Intervention(s)	Comparator	Outcome	Method
4.1.1	21	22, 29	Patients with a history of noncardioembolic ischemic stroke or TIA	Triflusal	Aspirin	Same as above	R
4.1.1	22	30, 31	Patients with a history of noncardioembolic ischemic stroke or TIA	Oral anticoagulation	Aspirin	Same as above	R
4.2.1	23		Patients with AF and a history of stroke or TIA	Oral anticoagulation	No Oral anticoagulation	Same as above	R
4.2.2	See You et al[3]		Patients with AF and a history of stroke or TIA	Dabigatran	No antiplatelets	Same as above	R
4.2.3			Patients with AF and a history of stroke or TIA	Aspirin and clopidogrel	Aspirin	Same as above	R
4.3			Patients with a history of a primary ICH and an indication for Coumadin for ischemic stroke prevention	Antithrombotic therapy	No antithrombotic therapy	QALY	D
			Cerebral venous sinus thrombosis				
5.1	24	32, 33	Patients with cerebral venous sinus thrombosis	Therapeutic anticoagulation	No therapeutic anticoagulation	Mortality, good functional outcome, nonfatal major bleeding	R

AF = atrial fibrillation; C = cohort study; D = decision model; ICH = intracerebral hemorrhage; MI = myocardial infarction; PE = pulmonary embolism; QALY = quality-adjusted life-year; Rec. = recommendation; R = randomized controlled trial; r-tPA = recombinant tissue plasminogen activator; TIA = transient ischemic attack.

[a]See supplemental tables in the online supplement.

for IV thrombolysis. We did not consider stroke recurrence or symptomatic intracerebral hemorrhage (ICH) as separate outcomes because the consequences of clinically relevant recurrent strokes are captured by the mortality and functional outcome measures. However, because ICH is the most feared complication in this setting, we reported rates of symptomatic ICH in the footnotes of the summary of findings tables. We did not consider major extracranial bleeding because of the relatively low incidence.[9] We did not consider surrogate outcomes (eg, radiographic recanalization with thrombectomy) when data on the corresponding patient-important outcomes (eg, functional status) were available.

2.1 IV r-tPA for Acute Ischemic Stroke

Systematic reviews summarizing the findings of nine randomized, placebo-controlled trials of IV r-tPA (Table S1) were used to generate the evidence tables. (Tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement. See the "Acknowledgments" for more information.) Please refer to Tables 2-4 and Tables S2-S4.[10,11]

2.1.1 Treatment With IV r-tPA Within 3 h: There is high-quality evidence that thrombolytic therapy, administered within 3 h of symptom onset, increases the likelihood of a good functional outcome but has little or no effect on mortality. These data are based on a pooled analysis of individual patient data from four trials (Table 2, Table S2).[10,11] In addition, the safety results of three large phase 4 studies of IV r-tPA therapy in routine clinical practice were similar to those of the major randomized trials of IV r-tPA.[12-14] In Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), the largest phase 4 study, the incidence of symptomatic ICH defined as any intracerebral bleeding with neurologic worsening was 7.3% compared with 5.9% in the stroke trials.[14] Additional studies of r-tPA use in routine clinical practice have typically reported symptomatic ICH rates $<7\%$.[15-21] These studies also demonstrated similar results in academic centers and community hospitals and in sites with frequent and infrequent use of r-tPA.

2.1.2 Treatment With IV r-tPA Between 3 and 4.5 h: There is high-quality evidence that IV r-tPA administered within the 3- to 4.5-h time window is associated with an increased chance of favorable functional outcome. The effect is, however, smaller than for treatment administered within 3 h (69 more favorable events per 1,000 patients in the 3-4.5-h window compared with 154 per 1,000 in the <3-h window). Results failed to show or exclude a beneficial or detrimental effect on mortality (Table 3, Table S3).

Table 2—*[Section 2.1.1] Summary of Findings: IV r-tPA Initiated Within 3 h in Patients With Acute Ischemic Stroke*[10-11]

Outcomes	No. of Participants (Studies) Follow-Up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk With No IV r-tPA	Risk Difference With IV r-tPA (95% CI)
Overall mortality[a]	930 (4 studies[b]) 90 d	High[c-e]	RR, 1.00 (0.76-1.33)[f,g]	120 deaths per 1,000[h]	0 fewer deaths per 1,000 (from 29 fewer to 40 more)
Good functional outcome,[i] mRS 0-1	930 (4 studies[b]) 90 d	High[c,j]	RR, 1.44 (1.21-1.72)[k,l]	350 excellent outcomes per 1,000[m]	154 more excellent outcomes per 1,000 (from 74 more to 252 more)

ECASS = The European Cooperative Acute Stroke Study; EPITHET = Echoplanar Imaging Thrombolytic Evaluation Trial; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; mRS = modified Rankin Scale; NINDS = National Institute of Neurological Disorders and Stroke; RR = relative risk. See Table 1 legend for expansion of other abbreviations.

[a]Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h, OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with tPA and 0.8% with placebo; seven studies.

[b]NINDS (1995), ATLANTIS, ECASS I (1995), and ECASS II (1998).

[c]Allocation unclear in two studies.

[d]$I^2 = 38\%$.

[e]The CI for mortality is borderline for the judgment of imprecision for RR. We thus judged imprecision for the mortality outcome by comparing the values across its CI to the point estimate for the outcome against which it is being considered (ie, good functional outcome) and whether the balance allows a recommendation in favor of IV tPA. Considering the value of 0.4 given to disability (see results of the values and preference exercise), 154 additional patients with good outcome (point estimate for good functional outcome) balances favorably with 40 additional deaths (upper boundary for the mortality outcome). Consequently, we did not rate down for imprecision.

[f]Data from Wardlaw et al.[11]

[g]Fixed effect model because NINDS (1995) judged to be dominant.

[h]Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trial (NINDS [1995], ECASS, ATLANTIS, and EPITHET).

[i]Symptomatic nonfatal ICH not reported separately because this outcome is captured under good functional outcome. Symptomatic nonfatal ICH more likely with tPA (8.6%) than placebo (1.5%). OR = 4.28; 95% CI, 2.4-7.8.

[j]$I^2 = 0\%$ (based on Wardlaw et al,[11] mRS 3-5 outcome).

[k]Data from Lees et al.[10]

[l]Calculated based on total numbers of mRS 0-1 in all trials combined, because numbers for individual trials on this outcome were not available for this time window.

[m]Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS, ECASS, ATLANTIS, and EPITHET).

One trial (The European Cooperative Acute Stroke Study [ECASS] III) enrolled patients exclusively during the 3- to 4.5-h time window, whereas only subsets of the patients from four other trials were treated in this time window.[22-26] The ECASS III trial, which is the dominant study in our analysis, had two exclusion criteria that were not present in most previous trials of IV r-tPA; patients > 80 years old and those with a history of the combination of prior stroke and diabetes mellitus were excluded. In addition, patients with a severe stroke assessed clinically (ie, National Institutes of Health Stroke Scale [NIHSS] > 25) or radiographically (ie, a stroke involving more than one-third of the middle cerebral artery [MCA] territory) were excluded from the study.[22] The effect of IV r-tPA in the 3- to 4.5-h time window on patients with these characteristics is therefore less certain.

2.1.3 Treatment With IV r-tPA Beyond 4.5 h: A recent meta-analysis, which included data from the European Cooperative Acute Stroke Study (ECASS) I, ECASS II, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) studies, provides moderate-quality evidence that IV r-tPA administered between 4.5 and 6 h after symptom onset is associated with an increased chance of death (49 more deaths per 1,000 patients treated).[10,23-26] There is also moderate-quality evidence of an increased chance of favorable functional outcome (46 more per 1,000 patients treated) (Table 4, Table S4).

Population: Imaging Exclusion Criteria for IV r-tPA—A CT scan (or MRI) of the brain is required prior to administration of thrombolytic therapy to exclude brain hemorrhage. The baseline CT scan may detect minor ischemic changes (often referred to as early ischemic changes or early infarct signs) defined as small areas of brain tissue that exhibit early signs of cerebral ischemia, such as a subtle loss of the differentiation between the cortical gray matter and the subcortical white matter. This is not a contraindication for r-tPA therapy. A post hoc analysis of the National Institute of Neurological Disorders and Stroke (NINDS) trial found early ischemic changes in 31% of baseline scans.[27] The benefits and risks associated with r-tPA were not different in patients with early ischemic changes compared with patients

Table 3—*[Section 2.1.2] Summary of Findings: IV r-tPA Initiated Between 3 and 4.5 h in Patients With Acute Ischemic Stroke*[10-11]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk With No IV r-tPA	Risk Difference With IV r-tPA (95% CI)
Overall mortality[a]	1,620 (5 studies[b]) 90 d	Low[c,d] due to inconsistency, imprecision	OR, 1.22 (0.87-1.71)[e,f]	120 deaths per 1,000[g]	23 more deaths per 1,000 (from 14 fewer to 69 more)
Good functional outcome,[h] mRS 0-1	1,620 (5 studies[b]) 90 d	High	OR 1.34 (1.06-1.68)[e,f]	350 excellent outcomes per 1,000[i]	69 more excellent outcomes per 1,000 (from 13 more to 125 more)

NIHSS = National Institutes of Health Stroke Scale. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time to treatment strata up to 6 h; OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with tPA and 0.8% with placebo; seven studies.

[b]ATLANTIS, ECASS I (1995), ECASS II (1998), ECASS III (2008), and EPITHET.

[c]$I^2 = 70\%$.

[d]95% CI includes both (1) no effect and (2) appreciable benefit or appreciable harm.

[e]Based on Lees et al.[10]

[f]This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

[g]Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trial (NINDS, ECASS, ATLANTIS, and EPITHET).

[h]Symptomatic nonfatal ICH not reported separately in table as it is captured by good functional outcome. Symptomatic nonfatal ICH more likely than placebo in the 3-6-h time window. OR = 3.34; 95% CI, 2.4-4.7; 8.4% vs 2.5%; six studies (three ECASS trials, two ATLANTIS trials, and EPITHET 2008). Data from Wardlaw et al.[11]

[i]Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS, ECASS, ATLANTIS, and EPITHET).

without early ischemic changes.[27,28] In contrast, the presence of major and extensive early infarct signs on the baseline CT scan, defined as substantial mass effect or well-defined hypodensity involving greater than one-third of the MCA, is associated with poor outcomes regardless of therapy. Only 2% of the patients in the NINDS study had extensive hypodensity (> 1/3 of the MCA territory) on the pretreatment CT scan.[27] In the NINDS study, major early infarct signs on CT scan were associated with an increased risk of symptomatic ICH in r-tPA-treated patients (OR, 7.8; 95% CI, 2.2-27.1).[29] Major early infarct signs are therefore a contraindication for IV r-tPA therapy.

Table 4—*[Section 2.1.3] Summary of Findings: IV r-tPA Initiated after 4.5 h in Patients With Acute Ischemic Stroke*[10-11]

Outcomes	No of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk With Control	Risk Difference With IV r-tPA (95% CI)
Overall mortality[a]	1,117 (4 studies[b]) 90 d	Moderate[c] due to imprecision	OR, 1.49 (1-2.21)[d]	120 deaths per 1,000[e]	49 more deaths per 1,000 (from 0 more to 112 more)
Good functional outcome,[f] mRS 0-1	1,117 (4 studies[b]) 90 d	Moderate[g] due to imprecision	OR, 1.22 (0.96-1.54)[d]	350 excellent outcomes per 1,000[h]	46 more excellent outcomes per 1,000 (from 9 fewer to 103 more)

See Table 1-3 legends for expansion of abbreviations.

[a]Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h; OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with tPA and 0.8% with placebo; seven studies.

[b]ATLANTIS A (2000), ECASS I (1995), ECASS II (1998), and EPITHET.

[c]Rated down for imprecision because recommendation would be in favor of tPA if the effect of tPA matched the lower bound of the CI (ie, OR = 1 indicating no effect on mortality).

[d]This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

[e]Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trial (NINDS, ECASS, ATLANTIS, and EPITHET).

[f]Symptomatic nonfatal ICH not reported separately in table as it is captured by good functional outcome. Symptomatic nonfatal ICH more likely than placebo in the 3-6-h time window. OR = 3.34; 95% CI, 2.4-4.7; 8.4% vs 2.5%, six studies (three ECASS trials, two ATLANTIS trials, and EPITHET 2008). Data from Wardlaw et al.[11]

[g]CI includes the possibility of harm and benefit.

[h]Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS, ECASS, ATLANTIS, and EPITHET).

Intervention: Timing of Treatment With IV r-tPA—Treatment should be initiated as early as possible because the benefits of r-tPA are greater for shorter onset-to-treatment times.[10,30,31] Implementation requires public awareness, rapid transport to hospital, immediate ED assessment and activation of the local stroke team, rapid access to brain imaging, and clearly defined stroke protocols.

Resource Implications for IV r-tPA—Cost-effectiveness analyses with a long (> 1 year) time horizon support the cost-effectiveness of r-tPA in acute stroke when given within 3 h of symptom onset. Analyses from the United States, Canada, and the United Kingdom have concluded that using r-tPA is economically dominant—both more effective and cost saving compared with not using r-tPA.[32-35] These analyses omitted the costs of establishing specialized stroke services. However, "stroke reorganization" in hospitals is an emerging standard of care, irrespective of r-tPA.[35,36]

An analysis of acute stroke treatments suggests that the economic case for r-tPA—at least for developed countries—does not depend on dramatic reductions in stroke-related disability.[37] Even treatments that are modestly effective (eg, those that shift the distribution of Rankin disability by 5%) may be cost-effective from a societal perspective because reduced disability is associated with decreased long-term care costs. In developed countries, r-tPA is similar in price to a few days of nursing home care. However, in an environment in which long-term care costs are small relative to the cost of r-tPA, this long-term savings will not be as salient.

Recommendations

2.1.1. In patients with acute ischemic stroke in whom treatment can be initiated within 3 h of symptom onset, we recommend IV r-tPA over no IV r-tPA (Grade 1A)**.**

2.1.2. In patients with acute ischemic stroke in whom treatment can be initiated within 4.5 h but not within 3 h of symptom onset, we suggest IV r-tPA over no IV r-tPA (Grade 2C)**.**

2.1.3. In patients with acute ischemic stroke in whom treatment cannot be initiated within 4.5 h of symptom onset, we recommend against IV r-tPA (Grade 1B)**.**

2.2 Intraarterial Thrombolysis in Acute Ischemic Stroke

Intraarterial (IA) thrombolytic therapy is delivered by local infusion adjacent or into the thrombus. This approach has the potential to increase recanalization rates and enhance safety due to targeted administration of a lower dose of thrombolytic. Disadvantages include the need for specialized facilities and personnel, delays in drug administration related to the logistics of assembling an appropriate team and performing an angiogram, the risks inherent in performing an invasive procedure within the cerebral vasculature, and the risk of general anesthesia that may be used for the procedure.

2.2.1 IA Thrombolysis Compared With No Thrombolytic Therapy in Patients With Ischemic Stroke and Contraindication for IV r-tPA: There is moderate-quality evidence that in patients with an ischemic stroke with a demonstrable cerebral artery occlusion, IA thrombolysis is associated with an increased chance of good functional outcome, whereas results failed to show or exclude a beneficial or detrimental effect on mortality (Table 5, Tables S5, S6). With IA thrombolysis, as with IV r-tPA, the increased chance of good functional outcome at day 90 is observed despite an increased risk of symptomatic ICH (OR, 4.7; 95% CI, 1.3-16).[38]

These data are derived from three trials (Prolyse in Acute Cerebral Thromboembolism [PROACT] 1, PROACT 2, and Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial [MELT]) that evaluated IA thrombolysis in patients with acute stroke due to MCA occlusions of < 6 h duration.[39-41] A subset of these study populations would have been eligible for treatment with IV r-tPA based on current treatment criteria, but the majority would have been ineligible because treatments were initiated outside the 4.5-h time window. The drug used in these studies, recombinant prourokinase, was never approved by the Food and Drug Administration for IA thrombolysis in acute stroke and is not currently available for use in most countries. Most centers therefore use r-tPA for IA thrombolysis, a therapy that has not been directly tested in clinical trials. Although our PICO questions focus on the use of IA r-tPA in patients with contraindications to IV r-tPA, we relied on the indirect evidence from the IA pro-urokinase literature and rated down the quality of the evidence for indirectness (Table 5, Tables S5, S6).

There are no data available from head-to-head trials comparing IA thrombolysis to IV thrombolysis for patients with acute ischemic stroke. Although the relative effect on good functional outcome and mortality appear similar for IV r-tPA and IA thrombolysis, the evidence for IV r-tPA is of higher quality than the evidence for IA thrombolysis. Treatment with IV r-tPA is therefore favored over IA r-tPA for patients who meet eligibility criteria for both.

Population: Target Blood Vessels for IA Thrombolysis—The benefit of IA thrombolysis was

Table 5—*[Section 2.2.1] Summary of Findings: IA Thrombolysis in Patients With Acute Ischemic Stroke*[h,39,40]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk With No IA tPA	Risk Difference With IA tPA (95% CI)
Overall mortality	334 (3 studies[a]) 90 d	Low[b-d] due to indirectness, imprecision	RR, 0.86 (0.56-1.33)	210 deaths per 1,000[e]	29 fewer deaths per 1,000 (from 92 fewer to 69 more)
Good functional outcome,[f] mRS 0-2	334 (3 studies[a]) 90 d	Moderate[b,c] due to indirectness	RR, 1.44 (1.06-1.95)	290 good outcomes per 1,000[g]	128 more good outcomes per 1,000 (from 17 more to 275 more)

IMS = Interventional Management of Stroke. See Table 1-3 legends for expansion of abbreviations.

[a]PROACT I (1998), PROACT II (1999), MELT (2007).

[b]$I^2 = 0\%$.

[c]Studies conducted in patients without contraindication for IV tPA; studies used thrombolytics other than rtPA; control patients received heparin in PROACT I (1998) and PROACT II (1999).

[d]CI includes both clinically significant harms and benefits.

[e]Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the control arm of NINDS (1995) as reported in the IMS (2004) study (153 of 727 = 21%). Intervention and control rates were averaged to determine the baseline rate, because the interventions did not have a notable effect on mortality.

[f]sICH not listed as a separate outcome because it is captured within the good functional outcome and mortality outcomes. sICH occurred in 20 of 191 (10%) patients treated with IA and 3 of 126 (2%) control patients.

[g]Baseline good functional outcome rate derived from control arms of PROACT I (1998) and PROACT II (1999), MELT (2007), and the control arm of NINDS as reported in the IMS study (99 of 341 = 29%).

[h]IA thrombolysis administered median time of 5.5 h PROACT (1998), 5.3 h PROACT II (1999), and 3.8 h MELT (2007) from symptom onset.

observed in studies that exclusively enrolled patients with MCA occlusions. Data on IA thrombolysis for treatment of patients with other vascular occlusions are limited. In a large multicenter observational cohort study of patients with basilar occlusions, IA thrombolysis was associated with better results than antithrombotic therapy among patients with severe clinical deficits, but poorer outcomes than antithrombotic therapy in patients with mild to moderate baseline deficits.[42]

Despite the lack of direct evidence for arterial locations other than the MCA, our recommendations include patients with acute occlusions of any proximal cerebral blood vessel (ie, internal carotid artery, MCA, vertebral artery, and basilar artery). We generalized the recommendations because pathophysiology and accessibility were believed to be similar for all major intracranial arterial locations.

Intervention: Timing of IA Thrombolysis—The IA thrombolysis trials initiated treatment within 6 h of symptom onset. A post hoc analysis of single-arm pilot trials of combined IV/IA therapy has shown that the probability of good clinical outcome decreases as time to angiographic reperfusion increases; this probability approaches that of patients without angiographic reperfusion when treatment is completed at approximately 7 h.[43] Indirect evidence from the IV r-tPA literature further supports the time sensitivity of IA r-tPA administration.[10,31]

2.2.2 Combination IV/IA Thrombolysis Compared With IV Thrombolysis Alone in Ischemic Stroke: A minority of patients treated with IV r-tPA alone benefit from this treatment. The number needed to treat for benefit is estimated to be between four and eight, depending on time to treatment.[44] The lack of universal efficacy of IV r-tPA is explained in part by a relatively low rate of recanalization following its administration. When IV r-tPA fails to recanalize the occluded artery, additional therapy with IA thrombolysis may increase the chances of recanalization and good clinical outcome. Two single-arm cohort studies (IMS [Interventional Management of Stroke] I and II) provide very low-quality evidence regarding the combination of IV plus IA r-tPA compared with IV r-tPA alone in patients presenting within 3 h of symptom onset (Table 6, Tables S5, S7) .[45,46] The CIs are wide and failed to demonstrate or exclude a beneficial effect or a detrimental effect on mortality and functional outcome. The special expertise and equipment that are needed to treat stroke with IA thrombolysis are currently not available at most hospitals. This provides additional grounds against using combination IV/IA r-tPA.

Recommendations

2.2.1. In patients with acute ischemic stroke due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV r-tPA, we suggest intraarterial (IA) r-tPA initiated within 6 h of symptom onset over no IA r-tPA (Grade 2C)**.**

2.2.2. In patients with acute ischemic stroke we suggest IV r-tPA over the combination IV/IA r-tPA (Grade 2C)**.**

Table 6—*[Section 2.2.2] Summary of Findings: Combination IV + IA Thrombolysis vs IV Thrombolysis Alone in Patients With Acute Ischemic Stroke*[45-46]

Outcomes[a,b]	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk with IV tPA Alone	Risk Difference With IA tPA in Addition to IV tPA (95% CI)
Overall mortality	343 (2 studies[c]) 90 d	Low[d] due to risk of bias, imprecision	RR, 0.77 (0.49-1.22)[c]	210 deaths per 1,000[e]	48 fewer deaths per 1,000 (from 107 fewer to 46 more)
Good functional outcome, mRS 0–2	343 (2 studies[c]) 90 d	Low[d] due to risk of bias, imprecision	RR, 1.13 (0.88-1.45)[c]	290 good outcomes per 1,000[c]	38 more good outcomes per 1,000 (from 35 fewer to 131 more)

See Table 1-3 and 5 legends for expansion of abbreviations.

[a]Major extracranial bleeding not reported as separate outcome because it is captured in the other listed outcomes. Major extracranial bleeding occurred in 2.5% of IV + IA-treated patients and 1.1% of IV tPA alone-treated patients (RR, 2.3; 95% CI, 0.4-12.1).

[b]sICH not reported as separate outcome because it is captured in the other listed outcomes. sICH occurred in 13 of 161 patients (8.0%) treated with combined IV + IA tPA and in 12 of 182 patients (6.6%) treated with IV tPA alone (RR, 1.23; 95% CI, 0.58-2.57).

[c]IMS I (2004) and IMS II (2007). Both studies used the same historical data for their control groups. Historical controls were obtained from the active treatment arm of the NINDS (1995) tPA trial. Control population was limited to patients with baseline NIHSS > 9 and age < 81 y to match the IMS cohorts. We thus combined data from the two studies for the intervention group and compared with the data from the same historical control group. Baseline Good Functional Outcome rate derived from control arms of PROACT I (1998) and PROACT II (1999), MELT (2007) and the placebo control arms of NINDS as reported in the IMS study (99 of 341 = 29%).

[d]CI includes both values indicating harms and benefit.

[e]Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the placebo and control arms of NINDS (1995) as reported in the IMS (2004) study (153 of 727 = 21%). Intervention and control rates were averaged to determine the baseline rate, because the interventions did not have notable effect on mortality.

Remarks: Carefully selected patients who value the uncertain benefits of combination IV/IA thrombolysis higher than the associated risks may choose this intervention. Patients who prefer to avoid risk in the setting of uncertain benefits are more likely to choose IV r-tPA alone.

2.3 Mechanical Thrombectomy in Acute Ischemic Stroke

Mechanical thrombectomy is the removal of blood clots from the cerebral circulation using endovascular retrieval devices. A potential advantage of mechanical thrombectomy is the higher recanalization rate compared with IV thrombolysis. The US Food and Drug Administration, through its 510(k) process, has cleared two catheter devices, the MERCI retriever (Concentric Medical) and the Penumbra device (Penumbra Inc) for clot retrieval in acute ischemic stroke. Their clearance was based on safety and recanalization data derived from single-arm observational cohort studies.

For the clinical outcomes of interest, mortality, and good functional outcome (defined as a mRS 0-2), we considered four different analyses. First, we compared the clinical outcomes that were observed in six cohort studies of mechanical thrombectomy[47-52] to the clinical outcomes of patients randomized to the control arms of the three IA thrombolysis trials (Tables S8, S9).[39-41] This comparison demonstrates an increased risk of mortality (32.9% vs 18.5%) and a similar rate of good clinical outcome (29.0% vs 31.9%) with mechanical thrombectomy compared with no intervention. However, differences in patient characteristics between the two populations may have obscured any potential benefits of mechanical thrombectomy. Specifically, the historical controls consisted exclusively of patients with MCA occlusions, whereas the mechanical thrombectomy studies also included patients with more severe strokes due to internal carotid artery or basilar artery occlusions. The second analysis that we considered was therefore limited to patients with MCA occlusions.[53] Patients with MCA occlusions who were treated with mechanical thrombectomy had a similar risk of mortality (26.8% with mechanical thrombectomy vs 27.1% with control) and a higher probability of good functional outcome (37.6% with mechanical thrombectomy vs 25.4% with control) compared with historic controls (Table S10). The third analysis compared mechanical thrombectomy to IA thrombolysis in patients with MCA occlusions and showed similar probabilities of good functional outcome and mortality with these two treatment modalities.[53] A fourth line of evidence comes from a meta-analysis demonstrating that recanalization in acute stroke is associated with an increase in good functional outcome (OR, 4.4; 95% CI, 3.3-5.9) and a decrease in mortality (OR, 0.24; 95% CI, 0.16-0.35).[54] This

provides weak indirect evidence in favor of mechanical thrombectomy, as recanalization rates are higher with mechanical thrombectomy than without.[48,50,51] It does not, however, exclude the possibility that those who did not achieve recanalization were harmed by the intervention.

Together, the data are of low quality and leave considerable uncertainty about the direction of the effect of mechanical thrombectomy on survival and functional outcomes. Given this uncertainty, mechanical thrombectomy is not recommended for stroke patients in general. Selected stroke patients with contraindications to IV r-tPA or persistent severe deficits despite IV r-tPA could be considered for thrombectomy if they have a proximal arterial occlusion that is amenable to IA thrombectomy and a relatively small burden of irreversible ischemic injury. Poor candidates for thrombectomy are those with evidence of major infarction or hemorrhage on brain imaging.

Recommendation

2.3. In patients with acute ischemic stroke, we suggest against the use of mechanical thrombectomy (Grade 2C)**.**

Remarks: Carefully selected patients who value the uncertain benefit of mechanical thrombectomy higher than the associated risks may choose this intervention.

2.4 Aspirin in Acute Ischemic Stroke

Two large randomized controlled trials, IST (International Stroke Trial) and Chinese Acute Stroke Trial (CAST), contributed > 98% of the data to a Cochrane systematic review of four trials assessing the effect of early aspirin administration in patients with acute stroke.[55] High-quality evidence shows that aspirin results in fewer deaths (nine per 1,000) and more patients with a good functional outcome (seven per 1,000) at 30 days after ischemic stroke (Table 7,

Table 7—*[Section 2.4] Summary of Findings: Aspirin (160-300 mg) Within 48 h Compared With No Aspirin in Patients With Acute Ischemic Stroke or TIA*[55]

Outcomes	No of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk With No Aspirin	Risk Difference With Aspirin (160-300 mg) (95% CI)
Overall mortality[a]	41,291 (4 studies[b]) 4-24 wk[c,d]	High[e,f]	OR, 0.92 (0.87-0.98)	120 deaths per 1,000[g]	9 fewer deaths per 1,000 (from 2 fewer to 14 fewer)
Good functional outcome[h] mRS 0-1	41,291 (4 studies[b]) 4-24 wk[c,d]	High[ij]	RR, 1.02 (1.01-1.04)[k]	350 good outcomes per 1,000[l]	7 more good outcomes per 1,000 (from 3 more to 14 more)
Nonfatal major extracranial hemorrhage, bleeding requiring transfusion	40,850 (4 studies[b]) 2-4 wk[m]	High	OR, 1.69 (1.35-2.11)[m,n]	6 bleeding events per 1,000[o]	4 more bleeding events per 1,000 (from 2 more to 7 more)

ADLs = activities of daily living; IST = International Stroke Trial. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Fatal ICH is captured in mortality outcome and is, therefore, not reported separately. Only IST (1997) reports fatal ICH (0.2% in both arms at 14 d). However, fatal ICH rates are not reliably reported in IST (1997) and CAST (1997) because 4% of patients in IST (1997) did not have a CT scan and 12% of the patients in CAST (1997) never underwent neuroimaging.

[b]IST (1997), CAST (1997), MAST (1995), and Roden-Jullig (2003).

[c]Events based on those observed during follow-up (4 wk in CAST [1997], 24 wk in IST [1997]).

[d]Although the IST (1997) trial followed patients for as long as 6 mo and CAST (1997) for only 1 mo, the closest shared outcome window is 2 wk for IST (1997) and 4 wk for CAST (1997).

[e]Minimal loss to follow-up, well blinded and concealed.

[f]$I^2 = 21\%$.

[g]Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trials (NINDS [1995], ECASS, ATLANTIS, and EPITHET).

[h]Symptomatic nonfatal ICH not listed separately in table because it is captured in the good functional outcome measure. Symptomatic ICH are higher in the treatment arm of IST (1997) and CAST (1997) (OR = 1.22; 95% CI, 1.00-1.50).

[i]Minimal loss to follow-up, well blinded and concealed.

[j]$I^2 = 0\%$.

[k]Rate of good functional outcome in intervention and control groups used to determine the RR is based on outcomes that roughly correspond to an mRS 0-2. Both IST (1997) and CAST (1997) used a four-level scale to measure functional outcome. Good functional outcome on this scale was defined as independent for all ADLs. The RR for good functional outcome defined as mRS 0-2 was assumed to be the same as the RR for good functional outcome defined as mRS 0-1 (a more strict definition of good functional outcome).

[l]Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS [1995], ECASS, ATLANTIS, and EPITHET).

[m]Events based on those observed during treatment period (2 wk in IST [1997] and 4 wk in CAST [1997]).

[n]OR obtained from Sandercock et al[55] is for any major extracranial hemorrhage (fatal plus nonfatal). OR for nonfatal major extracranial hemorrhage is assumed to be identical.

[o]Rate for fatal and nonfatal major extracranial hemorrhages used as the baseline rate for nonfatal major extracranial hemorrhages as the proportion of fatal major extracranial hemorrhages is small (4%, based on CAPRIE data) in comparison with all major extracranial hemorrhages.

Tables S11, S12). This occurs at the expense of a small increase in nonfatal major extracranial bleeding events (four per 1,000). The modest overall benefit of aspirin in terms of mortality and functional outcome is probably in large part due to a reduction in recurrent strokes (seven per 1,000) despite a small increase (two per 1,000) in symptomatic intracranial hemorrhages. An additional benefit of aspirin, not captured in our table (Table 7), is its reduction of VTE.[56]

Intervention: The optimal dose of initial aspirin therapy has not been studied in a head-to-head comparison. Eligible studies included in the meta-analysis used daily aspirin doses of 160 mg to 326 mg, and the meta-analysis found no heterogeneity in the effect on the different outcomes.[55] Similarly, optimal timing of initiation of aspirin therapy has not been studied in randomized trials. In the included studies, the median time to initiating aspirin therapy varied from 19 to 24 h. Based on these data we suggest starting aspirin at a dose of 160 to 326 mg per day, as early as possible after intracranial hemorrhage has been excluded and, ideally, within the first 48 h after symptom onset. To reduce bleeding complications, the aspirin dose may be reduced to secondary prevention dosing (75-100 mg/d; see Section 4) after 1 to 2 weeks of acute treatment.

Few studies have evaluated the combination of aspirin with other antiplatelet agents for acute ischemic stroke. The largest pilot study to date (N = 392) failed to demonstrate or exclude a beneficial or detrimental effect of the combination of aspirin with clopidogrel initiated within 24 h after symptom onset and continued for 90 days (7.1% recurrent stroke on combination vs 10.8% on aspirin alone; RR, 0.7; 95% CI, 0.3-1.2).[57] This approach is currently being investigated in large-scale clinical trials.[58] Aspirin may be used safely in combination with low doses of subcutaneous heparin for DVT prophylaxis but should not be given for the first 24 h after administration of r-tPA.

Recommendation

2.4. In patients with acute ischemic stroke or TIA, we recommend early (within 48 h) aspirin therapy at a dose of 160 to 325 mg over no aspirin therapy (Grade 1A)**.**

2.5 Anticoagulation in Acute Ischemic Stroke

A Cochrane systematic review compared parenteral anticoagulation to aspirin initiated within 48 h of ischemic stroke.[59] It provides high-quality evidence that treatment with treatment-dose anticoagulation

Table 8—*[Section 2.5] Summary of Findings: Anticoagulants Compared With Antiplatelets in Patients With Acute Ischemic Stroke or TIA*[59]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d	
				Risk with Antiplatelets	Risk Difference With Anticoagulants (95% CI)
Overall mortality	11,989 (5 studies[a]) 3-6 mo	High[b]	RR, 1.08 (1.01-1.16)	120 deaths per 1,000[c]	10 more deaths per 1,000 (from 1 more to 19 more)
Good functional outcome, mRS 0-1	12,235 (6 studies[a]) 3-6 mo	High[b]	RR, 0.98 (0.95-1.01)[d]	350 good outcomes per 1,000[e]	7 fewer good outcomes per 1,000 (from 18 fewer to 3 more)
Nonfatal recurrent stroke (ischemic or hemorrhagic)	11,715 (4 studies[f]) 3-6 mo	High[b]	RR, 1.20 (1.00-1.45)	30 strokes per 1,000[g]	6 more strokes per 1,000 (from 0 more to 14 more)
Nonfatal major extracranial hemorrhage	12,076 (5 studies[h]) 10-180 d	High[i]	RR, 1.74 (1.16-2.61)[j]	10 bleeding events per 1,000[g]	7 more bleeding events per 1,000 (from 2 more to 16 more)

See Table 1, 2, and 7 legends for expansion of abbreviations.

[a]IST (1997), RAPID (2005), TAIST (2001), HAEST (2000), FISS-tris (2007).

[b]$I^2 = 0\%$.

[c]Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trial (NINDS [1995], ECASS, ATLANTIS, and EPITHET).

[d]Rate of good functional outcome in intervention and control groups used to determine the RR is based on outcomes that roughly correspond to an mRS 0-2. IST (1997) used a four-level scale to measure functional outcome. Good functional outcome on this scale was defined as independent for all ADLs. The RR for good functional outcome defined as mRS 0-2 was assumed to be the same as the RR for good functional outcome defined as mRS 0-1 (a more strict definition of good functional outcome).

[e]Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS [1995], ECASS, ATLANTIS, and EPITHET).

[f]IST (1997), RAPID (2005), HAEST (2000), TAIST (2001).

[g]Baseline risk derived from IST.

[h]IST (1997), Pince (1981), TAIST (2001), HAEST (2000), FISS-tris (2007).

[i]$I^2 = 11\%$.

[j]RR based on all major extracranial bleeding events.

compared with aspirin results in more deaths, fewer patients with a favorable outcome, and more nonfatal major extracranial bleeding events.[59] These worse outcomes with anticoagulation resulted from an increase in patients with intracerebral hemorrhage that was not offset by a small decrease in recurrent ischemic strokes.[59] Table 8 and Tables S13, S14 summarize the effect of parenteral anticoagulation compared with antiplatelet therapy according to data from a Cochrane review updated with data from recent trials.[59]

Population: Anticoagulation in Subpopulations: Anticoagulation has been suggested as the preferred acute stroke treatment strategy for certain patient populations. These include, for example, patients with AF, cervical artery dissection, and large artery stenoses. Our review of the literature failed to identify studies that support the use of anticoagulation in these subgroups. Specifically, a meta-analysis reported no net benefit of acute anticoagulant therapy over antiplatelet therapy in stroke patients with AF.[60] In the only trial to exclusively recruit participants with ischemic stroke and AF (Heparin in Acute Embolic Stroke Trial),[61] the risk for extracerebral hemorrhages was greater with anticoagulation than with antiplatelet therapy (5.8% vs 1.8%, $P = .028$). Similarly, a recent systematic review based on observational studies failed to demonstrate a significant difference between antiplatelet therapy and anticoagulation for the acute treatment of patients with stroke secondary to cervical artery dissection.[62] Finally, for patients with stroke due to large artery atherosclerosis, no convincing evidence supports anticoagulation. Although the Trial of Org 10172 in Acute Stroke Treatment (TOAST) reported that a favorable functional outcome at 3 months occurred more frequently in the subgroup of patients with large artery atherosclerotic stroke who were treated with danaparoid (68.1% vs 54.7%, $P = .04$), the rates of recurrent stroke were similar between treatment regimens, and there was no benefit of danaparoid in the overall trial population.[63]

Aspirin therapy is therefore recommended for all patients with acute ischemic stroke based on high-quality evidence in favor of antiplatelet therapy and the lack of evidence to support anticoagulation over antiplatelet therapy for any subpopulation of ischemic stroke patients thus far investigated. There are, however, some patients at particularly high risk for recurrent embolic events (eg, those with mechanical heart valves or intracardiac thrombi) who were either not included or underrepresented in the acute antithrombotic therapy stroke trials. Although long-term anticoagulation for secondary stroke prevention may be indicated for these patients,[4] the optimal choice of acute antithrombotic therapy is uncertain. As a result, there is considerable variation in clinical practice. Acute anticoagulation could be considered in this setting when the risk of hemorrhagic complications is low (eg, small ischemic burden and no evidence of hemorrhage on imaging).

Recommendation

2.5. In patients with acute ischemic stroke or TIA, we recommend early (within 48 h) aspirin therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation (Grade 1A)**.**

3.0 VTE Prevention in Ischemic and Hemorrhagic Stroke

Patients who are hospitalized for stroke and have impaired mobility are at high risk of DVT and PE.[64] In the following sections we address the use of prophylactic-dose anticoagulation and mechanical methods for thromboprophylaxis in patients with ischemic stroke (Section 3.1) and hemorrhagic stroke (Section 3.2).

We derived the baseline risks for most outcomes from the control arm of a randomized study of the effectiveness of graduated compression stockings for VTE prevention after stroke (Clots in Legs or Stockings after Stroke [CLOTS]).[65] We judged that the CLOTS control group would be more representative than the control group of randomized controlled trials (RCTs) comparing heparin to no heparin and also more representative than the low-quality observational studies we identified. In CLOTS, surveillance for DVT by compression ultrasound may have biased (either underestimated or overestimated) the risk of symptomatic DVT and PE.[66] In addition, the treatment of approximately 8% of patients with heparin, warfarin, or alteplase likely resulted in a lower risk than would have been observed without use of these agents. It is unclear whether the overall effect of the potential biases is that of underestimation or overestimation of the baseline rate. We estimated the relative risk (RR) reduction for symptomatic DVT based on rates of any proximal DVT (symptomatic or asymptomatic) observed with the alternative antithrombotic regimens.[66]

3.1 VTE Prevention in Ischemic Stroke

Prophylactic-Dose Heparin: A meta-analysis provided estimates of the relative effects of prophylactic-dose anticoagulation for VTE prophylaxis in patients with acute ischemic stroke and restricted mobility.[67,68] Heparin prophylaxis, in comparison with no heparin

Table 9—*[Section 3.1.1] Summary of Findings: Prophylactic-Dose Anticoagulation (LMWH or UFH) for VTE Prevention Compared With No Anticoagulation in Patients With Acute Ischemic Stroke and Restricted Mobility*[o,67]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
				Risk With No Prophylactic-Dose Heparin	Risk Difference With Prophylactic-Dose Heparin (UFH or LMWH) (95% CI)
Overall mortality	15,594 (8 studies[a]) 2-26 wk[b]	Moderate[c,d] due to imprecision	RR, 0.86 (0.59-1.22)[e]	87 deaths per 1,000[f]	12 fewer deaths per 1,000 (from 36 fewer to 19 more)[g]
PE (fatal and nonfatal)	10,681 (8 studies[h]) 14-90 d	Moderate[c,d,i] due to imprecision	RR, 0.7 (0.47-1.03)[j]	16 PEs per 1,000[f]	5 fewer PEs per 1,000 (from 8 fewer to 0 more)
Symptomatic DVT	914 (8 studies[k]) 2-52 wk	Moderate[c,i,l] due to inconsistency	RR, 0.31 (0.21-0.42)	48 DVTs per 1,000[f]	33 fewer DVTs per 1,000 (from 28 fewer to 38 fewer)
Symptomatic intracranial hemorrhage	10,696 (8 studies[h]) 14-90 d[b]	Moderate[c,d,i,m] due to imprecision	RR, 1.52 (0.96-2.39)	5 bleeding events per 1,000	3 more bleeding events per 1,000 (from 0 fewer to 7 more)
Symptomatic extracranial hemorrhage	10,351 (8 studies[n]) 2-52 wk[b]	Moderate[c,d,i] due to imprecision	RR, 1.62 (0.93-2.81)	4 bleeding events per 1,000	2 more bleeding events per 1,000 (from 0 fewer to 7 more)

ITT = intention to treat; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; UFH = unfractionated heparin. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Turpie (1987), Sandset (1990), McCarthy (1986), McCarthy (1977), Pambianco (1995), Prins (1989), FISS (1995), and IST (1997).

[b]Not clearly reported in all studies, presumed to be during hospital stay following acute ischemic stroke.

[c]IST (1997) is the dominant study in the meta-analysis. In IST (1997) allocation was concealed, outcome assessors were blinded; follow-up > 99%; study not stopped early for benefit; not clear whether analysis was ITT.

[d]95% CI includes both no effect and appreciable benefit or appreciable harm.

[e]Since "there was no interaction between aspirin and heparin in the main outcomes" of the IST (1997) study, we combined data from patients with and without aspirin in the low-heparin group (2,432 + 2,426 = 4,858) and data from patients with and without aspirin in the no heparin group (4,858 + 4,860 = 9,718).

[f]Control rate derived from CLOTS trial judged to provide the most representative estimates of baseline risk in the population of patients with stroke and limited mobility.

[g]Death from bleeding occurred in 0.55% of 4,860 patients on low-dose heparin and 0.21% of 10,176 control patients (RR, 2.68; 95% CI, 1.5-4.7). Absolute effect equals 3 more per 1,000 (from 1 more to 7 more). Data are based on six RCTs.

[h]Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), IST (1997), and FISS-bis (1998).

[i]Fewer than 300 events occurred, but quality was not downgraded because of this.

[j]Based on meta-analysis by Kamphuisen (2006).

[k]McCarthy (1977), Duke (1980), McCarthy (1986), Turpie (1987), Prins (1989), Sandset (1990), FISS (1995), and Pambianco (1995).

[l]Statistical heterogeneity: $P = .003$; $I^2 = 74.3\%$.

[m]The IST (1997) contributed up 90% of the patients in the meta-analysis. IST did not require a CT scan for patient enrolment and a small proportion of patients with ICH were included. This could have overestimated, but not underestimated, the symptomatic ICH risk associated with prophylactic anticoagulation. Therefore, we did not downgrade the quality of the evidence for indirectness.

[n]Duke (1980), Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), and IST (1997).

[o]Data on the concomitant use of aspirin were generally insufficiently provided. In most studies, like the IST (1997), aspirin use was permitted, but exact numbers of patients using antiplatelet agents were lacking. In IST (1997), the dominant study, treatment was started within 48 h.

prophylaxis, results in 33 fewer symptomatic DVTs, five fewer pulmonary emboli, and five additional major hemorrhages (three intracranial and two extracranial) per 1,000 treated patients (Table 9, Tables S15, S16). The overall quality of the evidence is moderate due to imprecision. Patients with additional risk factors for venous thrombosis are more likely to benefit from heparin thromboprophylaxis, whereas patients with risk factors for bleeding are less likely to benefit.

Dosing and Timing of Prophylactic-Dose Heparin: Prophylactic-dose heparin is treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) at a lower dose than what is typically used for therapeutic anticoagulation. The definition for prophylactic dose was adapted from a review of pharmacologic prophylaxis of VTE in stroke patients.[67] Prophylactic-dose UFH was defined as 10,000 to 15,000 units/d and prophylactic-dose LMWH as 3,000 to 6,000 International Units/day. Prophylactic-dose heparin therapy is typically initiated within 48 h after onset of stroke and continued throughout the hospital stay or until the patient regains mobility. Prophylactic-dose heparin should not be used within the first 24 h after administration of thrombolytic therapy.

Prophylactic-Dose Unfractionated Heparin vs Low-Molecular-Weight Heparin: Compared with UFH, the use of LMWH in patients with restricted mobility

Table 10—*[Sections 3.1.2 and 3.2.2] Summary of Findings: LMWH Compared With Unfractionated Heparin for VTE Prevention in Patients With Acute Ischemic Stroke and Restricted Mobility*[k,68]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
				Risk With Prophylactic-Dose LMWH	Risk Difference With Prophylactic-Dose UFH (95% CI)
Overall mortality	2,506 (3 studies[a]) 14-90 d	Moderate[b] due to imprecision	RR, 0.96 (0.72-1.2)[c]	75 deaths per 1,000[d]	3 fewer deaths per 1,000 (from 21 fewer to 15 more)
PE (fatal and nonfatal)	2,092 (3 studies[a]) 14-90 d	Moderate[e] due to imprecision	RR, 0.26 (0.07-0.95)	11 PEs per 1,000[f]	8 fewer PEs per 1,000 (from 1 fewer to 10 fewer)
Symptomatic DVT	2,092 (3 studies[a]) 14-90 d	Moderate[e] due to imprecision	RR, 0.56 (0.4-0.77)[g]	15 DVTs per 1,000[f]	7 fewer DVTs per 1,000 (from 3 fewer to 9 fewer)
Symptomatic intracranial hemorrhage	1,749 (3 studies[a]) 14-90 d	Moderate[b] due to imprecision	RR, 0.7 (0.26-1.83)	7 bleeding events per 1,000[h]	2 fewer bleeding events per 1,000 (from 5 fewer to 6 more)
Symptomatic extracranial hemorrhage	2,506 (3 studies[a]) 14-90 d	Moderate[b] due to imprecision	RR, 2.12 (0.09-43.78)[i]	5 bleeding events per 1,000[j]	6 more bleeding events per 1,000 (from 5 fewer to 214 more)

See Tables 1, 2, and 9 legends for expansion of abbreviations.

[a]Hillbom (2002), PROTECT (2006), and PREVAIL (2006).

[b]95% CI includes both no effect and appreciable benefit or appreciable harm.

[c]0.40% mortality due to bleeding in both groups (5 of 1,255 LMWH, 5 of 1,251 UFH).

[d]Control rate derived from CLOTS trial judged to provide the most representative estimates of baseline risk in the population of patients with stroke and limited mobility.

[e]Fewer than 300 events occurred.

[f]Baseline risk calculated by multiplying baseline risk in CLOTS study times the RR with any heparin prophylaxis.

[g]Data for any proximal DVT.

[h]Based on PREVAIL study data.

[i]Percent due to GI bleeding not reported.

[j]Based on data from heparin for VTE prevention profile.

[k]Treatment started within 48 h from stroke symptom onset. PREVAIL, the dominant study, compared enoxaparin 40 mg once daily to UFH 5,000 units bid for 10 d.

reduces VTE events (eight fewer PE and seven fewer symptomatic DVTs per 1,000 patients treated) without an influence on mortality and bleeding complications. Please refer to Table 10, Tables S15 and S17.

Resource Implications for LMWH vs UFH for Prevention of VTE: We identified no cost-effectiveness analyses comparing LMWH to UFH in patients following a stroke. A high-quality cost-effectiveness analysis in acutely ill medical patients showed dominance of LMWH over UFH.[69] This was based on fewer VTEs and fewer complications (bleeding and heparin-induced thrombocytopenia) with LMWH at lower overall costs. In sensitivity analysis, even when the efficacy and risk of bleeding with LMWH and UFH were set equal, LMWH still dominated UFH because of the lower risk of heparin-induced thrombocytopenia.

Intermittent Pneumatic Compression Devices: Intermittent pneumatic compression devices are designed to intermittently apply external pressure on the calf muscles and vasculature. There is low-quality direct evidence of the effect of intermittent pneumatic compression devices in patients with stroke and impaired mobility (Table 11, Tables S15, S18).[70,71] We based our recommendation on indirect but higher-quality evidence from other populations, such as postoperative patients. In brief, trials that compared intermittent pneumatic compression devices to no treatment have shown an approximate 50% reduction in DVT detected by a systematic method such as venography. Since patients with stroke and restricted mobility fall into the high-risk category for symptomatic VTE events, this translates in a reduction of 36 symptomatic VTEs per 1,000 patients treated with intermittent pneumatic compression devices compared with no treatment.[70] Data for the effect of intermittent pneumatic compression devices on skin complications are lacking.

Elastic Compression Stockings: Elastic compression stocking, also referred to as graduated compression stockings, are stockings designed to apply greater pressure at the ankle than more proximally, thereby promoting venous emptying and blood return. One large RCT (N = 2,518) assessed the effect of elastic compression stockings in acute stroke patients (CLOTS) (Table 12, Tables S15, S19).[65] CLOTS demonstrated an increase in skin complications with elastic compression stockings, whereas results failed

Table 11—*[Sections 3.1.1 and 3.2.1] Summary of Findings: Intermittent Pneumatic Compression Devices for VTE Prevention in Patients With Acute Stroke and Restricted Mobility*[71]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (Grade)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
				Risk With Control	Risk Difference With IPC Stockings (95% CI)
Overall mortality	177 (2 studies[a]) 7-10 d	Moderate[b-e] due to imprecision	RR, 1.03 (0.33-3.23)	87 Deaths per 1,000[f]	3 more deaths per 1,000 (from 58 fewer to 194 more)
PE (fatal and nonfatal)	2,255 (19 studies[g]) 7-10 d	Moderate[h,i] due to indirectness	RR, 0.43 (0.35-0.53)[h]	16 PEs per 1,000[f]	9 fewer PEs per 1,000 (from 8 fewer to 10 fewer)
Symptomatic DVT	2,255 (19 studies[g]) 7-10 d	Moderate[b,h,j] due to indirectness	RR, 0.43 (0.35-0.53)[h,g]	48 DVTs per 1,000[f]	27 fewer DVTs per 1,000 (from 23 fewer to 31 fewer)

IPC = intermittent pneumatic compression. See Table 1, 2, and 9 legends for expansion of other abbreviations.
[a]Prasad (1982) and Lacut (2005).
[b]Lacut (2005): allocation was concealed, outcome assessor blinded, 88% follow-up, ITT analysis, and no early stoppage for benefit. Prasad (1982): unclear whether allocation concealed; no details provided regarding blinding of outcome assessors, the percentage of follow-up, and the type of analysis used.
[c]$I^2 = 28\%$.
[d]In Lacut (2005), restricted mobility was not an inclusion criterion, but 72% of patients were either comatose/sedated/ventilated or hemiplegic. In Prasad (1982), eligible patients had weakness of up to 2 of 6 motor power (Medical Research Council grade) in one or both limbs.
[e]CI interval includes both no effect and appreciable benefit or appreciable harm.
[f]Control rate derived from CLOTS trial judged to provide the most representative estimates of baseline risk in the population of patients with stroke and limited mobility.
[g]Based on meta-analysis in Roderick et al.[71]
[h]RR for symptomatic DVT and RR for PE inferred from rates reported for proximal DVT in 19 studies of postsurgical patients.
[i]Lacut (2005) reported that no PE occurred during follow-up. Prasad (1982) did not report on this outcome.
[j]Lacut (2005) reported that no symptomatic DVT occurred during follow-up. Prasad (1982) did not report on this outcome.

to show or exclude a beneficial or detrimental effect on the occurrence of symptomatic proximal DVT or PE.

Combination Treatment of VTE Prevention: Addition of elastic stockings to intermittent compression devices has been evaluated in a few studies, but the overall number of patients included is small. These studies failed to demonstrate or exclude a beneficial or detrimental effect of adding elastic stockings to intermittent pneumatic compression devices.[71] Trials in postsurgical patients that compared the combination of intermittent pneumatic compression devices with a pharmacologic method to pharmacologic therapy used alone showed a strong trend toward fewer DVTs with combination therapy (OR, 0.45; 95% CI, 0.20-1.03).[70] Studies that compared the combination of elastic stockings and pharmacologic prophylaxis to pharmacologic therapy alone showed a reduction in symptomatic or asymptomatic DVT (OR, 0.40; 95% CI, 0.25-0.65); this benefit should be weighed against the increase in skin complications (RR, 4.18; 95% CI, 2.4-7.3) that has been observed in stroke patients treated with elastic compression stockings (Table 12, Tables S15, S19).[65,70]

Recommendations

3.1.1. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose subcutaneous heparin (UFH or LMWH) or intermittent pneumatic compression devices over no prophylaxis (Grade 2B)**.**

3.1.2. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B)**.**

3.1.3. In patients with acute stroke and restricted mobility, we suggest against elastic compression stockings (Grade 2B)**.**

Remarks: Pharmacologic and mechanical prophylaxis should be initiated as early as possible and should be continued throughout the hospital stay or until the patient regains mobility. Mechanical devices should be temporarily removed as often as needed to allow for early mobilization and screening for skin complications.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

3.2 VTE Prevention in Hemorrhagic Stroke

Prophylactic-Dose Heparin: The use of heparin in patients with hemorrhagic stroke is addressed separately from patients with ischemic stroke because of the risk of extension of the bleeding and/or

Table 12—*[Section 3.1.3, 3.2.3] Summary of Findings: Elastic Compression Stockings for VTE Prevention in Patients With Acute Stroke and Restricted Mobility*[65,144]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
				Risk With No Graduated Compression Stockings	Risk Difference With Graduated Compression Stockings (95% CI)
Overall mortality	2,615 (2 studies[a]) 7-30 d[b]	Moderate[c-e] due to imprecision	RR, 1.11 (0.88-1.42)	87 deaths per 1,000[f]	10 more deaths per 1,000 (from 10 fewer to 37 more)
PE (fatal and nonfatal)	2,518 (1 study[g]) 30 d	Moderate[c,e] due to imprecision	RR, 0.65 (0.33-1.31)	16 PEs per 1,000[f]	6 fewer PEs per 1,000 (from 11 fewer to 5 more)
Symptomatic DVT	2,518 (1 study[g]) 30 d	Moderate[c,e] due to imprecision	RR, 0.91 (0.63-1.29)[h]	48 DVTs per 1,000[f]	4 fewer DVTs per 1,000 (from 18 fewer to 14 more)
Skin complications of elastic compression stockings[i]	2,518 (1 study[g]) 30 d	Moderate[j,k] due to risk of bias	RR, 4.02 (2.34-6.91)	13 Skin complications per 1,000[f]	39 more complications per 1,000 (from 17 more to 77 more)

See Table 1, 2, and 9 legends for expansion of abbreviations.

[a]CLOTS trial I (2009) and Muir et al[144] (2000).

[b]Follow-up was 30 d in CLOTS and 7 ± 2 d in Muir.

[c]Allocation concealed in both studies. Outcome adjudicator blinded in both studies. ITT analysis reported in one study (CLOTS). High rates of follow-up in both studies (100% and 99% for mortality). No study stopped early for benefit.

[d]$I^2 = 0\%$.

[e]CI includes both negligible effect and appreciable benefit or appreciable harm.

[f]Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria (see above).

[g]CLOTS trial I (2009).

[h]CLOTS, the primary study for this analysis, found no effect on "Proximal DVT" (adjusted OR, 0.98; 95% CI, 0.76-1.27).

[i]Includes: skin breaks, ulcers, blisters, and skin necrosis.

[j]Assessment of outcomes was based on case-note review and was not blinded to treatment allocation.

[k]Although CI excludes no effect, the number of events is low. This along with study limitations warranted rating down of the quality of evidence by one level.

rebleeding in patients with hemorrhagic stroke. This section addresses VTE prevention in patients with primary ICH, defined as a hemorrhage that occurs within the brain parenchyma without an underlying lesion, such as a tumor or vascular malformation.

Data on prevention of VTE is of higher quality for patients with ischemic stroke than for patients with ICH. We therefore used indirect data from the ischemic stroke literature to estimate control rates for the incidence of DVT and PE in patients with ICH and to estimate the effect of heparin on this incidence. (Section 3.1) We judged the indirectness to be insignificant and therefore did not rate down the quality of the evidence. The control rate of rebleeding and the effect of heparin on rebleeding were derived from three small randomized studies in patients with ICH.[72-74]

The table shows an imprecise estimate of the effect of heparin prophylaxis on rebleeding (Table 13, Tables S15, S20). However, the upper bound of the CI (one more rebleeding event per 1,000) indicates that heparin prophylaxis does not increase the risk of rebleeding significantly. Heparin prophylaxis is associated with 33 fewer symptomatic DVTs and five fewer PEs per 1,000 patients treated. The overall quality of the evidence is low.

One small study compared early (second hospital day) initiation of prophylactic heparin to late (fourth hospital day) initiation (Table 14, Tables S15, S21).[72] Due to the small sample size (N = 45), the study failed to demonstrate a harmful or beneficial effect on any of the outcomes. Rebleeding occurred in one of the 23 patients started on day 4 and in none of the 22 patients started on day 2, providing very low-quality evidence that early use of prophylactic-dose heparin is safe in patients with a primary ICH.

UFH vs LMWH: The comparative effect of UFH vs LMWH has not been studied in patients with primary intracerebral hemorrhage. Recommendations are therefore based on evidence from patients with ischemic stroke. (Section 3.1) (Table 10, Tables S15, S17)

Mechanical Prophylaxis: The effect of mechanical prophylaxis has not been studied exclusively in patients with primary intracerebral hemorrhage. Recommendations are therefore based on evidence

Table 13—*[Section 3.2.1] Summary of Findings: Prophylactic-Dose Heparin for VTE Prevention in Patients With Acute Hemorrhagic Stroke and Restricted Mobility*[72-74]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
				Risk With No Prophylactic Low-Dose Heparin[n]	Risk Difference With Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
Overall mortality	114 (2 studies[a]) 10 d	Low[b-d] due to risk of bias, imprecision	RR, 1.05 (0.46-2.36)	400 deaths per 1,000	20 more deaths per 1,000 (from 216 fewer to 544 more)
PE (fatal and nonfatal)	10,681 (8 studies[e]) 14-90 d	Moderate[e,d,f] due to imprecision	RR, 0.7 (0.47-1.03)[e]	16 PEs per 1,000[g]	5 fewer PEs per 1,000 (from 8 fewer to 0 more)
Symptomatic DVT	914 (8 studies[e]) 2-52 wk	Moderate[d,f,h] due to inconsistency	RR, 0.31 (0.21-0.42)[e]	48 DVTs per 1,000[g]	33 fewer DVTs per 1,000 (from 28 fewer to 38 fewer)
Rebleeding	189 (3 studies[i]) 7-10 d[j]	Low[c,d,k] due to risk of bias, imprecision	RR, 0.24 (0.05-1.13)[l]	10 rebleeding events per 1,000[m]	8 fewer rebleeding events per 1,000 (from 9 fewer to 1 more)

See Table 1, 2, and 7-9 legends for expansion of abbreviations.

[a]We excluded Orken (2009) from this analysis given the control group received compression stockings, which is a confounding factor. Included studies: Boeer (1991) and Dickman (1988).

[b]Allocation: unclear whether concealed in both studies (Boeer 1991, Dickmann 1988). Unclear whether ITT analysis in both studies. Neither of the two studies stopped early for benefit. Neither of the studies reported blinding patients.

[c]95% CI includes both no effect and appreciable benefit or appreciable harm.

[d]Fewer than 300 events occurred, but quality was not downgraded for this.

[e]Indirect data from studies of the effects of heparin on DVT and PE in patients with ischemic stroke. For PE: Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), IST (1997), and FISS-bis (1998); for DVT: McCarthy (1977), Duke (1980), McCarthy (1986), Turpie (1987), Prins (1989), Sandset (1990), FISS (1995), and Pambianco (1995). Also see Summary of Findings Table 9 on VTE prophylaxis in patients with ischemic stroke.

[f]Although relative risks for PE and DVT are taken from studies of patients with ischemic stroke, we judged that the indirectness is not significant enough to warrant rating down the quality of the evidence.

[g]Baseline risks derived from the control arm of CLOTS (*Lancet Neurol*. 2010). Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria: patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom graduated compression stockings might cause skin damage; those with subarachnoid hemorrhage.

[h]Statistical heterogeneity: $P = .003$; $I^2 = 74.3\%$.

[i]Included studies: Orken (2009) (LMWH started > 48 h after hemorrhage; although it compares LMWH to long compression stockings, the effect on rebleeding should be similar to that of a comparison of heparin vs no heparin); Boeer (1991) (UFH started between day 2 and 4 compared with UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10); and Dickman (1988) (UFH started on day 4 compared with UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10).

[j]We considered the time frame during which patients are exposed to heparin and consequently at risk for rebleeding.

[k]Allocation: not concealed in one study (Orken 2009) and unclear whether concealed in two studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in the each of the three studies. None of the three studies stopped early for benefit. In Orken 2009, patients who died prior to day 7 (n = 4) were excluded from the study after randomization; however, none of them had hematoma enlargement after randomization (author contact). None of the studies reported blinding patients. Only one study (Orken 2009) reported blinding assessors of bleeding outcome.

[l]Indirect evidence from an observational study (Warsay 2008): very low incidence in rebleeding with no difference between heparin and no heparin: 1 of 200 vs 0 of 258.

[m]Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT scan 24 h after admission excluding a progressive hematoma, none experienced major bleeding after being started on LMWH. In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH. We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these two studies.

[n]Baseline risk of mortality is derived from observational studies.

from patients with ischemic stroke (Section 3.1) (Tables 11, 12, Tables S15, S18, S19).

Recommendations

3.2.1. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose subcutaneous heparin (UFH or LMWH) started between days 2 and 4 or intermittent pneumatic compression devices over no prophylaxis (Grade 2C)**.**

3.2.2. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B)**.**

Table 14—*[Section 3.2.1] Summary of Findings: Early (Day 2-4) Compared With Late Prophylactic-Dose Anticoagulation for VTE Prevention in Patients With Acute Hemorrhagic Stroke and Restricted Mobility*[74]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d: Risk with Late Prophylactic Low-Dose Heparin (UFH or LMWH)	Anticipated Absolute Effects, Time Frame 30 d: Risk Difference With Early (Day 2-4) Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
Overall mortality	45 (1 study[a]) 10 d	Low[b,c] due to risk of bias, imprecision	RR, 0.42 (0.1-1.69)	400 deaths per 1,000[d,e]	232 fewer deaths per 1,000 (from 360 fewer to 276 more)
PE (fatal and nonfatal)	45 (1 study[a]) 10 d	Low[b,c] due to risk of bias, imprecision	RR, 0.35 (0.01-8.11)	11 PEs per 1,000[e,f]	7 fewer PEs per 1,000 (from 11 fewer to 78 more)
Symptomatic DVT	45 (1 study[a]) 10 d	Low [b,c,g] due to risk of bias, indirectness, imprecision	RR, 0.65 (0.25-1.69)	15 DVTs per 1,000[f]	5 fewer DVTs per 1,000 (from 11 fewer to 10 more)
Rebleeding	45 (1 study[a]) 10 d[h]	Low[b,c] due to risk of bias, imprecision	RR, 0.35 (0.01-8.11)	10 rebleeding events per 1,000[i]	7 fewer rebleeding events per 1,000 (from 10 fewer to 71 more)

See Table 1, 2, and 9 for expansion of abbreviations.

[a]Boeer (1991).

[b]Day 2 group not randomly defined. Allocation: unclear whether concealed. Unclear whether ITT analysis used. Study not stopped early for benefit. No reporting of blinding of patients or outcome assessors.

[c]CI includes both negligible effect and appreciable benefit or appreciable harm.

[d]Baseline risk of mortality is derived from observational studies.

[e]The single reported symptomatic PE event was fatal; has been included in both mortality and PE outcome in this evidence profile.

[f]Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria: patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom graduated compression stockings might cause skin damage; those with subarachnoid hemorrhage.

[g]DVT measured through routine perfusion scintigraphy by day 10. Not reported whether symptomatic and whether proximal vs distal.

[h]We considered the time frame during which patients are exposed to heparin and consequently at risk for rebleeding.

[i]Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT scan 24 h after admission excluding a progressive hematoma, none experienced major bleeding after being started on LMWH. In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH. We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these two studies.

3.2.3. In patients with primary intracerebral hemorrhage and restricted mobility, we suggest against elastic compression stockings (Grade 2B).

Remarks: Patients who prefer to avoid a theoretically increased risk of rebleeding with heparin would favor mechanical prophylaxis with intermittent pneumatic compression devices over pharmacologic prophylaxis.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

4.0 Secondary Stroke Prevention

Secondary stroke prevention studies, which have generally included patients with a history of stroke or TIA, have consistently shown similar relative effects for these two patient groups. The treatment recommendations made in this section therefore apply to both groups (stroke and TIA). Although patients who experience a stroke or TIA are most likely to have a stroke as their next serious vascular outcome,[75] they also often die of MI.[76-78] For the secondary prevention recommendations we therefore considered the following patient-important outcomes: mortality, recurrent nonfatal stroke (ischemic or hemorrhagic), nonfatal MI, and nonfatal major extracranial bleeding events. We did not consider intracranial bleeding events separately, because they are captured under the recurrent stroke outcome. We opted to list the effect of aspirin on cancer-specific mortality in a footnote but not as a separate row in the tables to avoid double counting along all-cause mortality.[79,80] Also, the median survival of patients with stroke is relatively short (5 years) compared with the 5- to 10-year duration of aspirin use required to achieve a reduction in cancer mortality.[79-81]

4.1 Antithrombotic Therapy for the Secondary Prevention of Noncardioembolic Stroke

A meta-analysis of antiplatelet drugs for secondary cardiovascular prevention in high-risk patients has shown a benefit of antiplatelet drugs compared with placebo. The pooled effect of various antiplatelet agents was a reduction in the odds of the composite outcome of stroke, MI, or vascular death by 25%,

Table 15—*[Section 4.1.1] Summary of Findings: Aspirin Compared With No Aspirin for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[f,82]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With No Aspirin	Risk Difference With Aspirin (95% CI)
Overall mortality	9,469 (11 studies) 1.5-6 y	High[a]	RR, 0.91 (0.81-1)[b]	55 deaths per 1,000[c]	5 fewer deaths per 1,000 (from 10 fewer to 0 more)[d]
Nonfatal recurrent stroke (ischemic and hemorrhagic)	10,126 (11 studies) 1.5-6 y	High[a]	RR, 0.81 (0.71-0.92)[e]	130 strokes per 1,000[c]	25 fewer strokes per 1,000 (from 10 fewer to 38 fewer)
Nonfatal MI	10,126 (11 studies) 1.5-6 y	High[a]	RR, 0.69 (0.6-0.8)	18 MIs per 1,000[c]	6 fewer MIs per 1,000 (from 4 fewer to 7 fewer)
Nonfatal major extracranial hemorrhage	10,126 (11 studies) 1.5-6 y	High[a]	RR, 2.69 (1.25-5.76)	4 bleeding events per 1,000[c]	7 more bleeding events per 1,000 (from 1 more to 19 more)

HR = hazard ratio. See Table 1, 2, and 7 legends for expansion of other abbreviations.

[a]Includes a number of small, open-label RCTs. However, summary estimate for large high-quality RCTs consistent with overall estimate.

[b]Estimate calculated from original data included in trials.

[c]Baseline event rates derived from aspirin arm of the CAPRIE study, adjusted for 2-y time frame and adjusted for the ASA treatment effect as reported in this profile.

[d]Aspirin (≥ 75 mg/d) reduces cancer-related mortality (HR = 0.8) with long-term use (> 5 y). Cancer-related mortality was not listed separately as an outcome because survival of stroke patients is relatively short (median survival 5 y) and because cancer-related mortality is captured by all-cause mortality.

[e]RR for nonfatal stroke based on RR for any (fatal and nonfatal) stroke. Incidence of ICH was low (about 0.1%) with RR, 1.67 (95% CI, 0.97-2.9) and absolute effect of one more ICH per 1,000 (from 0 fewer to 1 more).

[f]Trials evaluated aspirin in unselected patients following ischemic stroke or TIA. Comparators were placebo in three trials and control in all others. Aspirin dose ranged from 50 mg/d to 1,500 mg/d. The proportion of participants with TIA ranged from 0-100% among trials.

nonfatal stroke by 25%, nonfatal MI by 34%, and vascular mortality by 15%.[82]

Aspirin Compared With No Aspirin: The evidence supporting the use of aspirin over no aspirin for secondary stroke prevention is of high quality. Aspirin therapy of 1,000 patients with a history of stroke or TIA for 2 years results in five fewer deaths, 25 fewer recurrent nonfatal strokes, and six fewer nonfatal MIs, at the cost of seven additional nonfatal major extracranial bleeding events (Table 15, Tables S22, S23). These estimates do not include the one-third reduction in cancer-related mortality that is seen with long-term (> 5 years) aspirin use.[79-81] This effect translates to 20 fewer cancer-related deaths per 1,000 stroke patients treated for 10 years, assuming a 10-year post-stroke mortality risk of 50%, with 72% of deaths attributable to vascular causes and 12% to cancer.[83,84] The balance of benefits and harms is clearly in favor of aspirin use in patients with a history of stroke or TIA.

Evidence of the effects of different aspirin doses on vascular events stems from several meta-analyses that are summarized in the accompanying article on the prevention of cardiovascular disease by Vandvik et al.[1,85-87] These studies suggest an increase in bleeding complications with doses > 100 mg and leave uncertainty about the reduction in MI and stroke with doses < 75 mg. Based on these data, an aspirin dose of 75 to 100 mg/d is recommended for secondary stroke prevention.

Clopidogrel Compared With Aspirin: The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial compared clopidogrel to aspirin in patients with a history of stroke, MI, or peripheral vascular disease (Table 16, Tables S22, S24).[88] Effect estimates for the subpopulation of patients with a history of stroke were assumed equal to the effect estimates of clopidogrel observed in the overall cohort. Clopidogrel results in two fewer nonfatal MIs per 1,000 patients with a history of stroke or TIA treated for 2 years. Clopidogrel appears to have little or no effect on overall mortality and major nonfatal extracranial hemorrhage. Results failed to show or exclude a beneficial or harmful effect of clopidogrel on recurrent stroke. The overall quality of the evidence was moderate due to imprecision.

Combination Dipyridamole Plus Aspirin Compared With Aspirin Alone: The combination of aspirin and dipyridamole has been compared with aspirin. Table S22 presents the description of the individual trials,[89-94] which have been included in two reviews.[95,96] Based on meta-analyses of these trials, the combination of dipyridamole plus aspirin results in 24 fewer nonfatal recurrent strokes per 1,000 patients treated over 2 years and has little or no effect on mortality

Table 16—*[Sections 4.1.1 and 4.1.2] Summary of Findings: Clopidogrel Compared With Aspirin for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[88]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk with Aspirin	Risk Difference With Clopidogrel (95% CI)
Overall mortality	19,185 (1 study[a]) 1.9 y	Moderate[b,c] due to imprecision	RR, 0.98 (0.89-1.1)[b]	50 deaths per 1,000[d]	1 fewer death per 1,000 (from 6 fewer to 5 more)[e]
Nonfatal recurrent stroke (ischemic and hemorrhagic)	6,431 (1 study[a]) 1.9 y	Moderate[c] due to imprecision	RR, 0.91 (0.78-1.07)[f,g]	106 strokes per 1,000[d,h,f]	10 fewer strokes per 1,000 (from 23 fewer to 7 more)
Nonfatal MI	19,185 (1 study[a]) 1.9 y	High[c]	RR, 0.83 (0.7-0.99)[i]	13 MIs per 1,000[d,i]	2 fewer MIs per 1,000 (from 0 fewer to 4 fewer)
Nonfatal major extracranial hemorrhage	19,185 (1 study[a]) 1.9 y	Moderate[c] due to imprecision	RR, 0.94 (0.72-1.23)[j]	10 bleeding events per 1,000[d,j]	1 fewer bleeding events per 1,000 (from 3 fewer to 2 more)

See Table 1, 2, 7, and 15 legends for expansion of abbreviations.

[a]CAPRIE (1996).

[b]Population of CAPRIE included three patient populations (ischemic stroke, MI, and peripheral vascular disease). Estimates are provided for the entire population and are consistent with estimates in the ischemic stroke subgroup. All ischemic strokes were nonsevere (no TIA patients) and patients were enrolled within 6 mo of event.

[c]CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.

[d]Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

[e]Aspirin ($\geq$75 mg/d) reduces cancer-related mortality (HR = 0.8) with long-term use ($>$5 y). Cancer-related mortality was not listed separately as an outcome because survival of stroke patients is relatively short (median survival, 5 y) and because cancer-related mortality is captured by all-cause mortality.

[f]Based on individual first-outcome nonfatal strokes in CAPRIE's stroke subpopulation.

[g]ICH incidence was low in the aspirin group (0.4%); RR with clopidogrel was 0.79 (95% CI, 0.49-1.27), with an absolute reduction of 1 fewer ICH per 1,000 (from 2 fewer to 1 more).

[h]96.8% of events are nonfatal ischemic stroke.

[i]Based on individual first-outcome nonfatal MI in the overall CAPRIE population.

[j]Based on any (fatal and nonfatal) severe extracranial hemorrhage in the overall CAPRIE population.

and extracranial hemorrhages compared with aspirin alone (Table 17, Tables S22, S25). However, indirect data from two trials suggest that the beneficial effect on recurrent stroke with the combination dipyridamole plus aspirin may be more modest than the estimates reported by these meta-analyses. Specifically, the CAPRIE study failed to show a benefit of clopidogrel compared with aspirin on recurrent stroke (see previous section) and the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) study has shown that the combination dipyridamole plus aspirin is comparable to clopidogrel (see next section).[88,97] The overall quality of the evidence was moderate due to imprecision.

Studies that evaluated the effect of aspirin at doses of $\geq$75 mg/d have shown a protective effect of long-term aspirin use ($>$5 years) on cancer-related mortality.[79,80] It is unknown if the typical aspirin dose used in the combination of dipyridamole plus aspirin (50 mg/d) has the same effect.

Clopidogrel Compared With the Combination of Dipyridamole Plus Aspirin: The PRoFESS trial compared clopidogrel to the combination of extended-release dipyridamole plus aspirin.[98] The results of this study failed to show or exclude a beneficial effect of either drug compared with the other on mortality and vascular outcomes (Table 18, Tables S22, S26). Factors not considered in the table that may influence patient preferences are: a lower incidence of headache with clopidogrel (10% vs 30% with dipyridamole/aspirin),[98] single daily dosing with clopidogrel vs bid with dipyridamole/aspirin, and potential reduction of cancer-related mortality with long-term use of dipyridamole/aspirin.

Clopidogrel Plus Aspirin Compared With Clopidogrel: The Management of Atherothrombosis With Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) study evaluated the efficacy and safety of clopidogrel plus aspirin compared with clopidogrel alone for 18 months in 7,599 patients with recent stroke or TIA and one other vascular risk factor.[99] The results favor clopidogrel used alone, as there was no significant difference in the rates of mortality, recurrent stroke (fatal or nonfatal), or MI (fatal or nonfatal), whereas the risk of nonfatal major extracranial bleeding was higher with combination therapy (RR, 2.55; 95% CI, 1.88-3.46) (Table 19, Tables S22, S27). The overall quality of evidence is rated as moderate given imprecision of the point estimates.

Table 17—*[Sections 4.1.1 and 4.1.2] Summary of Findings: Aspirin Plus Dipyridamole Compared With Aspirin for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[95,96]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With Aspirin	Risk Difference With Aspirin Plus Dipyridamole (95% CI)
Overall mortality	6,038 (2 studies[a]) 2-5 y[b,c]	Moderate[d] due to imprecision	RR, 0.97 (0.83-1.13)	50 deaths per 1,000[b]	1 fewer deaths per 1,000 (from 9 fewer to 6 more)[e]
Nonfatal recurrent stroke (ischemic and hemorrhagic)	7,659 (6 studies) 2.6 y[c]	High	RR, 0.77 (0.67-0.89)[f,g]	106 strokes per 1,000[b]	24 fewer strokes per 1,000 (from 12 fewer to 35 fewer)
Nonfatal MI	6,038 (2 studies[a]) 2-5 y[b,c]	Moderate[d] due to imprecision	RR, 0.79 (0.59-1.06)[g]	13 MIs per 1,000[b]	3 fewer MIs per 1,000 (from 5 fewer to 1 more)
Nonfatal major extracranial hemorrhage	6,981 (9 studies[h]) 0.5-5 y[b,c]	Moderate[d] due to imprecision	RR, 1.08 (0.75-1.54)[g,h]	10 bleeding events per 1,000[b]	1 more bleeding event per 1,000 (from 2 fewer to 5 more)

AICLA = Accidents Ischemiques Cerebraux Lies a l' Atherosclerose. See Table 1, 2, 7, 15, and 16 legends for expansion of other abbreviations.
[a]ESPS-2 (1997), and ESPRIT (2006).
[b]Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.
[c]Included studies that followed up patients for a mean of 2.6 y.
[d]CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.
[e]Aspirin ($\geq$75 mg/d) reduces cancer-related mortality (HR = 0.8) with long-term use (>5 y). Cancer-related mortality was not listed separately as an outcome because survival of stroke patients is relatively short (median survival, 5 y) and because cancer-related mortality is captured by overall mortality.
[f]Incidence of ICH was low (about 0.1%) with RR 1.67 (95% CI, 0.97-2.9) and absolute effect of 1 more ICH per 1,000 (from 0 fewer to 1 more).
[g]RR based on fatal and nonfatal events. RR for only nonfatal events assumed to be the same.
[h]Estimate for major extracranial bleeding derived from Cochrane review (2008), which included nine trials (three nonstroke trials): AICLA (1983), Caneschi (1985), Chairangsarit (2005), ESPRIT (2006), ESPS-2 (1997), Hess (1985), Libretti (1986), Schoop-I (1983), Sreedhara (1994).

Cilostazol Compared With Aspirin: A meta-analysis comparing cilostazol to placebo in patients with atherothrombotic disease has shown a reduction in total vascular events (RR, 0.9; 95% CI, 0.7-1.0) mostly driven by fewer cerebrovascular events in the cilostazol group (RR, 0.6; 95% CI, 0.4-0.8).[100] Cilostazol has been compared with aspirin in two secondary stroke prevention studies conducted in Japan.[101,102] Cilostazol results in 35 fewer recurrent strokes and three fewer nonfatal major extracranial hemorrhages per 1,000 patients treated for 2 years (Table 20, Tables S22, S28).[103] The trials failed to demonstrate or exclude an effect on mortality and MI. Cilostazol caused higher rates of side effects, including headache (RR, 1.5; 95% CI, 1.3-1.8), gastrointestinal intolerance (RR, 1.9; 95% CI, 1.5-2.5), palpitations (RR, 1.5; 95% CI, 1.2-1.9), tachycardia (RR, 4.0; 95% CI, 2.6-6.0), and dizziness (RR, 1.4; 95% CI, 1.1-1.8).[103] The quality of evidence was low as a result of serious methodologic limitations of the primary studies that may have biased the results in favor of cilostazol and due to imprecision of the overall effects. The cilostazol studies were limited to Asian patients. The quality of evidence was not downgraded for indirectness, however, because there are no data demonstrating that relative effects differ between racial groups. As a result of the low quality, we judged there to be insufficient evidence to determine superiority of cilostazol over aspirin. However, these trials added strength to the recommendation for cilostazol over no antiplatelet therapy.

Triflusal Compared With Aspirin: Triflusal has been compared with aspirin in three secondary stroke prevention studies (Table 21).[104] These studies showed a reduction in nonfatal major extracranial hemorrhages (six fewer per 1,000) but failed to demonstrate or exclude an effect on other more important outcomes, including mortality, recurrent stroke, and MI (Table 21, Table S29). The quality of evidence is limited due to imprecision.

Ticlopidine Compared With Aspirin: In stroke and TIA patients, ticlopidine reduces the risk of stroke, MI, and vascular death by about 8% compared with aspirin.[105] However, ticlopidine also has a 5% incidence of bothersome adverse effects, a 0.9% incidence of severe neutropenia, and a small risk of thrombotic thrombocytopenic purpura, which can be life-threatening.[106,107] Because of the risk of serious side effects and the availability of safer antiplatelet agents, the use of ticlopidine for secondary stroke prevention has become severely limited.

Terutroban Compared With Aspirin: The effect of terutroban in secondary stroke prevention was assessed in the Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin With Terutroban in

Table 18—*[Section 4.1.1, 4.1.2] Summary of Findings: Aspirin Plus Dipyridamole Compared With Clopidogrel for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[98]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With Clopidogrel	Risk Difference With Aspirin Plus Dipyridamole (95% CI)
Overall mortality	20,332 (1 study[a]) 2.5 y	Moderate[b] due to imprecision	HR, 0.97 (0.87-1.07)	49 deaths per 1,000[c]	1 fewer deaths per 1,000 (from 6 fewer to 3 more)[d]
Nonfatal recurrent stroke (ischemic and hemorrhagic)	20,332 (1 study[a]) 2.5 y	Moderate[b] due to imprecision	HR, 0.97 (0.88-1.07)	97 strokes per 1,000[c]	3 fewer strokes per 1,000 (from 11 fewer to 6 more)
Nonfatal MI	20,332 (1 study[a]) 2.5 y	High[b,e]	HR, 0.90 (0.73-1.1)	10 MIs per 1,000[c]	1 fewer MIs per 1,000 (from 3 fewer to 1 more)
Nonfatal major extracranial hemorrhage	20,332 (1 study[a]) 2.5 y	Moderate[b,e] due to imprecision	RR, 1.04 (0.88-1.22)[f]	10 bleeding events per 1,000[c]	0 more bleeding events per 1,000 (from 1 fewer to 2 more)

See Table 1, 2, 7, and 15 legends for expansion of abbreviations.
[a]Sacco (2008).
[b]CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.
[c]Baseline rates are derived from CAPRIE and adjusted for 2-y time frame.
[d]Aspirin ($\geq$75 mg/d) reduces cancer-related mortality (HR = 0.8) with long-term use ($>$5 y). Cancer-related mortality was not listed separately as an outcome because survival of stroke patients is relatively short (median survival, 5 y) and because cancer-related mortality is captured by overall mortality.
[e]The absolute number of events at the extremes of the CI are small; therefore, not rated down for imprecision.
[f]RR based on fatal and nonfatal major extracranial hemorrhages.

Patients With a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) trial.[108] This trial was stopped early based on an interim analysis. The results did not meet predefined criteria for noninferiority compared with aspirin. Consequently, development of terutroban was stopped, and it is therefore not included in these secondary stroke prevention recommendations.

Oral Anticoagulants: A meta-analysis has summarized the findings of five well-designed, randomized trials that have assessed the efficacy of oral anticoagulants for secondary prevention in patients with a history of noncardioembolic stroke.[109] These studies included patients with various stroke causes, such as large artery atherosclerosis, intracranial artery stenosis, small penetrating artery disease, and strokes

Table 19—*[Section 4.1.1] Summary of Findings: Aspirin Plus Clopidogrel Compared With Clopidogrel for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[99]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With Clopidogrel	Risk Difference With Aspirin Plus Clopidogrel (95% CI)
Overall mortality	7,599 (1 study[a]) 18 mo	Moderate[b] due to imprecision	RR, 1.00 (0.83-1.21)	49 deaths per 1,000[c]	0 fewer deaths per 1,000 (from 8 fewer to 10 more)
Nonfatal recurrent stroke (ischemic and hemorrhagic)	7,599 (1 study[a]) 18 mo	Moderate[b] due to imprecision	RR, 0.95 (0.82-1.1)[d]	97 strokes per 1,000[c,d]	5 fewer strokes per 1,000 (from 17 fewer to 10 more)
Nonfatal MI	7,599 (1 study[a]) 18 mo	Moderate[b] due to imprecision	RR, 0.98 (0.68-1.41)[e]	10 MIs per 1,000[c,e]	0 fewer MIs per 1,000 (from 3 fewer to 4 more)
Nonfatal major extracranial hemorrhage	7,540 (1 study[a]) 18 mo	High	RR, 2.55 (1.88-3.46)[f]	10 bleeding events per 1,000[c,f]	15 more bleeding events per 1,000 (from 9 more to 25 more)

ASA = acetylsalicylic acid; Clop = clopidogrel. See Table 1, 2, and 7 legends for expansion of other abbreviations.
[a]Diener (2004).
[b]CI includes possible benefit and possible harm or few events.
[c]Baseline rates for nonfatal events and overall mortality are derived from CAPRIE and adjusted for 2-y time frame.
[d]Based on data provided by the sponsor of the MATCH trial. Included in this outcome are all nonfatal ischemic strokes (Clop + ASA = 298; Clop = 325) and all nonfatal symptomatic intracranial hemorrhages (Clop + ASA = 27; Clop = 15).
[e]Based on data provided by the sponsor of the MATCH trial.
[f]Based on data provided by the sponsor of the MATCH trial. This includes all patients who had a nonfatal major or life-threatening extracranial hemorrhage. Patients who had more than one event were only counted once.

Table 20—*[Section 4.1.1, 4.1.2] Summary of Findings: Cilostazol Compared With Aspirin for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[103]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (Grade)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With Aspirin	Risk Difference With Cilostazol (95% CI)
Overall mortality	3,391 (2 studies[a]) 12-28 mo	Low[b-d] due to risk of bias, imprecision	RR, 0.89 (0.45-1.74)	50 deaths per 1,000[e]	6 fewer deaths per 1,000 (from 28 fewer to 37 more)
Nonfatal recurrent stroke (ischemic and hemorrhagic)	3,391 (2 studies[a]) 12-28 mo	Moderate[b,c] due to risk of bias	RR, 0.67 (0.52-0.86)[f]	106 strokes per 1,000[e]	35 fewer strokes per 1,000 (from 15 fewer to 51 fewer)
Nonfatal MI	3,391 (2 studies[a]) 12-28 mo	Low[b-d] due to risk of bias, imprecision	RR, 1.15 (0.55-2.41)[g]	13 MIs per 1,000[e]	2 more MIs per 1,000 (from 6 fewer to 18 more)
Nonfatal major extracranial hemorrhage	3,391 (2 studies[a]) 12-28 mo	Moderate[b,c] due to risk of bias	RR, 0.74 (0.61-0.9)[h]	10 bleeding events per 1,000[e]	3 fewer bleeding events per 1,000 (from 1 fewer to 4 fewer)

See Table 1, 2, 7, and 9 legends for expansion of abbreviations.

[a]CASISP (2008) and CSPS 2 (2010).

[b]Incomplete accounting of patients and outcome events by failing to adhere to ITT principle. In the CSPS 2 study, patients who discontinued drug were censored and no long-term follow-up data were acquired after discontinuation. In cilostazol arm, 457 (34%) patients discontinued the study drug, compared with 336 (25%) in aspirin arm.

[c]Evaluated in Asian population only: CASISP in China and CSPS 2 in Japan.

[d]CI is wide and includes possible benefit and possible harm.

[e]Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

[f]Incidence of ICH was 0.5% with cilostazol and 2.0% with aspirin (RR, 0.26; 95% CI, 0.13-0.55) and absolute effect of 14 fewer ICH per 1,000 patients treated with cilostazol.

[g]Based on any MI (fatal and nonfatal).

[h]Based on any extracranial hemorrhage (fatal and nonfatal, major and nonmajor).

of unknown cause (ie, cryptogenic strokes). Moderate-quality evidence suggests that oral anticoagulation is associated with higher all-cause mortality and major bleeding events. (Table 22, Tables S30, S31).

Special Populations: Subgroup analyses of secondary prevention studies have not identified effects that warrant separate recommendations for any specific subset of patients with noncardioembolic stroke. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) failed to find a benefit of anticoagulation over aspirin for secondary prevention in patients with antiphospholipid antibodies and in other investigated subgroups, including age, sex, race, prior TIA/stroke, hypertension, diabetes, cardiac disease, and smokers.[110-112] A Cochrane systematic review did not find a significant difference between anticoagulation and antiplatelet therapy in patients with stroke secondary to cervical artery dissection.[62] Recommendations for all subgroups therefore follow the general recommendations regarding patients with noncardioembolic stroke.

Resource Implications for Newer Antiplatelet Drugs vs Aspirin for Stroke Prevention: Since aspirin is inexpensive and newer antiplatelet agents such as clopidogrel and the combination of aspirin plus extended-release dipyridamole are more expensive, we evaluated if the more expensive agents are worth the cost. Since the lifetime cost of stroke is high (and thus the potential cost savings of stroke prevented is high), even a modestly effective drug that is not inordinately more expensive may be cost-effective.[113,114]

A cost-effectiveness analysis that compared aspirin to placebo showed that aspirin was cost-effective compared with placebo with a base-case incremental cost-effectiveness ratio of $2,176/quality-adjusted life-years (QALY) (in 2010 $US).[113] An analysis comparing clopidogrel with aspirin for secondary prevention of vascular events, including stroke, concluded that clopidogrel increased quality-adjusted life expectancy at an incremental cost-effectiveness ratio of $37,768/QALY (in 2010 $US).[115] Given the similar effectiveness of dipyridamole/aspirin and clopidogrel (Table 18, Table S26) and their similar cost in the United States, cost-effectiveness estimates from this study apply to both agents. In settings where there is a cost difference between clopidogrel and dipyridamole/aspirin, the less costly of the two treatment options is preferred from a cost-effectiveness perspective.

Recommendations

4.1.1. In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend

Table 21—*[Section 4.1.1] Summary of Findings: Triflusal Compared With Aspirin for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[104]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With Aspirin	Risk Difference With Triflusal (95% CI)
Overall mortality	2,753 (3 studies[a]) 1.5-3 y	Moderate due to imprecision	OR, 1.03 (0.75-1.43)[b]	50 deaths per 1,000[c]	1 more deaths per 1,000 (from 12 fewer to 20 more)
Nonfatal recurrent stroke (ischemic and hemorrhagic)	2,753 (3 studies[a]) 1.5-3 y	Moderate[d] due to imprecision	OR, 0.97 (0.76-1.25)[b,e]	106 strokes per 1,000[c]	3 fewer strokes per 1,000 (from 23 fewer to 23 more)
Nonfatal MI	2,753 (3 studies[a]) 1.5-3 y	Moderate[d] due to imprecision	OR, 0.8 (0.48-1.33)	13 MIs per 1,000[c]	3 fewer MIs per 1,000 (from 7 fewer to 4 more)
Nonfatal major extracranial hemorrhage	2,753 (3 studies[a]) 1.5-3 y	High	OR, 0.38 (0.22-0.65)[b,f]	10 bleeding events per 1,000[c]	6 fewer bleeding events per 1,000 (from 3 fewer to 8 fewer)

See Table 1, 7, and 15 legends for expansion of abbreviations.

[a]Matias-Guiu (1994), TACIP (2003), and TAPIRSS (2004).

[b]ORs obtained from Cochrane analysis were inverted to obtain estimate for effect relative to aspirin.

[c]Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

[d]CIs wide and include 1.00.

[e]Incidence of ICH was 1.3% with aspirin and 0.7% with triflusal (OR, 0.51; 95% CI, 0.2-1.1) and absolute effect of 7 fewer (95% CI from 12 fewer to 1 more) ICH per 1,000 patients treated with triflusal.

[f]OR for nonfatal major extracranial hemorrhages based on data for any (fatal and nonfatal) major extracranial hemorrhages.

long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A), **oral anticoagulants** (Grade 1B), **the combination of clopidogrel plus aspirin** (Grade 1B), **or triflusal** (Grade 2B)**.**

4.1.2. Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin (Grade 2B) **or cilostazol** (Grade 2C)**.**

Remarks: With long-term use (>5 years), the benefit of clopidogrel over aspirin in preventing major vascular events may be offset by a reduction in cancer-related mortality with regimens that contain aspirin.

4.2 Antithrombotic Therapy for the Secondary Prevention of Cardioembolic Stroke

AF is the most common cause of cardiac embolism and is responsible for about half of all cardiogenic strokes. Other potential cardiac sources of emboli include patent foramen ovale (PFO), atrial septal aneurysm, aortic arch atheroma, and mitral valvular strands. The cause of 30% to 40% of all ischemic strokes remains undetermined, and cardiac mechanisms are suspected to account for a percentage of these cryptogenic strokes.[116,117]

Atrial Fibrillation: Recommendations for patients with AF and a history of stroke or TIA are based on the pooled effect of anticoagulation in primary and secondary prevention studies as the data exclusively on secondary prevention are limited to only two trials.[118,119] Pooled data from these anticoagulation trials are summarized in the accompanying article on antithrombotic therapy in AF by You et al[3] and provide high-quality evidence that anticoagulation reduces recurrent stroke and mortality in patients with a history of stroke or TIA and AF (Table 23)[120] (You et al,[3] Section 2.1.10). You et al[3] also discuss antiplatelet therapy for patients with contraindications to anticoagulant therapy and the comparative effectiveness of newer anticoagulants and VKAs.

The risk of recurrent stroke in patients with AF depends on multiple risk factors. $CHADS_2$ (Congestive heart failure, Hypertension, Age $\geq$ 75, Diabetes mellitus, Stroke or TIA history) is a commonly used risk-stratification scale for patients with AF.[120] For information on how to calculate the $CHADS_2$ score, see You et al[3] in this guideline supplement. Anticoagulation is recommended for patients with AF, including paroxysmal AF, who are at high risk of stroke ($CHADS_2 \geq 2$). This includes all patients with a history of stroke or TIA, as a history of stroke or TIA alone accounts for two points on the $CHADS_2$ score. Recommendations for antithrombotic therapy in patients with AF with a history of stroke or TIA therefore follow the recommendations for patients with AF at high risk of stroke (Section 2.1.10 in You et al).[3] The high risk of stroke in patients with AF with a history of stroke or TIA is demonstrated by a much higher stroke rate in the two secondary prevention trials (8.0% per year)[118,119] compared with the nine mainly primary prevention trials (2.6% per year).[119,121-128]

Table 22—*[Section 4.1.1] Summary of Findings: Anticoagulation Compared With Antiplatelet Therapy for Secondary Prevention in Patients With a History of Noncardioembolic Ischemic Stroke or TIA*[n,109]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
				Risk With Antiplatelet	Risk Difference With Oral Anticoagulation (95% CI)
Overall mortality	5,400 (5 studies[a]) 0-5 y	Moderate[b-e] due to inconsistency	RR, 1.36 (1.09-1.7)	50 deaths per 1,000[f]	18 more deaths per 1,000 (from 5 more to 35 more)[g]
Nonfatal recurrent stroke (ischemic and hemorrhagic)	5,400 (5 studies[a]) 0-5 y	High[b,d]	RR, 1.03 (0.88-1.22)	106 strokes per 1,000[f]	3 more strokes per 1,000 (from 13 fewer to 23 more)
Nonfatal MI	1,637 (2 studies[a]) 3-5 y	Moderate[i-k] due to imprecision	RR, 0.91 (0.59-1.4)	13 MIs per 1,000[f]	1 fewer MIs per 1,000 (from 5 fewer to 5 more)
Nonfatal major extracranial hemorrhage	3,194 (4 studies[l]) 0-5 y	High[b,d,m]	RR, 3.60 (2.29-5.66)	10 bleeding events per 1,000[f]	26 more bleeding events per 1,000 (from 13 more to 47 more)

See Table 1, 2, 15, and 17 legends for expansion of abbreviations.

[a]Garde (1983), SPIRIT (1997), WASID (2000), WARSS (2001), and ESPRIT (2007).

[b]Of the five studies, allocation was concealed in four (unclear in Garde 1983), outcome adjudicators were blinded in four (not blinded in Garde 1983), analysis was ITT in four (unclear in Garde 1983), and follow-up ranged from 97% to 100%.

[c]$I^2 = 62\%$.

[d]INR target range was 2-3 in two studies (WASID, ESPRIT), 1.4-2.8 in one study (WARSS), 3-4.5 in one study (SPIRIT). Thrombin time was 7%-15% in one study (Garde). We did not downgrade for indirectness.

[e]CI includes both values suggesting anticoagulation is harmful and values suggesting anticoagulation is no different from antiplatelets. The quality of evidence could be considered as moderate if considering mortality as either unchanged or worsened with anticoagulation given a lower CI of 0.98.

[f]Baseline event rates based on aspirin arm of the CAPRIE trial and adjusted for 2-y time frame.

[g]Aspirin ($\geq$ 75 mg/d) reduces cancer-related mortality (HR = 0.8) with long-term use ($>$ 5 y). Cancer-related mortality was not listed separately as an outcome because survival of stroke patients is relatively short (median survival, 5 y) and because cancer-related mortality is captured by overall mortality.

[h]WASID (2000) and ESPRIT (2007).

[i]Of the two studies (WASID, ESPRIT), allocation was concealed in both, outcome adjudicators were blinded in both, analysis was ITT in both, and follow-up ranged from 97% to 98%.

[j]INR target range was 2-3 in both studies (WASID, ESPRIT).

[k]CI includes both values suggesting harm and benefit.

[l]Garde (1983), SPIRIT (1997), WASID (2000), and ESPRIT (2007).

[m]Although $I^2 = 80\%$, we did not downgrade for inconsistency as all point estimates suggest increased major bleeding.

[n]The antiplatelet used in all studies was aspirin.

The benefit of anticoagulation in the two secondary-prevention trials was driven by a lower incidence of any (ischemic or hemorrhagic) recurrent stroke (52 fewer per 1,000 over 1-2.3 years); this came at a cost of more major extracranial bleeding events (12 more per 1,000 over 1-2.3 years).[129] Both primary and secondary prevention studies failed to show or exclude a beneficial or detrimental effect of anticoagulation therapy on mortality.[129]

The optimal time to begin oral anticoagulation following a cardioembolic stroke depends primarily on the balance of risks of early ischemic stroke recurrence and hemorrhagic transformation of the index stroke. For patients with AF there is an approximately 5% risk of symptomatic hemorrhagic transformation in the 2 weeks after presentation with an acute ischemic stroke and the risk is greater in patients with larger infarcts.[130]

A few studies can help guide the timing of anticoagulation after stroke secondary to AF. In the European Atrial Fibrillation Trial (EAFT),[118] patients with stroke or TIA in the previous 3 months who also were diagnosed with AF were randomized to oral anticoagulation, 300 mg aspirin daily, or placebo. About half of the patients receiving anticoagulation were randomized within 2 weeks after symptom onset. No increase in brain hemorrhage was apparent in patients started early ($<$2 weeks) vs later (2 weeks to 3 months). The Heparin in Acute Embolic Stroke Trial (HAEST) study randomized patients with AF presenting with acute ischemic stroke to early treatment (within 30 h of stroke onset) with LMWH or aspirin and did not find evidence of a statistically significant difference in recurrent ischemic stroke (the primary outcome) or intracerebral hemorrhage.[61] A subgroup analysis of 3,169 patients with AF enrolled in the IST showed no net advantage to early treatment with UFH compared with no heparin; patients who received heparin experienced reductions in ischemic stroke that were offset by an increase in hemorrhagic stroke within the first 14 days.[131]

In summary, there is low-quality evidence suggesting no net benefit or harm associated with the early initiation of anticoagulation, but that the risk of

Table 23—*[Section 4.2.1] Summary of Findings: Anticoagulation Compared With No Anticoagulation for Secondary Prevention in Patients With AF and a History of Ischemic Stroke or TIA*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects, 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With No Therapy	With VKA	Relative Effect (95% CI)[j]	With No Therapy	With VKA (95% CI)	Quality of Evidence
Death (critical outcome), mean follow-up 1.7 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	136 of 1,425 (9.5)	103 of 1,429 (7.2)	RR, 0.72 (0.55-0.94)	53 per 1,000[a]	15 fewer deaths per 1,000[b] (from 3 fewer to 24 fewer)	High
Nonfatal stroke (critical outcome), mean follow-up 1.7 y. Ischemic stroke and intracranial hemorrhage[c,k]											
6 RCTs	No serious limitations	No serious inconsistency	No serious Indirectness	No serious imprecision	Undetected	108 of 1,425[d] (7.6)	36 of 1,429[e] (2.5)	RR, 0.34 (0.23-0.49)	CHADS 2 points		High
									45 per 1,000	30 fewer strokes per 1,000 (from 23 fewer to 35 fewer)	
									CHADS 3-6 points		
									96 per 1,000	63 fewer strokes per 1,000 (from 49 fewer to 74 fewer)	
Nonfatal major extracranial bleeding events (important outcome), mean follow-up 1.7 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	7 of 1,425 (0.5)	23 of 1,429 (1.6)	RR, 2.58 (1.12-5.97)	5 per 1,000[f]	8 more bleeding events per 1,000 (from 1 more to 25 more)	High[g]
Systemic embolism (important outcome), mean follow-up 1.7 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[h]	Undetected	10 of 1,425 (0.7)	4 of 1,429 (0.3)	RR, 0.42 (0.15-1.20)	4 per 1,000[i]	2 fewer systemic emboli per 1,000 (from 3 fewer to 1 more)	Moderate
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	N/A	N/A	N/A	VKA > no therapy	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits		High

ATRIA = Anticoagulation and Risk Factors In Atrial Fibrillation; $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥ 75, diabetes mellitus, stroke or TIA; N/A = not applicable; VKA = vitamin K antagonist. See Table 1, 2, and 9 legends for expansion of other abbreviations.

[a]From Go et al. (2003), which reported a mortality rate of 5.33 per 100 person-years in untreated (no warfarin) patients from an observational study (ATRIA cohort). The majority of the patients in ATRIA (78%) had a $CHADS_2$ score ≥ 1 or higher.

[b]VKA therapy likely does not lead to any reductions in all-cause mortality compared with no therapy in low risk patients with a $CHADS_2$ of 0, since there is evidence suggesting that absolute reductions in ischemic stroke are heavily dependent on stroke risk (eg, small reductions at low $CHADS_2$ score), whereas the absolute increase in intracranial hemorrhage is relatively consistent across $CHADS_2$ categories (Singer et al. [2009]).

[c]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeding events. For papers that did not report the number of strokes that were fatal and nonfatal (CAFA, EAFT), we imputed values for the number of fatal and nonfatal strokes to estimate the pooled relative risk for nonfatal stroke across all eligible studies. Assumptions underlying these estimates are detailed in section 1.3.

[d]Of the 108 nonfatal strokes on no therapy, an estimated 106 (98%) were ischemic and two (2%) were hemorrhagic.

[e]Of the 36 nonfatal strokes on VKA therapy, an estimated 34 (94%) were ischemic and two (6%) were hemorrhagic.

[f]Estimate of the rate of nonfatal major extracranial bleeding on no therapy is derived from rates observed in observational cohorts of predominantly patients with AF receiving adjusted-dose VKA therapy (median of 1.3% per year) and dividing by the relative risk of major bleeding on adjusted-dose VKA therapy observed in the randomized clinical trials (section 1.6).

[g]Quality of evidence is moderate for patients with a $CHADS_2$ score of 0, since the recommendation would differ if the true increase in nonfatal major extracranial bleeding was one vs 25 bleeding events per 1,000 patients in a given year.

[h]95% CI does not exclude the possibility of no effect.

[i]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-years reported in IPD meta-analysis of warfarin vs aspirin by van Walraven et al. (2002), and an RR of 0.80 for aspirin vs no therapy for systemic embolism.

[j]Pooled estimates of treatment effect in this evidence profile are from a meta-analysis conducted for these guidelines, including data from six RCTs of adjusted-dose VKA therapy vs no antithrombotic therapy (AFASAK I, BAATAF, CAFA, EAFT, SPAF I, SPINAF).

[k]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on no therapy by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of sox historical RCTs in AF patients (Gage et al[120]). Assumptions underlying these estimates are detailed in section 1.4.4.

symptomatic hemorrhagic transformation is greater with large infarcts. We therefore recommend initiation of oral anticoagulation therapy within 2 weeks of a cardioembolic stroke; however, for patients with large infarcts or other risk factors for hemorrhage, additional delays are appropriate.

Before anticoagulation is initiated and during the time that anticoagulation is started but has not yet reached therapeutic levels (ie, INR < 2.0), treatment with aspirin is recommended. This is based on data that aspirin is beneficial in the early treatment of acute stroke (see Section 2.4) and indirect data from randomized trials of aspirin in patients with AF who have not yet had a stroke that suggest a relative risk reduction of recurrent stroke of approximately 20% (Section 2.1.2 in You et al).[3] EAFT provides additional data that suggest benefit of aspirin over placebo. It compared the long-term efficacy of aspirin (300 mg/d) to placebo in patients with AF who had suffered a stroke or TIA.[118] In this trial, aspirin was associated with a 14% reduction in the annual rate of stroke (HR, 0.86; 95% CI, 0.64-1.15); this difference was not statistically significant.

Other Cardioembolic Sources: Vandvik et al[1] and You et al[3] in this supplement address long-term antithrombotic therapy for patients with other potential cardioembolic sources for stroke. The special populations covered in Vandvik et al[1] include recent MI, left ventricular thrombus, and low ejection fraction. The special conditions covered by Whitlock et al[4] include mechanical heart valves, nonbacterial thrombotic endocarditis, infective endocarditis, mitral valve prolapse, mitral valve strands, and aortic arch atheroma. Although the recommendations in the accompanying articles focus on long-term antithrombotic therapy for primary stroke prevention, they also apply to patients who have suffered a stroke in the setting of one of these conditions (ie, secondary stroke prevention).

Patent Foramen Ovale: Among stroke patients with a PFO, the risk of stroke recurrence is estimated to be only 1% to 2% per year.[132,133] In the PICSS (PFO in Cryptogenic Stroke Study) trial, stroke patients with PFO did not have a significantly increased 2-year risk of recurrent stroke or death compared with those without a PFO, and there was no significant difference in the 2-year event rates among those treated with warfarin vs aspirin.[134] Given the known increased risk of bleeding complications with anticoagulation and the lack of data to demonstrate a benefit in terms of reduction of recurrent ischemic cardiovascular events, anticoagulation is not indicated for this population. PFO closure is an alternative to antithrombotic therapy. A large clinical trial of PFO closure in stroke patients has been conducted recently but results have not been published.[135] Consequently, we suggest that patients with stroke and PFO are treated with antiplatelet therapy following the recommendations for patients with noncardioembolic stroke (see Recommendations 4.1.1 and 4.1.2).

Recommendations

4.2.1. In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we recommend oral anticoagulation over no antithrombotic therapy (Grade 1A)**, aspirin** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)**.**

4.2.2. In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we suggest oral anticoagulation with dabigatran 150 mg bid over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0) (Grade 2B)**.**

4.2.3. In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel over aspirin (Grade 1B)**.**

Remarks: Patients should be treated (ie, bridged) with aspirin until anticoagulation has reached a therapeutic level.

Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset. Earlier anticoagulation can be considered for patients at low risk of bleeding complications (eg, those with a small infarct burden and no evidence of hemorrhage on brain imaging). Delaying anticoagulation should be considered for patients at high risk of hemorrhagic complications (eg, those with extensive infarct burden or evidence of significant hemorrhagic transformation on brain imaging).
Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less).

4.3 Antithrombotic Therapy for Stroke Prevention in Patients With a History of ICH

There is considerable overlap in the risk factors for primary ICH and other cardiovascular disorders, such as ischemic stroke. Common risk factors for ICH include hypertension, smoking, and diabetes. Patients with a history of a primary ICH

are therefore often not only at risk for recurrent hemorrhagic stroke but also at increased risk of ischemic stroke and ischemic heart disease. Occasionally, patients with a history of an ICH have AF or another indication for long-term oral anticoagulation therapy.

The recommendations listed in this section relate specifically to patients with a primary ICH, typically those with hypertension and/or cerebral amyloid angiopathy. This includes patients who had an ICH while taking an antiplatelet agent or while taking anticoagulation and being in a therapeutic range. It excludes patients with an underlying vascular malformation or tumor. Similarly, the recommendations do not address patients with a hemorrhage due to an overdose of anticoagulation therapy.

We identified no clinical trials that compared anticoagulation to no anticoagulation in patients with a history of ICH and an indication for long-term anticoagulation. One published clinical decision analysis on this topic formed the basis for our recommendation.[136] The primary outcome considered was QALY. No antithrombotic therapy was preferred over anticoagulation as it resulted in a lifetime gain of 0.3 QALY for patients with deep hemorrhages and a gain of 1.9 QALY with lobar hemorrhages.

Only in patients with deep hemorrhages who are at very high risk of cardiac embolism without antithrombotic therapy (>7% per year) should anticoagulation be considered.[136] This is generally the case for patients with mechanical heart valves and for patients with AF and high $CHADS_2$ scores (≥4 points). In patients with deep ICH and intermediate risk of cardiac thromboembolic events (5%-7% per year), antiplatelet therapy with aspirin may be preferred over no antithrombotic therapy or anticoagulation.[136] For patients with a history of ICH who only have an indication for antiplatelet therapy, the risk of thromboembolic events is generally low (<5% per year), and the benefit of antiplatelet therapy is therefore unlikely to outweigh its potential harmful effect for most patients in this setting.

Recommendation

4.3. In patients with a history of a symptomatic primary ICH, we suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke (Grade 2C)**.**

Remarks: Patients with a history of ICH who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep

Table 24—*[Section 5.1] Summary of Findings: Therapeutic-Dose Anticoagulation Compared With No Anticoagulation in Patients With Symptomatic Cerebral Venous Sinus Thrombosis*[143,i]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 6 mo: Risk With No Therapeutic Anticoagulation	Anticipated Absolute Effects, Time Frame 6 mo: Risk Difference With Therapeutic Anticoagulation (95% CI)
Overall mortality or disability[e]	79 (2 studies[a]) 3 mo	Low[b,c,f] due to risk of bias, imprecision	RR, 0.43 (0.12-1.41)	140 deaths or disability per 1,000[d]	80 fewer deaths or disability per 1,000 (from 123 fewer to 57 more)
Nonfatal major extracranial hemorrhage	79 (2 studies[a]) 3 mo	Low[b,c,f] due to risk of bias, imprecision	RR, 2.9 (0.12-68.5)[g]	10 bleeding events per 1,000[d]	19 more bleeding events per 1,000 (from 9 fewer to 675 more)

ISCVT = International Study on Cerebral Vein and Dural Sinus Thrombosis. See Tables 2 and 7 for expansion of abbreviations.

[a]Einhaupl (1991) and de Bruijn (1999).

[b]Allocation was concealed in both studies. In one study (Einhaupl 1991), patients and outcome assessors but not providers were blinded. In the other study (CVST group 1999), patients, providers, and outcome assessors were blinded for 3 wk then unblinded. No postrandomization exclusion in the Einhaupl (1991) and one patient excluded for "wrong diagnosis" in CVST group 1999. Einhaupl (1991) was stopped early (after 20 patients) because a statistically significant effect in favor of heparin was found, based upon scores on the CVST severity scale.

[c]CI includes both negligible effect and appreciable benefit or appreciable harm.

[d]Baseline risk of mortality or disability at 6 mo is 70 per 1,000 and baseline risk of disability is also 70 per 1,000 (ISCVT, 2004).

[e]No disability in Einhaupl defined as complete recovery or slight neurologic deficits. In de Bruijn, defined as BI<15.

[f]Effect estimate based on few events.

[g]In Einhaupl three of 10 patients and in de Bruijn 15 of 30 patients had some degree of intracerebral hemorrhage on their pretreatment CT scans. No new or worsening of existing intracerebral hemorrhages were observed during treatment. No fatal hemorrhages occurred. Nonfatal extracranial major hemorrhages occurred in 1 of 40 patients (2.5%) treated with anticoagulation and 0 of 39 patients (0%) treated without anticoagulation.

[h]Baseline risk derived from IST.

[i]Both studies generally applied inclusions/exclusions criteria routinely used in clinical practice. However, the Einhaupl study excluded patients with known malignancy and or pretreatment with antiplatelet medications. Patients with malignancy represent approximately 7% of all patients with cerebral sinus thromboses (ISCVT, 2004).

hemorrhages) and relatively high risk (>7% per year) of cardiac thromboembolic events (eg, with mechanical heart valves or $CHADS_2$ score ≥ 4 points).

5.0 Cerebral Venous Sinus Thrombosis

5.1 Anticoagulation for Symptomatic Cerebral Venous Sinus Thrombosis

A Cochrane systematic review summarized two randomized trials of anticoagulation for patients with symptomatic cerebral sinus thrombosis.[137] This includes patients who present with headache, focal neurologic deficits, seizures, alterations of consciousness, and/or papilledema.[138] Due to small sample size, the effect estimates had wide CIs (Table 24, Tables S32, S33). Neither benefit nor harm could be confirmed or excluded for any of the outcomes. The overall quality of evidence was low as a result of imprecision. The suggestion to treat patients with symptomatic cerebral sinus thrombosis with anticoagulation therefore reflects the panel's judgment based on the best available, albeit low-quality, evidence.

The two trials included in the meta-analysis had a relatively high percentage of patients who had some degree of ICH prior to anticoagulation therapy (three of 10 in one trial and 15 of 30 in the second trial). Despite this, no occurrences of new symptomatic ICH were observed in patients treated with anticoagulation. Anticoagulation is therefore recommended even in the presence of hemorrhage within a venous infarction. However, for patients with venous infarcts and large parenchymal hematomas the risk of hemorrhage extension is likely high. The uncertain benefits of anticoagulation do not outweigh the potential for harm.

Either dose-adjusted heparin or LMWH can be used for the initial treatment of patients with cerebral venous sinus thrombosis. Heparin should be continued until the patient has stabilized clinically. For patients who demonstrate progressive neurologic deterioration despite adequate anticoagulation, other options, such as endovascular thrombectomy or local intrathrombus infusion of a thrombolytic agent, together with IV heparin, can be considered.[139,140] Patients who have stabilized can be switched from heparin to oral anticoagulation. Oral anticoagulation is generally recommended for a period of 3 to 6 months.[141] Lifelong anticoagulation could be considered in the presence of permanent risk factors for recurrent events.[141]

Recommendation

5.1. In patients with cerebral venous sinus thrombosis, we suggest anticoagulation over no anticoagulant therapy during the acute and chronic phases (Grade 2C)**.**

Research Recommendation: The efficacy of mechanical thrombectomy is uncertain as outcome data are limited to single-arm prospective cohort studies. Several RCTs are currently ongoing and may provide the data needed to determine if mechanical thrombectomy is efficacious and, if so, what subset of patients with stroke benefits. This is of particular relevance as mechanical thrombectomy for acute stroke is on the rise in the United States.[142]

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Dr Lansberg: contributed as Deputy Editor.
Dr O'Donnell: contributed as a panelist.
Dr Khatri: contributed as a panelist.
Dr Lang: contributed as a panelist.
Dr Nguyen-Huynh: contributed as a panelist.
Dr Schwartz: contributed as frontline clinician.
Dr Sonnenberg: contributed as a resource consultant.
Dr Schulman: contributed as a panelist.
Dr Vandvik: contributed as a panelist.
Dr Spencer: contributed as a panelist.
Dr Alonso-Coello: contributed as a panelist.
Dr Guyatt: contributed as a panelist.
Dr Akl: contributed as Topic Editor.

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