

# CHEST<sup>®</sup>

Official publication of the American College of Chest Physicians



## **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**

Maarten G. Lansberg, Martin J. O'Donnell, Pooja Khatri, Eddy S. Lang,  
Mai N. Nguyen-Huynh, Neil E. Schwartz, Frank A. Sonnenberg, Sam  
Schulman, Per Olav Vandvik, Frederick A. Spencer, Pablo  
Alonso-Coello, Gordon H. Guyatt and Elie A. Akl

*Chest* 2012;141:e601S-e636S

DOI 10.1378/chest.11-2302

The online version of this article, along with updated information and  
services can be found online on the World Wide Web at:

[http://chestjournal.chestpubs.org/content/141/2\\_suppl/e601S.full.html](http://chestjournal.chestpubs.org/content/141/2_suppl/e601S.full.html)

Supplemental material related to this article is available at:

[http://chestjournal.chestpubs.org/content/suppl/2012/02/03/141.2\\_suppl.e601S.DC1.html](http://chestjournal.chestpubs.org/content/suppl/2012/02/03/141.2_suppl.e601S.DC1.html)

*Chest* is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2012 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder. (<http://chestjournal.chestpubs.org/site/misc/reprints.xhtml>)  
ISSN:0012-3692

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S<sup>®</sup>



## 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

Maarten G. Lansberg, MD, PhD; Martin J. O'Donnell, PhD; Pooja Khatri, MD; Eddy S. Lang, MDCM; Mai N. Nguyen-Huynh, MD; Neil E. Schwartz, MD, PhD; Frank A. Sonnenberg, MD; Sam Schulman, MD, PhD; Per Olav Vandvik, MD, PhD; Frederick A. Spencer, MD; Pablo Alonso-Coello, MD, PhD; Gordon H. Guyatt, MD, FCCP; and Elie A. Akl, MD, MPH, PhD

**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<sub>2</sub> = 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

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**

Revision accepted August 31, 2011.

**Affiliations:** From the Stanford Stroke Center (Drs Lansberg and Schwartz), Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, CA; the HRB-Clinical Research Faculty (Dr O'Donnell), National University of Ireland Galway, Galway, Ireland; the Department of Neurology (Dr Khatri), University of Cincinnati, Cincinnati, OH; the University of Calgary (Dr Lang), Calgary, AB, Canada; the Department of Neurology (Dr Nguyen-Huynh), University of California, San Francisco, CA; the Division of General Internal Medicine (Dr Sonnenberg), UMDNJ/Robert Wood Johnson Medical School, New Brunswick, NJ; the Department of Medicine (Drs Schulman and Guyatt), McMaster University, ON, Canada; the Norwegian Knowledge Centre for the Health Services (Dr Vandvik), Oslo, Norway; St. Joseph's Healthcare (Dr Spencer), Hamilton, ON, Canada; the Iberoamerican Cochrane Centre (Dr Alonso-Coello), CIBERESP-IIB Sant Pau, Barcelona, Spain; the State University of New York at Buffalo (Dr Akl), Buffalo, NY; and the Department of Clinical Epidemiology and Biostatistics (Drs Akl and Guyatt), McMaster University, Hamilton, ON, Canada.

**Funding/Support:** The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines received support from the National Heart, Lung, and Blood Institute [R13 HL104758] and Bayer Schering Pharma AG. Support in the form of educational grants were also provided by Bristol-Myers Squibb; Pfizer, Inc; Canyon Pharmaceuticals; and sanofi-aventis US.

**Disclaimer:** American College of Chest Physician guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at [http://chestjournal.chestpubs.org/content/141/2\\_suppl/1S](http://chestjournal.chestpubs.org/content/141/2_suppl/1S).

**Correspondence to:** Elie A. Akl, MD, MPH, PhD, State University of New York at Buffalo, ECMC, DK Miller bldg C216, 462 Grider St, Buffalo, NY 14228; e-mail: [elieakl@buffalo.edu](mailto:elieakl@buffalo.edu)

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (<http://www.chestpubs.org/site/misc/reprints.xhtml>).

DOI: 10.1378/chest.11-2302

**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

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<sub>2</sub> (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<sup>1</sup> (coronary artery disease), Alonso-Coello et al<sup>2</sup> (peripheral arterial disease), You et al<sup>3</sup> (atrial fibrillation [AF]), and Whitlock et al<sup>4</sup> (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.<sup>2</sup>

## 1.0 METHODS

Guideline development for this article followed the procedures set forward in the article by Guyatt et al<sup>5</sup> 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.<sup>6</sup> 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 com-

puter program designed for guideline development according to GRADE criteria.<sup>7</sup>

### 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,<sup>5</sup> we used ratings from participating guideline panelists informed by a systematic review of the literature.<sup>8</sup> 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.<sup>8</sup>

## 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  $\leq 1$  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  $\leq 2$ , 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 <sup>a</sup>	Population	Intervention(s)	Comparator	Outcome	Method
				Ischemic stroke: acute management			
2.1.1	2, 3, 4	1, 2, 3, 4	Patients with acute ischemic stroke	IV r-tPA	No IV r-tPA	Mortality, good functional outcome	R
2.1.2							
2.1.3							
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		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	10	15, 17	Patients with acute stroke (ischemic or hemorrhagic) and restricted mobility	Prophylactic-dose unfractionated heparin	Prophylactic-dose LMWH	Same as above	R
3.2.2							
3.1.1	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
3.2.1							
3.1.3	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
3.2.3							
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	16	22, 24	Patients with a history of noncardioembolic ischemic stroke or TIA	Clopidogrel	Aspirin	Same as above	R
4.1.2							
4.1.1	17	22, 25	Patients with a history of noncardioembolic ischemic stroke or TIA	Aspirin plus dipyridamole	Aspirin	Same as above	R
4.1.2							
4.1.1	18	22, 26	Patients with a history of noncardioembolic ischemic stroke or TIA	Aspirin plus dipyridamole	Clopidogrel	Same as above	R
4.1.2							
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	20	22, 28	Patients with a history of noncardioembolic ischemic stroke or TIA	Cilostazol	Aspirin	Same as above	R
4.1.2							

(Continued)

**Table 1—Continued**

Rec.	Table	S-Table <sup>a</sup>	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 <sup>3</sup>		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
5.1	24	32, 33	Patients with cerebral venous sinus thrombosis	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.  
<sup>a</sup>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.<sup>9</sup> 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.<sup>10,11</sup>

**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).<sup>10,11</sup> 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.<sup>12-14</sup> 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.<sup>14</sup> Additional studies of r-tPA use in routine clinical practice have typically reported symptomatic ICH rates < 7%.<sup>15-21</sup> 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<sup>10-11</sup>**

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 <sup>a</sup>	930 (4 studies <sup>b</sup> ) 90 d	High <sup>c-e</sup>	RR, 1.00 (0.76-1.33) <sup>f,g</sup>	120 deaths per 1,000 <sup>h</sup>	0 fewer deaths per 1,000 (from 29 fewer to 40 more)
Good functional outcome, <sup>i</sup> mRS 0-1	930 (4 studies <sup>b</sup> ) 90 d	High <sup>c,j</sup>	RR, 1.44 (1.21-1.72) <sup>k,l</sup>	350 excellent outcomes per 1,000 <sup>m</sup>	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.

<sup>a</sup>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.

<sup>b</sup>NINDS (1995), ATLANTIS, ECASS I (1995), and ECASS II (1998).

<sup>c</sup>Allocation unclear in two studies.

<sup>d</sup> $I^2 = 38\%$ .

<sup>e</sup>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.

<sup>f</sup>Data from Wardlaw et al.<sup>11</sup>

<sup>g</sup>Fixed effect model because NINDS (1995) judged to be dominant.

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

<sup>i</sup>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.

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

<sup>k</sup>Data from Lees et al.<sup>10</sup>

<sup>l</sup>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.

<sup>m</sup>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.<sup>22-26</sup> 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.<sup>22</sup> 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 Noninterventive 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).<sup>10,23-26</sup> 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.<sup>27</sup> 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<sup>10-11</sup>**

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 <sup>a</sup>	1,620 (5 studies <sup>b</sup> ) 90 d	Low <sup>c,d</sup> due to inconsistency, imprecision	OR, 1.22 (0.87-1.71) <sup>e,f</sup>	120 deaths per 1,000 <sup>g</sup>	23 more deaths per 1,000 (from 14 fewer to 69 more)
Good functional outcome, <sup>h</sup> mRS 0-1	1,620 (5 studies <sup>b</sup> ) 90 d	High	OR 1.34 (1.06-1.68) <sup>e,f</sup>	350 excellent outcomes per 1,000 <sup>i</sup>	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.

<sup>a</sup>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.

<sup>b</sup>ATLANTIS, ECASS I (1995), ECASS II (1998), ECASS III (2008), and EPITHET.

<sup>c</sup> $I^2 = 70\%$ .

<sup>d</sup>95% CI includes both (1) no effect and (2) appreciable benefit or appreciable harm.

<sup>e</sup>Based on Lees et al.<sup>10</sup>

<sup>f</sup>This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

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

<sup>h</sup>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.<sup>11</sup>

<sup>i</sup>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.<sup>27,28</sup> 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 hypoden-

sity (> 1/3 of the MCA territory) on the pretreatment CT scan.<sup>27</sup> 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).<sup>29</sup> 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<sup>10-11</sup>**

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 <sup>a</sup>	1,117 (4 studies <sup>b</sup> ) 90 d	Moderate <sup>c</sup> due to imprecision	OR, 1.49 (1-2.21) <sup>d</sup>	120 deaths per 1,000 <sup>e</sup>	49 more deaths per 1,000 (from 0 more to 112 more)
Good functional outcome, <sup>f</sup> mRS 0-1	1,117 (4 studies <sup>b</sup> ) 90 d	Moderate <sup>g</sup> due to imprecision	OR, 1.22 (0.96-1.54) <sup>d</sup>	350 excellent outcomes per 1,000 <sup>h</sup>	46 more excellent outcomes per 1,000 (from 9 fewer to 103 more)

See Table 1-3 legends for expansion of abbreviations.

<sup>a</sup>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.

<sup>b</sup>ATLANTIS A (2000), ECASS I (1995), ECASS II (1998), and EPITHET.

<sup>c</sup>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).

<sup>d</sup>This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

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

<sup>f</sup>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.<sup>11</sup>

<sup>g</sup>CI includes the possibility of harm and benefit.

<sup>h</sup>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.<sup>10,30,31</sup> 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.<sup>32-35</sup> 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.<sup>35,36</sup>

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.<sup>37</sup> 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 administra-

tion 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).<sup>38</sup>

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.<sup>39-41</sup> 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<sup>h,39,40</sup>**

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 <sup>a</sup> ) 90 d	Low <sup>b,d</sup> due to indirectness, imprecision	RR, 0.86 (0.56-1.33)	210 deaths per 1,000 <sup>e</sup>	29 fewer deaths per 1,000 (from 92 fewer to 69 more)
Good functional outcome, <sup>f</sup> mRS 0-2	334 (3 studies <sup>a</sup> ) 90 d	Moderate <sup>b,c</sup> due to indirectness	RR, 1.44 (1.06-1.95)	290 good outcomes per 1,000 <sup>e</sup>	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.

<sup>a</sup>PROACT I (1998), PROACT II (1999), MELT (2007).

<sup>b</sup>*I*<sup>2</sup> = 0%.

<sup>c</sup>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).

<sup>d</sup>CI includes both clinically significant harms and benefits.

<sup>e</sup>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.

<sup>f</sup>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.

<sup>g</sup>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%).

<sup>h</sup>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.<sup>42</sup>

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.<sup>43</sup> Indirect evidence from the IV r-tPA literature further supports the time sensitivity of IA r-tPA administration.<sup>10,31</sup>

**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 ben-

efit from this treatment. The number needed to treat for benefit is estimated to be between four and eight, depending on time to treatment.<sup>44</sup> 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).<sup>45,46</sup> 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<sup>45-46</sup>**

Outcomes <sup>a,b</sup>	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) <sup>c</sup> 90 d	Low <sup>d</sup> due to risk of bias, imprecision	RR, 0.77 (0.49-1.22) <sup>e</sup>	210 deaths per 1,000 <sup>e</sup>	48 fewer deaths per 1,000 (from 107 fewer to 46 more)
Good functional outcome, mRS 0-2	343 (2 studies) <sup>c</sup> 90 d	Low <sup>d</sup> due to risk of bias, imprecision	RR, 1.13 (0.88-1.45) <sup>e</sup>	290 good outcomes per 1,000 <sup>e</sup>	38 more good outcomes per 1,000 (from 35 fewer to 131 more)

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

<sup>a</sup>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).

<sup>b</sup>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).

<sup>c</sup>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%).

<sup>d</sup>CI includes both values indicating harms and benefit.

<sup>e</sup>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<sup>47-52</sup> to the clinical outcomes of patients randomized to the control arms of the three IA thrombolysis trials

(Tables S8, S9).<sup>39-41</sup> 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.<sup>53</sup> 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.<sup>53</sup> 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).<sup>54</sup> This

provides weak indirect evidence in favor of mechanical thrombectomy, as recanalization rates are higher with mechanical thrombectomy than without.<sup>48,50,51</sup> 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.<sup>55</sup> 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<sup>55</sup>**

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 <sup>a</sup>	41,291 (4 studies <sup>b</sup> ) 4-24 wk <sup>c,d</sup>	High <sup>e,f</sup>	OR, 0.92 (0.87-0.98)	120 deaths per 1,000 <sup>g</sup>	9 fewer deaths per 1,000 (from 2 fewer to 14 fewer)
Good functional outcome <sup>h</sup> mRS 0-1	41,291 (4 studies <sup>b</sup> ) 4-24 wk <sup>c,d</sup>	High <sup>i</sup>	RR, 1.02 (1.01-1.04) <sup>k</sup>	350 good outcomes per 1,000 <sup>l</sup>	7 more good outcomes per 1,000 (from 3 more to 14 more)
Nonfatal major extracranial hemorrhage, bleeding requiring transfusion	40,850 (4 studies <sup>b</sup> ) 2-4 wk <sup>m</sup>	High	OR, 1.69 (1.35-2.11) <sup>n,o</sup>	6 bleeding events per 1,000 <sup>p</sup>	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.

<sup>a</sup>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.

<sup>b</sup>IST (1997), CAST (1997), MAST (1995), and Roden-Jullig (2003).

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

<sup>d</sup>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).

<sup>e</sup>Minimal loss to follow-up, well blinded and concealed.

<sup>f</sup> $I^2 = 21\%$ .

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

<sup>h</sup>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).

<sup>i</sup>Minimal loss to follow-up, well blinded and concealed.

<sup>j</sup> $I^2 = 0\%$ .

<sup>k</sup>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).

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

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

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

<sup>o</sup>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.<sup>56</sup>

**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.<sup>55</sup> 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).<sup>57</sup> This approach is currently being investigated in large-scale clinical trials.<sup>58</sup> 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.<sup>59</sup> 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<sup>59</sup>**

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 <sup>a</sup> ) 3-6 mo	High <sup>b</sup>	RR, 1.08 (1.01-1.16)	120 deaths per 1,000 <sup>c</sup>	10 more deaths per 1,000 (from 1 more to 19 more)
Good functional outcome, mRS 0-1	12,235 (6 studies <sup>a</sup> ) 3-6 mo	High <sup>b</sup>	RR, 0.98 (0.95-1.01) <sup>d</sup>	350 good outcomes per 1,000 <sup>e</sup>	7 fewer good outcomes per 1,000 (from 18 fewer to 3 more)
Nonfatal recurrent stroke (ischemic or hemorrhagic)	11,715 (4 studies <sup>f</sup> ) 3-6 mo	High <sup>b</sup>	RR, 1.20 (1.00-1.45)	30 strokes per 1,000 <sup>g</sup>	6 more strokes per 1,000 (from 0 more to 14 more)
Nonfatal major extracranial hemorrhage	12,076 (5 studies <sup>h</sup> ) 10-180 d	High <sup>i</sup>	RR, 1.74 (1.16-2.61) <sup>j</sup>	10 bleeding events per 1,000 <sup>k</sup>	7 more bleeding events per 1,000 (from 2 more to 16 more)

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

<sup>a</sup>IST (1997), RAPID (2005), TAIST (2001), HAEST (2000), FISS-tris (2007).

<sup>b</sup> $I^2 = 0\%$ .

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

<sup>d</sup>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).

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

<sup>f</sup>IST (1997), RAPID (2005), HAEST (2000), TAIST (2001).

<sup>g</sup>Baseline risk derived from IST.

<sup>h</sup>IST (1997), Pince (1981), TAIST (2001), HAEST (2000), FISS-tris (2007).

<sup>i</sup> $I^2 = 11\%$ .

<sup>j</sup>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.<sup>59</sup> 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.<sup>59</sup> 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.<sup>59</sup>

*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.<sup>60</sup> In the only trial to exclusively recruit participants with ischemic stroke and AF (Heparin in Acute Embolic Stroke Trial),<sup>61</sup> 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.<sup>62</sup> 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.<sup>63</sup>

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,<sup>4</sup> the optimal choice of acute anti-

thrombotic 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.<sup>64</sup> 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]).<sup>65</sup> 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.<sup>66</sup> 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.<sup>66</sup>

### 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.<sup>67,68</sup> 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<sup>a,67</sup>**

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 <sup>a</sup> ) 2-26 wk <sup>b</sup>	Moderate <sup>c,d</sup> due to imprecision	RR, 0.86 (0.59-1.22) <sup>e</sup>	87 deaths per 1,000 <sup>f</sup>	12 fewer deaths per 1,000 (from 36 fewer to 19 more) <sup>g</sup>
PE (fatal and nonfatal)	10,681 (8 studies <sup>h</sup> ) 14-90 d	Moderate <sup>c,d,i</sup> due to imprecision	RR, 0.7 (0.47-1.03) <sup>j</sup>	16 PEs per 1,000 <sup>f</sup>	5 fewer PEs per 1,000 (from 8 fewer to 0 more)
Symptomatic DVT	914 (8 studies <sup>k</sup> ) 2-52 wk	Moderate <sup>c,i,l</sup> due to inconsistency	RR, 0.31 (0.21-0.42)	48 DVTs per 1,000 <sup>f</sup>	33 fewer DVTs per 1,000 (from 28 fewer to 38 fewer)
Symptomatic intracranial hemorrhage	10,696 (8 studies <sup>h</sup> ) 14-90 d <sup>b</sup>	Moderate <sup>c,d,i,m</sup> 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 <sup>n</sup> ) 2-52 wk <sup>b</sup>	Moderate <sup>c,d,j</sup> 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.

<sup>a</sup>Turpie (1987), Sandset (1990), McCarthy (1986), McCarthy (1977), Pambianco (1995), Prins (1989), FISS (1995), and IST (1997).

<sup>b</sup>Not clearly reported in all studies, presumed to be during hospital stay following acute ischemic stroke.

<sup>c</sup>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.

<sup>d</sup>95% CI includes both no effect and appreciable benefit or appreciable harm.

<sup>e</sup>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).

<sup>f</sup>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.

<sup>g</sup>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.

<sup>h</sup>Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), IST (1997), and FISS-bis (1998).

<sup>i</sup>Fewer than 300 events occurred, but quality was not downgraded because of this.

<sup>j</sup>Based on meta-analysis by Kamphuisen (2006).

<sup>k</sup>McCarthy (1977), Duke (1980), McCarthy (1986), Turpie (1987), Prins (1989), Sandset (1990), FISS (1995), and Pambianco (1995).

<sup>l</sup>Statistical heterogeneity:  $P = .003$ ;  $I^2 = 74.3\%$ .

<sup>m</sup>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.

<sup>n</sup>Duke (1980), Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), and IST (1997).

<sup>o</sup>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.<sup>67</sup> 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<sup>k,68</sup>**

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 <sup>a</sup> ) 14-90 d	Moderate <sup>b</sup> due to imprecision	RR, 0.96 (0.72-1.2) <sup>c</sup>	75 deaths per 1,000 <sup>d</sup>	3 fewer deaths per 1,000 (from 21 fewer to 15 more)
PE (fatal and nonfatal)	2,092 (3 studies <sup>a</sup> ) 14-90 d	Moderate <sup>c</sup> due to imprecision	RR, 0.26 (0.07-0.95)	11 PEs per 1,000 <sup>f</sup>	8 fewer PEs per 1,000 (from 1 fewer to 10 fewer)
Symptomatic DVT	2,092 (3 studies <sup>a</sup> ) 14-90 d	Moderate <sup>c</sup> due to imprecision	RR, 0.56 (0.4-0.77) <sup>g</sup>	15 DVTs per 1,000 <sup>f</sup>	7 fewer DVTs per 1,000 (from 3 fewer to 9 fewer)
Symptomatic intracranial hemorrhage	1,749 (3 studies <sup>a</sup> ) 14-90 d	Moderate <sup>b</sup> due to imprecision	RR, 0.7 (0.26-1.83)	7 bleeding events per 1,000 <sup>h</sup>	2 fewer bleeding events per 1,000 (from 5 fewer to 6 more)
Symptomatic extracranial hemorrhage	2,506 (3 studies <sup>a</sup> ) 14-90 d	Moderate <sup>b</sup> due to imprecision	RR, 2.12 (0.09-43.78) <sup>i</sup>	5 bleeding events per 1,000 <sup>j</sup>	6 more bleeding events per 1,000 (from 5 fewer to 214 more)

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

<sup>a</sup>Hillbom (2002), PROTECT (2006), and PREVAIL (2006).

<sup>b</sup>95% CI includes both no effect and appreciable benefit or appreciable harm.

<sup>c</sup>0.40% mortality due to bleeding in both groups (5 of 1,255 LMWH, 5 of 1,251 UFH).

<sup>d</sup>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.

<sup>e</sup>Fewer than 300 events occurred.

<sup>f</sup>Baseline risk calculated by multiplying baseline risk in CLOTS study times the RR with any heparin prophylaxis.

<sup>g</sup>Data for any proximal DVT.

<sup>h</sup>Based on PREVAIL study data.

<sup>i</sup>Percent due to GI bleeding not reported.

<sup>j</sup>Based on data from heparin for VTE prevention profile.

<sup>k</sup>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.<sup>69</sup> 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).<sup>70,71</sup>

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.<sup>70</sup> 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).<sup>65</sup> 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<sup>71</sup>**

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 <sup>a</sup> ) 7-10 d	Moderate <sup>b,c</sup> due to imprecision	RR, 1.03 (0.33-3.23)	87 Deaths per 1,000 <sup>f</sup>	3 more deaths per 1,000 (from 58 fewer to 194 more)
PE (fatal and nonfatal)	2,255 (19 studies <sup>e</sup> ) 7-10 d	Moderate <sup>b,h,i</sup> due to indirectness	RR, 0.43 (0.35-0.53) <sup>h</sup>	16 PEs per 1,000 <sup>f</sup>	9 fewer PEs per 1,000 (from 8 fewer to 10 fewer)
Symptomatic DVT	2,255 (19 studies <sup>e</sup> ) 7-10 d	Moderate <sup>b,h,j</sup> due to indirectness	RR, 0.43 (0.35-0.53) <sup>h,g</sup>	48 DVTs per 1,000 <sup>f</sup>	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.

<sup>a</sup>Prasad (1982) and Lacut (2005).

<sup>b</sup>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.

<sup>c</sup> $I^2 = 28\%$ .

<sup>d</sup>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.

<sup>e</sup>CI interval includes both no effect and appreciable benefit or appreciable harm.

<sup>f</sup>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.

<sup>g</sup>Based on meta-analysis in Roderick et al.<sup>71</sup>

<sup>h</sup>RR for symptomatic DVT and RR for PE inferred from rates reported for proximal DVT in 19 studies of postsurgical patients.

<sup>i</sup>Lacut (2005) reported that no PE occurred during follow-up. Prasad (1982) did not report on this outcome.

<sup>j</sup>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.<sup>71</sup> 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).<sup>70</sup> 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).<sup>65,70</sup>

## 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<sup>65,144</sup>**

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 <sup>a</sup> ) 7-30 d <sup>b</sup>	Moderate <sup>c,e</sup> due to imprecision	RR, 1.11 (0.88-1.42)	87 deaths per 1,000 <sup>f</sup>	10 more deaths per 1,000 (from 10 fewer to 37 more)
PE (fatal and nonfatal)	2,518 (1 study <sup>g</sup> ) 30 d	Moderate <sup>c,e</sup> due to imprecision	RR, 0.65 (0.33-1.31)	16 PEs per 1,000 <sup>f</sup>	6 fewer PEs per 1,000 (from 11 fewer to 5 more)
Symptomatic DVT	2,518 (1 study <sup>g</sup> ) 30 d	Moderate <sup>c,e</sup> due to imprecision	RR, 0.91 (0.63-1.29) <sup>h</sup>	48 DVTs per 1,000 <sup>f</sup>	4 fewer DVTs per 1,000 (from 18 fewer to 14 more)
Skin complications of elastic compression stockings <sup>i</sup>	2,518 (1 study <sup>g</sup> ) 30 d	Moderate <sup>j,k</sup> due to risk of bias	RR, 4.02 (2.34-6.91)	13 Skin complications per 1,000 <sup>f</sup>	39 more complications per 1,000 (from 17 more to 77 more)

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

<sup>a</sup>CLOTS trial I (2009) and Muir et al<sup>144</sup> (2000).

<sup>b</sup>Follow-up was 30 d in CLOTS and 7 ± 2 d in Muir.

<sup>c</sup>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.

<sup>d</sup>I<sup>2</sup> = 0%.

<sup>e</sup>CI includes both negligible effect and appreciable benefit or appreciable harm.

<sup>f</sup>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).

<sup>g</sup>CLOTS trial I (2009).

<sup>h</sup>CLOTS, the primary study for this analysis, found no effect on “Proximal DVT” (adjusted OR, 0.98; 95% CI, 0.76-1.27).

<sup>i</sup>Includes: skin breaks, ulcers, blisters, and skin necrosis.

<sup>j</sup>Assessment of outcomes was based on case-note review and was not blinded to treatment allocation.

<sup>k</sup>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.<sup>72-74</sup>

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).<sup>72</sup> 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<sup>72-74</sup>**

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 <sup>a</sup>	Risk Difference With Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
Overall mortality	114 (2 studies <sup>a</sup> ) 10 d	Low <sup>b,d</sup> 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 <sup>c</sup> ) 14-90 d	Moderate <sup>c,d,f</sup> due to imprecision	RR, 0.7 (0.47-1.03) <sup>e</sup>	16 PEs per 1,000 <sup>g</sup>	5 fewer PEs per 1,000 (from 8 fewer to 0 more)
Symptomatic DVT	914 (8 studies <sup>c</sup> ) 2-52 wk	Moderate <sup>d,f,h</sup> due to inconsistency	RR, 0.31 (0.21-0.42) <sup>e</sup>	48 DVTs per 1,000 <sup>g</sup>	33 fewer DVTs per 1,000 (from 28 fewer to 38 fewer)
Rebleeding	189 (3 studies <sup>i</sup> ) 7-10 d <sup>j</sup>	Low <sup>c,d,k</sup> due to risk of bias, imprecision	RR, 0.24 (0.05-1.13) <sup>l</sup>	10 rebleeding events per 1,000 <sup>m</sup>	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.

<sup>a</sup>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).

<sup>b</sup>Allocation: unclear whether concealed in both studies (Boeer 1991, Dickman 1988). Unclear whether ITT analysis in both studies. Neither of the two studies stopped early for benefit. Neither of the studies reported blinding patients.

<sup>c</sup>95% CI includes both no effect and appreciable benefit or appreciable harm.

<sup>d</sup>Fewer than 300 events occurred, but quality was not downgraded for this.

<sup>e</sup>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.

<sup>f</sup>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.

<sup>g</sup>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.

<sup>h</sup>Statistical heterogeneity:  $P = .003$ ;  $I^2 = 74.3\%$ .

<sup>i</sup>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).

<sup>j</sup>We considered the time frame during which patients are exposed to heparin and consequently at risk for rebleeding.

<sup>k</sup>Allocation: not concealed in one study (Orken 2009) and unclear whether concealed in two studies (Boeer 1991; Dickman 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.

<sup>l</sup>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.

<sup>m</sup>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.

<sup>n</sup>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<sup>74</sup>**

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)	Risk Difference With Early (Day 2-4) Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
Overall mortality	45 (1 study <sup>a</sup> ) 10 d	Low <sup>b,c</sup> due to risk of bias, imprecision	RR, 0.42 (0.1-1.69)	400 deaths per 1,000 <sup>d,e</sup>	232 fewer deaths per 1,000 (from 360 fewer to 276 more)
PE (fatal and nonfatal)	45 (1 study <sup>a</sup> ) 10 d	Low <sup>b,c</sup> due to risk of bias, imprecision	RR, 0.35 (0.01-8.11)	11 PEs per 1,000 <sup>e,f</sup>	7 fewer PEs per 1,000 (from 11 fewer to 78 more)
Symptomatic DVT	45 (1 study <sup>a</sup> ) 10 d	Low <sup>b,c,g</sup> due to risk of bias, indirectness, imprecision	RR, 0.65 (0.25-1.69)	15 DVTs per 1,000 <sup>f</sup>	5 fewer DVTs per 1,000 (from 11 fewer to 10 more)
Rebleeding	45 (1 study <sup>a</sup> ) 10 d <sup>h</sup>	Low <sup>b,c</sup> due to risk of bias, imprecision	RR, 0.35 (0.01-8.11)	10 rebleeding events per 1,000 <sup>i</sup>	7 fewer rebleeding events per 1,000 (from 10 fewer to 71 more)

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

<sup>a</sup>Boer (1991).

<sup>b</sup>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.

<sup>c</sup>CI includes both negligible effect and appreciable benefit or appreciable harm.

<sup>d</sup>Baseline risk of mortality is derived from observational studies.

<sup>e</sup>The single reported symptomatic PE event was fatal; has been included in both mortality and PE outcome in this evidence profile.

<sup>f</sup>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.

<sup>g</sup>DVT measured through routine perfusion scintigraphy by day 10. Not reported whether symptomatic and whether proximal vs distal.

<sup>h</sup>We considered the time frame during which patients are exposed to heparin and consequently at risk for rebleeding.

<sup>i</sup>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,<sup>75</sup>

they also often die of MI.<sup>76-78</sup> 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.<sup>79,80</sup> 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.<sup>79-81</sup>

### 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<sup>f,82</sup>**

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 <sup>a</sup>	RR, 0.91 (0.81-1) <sup>b</sup>	55 deaths per 1,000 <sup>c</sup>	5 fewer deaths per 1,000 (from 10 fewer to 0 more) <sup>d</sup>
Nonfatal recurrent stroke (ischemic and hemorrhagic)	10,126 (11 studies) 1.5-6 y	High <sup>a</sup>	RR, 0.81 (0.71-0.92) <sup>e</sup>	130 strokes per 1,000 <sup>c</sup>	25 fewer strokes per 1,000 (from 10 fewer to 38 fewer)
Nonfatal MI	10,126 (11 studies) 1.5-6 y	High <sup>a</sup>	RR, 0.69 (0.6-0.8)	18 MIs per 1,000 <sup>c</sup>	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 <sup>a</sup>	RR, 2.69 (1.25-5.76)	4 bleeding events per 1,000 <sup>c</sup>	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.

<sup>a</sup>Includes a number of small, open-label RCTs. However, summary estimate for large high-quality RCTs consistent with overall estimate.

<sup>b</sup>Estimate calculated from original data included in trials.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>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).

<sup>f</sup>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%.<sup>82</sup>

**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.<sup>79-81</sup> 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.<sup>83,84</sup> 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.<sup>1,85-87</sup> 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).<sup>88</sup> 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,<sup>89-94</sup> which have been included in two reviews.<sup>95,96</sup> 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<sup>88</sup>**

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 <sup>a</sup> ) 1.9 y	Moderate <sup>b,c</sup> due to imprecision	RR, 0.98 (0.89-1.1) <sup>b</sup>	50 deaths per 1,000 <sup>d</sup>	1 fewer death per 1,000 (from 6 fewer to 5 more) <sup>e</sup>
Nonfatal recurrent stroke (ischemic and hemorrhagic)	6,431 (1 study <sup>a</sup> ) 1.9 y	Moderate <sup>c</sup> due to imprecision	RR, 0.91 (0.78-1.07) <sup>f,g</sup>	106 strokes per 1,000 <sup>d,h,f</sup>	10 fewer strokes per 1,000 (from 23 fewer to 7 more)
Nonfatal MI	19,185 (1 study <sup>a</sup> ) 1.9 y	High <sup>c</sup>	RR, 0.83 (0.7-0.99) <sup>i</sup>	13 MIs per 1,000 <sup>d,i</sup>	2 fewer MIs per 1,000 (from 0 fewer to 4 fewer)
Nonfatal major extracranial hemorrhage	19,185 (1 study <sup>a</sup> ) 1.9 y	Moderate <sup>c</sup> due to imprecision	RR, 0.94 (0.72-1.23) <sup>j</sup>	10 bleeding events per 1,000 <sup>d,j</sup>	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.

<sup>a</sup>CAPRIE (1996).

<sup>b</sup>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.

<sup>c</sup>CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.

<sup>d</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>e</sup>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.

<sup>f</sup>Based on individual first-outcome nonfatal strokes in CAPRIE's stroke subpopulation.

<sup>g</sup>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).

<sup>h</sup>96.8% of events are nonfatal ischemic stroke.

<sup>i</sup>Based on individual first-outcome nonfatal MI in the overall CAPRIE population.

<sup>j</sup>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).<sup>88,97</sup> 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.<sup>79,80</sup> 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.<sup>98</sup> 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),<sup>98</sup> 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.<sup>99</sup> 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<sup>95,96</sup>**

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 <sup>a</sup> ) 2-5 y <sup>b,c</sup>	Moderate <sup>d</sup> due to imprecision	RR, 0.97 (0.83-1.13)	50 deaths per 1,000 <sup>b</sup>	1 fewer deaths per 1,000 (from 9 fewer to 6 more) <sup>e</sup>
Nonfatal recurrent stroke (ischemic and hemorrhagic)	7,659 (6 studies) 2.6 y <sup>c</sup>	High	RR, 0.77 (0.67-0.89) <sup>f,g</sup>	106 strokes per 1,000 <sup>b</sup>	24 fewer strokes per 1,000 (from 12 fewer to 35 fewer)
Nonfatal MI	6,038 (2 studies <sup>a</sup> ) 2-5 y <sup>b,c</sup>	Moderate <sup>d</sup> due to imprecision	RR, 0.79 (0.59-1.06) <sup>g</sup>	13 MIs per 1,000 <sup>b</sup>	3 fewer MIs per 1,000 (from 5 fewer to 1 more)
Nonfatal major extracranial hemorrhage	6,981 (9 studies <sup>h</sup> ) 0.5-5 y <sup>b,c</sup>	Moderate <sup>d</sup> due to imprecision	RR, 1.08 (0.75-1.54) <sup>g,h</sup>	10 bleeding events per 1,000 <sup>b</sup>	1 more bleeding event per 1,000 (from 2 fewer to 5 more)

AICLA = Accidents Ischémiques Cerebraux Lies à l'Atherosclérose. See Table 1, 2, 7, 15, and 16 legends for expansion of other abbreviations.

<sup>a</sup>ESPS-2 (1997), and ESPRIT (2006).

<sup>b</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>c</sup>Included studies that followed up patients for a mean of 2.6 y.

<sup>d</sup>CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.

<sup>e</sup>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.

<sup>f</sup>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).

<sup>g</sup>RR based on fatal and nonfatal events. RR for only nonfatal events assumed to be the same.

<sup>h</sup>Estimate for major extracranial bleeding derived from Cochrane review (2008), which included nine trials (three nonstroke trials): AICLA (1983), Caneschi (1985), Chairangarit (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).<sup>100</sup> Cilostazol has been compared with aspirin in two secondary stroke prevention studies conducted in Japan.<sup>101,102</sup> 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).<sup>103</sup> 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).<sup>103</sup> 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).<sup>104</sup> 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.<sup>105</sup> 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.<sup>106,107</sup> 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<sup>98</sup>**

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 <sup>a</sup> ) 2.5 y	Moderate <sup>b</sup> due to imprecision	HR, 0.97 (0.87-1.07)	49 deaths per 1,000 <sup>c</sup>	1 fewer deaths per 1,000 (from 6 fewer to 3 more) <sup>d</sup>
Nonfatal recurrent stroke (ischemic and hemorrhagic)	20,332 (1 study <sup>a</sup> ) 2.5 y	Moderate <sup>b</sup> due to imprecision	HR, 0.97 (0.88-1.07)	97 strokes per 1,000 <sup>c</sup>	3 fewer strokes per 1,000 (from 11 fewer to 6 more)
Nonfatal MI	20,332 (1 study <sup>a</sup> ) 2.5 y	High <sup>b,c</sup>	HR, 0.90 (0.73-1.1)	10 MIs per 1,000 <sup>c</sup>	1 fewer MIs per 1,000 (from 3 fewer to 1 more)
Nonfatal major extracranial hemorrhage	20,332 (1 study <sup>a</sup> ) 2.5 y	Moderate <sup>b,e</sup> due to imprecision	RR, 1.04 (0.88-1.22) <sup>f</sup>	10 bleeding events per 1,000 <sup>c</sup>	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.

<sup>a</sup>Sacco (2008).

<sup>b</sup>CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.

<sup>c</sup>Baseline rates are derived from CAPRIE and adjusted for 2-y time frame.

<sup>d</sup>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.

<sup>e</sup>The absolute number of events at the extremes of the CI are small; therefore, not rated down for imprecision.

<sup>f</sup>RR based on fatal and nonfatal major extracranial hemorrhages.

Patients With a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) trial.<sup>105</sup> 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.<sup>109</sup> 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<sup>99</sup>**

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 <sup>a</sup> ) 18 mo	Moderate <sup>b</sup> due to imprecision	RR, 1.00 (0.83-1.21)	49 deaths per 1,000 <sup>c</sup>	0 fewer deaths per 1,000 (from 8 fewer to 10 more)
Nonfatal recurrent stroke (ischemic and hemorrhagic)	7,599 (1 study <sup>a</sup> ) 18 mo	Moderate <sup>b</sup> due to imprecision	RR, 0.95 (0.82-1.1) <sup>d</sup>	97 strokes per 1,000 <sup>c,d</sup>	5 fewer strokes per 1,000 (from 17 fewer to 10 more)
Nonfatal MI	7,599 (1 study <sup>a</sup> ) 18 mo	Moderate <sup>b</sup> due to imprecision	RR, 0.98 (0.68-1.41) <sup>e</sup>	10 MIs per 1,000 <sup>c,e</sup>	0 fewer MIs per 1,000 (from 3 fewer to 4 more)
Nonfatal major extracranial hemorrhage	7,540 (1 study <sup>a</sup> ) 18 mo	High	RR, 2.55 (1.88-3.46) <sup>f</sup>	10 bleeding events per 1,000 <sup>c,f</sup>	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.

<sup>a</sup>Diener (2004).

<sup>b</sup>CI includes possible benefit and possible harm or few events.

<sup>c</sup>Baseline rates for nonfatal events and overall mortality are derived from CAPRIE and adjusted for 2-y time frame.

<sup>d</sup>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).

<sup>e</sup>Based on data provided by the sponsor of the MATCH trial.

<sup>f</sup>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<sup>103</sup>**

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 <sup>a</sup> ) 12-28 mo	Low <sup>b-d</sup> due to risk of bias, imprecision	RR, 0.89 (0.45-1.74)	50 deaths per 1,000 <sup>e</sup>	6 fewer deaths per 1,000 (from 28 fewer to 37 more)
Nonfatal recurrent stroke (ischemic and hemorrhagic)	3,391 (2 studies <sup>a</sup> ) 12-28 mo	Moderate <sup>b,c</sup> due to risk of bias	RR, 0.67 (0.52-0.86) <sup>f</sup>	106 strokes per 1,000 <sup>e</sup>	35 fewer strokes per 1,000 (from 15 fewer to 51 fewer)
Nonfatal MI	3,391 (2 studies <sup>a</sup> ) 12-28 mo	Low <sup>b-d</sup> due to risk of bias, imprecision	RR, 1.15 (0.55-2.41) <sup>g</sup>	13 MIs per 1,000 <sup>e</sup>	2 more MIs per 1,000 (from 6 fewer to 18 more)
Nonfatal major extracranial hemorrhage	3,391 (2 studies <sup>a</sup> ) 12-28 mo	Moderate <sup>b,c</sup> due to risk of bias	RR, 0.74 (0.61-0.9) <sup>h</sup>	10 bleeding events per 1,000 <sup>e</sup>	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.

<sup>a</sup>CASISP (2008) and CSPS 2 (2010).

<sup>b</sup>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.

<sup>c</sup>Evaluated in Asian population only: CASISP in China and CSPS 2 in Japan.

<sup>d</sup>CI is wide and includes possible benefit and possible harm.

<sup>e</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>f</sup>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.

<sup>g</sup>Based on any MI (fatal and nonfatal).

<sup>h</sup>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.<sup>110-112</sup> A Cochrane systematic review did not find a significant difference between anticoagulation and antiplatelet therapy in patients with stroke secondary to cervical artery dissection.<sup>62</sup> 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.<sup>113,114</sup>

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).<sup>113</sup> 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).<sup>115</sup> 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<sup>104</sup>**

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 <sup>a</sup> ) 1.5-3 y	Moderate due to imprecision	OR, 1.03 (0.75-1.43) <sup>b</sup>	50 deaths per 1,000 <sup>c</sup>	1 more deaths per 1,000 (from 12 fewer to 20 more)
Nonfatal recurrent stroke (ischemic and hemorrhagic)	2,753 (3 studies <sup>a</sup> ) 1.5-3 y	Moderate <sup>d</sup> due to imprecision	OR, 0.97 (0.76-1.25) <sup>b,e</sup>	106 strokes per 1,000 <sup>c</sup>	3 fewer strokes per 1,000 (from 23 fewer to 23 more)
Nonfatal MI	2,753 (3 studies <sup>a</sup> ) 1.5-3 y	Moderate <sup>d</sup> due to imprecision	OR, 0.8 (0.48-1.33)	13 MIs per 1,000 <sup>c</sup>	3 fewer MIs per 1,000 (from 7 fewer to 4 more)
Nonfatal major extracranial hemorrhage	2,753 (3 studies <sup>a</sup> ) 1.5-3 y	High	OR, 0.38 (0.22-0.65) <sup>b,f</sup>	10 bleeding events per 1,000 <sup>c</sup>	6 fewer bleeding events per 1,000 (from 3 fewer to 8 fewer)

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

<sup>a</sup>Matias-Guiu (1994), TACIP (2003), and TAPIRSS (2004).

<sup>b</sup>ORs obtained from Cochrane analysis were inverted to obtain estimate for effect relative to aspirin.

<sup>c</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>d</sup>CI is wide and include 1.00.

<sup>e</sup>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.

<sup>f</sup>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 cardioembolic 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.<sup>116,117</sup>

*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.<sup>118,119</sup> Pooled data from these anticoagulation trials are summarized in the accompanying article on antithrombotic therapy in AF by You et al<sup>3</sup> 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)<sup>120</sup> (You et al,<sup>3</sup> Section 2.1.10). You et al<sup>3</sup> 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<sub>2</sub> (Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke or TIA history) is a commonly used risk-stratification scale for patients with AF.<sup>120</sup> For information on how to calculate the CHADS<sub>2</sub> score, see You et al<sup>3</sup> in this guideline supplement. Anticoagulation is recommended for patients with AF, including paroxysmal AF, who are at high risk of stroke (CHADS<sub>2</sub> ≥ 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<sub>2</sub> 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).<sup>3</sup> 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)<sup>118,119</sup> compared with the nine mainly primary prevention trials (2.6% per year).<sup>119,121-125</sup>

**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<sup>a,109</sup>**

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 <sup>a</sup> ) 0-5 y	Moderate <sup>b,c</sup> due to inconsistency	RR, 1.36 (1.09-1.7)	50 deaths per 1,000 <sup>f</sup>	18 more deaths per 1,000 (from 5 more to 35 more) <sup>g</sup>
Nonfatal recurrent stroke (ischemic and hemorrhagic)	5,400 (5 studies <sup>a</sup> ) 0-5 y	High <sup>b,d</sup>	RR, 1.03 (0.88-1.22)	106 strokes per 1,000 <sup>f</sup>	3 more strokes per 1,000 (from 13 fewer to 23 more)
Nonfatal MI	1,637 (2 studies <sup>a</sup> ) 3-5 y	Moderate <sup>e,k</sup> due to imprecision	RR, 0.91 (0.59-1.4)	13 MIs per 1,000 <sup>f</sup>	1 fewer MIs per 1,000 (from 5 fewer to 5 more)
Nonfatal major extracranial hemorrhage	3,194 (4 studies <sup>l</sup> ) 0-5 y	High <sup>b,d,m</sup>	RR, 3.60 (2.29-5.66)	10 bleeding events per 1,000 <sup>f</sup>	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.

<sup>a</sup>Garde (1983), SPIRIT (1997), WASID (2000), WARSS (2001), and ESPRIT (2007).

<sup>b</sup>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%.

<sup>c</sup> $I^2 = 62\%$ .

<sup>d</sup>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.

<sup>e</sup>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.

<sup>f</sup>Baseline event rates based on aspirin arm of the CAPRIE trial and adjusted for 2-y time frame.

<sup>g</sup>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.

<sup>h</sup>WASID (2000) and ESPRIT (2007).

<sup>i</sup>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%.

<sup>j</sup>INR target range was 2-3 in both studies (WASID, ESPRIT).

<sup>k</sup>CI includes both values suggesting harm and benefit.

<sup>l</sup>Garde (1983), SPIRIT (1997), WASID (2000), and ESPRIT (2007).

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

<sup>n</sup>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).<sup>129</sup> Both primary and secondary prevention studies failed to show or exclude a beneficial or detrimental effect of anticoagulation therapy on mortality.<sup>129</sup>

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.<sup>130</sup>

A few studies can help guide the timing of anticoagulation after stroke secondary to AF. In the European Atrial Fibrillation Trial (EAFT),<sup>118</sup> 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.<sup>61</sup> 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.<sup>131</sup>

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**

No. of Studies	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Study Event Rates (%)	Relative Effect (95% CI) <sup>b</sup>	Estimation of Absolute Effects, 1-y Time Frame	Quality of Evidence	
						With No Therapy	With VKA	With No Therapy	With VKA (95% CI)	
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)	15 fewer deaths per 1,000 <sup>b</sup> (from 3 fewer to 24 fewer)	High
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	108 of 1,425 <sup>d</sup> (7.6)	36 of 1,429 <sup>e</sup> (2.5)	RR, 0.34 (0.23-0.49)	CHADS <sub>2</sub> 2 points 30 fewer strokes per 1,000 (from 23 fewer to 35 fewer)	High
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)	8 more bleeding events per 1,000 (from 1 more to 25 more)	High <sup>g</sup>
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	10 of 1,425 (0.7)	4 of 1,429 (0.3)	RR, 0.42 (0.15-1.20)	2 fewer systemic emboli per 1,000 (from 3 fewer to 1 more)	Moderate
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<sub>2</sub> = Congestive heart failure, Hypertension, Age  $\geq$  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.

<sup>a</sup>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<sub>2</sub> score  $\geq$  1 or higher.

<sup>b</sup>VKA therapy likely does not lead to any reductions in all-cause mortality compared with no therapy in low risk patients with a CHADS<sub>2</sub> 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<sub>2</sub> score), whereas the absolute increase in intracranial hemorrhage is relatively consistent across CHADS<sub>2</sub> categories (Singer et al. [2009]).  
<sup>c</sup>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.  
<sup>d</sup>Of the 108 nonfatal strokes on no therapy, an estimated 106 (98%) were ischemic and two (2%) were hemorrhagic.  
<sup>e</sup>Of the 36 nonfatal strokes on VKA therapy, an estimated 34 (94%) were ischemic and two (6%) were hemorrhagic.

<sup>f</sup>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).  
<sup>g</sup>Quality of evidence is moderate for patients with a CHADS<sub>2</sub> 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.

<sup>h</sup>95% CI does not exclude the possibility of no effect.  
<sup>i</sup>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.

<sup>j</sup>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).

<sup>k</sup>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<sub>2</sub> score, in the aspirin arms of six historical RCTs in AF patients (Cage et al.<sup>120</sup>). 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).<sup>3</sup> 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.<sup>118</sup> 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<sup>1</sup> and You et al<sup>3</sup> 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<sup>1</sup> include recent MI, left ventricular thrombus, and low ejection fraction. The special conditions covered by Whitlock et al<sup>4</sup> 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.<sup>132,133</sup> 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.<sup>134</sup> 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.<sup>135</sup> 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.<sup>136</sup> 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.<sup>136</sup> This is generally the case for patients with mechanical heart valves and for patients with AF and high CHADS<sub>2</sub> 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.<sup>136</sup> 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<sup>143,i</sup>**

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	Risk Difference With Therapeutic Anticoagulation (95% CI)
Overall mortality or disability <sup>c</sup>	79 (2 studies <sup>a</sup> ) 3 mo	Low <sup>b,e,f</sup> due to risk of bias, imprecision	RR, 0.43 (0.12-1.41)	140 deaths or disability per 1,000 <sup>d</sup>	80 fewer deaths or disability per 1,000 (from 123 fewer to 57 more)
Nonfatal major extracranial hemorrhage	79 (2 studies <sup>a</sup> ) 3 mo	Low <sup>b,e,f</sup> due to risk of bias, imprecision	RR, 2.9 (0.12-68.5) <sup>g</sup>	10 bleeding events per 1,000 <sup>d</sup>	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.

<sup>a</sup>Einhaupl (1991) and de Bruijn (1999).

<sup>b</sup>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.

<sup>c</sup>CI includes both negligible effect and appreciable benefit or appreciable harm.

<sup>d</sup>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).

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

<sup>f</sup>Effect estimate based on few events.

<sup>g</sup>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.

<sup>h</sup>Baseline risk derived from IST.

<sup>i</sup>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<sub>2</sub> 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.<sup>137</sup> This includes patients who present with headache, focal neurologic deficits, seizures, alterations of consciousness, and/or papilledema.<sup>138</sup> 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.<sup>139,140</sup> 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.<sup>141</sup> Lifelong anticoagulation could be considered in the presence of permanent risk factors for recurrent events.<sup>141</sup>

#### 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.<sup>142</sup>

## ACKNOWLEDGMENTS

**Author contributions:** As Topic Editor, Dr Akl oversaw the development of this article, including the data analysis and subsequent development of the recommendations contained herein.

*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.

**Financial/nonfinancial disclosures:** The authors of this guideline provided detailed conflict of interest information related to each individual recommendation made in this article. A grid of these disclosures is available online at [http://chestjournal.chestpubs.org/content/141/2\\_suppl/e601S/suppl/DC1](http://chestjournal.chestpubs.org/content/141/2_suppl/e601S/suppl/DC1). In summary, the authors have reported to CHEST the following conflicts of interest: Dr O'Donnell has received university grants; received grants, speaking fees, and travel accommodations from Boehringer Ingelheim, and has received speaking fees from sanofi-aventis. Dr Khatri will receive funding from Penumbra, Inc as THERAPY Trial Neurology PI; received research support for third-party survey services and travel support for a 1-day summit in Chicago from Genentech, Inc to study RISS; participated in a one-time advisory board for Otsuka Pharmaceuticals regarding cilostazol; and provided expert witnessing regarding cases related to stroke treatment. Drs Lansberg and Schwartz have served as expert witnesses in cases related to stroke. Dr Nguyen-Huynh received a research grant from Concentric Medical. Dr Lang is a member of the GRADE Working Group. Dr Guyatt is co-chair of the GRADE Working Group, and the following authors have been prominent contributors to the groups work: Drs Vandvik, Alonso-Coello, and Akl. Drs Sonnenberg, Spencer, and Schulman have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Role of sponsors:** The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at <http://chestnet.org>.

**Other contributions:** We thank the writing groups of the article on antithrombotic and thrombolytic therapy for ischemic stroke in previous iterations of the ACCP evidence-based clinical practice guidelines for providing the framework for the current article; Mark Eckman, MD, for his contribution to the section that deals with antithrombotic therapy for stroke prevention following intracerebral hemorrhage; Aman Rajpal, MD, for his help with reviewing the proofs; and Peter Pellionisz for his contributions in editing the online tables.



**Endorsements:** This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hematosis.

**Additional information:** The supplement Tables can be found in the Online Data Supplement at [http://chestjournal.chestpubs.org/content/141/2\\_suppl/e601S/suppl/DC1](http://chestjournal.chestpubs.org/content/141/2_suppl/e601S/suppl/DC1).

## REFERENCES

1. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e637S-e668S.
2. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e669S-e690S.
3. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e531S-e575S.
4. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e576S-e600S.
5. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):53S-70S.
6. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
7. Brozek J, Oxman AD, Schünemann H. GRADE profiler [Computer Program] Version 3.6 for Windows, 2011. <http://ims.cochrane.org/revman/gradepr>.
8. MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e1S-e23S.
9. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
10. Lees KR, Bluhmki E, von Kummer R, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375(9727):1695-1703.
11. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2009;(4):CD000213.
12. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA*. 2000;283(9):1145-1150.
13. Hill MD, Buchan AM; Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ*. 2005;172(10):1307-1312.
14. Wahlgren N, Ahmed N, Dávalos A, et al; SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study [erratum appears in *Lancet*. 2007;369(9564):826]. *Lancet*. 2007;369(9558):275-282.
15. Grond M, Stenzel C, Schmülling S, et al. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke*. 1998;29(8):1544-1549.
16. Chiu DKD, Krieger D, Villar-Cordova C, et al. Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. *Stroke*. 1998;29(1):18-22.
17. Trouillas P, Nighoghossian N, Derex L, et al. Thrombolysis with intravenous rTPA in a series of 100 cases of acute carotid territory stroke: determination of etiological, topographic, and radiological outcome factors. *Stroke*. 1998;29(12):2529-2540.
18. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. The t-PA Stroke Survey Group. *Neurology*. 1999;53(2):424-427.
19. Akins PT, Delemos C, Wentworth D, Byer J, Schorer SJ, Atkinson RP. Can emergency department physicians safely and effectively initiate thrombolysis for acute ischemic stroke? *Neurology*. 2000;55(12):1801-1805.
20. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA*. 2000;283(9):1151-1158.
21. Katzan IL, Hammer MD, Furlan AJ, Hixson ED, Nadzam DM; Cleveland Clinic Health System Stroke Quality Improvement Team. Quality improvement and tissue-type plasminogen activator for acute ischemic stroke: a Cleveland update. *Stroke*. 2003;34(3):799-800.
22. Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
23. Hacke W, Kaste M, Fieschi C, et al; The European Cooperative Acute Stroke Study (ECASS). Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*. 1995;274(13):1017-1025.
24. Hacke W, Kaste M, Fieschi C, et al; Second European-Australasian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*. 1998;352(9136):1245-1251.
25. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke. *JAMA*. 1999;282(21):2019-2026.
26. Davis SM, Donnan GA, Parsons MW, et al; EPITHET investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol*. 2008;7(4):299-309.

27. Patel SC, Levine SR, Tilley BC, et al; National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA*. 2001;286(22):2830-2838.
28. Demchuk AM, Hill MD, Barber PA, Silver B, Patel SC, Levine SR; NINDS rtPA Stroke Study Group, NIH. Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. *Stroke*. 2005;36(10):2110-2115.
29. Intracerebral Hemorrhage After Intravenous t-PA Therapy for Ischemic Stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *Stroke*. 1997;28(11):2109-2118.
30. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*. 2000;55(11):1649-1655.
31. Hacke W, Donnan G, Fieschi C, et al; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363(9411):768-774.
32. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology*. 1998;50(4):883-890.
33. Ehlers L, Andersen G, Clausen LB, Bech M, Kjølbj M. Cost-effectiveness of intravenous thrombolysis with alteplase within a 3-hour window after acute ischemic stroke. *Stroke*. 2007;38(1):85-89.
34. Sinclair SE, Frighetto L, Loewen PS, et al. Cost-utility analysis of tissue plasminogen activator therapy for acute ischaemic stroke: a Canadian healthcare perspective. *Pharmacoeconomics*. 2001;19(9):927-936.
35. Chung H, Refoios Camejo R, Barnett D. Alteplase for the treatment of acute ischaemic stroke: NICE technology appraisal guidance. *Heart*. 2007;93(12):1616-1617.
36. Lindley RI. Commentary on NICE guidelines for alteplase for the treatment of acute ischaemic stroke. *Heart*. 2007;93(12):1617-1618.
37. Matchar DB. The value of stroke prevention and treatment. *Neurology*. 1998;51(suppl 3):S31-S35.
38. Fields JD, Khatri P, Nesbit GM, et al. Meta-analysis of randomized intra-arterial thrombolytic trials for the treatment of acute stroke due to middle cerebral artery occlusion. *J Neurointerv Surg*. 2011;3(2):151-155.
39. del Zoppo GJHR, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct delivery in acute middle cerebral artery stroke. PROACT Investigators. *Stroke*. 1998;29(1):4-11.
40. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial pro-urokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Stroke*. 1999;28(21):2003-2011.
41. Ogawa A, Mori E, Minematsu K, et al; MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007;38(10):2633-2639.
42. Schonewille WJ, Wijman CA, Michel P, et al; BASICS study group. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. *Lancet Neurol*. 2009;8(8):724-730.
43. Khatri P, Abruozzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA; IMS I and II Investigators. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology*. 2009;73(13):1066-1072.
44. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke*. 2009;40(6):2079-2084.
45. Investigators IIT; IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. *Stroke*. 2007;38(7):2127-2135.
46. IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke*. 2004;35(4):904-911.
47. Struffert T, Köhrmann M, Engelhorn T, et al. Penumbra Stroke System as an "add-on" for the treatment of large vessel occlusive disease following thrombolysis: first results. *Eur Radiol*. 2009;19(9):2286-2293.
48. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke*. 2009;40(8):2761-2768.
49. Grunwald IQ, Walter S, Papanagiotou P, et al. Revascularization in acute ischaemic stroke using the penumbra system: the first single center experience. *Eur J Neurol*. 2009;16(11):1210-1216.
50. Smith WS, Sung G, Starkman S, et al; MERCI Trial Investigators. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke*. 2005;36(7):1432-1438.
51. Smith WS, Sung G, Saver J, et al; Multi MERCI Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008;39(4):1205-1212.
52. Lee W, Sitoh Y-Y, Lim CCT, Lim WE, Hui FK. The MERCI Retrieval System for the management of acute ischaemic stroke—the NNI Singapore experience. *Ann Acad Med Singapore*. 2009;38(9):749-755.
53. Josephson SA, Saver JL, Smith WS; Merci and Multi Merci Investigators. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi MERCI compared to PROACT II. *Neurocrit Care*. 2009;10(1):43-49.
54. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38(3):967-973.
55. Sandercock PAG, Counsell C, Gubitz GJ, Tseng MC. Antiplatelet therapy for acute ischaemic stroke [update of Cochrane Database Syst Rev. 2003;(2):CD000029; PMID: 12804384]. *Cochrane Database Syst Rev*. 2008;(3):CD000029.
56. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e195S-e226S.
57. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6(11):961-969.
58. Wang Y, Johnston SC; CHANCE Investigators. Rationale and design of a randomized, double-blind trial comparing the effects of a 3-month clopidogrel-aspirin regimen versus aspirin alone for the treatment of high-risk patients with acute non-disabling cerebrovascular event. *Am Heart J*. 2010;160(3):380-386.e1.

59. Berge E, Sandercock P. Anticoagulants versus antiplatelet agents for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2002;(4):CD003242.
60. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials [see comment]. *Stroke.* 2007;38(2):423-430.
61. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet.* 2000;355(9211):1205-1210.
62. Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev.* 2010;(10):CD000255.
63. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *JAMA.* 1998;279(16):1265-1272.
64. Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. *Stroke.* 2001;32(1):262-267.
65. Dennis M, Sandercock PA, Reid J, et al; CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet.* 2009;373(9679):1958-1965.
66. Guyatt GH, Eikelboom JW, Gould MK, et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2)(suppl):e185S-e194S.
67. Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep-vein thrombosis and pulmonary embolism in patients with acute ischemic stroke? *Thromb Res.* 2007;119(3):265-274.
68. Shorr AF, Jackson WL, Sherner JH, Moores LK. Differences between low-molecular-weight and unfractionated heparin for venous thromboembolism prevention following ischemic stroke: a metaanalysis. *Chest.* 2008;133(1):149-155.
69. McGarry LJ, Thompson D, Weinstein MC, Goldhaber SZ. Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients. *Am J Manag Care.* 2004;10(9):632-642.
70. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2)(suppl):e227S-e277S.
71. Roderick P, Ferris G, Wilson K, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. *Health Technol Assess.* 2005;9(49):1-78.
72. Boer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry.* 1991;54(5):466-467.
73. Orken DN, Kenangil G, Ozkurt H, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. *Neurologist.* 2009;15(6):329-331.
74. Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. *Klin Wochenschr.* 1988;66(23):1182-1183.
75. Albers GW. Choice of endpoints in antiplatelet trials: which outcomes are most relevant to stroke patients? *Neurology.* 2000;54(5):1022-1028.
76. Sacco RL. Risk factors and outcomes for ischemic stroke. *Neurology.* 1995;45(2 suppl 1):S10-S14.
77. Hartmann A, Rundek T, Mast H, et al. Mortality and causes of death after first ischemic stroke: the Northern Manhattan Stroke Study. *Neurology.* 2001;57(11):2000-2005.
78. Brønnum-Hansen H, Davidsen M, Thorvaldsen P; Danish MONICA Study Group. Long-term survival and causes of death after stroke. *Stroke.* 2001;32(9):2131-2136.
79. Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet.* 2011;377(9759):31-41.
80. Rothwell PM, Wilson M, Elwin C-E, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet.* 2010;376(9754):1741-1750.
81. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Anderson CS. Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989-1990. *Stroke.* 2002;33(4):1034-1040.
82. Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373(9678):1849-1860.
83. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry.* 1991;54(12):1044-1054.
84. van Wijk I, Kappelle LJ, van Gijn J, et al; LiLAC study group. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet.* 2005;365(9477):2098-2104.
85. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324(7329):71-86.
86. Campbell CL, Smyth S, Montalescot G, et al. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA.* 2007;297(18):2018-2024.
87. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol.* 2005;95(10):1218-1222.
88. Steering Committee CAPRIE; CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348(9038):1329-1339.
89. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996;143(1-2):1-13.
90. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A; ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial [erratum appears in *Lancet.* 2007;369(9558):274]. *Lancet.* 2006;367(9523):1665-1673.
91. Guiraud-Chaumeil B, Rascol A, David J, Boneu B, Clanet M, Bierme R. Prevention of recurrences of cerebral ischemic vascular accidents by platelet antiaggregants. Results of a 3-year controlled therapeutic trial [in French]. *Rev Neurol (Paris).* 1982;138(5):367-385.
92. Boussier MG, Eschwege E, Haguenu M, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary

- prevention of athero-thrombotic cerebral ischemia. *Stroke*. 1983;14(1):5-14.
93. Persantine Aspirin Trial in cerebral ischemia. Part II: end-point results. The American-Canadian Co-Operative Study group. *Stroke*. 1985;16(3):406-415.
  94. Caneschi S, Bonaventuri C, Finzi F. Ischemic cerebrovascular disease: treatment with various anti-platelet aggregation drugs. Clinical follow-up of 80 patients (22-34 months) [in Italian]. *Minerva Med*. 1985;76(41):1933-1943.
  95. Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke*. 2008;39(4):1358-1363.
  96. De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Syst Rev*. 2007; (3):CD001820.
  97. Diener HC, Sacco RL, Yusuf S, et al; Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study group. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol*. 2008;7(10):875-884.
  98. Sacco RL, Diener H-C, Yusuf S, et al; PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008; 359(12):1238-1251.
  99. Diener HC, Bogousslavsky J, Brass LM, et al; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331-337.
  100. Uchiyama S, Demaerschalk BM, Goto S, et al. Stroke prevention by cilostazol in patients with atherothrombosis: meta-analysis of placebo-controlled randomized trials. *J Stroke Cerebrovasc Dis*. 2009;18(6):482-490.
  101. Huang Y, Cheng Y, Wu J, et al; Cilostazol versus Aspirin for Secondary Ischaemic Stroke Prevention cooperation investigators. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study [erratum appears in *Lancet Neurol*. 2008;7(8):675]. *Lancet Neurol*. 2008;7(6):494-499.
  102. Shinohara Y, Katayama Y, Uchiyama S, et al; CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9(10):959-968.
  103. Kamal AK, Naqvi I, Husain MR, Khealani BA. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Cochrane Database Syst Rev*. 2011;(1):CD008076.
  104. Costa J, Ferro JM, Matias-Guiu J, Alvarez-Sabin J, Torres F. Triflusal for preventing serious vascular events in people at high risk. *Cochrane Database Syst Rev*. 2005; (3):CD004296.
  105. Sudlow CL, Mason G, Maurice JB, Wedderburn CJ, Hankey GJ. Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database Syst Rev*. 2009;(4):CD001246.
  106. Chen DK, Kim JS, Sutton DM. Thrombotic thrombocytopenic purpura associated with ticlopidine use: a report of 3 cases and review of the literature. *Arch Intern Med*. 1999;159(3):311-314.
  107. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet*. 1989;1(8649):1215-1220.
  108. Bousser MG, Amarenco P, Chamorro A, et al; PERFORM Study Investigators. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. *Lancet*. 2011;377(9782): 2013-2022.
  109. Algra A, De Schryver ELLM, van Gijn J, Kappelle LJ, Koudstaal PJ. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. *Cochrane Database of Systematic Reviews*. 2006; (3):CD001342.
  110. Sacco RL, Prabhakaran S, Thompson JL, et al; WARSS Investigators. Comparison of warfarin versus aspirin for the prevention of recurrent stroke or death: subgroup analyses from the Warfarin-Aspirin Recurrent Stroke Study. *Cerebrovasc Dis*. 2006;22(1):4-12.
  111. Levine SR, Brey RL, Tilley BC, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA*. 2004;291(5):576-584.
  112. Mohr JP, Thompson JLP, Lazar RM, et al; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345(20):1444-1451.
  113. Matchar DB, Samsa GP, Liu S. Cost-effectiveness of antiplatelet agents in secondary stroke prevention: the limits of certainty. *Value Health*. 2005;8(5):572-580.
  114. Shah H, Gondek K. Aspirin plus extended-release dipyridamole or clopidogrel compared with aspirin monotherapy for the prevention of recurrent ischemic stroke: a cost-effectiveness analysis. *Clin Ther*. 2000;22(3):362-370.
  115. Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. *Am J Med*. 2004;116(12):797-806.
  116. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol*. 1989;25(4):382-390.
  117. Bogousslavsky J, Cachin C, Regli F, Despland PA, Van Melle G, Kappenberg L. Cardiac sources of embolism and cerebral infarction—clinical consequences and vascular concomitants: the Lausanne Stroke Registry. *Neurology*. 1991;41(6):855-859.
  118. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342(8882):1255-1262.
  119. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343(8899):687-691.
  120. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110(16): 2287-2292.
  121. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1(8631):175-179.
  122. Gulløv AL, Koefoed BG, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med*. 1998;158(14):1513-1521.
  123. Hellemons BSP, Langenberg M, Lodder J, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ*. 1999;319(7215):958-964.

124. Pérez-Gómez F, Alegría E, Berjón J, et al; NASPEAF Investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol*. 2004;44(8):1557-1566.
125. Vemmos KN, Tsiygoulis G, Spengos K, et al. Primary prevention of arterial thromboembolism in the oldest old with atrial fibrillation—a randomized pilot trial comparing adjusted-dose and fixed low-dose coumadin with aspirin. *Eur J Intern Med*. 2006;17(1):48-52.
126. Connolly S, Pogue J, Hart R, et al; ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367(9526):1903-1912.
127. Hu DY, Zhang HP, Sun YH, Jiang LQ; Antithrombotic Therapy in Atrial Fibrillation Study Group. The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin [in Chinese]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2006;34(4):295-298.
128. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing*. 2007;36(2):151-156.
129. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867.
130. Lee JH, Park KY, Shin JH, et al. Symptomatic hemorrhagic transformation and its predictors in acute ischemic stroke with atrial fibrillation. *Eur Neurol*. 2010;64(4):193-200.
131. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke*. 2001;32(10):2333-2337.
132. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med*. 1988;318(18):1148-1152.
133. Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G; Lausanne Stroke with Paradoxal Embolism Study Group. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. *Neurology*. 1996;46(5):1301-1305.
134. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105(22):2625-2631.
135. Furlan AJ, Reisman M, Massaro J, et al; CLOSURE I Investigators. Study design of the CLOSURE I Trial: a prospective, multicenter, randomized, controlled trial to evaluate the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. *Stroke*. 2010;41(12):2872-2883.
136. Eckman MH, Wong LKS, Soo YOY, et al. Patient-specific decision-making for warfarin therapy in nonvalvular atrial fibrillation: how will screening with genetics and imaging help? *Stroke*. 2008;39(12):3308-3315.
137. Stam J, De Bruijn SF, DeVeber G. Anticoagulation for cerebral sinus thrombosis. *Cochrane Database Syst Rev*. 2002;(4):CD002005.
138. Bousser MG, Chiras J, Bories J, Castaigne P. Cerebral venous thrombosis—a review of 38 cases. *Stroke*. 1985;16(2):199-213.
139. Bousser MG. Cerebral venous thrombosis: nothing, heparin, or local thrombolysis? *Stroke*. 1999;30(3):481-483.
140. Frey JL, Muro GJ, McDougall CG, Dean BL, Jahnke HK. Cerebral venous thrombosis: combined intrathrombus rtPA and intravenous heparin. *Stroke*. 1999;30(3):489-494.
141. Ageno W, Dentali F, Squizzato A, et al. Evidence and clinical judgment: Treatment of cerebral vein thrombosis. *Thromb Haemost*. 2010;103(6):1109-1115.
142. Hirsch JA, Yoo AJ, Nogueira RG, et al. Case volumes of intra-arterial and intravenous treatment of ischemic stroke in the USA. *J Neurointerv Surg*. 2009;1(1):27-31.
143. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670.
144. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *Q J Med*. 2000;93(6):359-64.



### **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**

*Maarten G. Lansberg, MD, PhD; Martin J. O'Donnell, PhD; Pooja Khatri, MD;  
Eddy S. Lang, MDCM; Mai N. Nguyen-Huynh, MD; Neil E. Schwartz, MD, PhD;  
Frank A. Sonnenberg, MD; Sam Schulman, MD, PhD; Per Olav Vandvik, MD, PhD;  
Frederick Spencer, MD; Pablo Alonso-Coello, MD, PhD; Gordon Guyatt, MD, FCCP;  
and Elie A. Akl, MD, MPH, PhD*

**Table S1—Randomized Controlled Trials of rt-PA in Acute Stroke: Clinical Description and Results**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Favorable Outcome at 90 d, RR (95% CI)			90-d Mortality, RR (95% CI)	90-d Death and Dependency	Comments
				NIHSS 0-1	mRS 0-1	BI $\geq$ 95			
NINDS/1995	r-tPA 0.9 mg/kg	Part 1: r-tPA: 144 of 144	Part 1: 24 h	Part 1: r-tPA: 78 of 144 (54%)	Part 1: r-tPA: 54 of 144 (38%)	Parts 1 and 2: r-tPA: 54 of 312 (17%)			
		Placebo: 147 of 147		Placebo: 57 of 147 (39%)	Placebo: 31 of 147 (21%)	Placebo: 64 of 312 (21%)			
	Placebo	Part 2: 90 d	RR, 1.40 (1.09-1.80)	RR, 1.75 (1.27-2.42)	RR, 1.78 (1.22-2.59)	RR, 0.84 (0.61-.17)			
		Part 2: r-tPA: 168 of 168	Part 2: 90 d	Part 2: r-tPA: 84 of 168 (50%)	Part 2: r-tPA: 52 of 168 (31%)				
		Placebo: 165 of 165		Placebo: 62 of 165 (38%)	Placebo: 33 of 165 (20%)				
				RR, 1.33 (1.04-1.71)	RR, 1.48 (1.08-2.04)	RR, 1.55 (1.06-2.26)			
Hacke, ECASS III <sup>2</sup> /2008	r-tPA 0.9 mg/kg	ITT r-tPA: 418 of 418	90 d	ITT r-tPA: 265 of 418 (63.4%)	ITT r-tPA: 210 of 418 (50.2%)	ITT r-tPA: 28 of 418 (6.7%)	ITT r-tPA: 101 of 418 (24.2%)	Symptom onset within 3-4.5 h	
				Placebo: 236 of 403 (58.6%)	Placebo: 174 of 403 (43.2%)	Placebo: 31 of 403 (7.7%)			Placebo: 155 of 403 (38.5%)
	Placebo	TPP r-tPA: 375 of 375	TPP r-tPA: 248 of 375 (66.1%)	TPP r-tPA: 206 of 375 (54.9%)	TPP r-tPA: 197 of 375 (52.5%)	TPP r-tPA: 115 of 375 (30.7%)	TPP r-tPA: 115 of 375 (30.7%)	TPP r-tPA: 115 of 375 (30.7%)	
			RR, 1.08 (0.97-1.21)	RR, 1.16 (1.01-1.34)	RR, 1.16 (1.01-1.35)	RR, 0.87 (0.53-1.42)	RR, 0.63 (0.51-0.77)		
			TPP r-tPA: 375 of 375	TPP r-tPA: 206 of 375 (54.9%)	TPP r-tPA: 197 of 375 (52.5%)	TPP r-tPA: 115 of 375 (30.7%)	TPP r-tPA: 115 of 375 (30.7%)		
			Placebo: 355 of 355	Placebo: 161 of 355 (45.4%)	Placebo: 155 of 355 (43.7%)	Placebo: 134 of 355 (37.7%)	Placebo: 134 of 355 (37.7%)		
			RR, 1.11 (1.00-1.24)	RR, 1.21 (1.05-1.40)	RR, 1.20 (1.03-1.40)	RR, 0.81 (0.66-0.99)	RR, 0.81 (0.66-0.99)		
									(Continued)

**Table S1—Continued**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Favorable Outcome at 90 d, RR (95% CI)				90-d Mortality, RR (95% CI)	90-d Death and Dependency	Comments
				BI $\geq$ 95	mRS 0-1	NIHSS 0-1	ITT			
Clark, ATLANTIS B/1999	r-tPA	ITT	90 d	ITT	ITT	ITT	ITT	r-tPA: 136 of 297 (45.8%) Placebo: 140 of 312 (45.9%) RR, 0.66 (0.56-0.77)	Death and dependency results taken from Wardlaw et al <sup>a</sup>	
	0.9 mg/kg	r-tPA: 307 of 307	r-tPA: 128 of 307 (42%)	r-tPA: 105 of 307 (34%)	r-tPA: 34 of 307 (11%)	r-tPA: 136 of 297 (45.8%)				
Clark, ATLANTIS A/2000	Placebo	TP	90 d	TP	TP	TP	TP	r-tPA: 62 of 71 (87.3%) Placebo: 54 of 71 (76.1%) RR, 1.15 (0.98-1.34)	Death and dependency results taken from Wardlaw et al <sup>a</sup>	
	0.9 mg/kg	r-tPA: 272 of 272	r-tPA: 115 of 272 (42%)	r-tPA: 92 of 272 (34%)	r-tPA: 30 of 272 (11%)	r-tPA: 62 of 71 (87.3%)				
Clark, ATLANTIS A/2000	Placebo	TP	90 d	TP	TP	TP	TP	r-tPA: 62 of 71 (87.3%) Placebo: 54 of 71 (76.1%) RR, 1.15 (0.98-1.34)	Death and dependency results taken from Wardlaw et al <sup>a</sup>	
	0.9 mg/kg	r-tPA: 275 of 275	r-tPA: 106 of 275 (39%)	r-tPA: 88 of 275 (32%)	r-tPA: 19 of 275 (7%)	r-tPA: 62 of 71 (87.3%)				

(Continued)



**Table S1—Continued**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Favorable Outcome at 90 d, RR (95% CI)			90-d Mortality, RR (95% CI)	90-d Death and Dependency	Comments
				BI $\geq$ 95	mRS 0-1	NIHSS 0-1			
Hacke, ECASS I <sup>15</sup> /1995	r-tPA	ITT	90 $\pm$ 14 d	ITT	ITT	ITT	r-tPA: 171 of 313 (54.6%)	Death and dependency results taken from Wardlaw et al <sup>b</sup>	
	1.1 mg/kg	r-tPA: 313 of 313		r-tPA: 112 of 313 (36%)	r-tPA: 56 of 313 (18%)	r-tPA: 36 of 247 (15%)			
	Placebo	Placebo: 307 of 307		Placebo: 90 of 307 (29%)	Placebo: 39 of 307 (13%)	Placebo: 31 of 264 (12%)	Placebo: 185 of 307 (60.3%)		
				RR, 1.22 (0.97-1.53)	RR, 1.41 (0.97-2.05)	RR, 1.24 (0.79-1.94)	RR, 0.91 (0.79-1.04)		
		TP		TP	TP				
		r-tPA: 247 of 247		r-tPA: 101 of 247 (41%)	r-tPA: 36 of 247 (15%)				
		Placebo: 264 of 264		Placebo: 77 of 264 (29%)	Placebo: 31 of 264 (12%)				
				RR, 1.40 (1.10-1.78)	RR, 1.24 (0.79-1.94)				
Hacke, ECASS II <sup>9</sup> /1998	r-tPA	r-tPA: 409 of 409	90 d	r-tPA: 165 of 409 (40%)	r-tPA: 43 of 409 (11%)	r-tPA: 43 of 409 (11%)	r-tPA: 196 of 409 (47.9%)	Death and dependency results taken from Wardlaw et al <sup>b</sup>	
	1.1 mg/kg	Placebo: 391 of 391		Placebo: 143 of 391 (37%)	Placebo: 42 of 391 (11%)	Placebo: 42 of 391 (11%)	Placebo: 211 of 391 (53.9%)		
	Placebo			RR, 1.09 (0.94-1.26)	RR, 1.10 (0.93-1.32)	RR, 0.98 (0.64-1.46)	RR, 0.89 (0.77-1.02)		

BI = Barthel Index; ITT = Intention-to-treat population; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; RR = risk ratio; r-tPA = recombinant tissue plasminogen activator; TP = per treatment protocol population.

<sup>a</sup>Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2009, Issue 4.

**Table S2—[Section 2.1.1] Evidence Profile: Should IV t-PA vs No IV t-PA Be Used in Patients With Ischemic Stroke Within 3 h of Symptom Onset?**

Quality Assessment				Summary of Findings					
No. of Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 90 d	
						With No IV t-PA	With IV t-PA		Relative Effect (95% CI)
930 (4 studies) <sup>a</sup>	No	No serious inconsistency <sup>e</sup>	No serious indirectness	No serious imprecision <sup>d</sup>	Undetected	Overall mortality (critical outcome) High <sup>b,c,d</sup>	82 of 465 (17.2) <sup>f,g</sup>	RR, 1.00 (0.76-1.33) <sup>h</sup>	Moderate <sup>h</sup>
90 d	serious risk of bias <sup>b</sup>						465 (17.2) <sup>f,g</sup>		0 fewer deaths per 1,000 <sup>f,g,e</sup> per 1,000 <sup>f,g</sup> (from 29 fewer to 40 more)
930 (4 studies)	No	No serious inconsistency <sup>h</sup>	No serious indirectness	No serious imprecision	Undetected	Good functional outcome (critical outcome; assessed with: mRS 0-1)	194 of 466 (29) <sup>j,k</sup>	RR, 1.44 (1.21-1.72) <sup>l</sup>	Moderate <sup>m</sup>
90 d	serious risk of bias <sup>a</sup>						464 (41.8) <sup>j,k</sup>		350 excellent outcomes per 1,000 (from 74 more to 252 more)

Bibliography: Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375(9727):1695-1703. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2009;(4):000213. ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS = European Cooperative Acute Stroke Study; ICH = intracerebral hemorrhage; NINDS = National Institute of Neurological Disorders and Stroke. See Table S1 legend for expansion of other abbreviations.

<sup>a</sup>NINDS (1995), ATLANTIS, ECASS I (1995), and ECASS II (1998).

<sup>b</sup>Allocation unclear in two studies.

<sup>c</sup> $I^2 = 38\%$ .

<sup>d</sup>The CI for mortality is borderline for the judgment of imprecision for relative risk. 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 the results of the values and preference exercise), 179 additional patients with good outcome (point estimate for good functional outcome) balances favorably with 50 additional deaths (upper boundary for the mortality outcome). Consequently, we did not rate down for imprecision.

<sup>e</sup>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.

<sup>f</sup>Data from Wardlaw et al.

<sup>g</sup>Fixed effect model because NINDS (1995) judged to be dominant.

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

<sup>i</sup> $I^2 = 0\%$  (based on Wardlaw et al, mRS 3-5 outcome).

<sup>j</sup>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.

<sup>k</sup>Data from Lees et al.

<sup>l</sup>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.

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

**Table S3—[Section 2.1.2] Evidence Profile: Should IV t-PA vs No IV t-PA Be Used in Patients With Ischemic Stroke Within 3-4.5 h of Symptom Onset?**

No. of Participants (Studies) Follow up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 90 d		
	Serious <sup>b</sup>	No serious	No serious	Serious <sup>c</sup>	Undetected	Low <sup>b,c</sup>	No IV t-PA	With IV t-PA	Relative Effect (95% CI)	Risk With No IV t-PA	Risk Difference With IV t-PA (95% CI)
1,620 (5 studies <sup>a</sup> ) 90 d	No serious risk of bias	No serious indirectness	No serious indirectness	Serious <sup>c</sup>	Undetected	Low <sup>b,c</sup> due to inconsistency, imprecision	82 of 811 (10.1) <sup>d,e</sup>	89 of 809 (11) <sup>d,e</sup>	OR, 1.22 (0.87-1.71) <sup>e,f</sup>	120 deaths per 1,000 <sup>d,e</sup>	Moderate <sup>g</sup> 23 more deaths per 1,000 (from 14 fewer to 69 more)
1,620 (5 studies <sup>a</sup> ) 90 d	No serious risk of bias	No serious indirectness	No serious indirectness	No serious imprecision	Undetected	High	306 of 811 (37.7) <sup>h,i</sup>	361 of 809 (44.6) <sup>h,i</sup>	OR 1.34 (1.06-1.68) <sup>e,f</sup>	350 excellent outcomes per 1,000 <sup>h,i</sup>	Moderate <sup>i</sup> 69 more excellent outcomes per 1,000 (from 13 more to 125 more)

Bibliography: Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375(9727):1695-1703. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischemic stroke. *Cochrane Database Syst Rev*. 2009;(4):000213. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>ATLANTIS, ECASS I (1995), ECASS II (1998), ECASS III (2008), and EPITHET.

<sup>b</sup>I<sup>2</sup> = 70%.

<sup>c</sup>Wide CIs ranging from 0.78-1.39 on mortality.

<sup>d</sup>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.

<sup>e</sup>Based on Lees et al.

<sup>f</sup>This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

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

<sup>h</sup>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.

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

**Table S4—[Section 2.1.3] Should IV t-PA Be Used in Patients With Ischemic Stroke Within 4.5 to 6 h of Symptom Onset?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Risk with Control	Anticipated Absolute Effects, Time Frame 90 d
1,117 (4 studies) <sup>a</sup> 90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b</sup> imprecision	Undetected	Moderate <sup>b</sup> due to imprecision	55 of 542 (10.1) <sup>c</sup> 86 of 575 (15) <sup>c</sup>	OR, 1.49 (1-2.21) <sup>d</sup>	Risk with Control	Moderate <sup>e</sup> 49 more deaths per 1,000 (from 0 more to 112 more)
1,117 (4 studies) <sup>a</sup> 90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>f</sup> imprecision	Undetected	Moderate <sup>f</sup> due to imprecision	193 of 542 (35.6) 215 of 575 (37.4)	OR, 1.22 (0.96-1.54) <sup>d</sup>	350 excellent outcomes per 1,000	Moderate <sup>g</sup> 46 more excellent outcomes per 1,000 (from 9 fewer to 103 more)

Bibliography: Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375(9727):1695-1703. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischemic stroke. *Cochrane Database Syst Rev*. 2009;(4):000213. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>ATLANTIS A (2000), ECASS I (1995), ECASS II (1998), and EPITHET.  
<sup>b</sup>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).  
<sup>c</sup>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.  
<sup>d</sup>This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.  
<sup>e</sup>Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trial (NINDS, ECASS, ATLANTIS, and EPITHET).  
<sup>f</sup>CI includes the possibility of harm and benefit.  
<sup>g</sup>Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS, ECASS, ATLANTIS, and EPITHET).

**Table S5—Randomized Controlled Trials of IA Thrombolysis in Acute Stroke: Clinical Description and Results**

Study/Year	Interventions	No. of Patients Analyzed	Favorable Outcome at 3 mo <sup>a</sup>	Total Mortality	sICH	Comments
Trials of IA thrombolysis as monotherapy						
Del Zoppo, PROACT I/1998	pro-urokinase, 6 mg	26	12 (46%)	7 (27%)	4 (15%)	M1 or M2 occlusions, median baseline NIHSS 18 Study drug started at median of 5.5 h
	Heparin	14	3 (21%)	6 (43%)	1 (7%)	Revascularization rate 58% with pro-urokinase and 14% with heparin ( $P = .02$ )
			$P = .18$	$P = .48$	$P = .64$	All patients received IV heparin. The protocol initially specified a heparin dose of a 100 International Units/kg bolus and 1,000 units/h for 4 h. After 16 patients were randomized, the heparin dose was reduced to a 2,000 International Units/kg bolus and 500 International Units/h 4-h infusion on recommendations of the safety committee.
Furlan, PROACT II <sup>11</sup> /1999	r-prourokinase, 9 mg	121	48 (40%)	30 (25%)	11 (9%)	M1 or M2 occlusions, median baseline NIHSS 17 Study drug started at median of 5.3 h
	Heparin, Y mg/kg	59	15 (25%)	16 (27%)	1 (2%)	Heparin (2,000 unit bolus and a 500 unit/h infusion for 4 h) for both groups
			$P = .07$	$P = .72$	$P = .11$	Revascularization rate (TIMI 2 or 3) was 66% with pro-urokinase and 18% with heparin ( $P < .01$ )
Ogawa, MELT <sup>9</sup> /2007	Urokinase, X mg/kg	57	28 (49%)	3 (5%)	5 (9%)	Included only M1 and M2 occlusions, median NIHSS 14 Recanalization rate (TIMI 2 or 3) 74% in treatment group
	Heparin, Y mg/kg	57	22 (39%)	2 (4%)	1 (2%)	Heparin (5,000 u bolus) for both groups
			$P = .35$	$P = 1.00$	$P = .21$	
Trials of combined IV and IA thrombolysis						
IMS investigators, IMS I <sup>10</sup> /2004	IV 0.6 mg/kg r-tPA plus IA r-tPA (up to 22 mg)	80	34 (43%)	13 (16%)	5 (6%)	All proximal occlusions, median NIHSS 19 Revascularization rate (TICI 2 or 3) 60%
IMS investigators, IMS II <sup>11</sup> /2007	IV 0.6 mg/kg r-tPA plus IA r-tPA (up to 22 mg) ± ultrasound	81	37 (46%)	13 (16%)	8 (10%)	Heparin (2,000 unit bolus and a 450 unit/h infusion for up to 2 h) All proximal occlusions, median NIHSS 19 Revascularization rate (TICI 2 or 3) 60%

All statistical  $P$  values are calculated with two-tailed Fisher exact tests. IA = intraarterial; M1 = primary branch of middle cerebral artery; M2 = secondary branch of middle cerebral artery; sICH = symptomatic intracranial hemorrhage; TICI = thrombolysis in cerebral ischemia scale; TIMI = thrombolysis in myocardial ischemia scale. See Table 1 legend for expansion of other abbreviations.

<sup>a</sup>Favorable outcome defined as mRS 0-2.

**Table S6—[Section 2.2.1] Evidence Profile: Should IA tPA vs no IA tPA Be Used for Patients With Ischemic Stroke and Contraindication for IV tPA?**

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence		Anticipated Absolute Effects, Time Frame 90 d		
						No IA tPA	With IA tPA	Relative Effect (95% CI)	Risk With No IA tPA	Risk Difference With IA tPA (95% CI)
334 (3 studies <sup>a</sup> ) 90 d	No serious risk of bias	No serious inconsistency <sup>b</sup>	Serious <sup>c</sup>	Serious <sup>d</sup>	Undetected	Low <sup>b,d</sup> due to indirectness, imprecision	40 of 130 (18.5)	40 of 204 (19.6) <sup>e</sup>	RR, 0.86 (0.56-1.33)	Moderate <sup>f</sup> 210 deaths per 1,000 (from 92 fewer to 69 more)
334 (3 studies <sup>a</sup> ) 90 d	No serious risk of bias	No serious inconsistency <sup>b</sup>	Serious <sup>c</sup>	No serious imprecision	Undetected	Moderate <sup>b,c</sup> due to indirectness	40 of 130 (30.8) <sup>g</sup>	88 of 204 (43.1) <sup>g</sup>	RR, 1.44 (1.06-1.95)	Moderate <sup>h</sup> 290 good outcomes per 1,000 (from 17 more to 275 more)

**Bibliography:** Ogawa A, Mori E, Minematsu K, et al; MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 h of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007;38(10):2633-2639. Del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase 2 randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *PROACT Investigators. Polysy in Acute Cerebral Thromboembolism. Stroke*. 1998;29(1):4-11. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Polysy in Acute Cerebral Thromboembolism. JAMA*. 1999;282(21):2003-2011. The IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke*. 2004;35(4):904-911. IA thrombolysis administered median time of 5.5 h PROACT (1999), 5.3 h PROACT II (1999), and 3.8 h MELT (2007) from symptom onset. See Table S1 and S5 legends for expansion of abbreviations.

<sup>a</sup>PROACT I (1998), PROACT II (1999), MELT (2007).

<sup>b</sup>P<sub>2</sub> = 0%.

<sup>c</sup>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).

<sup>d</sup>CI includes both clinically significant harms and benefits.

<sup>e</sup>Higher risk in intervention group despite an RR < 1 explained by Simpson's paradox.

<sup>f</sup>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.

<sup>g</sup>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%) IA-treated patients and 3 of 126 (2%) control patients.

<sup>h</sup>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%).

**Table S7—[Section 2.2.2] Evidence Profile: Should IA tPA Alone Be Used for Patients With Ischemic Stroke?**

No. of Participants (Studies)	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d
343 (2 studies <sup>a,b</sup> )	Serious <sup>c</sup>	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	Low <sup>e,d</sup> due to risk of bias, imprecision	38 of 182 (20.9) <sup>e</sup> With IA tPA in Addition to IV tPA Alone	RR, 0.77 (0.49-1.22)	Risk Difference With IA tPA in Addition to IV tPA (95% CI)
90 d							26 of 161 (16.1)	210 deaths per 1,000 <sup>f</sup>	48 fewer deaths per 1,000 (from 107 fewer to 46 more)
343 (2 studies <sup>a,b</sup> )	Serious <sup>c</sup>	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	Good functional outcome (critical outcome); assessed with mRS 0–2)	71 of 182 (39) <sup>e,g,h</sup> With IA tPA in Addition to IV tPA Alone	RR, 1.13 (0.88-1.45)	38 more good outcomes per 1,000 (from 35 fewer to 131 more)
90 d							71 of 161 (44.1) <sup>g,h</sup>	290 good outcomes per 1,000 <sup>e,g,h</sup>	

**Bibliography:** The IMS Study Investigators. Combined intravenous and intraarterial recanalization for acute ischemic stroke: the interventional management of stroke study. *Stroke*. 2004;35(4):904-912. The IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II study. *Stroke*. 2007;38(7):2127-2135. See Tables S1 and S5 legends for expansion of abbreviations.

<sup>a</sup>IMS I (2004) and IMS II (2007) used the same data for their control groups. We, thus, combined data from the two studies for the intervention group and compared with the data from the same control group.

<sup>b</sup>IMS I (2004) and IMS II (2007).

<sup>c</sup>No handling of confounding reported and no blinding of outcome assessors reported.

<sup>d</sup>CI includes values indicating both harms and benefit.

<sup>e</sup>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 old to match the IMS cohorts.

<sup>f</sup>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.

<sup>g</sup>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 patients treated with IV + IA tPA and 1.1% of patients treated with IV tPA alone (RR, 2.3; 95% CI, 0.4-12.1).

<sup>h</sup>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 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).

**Table S8—Studies of Mechanical Thrombectomy in Acute Stroke: Clinical Description and Results**

Study/Year, Country	Intervention	No. of Patients	Follow-up	Population	Modified Rankin Score at 3 mo	NIHSS at 3 mo	Mortality at 3 mo	sfCH Within 24 h
Struffert <sup>12</sup> /2009, Germany	Penumbra System	15	90 d	Patients with acute ischemic stroke treated with PS after IV or IA standard treatment with tPA (n = 14) or ReoPro (n = 1) and admitted within 6 h after symptom onset Age (mean ± SD): 60.3 ± 18.7 y Median baseline NIHSS in patients with occlusions of the anterior circulation (n = 12): 15; all patients with BA occlusions (n = 3) presented with coma	Median 90-d mRS: 2	NR	3 of 15 (20%)	0 of 15 (0%)
Penumbra Pivotal Stroke Trial Investigators <sup>13</sup> /2009, United States	Penumbra treatment	125	90 d	Patients with neurologic deficits (NIHSS score ≥ 8), presented within 8 h of symptom onset, and an angiographic occlusion (TIMI grade 0 or 1) of a treatable large intracranial vessel Age (mean ± SD): 63.5 ± 13.5 y NIHSS (mean ± SD): 17.6 ± 5.2	mRS ≤ 2 at 90 d: 25 of 125 (20%)	Discharge NIHSS 0-1 or improved by ≥ 10: 27 of 125 (21.6%)	33 of 125 (26.4%)	14 of 125 (11%)
Grunwald <sup>14</sup> /2009, Germany	Penumbra as monotherapy	Overall: 29	90 d	Patients with acute ischemic stroke who underwent mechanical revascularization with the PS either as monotherapy or adjunctive therapy, had NIHSS score ≥ 8, presentation within 8 h of symptom onset, and occlusion (TIMI 0 or 1) of a treatable intracranial vessel Mean age ± SD: 58.4 ± 17.8 y	mRS ≤ 2 at 3 mo:	≥ 4-point improvement	Death at 30 d (not 3 mo):	2 of 29 (7%)
	Penumbra as adjunct therapy	IV + mech: 12 IA + mech: 11 Bridge + mech: 3 Mech only: 3		Mean NIHSS score at baseline: 20	IV + mech: 3 of 12 (25%) IA + mech: 5 of 11 (45.5%) Bridging + mech: 2 of 3 (66.7%) Mech only: 1 of 3 (33.3%)	IV + mech: 7 of 12 (58%) IA + mech: 6 of 11 (54.5%) Bridging + mech: 3 of 3 (100%) Mech only: 3 of 3 (100%)	IV + mech: 3 of 12 (25%) IA + mech: 1 of 11 (9%) Bridging + mech: 0 of 3 (0%) Mech only: 0 of 3 (0%)	

(Continued)



**Table S8—Continued**

Study/Year, Country	Intervention	No. of Patients	Follow-up	Population	Modified Rankin Score at 3 mo	NIHSS at 3 mo	Mortality at 3 mo	sfICH Within 24 h
Smith, MERCI Trial <sup>16</sup> /2005, United States	MERCI	151 (device deployed in 141)	90 d	Patients with occluded intracranial vessels within the first 8 h of acute ischemic stroke, NIHSS score $\geq$ 8, and occlusion of a treatable vessel Age (mean $\pm$ SD): 67.0 $\pm$ 15.5 y Baseline NIHSS (mean $\pm$ SD): 20.1 $\pm$ 6.6 Recanalization: 69 of 151 (46%)	mRS score $\leq$ 2: Overall: 27.7% Recanalized: 46.0%	NIHSS improved $\geq$ 10: Overall: 32.4% Recanalized: 50.0%	Mortality: Overall: 61 of 141 (43%) Recanalized: 29.9%	11 of 141 (8%)
Smith, Multi MERCI Trial <sup>16</sup> /2008, United States	MERCI	Overall: 164	90 d	Patients with large vessel stroke treated within 8 h of symptom onset Age (mean $\pm$ SD): 68.1 $\pm$ 16.0 y Baseline NIHSS (median [IQR]): 19 (15-23) Baseline mRS (mean $\pm$ SD): 0.34 $\pm$ 0.95	mRS score $\leq$ 2 (95% CI): NR Overall: 36% (29-44) Recan: 49% (40-59) No recan: 10% (2-18) RR recan vs no recan: 5.1 (95% CI, 2.2-12)	NR Overall: 34% (26-41) Recan: 25% (17-33) No recan: 52% (38-66) RR recan vs no recan: 0.48 (95% CI: 0.3-0.7)	90d mortality (95% CI): 16 of 164 (10%)	
Lee <sup>17</sup> /2009, Singapore Results	MERCI device	15	30 d	Patients who underwent treatment with MERCI thrombectomy device, after confirmed large vessel stroke (initial NIHSS score $\geq$ 8) presenting within the 8-h window period from stroke onset Age (median IQR): 67 (61.5-76 y) NIHSS before treatment: 17.88	Mean mRS at 30 d: Post-MERCI NIHSS: Mean: 9.5 Overall: 4.4 Complete recan: 2.6 No or partial recan: 4.5	Deaths: Overall: 4 of 15 (26%) Complete recan: 22% No or part. recan: 33%	1 of 15 (7%)	

BA = basilar artery; IQR = interquartile range; mech = mechanical revascularization; NR = not reported; PS = Penumbra System; recan = recanalization.

**Table S9—[Section 2.3] Evidence Profile: Should Mechanical Thrombectomy vs Standard Medical Therapy Be Used in Acute Stroke Patients With Large Artery Occlusion?**

Quality Assessment				Summary of Findings					
No. of Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 90 d	
						Overall Quality of Evidence	With Standard Medical Therapy	With Mechanical Thrombectomy	Risk With Standard Medical Therapy
619 (6 studies) <sup>a</sup> 30-90 d	Serious <sup>b</sup> No serious inconsistency <sup>c</sup>	No No serious indirectness	No No serious indirectness	No No serious imprecision	Undetected No serious imprecision	Overall mortality (critical outcome) Low <sup>b,c</sup> due to risk of bias	161 of 24 of 130 (18.5) <sup>d</sup> 489 (32.9)	RR, 1.78 (1.24-2.64)	Moderate <sup>e</sup> 210 deaths per 1,000 <sup>d</sup> (from 50 more to 344 more)
604 (5 studies) <sup>f</sup> 90 d	Serious <sup>b</sup> No serious inconsistency	No No serious indirectness	No No serious indirectness	No No serious imprecision	Undetected No serious imprecision	Good functional outcome (critical outcome; assessed with: mRS 0-2) Low <sup>b</sup> due to risk of bias	139 of 40 of 130 (30.8) <sup>h,g</sup> 474 (29.3) <sup>g</sup>	RR, 0.95 (0.72-1.29)	Moderate <sup>h</sup> 290 good outcomes per 1,000 <sup>d,g</sup> fewer to 84 more)

ICA = internal carotid artery; MCA = middle cerebral artery. See Table S1 and S5 legends for expansion of other abbreviations.

<sup>a</sup> Intervention data derived from Penumbra studies (Struffert 2009, Penumbra Pivotal Stroke Trial 2009, and Grunwald 2009) and MERCI studies (Smith 2006, Smith 2008, and Lee 2009). Patients with strokes secondary to ICA, MCA, and basilar occlusions were included in these studies.

<sup>b</sup> Patients were not randomized.

<sup>c</sup> No explanation was provided.

<sup>d</sup> Control data derived from placebo arms of three trials (MELT 2007, PROACT I 1998, PROACT II 1999). These studies only included patients with MCA occlusions. In PROACT the placebo arm received IA heparin.

<sup>e</sup> 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 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.

<sup>f</sup> sICH not listed as a separate outcome as it is captured in the other listed outcomes. sICH occurred in 44 of 489 patients (9.0%) treated with mechanical thrombectomy and three of 126 patients (2.4%) treated with medical therapy.

<sup>g</sup> Penumbra (Struffert 2009, Pivotal Trial 2009, and Grunwald 2009), MERCI (Smith 2006 and Smith 2008).

<sup>h</sup> Baseline good functional outcome rate derived from control arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the placebo control arms of NINDS as reported in the IMS study (99 of 341 = 29%).

**Table S10—[Section 2.3] Evidence Profile: Should Mechanical Thrombectomy vs No Mechanical Thrombectomy Be Used for Acute Stroke Secondary to MCA Occlusion?**

No. of Participants (Studies)	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 90 d
							With Mechanical Thrombectomy	With Mechanical Thrombectomy	
208 (2 studies <sup>a,b</sup> ) 90 d	Very serious <sup>c</sup> No serious inconsistency	No serious inconsistency	Serious <sup>d</sup>	Serious <sup>e</sup>	Undetected	Overall mortality (critical outcome) Low <sup>e,e</sup> due to risk of bias, indirectness, imprecision	40 of 16 of 149 (26.8) <sup>f</sup> 59 (27.1)	RR, 0.99 (0.617-1.648)	Moderate <sup>g</sup> 210 deaths per 1,000 (from 80 fewer to 136 more)
200 (2 studies <sup>a,b</sup> ) 90 d	Very serious <sup>c</sup> No serious inconsistency	No serious inconsistency	Serious <sup>d</sup>	Serious <sup>g</sup>	Undetected	Good functional outcome (critical outcome; assessed with: mRS 0-2) Low <sup>e,d,h</sup> due to risk of bias, indirectness, imprecision	53 of 15 of 141 (37.6) <sup>j,k</sup> 59 (25.4) <sup>e</sup>	RR, 1.478 (0.935-2.443)	Moderate <sup>l</sup> 139 more good outcomes per 1,000 (from 19 fewer to 418 more)

Bibliography: Josephson SA, Saver JL, Smith WS. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi MERCI compared to PROACT II. *Neurocritical Care*. 2009;10(1):43-49. See Table S1 and S5 legends for expansion of other abbreviations.

<sup>a</sup>Intervention data derived from a subset of patients from the MERCI (2007) and Multi-MERCI cohorts. The subset was defined as patients who met inclusion criteria for the PROACT II (1999) trial.

<sup>b</sup>Control data derived from the control arm of PROACT II (1999).

<sup>c</sup>Outcome rates with mechanical thrombectomy compared with historical controls obtained from the placebo arm of the PROACT II (1999) trial. Consequently, there may be important systematic differences in the intervention and control populations.

<sup>d</sup>Analysis restricted to MCA patients.

<sup>e</sup>Boundaries of the CI lie outside 0.8 and 1.2.

<sup>f</sup>After adjusting for more severe symptoms (higher baseline NIHSS) in the intervention group, the mortality in the intervention group is 23.0%.

<sup>g</sup>Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998) and II (1999), MELT (2007), and the placebo and control arms of NINDS (1995) as reported in the IMS 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.

<sup>h</sup>Boundaries of the confidence interval overlap 1.

<sup>i</sup>After adjustment for more severe symptoms (higher baseline NIHSS) in the intervention group, the proportion with good outcome in the intervention group increases to 39.9%.

<sup>j</sup>Baseline good functional outcome rate derived from control arms of PROACT I and II, MELT, and the placebo control arms of NINDS as reported in the IMS study (99 of 341 = 29%).

**Table S11—Randomized Controlled Trials of Aspirin in Acute Stroke: Clinical Description and Results**

Study/Year, Country	Intervention	No. of Patients	Follow-up	Population	Death or Dependence at End of Follow-up	Mortality at End of Follow-up	sICH During Treatment Period	Comments
CAST <sup>19</sup> /1997 (Chinese Acute Stroke Trial), China	ASA 160 mg/d  Started within 48 h of stroke onset	ASA: 10,554  Placebo: 10,552  Total: 21,106	4 wk	Patients with acute ischemic stroke treated with symptom onset within 48 h of presentation to hospital and with no contraindications to ASA as judged by the treating physician  Age (mean ± SD): 63.1 y Median baseline NIHSS not reported 13% of patients did not undergo CT scan prior to randomization	ASA: 3,153 (29.9%)  Placebo: 3,266 (31.0%)	ASA: 343 (3.2%)  Placebo: 398 (3.8%)	ASA: 115 (1.1%)	Mean time to randomization, 25 h  ASA arm had fewer early deaths (3.3% vs 3.9%; <i>P</i> = .04)  ASA arm had fewer recurrent strokes (1.6% vs 2.1%; <i>P</i> = .01)
IST <sup>10</sup> /1997, United States	ASA 300 mg/d	ASA: 9,720  Placebo: 9,715  Total: 19,435	14 d and 6 mo	Patients with acute ischemic stroke treated with symptom onset within 48 h of presentation to hospital  Age (mean ± SD): 63.1 y  Median baseline NIHSS not reported  33% of patients did not undergo CT scan prior to randomization	ASA: 6,000 (61.7%)  Placebo: 6,125 (63.0%)	ASA: 2,073 (21.3%)  Placebo: 2,168 (22.3%)	ASA: 87 (0.90%)  Placebo: 74 (0.76%)	Median time to randomization, 19 h  ASA arm had fewer deaths within 14 d (9.0% vs 9.4%)  ASA arm had fewer recurrent strokes (2.8% vs 3.9%)  2 × 2 factorial design with ASA and heparin. Only ASA and placebo groups included in this table.

(Continued)

**Table S11—Continued**

Study/Year, Country	Intervention	No. of Patients	Follow-up	Population	Death or Dependence at End of Follow-up	Mortality at End of Follow-up	sfCH During Treatment Period	Comments
MAST <sup>20</sup> /1995, Germany	ASA 300 mg/d × 10 d	ASA: 309 Placebo: 313 Total: 622	6 mo	Patients with acute ischemic stroke presenting within 6 h of symptom onset Mean age not reported but most patients between 60 and 75 y Mean NIHSS score not reported	ASA: 98 (31.7%) Placebo: 89 (28%)	ASA: 98 (31.7%) Placebo: 89 (28.4%)	ASA (2%) Placebo (0.6%)	2 × 2 factorial design with ASA and streptokinase. Only ASA and placebo groups included in this table.
Roden-Jullig <sup>21</sup> /2003, Sweden	ASA 325 mg po × 5 d	ASA: 221 Placebo: 220 Total: 441	90 d	Patients of all ages were included if they had an acute ischemic stroke (CT scan confirmed) Focal neurologic impairment of at least one point severity according to the SSSS Median SSSS at baseline: 13.2 in ASA group, 12.3 in placebo	ASA: 52.9% Placebo: 49.4% Defined as dead or in need of increased help with ADLs	ASA: 6.8% Placebo: 5.4%	Not reported	

ADL = activities of daily living; HT = hemorrhagic transformation; SSSS = Scandinavian Stroke Supervision Scale

**Table S12—[Section 2.4] Evidence Profile: Should Aspirin (160-300 mg) vs No Aspirin Be Used for Acute Ischemic Stroke (Prescribed Within 48 h)**

Quality Assessment				Summary of Findings						
No. of Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence		Relative Effect (95% CI)	Risk With No Aspirin (160-300 mg) (95% CI)	Risk Difference With Aspirin (160-300 mg) (95% CI)
						Overall Quality of Evidence	Study Event Rates (%)			
41,291 (4 studies <sup>a</sup> ) 4-24 wk <sup>b,c,d</sup>	No serious risk of bias <sup>d</sup>	No serious inconsistency <sup>e</sup>	No serious indirectness	No serious imprecision	Undetected	High <sup>b,e</sup>	2,661 of 20,644 (12.9) <sup>b,f</sup>	OR, 0.92 (0.87-0.98)	120 deaths per 1,000 <sup>b,f</sup> from 2 fewer to 14 fewer <sup>g</sup>	Moderate <sup>g</sup>
41,291 (4 studies <sup>b</sup> ) 4-24 wk <sup>b,c,e</sup>	No serious risk of bias <sup>d</sup>	No serious inconsistency <sup>f</sup>	No serious indirectness	No serious imprecision	Undetected	High <sup>b,h</sup>	11,115 of 20,644 (53.8) <sup>h</sup>	RR, 1.02 (1.01-1.04)	350 good outcomes per 1,000 <sup>h</sup> to 14 more <sup>h</sup>	Moderate <sup>h,k</sup>
40,850 (4 studies <sup>c</sup> ) 2-4 wk <sup>i</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	115 of 20,423 (0.56) <sup>j</sup>	OR, 1.69 (1.35-2.11) <sup>jm</sup>	6 bleeding events per 1,000 <sup>l</sup> to 7 more <sup>l</sup>	Moderate <sup>l,n</sup>

Bibliography: Sandercock PAG, Counsell C, Grubitz GJ, Tseng MC. Antiplatelet therapy for acute ischemic stroke. *Cochrane Database Syst Rev*. 2008;(3):CD000029. TIA = transient ischemic attack. See Table 1 legend for expansion of other abbreviations.

<sup>a</sup>IST (1997), CAST (1997), MAST (1995), and Roden-Jullig (2003).  
<sup>b</sup>Events based on those observed during follow-up (4 wk in CAST [1997], 24 wk in IST [1997]).  
<sup>c</sup>Although the IST (1997) trial followed patients for as long as 6 mo and CAST (1997) for only 1 month, the closest shared outcome window is 2 wk for IST (1997) and 4 wk for CAST (1997).  
<sup>d</sup>Minimal loss to follow-up, well blinded and concealed.  
<sup>e</sup> $I^2 = 21\%$ .  
<sup>f</sup>Fatal ICH captured in mortality outcome and therefore is 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 and 12% of the patients in CAST (1997) never underwent neuroimaging.  
<sup>g</sup>Baseline mortality rate (217 of 1,822 = 11.9%) derived from placebo arms of tPA trials (NINDS [1995], ECASS, ATLANTIS, and EPITHET).  
<sup>h</sup> $I^2 = 0\%$ .  
<sup>i</sup>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).  
<sup>j</sup>Symptomatic nonfatal ICH not listed separately in table because it is captured in the good functional outcome measure. Symptomatic ICH is higher in the treatment arm of IST (1997) and CAST (1997) (OR = 1.22; 95% CI, 1.00-1.50).  
<sup>k</sup>Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS [1995], ECASS, ATLANTIS, and EPITHET).  
<sup>l</sup>Events based on those observed during treatment period (2 wk in IST [1997] and 4 wk in CAST [1997]).  
<sup>m</sup>RR obtained from Sandercock et al is for any major extracranial hemorrhage (fatal plus nonfatal). RR for nonfatal major extracranial hemorrhage is assumed to be identical.  
<sup>n</sup>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.

**Table S13—Randomized Controlled Trials of Anticoagulation vs Antiplatelet in Acute Stroke: Clinical Description and Results**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Population	Mortality	Outcome			Comments
						Good Functional Outcome*	Ischemic	Hemorrhagic	
IST <sup>19</sup> /1997	Heparin	4,818	6 mo	Patients with suspected acute ischemic stroke	1,757 of 4,818 (36.5%)	217 of 4,855 (4.5%)	16 of 487 (3.3%)	Heparin is 12,500 or 5,000 International Units sc bid without aspirin Aspirin is 300 mg daily without heparin	
	Aspirin 300 mg/d	4,816		Presentation within 48 h of symptom onset	1,818 of 4,816 (37.7%)	182 of 4,858 (3.7%)	N/A		
		Total: 9634		67% CT scan prior to randomization, 29% CT scan after randomization					
Bath, TAI <sup>22</sup> /2001	Timzaparin HD	487	6 mo	Patients with acute ischemic stroke	71 of 487 (14.6%)	16 of 487 (3.3%)	Drug administered for up to 10 d Dosage: HD: 175 anti-Xa International Units/kg daily; LD: 100 anti-Xa International Units/kg daily		
	Timzaparin LD	508		Presentation within 48 h of symptom onset	72 of 508 (14.2%)	24 of 508 (4.7%)			
	Aspirin 300 mg/d	491		Age: 18-90 y	73 of 491 (14.9%)	15 of 491 (3.1%)			
		Total: 1,486				(Ischemic or unknown)			
LaMonte, ARGIS-1 <sup>29</sup> /2004	Argatroban HD	59 of 59	90 d	Patients with mild to moderate ischemic stroke	7 of 59 (11.1%)	N/A	Dosage: HD: 100 µg/kg bolus followed by low-dose arm 1 µg/kg/min, or LD: high-dose arm 3 µg/kg/min, for 5 d vs Placebo. Treatment continued for 10 d		
	Argatroban LD	54 of 54		Presentation within 12 h of symptom onset	58 (19.3%)	2 of 58 (3.4%)			
	Aspirin	54 of 54		NIHSS score 5-22	5 of 54 (9.3%)	0 of 54 (0.0%)			
		Total: 171							

(Continued)

**Table S13—Continued**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Population	Mortality	Outcome		
						Good Functional Outcome <sup>a</sup>	Recurrent Stroke at 14 Days	Comments
					Ischemic	Hemorrhagic		
Pince, Toulouse <sup>24/1981</sup>	Heparin No treatment	10 of 40 5 of 40 Total: 80	10 d	Patients with ischemic stroke affecting the leg Presentation within 7 d of symptom onset No CT scan, 100% LP before entry Age: 30-92 y				Heparin (5,000 International Units sc 8 hourly) × 10 d
Berge, HAE <sup>25/2000</sup>	Dalteparin	244 of 244	3 mo	Patients with atrial fibrillation and acute ischemic stroke Presentation within 30 h of symptom onset CT scan mandatory for all patients	9 of 179 (5%) P = .048	6 of 224 (2.7%) P = .73	51 of 224 (22.8%) P = .73	Dosage: 100 International Units/kg sc bid
Wong, FISS-tris <sup>26/2007</sup>	Subcutaneous nadroparin Aspirin 160 mg/d	180 of 180 173 of 173 Total: 353	6 mo	Patients with confirmed large artery occlusive disease Presenting within 48 h of symptom onset	179 (5%) P = .88	180 (4%) P = .74	55 of 101 (54.5%) P = .16	Dosage: (3,800 anti-factor Xa International Units/0.4 mL) bid
Chamorro, RAPID <sup>27/2005</sup>	ASA UH + aspirin	35 of 35 32 of 32 Total: 67	90 d	Patients with suspected ischemic stroke Symptoms lasting < 12 h	4 of 35 (11.4%) P = .50	6 of 35 (%) P = .36	19 of 35 (54.3%) P = .33	Not reported
Sarna, India <sup>28/2003</sup>	Subcutaneous nadroparin + aspirin Aspirin 325 mg/d	20 of 20 20 of 20 Total: 40		Patients with acute ischemic stroke Presented within 24 h of symptom onset CT scan on all patients				Dosage: sc nadroparin 4,100 units/d combined with aspirin 325 mg/d Nadroparin stopped after 10 d of study Primary outcome considered complete recovery on BI

HD = high dose; LD = low dose; sc = subcutaneous. See Table 1 legend for expansion of other abbreviations. Good functional outcome refers to a score of 0-2 on the mRS unless otherwise noted.



**Table S14—[Section 2.5] Evidence Profile: Acute Anticoagulation Therapy in Patients With Acute Ischemic Stroke or TIA: Should Anticoagulants vs Antiplatelets Be Used in Patients With Acute Ischemic Stroke?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias of Evidence	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 90 d
11,989 (5 studies <sup>a</sup> ) 3-6 mo	No serious risk of bias	No serious inconsistency <sup>b</sup>	No serious indirectness	No serious imprecision	Undetected	High <sup>b</sup>	With Antiplatelets 1,140 of 5,740 (19.9)	RR, 1.08 (1.01-1.16)	Moderate <sup>c</sup> 120 deaths per 1,000 (from 1 more to 19 more)
12,235 (5 studies <sup>a</sup> ) 3-6 mo	No serious risk of bias	No serious inconsistency <sup>b</sup>	No serious indirectness	No serious imprecision	Undetected	High <sup>b</sup>	With Anticoagulants 2,335 of 5,861 (39.8)	RR, 0.98 (0.95-1.01)	Moderate <sup>d,e</sup> 350 good outcomes per 1,000 (from 18 fewer to 3 more)
11,715 (4 studies <sup>a</sup> ) 3-6 mo	No serious risk of bias	No serious inconsistency <sup>b</sup>	No serious indirectness	No serious imprecision	Undetected	High <sup>b</sup>	With Anticoagulants 225 of 5,609 (4)	RR, 1.20 (1-1.45)	Moderate <sup>g</sup> 30 strokes per 1,000 (from 0 more to 14 more)

(Continued)

**Table S14—Continued**

No. of Participants (Studies)	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Relative Effect (95% CI)	Risk With Antiplatelets	Anticipated Absolute Effects, Time Frame 90 d
12,076 (5 studies <sup>b</sup> ) 10-180 d	No serious risk of bias	No serious inconsistency <sup>d</sup>	No serious indirectness	No serious imprecision	Undetected	High <sup>a</sup>	40 of 5,782 (0.69)	77 of 6,294 (1.2)	RR, 1.74 (1.16-2.61) <sup>e</sup>	10 bleeding events per 1,000	Moderate <sup>g</sup> 7 more bleeding events per 1,000 (from 2 more to 16 more)

Bibliography: Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. *Cochrane Database of Systematic Reviews*. 2008;(4):CD000024. See Table S1, S11, and S12 legends for expansion of abbreviations.

<sup>a</sup>IST (1997), RAPID (2005), TAIIST (2001), HAEIST (2000), FISS-tris (2007).

<sup>b</sup> $I^2 = 0\%$ .

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

<sup>d</sup>Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of tPA trials (NINDS [1995], ECASS, ATLANTIS, and EPITHEAT).

<sup>e</sup>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).

<sup>f</sup>IST (1997), RAPID (2005), HAEIST (2000), TAIIST (2001).

<sup>g</sup>Baseline risk derived from IST.

<sup>h</sup>IST (1997), Pince (1981), TAIIST (2001), HAEIST (2000), FISS-tris (2007).

<sup>i</sup> $I^2 = 11\%$ .

<sup>j</sup>RR based on all major extracranial bleeding events.

**Table S15—Trials of VTE Prophylaxis in Acute Stroke: Clinical Description and Results**

Study/Year	Population	Interventions	No. of Patients Analyzed	Follow-up	Outcome				Comments
					DVT	PE	Mortality	Other	
McCarthy <sup>29</sup> /1977	Acute ischemic stroke	UFH 5,000 International Units tid sc	Total: 32 Tx: 16 Cx: 16	1 mo	Scintigraphy: Tx: 2 of 16 Cx: 12 of 16	NR		NR	
Duke <sup>30</sup> /1980	Acute ischemic stroke	UFH 5,000 International Units tid sc	Total: 65 Tx: 35 Cx: 30	1 y	Scintigraphy: Tx: 0 of 35 Cx: 3 of 30	NR		NR	
McCarthy <sup>31</sup> /1986	Acute ischemic stroke	UFH 5,000 International Units tid sc	Total: 305 Tx: 144 Cx: 161	3 mo	Scintigraphy: Tx: 32 of 144 Cx: 117 of 161	NR		NR	
Turpie <sup>32</sup> /1987	Acute ischemic stroke	Danaparoid 750 International Units bid sc	Total: 75 Tx: 50 Cx: 25	3 mo	Scintigraphy: Tx: 2 of 50 Cx: 7 of 25	Tx: 0 of 50 Cx: 2 of 25		sICH: Tx: 1 of 50 Cx: 0 of 25	
Cazzato <sup>33</sup> /1989	Acute ischemic stroke	Mesoglycan 50 mg tid IM (5 d) then 144 mg od po	Total: 57 Tx: 28 Cx: 29	1 mo	NR	Tx: 1 of 28 Cx: 0 of 29		sICH: Tx: 0 of 28 Cx: 0 of 29	
Prins <sup>34</sup> /1989	Acute ischemic stroke	Dalteparin 2,500 International Units bid sc	Total: 60 Tx: 30 Cx: 30	2 wk	Scintigraphy: Tx: 6 of 30 Cx: 15 of 30	Tx: 1 of 30 Cx: 2 of 30		sICH: Tx: 1 of 30 Cx: 0 of 30	
Sandset <sup>35</sup> /1990	Acute ischemic stroke	Dalteparin 3,000-5,500 International Units od sc	Total: 103 Tx: 50 Cx: 53	1 mo	Venography: Tx: 15 of 42 Cx: 17 of 50	Tx: 2 of 42 Cx: 2 of 50		sICH: Tx: 2 of 50 Cx: 1 of 53	
FISS <sup>36</sup> /1995	Acute ischemic stroke	Nadroparin 4,100 International Units od sc	Total: 154 Tx: 101 Cx: 53	6 mo	Sympt DVT: Tx: 0 of 101 Cx: 1 of 53	Tx: 0 of 101 Cx: 1 of 53		sICH: Tx: 0 of 101 Cx: 1 of 53	
FISS-bis <sup>36</sup> /1998	Acute ischemic stroke	Nadroparin 86 International Units/kg od or tid sc	Total: 397 Tx: 272 Cx: 25	6 mo	NR	Tx: 4 of 272 Cx: 7 of 125		sICH: Tx: 10 of 272 Cx: 4 of 125	
IST <sup>39</sup> /1997	Acute ischemic stroke	UFH 5,000 International Units bid sc	Total: 9,719 Tx: 4,860 Cx: 4,859	6 mo	NR	Tx: 33 of 4,856 Cx: 41 of 4,859		sICH: Tx: 35 of 4,856 Cx: 21 of 4,859	

(Continued)

**Table S15—Continued**

Study/Year	Population	Interventions	No. of Patients Analyzed	Follow-up	Outcome				Comments
					DVT	PE	Mortality	Other	
Pambianco <sup>37</sup> /1995	Acute ischemic stroke	UFH 5,000 International Units tid sc	Total: 131 Tx: 64 Cx: 67	1 mo	Leg ultrasound: Tx: 3 of 64 Cx: 3 of 67	Tx: 2 of 64 Cx: 1 of 67	sICH: Tx: 0 of 64 Cx: 0 of 67		
Trials comparing LMWH to UFH in ischemic stroke									
Hillbom <sup>38</sup> /2002	Acute ischemic stroke necessitating bedrest	LMWH: enoxaparin 40 mg od sc UFH: 5,000 International Units tid sc	Total: 212  LMWH: 106 UFH: 106	3 mo	Phlebography at day 10: LMWH: 17 of 106 UFH: 26 of 106	PE: LMH: 2 of 106 UFH: 4 of 106	All cause: sICH: LMH: 1 of 106 UFH: 0 of 106		
Diener <sup>39</sup> /2006 PROTECT	Acute ischemic stroke with at least mild leg paresis	LMWH: certoparin 3,000 International Units UFH: 5,000 International Units tid sc	Total: 545  LMWH: 272 UFH: 273	14 d	Ultrasound proximal DVT: LMWH: 18 of 272 UFH: 23 of 273	PE: LMWH: 0 of 272 UFH: 0 of 273	All cause: sICH: LMWH: 7 of 272 UFH: 3 of 273		1 death related to VTE in UFH group
Sherman <sup>40</sup> /2006 PREVAIL	Acute ischemic stroke and unable to walk unassisted	LMWH: enoxaparin 40 mg od sc UFH: 5,000 International Units bid sc	Total: 1,762  LMWH: 884 UFH: 878	14 d	Leg ultrasound: LMWH: 30 of 666 UFH: 64 of 669	PE: LMWH: 1 of 666 UFH: 6 of 669	All cause: sICH: LMWH: 48 of 877 UFH: 45 of 872		Safety population = 1,749; Efficacy population = 1,335 Treatment started within 48 h of stroke onset Only proximal DVTs reported in this table

(Continued)

**Table S15—Continued**

Study/Year	Population	Interventions	No. of Patients Analyzed	Follow-up	Outcome				
					DVT	PE	Mortality	Other	Comments
Trials using heparin in hemorrhagic stroke									
Boeer <sup>†1</sup> /1991	Primary ICH	Heparin 5,000 International Units tid sc: Early = start day 2 Late = start day 4 Cx = start day 10	Total: 68  Early: 22  Late: 23  Cx: 23	10 d	Scintigraphy:  Early: 5 of 22 Late: 8 of 23 Cx: 10 of 23	Sympt PE:  Early: 0 of 22 Late: 1 of 23 Cx: 3 of 23	All cause:  Early: 2 of 22 Late: 5 of 23 Cx: 4 of 23	Rebleeding:  Early: 0 of 22 Late: 1 of 23 Cx: 3 of 23	All patients with rebleeding died Most DVTs (20 of 23) were already present at baseline scintigraphy
Orken <sup>‡2</sup> /2009	Primary ICH	Tx: enoxaparin 40 mg/d sc started > 48 h  Cx: GCS	Total: 75  Tx: 39  Cx: 36	7 d	Leg ultrasound:  Tx: 3 of 39 Cx: 1 of 36	Pulmonary CTA:  Tx: 1 of 39 Cx: 1 of 36	All cause:  Tx: 1 of 39 Cx: 3 of 36	Rebleeding:  Tx: 0 of 39 Cx: 0 of 36	All PEs were asymptomatic detected on screening CTA All DVTs were asymptomatic None of the deaths were due to hematoma enlargement (personal communication with Dr Orken)

(Continued)

**Table S15—Continued**

Study/Year	Population	Interventions	No. of Patients Analyzed	Follow-up	Outcome				Comments
					DVT	PE	Mortality	Other	
Dickmann <sup>49</sup> /1988	Primary ICH	Heparin 5,000 International Units tid sc Tx: start day 4	Total: 46  Tx: 23	10 d	Scintigraphy: Tx: 8 of 23	Scintigraphy: Tx: 5 of 23	All cause: Tx: 5 of 23	Rebleeding: Tx: 1 of 23	All patients with rebleeding died Most DVTs (15 of 18) already present on day 2 scintigraphy No data on symptomatic VTEs
		Cx: start day 10	Cx: 23		Cx: 10 of 23	Cx: 9 of 23	Cx: 4 of 23	Cx: 3 of 23	
Trials using mechanical devices in ischemic or hemorrhagic stroke									
Muir <sup>44</sup> /2000	Acute stroke with leg weakness of $\geq 1$ on the NIHSS	Tx: GCS  Cx: no GCS	Total: 97  Tx: 65 Cx: 32	7 d	Leg ultrasound: Tx: 3 of 65 Cx: 2 of 32	Any PE: Tx: 0 of 65 Cx: 0 of 32	All cause: Tx: 9 of 65 Cx: 4 of 32		7 patients in stocking group withdrew, 3 because they were intolerant 1 of the 5 proximal DVTs was symptomatic, unknown which group
CLOTS <sup>45</sup> /2009	Acute stroke with restricted mobility	Tx: GCS  Cx: no GCS	Total: 2,518  Tx: 1,256 Cx: 1,262	30 d	Sympt DVT: Tx: 55 of 1,256 Cx: 61 of 1,262	Sympt PE: Tx: 12 of 1,256 Cx: 20 of 1,262	All cause: Tx: 122 of 1,256 Cx: 110 of 1,262	Skin complications: Tx: 64 of 1,256 Cx: 16 of 1,262	Restricted mobility defined as inability to walk independently to the toilet PE was confirmed in all cases on imaging or autopsy (Continued)

Table S15—Continued

Study/Year	Population	Interventions	No. of Patients Analyzed	Follow-up	Outcome				Comments
					DVT	PE	Mortality	Other	
Lacut <sup>46</sup> /2005	ICH	Tx: GCS + IPC Cx: GCS	Total: 151 Tx: 64	10 d	Symp DVT: Tx: 0 of 64 Cx: 0 of 69	Any PE: Tx: 0 of 74 Cx: 0 of 77	All cause: Tx: 6 of 74 Cx: 8 of 77		126 of 151 patients had restricted mobility; 63 in each group (personal communication with Dr Lacut) Prophylactic heparin not allowed (personal communication) 3 asymptomatic DVTs in control group
Prasad <sup>47</sup> /1982	Any stroke with leg weakness graded 2 of 6 or worse	Tx: IPC Cx: no IPC	Total: 26 Tx: 13 Cx: 13	7 d	Not reported	Not reported	All cause: Tx: 2 of 13 Cx: 0 of 13		1 symptomatic DVT. Not reported in which group

Cx = control; CTA = CT angiogram; GCS = graduated compression stockings; IPC = intermittent pneumatic compression; od = once daily; PE = pulmonary embolism; Sympt = symptomatic; Tx = treatment.

**Table S16—[Section 3.1.1] Evidence Profile: Should Prophylactic-Dose Heparin (UFH or LMWH) vs No Prophylactic-Dose Heparin Be Used in Patients With Acute Ischemic Stroke and Restricted Mobility?**

No. of Participants (Studies) Follow-up	Quality Assessment										Summary of Findings		
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Prophylactic-Dose Heparin	With Prophylactic-Dose Heparin (UFH or LMWH)	Relative Effect (95% CI)	Risk With No Prophylactic-Dose Heparin	Risk Difference With Prophylactic-Dose Heparin (UFH or LMWH) (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
15,594 (8 studies) <sup>b</sup> 2-26 wk <sup>c</sup>	No serious risk of bias <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>e</sup>	Undetected	Moderate <sup>d,e</sup> due to imprecision	993 of 10,222 (9.7) <sup>f</sup>	493 of 5,372 (9.2) <sup>g</sup>	RR, 0.86 (0.59-1.22)	87 deaths per 1,000 <sup>h</sup>	Moderate <sup>h</sup>	12 fewer deaths per 1,000 (from 36 fewer to 19 more) <sup>i</sup>	
10,681 (8 studies) <sup>b</sup> 14-90 d	No serious risk of bias <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>e,k</sup>	Undetected	Moderate <sup>d,k</sup> due to imprecision	56 of 5,238 (1.1) <sup>j</sup>	43 of 5,443 (0.79) <sup>j</sup>	RR, 0.7 (0.47-1.03)	16 PEs per 1,000 <sup>h</sup>	Moderate <sup>h</sup>	5 fewer PEs (from 8 fewer to 0 more)	
914 (8 studies) <sup>b</sup> 2-52 wk	No serious risk of bias <sup>d</sup>	Serious <sup>e</sup>	No serious indirectness	No serious imprecision <sup>k</sup>	Undetected	Moderate <sup>d,k,n</sup> due to inconsistency	175 of 432 (40.5)	60 of 482 (12.4)	RR, 0.31 (0.21-0.42)	48 DVTs per 1000	Moderate <sup>h</sup>	33 fewer DVTs (from 28 fewer to 38 fewer)	
10,696 (8 studies) <sup>b</sup> 14-90 d <sup>c</sup>	No serious risk of bias <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>e,k</sup>	Undetected	Moderate <sup>d,k,o</sup> due to imprecision	27 of 5,241 (0.52)	49 of 5,455 (0.9)	RR, 1.52 (0.96-2.39)	5 bleeding events per 1,000	Moderate <sup>h</sup>	3 more bleeding events (from 0 fewer to 7 more) <sup>i</sup>	

(Continued)



Table S16—Continued

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings						
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Prophylactic-Dose Heparin	With Prophylactic-Dose Heparin (UFH or LMWH)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	Risk Difference With Prophylactic-Dose Heparin (UFH or LMWH) (95% CI)
10,351 (8 studies) <sup>a</sup> 2-52 wk <sup>c</sup>	No serious risk of bias <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>k</sup> imprecision	Undetected	Moderate <sup>l,m</sup> due to imprecision	19 of 5,135 (0.37)	32 of 5,216 (0.61) <sup>n</sup>	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)

Symptomatic extracranial hemorrhage (critical outcome; assessed with: not clearly reported)

Bibliography: Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep-vein thrombosis and pulmonary embolism in patients with acute ischemic stroke? *Thromb Res.* 2007;119(3):265-274. 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. LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; UFH = unfractionated heparin. See Table S1, S2, S15 legends for expansion of other abbreviations.

<sup>a</sup>We have rated the importance of the mortality outcome as important (and not critical) because of random error (ie, the intervention-related effect on mortality is assumed to be negligible in comparison with other causes).

<sup>b</sup>Turpie (1987), Sandset (1990), McCarthy (1986), McCarthy (1977), Pambianco (1995), Prins (1989), FISS (1995), and IST (1997).

<sup>c</sup>Not clearly reported in all studies, presumed to be during hospital stay following acute ischemic stroke.

<sup>d</sup>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.

<sup>e</sup>95% CI includes both no effect and appreciable benefit or appreciable harm.

<sup>f</sup>% Due to bleeding: 27 of 4,860 (56%) heparin; 21 of 10,175 (21%) placebo.

<sup>g</sup>IST (1997) data: since "there was no interaction between aspirin and heparin in the main outcomes," 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).

<sup>h</sup>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.

<sup>i</sup>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.

<sup>j</sup>Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), IST (1997), and FISS-bis (1998).

<sup>k</sup>Fewer than 300 events occurred, but quality was not downgraded because of this.

<sup>l</sup>Based on meta-analysis by Kamphuisen (2006).

<sup>m</sup>McCarthy (1977), Duke (1980), McCarthy (1986), Turpie (1987), Prins (1989), Sandset (1990), FISS (1995), and Pambianco (1995).

<sup>n</sup>Statistical heterogeneity:  $P = .003$ ;  $I^2 = 74.3\%$ .

<sup>o</sup>The international stroke study, IST (1997), contributed up to 90% of the patients in the meta-analysis. IST did not require a CT scan for patient enrollment, 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.

<sup>p</sup>Duke (1980), Turpie (1987), Cazzato (1989), Prins (1989), Sandset (1990), FISS (1995), Pambianco (1995), and IST (1997).

<sup>q</sup>% Due to GI bleeding: 0 of 152 (0%) heparin; 0 of 157 placebo (0%).

**Table S17—[Sections 3.1.2, 3.2.2] Evidence Profile: Should Prophylactic-Dose UFH vs Prophylactic-Dose LMWH Be Used in Patients With Acute Ischemic Stroke and Restricted Mobility?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 30 d	
							With Prophylactic-Dose LMWH	With Prophylactic-Dose UFH	Relative Effect (95% CI)	Risk With Prophylactic-Dose LMWH
2,506 (3 studies <sup>b</sup> ) 14-90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Moderate <sup>c</sup> due to imprecision	139 of 1,251 (11.1)	135 of 1,255 (10.8)	RR, 0.96 (0.72-1.2) <sup>d</sup>	Moderate <sup>e</sup> 3 fewer deaths per 1,000 (from 24 fewer to 17 more)
2,092 (3 studies <sup>b</sup> ) 14-90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	Undetected	Moderate <sup>f</sup> due to imprecision	10 of 1,048 (0.95)	3 of 1,044 (0.29)	RR, 0.26 (0.07-0.95)	Moderate <sup>f</sup> 11 PEs per 1,000 8 fewer PEs per 1,000 (from 1 fewer to 10 fewer)
2,092 (3 studies <sup>b</sup> ) 14-90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	Undetected	Moderate <sup>f</sup> due to imprecision	113 of 1,048 (10.8) <sup>h</sup>	65 of 1,044 (6.2) <sup>h</sup>	RR, 0.56 (0.4-0.77)	Moderate <sup>g</sup> 15 DVTs per 1,000 <sup>h</sup> 7 fewer DVTs per 1,000 (from 3 fewer to 9 fewer)

(Continued)

**Table S17—Continued**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence		Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 30 d
						With Prophylactic-Dose LMWH	With Prophylactic-Dose UFH	Relative Effect (95% CI)	Risk With Prophylactic-Dose LMWH	
1,749 (3 studies) <sup>b</sup> 14-90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Moderate <sup>d</sup> due to imprecision	4 of 877 (0.46) <sup>b</sup>	6 of 872 (0.69)	RR, 0.7 (0.26-1.83)	Moderate <sup>e</sup> 2 fewer bleeding events per 1,000 (from 5 fewer to 6 more)
2,506 (3 studies) <sup>b</sup> 14-90 d	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Moderate <sup>d</sup> due to imprecision	2 of 1,251 (0.16)	6 of 1,255 (0.48)	RR, 2.12 (0.09-43.75) <sup>h</sup>	Moderate <sup>k</sup> 6 more bleeding events per 1,000 (from 5 fewer to 214 more)

**Bibliography:** Shorr AF, Jackson WL, Sherner JH, Moores LK. Differences between low-molecular-weight and unfractionated heparin for venous thromboembolism prevention following ischemic stroke: a metaanalysis. *Chest*. 2008;133(1):149-155. 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. See Table S1, S15, and S16 legends for expansion of abbreviations.

<sup>a</sup>We have rated the importance of the mortality outcome as important (and not critical) because of random error (ie, the intervention-related effect on mortality is assumed to be negligible in comparison with other causes).

<sup>b</sup>Hillbom (2002), PROTECT (2006), and PREVAIL (2006).

<sup>c</sup>95% CI includes both no effect and appreciable benefit or appreciable harm.

<sup>d</sup>0.40% mortality due to bleeding in both groups (5 of 1,255 LMWH, 5 of 1,251 UFH).

<sup>e</sup>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.

<sup>f</sup>Fewer than 300 events occurred.

<sup>g</sup>Baseline risk calculated by multiplying baseline risk in CLOTS study times the RR with any heparin prophylaxis.

<sup>h</sup>Data for any proximal DVT.

<sup>i</sup>Based on PREVAIL study data.

<sup>j</sup>% Due to GI bleeding not reported.

<sup>k</sup>Based on data from heparin for VTE prevention profile.

**Table S18—[Sections 3.1.1, 3.2.1] Evidence Profile: Should IPC Stockings Be Used in Patients With Acute Stroke (Ischemic and Hemorrhagic) and Restricted Mobility?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings			Anticipated Absolute Effects, Time Frame 30 d		
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Study Event Rates (%)		Relative Effect (95% CI)		Risk With Control	Risk Difference With IPC Stockings (95% CI)
						Overall Quality of Evidence	With Control				
177 (2 studies <sup>b</sup> ) 7-10 d	No serious risk of bias <sup>c</sup>	No serious inconsistency <sup>d</sup>	No serious indirectness <sup>e</sup>	Serious <sup>f</sup>	Undetected	Moderate <sup>g-f</sup> due to imprecision	8 of 90 (8.9)	8 of 87 (9.2)	RR, 1.03 (0.33-3.23)	Moderate <sup>g</sup> 87 deaths per 1,000 (from 58 fewer to 194 more)	
2,255 (19 studies <sup>h</sup> ) 7-10 d	No serious risk of bias	No serious inconsistency	Serious <sup>i</sup>	No serious imprecision <sup>j</sup>	Undetected	Moderate <sup>g-h</sup> due to indirectness	268 of 1,147 (23.4)	112 of 1,108 (10.1)	RR, 0.43 (0.35-0.53) <sup>h,i</sup>	Moderate <sup>g</sup> 16 PEs per 1,000 (from 8 fewer to 10 fewer)	
2,255 (19 studies <sup>h</sup> ) 7-10 d	No serious risk of bias	No serious inconsistency	Serious <sup>i</sup>	No serious imprecision <sup>k</sup>	Undetected	Moderate <sup>g-h,k</sup> due to indirectness	268 of 1,147 (23.4)	112 of 1,108 (10.1)	RR, 0.43 (0.35-0.53) <sup>h,i</sup>	Moderate <sup>g</sup> 48 DVTs per 1,000 (from 23 fewer to 31 fewer)	

Bibliography: Roderick P, Ferris G, Wilson K, et al. Toward evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anesthesia as thromboprophylaxis. *Health Technol Assess*. 2005;9(49):iii-iv, ix-x, 1-78. See Table S1 and S15 legends for expansion of abbreviations.

<sup>a</sup>We have rated the importance of the mortality outcome as important (and not critical) because of random error (ie, the intervention-related effect on mortality is assumed to be negligible in comparison with other causes).

<sup>b</sup>Prasad (1982) and Lacut (2005).

<sup>c</sup>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.

<sup>d</sup> $P = 28\%$  ( $P = .24$ ).

<sup>e</sup>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 (MRC grade) in one or both limbs.

<sup>f</sup>CI interval includes both no effect and appreciable benefit or appreciable harm.

<sup>g</sup>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.

<sup>h</sup>RR for symptomatic DVT and RR for PE inferred from rates reported for proximal DVT in 19 studies of postsurgical patients.

<sup>i</sup>Lacut (2005) reported that no PE occurred during follow-up. Prasad (1982) did not report on this outcome.

<sup>j</sup>Based on meta-analysis in Roderick.

<sup>k</sup>Lacut (2005) reported that no symptomatic DVT occurred during follow-up. Prasad (1982) did not report on this outcome.

**Table S19—[Sections 3.1.3, 3.2.3] Evidence Profile: Should GCS vs No GCS Be Used in Patients With Acute Stroke and Restricted Mobility?**

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 30 d	
					With No GCS	With GCS			Risk With No GCS	Risk Difference With GCS (95% CI)
2,615 (2 studies) <sup>b</sup> 7-30 d <sup>c</sup>	No serious risk of bias <sup>d</sup>	No serious inconsistency <sup>e</sup>	No serious indirectness	Serious <sup>f</sup>	Undetected	Moderate <sup>g,h</sup> due to imprecision	114 of 1,294 (8.8) I3I of 1,321 (9.9)	RR, 1.11 (0.88-1.42)	87 deaths per 1,000	Moderate <sup>g</sup> 10 more deaths per 1,000 (from 10 fewer to 37 more)
2,518 (1 study) <sup>b</sup> 30 d	No serious risk of bias <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	Undetected	Moderate <sup>g,h</sup> due to imprecision	20 of 1,262 (1.6) I3 of 1,256 (1)	RR, 0.65 (0.33-1.31)	16 PEs per 1,000	Moderate <sup>g</sup> 6 fewer PEs per 1,000 (from 11 fewer to 5 more)
2,518 (1 study) <sup>b</sup> 30 d	No serious risk of bias <sup>d</sup>	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	Undetected	Moderate <sup>g,h</sup> due to imprecision	61 of 1,262 (4.8) I5 of 1,256 (4.4)	RR, 0.91 (0.63-1.29) <sup>i</sup>	48 DVTs per 1,000	Moderate <sup>g</sup> 4 fewer DVTs per 1,000 (from 18 fewer to 14 more)
2,518 (1 study) <sup>b</sup> 30 d	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision <sup>l</sup>	Undetected	Moderate <sup>g,h</sup> due to bias	16 of 1,262 (1.3) I6 of 1,256 (5.1)	RR, 4.02 (2.34-6.91)	13 complications per 1,000	Moderate <sup>g</sup> 39 more complications per 1,000 (from 17 more to 77 more)

**Bibliography:** CLOTS Trials Collaboration, Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomized controlled trial. *Lancet*. 2009;373(9679):1958-1965. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *QJM*. 2000;93(6):359-364. See Table S1 and S15 legends for expansion of abbreviations.

<sup>a</sup>We have rated the importance of the mortality outcome as important (and not critical) because of random error (ie, the intervention-related effect on mortality is assumed to be negligible in comparison with other causes). Also, mortality is unlikely to be increased by the intervention as PE and DVT both trended lower in intervention group.

<sup>b</sup>CLOTS trial I and Muir et al.

<sup>c</sup>Follow-up was 30 d in CLOTS and 7 ± 2 d in Muir et al.

<sup>d</sup>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.

<sup>e</sup> $I^2 = 0\%$ .

<sup>f</sup>CI includes both negligible effect and appreciable benefit or appreciable harm.

<sup>g</sup>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).

<sup>h</sup>CLOTS trial I.

<sup>i</sup>CLOTS, the primary study for this analysis found no effect on "Proximal DVT" (adjusted OR, 0.98; 95% CI, 0.76-1.27).

<sup>j</sup>skin breaks, ulcers, blisters, and skin necrosis.

<sup>k</sup>Assessment of outcomes was based on case-note review and was not blinded to treatment allocation.

<sup>l</sup>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.

**Table S20—[Section 3.2.1] Evidence Profile: Should Prophylactic Low-Dose Heparin (UFH or LMWH) vs No Prophylactic Low-Dose Heparin Be Used in Patients With Acute Hemorrhagic Stroke and Restricted Mobility?**

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence
114 (2 studies <sup>b</sup> ) 10 d	Serious <sup>e</sup>	No serious inconsistency	No serious indirectness	Serious <sup>d,e</sup>	Undetected	Overall mortality (important outcome) <sup>e</sup> Low <sup>e-c</sup> due to risk of bias, imprecision
					8 of 46 (17.4)	12 of 68 (17.6)
					RR, 1.05 (0.46-2.36)	RR, 1.05 (0.46-2.36)
					400 deaths per 1,000	400 deaths per 1,000
					20 more deaths (from 216 fewer to 544 more)	20 more deaths (from 216 fewer to 544 more)
						Moderate <sup>f</sup>
						Risk With No Prophylactic Low-Dose Heparin
						Risk Difference With Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
10,681 (8 studies <sup>c</sup> ) 30 d	No serious risk of bias	No serious inconsistency	No serious indirectness <sup>i</sup>	Serious <sup>d,e</sup>	Undetected	PE (fatal and nonfatal) (critical outcome) Moderate <sup>e,d,h</sup> due to imprecision
					56 of 5,238 (1.1)	43 of 5,443 (0.79)
					RR, 0.7 (0.47-1.03) <sup>g</sup>	RR, 0.7 (0.47-1.03) <sup>g</sup>
					16 PEs per 1,000	16 PEs per 1,000
					5 fewer PEs (from 8 fewer to 0 more)	5 fewer PEs (from 8 fewer to 0 more)
						Moderate <sup>i</sup>
						Risk With No Prophylactic Low-Dose Heparin
						Risk Difference With Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
914 (8 studies <sup>c</sup> ) 30 d	No serious risk of bias	Serious <sup>i</sup>	No serious indirectness <sup>h</sup>	No serious imprecision <sup>e</sup>	Undetected	Symptomatic DVT (critical outcome) Moderate <sup>e,h,j</sup> due to inconsistency
					175 of 432 (40.5)	60 of 482 (12.4)
					RR, 0.31 (0.21-0.42) <sup>g</sup>	RR, 0.31 (0.21-0.42) <sup>g</sup>
					48 DVTs per 1,000	33 fewer DVTs per 1,000
					28 fewer (from 28 fewer to 38 fewer)	28 fewer (from 28 fewer to 38 fewer)
						Moderate <sup>i</sup>
						(Continued)

Table S20—Continued

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Prophylactic Low-Dose Heparin	With Prophylactic Low-Dose Heparin (UFH or LMWH)	Anticipated Absolute Effects, Time Frame 30 d
	Follow-up	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Prophylactic Low-Dose Heparin	With Prophylactic Low-Dose Heparin (UFH or LMWH)	Risk Difference With Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
189 (3 studies) <sup>h</sup> 7-10 d <sup>i</sup>	Serious <sup>m</sup>	No serious inconsistency	No serious indirectness	Serious <sup>n,o</sup>	Undetected	Low <sup>p,q,r</sup> due to risk of bias, imprecision	6 of 82 (7.3)	2 of 107 (1.9)	RR, 0.24 (0.05-1.13) <sup>n</sup> Moderate <sup>o</sup> 10 rebleeding events per 1,000 8 fewer rebleeding events per 1,000 (from 9 fewer to 1 more)

**Bibliography:** Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. *Klin Wochenschr.* 1988;66(23):1182-1183. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral hemorrhage. *J Neurol Neurosurg Psychiatry.* 1991;54(5):466-467. Orken DN, Kenangil G, Ozkurt H, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. *Neurologist.* 2009;15(6):329-331. Wasay M, Khan S, Zaki KS, et al. A non-randomized study of safety and efficacy of heparin for DVT prophylaxis in intracerebral haemorrhage. *JAMA.* 2008;58:362-364. Kipluth IC, Staykov D, Kohrman M, et al. Early administration of low molecular weight heparin after spontaneous intracerebral hemorrhage. A safety analysis. *Cerebrovasc Dis.* 2009;27:146-150. See Table S1, S2, S15, and S16 legends for expansion of abbreviations.

<sup>a</sup>We have rated the importance of the mortality outcome as important (and not critical) because of random error (ie, the intervention-related effect on mortality is assumed to be negligible in comparison with other causes).

<sup>b</sup>We excluded Orken et al from this analysis given the control group received compression stockings, which is a confounding factor. Included studies: Boeer et al and Dickman et al.

<sup>c</sup>Allocation: unclear whether concealed in both studies (Boeer et al, Dickmann et al). Unclear whether ITT analysis in both studies. Neither of the two studies stopped early for benefit. None of the studies reported blinding patients.

<sup>d</sup>95% CI includes both no effect and appreciable benefit or appreciable harm.

<sup>e</sup>Fewer than 300 events occurred, but quality was not rated down for this.

<sup>f</sup>Baseline risk of mortality is derived from: *Lancet Neurol.* 2010;9(2):167-176.

<sup>g</sup>Indirect data from studies of the effects of heparin on DVT and PE in patients with ischemic stroke (see corresponding Evidence Profile).

<sup>h</sup>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.

<sup>i</sup>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 GCS might cause skin damage, those with subarachnoid hemorrhage.

<sup>j</sup>Statistical heterogeneity:  $P = .003$ ;  $I^2 = 74.3\%$ .

<sup>k</sup>Included studies: Orken et al (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 et al (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 et al (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).

<sup>l</sup>We considered the time frame during which patients are exposed to heparin and consequently at risk for rebleeding.

<sup>m</sup>Allocation: not concealed in one study (Orken et al) and unclear whether concealed in two studies (Boeer et al, Dickmann et al). Unclear whether ITT analysis in the each of the three studies. None of the three studies stopped early for benefit. In Orken et al, 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 (personal communication with the author). None of the studies reported blinding patients. Only one study (Orken et al) reported blinding assessors of bleeding outcome.

<sup>n</sup>Indirect evidence from an observational study (Wasay *JAMA.* 2008;58:362); very low incidence in rebleeding with no difference between heparin and no heparin: 1 of 200 vs 0 of 258.

<sup>o</sup>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 (Kleindienst. *Acta Neurochir (Wien).* 2003;145:1085-1091. 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 (Kipluth. *Cerebrovasc Dis.* 2009;27:146-150). We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these two studies.

**Table S21—[Section 3.2.1] Evidence Profile: Should Early (Day 2-4) Prophylactic Low-Dose Heparin (UFH or LMWH) vs Late Prophylactic Low-Dose Heparin (UFH or LMWH) Be Used for Patients With Acute Hemorrhagic Stroke and Restricted Mobility?**

		Quality Assessment										Summary of Findings	
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Late Prophylactic Low-Dose Heparin (UFH or LMWH)	With Early Prophylactic Low-Dose Heparin (UFH or LMWH)	Study Event Rates (%)	Anticipated Absolute Effects, Time Frame 30 d		
No. of Participants (Studies)	Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence <td>With Late Prophylactic Low-Dose Heparin (UFH or LMWH)</td> <td>With Early Prophylactic Low-Dose Heparin (UFH or LMWH)</td> <td>Study Event Rates (%)</td> <td>Anticipated Absolute Effects, Time Frame 30 d</td>	With Late Prophylactic Low-Dose Heparin (UFH or LMWH)	With Early Prophylactic Low-Dose Heparin (UFH or LMWH)	Study Event Rates (%)	Anticipated Absolute Effects, Time Frame 30 d		
45 (1 study) <sup>a</sup>	10 d	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Overall mortality (critical outcome) Low <sup>b,c</sup> due to risk of bias, imprecision	5 of 23 (21.7) <sup>a</sup>	2 of 22 (9.1)	RR, 0.42 (0.1-1.69)	Moderate <sup>e</sup> 400 deaths per 1,000 (from 360 fewer to 276 more)		
45 (1 study) <sup>a</sup>	10 d	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	Undetected	PE (critical outcome) Low <sup>b,c</sup> due to risk of bias, imprecision	1 of 23 (4.3) <sup>d</sup>	0 of 22 (0)	RR, 0.35 (0.01-8.11)	Moderate <sup>f</sup> 11 PEs per 1,000 (from 7 fewer to 11 more)		
45 (1 study) <sup>a</sup>	10 d	Serious <sup>b</sup>	No serious inconsistency	Serious <sup>c</sup>	Serious <sup>c</sup>	Undetected	Symptomatic DVT (critical outcome) Low <sup>b,c,g</sup> due to risk of bias, indirectness, imprecision	8 of 23 (34.8)	5 of 22 (22.7) <sup>h</sup>	RR, 0.65 (0.25-1.69)	Moderate <sup>f</sup> 15 DVTs per 1,000 (from 5 fewer to 10 more)		

(Continued)



**Table S21—Continued**

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings		Anticipated Absolute Effects, Time Frame 30 d		
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence		Study Event Rates (%)	Relative Effect (95% CI)
45 (1 study) <sup>a</sup> 10 d <sup>b</sup>	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Very serious <sup>c</sup>	Undetected	Rebleeding (critical outcome) Low <sup>b,c</sup> due to risk of bias, imprecision	With Late Prophylactic Low-Dose Heparin (UFH or LMWH) With Early Prophylactic Low-Dose Heparin (UFH or LMWH)	RR, 0.35 (0.01-8.11)	Risk With Late Prophylactic Low-Dose Heparin (UFH or LMWH) Risk Difference With Early (Day 2-4) Prophylactic Low-Dose Heparin (UFH or LMWH) (95% CI)
									10 rebleeding events per 1,000 7 fewer rebleeding events per 1,000 (from 10 fewer to 71 more)

**Bibliography:** Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral hemorrhage. *J Neurol Neurosurg Psychiatry*. 1991;54(5):466-467. Kleindienst A, Harvey HB, Mater E, et al. Early antithrombotic prophylaxis with low molecular weight heparin in neurosurgery. *Acta Neurochir (Wien)*. 2003;145:1085-1091. Kiphuth IC, Staykov D, Kohrmann M, et al. Early administration of low molecular weight heparin after spontaneous intracerebral hemorrhage. A safety analysis. *Cerebrovasc Dis*. 2009;27:146-150. See Table S1, S2, S15, and S16 legends for expansion of abbreviations.

<sup>a</sup>Boeer et al.  
<sup>b</sup>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.  
<sup>c</sup>CI includes both negligible effect and appreciable benefit or appreciable harm.  
<sup>d</sup>The single reported symptomatic PE event was fatal; has been included in both mortality and PE outcome in this evidence profile.  
<sup>e</sup>Baseline risk of mortality is derived from van Asch CJ, Luitse MJ, Rinkel CJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167-176.  
<sup>f</sup>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 GCS was might cause skin damage; those with subarachnoid hemorrhage.  
<sup>g</sup>DVT measured through routine perfusion scintigraphy by day 10. Not reported whether symptomatic and whether proximal vs distal.  
<sup>h</sup>In the early group 5 of 5 DVTs were already detected on day 2, whereas in the late group 7 out of 8 were already detected on day 2.  
<sup>i</sup>We considered the time frame during which patients are exposed to heparin and consequently at risk for rebleeding.  
<sup>j</sup>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 (Kleindienst et al). 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 (Kiphuth et al). We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these two studies.

**Table S22—Randomized Trials of Antiplatelet Agents for the Secondary Prevention of Noncardioembolic Stroke:<sup>a</sup> Clinical Description and Results**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Major Bleeding, <sup>b</sup> RR (95% CI)	Total Mortality, RR (95% CI)	Composite Primary Outcome, <sup>c</sup> RR (95% CI)	Comments
The Dutch TIA Trial Study Group <sup>49</sup> /1991	Aspirin 283 mg  Aspirin 30 mg	Aspirin 283 mg: 1,576 of 1,576  Aspirin 30 mg: 1,555 of 1,555	52 mo	Aspirin 283 mg: 53 of 1,576 (3.4%)  Aspirin 30 mg: 40 of 1,555 (2.6%)  RR: 1.31 (0.87-1.90)	Aspirin 283 mg: 391 of 1,576 (24.8%)  Aspirin 30 mg: 388 of 1,555 (25.0%)  RR: 0.99 (0.88-1.12)	Aspirin 283 mg: 240 of 1,576 (15.2%)  Aspirin 30 mg: 228 of 1,555 (14.7%)  RR: 1.04 (0.88-1.23)	Nonfatal episodes of bleeding were considered major if a hospital visit and treatment were necessary.
UK-TIA Study Group <sup>50</sup> /1991	Aspirin 1,200 mg/d  Aspirin 300 mg/d	Aspirin 1,200 mg: 815 of 815  Aspirin 300 mg: 806 of 806	7 y		Aspirin 1,200 mg: 112 of 815 (13.7%) 815 (19.9%)  Aspirin 300 mg: 109 of 806 (13.5%) 806 (20.1%)  RR: 1.02 (0.80-1.30)	Aspirin 1,200 mg: 162 of 815 (19.9%)  Aspirin 300 mg: 162 of 806 (20.1%)  RR: 0.99 (0.81-1.20)	
Diener, MATCH <sup>50</sup> /2004	Clopidogrel 75 mg/d + aspirin 75 mg/d  Clopidogrel 75 mg/d	C-A: 3,797 of 3,797  Clopidogrel: 3,802 of 3,802	18 mo	C-A: 73 of 3,759 (1.9%)  Clopidogrel: 22 of 3,781 (0.6%)  RR: 3.34 (2.08-5.36)	C-A: 01 of 3,797 (5.3%)  Clopidogrel: 201 of 3,802 (5.3%)  RR: 1.00 (0.83-1.21)	C-A: 596 of 3,797 (15.7%)  Clopidogrel: 636 of 3,802 (16.7%)  RR: 0.94 (0.85-1.04)	
Bhatt <sup>51</sup> /2006	C-A: clopidogrel 75 mg/d + aspirin 75-162 mg/d  Aspirin 75-162 mg/d	C-A: 7,802 of 7,802  Aspirin: 7,801 of 7,801	18-42 mo	C-A: 130 of 7,802 (1.7%) Aspirin: 104 of 7,801 (1.3%)  RR: 1.25 (0.97-1.61)	C-A: 371 of 7,802 (4.8%) Aspirin: 374 of 7,801 (4.8%)  RR: 0.99 (0.86-1.14)	C-A: 534 of 7,802 (6.8%) Aspirin: 573 of 7,801 (7.3%)  RR: 0.93 (0.83-1.05)	Major bleeding: fatal bleeding and primary intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, ionotropic support, or surgical intervention. (GUSTO IV definition)

(Continued)

Table S22—Continued

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Major Bleeding, <sup>b</sup> RR (95% CI)	Total Mortality, RR (95% CI)	Composite Primary Outcome, <sup>c</sup> RR (95%CI)	Comments
Diener, ESPS2 <sup>53</sup> /1996	D-A: dipyridamole 400 mg/d + Aspirin 50 mg/d Dipyridamole 400 mg/d	D-A: 1,650 of 1,650  Dipyridamole: 1,654 of 1,654	2 y	Severe or fatal: D-A: 27 of 1,650 (1.6%)  Dipyridamole: 6 of 1,654 (0.36%) RR: 4.51 (1.87-10.90)	D-A: 185 of 1,650 (11.2%)  Dipyridamole: 188 of 164 (11.4%) RR: 0.99 (0.81-1.19)	D-A: 206 of 1,650 (12.5%)  Dipyridamole: 271 of 1,654 (16.4%) RR: 0.76 (0.64-0.90)	ESPS2 Major bleeding: significantly disabling with persistent sequel; intraocular bleed lead to significant loss of vision; or transfusion of $\leq$ 3 units of RBC or equivalent whole blood
Diener, ESPS2 <sup>53</sup> /1996	Dipyridamole 400 mg/d  Aspirin 50 mg/d	Dipyridamole: 1,654 of 1,654  Aspirin: 1,649 of 1,649	2 y	Severe or fatal: dipyridamole: 6 of 1,654 (0.36%) Aspirin: 20 of 1,649 (1.2%) RR: 0.30 (0.12-0.74)	Dipyridamole: 188 of 1,654 (11.4%)  Aspirin: 182 of 1,649 (11.0%) RR: 1.03 (0.85-1.25)	Dipyridamole: 271 of 1,654 (16.4%)  Aspirin: 266 of 1,649 (16.1%) RR: 1.02 (0.87-1.19)	ESPS2
American Canadian Cooperative Study Group <sup>54</sup> /1985	Persantine 75 mg + aspirin 325 mg/d Aspirin 325 mg/d	P-A: persantine + aspirin: 448 of 448  Aspirin: 442 of 442	5 y	NR	P-A: 46 of 448 (10.3%)  Aspirin: 38 of 442 (8.6%) RR: 1.19 (0.79-1.80)	P-A: 79 of 448 (17.6%)  Aspirin: 85 of 442 (19.2%) RR: 0.92 (0.70, 1.21)	17 Patients had stroke, but the article does not classify to which group they belong
Bousser <sup>55</sup> /1983	D-A: dipyridamole 225 mg/d + Aspirin 990 mg/d Aspirin 990 mg/d	D-A: 202 of 202  Aspirin: 198 of 198	3 y	NR	D-A: 8 of 202 (3.9%)  Aspirin: 10 of 198 (5.1%) RR: 0.78 (0.32-1.95)	D-A: 30 of 202 (14.8%)  Aspirin: 31 of 198 (19.2%) RR: 0.95 (0.00-1.51)	ESPS2
Diener, ESPS2 <sup>53</sup> /1996	D-A: dipyridamole 400 mg/d + aspirin 50 mg/d A: Aspirin 50 mg/d	D-A: 1,650 of 1,650  Aspirin: 1,649 of 1,649	2 y	Severe or fatal D-A: 27 of 1,650 (1.6%)  Aspirin: 20 of 1,649 (1.2%) RR: 1.35 (0.76-2.40)	D-A: 185 of 1,650 (11.2%)  Aspirin: 182 of 1,649 (11.0%) RR: 1.02 (0.84-1.23)	D-A: 246 of 1,650 (14.9%)  Aspirin: 314 of 1,649 (19.0%) RR: 0.78 (0.67-0.91)	ESPS2

(Continued)

**Table S22—Continued**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Major Bleeding, <sup>b</sup> RR (95% CI)	Total Mortality, RR (95% CI)	Composite Primary Outcome, <sup>c</sup> RR (95%CI)	Comments
The ESPRIT Study Group <sup>57/2006</sup>	D-A: dipyridamole 400 mg/d + aspirin 30-325 mg/d Aspirin 30-325 mg/d	D-A: 1,363 of 1,363 Aspirin: 1,376 of 1,376	5 y	D-A: 35 of 1,363 (2.6%) Aspirin: 53 of 1,376 (3.9%) RR: 0.67 (0.44-1.01)	D-A: 93 of 1,363 (6.8%) Aspirin: 107 of 1,376 (7.8%) RR: 0.88 (0.67-1.15)	D-A: 149 of 1,363 (10.9%) Aspirin: 192 of 1,376 (13.9%) RR: 0.78 (0.64-0.96)	Major bleeding: all intracranial bleeding, or any fatal bleeding, or hospital admission
Hass <sup>58/1989</sup>	Ticlopidine 500 mg/d Aspirin 1,300 mg/d	Ticlopidine: 1,529 of 1,529 Aspirin: 1,540 of 1,540	6 y	Ticlopidine: 0 of 1,529 (0%) Aspirin: 0 of 1,540 (0%) RR: 0.90 (0.74-1.09)	Ticlopidine: 175 of 1,529 (11.4%) Aspirin: 196 of 1,540 (12.7%) RR: 0.88 (0.74-1.09)	Ticlopidine: 306 of 1,529 (20.0%) Aspirin: 349 of 1,540 (22.7%) RR: 0.88 (0.77-1.01)	
Gorelick <sup>59/2003</sup>	Ticlopidine 500 mg/d Aspirin 650 mg/d	Ticlopidine: 902 of 902 Aspirin: 907 of 907	2 y	Ticlopidine: 10 of 902 (1.1%) Aspirin: 19 of 907 (2.1%) RR: 0.53 (0.25-1.13)	Ticlopidine: 45 of 902 (5.0%) Aspirin: 40 of 907 (4.4%) RR: 1.13 (0.75-1.71)	Ticlopidine: 133 of 902 (14.7%) Aspirin: 112 of 907 (12.3%) RR: 1.19 (0.95-1.51)	
Gent <sup>60/1989</sup>	Ticlopidine 500 mg/d Heparin	Ticlopidine: 525 of 525 Heparin: 528 of 528	3 y	Ticlopidine: 2 of 525 (0.4%) Heparin: 1 of 528 (0.2%) RR: 2.01 (0.18-22.12)	Ticlopidine: 64 of 525 (12.2%) Heparin: 64 of 528 (12.1%) RR: 1.01 (0.73-1.39)	Ticlopidine: 106 of 525 (20.2%) Heparin: 134 of 528 (25.4%) RR: 0.80 (0.64-1.00)	
CAPRIE <sup>61/1996</sup>	Clopidogrel (75 mg/d) Aspirin (325 mg/d)	Clopidogrel: 9,599 Aspirin: 9,586	1.9 y	Clopidogrel: 132 of 9,599 (1.4%) Aspirin: 149 of 9,586 (1.6%) RR: 0.89 (0.70-1.12)	Clopidogrel: 560 of 9,599 (5.8%) Aspirin: 571 of 9,586 (6.0%) RR: 0.98 (0.87-1.10)	Clopidogrel: 939 of 9,599 (9.8%) Aspirin: 1,021 of 9,586 (10.6%) RR: 0.91 (0.84-1.00)	Study included patients with stroke (n = 6,431), MI (n = 6,302) and PAD (n = 6,452). Data are for all 19,185 patients enrolled in the study

(Continued)

**Table S22—Continued**

Study/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Major Bleeding, <sup>b</sup> RR (95% CI)	Total Mortality, RR (95% CI)	Composite Primary Outcome, <sup>c</sup> RR (95%CI)	Comments
ProFESS <sup>62</sup>	D-A: extended-release dipyridamole + aspirin Clopidogrel	D-A: 10,181 Clopidogrel: 10,151	2.5 y	D-A: 419 of 10,181 (4.1%) Clopidogrel: 365 of 10,151 (3.6%) HR: 1.15 (1.00-1.32)	D-A: 739 of 10,181 (7.3%) Clopidogrel: 756 of 10,151 (7.4%) HR: 0.97 (0.87-1.07)	D-A: 1,333 of 10,181 (13.1%) Clopidogrel: 1,333 of 10,151 (13.1%) HR: 0.99 (0.92-1.07)	
CASIP <sup>63/2008</sup>	Cilostazol (200 mg × 2/d) Aspirin (100 mg/d)	Cilostazol: 360 Aspirin: 359	12-18 mo	Cilostazol: 10 of 360 (2.8%) Aspirin: 17 of 359 (4.7%)	Cilostazol: 3 of 360 (0.8%) Aspirin: 5 of 359 (1.4%)	Cilostazol: 13 of 360 (3.6%) Aspirin: 24 of 359 (6.7%)	
CSPS II <sup>64/2010</sup>	Cilostazol (100 mg × 2/d) Aspirin (81 mg/d)	Cilostazol: 1,337 Aspirin: 1,335	29 mo	Cilostazol: 23 of 1,337 (1.7%) Aspirin: 57 of 1,335 (4.2%)	Cilostazol: 13 of 1,337 (1%) Aspirin: 13 of 1,335 (1%)	Cilostazol: 82 of 1,337 (6.1%) Aspirin: 119 of 1,335 (8.9%)	
Matias-Guini, TACIP <sup>65/2003</sup>	Aspirin 325 mg/d  Triflusal 600 mg/d	Triflusal: 1,055 of 1,055 Aspirin: 1,052 of 1,052	3 y	Triflusal: 13 of 1,055 (1.2%) Aspirin: 31 of 1,052 (2.9%) RR: 0.42 (0.22-0.79)	Triflusal: 68 of 1,055 (6.4%) Aspirin: 57 of 1,052 (5.4%) RR: 1.19 (0.85-1.67)	Triflusal: 138 of 1,055 (13.1%) Aspirin: 130 of 1,052 (12.4%) RR: 1.06 (0.85-1.32)	Major systemic hemorrhage: bleeding episode requiring hospital admission and/or blood transfusion
TAPIRSS <sup>66/2004</sup>	Triflusal (600 mg/d)  Aspirin (325 mg/d)	Triflusal: 213 Aspirin: 216	1-2 y	Triflusal: 1 of 213 (0.5%) Aspirin: 7 of 216 (3.2%)	Triflusal: 6 of 213 (2.8%) Aspirin: 13 of 216 (13%)	Triflusal: 27 of 213 (12.7%) Aspirin: 30 of 216 (13.9%)	

C-A = clopidogrel + aspirin; D-A = dipyridamole + aspirin; HR = hazard ratio; MI = myocardial infarction; PAD = peripheral artery disease. See Table S1 and S8 for expansion of abbreviations.

<sup>a</sup> Does not include trials of only aspirin vs heparin.

<sup>b</sup> Major bleeding defined as requiring transfusion or hospitalization or resulting in death.

<sup>c</sup> Composite primary outcome: death from all vascular causes, nonfatal stroke, nonfatal MI, major bleeding.

**Table S23—[Section 4.1.1] Evidence Profile: Should Aspirin vs No Aspirin Be Used for Secondary Prevention After Noncardioembolic Ischemic Stroke or TIA?**

Quality Assessment				Summary of Findings						
No. of Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 2 y	
							With No Aspirin	With Aspirin	Risk With No Aspirin	Risk difference With Aspirin (95% CI)
9,469 (10 studies) 1.5-6 y	No serious risk of bias <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High <sup>a</sup>	628 of 4,488 (14)	565 of 4,981 (11.3)	RR, 0.91 (0.81-1) <sup>b</sup>	Moderate <sup>c</sup> 5 fewer deaths per 1,000 (from 10 fewer to 0 more) <sup>d</sup>
10,126 (11 studies) 1.5-6 y	No serious risk of bias <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High <sup>a</sup>	580 of 5,001 (11.6)	480 of 5,125 (9.4)	RR, 0.81 (0.71-0.92) <sup>b</sup>	Moderate <sup>c</sup> 130 strokes per 1,000 (from 10 fewer to 38 fewer)
10,126 (11 studies) 1.5-6 y	No serious risk of bias <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High <sup>a</sup>	505 of 5,001 (10.1)	357 of 5,125 (7)	RR, 0.69 (0.6-0.8)	Moderate <sup>c</sup> 18 MIs per 1,000 (from 4 fewer to 7 fewer)
10,126 (11 studies) 1.5-6 y	No serious risk of bias <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High <sup>a</sup>	6 of 5,001 (0.12)	23 of 5,125 (0.45%)	RR, 2.69 (1.25-5.76)	Moderate <sup>c</sup> 4 bleeding events per 1,000 (from 1 more to 19 more)

**Bibliography:** Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-1860. 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. See Table S1, S2, S12, S16, and S22 legends for expansion of abbreviations.

<sup>a</sup>Includes a number of small, open-label RCTs. However, summary estimate for large, high-quality RCTs consistent with overall estimate.  
<sup>b</sup>Estimate not included in ATT and calculated from original data included in trials.  
<sup>c</sup>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.  
<sup>d</sup>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.  
<sup>e</sup>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 (0.97-2.9) and absolute effect of 1 more ICH per 1000 (from 0 fewer to 1 more).

**Table S24—[Sections 4.1.1, 4.1.2] Evidence Profile: Should Clopidogrel vs Aspirin Be Used for Secondary Prevention After Ischemic Stroke?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 2 y		
							With Aspirin	With Clopidogrel	Relative Effect (95% CI)	Risk With Aspirin	Risk Difference With Clopidogrel (95% CI)
19,185 (1 study) <sup>a</sup> 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Moderate <sup>b,c</sup> due to imprecision	571 of 9,586 (6)	560 of 9,599 (5.8)	RR <sub>1</sub> , 0.98 (0.89-1.1) <sup>b</sup>	50 deaths per 1,000	Moderate <sup>d</sup> 1 fewer deaths per 1,000 (from 6 fewer to 5 more) <sup>e</sup>
6,431 (1 study) <sup>a</sup> 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Moderate <sup>c</sup> due to imprecision	322 of 3,198 (10.1) <sup>g</sup>	298 of 3,233 (9.2) <sup>f</sup>	RR <sub>2</sub> , 0.91 (0.78-1.07) <sup>h</sup>	106 strokes per 1,000 <sup>g</sup>	Moderate <sup>d</sup> 10 fewer strokes per 1,000 (from 23 fewer to 7 more)
19,185 (1 study) <sup>a</sup> 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision <sup>e</sup>	Undetected	High <sup>f</sup>	270 of 9,586 (2.8) <sup>i</sup>	226 of 9,599 (2.4) <sup>j</sup>	RR <sub>3</sub> , 0.83 (0.7-0.99) <sup>i</sup>	13 MIs per 1,000 <sup>b</sup>	Moderate <sup>d</sup> 2 fewer MIs per 1,000 (from 0 fewer to 4 fewer)
19,185 (1 study) <sup>a</sup> 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Moderate <sup>c</sup> due to imprecision	108 of 9,586 (1.1) <sup>k</sup>	102 of 9,599 (1.1) <sup>l</sup>	RR <sub>4</sub> , 0.94 (0.72-1.23) <sup>j</sup>	10 bleeding events per 1,000	Moderate <sup>d</sup> 1 fewer bleeding events per 1,000 (from 3 fewer to 2 more)

Bibliography: CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-1339. See Tables S1, S2, S12, S16, and S22 legends for expansion of abbreviations.

<sup>a</sup>CAPRIE (1996).

<sup>b</sup>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.

<sup>c</sup>CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.

<sup>d</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>e</sup>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.

<sup>f</sup>Based on individual first-outcome nonfatal strokes in CAPRIE's stroke subpopulation.

<sup>g</sup>96.8% of events are nonfatal ischemic stroke.

<sup>h</sup>ICH incidence was low in the aspirin group (0.4%); RR with clopidogrel was 0.79 (0.49-1.27) with an absolute reduction of 1 fewer ICH per 1,000 (from 2 fewer to 1 more).

<sup>i</sup>Based on individual first outcome nonfatal MI in the overall CAPRIE population.

<sup>j</sup>Based on any (fatal and nonfatal) severe extracranial hemorrhage in the overall CAPRIE population.

**Table S25—[Sections 4.1.1, 4.1.2] Evidence Profile: Should Aspirin Plus Dipyridamole vs Aspirin Be Used for Secondary Prevention After Ischemic Stroke?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 2 y	
							With Aspirin	With Aspirin Plus Dipyridamole	Risk With Aspirin (95% CI)	Risk Difference With Aspirin Plus Dipyridamole (95% CI)
6,038 (2 studies) <sup>a</sup> 2-5 y <sup>b,c</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	Moderate <sup>d</sup> due to imprecision	289 of 3,025 (9.6)	278 of 3,013 (9.2)	50 deaths per 1,000	Moderate <sup>b</sup> 1 fewer deaths per 1,000 (from 9 fewer-6 more) <sup>e</sup>
7,649 (6 studies) 2 y <sup>b,c</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	381 of 3,826 (10)	294 of 3,823 (7.7)	106 strokes per 1,000	Moderate <sup>b</sup> 24 fewer strokes per 1,000 (from 12 fewer to 35 fewer)
6,038 (2 studies) 2-5 y <sup>b,c</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	Moderate <sup>d</sup> due to imprecision	99 of 3,025 (3.3)	78 of 3,013 (2.6)	13 MIs per 1,000	Moderate <sup>b</sup> 3 fewer MIs per 1,000 (from 5 fewer to 1 more)
6,981 (9 studies) <sup>b</sup> 0.5-5 y <sup>b,c</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	Moderate <sup>d</sup> due to imprecision	56 of 3,488 (1.6)	61 of 3,493 (1.7)	10 bleeding events per 1,000	Moderate <sup>b</sup> 1 more bleeding event per 1,000 (from 2 fewer to 5 more)

**Bibliography:** Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke*. 2008;39(4):1358-1363. de Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Syst Rev*. 2007;(3):CD001820. See Tables S1, S2, S12, S16, and S22M legends for expansion of abbreviations.

<sup>a</sup>ESPS-2 (1997) and ESPRIT (2006).  
<sup>b</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.  
<sup>c</sup>Included studies following up patients for a mean of 2.6 y.  
<sup>d</sup>CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.  
<sup>e</sup>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 overall mortality.  
<sup>f</sup>Incidence of ICH was low (about 0.1%) with RR 1.67 (0.97-2.9) and absolute effect of 1 more ICH per 1,000 (from 0 fewer to 1 more).  
<sup>g</sup>RR based on fatal and nonfatal events. RR for only nonfatal events assumed to be the same.  
<sup>h</sup>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).



**Table S26—[Sections 4.1.1, 4.1.2] Evidence Profile: Should Aspirin Plus Dipyridamole vs Clopidogrel Be Used for Secondary Prevention After Ischemic Stroke?**

Participants (Studies) Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Risk With Clopidogrel	Anticipated Absolute Effects, Time Frame 2 y
						Overall mortality (critical outcome)	With Clopidogrel	With Aspirin Plus Dipyridamole	Risk Difference With Aspirin Plus Dipyridamole (95% CI)	
20,332 (1 study) <sup>a</sup> 2.5 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	Undetected	Moderate <sup>b</sup> due to imprecision	756 of 10,151 (7.4)	739 of 10,181 (7.3)	HR, 0.97 (0.87-1.07)	49 deaths per 1,000 (from 6 fewer to 3 more) <sup>d</sup>
20,332 (1 study) <sup>a</sup> 2.5 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	Undetected	Moderate <sup>b</sup> due to imprecision	898 of 10,151 (8.8)	916 of 10,181 (9)	HR, 0.97 (0.88-1.07)	97 strokes per 1,000 from 11 fewer to 6 more
20,332 (1 study) <sup>a</sup> 2.5 y	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision <sup>b,e</sup>	Undetected	High <sup>b,e</sup>	178 of 10,181 (1.7)	197 of 10,151 (1.9)	HR, 0.90 (0.73-1.1)	10 MIs per 1,000 (from 3 fewer to 1 more)
20,332 (1 study) <sup>a</sup> 2.5 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b,e</sup>	Undetected	Moderate <sup>b,e</sup> due to imprecision	262 of 10,151 (2.6)	272 of 10,181 (2.7)	RR, 1.04 (0.88-1.22) <sup>f</sup>	10 bleeding events per 1,000 (from 1 fewer to 2 more)

Bibliography: Sacco RL, Diener H-C, Yusuf S, et al; PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359(12):1238-1251. See Tables S1, S12, and S22 legends for expansion of abbreviations.

<sup>a</sup>Sacco et al.

<sup>b</sup>CI included values indicating no effect and values indicating either appreciable harm or appreciable benefit.

<sup>c</sup>Baseline rates are derived from CAPRIE and adjusted for 2-y time frame.

<sup>d</sup>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 overall mortality.

<sup>e</sup>The absolute number of events at the extremes of the CI are small. Therefore, not rated down for imprecision.

<sup>f</sup>RR based on fatal and nonfatal major extracranial hemorrhages.

**Table S27—[Section 4.1.1] Evidence Profile: Should Aspirin Plus Clopidogrel vs Clopidogrel Be Used for Patients With Recent Noncardioembolic Ischemic Stroke or TIA?**

No. of Participants (Studies) Follow up	Quality Assessment										Summary of Findings		
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Clopidogrel Plus Clopidogrel	With Aspirin Plus Clopidogrel	Relative Effect (95% CI)	Risk With Clopidogrel	Risk Difference With Aspirin Plus Clopidogrel (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
						Overall mortality (important outcome)							
7,599 (1 study) <sup>a</sup> 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	Undetected	Moderate <sup>b</sup> due to imprecision	201 of 3,802 (5.3)	201 of 3,797 (5.3)	RR, 1.00 (0.83-1.21)	49 deaths per 1,000	Moderate <sup>c</sup>	0 fewer deaths per 1,000 (from 8 fewer to 10 more)	
7,599 (1 study) <sup>a</sup> 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	Undetected	Moderate <sup>b</sup> due to imprecision	340 of 3,802 (8.9) <sup>d</sup>	325 of 3,797 (8.6) <sup>d</sup>	RR, 0.95 (0.82-1.1) <sup>d</sup>	97 strokes per 1,000	Moderate <sup>c</sup>	5 fewer strokes per 1,000 (from 17 fewer to 10 more)	
7,599 (1 study) <sup>a</sup> 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>b</sup>	Undetected	Moderate <sup>b</sup> due to imprecision	59 of 3,802 (1.6) <sup>e</sup>	58 of 3,797 (1.5) <sup>e</sup>	RR, 0.98 (0.68-1.41) <sup>e</sup>	10 MIs per 1,000	Moderate <sup>c</sup>	0 fewer MIs per 1,000 (from 3 fewer to 4 more)	
7,540 (1 study) <sup>a</sup> 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	60 of 3,781 (1.6) <sup>f</sup>	152 of 3,759 (4) <sup>f</sup>	RR, 2.55 (1.88-3.46) <sup>f</sup>	10 bleeding events per 1,000	Moderate <sup>c</sup>	15 more bleeding events per 1,000 (from 9 more to 25 more)	

Bibliography: Diener HC, Bogousslavsky J, Brass LM, et al (2004). Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 364(9431):331-337. See Tables S1, S12, and S22 legends for expansion of abbreviations.

<sup>a</sup>Diener et al

<sup>b</sup>CI includes possible benefit and possible harm or few events.

<sup>c</sup>Baseline rates for nonfatal events and overall mortality are derived from CAPRIE and adjusted for 2-y time frame.

<sup>d</sup>Based on unpublished data provided by the sponsor of the MATCH trial. Included in this outcome are all nonfatal ischemic strokes (clopidogrel + aspirin = 298; clopidogrel = 325) and all nonfatal symptomatic intracranial hemorrhages (clopidogrel + aspirin = 27; clopidogrel = 15).

<sup>e</sup>Based on unpublished data provided by the sponsor of the MATCH trial.

<sup>f</sup>Based on unpublished 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 S28—[Sections 4.1.1, 4.1.2] Evidence Profile: Should Cilostazol vs Aspirin Be Used for Secondary Prevention After Noncardioembolic Ischemic Stroke or TIA?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects, Time Frame 2 y		
							With Aspirin	With Cilostazol	Relative Effect (95% CI)	Risk With Aspirin	Risk Difference With Cilostazol (95% CI)
3,391 (2 studies <sup>a</sup> ) 12-28 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness <sup>c</sup>	Serious <sup>d</sup>	Undetected	Overall mortality (important outcome) Low <sup>b-d</sup> due to risk of bias, imprecision	18 of 1,694 (1.1)	16 of 1,697 (0.94)	RR, 0.89 (0.45-1.74)	50 deaths per 1,000	Moderate <sup>e</sup> 6 fewer deaths per 1,000 (from 26 fewer to 36 more)
3,391 (2 studies <sup>a</sup> ) 12-28 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness <sup>c</sup>	No serious imprecision	Undetected	Nonfatal recurrent stroke (ischemic and hemorrhagic) (critical outcome) Moderate <sup>b,c</sup> due to risk of bias	141 of 1,694 (8.3)	94 of 1,697 (5.5)	RR, 0.67 (0.52-0.86) <sup>f</sup>	106 strokes per 1,000 (from 14 fewer to 48 fewer)	Moderate <sup>e</sup> 35 fewer strokes per 1,000 (from 14 fewer to 48 fewer)
3,391 (2 studies <sup>a</sup> ) 12-28 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness <sup>c</sup>	Serious <sup>d</sup>	Undetected	Nonfatal MI (important outcome) Low <sup>b-d</sup> due to risk of bias, imprecision	13 of 1,694 (0.77)	15 of 1,697 (0.88)	RR, 1.15 (0.55-2.41) <sup>g</sup>	13 MIs per 1,000 (from 5 fewer to 17 more)	Moderate <sup>e</sup> 2 more MIs per 1,000 (from 5 fewer to 17 more)
3,391 (2 studies <sup>a</sup> ) 12-28 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness <sup>c</sup>	No serious imprecision	Undetected	Nonfatal major extracranial hemorrhage (critical outcome) Moderate <sup>b,c</sup> due to risk of bias	205 of 1,694 (12.1)	155 of 1,697 (9.1)	RR, 0.74 (0.61-0.9) <sup>h</sup>	10 bleeding events per 1,000 (from 1 fewer to 4 fewer)	Moderate <sup>e</sup> 3 fewer bleeding events per 1,000 (from 1 fewer to 4 fewer)

Bibliography: Kamal AK, Nagvi I, Husain, MR, Khealani BA, et al. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Cochrane Database Syst Rev.* 2011;(1):CD008076. See Table S1, S2, S12, and S22 legends for expansion of abbreviations.

<sup>a</sup>CASISP (2008) and CSPS II (2010).  
<sup>b</sup>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.

<sup>c</sup>Evaluated in Asian population only: CASISP in China and CSPS II in Japan.  
<sup>d</sup>CI is wide and includes possible benefit and possible harm.

<sup>e</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>f</sup>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.

<sup>g</sup>Based on any MI (fatal and nonfatal).  
<sup>h</sup>Based on any extracranial hemorrhage (fatal and nonfatal, major and nonmajor).

**Table S29—[Section 4.1.1] Evidence Profile: Should Triflusal vs Aspirin Be Used for Secondary Prevention After Noncardioembolic Ischemic Stroke or TIA?**

Quality Assessment				Summary of Findings						
No. of Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
						With Aspirin	With Triflusal		Risk With Aspirin	Risk Difference With Triflusal (95% CI)
2,753 (3 studies <sup>a</sup> ) 1.5-3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	Undetected	79 of 1,379 (5.7)	81 of 1,374 (5.9)	OR, 1.03 (0.75-1.43) <sup>b</sup>	Moderate <sup>c</sup>	50 deaths per 1,000 (from 12 fewer to 19 more)
Overall mortality (important outcome)										
Overall Quality of Evidence		Moderate due to imprecision		Moderate due to imprecision		Moderate due to imprecision				
Nonfatal recurrent stroke (ischemic and hemorrhagic) (critical outcome; assessed with: CT of brain)										
2,753 (3 studies <sup>a</sup> ) 1.5-3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	137 of 1,379 (9.9)	133 of 1,374 (9.7)	OR, 0.97 (0.76-1.25) <sup>b,e</sup>	Moderate <sup>c</sup>	106 strokes per 1,000 (from 22 fewer to 22 more)
Overall mortality (important outcome)										
Overall Quality of Evidence		Moderate <sup>d</sup> due to imprecision		Moderate <sup>d</sup> due to imprecision		Moderate <sup>d</sup> due to imprecision				
Nonfatal MI (important outcome) (assessed with: clinical)										
2,753 (3 studies <sup>a</sup> ) 1.5-3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	Undetected	34 of 1,379 (2.5)	27 of 1,374 (2)	OR, 0.8 (0.48-1.33)	Moderate <sup>c</sup>	13 MIs per 1,000 (from 16 fewer to 10 more)
Overall mortality (important outcome)										
Overall Quality of Evidence		Moderate <sup>d</sup> due to imprecision		Moderate <sup>d</sup> due to imprecision		Moderate <sup>d</sup> due to imprecision				

(Continued)

**Table S29—Continued**

No. of Participants (Studies) Follow-up	Quality Assessment						Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 2 y	
							With Aspirin	With Triflusal		Risk With Aspirin	Risk Difference With Triflusal (95% CI)
2,753 (3 studies) <sup>a</sup> 1.5-3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	40 of 1,379 (2.9)	23 of 1,374 (1.7)	OR, 0.38 (0.22-0.65) <sup>b,c</sup>	10 bleeding events per 1,000	Moderate <sup>e</sup> 6 fewer bleeding events per 1,000 (from 4 fewer to 8 fewer)

Bibliography: Costa J, Ferro JM, Matias-Guiu J, et al. Triflusal for preventing serious vascular events in people at high risk. *Cochrane Database of Systematic Reviews*. 2005;(3):CD004296. See Table S2, S12, and S22 legends for expansion of abbreviations.

<sup>a</sup>Matias-Guiu (1994), TACIP (2003), and TAPIRSS (2004).

<sup>b</sup>ORs obtained from Costa et al were inverted to obtain estimate for effect relative to aspirin.

<sup>c</sup>Baseline event rates derived from aspirin arm of CAPRIE trial and adjusted for 2-y time frame.

<sup>d</sup>CIIs wide and include 1.00.

<sup>e</sup>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. †OR for nonfatal major extracranial hemorrhages based on data for any (fatal and nonfatal) major extracranial hemorrhages.

**Table S30—Randomized Trials of Anticoagulation vs Antiplatelets for the Secondary Prevention of Presumed Noncardioembolic Stroke: Clinical Description and Results**

Author/Year	Interventions	No. of Patients Analyzed		Mean Length of Follow-up, mo	Major Bleeding, RR (95% CI)	Total Mortality, RR (95% CI)	Recurrent Ischemic Strokes, RR (95% CI)	Recurrent Ischemic Stroke and Intracerebral Hemorrhage, RR (95% CI)	Comments
		AC	ASA						
Garde <sup>67</sup> /1983	Warfarin vs ASA	114	127	20	AC: 8; ASA: 4 2.23 (0.69-7.20)	AC: 3; ASA: 3 1.11 (0.23-5.41)	AC: 7; ASA: 6 1.3 (0.45-3.75)	1.11 (0.4-3.08)	
SPRIT study group, SPIRIT <sup>68</sup> /1997	Phenprocoumon (INR 3-4.5) vs ASA (30 mg/d)	651	665	14	AC: 53; ASA: 6 10.66 (4.62-24.61)	AC: 35; ASA: 15 2.82 (1.55-5.10)	AC: 14; ASA: 14 1.21 (0.58-2.51)	2.41 (1.43-4.08)	Stopped prematurely because of a significant excess in the rate of major bleeding complications in the anticoagulation group
Chimowitz, WASID <sup>69</sup> /2000	Warfarin (INR 2-3) vs ASA (1,300 mg/d)	289	280	21.6	AC: 24; ASA: 9 2.78 (1.31-5.86)	AC: 28; ASA: 12 2.43 (1.26-4.68)	AC: 49; ASA: 57 0.89 (0.63-1.26)	0.92 (0.65-1.28)	Stopped prematurely by DSMB because of higher rate of adverse events and no benefit of anticoagulation over aspirin
Mohr, ARSS <sup>70</sup> /2001	Warfarin (INR 1.4-2.8) vs ASA (325 mg/d)	1,103	1,103	10.2	AC: 38; ASA: 30 1.27 (0.79-2.03)	AC: 47; ASA: 53 0.89 (0.6-1.3)	AC: 149; ASA: 123 1.21 (0.97-1.52)	N/A	Did not report ischemic stroke + ICH or ICH separately as an outcome
Algra, SPRIT <sup>71</sup> /2007	Phenprocoumon or warfarin (INR 2-3) vs ASA (30-325 mg/d)	536	532	55.2	AC: 45; ASA: 18 2.48 (1.46-4.23)	AC: 59; ASA: 44 1.33 (0.92-1.93)	AC: 41; ASA: 53 0.77 (0.52-1.13)	N/A	Median ASA dose 75 mg/d (nearly one-half the population used 30 mg/d) Did not report ischemic stroke + ICH or ICH separately as an outcome

(Continued)

**Table S30—Continued**

Author/Year	Interventions	No. of Patients Analyzed		Mean Length of Follow-up, mo	Major Bleeding, RR (95% CI)	Total Mortality, RR (95% CI)	Recurrent Ischemic Strokes, RR (95% CI)	Recurrent Ischemic Stroke and Intracerebral Hemorrhage, RR (95% CI)	Comments
		AC	ASA						
Algra, ESPRIT <sup>7</sup> /2007	Phenprocoumon or warfarin (INR 2-3) vs ASA (30-325 mg/d) + dipyridamole (200 mg bid)	523	509	55.2	AC: 47; ASA: 11 4.16 (2.18-7.93)	AC: 67; ASA: 48 1.36 (0.96-1.93)	AC: 45; ASA: 45 0.97 (0.66-1.44)	N/A	Median ASA dose 75 mg/d 83% of patients in the antiplatelet arm used extended-release dipyridamole This was a post hoc analysis Did not report ischemic stroke + ICH or ICH separately as an outcome

AC = anticoagulant; DSMB = data and safety monitoring board; INR = International Normalized Ratio. See Table S1, S2, and S11 legends for expansion of other abbreviations.

**Table S31—[Section 4.1.1] Evidence Profile: Should Oral Anticoagulation vs Antiplatelet Be Used for Secondary Stroke Prevention in Noncardioembolic Ischemic Stroke or TIA?**

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame, 2 y	
5,400 (5 studies <sup>a</sup> ) 0-5 y	No serious risk of bias <sup>b</sup>	Serious <sup>c</sup>	No serious indirectness <sup>d</sup>	No serious imprecision <sup>e</sup>	Undetected	Moderate <sup>b,c</sup> due to inconsistency	127 of 2,707 (4.7)	RR, 1.36 (1.09-1.7)	50 deaths per 1,000	Risk Difference With Oral Anticoagulation (95% CI)
							172 of 2,693 (6.4)		18 more deaths per 1,000 (from 5 more to 35 more) <sup>g</sup>	
5,400 (5 studies <sup>a</sup> ) 0-5 y	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness <sup>d</sup>	No serious imprecision	Undetected	High <sup>b,d</sup>	253 of 2,707 (9.3)	RR, 1.03 (0.88-1.22)	106 strokes per 1,000 (from 13 fewer to 23 more)	Moderate <sup>f</sup>
							260 of 2,693 (9.7)		3 more strokes per 1,000 (from 13 fewer to 23 more)	
1,637 (2 studies <sup>h</sup> ) 3-5 y	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness <sup>i</sup>	Serious <sup>k</sup>	Undetected	Moderate <sup>k</sup> due to imprecision	40 of 812 (4.9)	RR, 0.91 (0.59-1.4)	13 MIs per 1,000 (from 5 fewer to 5 more)	Moderate <sup>f</sup>
							37 of 825 (4.5)		1 fewer MIs per 1,000 (from 5 fewer to 5 more)	

(Continued)



**Table S31—Continued**

Participants (Studies) Follow-up	Quality Assessment				Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Anticipated Absolute Effects, Time Frame, 2 y		
No. of Participants (Studies) Follow-up						Relative Effect (95% CI)	Risk With Antiplatelet	Risk Difference With Oral Anticoagulation (95% CI)		
3,194 (4 studies) <sup>1</sup>	No serious risk of bias <sup>b</sup>	No serious inconsistency <sup>m</sup>	No serious indirectness <sup>d</sup>	No serious imprecision	Undetected	High <sup>low,m</sup>	23 of 1,604 (1.4)	82 of 1,590 (5.2)	RR, 3.60 (2.29-5.66)	10 bleeding events per 1,000 (from 13 more to 47 more)
0-5 y										Moderate <sup>r</sup>

Nonfatal major extracranial hemorrhage (critical outcome)

Bibliography: Algra A, De Schryver ELLM, van Gijn J, Kappelle LJ, Kondstaal PJ. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. *Cochrane Database of Systematic Reviews*. 2006;(3):CD001342.

The antiplatelet used in all studies was aspirin. See Table S1, S2, S12, and S22 legends for expansion of abbreviations.

<sup>a</sup>Garde (1983), SPIRIT (1997), WASID (2000), WARSS (2001), and ESPRIT (2007).

<sup>b</sup>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%.

<sup>c</sup> $I^2 = 62\%$ .

<sup>d</sup>INR target range was 2 to 3 in two studies (WASID, ESPRIT), 1.4 to 2.8 in one study (WARSS), 3 to 4.5 in one study (SPIRIT). TT was 7% to 15% in one study (Garde). We did not downgrade for indirectness.

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

<sup>f</sup>Baseline event rates based on aspirin arm of the CAPRIE trial and adjusted for 2-y time frame.

<sup>g</sup>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.

<sup>h</sup>WASID (2000) and ESPRIT (2007).

<sup>i</sup>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%.

<sup>j</sup>INR target range was 2 to 3 in both studies (WASID, ESPRIT).

<sup>k</sup>CI includes both values suggesting harm and benefit.

<sup>l</sup>Garde (1983), SPIRIT (1997), WASID (2000), and ESPRIT (2007).

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

**Table S32—Randomized Trials of Anticoagulation for Cerebral Sinus Thrombosis**

Author/Year	Interventions	No. of Patients Analyzed	Length of Follow-up	Major New Bleeding After Treatment, † RR (95% CI)	Total Mortality, RR (95% CI)	Composite Primary Outcome, RR (95% CI)	Comments
Einhaupl <sup>72</sup> /1991	IV heparin vs placebo	10 Treated, 10 placebo	12 wk	0 (0-28)	0 (0-28)	10 (72-100)	Primary outcome was complete recovery or slight neurologic deficits
				2 (6-51)	3 (11-60)	1 (2-40)	
De Bruijn, CVST study <sup>73</sup> /1999	SC nadroparin (180 anti-factor Xa units/kg per 24 h) vs placebo for 3 wk (blinded part); then 3 mo of oral anticoagulants (nadroparin; open part)	30 Treated, 29 placebo	12 wk	1 (1-17)	2 (2-21)	2 (2-21)	Primary outcome was BI of 95 or 100
				0 (0-12)	4 (6-31)	2 (2-22)	

See Table S1 for expansion of abbreviations.

**Table S33—[Section 5.1] Evidence Profile: Should Therapeutic Anticoagulation vs No Therapeutic Anticoagulation Be Used in Patients With Cerebral Venous Sinus Thrombosis?**

No. of Participants (Studies) Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame	
							With Therapeutic Anticoagulation	With No Therapeutic Anticoagulation			
79 (2 studies) <sup>a</sup> 3 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Low <sup>b,c</sup> due to risk of bias, imprecision	7 of 39 (17.9)	2 of 40 (5) <sup>d</sup>	RR, 0.33 (0.08-1.28)	Moderate <sup>e</sup> 70 deaths per 1,000 (from 64 fewer to 20 more)	Risk Difference With Therapeutic Anticoagulation (95% CI)
79 (2 studies) <sup>a</sup> 3 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	Undetected	Good functional outcome (independence) (critical outcome; assessed with: clinical examination) <sup>f</sup> Low <sup>b,g</sup> due to risk of bias, imprecision	30 of 39 (76.9)	36 of 40 (90) <sup>d</sup>	RR, 1.17 (0.96-1.35)	Moderate <sup>e</sup> 860 good outcomes per 1,000 (from 34 fewer to 301 more)	Risk Difference With Therapeutic Anticoagulation (95% CI)

(Continued)

**Table S33—Continued**

No. of Participants (Studies) Follow-up	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 6 mo
79 (2 studies) <sup>a</sup> 3 mo	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious <sup>c,g</sup>	Undetected	Low <sup>b,c,g</sup> due to risk of bias, imprecision	With Therapeutic Anticoagulation: 0 of 39 (0) <sup>h</sup> With Therapeutic Anticoagulation: 1 of 40 (2.5) <sup>h</sup>	RR, 2.9 (0.12-68.5)	Moderate <sup>e</sup> 19 more bleeding events per 1,000 (from 9 fewer to 675 more)

Nonfatal major extracranial hemorrhage (important outcome)

Bibliography: Stam J, de Bruijn SFTM, DeVeber G. Anticoagulation for cerebral sinus thrombosis. *Cochrane Database Syst Rev*. 2002;(4):CD002005. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670. de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. *Stroke*. 1999;30(3):484-488. Einhaupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, et al. Heparin treatment in sinus venous thrombosis. *Lancet*. 1991;338(8767):597-600. See Table S1 and S2 for expansion of abbreviations.

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 as per the ISCVT Study (Ferraro et al).

<sup>a</sup>Einhaupl (1991) and de Bruijn (1999).  
<sup>b</sup>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 post-randomization 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 on scores on the CVST severity scale.

<sup>c</sup>CI includes both negligible effect and appreciable benefit or appreciable harm.  
<sup>d</sup>In Einhaupl 1991, the intervention consisted of IV heparin started 33 d after first symptoms; no further details provided about anticoagulation. In the CVST Group (de Bruijn 1999), the intervention consisted of nadroparin bid (total 180 anti-factor Xa units/kg per 24 h) started 10 d after first symptoms and follow with warfarin (nonblinded) for 10 wk (total duration of anticoagulant treatment 13 wk).

<sup>e</sup>Baseline risk of mortality at 6 mo derived from the ISCVT study (Ferraro et al).  
<sup>f</sup>In Einhaupl defined as complete recovery or slight neurologic deficits. In de Bruijn et al defined as BI < 15.

<sup>g</sup>Effect estimate based on few events.

<sup>h</sup>In Einhaupl et al, three of 10 patients and in de Bruijn 15 of 30 patients had some degree of ICH 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.

<sup>i</sup>Baseline risk derived from IST.

## REFERENCES

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
2. Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
3. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA*. 1999;282(21):2019-2026.
4. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study: Thrombolytic Therapy in Acute Ischemic Stroke Study investigators. *Stroke*. 2000;31(4):811-816.
5. Hacke W, Kaste M, Fieschi C, et al; The European Cooperative Acute Stroke Study (ECASS). Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*. 1995;274(13):1017-1025.
6. Hacke W, Kaste M, Fieschi C, et al; Second European-Australasian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*. 1998;352(9136):1245-1251.
7. del Zoppo GJHR, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke*. 1998;29(1):4-11.
8. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA*. 1999;282(21):2003-2011.
9. Ogawa A, Mori E, Minematsu K, et al; MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007;38(10):2633-2639.
10. IMS Study Investigators. Combined intravenous and intraarterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke*. 2004;35(4):904-911.
11. IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II study. *Stroke*. 2007;38(7):2127-2135.
12. Struffert T, Köhrmann M, Engelhorn T, et al. Penumbra Stroke System as an "add-on" for the treatment of large vessel occlusive disease following thrombolysis: first results. *Eur Radiol*. 2009;19(9):2286-2293.
13. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke*. 2009;40(8):2761-2768.
14. Grunwald IQ, Walter S, Papanagiotou P, et al. Revascularization in acute ischaemic stroke using the penumbra system: the first single center experience. *Eur J Neurol*. 2009;16(11):1210-1216.
15. Smith WS, Sung G, Starkman S, et al; MERCI Trial Investigators. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke*. 2005;36(7):1432-1438.
16. Smith WS, Sung G, Saver J, et al; Multi MERCI Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008;39(4):1205-1212.
17. Lee W, Sitoh Y-Y, Lim CCT, Lim WE, Hui FK. The MERCI Retrieval System for the management of acute ischaemic stroke—the NNI Singapore experience. *Ann Acad Med Singapore*. 2009;38(9):749-755.
18. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349(9066):1641-1649.
19. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet*. 1997;31:349(9065):1569-1581.
20. Multicentre Acute Stroke Trial—Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet*. 1995;346(8989):1509-1514.
21. Rödén-Jülig A, Britton M, Malmkvist K, Leijd B. Aspirin in the prevention of progressing stroke: a randomized controlled study. *J Intern Med*. 2003;254(6):584-590.
22. Bath PM, Lindstrom E, Boysen G, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. *Lancet*. 2001;358(9283):702-710.
23. LaMonte MP, Nash ML, Wang DZ, et al; for the ARGIS-1 Investigators. Argatroban anticoagulation in patients with acute ischemic stroke (ARGIS-1): a randomized, placebo-controlled safety study. *Stroke*. 2004;35(7):1677-1682.
24. Prince J. *Thromboses veineuses des membres inferieurs et embolies pulmonaries au cours des accidents vasculaires cerebraux: a propos d'un essai comparatif de traitement preventif (these pour le doctorat d'etat en medecine)*. Toulouse, France: Universite Paul Sabatier; 1981.
25. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet*. 2000;355(9211):1205-1210.
26. Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC, et al; FISS-tris Study Investigators. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. *Lancet Neurol*. 2007;6(5):407-413.
27. Chamorro A, Busse O, Obach V, Toni D, Sandercock P, Reverter JC, et al; RAPID Investigators. The rapid anticoagulation prevents ischemic damage study in acute stroke—final results from the writing committee. *Cerebrovasc Dis*. 2005;19(6):402-404.
28. Sarma GR, Roy AK. Nadroparin plus aspirin versus aspirin alone in the treatment of acute ischemic stroke. *Neurol India*. 2003;51(2):208-210.
29. McCarthy ST, Turner JJ, Robertson D, Hawkey CJ, Macey DJ. Low-dose heparin as a prophylaxis against deep-vein thrombosis after acute stroke. *Lancet*. 1977;2(8042):800-801.
30. Duke RJ, Bloch RF, Turpie AG, Trebilcock R, Bayer N. Intravenous heparin for the prevention of stroke progression in acute partial stable stroke. *Ann Intern Med*. 1986;105(6):825-828.
31. McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. *Age Ageing*. 1986;15(2):84-88.
32. Turpie AG, Levine MN, Hirsh J, et al. Double-blind randomised trial of Org 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. *Lancet*. 1987;1(8532):523-526.
33. Cazzato G, Zorzon M, Mase G, Antonutti L, Iona LG. Mesoglycan in acute focal cerebral ischemia. *Riv Neurol*. 1989;59(3):121-126.

34. Prins MH, Gelsema E, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. *Haemostasis*. 1989;19(5):245-250.
35. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. *Semin Thromb Hemost*. 1990;16(suppl):25-33.
36. Hommel M for the FISS-bis Investigators Group. Fraxiparine in Ischemic Stroke Study (FISS bis) [Abstract]. *Cerebrovasc Dis*. 1998;8(suppl):19.
37. Pambianco G, Orchard T, Landau P. Deep vein thrombosis: prevention in stroke patients during rehabilitation. *Arch Phys Med Rehabil*. 1995;76(4):324-330.
38. Hillbom M, Eriola T, Sotaniemi K, Tatlisumak T, Sarna S, Kaste M. Enoxaparin vs heparin for prevention of deep-vein thrombosis in acute ischaemic stroke: a randomized, double-blind study. *Acta Neurol Scand*. 2002;106(2):84-92.
39. Diener HC, Ringelstein EB, von Kummer R, et al; for the PROTECT Trial Group. Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT trial. *Stroke*. 2006;37(1):139-144.
40. Sherman DG, Albers GW, Bladin C, et al; for the PREVAIL Investigators. Prevention of venous thromboembolism after acute ischemic stroke with enoxaparin versus unfractionated heparin and the impact of stroke severity [ASH Annual Meeting Abstracts]. *Blood*. 2006;108:713.
41. Boer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 1991;54(5):466-467.
42. Orken DN, Kenangil G, Ozkurt H, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. *Neurologist*. 2009;15(6):329-331.
43. Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and ulmonary embolism after intracerebral hemorrhage. *Klin Wochenschr*. 1988;66(23):1182-1183.
44. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *Q J Med*. 2000;93(6):359-364.
45. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, et al; The CLOTS Trial Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet*. 2009;373(9679):1958-1965.
46. Lacut K, Bressollette L, Le Gal G, et al; on behalf of the VICTORIAh. (Venous Intermittent Compression and Thrombosis Occurrence Related to Intra-cerebral Acute hemorrhage) investigators. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. *Neurology*. 2005;65(6):865-869.
47. Prasad BK, Banerjee AK, Howard H. Incidence of deep vein thrombosis and the effect of pneumatic compression of the calf in elderly hemiplegics. *Age Ageing*. 1982;11(1):42-44.
48. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med*. 1991;325(18):1261-1266.
49. Farrel B, Goodwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54(12):1044-1054.
50. Diener HC, Bogousslavsky J, Brass LM, et al; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331-337.
51. Bhatt DL, Fox KA, Hacke W, Berger P, Black HR, Boden WE, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354(16):1706-1717.
52. Bhatt DL. Identification of and management approaches for the high-risk patient. *Am J Cardiol*. 2006;98(12A):22Q-29Q.
53. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143(1-2):1-13.
54. Persantine Aspirin Trial in cerebral ischemia. Part II: endpoint results. The American-Canadian Co-Operative Study group. *Stroke*. 1985;16(3):406-415.
55. Bousser MG, Eschwege E, Haguenu M, et al. Controlled cooperative trial of secondary prevention of cerebral ischemic accidents caused by atherosclerosis, using aspirin and dipyridamole. *Presse Med*. 1983;12(48):3049-3057.
56. Diener HC. Dipyridamole trials in stroke prevention. *Neurology*. 1998;51(Suppl 3):S17-S19.
57. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A; ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial [erratum appears in *Lancet*. 2007;369(9558):274]. *Lancet*. 2006;367(9523):1665-1673.
58. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med*. 1989;321(8):501-507.
59. Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *JAMA*. 2003;289(22):2947-2957.
60. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet*. 1989;1(8649):1215-1220.
61. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel vs aspirin in patients at risk for ischemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-1339.
62. Sacco RL, Diener H-C, Yusuf S, et al; RoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359(12):1238-1251.
63. Huang Y, Cheng Y, Wu J, et al; Cilostazol versus Aspirin for Secondary Ischaemic Stroke Prevention cooperation investigators. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study [erratum appears in *Lancet Neurol*. 2008;7(8):675]. *Lancet Neurol*. 2008;7(6):494-499.
64. Shinohara Y, Katayama Y, Uchiyama S, et al; CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9(10):959-968.
65. Matías-Guio J, Ferro JM, Alvarez-Sabín J, et al; TACIP Investigators. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction: the TACIP Study: a randomized, double-blind, multicenter trial. *Stroke*. 2003;34(4):840-848.
66. Culebras A, Rotta-Escalante R, Vila J, Domínguez R, Abiusi G, Famulari A, et al; TAPIRSS investigators. Triflusal vs aspirin for prevention of cerebral infarction: a randomized stroke study. *Neurology*. 2004;13;62(7):1073-1080.

67. Gårde A, Samuelsson K, Fahlgren H, Hedberg E, Hjerne LG, Ostman J. Treatment after transient ischemic attacks: a comparison between anticoagulant drug and inhibition of platelet aggregation. *Stroke*. 1983;14(5):677-681.
68. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol*. 1997;42(6):857-865.
69. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352(13):1305-1316.
70. Mohr JP, Thompson JLP, Lazar RM, et al; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345(20):1444-1451.
71. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A; ESPRIT Study Group. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol*. 2007;6(2):115-124.
72. Einhäupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. *Lancet*. 1991;338(8767):597-600.
73. de Bruijn de SF, Stam J. Randomised placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. *Stroke*. 1999;30(3):484-488.

**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**

Maarten G. Lansberg, Martin J. O'Donnell, Pooja Khatri, Eddy S. Lang, Mai N. Nguyen-Huynh, Neil E. Schwartz, Frank A. Sonnenberg, Sam Schulman, Per Olav Vandvik, Frederick A. Spencer, Pablo Alonso-Coello, Gordon H. Guyatt and Elie A. Akl  
*Chest* 2012;141; e601S-e636S  
DOI 10.1378/chest.11-2302

**This information is current as of March 4, 2012**

**Supplementary Material**

View e-supplements related to this article at:

[http://chestjournal.chestpubs.org/content/suppl/2012/02/03/141.2\\_suppl.e601S.DC1.html](http://chestjournal.chestpubs.org/content/suppl/2012/02/03/141.2_suppl.e601S.DC1.html)

**Updated Information & Services**

Updated Information and services can be found at:

[http://chestjournal.chestpubs.org/content/141/2\\_suppl/e601S.full.html](http://chestjournal.chestpubs.org/content/141/2_suppl/e601S.full.html)

**References**

This article cites 132 articles, 75 of which can be accessed free at:

[http://chestjournal.chestpubs.org/content/141/2\\_suppl/e601S.full.html#ref-list-1](http://chestjournal.chestpubs.org/content/141/2_suppl/e601S.full.html#ref-list-1)

**Cited By**

This article has been cited by 5 HighWire-hosted articles:

[http://chestjournal.chestpubs.org/content/141/2\\_suppl/e601S.full.html#related-urls](http://chestjournal.chestpubs.org/content/141/2_suppl/e601S.full.html#related-urls)

**Permissions & Licensing**

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://www.chestpubs.org/site/misc/reprints.xhtml>

**Reprints**

Information about ordering reprints can be found online:

<http://www.chestpubs.org/site/misc/reprints.xhtml>

**Citation Alerts**

Receive free e-mail alerts when new articles cite this article. To sign up, select the "Services" link to the right of the online article.

**Images in PowerPoint format**

Figures that appear in *CHEST* articles can be downloaded for teaching purposes in PowerPoint slide format. See any online figure for directions.

