



### **Antithrombotic Therapy in Peripheral Artery Disease**

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

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**Table S1—[Introduction] Question Definition and Eligibility Criteria for Antithrombotic Treatments in PAD**

Section	Informal Question	PICO Question			Outcomes
		Population	Interventions	Comparator	
2.0 Asymptomatic PAD					
2.1	Choice of antithrombotic therapy	Patients with asymptomatic PAD (eg, ABPI <0.9)	Aspirin	Placebo	Total mortality Nonfatal MI Nonfatal stroke Major nonfatal extracranial bleed
3.0 Symptomatic PAD: prevention of cardiovascular events					
3.1	Choice of antithrombotic therapy	Patients with symptomatic PAD	Aspirin	Placebo	Total mortality
3.2			Clopidogrel	Aspirin	Nonfatal MI
3.3			Aspirin + clopidogrel	Aspirin	Nonfatal stroke
3.4			Aspirin + OACs	Aspirin	Major nonfatal extracranial bleed
4.0 Symptomatic PAD: management of claudication					
4.1	Choice of antithrombotic therapy	Patients with claudication	Heparins	Placebo	Quality of life
4.2			Cilostazol	Placebo or pentoxifylline	Maximum walking distance
4.3			Pentoxifylline	Placebo	Major nonfatal extracranial bleeding
4.4			Prostaglandins	Placebo	Mortality Adverse events
5.0 Symptomatic PAD: management of critical limb ischemia					
5.1	Choice of antithrombotic therapy	Patients with critical limb ischemia unable to undergo revascularization	Prostaglandins	Placebo	Rest pain relief  Ulcer healing Amputations Mortality Adverse events

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Table S1—Continued

Section	Informal Question	Population	PICO Question		
			Interventions	Comparator	Outcomes
6.0 Acute limb ischemia					
6.1	Choice of antithrombotic therapy	Patients with acute limb ischemia	Unfractionated heparin	No anticoagulation	Death
6.2			Intraarterial thrombolytic therapy	Surgery	Amputation
6.3			Urokinase or rt-PA	Streptokinase	Nonfatal stroke Major nonfatal extracranial bleed
7.0 Endovascular surgery					
7.1	Choice of antithrombotic therapy post PTA ± stent	Patients undergoing any graft	Aspirin plus dipyridamole	Placebo	Vessel restenosis/occlusion
			Aspirin/dipyridamole	Phenprocoumon	
			Ticlopidine	Phenprocoumon	
			Unfractionated heparin	Subcutaneous nadroparin (LMWH)	
8.0 Open lower-limb vascular surgery					
8.1	Choice of antithrombotic therapy	Patients undergoing PTA	Aspirin or aspirin/dipyridamole	Placebo	Vascular mortality
8.2		Patients undergoing below-knee prosthetic graft	Aspirin or aspirin/dipyridamole	Other agents	Nonfatal MI
8.3			Clopidogrel plus aspirin	Aspirin	Nonfatal stroke
8.4			OACs ± aspirin	Aspirin	Major nonfatal extracranial bleed
8.5			Aspirin plus clopidogrel	Aspirin	Amputation
9.0 Carotid stenosis					
9.1	Choice of antithrombotic therapy	Patients with asymptomatic carotid stenosis	Aspirin	Placebo	Total mortality
9.2		Patients with symptomatic carotid stenosis	Antiplatelet agents post endarterectomy	Placebo	Nonfatal MI
9.3		Patients with carotid stenosis undergoing endarterectomy			Nonfatal stroke Major nonfatal extracranial bleed

ABPI = ankle-brachial pressure index; LMWH = low-molecular-weight heparin; MI = myocardial infarction; OAC = oral anticoagulant; PAD = peripheral arterial disease; PICO = population, intervention, comparator, outcome; PTA = percutaneous transluminal angioplasty; rt-PA = recombinant tissue-type plasminogen activator.

**Table S2—[Section 1.1] Evidence Profile: Aspirin (75-100 mg) Compared With No Aspirin in the Primary Prevention of Cardiovascular Disease**

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings		Quality of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Anticipated Absolute Effects Time Frame: 10 y	
100,076 (9 RCTs), 3.8-10 y	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Overall mortality (critical outcome), including cancer mortality, vascular mortality, and fatal bleeds <sup>a</sup> No serious indirectness Serious imprecision CI includes no benefit	Undetected	RR 0.94 (0.89-1.00)	Without Aspirin 60-y-old man <sup>c</sup> 6 fewer deaths per 1,000 (from 12 fewer to 0 fewer)	Moderate due to imprecision
95,000 (6 RCTs), 3.8-10 y	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 0.77 (0.69-0.86)	Low-risk population <sup>e</sup> 6 fewer MI per 1,000 (from 8 fewer to 4 fewer)	High
					Undetected		Moderate-risk population <sup>e</sup> 19 fewer MI per 1,000 (from 26 fewer to 12 fewer)	
					Undetected		High-risk population <sup>e</sup> 31 fewer MI per 1,000 (from 42 fewer to 19 fewer)	
95,000 (6 RCTs), 3.8-10 y	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Nonfatal stroke (critical outcome), includes ischemic, hemorrhagic, and unknown cause <sup>f</sup> No serious indirectness No serious imprecision	Undetected	RR 0.95 (0.85-1.06)	Low-risk population <sup>e</sup> 1 fewer stroke per 1,000 (from 3 fewer to 1 more)	High
					Undetected		Moderate-risk population <sup>e</sup> 3 fewer strokes per 1,000 (from 10 fewer to 4 more)	
					Undetected		High-risk population <sup>e</sup> 5 fewer strokes per 1,000 (from 16 fewer to 6 more)	

(Continued)

**Table S2—Continued**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings		Quality of Evidence	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)		Anticipated Absolute Effects Time Frame: 10 y
95,000 (6 RCTs), 3.8-10 y	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 1.54 (1.30-1.82)	Without Aspirin 8 bleeds per 1,000 <sup>d</sup> Low-risk populations <sup>e</sup> 4 more bleeds per 1,000 (from 2 more to 7 more)	With Aspirin (95% CI) 16 more bleeds per 1,000 (from 7 more to 20 more) High
							Moderate-risk populations <sup>e</sup> 24 bleeds per 1,000 <sup>d</sup>	
							High-risk populations <sup>e</sup> 40 bleeds per 1,000 <sup>d</sup> 22 more bleeds per 1,000 (from 12 more to 33 more)	

**Bibliography:** Antithrombotic Trialists' (ATT) Collaboration; Gaigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet*. 2009;373(9678):1849-1860. Raju N, Sobieraj-Teague M, Hinsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in primary prevention of cardiovascular disease. *Am J Med*. 2011;124(7):621-629.<sup>a</sup> RCT = randomized controlled trial; RR = risk ratio. See Table S1 for expansion of other abbreviations.

<sup>a</sup>This systematic review reports total mortality and includes the most recent trials but does not report specific causes of mortality. Other meta-analyses that use individual patient data report relative risk estimates for vascular mortality (RR, 0.97; 95% CI, 0.87-1.09) cancer mortality (RR, 0.66; 95% CI, 0.50-0.87), and fatal intracranial bleeds (RR, 1.73; 95% CI, 0.96-3.13). The risk of a fatal bleed (including extracranial and intracranial) was low (0.3% with aspirin and 0.2% with control).

<sup>b</sup>Borderline decision where we did not rate down for risk of bias. Three of the trials did not blind patients, caregivers, or outcome adjudicator. Sensitivity analyses in meta-analysis by Raju et al did not show evidence of risk of bias.

<sup>c</sup>Control group risk estimate for 10-y mortality apply to a 60-y-old man and come from population-based data from Statistics Norway. Mortality increases with age (eg, 50-y-old man, 50 deaths per 1,000 in 10 y) and is lower in women than in men (eg, 3% in women aged 50 y vs 5% in men aged 50 y).

<sup>d</sup>Control group risk estimates in low-, moderate-, and high-risk cardiovascular groups are based on the Framingham score. As explained in the article, we have used data from an individual participant data (IPD) meta-analysis to provide estimated risks for patient-important outcomes not covered by the Framingham risk score. We have also adjusted for 20% overestimation associated with Framingham risk score.

<sup>e</sup>Risk groups correspond to low risk (5%), medium risk (15%), or high risk (25%) according to the Framingham score (or other risk tool) to estimate 10-y risk.

<sup>f</sup>Of the strokes in the trials, 89 of 682 (13%) without aspirin were hemorrhagic and 116 of 655 (18%) with aspirin were hemorrhagic.

<sup>g</sup>In the IPD meta-analysis, risk for future major bleeding correlated with risk for future cardiovascular events. Therefore, we make the assumption that a patient at low, medium, or high risk of future cardiovascular events (determined by Framingham score) will be at low, medium, or high risk of future major bleeding events, respectively.

**Table S3—[Section 3.1-3.4] Evidence Profile: Aspirin vs No Aspirin in Patients With Symptomatic PAD**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk Without Aspirin	Risk Difference With Aspirin (95% CI)	Quality of Evidence
17,000 (16 RCTs), 27 mo	No serious risk of bias	No serious limitations	No serious indirectness	Imprecise <sup>a</sup> CI includes benefit and no effect	Undetected	RR 0.90 (0.82-0.99)	133 per 1,000 <sup>b</sup>	13 fewer per 1,000 (from 24 fewer to 1 fewer)	Moderate due to imprecision <sup>a</sup>
17,000 (16 RCTs), 27 mo	No serious risk of bias	No serious limitations	No serious indirectness	Nonfatal MI (critical outcome) No serious imprecision	Undetected	RR 0.69 (0.60-0.80)	117 per 1,000 <sup>c</sup>	36 fewer per 1,000 (from 46 fewer to 23 fewer)	High
17,000 (16 RCTs), 27 mo	No serious risk of bias	No serious limitations	No serious indirectness	No serious imprecision	Undetected	RR 0.81 (0.71-0.92)	135 per 1,000 <sup>c</sup>	25 fewer per 1,000 (from 39 fewer to 11 fewer)	High
17,000 (16 RCTs), 27 mo	No serious risk of bias	No serious limitations	Indirectness: Bleeding only reported in stroke/TIA trials <sup>d</sup>	No serious imprecision	Undetected	RR 2.69 (1.25-5.76)	15 per 1,000 <sup>e</sup>	25 more per 1,000 (from 4 more to 71 more)	Moderate due to indirectness

**Bibliography:** Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet*. 2009;373(9678):1849-1860. CAPRIE = Clopidogrel vs Aspirin in Patients at Risk for Ischemic Events; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; TIA = transient ischemic attack. See Table S1 and S2 legends for expansion of other abbreviations.

<sup>a</sup>Rated down for imprecision because 95% CI suggests possible benefit and no effect on total mortality

<sup>b</sup>Control group risk estimates (without aspirin) come from observed yearly event rates in 16 RCTs reported in the meta-analysis, adjusted to a 5-y time frame. The control group risk estimate for total mortality without aspirin is derived from the event rate in the aspirin arm of the CHARISMA trial, using the RR of 0.90 to get to the control group risk estimate without aspirin.

<sup>c</sup>Of the strokes in the meta-analysis, 0.8% with aspirin were intracranial hemorrhages, and 0.4% of strokes without aspirin were intracranial hemorrhages.

<sup>d</sup>Rated down for indirectness because bleeding was only reported in subset of trials with stroke/TIA populations.

<sup>e</sup>To estimate control group risks for major bleeding events, we have used major bleeding estimates from the aspirin arm in the CAPRIE trial as the starting point (to ensure consistency across evidence profiles). We have then used the RR of 2.69 to get to the control group risk estimate without aspirin.

**Table S4—[Section 3.1-3.4] Evidence Profile: Clopidogrel vs Aspirin for the Secondary Prevention of Cardiovascular Events in Patients With Symptomatic PAD**

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings			Quality of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Anticipated Absolute Effects Time Frame: 5 y		
							Risk With Aspirin	Risk Difference With Clopidogrel (95% CI)	
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency Subgroup analysis suggested no benefit in patients with acute MI <sup>b</sup>	No serious indirectness	Serious imprecision CI includes benefit and harm with clopidogrel	Undetected	RR 0.98 (0.87-1.10)	120 per 1,000 <sup>c</sup>	2 fewer per 1,000 (from 16 fewer to 12 more)	Moderate due to imprecision
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and no benefit with clopidogrel	Undetected	RR 0.85 (0.72-1.0)	80 per 1,000 <sup>c</sup>	12 fewer per 1,000 (from 22 fewer to 0 more)	Moderate due to imprecision
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and harm with clopidogrel	Undetected	RR 0.94 (0.83-1.06)	110 per 1,000 <sup>c</sup>	6 fewer per 1,000 (from 18 fewer to 6 more)	Moderate due to imprecision
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and harm with clopidogrel	Undetected	RR 0.88 (0.7-1.12)	40 per 1,000 <sup>f</sup>	4 fewer per 1,000 (from 12 fewer to 4 more)	Moderate due to imprecision

Bibliography: 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.

<sup>a</sup>Of the deaths in CAPRIE, 27 of 571 (4.7%) with aspirin were fatal bleeds and 23 of 560 (4.1%) with clopidogrel were fatal bleeds. See Table S1, S2, and S3 legends for expansion of abbreviations.

<sup>b</sup>Subgroup analysis of composite end point reported relative risk reduction of 7.3% for patients with stroke and 23.8% for patients with PAD and relative risk increase of 3.7% for patients with MI (test for interaction  $P = .043$ ). Based on criteria for credibility, we did not believe the results from the subgroup analysis and, therefore, did not rate down for inconsistency.

<sup>c</sup>Control group risk estimates for total mortality comes from the aspirin arm of the CHARISMA trial. Estimates for MI and stroke come from observed events in a meta-analysis of 16 RCTs in secondary prevention (Baigent, see Table S3 legend) adjusted to 5-y time frame.

<sup>d</sup>Of the strokes in CAPRIE, 24 of 486 (4.9%) with aspirin were hemorrhagic, and 14 of 528 (2.6%) with clopidogrel were hemorrhagic.

<sup>e</sup>Of the major extracranial bleeds in CAPRIE, 68 of 149 (45.6%) with aspirin were GI and 47 of 132 (35.6%) with clopidogrel were GI ( $P = .05$ ).

<sup>f</sup>Control group risk estimates come from observed major bleeding events in the CAPRIE trial adjusted to 5-y time frame and not from the 16 studies included in the meta-analysis because these studies did not report major bleeds consistently.



**Table S5—[Section 3.1-3.4] Evidence Profile: Aspirin Plus Clopidogrel vs Aspirin for Secondary Prevention of Cardiovascular Events in Patients With Symptomatic PAD**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings			Quality of Evidence	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin		Risk Difference With Aspirin + Clopidogrel (95% CI)
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious Inconsistency <sup>b</sup>	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.99 (0.86-1.14)	120 per 1,000 <sup>d</sup>	1 fewer per 1,000 (from 16 fewer to 16 more)	Moderate due to imprecision
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.94 (0.75-1.18)	80 per 1,000 <sup>d</sup>	4 fewer per 1,000 (from 20 fewer to 14 more)	Moderate due to imprecision
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.81 (0.64-1.02)	110 per 1,000 <sup>d</sup>	20 fewer per 1,000 (from 39 fewer to 2 more)	Moderate due to imprecision
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 1.25 (0.97-1.61)	40 per 1,000 <sup>d</sup>	10 more per 1,000 (from 1 fewer to 24 more)	Moderate due to imprecision

Bibliography: Bhatt D, Fox KA, Hacke W, et al. Clopidogrel and aspirin vs aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354(16):1706-1717. GUSTO = Global Use of Strategies to Open Occluded Arteries. See Table S1, S2, and S3 legends for expansion of other abbreviations.

<sup>a</sup>Of the deaths in CHARISMA, 17 of 571 (3%) with aspirin were fatal bleeding events and 26 of 574 (4.5%) with clopidogrel and aspirin were fatal bleeding events.

<sup>b</sup>Subgroup analysis found no significant effect of clopidogrel on vascular mortality in patients with established cardiovascular disease, in contrast to increased mortality in asymptomatic patients. We judged claim of subgroup effect to be not credible (high number of subgroup hypotheses tested, unclear whether an appropriate test for interaction used).

<sup>c</sup>CI includes important benefit and harm (for mortality) and no benefit (for stroke).

<sup>d</sup>Control group risk estimates for total mortality comes from the aspirin arm of the CHARISMA trial. Estimates for MI and stroke come from observed events in a meta-analysis of 16 RCTs in secondary prevention (Baigent, see Table S3 legend) adjusted to 5-y time frame.

<sup>e</sup>Of the strokes in CHARISMA, 27 of 189 (14%) with aspirin were intracranial hemorrhages, and 26 of 150 (17%) with clopidogrel were intracranial hemorrhages.

<sup>f</sup>We excluded fatal bleeding and intracranial hemorrhage to avoid the double counting of events in the CHARISMA trial. Proportion of severe GI bleeds in CHARISMA was 0.65% (not reported separately for each treatment arm).

<sup>g</sup>CI includes no benefit and important harm.

<sup>h</sup>Control group risk estimates come from observed major bleeding events in the CAPRIE trial, adjusted to 5-yr time frame, and not from the 16 studies included in the meta-analysis or from CHARISMA as these studies did not report major bleeds consistently.



**Table S6—[Section 3.1-3.4] Evidence Profile: Moderate-Intensity Warfarin (INR 2.0-3.0) Plus Aspirin vs Aspirin Alone for Secondary Prevention of Cardiovascular Events in Patients With Symptomatic PAD**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings			Quality of Evidence	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Event Rate With Aspirin		Risk Difference With Warfarin + Aspirin (95% CI)
3,048 (3 RCTs), 35-60 mo	No serious risk of bias	Serious inconsistency <sup>a</sup> ( <i>P</i> = 63%)	No serious indirectness	Imprecise CI includes benefit and harm	Undetected	RR 1.11 (0.79-1.55)	120 per 1,000 <sup>b</sup>	13 more per 1,000 (from 25 fewer to 66 more)	Low due to imprecision and inconsistency
3,048 (3 RCTs), 35-60 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Imprecise CI includes benefit and harm	Undetected	RR 0.95 (0.64-0.1.41)	80 per 1,000 <sup>c</sup>	4 fewer per 1,000 (from 28 fewer to 32 more)	Moderate due to imprecision
3,048 (3 RCTs), 35-60 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Imprecise CI includes benefit and harm	Undetected	RR 0.92 (0.64-1.33)	110 per 1,000 <sup>c</sup>	8 fewer per 1,000 (from 39 fewer to 36more)	Moderate due to imprecision
2,994 (2 RCTs), 35-60 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 2.39 (1.50-3.82)	40 per 1,000 <sup>c</sup>	55 more per 1,000 (from 20 more to 112 more)	High
N/A <sup>f</sup>	Burden of treatment (important outcome)				Warfarin > aspirin	Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/monitoring, increased hospital/clinic visits. <sup>d</sup> Aspirin: daily medication only.			High

**Bibliography:** Johnson WC, Williford WO; Department of Veterans Affairs Cooperative Study #362. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg.* 2002;35(3):41-421. Sarac TP, Huber TS, Back MR, et al. Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk for failure. *J Vasc Surg.* 1998;28(3):446-457. Anand S, Yusuf S, Xie C, et al; Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med.* 2007;357(3):217-227. INR = international normalized ratio; N/A = not applicable. See Table S1, S2, and S3 legends for expansion of other abbreviations.

<sup>a</sup>Excess cancer deaths in one study with warfarin and aspirin.

<sup>b</sup>Control group risk estimates for total mortality comes from the aspirin arm of the CHARISMA trial.

<sup>c</sup>Control group risk estimates for nonfatal MI and nonfatal strokes (ischemic, hemorrhagic, and unknown cause) come from observed events in the aspirin arm of a meta-analysis of 16 RCTs in secondary prevention (Baigent et al, see Table S3 legend).

<sup>d</sup>Of total strokes, two of 48 (4%) with aspirin and 17 of 50 (34%) with warfarin plus aspirin were hemorrhagic.

<sup>e</sup>Control group risk estimates for major bleeds come from observed rates in the aspirin-alone arm of the CAPRIE trial.

<sup>f</sup>As far as we are aware, no studies have evaluated differences in burden of treatment between patients with PAD taking warfarin vs aspirin. There are studies evaluating quality of life in patients during warfarin treatment (with disparate findings), but these are limited by small sample size, lack of comparator, and other design issues.

**Table S7—[Section 4.1-4.4] Evidence Profile: Cilostazol vs Placebo in Patients With Symptomatic PAD and Claudication**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Estimation of Absolute Effects		Quality of Evidence
						Event rate With No Cilostazol <sup>a</sup>	Risk Difference With Cilostazol (95% CI)	
1,439 (1 RCT <sup>b</sup> ), 34 mo	Serious risk of bias. Unclear concealment of allocation	Single study only	No serious indirectness	Serious imprecision CIs are wide and only 101 events	Undetected	RR 0.94 (0.64-1.39)	68 per 1,000 <sup>a</sup> 4 less per 1,000 (27 fewer to 26 more)	Low due to bias and imprecision
1,890 (7 RCTs), 3-6 mo	Serious risk of bias. Unclear concealment of allocation in 4/7 studies	Serious inconsistency ( <i>P</i> = 69%)	Serious indirectness Use of surrogate end point	No serious imprecision	Undetected	1.09 (1.06-1.12)	800 per 1,000 <sup>c</sup> 79 more per 1,000 (55 more to 100 more)	Low due to bias, inconsistency, and indirectness
2,273 (2 RCTs), 1-6 mo	No serious risk of bias	No serious inconsistency	Serious indirectness <sup>d</sup>	Serious imprecision CIs are wide and border on no effect	Undetected	RR 0.89 (0.46-1.73) <sup>d</sup>	46 per 1,000 <sup>a</sup> 5 fewer per 1,000 (from 25 fewer to 33 more)	Low due to indirectness and imprecision
...	...	...	...	Nonfatal MI (critical outcome)	...	...	...	...
...	...	...	...	Nonfatal stroke (critical outcome)	...	...	...	...

Bibliography: Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database Syst Rev.* 2008;(1):CD003748. CASTLE = Cilostazol: A Study in Long-Term Effects. See Table S1 and S2 legends for expansion of other abbreviations.

<sup>a</sup>Control group risk estimates come from observed events reported in placebo arms of included studies.

<sup>b</sup>Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study. *J Vasc Surg.* 2008;47(2):330-336.

<sup>c</sup>Calculated from pooled standardized mean differences, converted into risk difference (assumed control response rate of 80%).

<sup>d</sup>Studies were conducted in patients with CAD undergoing stent placement and receiving aspirin and clopidogrel in addition to cilostazol and placebo.

**Table S8—[Section 4.1-4.4] Evidence Profile: Heparins vs Placebo in Patients With Symptomatic PAD and Claudication**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Event Rate With Control <sup>a</sup>	Risk Difference With Heparins (95% CI)	Quality of Evidence
221 (2 RCTs), <sup>b,c</sup> 6-18 mo	Serious risk of bias Dropout and withdrawal rate 29%	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	N/A. No events in either arm	N/A	N/A	Low due to bias and serious imprecision
Total mortality (critical outcome)									
221 (2 RCTs), <sup>b,c</sup> 6-18 mo	Serious risk of bias Dropout and withdrawal rate 29%	No serious inconsistency	No serious indirectness	Serious imprecision include benefit and harm	Undetected	RR 3.47 (0.74-16.28)	18 per 1,000	44 more per 1,000 (from 4 fewer to 275 more)	Low due to bias and serious imprecision
Cardiovascular events (TIA, stroke, unstable angina, MI [critical outcome])									
356 (5 RCTs), <sup>b,d</sup> 6 mo	Serious risk of bias Allocation concealment unclear in 4/5 studies	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	N/A. No events in either arm	N/A	N/A	Low due to bias and serious imprecision
Major bleeding events (critical outcome)									
201 (1 RCTs), <sup>b,g</sup> 18 mo	Serious risk of bias Dropout and withdrawal rate 32%	Single study only	Serious indirectness Use of surrogate endpoint	Serious imprecision include benefit and harm	Undetected	1.14 (1.07-1.18)	800 per 1,000	112 more per 1,000 (from 58 fewer to 149 more) <sup>h</sup>	Low due to study limitations, indirectness, and imprecision

Bibliography: Cosmi B, Conti E, Coccheri S. Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev.* 2001;(3):CD001999. See Table S1, S2, and S6 legends for expansion of abbreviations.

<sup>a</sup>Control group risk estimates for mortality, cardiovascular events, bleeding events, and walking distance come from observed events in control arms of RCTs.

<sup>b</sup>Antonicelli R, Sardina M, Scotti A, Bonizzoni E, Paciaroni E, Italian CAP Study Group. Randomized trial of the effects of low-dose calcium heparin in patients with peripheral arterial disease and claudication. *Am J Med.* 1999;107(3):234-239.

<sup>c</sup>Tesi M, Bronchi GF, Carini A, Morfini M, Cinotti S, Filiberti E. Efficacy and safety of a new low molecular weight heparin in the medium term treatment of atherosclerotic arteriopathy of the lower limbs. *J Drug Dev.* 1989;2(2):73-82.

<sup>d</sup>Calabrò A, Piarulli F, Milan D, Rossi A, Coscetti G, Crepaldi G. Clinical assessment of low molecular weight heparin effects in peripheral vascular disease. *Angiology.* 1993;44(3):188-195.

<sup>e</sup>Mannarino E, Pasqualini L, Innocente S, Orlandi U, Scricciolo V, Lombardini R, Giuffetti G. Efficacy of low-molecular weight heparin in the management of intermittent claudication. *Angiology.* 1991;42(1):1-7.

<sup>f</sup>Palmieri G, Ambrosi G, Agrati AM, Ferraro C, Marozzi S. A new low molecular weight heparin in the treatment of peripheral arterial disease. *Int Angiol.* 1988;7(suppl 3):41-47.

<sup>g</sup>In four of five studies, data on walking distance was presented in bar graph form only. Unable to assess mean difference between treatment arms in change in walking distance in these studies.

<sup>h</sup>Calculated from pooled standardized mean differences, converted into risk difference (assumed control response rate of 80%).

**Table S9—[Section 4.1-4.4] Evidence Profile: Prostaglandins vs Placebo in Patients With Intermittent Claudication**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Estimation of Absolute Effects Event Rate With No Prostaglandins <sup>a</sup>   Risk Difference With Prostaglandins (95% CI)	Quality of Evidence
1,354 (3 RCTs), 6-12 mo	Serious risk of bias Unclear concealment of allocation in all of the studies	No serious inconsistency	No serious indirectness	Serious imprecision CIs include benefit and harm; only 5 events	Undetected	RR 0.34 (0.08-2.39)	10 per 1,000   6 fewer per 1,000 (from 9 fewer to 14 more)	Low due to bias and imprecision
1,636 (5 RCTs), 3-12 mo	Serious risk of bias Unclear concealment of allocation in all of the studies	Serious inconsistency ( $I^2 = 46\%$ )	Serious indirectness Use of surrogate end point	No serious imprecision	Undetected	1.09 (1.07-1.12)	800 per 1,000 <sup>b</sup>   79 more per 1,000 (58 more to 98 more) <sup>c</sup>	Low due to bias, inconsistency, and indirectness
...	...	...	...	...	...	...	...	...
762 (1 RCT) 12 mo	Serious risk of bias Unclear concealment of allocation in all of the studies	Single study only	No serious indirectness	Very serious imprecision	Undetected	RR 0.09 (0.00-1.60)	13 per 1,000   11 fewer per 1,000 (from 13 fewer to 7 more)	Low due to bias and imprecision
762 (1 RCT) 12 mo	Serious risk of bias Unclear concealment of allocation in all of the studies	Single study only	No serious indirectness	Very serious imprecision	Undetected	RR 1.22 (0.33-4.52)	10 per 1,000   2 fewer per 1,000 (from 7 fewer to 37 more)	Low due to bias and imprecision

Bibliography: Momsen AH, Jensen MB, Norager CB, Madsen MR, Vestersgaard-Andersen T, Lindholt JS. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *Eur J Vasc Endovasc Surg*. 2009;38(4):463-474. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>Control group risk estimates come from median control rate or representative control group risk of the included studies.

<sup>b</sup>Assumed control response rate of 80%.

<sup>c</sup>Calculated from pooled standardized mean differences, converted into risk difference (assumed control response rate of 80%)

**Table S10—[Section 5.1] Evidence Profile: Prostanoids vs Placebo in Patients With Critical Limb Ischemia Ineligible for Revascularization Procedures**

Participants (studies), Follow-up	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Estimation of Absolute Effects		Quality of Evidence
							Event Rate With Placebo	Risk difference With Prostanoids (95% CI)	
1,116 (9 RCTs), 21.4 wk	Serious risk of bias. Allocation and blinding concerns	No serious inconsistency	No serious indirectness	No imprecision	Undetected	RR 1.32 (1.1-1.57)	243 per 1,000 <sup>a</sup>	77 more per 1,000 (from 24 more to 138 more)	Moderate due to risk of bias
Rest pain relief (any improvement on a validated scale) (important outcome)									
1,132 (8 RCTs), 17.5 wk	Serious risk of bias. Allocation and blinding concerns	Serious inconsistency ( $I^2 = 44\%$ )	No serious indirectness	No imprecision	Undetected	RR 1.54 (1.22-1.96)	253 per 1,000 <sup>a</sup>	136 more per 1,000 (from 55 more to 242 more)	Low due to risk of bias and inconsistency
Ulcer healing (any decrease in size of ulcer or presence of granulation tissue) (important outcome)									
1,790 (9 RCTs), 23.1 wk	Serious risk of bias. Allocation and blinding concerns	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	RR 0.89 (0.76-1.04)	313 per 1,000 <sup>a</sup>	34 fewer per 1,000 (from 75 fewer to 12 more)	Low due to risk of bias, inconsistency, and imprecision
Amputations (major or minor amputations) (critical outcome)									
1,391 (5 RCTs), 32 wk	Serious risk of bias. Allocation and blinding concerns	Serious inconsistency ( $I^2 = 40\%$ )	No serious indirectness	Serious imprecision	Undetected	RR 1.07 (0.65-1.75)	121 per 1,000 <sup>a</sup>	8 more per 1,000 (from 42 fewer to 90 more)	Low due to risk of bias, inconsistency, and imprecision
Mortality (critical outcome)									
716 (8 RCTs), 14.4 mo	Serious risk of bias. Allocation and blinding concerns	No serious inconsistency	No serious indirectness	No imprecision	Undetected	RR 2.35 (1.99-2.78)	77 per 1,000 <sup>a</sup>	103 more per 1,000 (from 76 more to 137 more)	Moderate due to risk of bias
Adverse events (important outcome)									
							394 per 1,000 <sup>a</sup>	531 more per 1,000 (from 390 more to 701 more)	

Bibliography: Ruffolo AJ, Romano M, Ciapponi A. Prostanoids for critical limb ischemia. *Cochrane Database of Syst Rev.* 2010;(1):CD006544. See Table S2 legend for expansion of abbreviations.

<sup>a</sup>Control group risk estimates come from median control rate or representative control group risk of the included studies. For rest pain relief or ulcer healing control rates represent number of subjects with improvement in control arm.

**Table S11—[Section 6.1-6.3] Evidence Profile: Thrombolysis vs Surgery for the Treatment of Acute Limb Ischemia**

Participants (Studies), Follow-up	Quality Assessment			Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	With Surgery	Risk Difference With Thrombolysis (95% CI)	Quality of Evidence
654 (2 RCTs), <sup>a</sup> 12 mo	No serious risk of bias	Serious inconsistency ( $I^2 = 49\%$ )	No serious indirectness	Limb salvage at 1 y (critical outcome) Serious imprecision CI includes harms and benefits	Undetected	RR 1.00 (0.86-1.17)	754 per 1,000 <sup>b</sup>	0 fewer per 1,000 (from 106 fewer to 128 more)	Low due to inconsistency and imprecision
768 (3 RCTs), <sup>a</sup> 12 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Amputation at 1 y (critical outcome) Serious imprecision CI includes harms and benefits Low number of events	Undetected	RR 1.10 (0.88-1.38)	190 per 1,000 <sup>b</sup>	19 more per 1,000 (from 22 fewer to 72 more)	Moderate due to imprecision
768 (3 RCTs), <sup>a</sup> 12 mo	No serious risk of bias	Serious inconsistency ( $I^2 = 80\%$ )	No serious indirectness	Death at 1 y (critical outcome) <sup>c</sup> Serious imprecision CI includes harms and benefits	Undetected	RR 0.74 (0.35-1.58)	169 per 1,000 <sup>b</sup>	43 fewer per 1,000 (from 109 fewer to 98 more)	Low due to inconsistency and imprecision
1,180 (5 RCTs), <sup>a,e</sup> 1-12 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Stroke at 30 d (critical outcome) <sup>d</sup> Serious inconsistency CI includes harms and benefits Low number of events (8)	Undetected	0.01 (0.00-0.02) <sup>f</sup>	0 per 1,000 <sup>b</sup>	10 more per 1,000 (from 0 fewer to 20 more)	Moderate due to imprecision
1,070 (4 RCTs), <sup>a</sup> 1-12 mo	No serious risk of bias <sup>g</sup>	No serious inconsistency	No serious indirectness <sup>h</sup>	Extracranial major hemorrhage at 30 d Serious imprecision CI includes harms and benefits Low number of events (60)	Undetected	RR 2.34 (1.32-4.14)	12 per 1,000 <sup>b</sup>	16 more per 1,000 (from 3 more to 37 more)	Moderate due to imprecision

Bibliography: Berridge DC, Kessel D, Robertson I. Surgery versus thrombolysis for acute limb ischaemia: initial management. *Cochrane Database Syst Rev*. 2002;(3):CD002784. Ouriel K, Veith FJ, Sasahara AA; Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. The STILE investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischaemia of the lower extremity. *Ann Surg*. 1994;220(3):251-268. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. *N Engl J Med*. 1998;338(16):1105-1111. See Table S2 legend for expansion of abbreviations.

<sup>a</sup>For one study using three different doses of the thrombolytic agent, only the optimal dose is used for comparison with surgery.

<sup>b</sup>Control group risk estimates from median or representative control group risk of included studies.

<sup>c</sup>Ouriel et al (1998) reported that one in 54 deaths in the thrombolysis group were from intracranial hemorrhage, whereas none of 46 in the surgery group were from intracranial hemorrhage.

<sup>d</sup>Of reported nonfatal strokes, all happened in the thrombolysis group and all were intracranial hemorrhages (8/8 [100%]).

<sup>e</sup>STILE investigators et al (1994) included patients with both acute and chronic limb ischemia.

<sup>f</sup>Pooled risk difference presented instead of relative risk.

<sup>g</sup>Concealment of allocation unclear in one study.



**Table S12—[Section 6.1-6.3] Evidence Profile: Intraarterial Urokinase vs Intraarterial rt-PA for Acute Limb Ischemia**

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings		
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Estimation of Absolute Effects		
						Event Rate With Intraarterial rt-PA	Risk Difference With Urokinase (95% CI)	Quality of Evidence
368 (3 RCTs), 1-6 mo	Serious risk of bias. Unclear concealment of allocation	No serious inconsistency	No serious indirectness	Serious imprecision CIs are wide and include benefit and harm	Undetected All-cause mortality (critical outcome)	RR 0.79 (0.26-2.46)	19 per 1,000 <sup>a</sup> 4 fewer per 1,000 (from 14 fewer to 27 more)	Low due to risk of bias and imprecision
368 (3 RCTs), 1-6 mo	Serious risk of bias. Unclear concealment of allocation	No serious inconsistency	No serious indirectness	Serious imprecision CIs are wide and include benefit and harm	Undetected Amputation (critical outcome)	RR 0.78 (0.23, 2.71)	89 per 1,000 <sup>a</sup> 20 fewer per 1,000 (from 68 fewer to 152 more)	Low due to risk of bias and imprecision
298 (3 RCTs), 1-6 mo	Serious risk of bias. Unclear concealment of allocation	No serious inconsistency	No serious indirectness	Serious imprecision CI includes harm and benefit	Undetected Major nonfatal extracranial bleed (important outcome)	RR 0.69 (0.23-2.06)	8 per 1,000 <sup>a</sup> 2 fewer per 1,000 (from 6 fewer to 8 more)	Low due to risk of bias and imprecision

Bibliography: Robertson I, Kessel DO, Berridge DC. Fibrinolytic agents for peripheral arterial occlusion. *Cochrane Database Syst Rev.* 2010;(3):CD001099. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>Control group risk estimate comes from median event rate in the rt-PA arm.



**Table S13—[Section 8.1-8.3] Evidence Profile: Aspirin plus Dipyridamole vs Placebo for Prevention of Thrombosis After Peripheral Bypass Surgery**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings				Quality of Evidence	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Event Rate With Control <sup>b</sup>	Estimation of Absolute Effects Time Period: 1 y		
								Difference With Aspirin + Dipyridamole (95% CI)		
966 (6 RCTs), 12 mo	Serious risk of bias <sup>b</sup>	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	RR 0.68 (0.55-0.83)	71 per 1,000	22 fewer per 1,000 (from 32 fewer to 12 fewer)	Low due to risk of bias and indirectness	
Amputation inferred from loss of primary graft patency (critical outcome)										
148 (1 RCT), 12 mo	Serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.52 (0.27-1.01)	71 per 1,000	34 fewer per 1,000 (from 51 fewer to 1 more)	Low due to risk of bias and imprecision	
Amputation (critical outcome)										
750 (3 RCTs), 12 mo	No risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.86 (0.6-1.22)	105 per 1,000	14 fewer per 1,000 (from 42 fewer to 23 more)	Moderate due to imprecision	
Death (critical outcome)										
667 (3 RCTs), 12 mo	No risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.65 (0.4-1.06)	28 per 1,000	9 fewer per 1,000 (from 16 fewer to 1 more)	Moderate due to imprecision	
MI (critical outcome)										
667 (3 RCTs), 12 mo	No risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 0.79 (0.42-1.49)	27 per 1,000	5 fewer per 1,000 (from 15 fewer to 13 more)	Moderate due to imprecision	
Stroke <sup>d</sup> (critical outcome)										
598 (2 RCTs), 12 mo	No risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision <sup>c</sup>	Undetected	RR 1.86 (0.85-4.04)	10 per 1,000	8 more per 1,000 (from 1 fewer to 30 more)	Moderate due to imprecision	
Major extracranial bleeding <sup>e</sup> (critical outcome)										

**Bibliography:** Brown J, Lethaby A, Maxwell H, Wawrzyniak AJ, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev.* 2008;(4):CD000535. Study Group on Pharmacological Treatment After TPA. Platelet inhibition with ASA/dipyridamole after percutaneous balloon angioplasty in patients with symptomatic lower limb arterial disease. A prospective double-blind trial. *Eur J Vasc Surg.* 1994;8(1):83-88. BOA = Dutch Bypass Oral Anticoagulants or Aspirin. See Table S1 and S2 legends for expansion of other abbreviations.

<sup>a</sup>Control group risk estimate derived from application of relative risk of placebo vs aspirin/dipyridamole to aspirin event rate in a large RCT (BOA) comparing warfarin to aspirin following peripheral artery bypass surgery (Study Group on Pharmacological Treatment After TPA, 1994).

<sup>b</sup>Problems with allocation concealment and blinding.

<sup>c</sup>Low number of events, CI includes important benefits and harms.

<sup>d</sup>None of the strokes was due to intracranial bleeding.

<sup>e</sup>Of these bleedings, five of 19 (26%) were GI.

**Table S14—[Section 8.1-8.3] Evidence Profile: Aspirin and Clopidogrel vs Aspirin Alone for Patients With PAD Postsurgical Below Knee Revascularization (Venous or Prosthetic Grafts)**

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings				Quality of Evidence	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin <sup>a</sup>	Risk Difference With Aspirin + Clopidogrel (95% CI)		Estimation of Absolute Effects Time Period: 1 y
851 (1 RCT), mean ~11 mo <sup>a</sup>	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events = 41)	Undetected	RR 1.42 (0.77-2.60)	90 per 1,000	37 more per 1,000 (from 20 fewer to 144 more)	Moderate due to imprecision	
...	...	...	...	MI (critical outcome): not reported	...	...	...	...	...	
...	...	...	...	Stroke (critical outcome): not reported	...	...	...	...	...	
851 (1 RCT), mean ~11 mo <sup>a</sup>	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision Extracranial major bleeding (critical outcome); severe GUSTO criteria <sup>c</sup>	Undetected	RR 1.73 (0.51-5.88)	19 per 1,000	13 more per 1,000 (from 9 fewer to 92 more)	Moderate due to imprecision	
...	...	...	...	Amputations (critical outcome)	...	...	...	...	...	
851 (1 RCT), mean ~11 mo <sup>a</sup>	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events = 76)	Undetected	HR 0.69 (0.45-1.07)	48 per 1,000	14 fewer per 1,000 (from 26 fewer to 3 more)	Moderate due to imprecision	

Bibliography: Belch JJ, Dormandy J, Biasi GM, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg.* 2010;52(4):825-833. See Table S1, S2, S5, and S14 legends for expansion of abbreviations.

<sup>a</sup>Control group rates obtained from event rates in aspirin arm of BOA study normalized to 1 y.

<sup>b</sup>Eight patients lost to follow-up in the intervention group (aspirin + clopidogrel) and 11 patients in the comparison group (aspirin group).

<sup>c</sup>Fatal bleeding events were two of 426 in the intervention group (aspirin + clopidogrel group) and one of 422 in the comparison group (aspirin group).

**Table S15—[Section 8.1-8.3] Evidence Profile: Aspirin and Clopidogrel vs Aspirin Alone for Patients With PAD Postsurgical Below Knee Revascularization With Prosthetic Grafts**

Participants (studies), Follow-up	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin <sup>a</sup>	Risk Difference With Aspirin + Clopidogrel (95% CI)	Quality of Evidence
253 (1 RCT), mean ~11 mo <sup>a</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision CIs include significant harm and benefit (no. events = 10)	Undetected	RR 1.46 (0.42-5.07)	90 per 1,000	41 more per 1,000 (from 52 fewer to 366 more)	Low due to imprecision
Stroke (critical outcome): not reported									
Extracranial major bleeding (critical outcome); severe GUSTO criteria <sup>b</sup>									
253 (1 RCT), mean ~11 mo <sup>a</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision (no. events = 3)	Undetected	RR 0.50 (0.05-5.44)	19 per 1,000	9 fewer per 1,000 (from 18 fewer to 84 more)	Low due to imprecision
Amputations (critical outcome)									
253 (1 RCT), mean ~11 mo <sup>a</sup>	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision CIs include significant harm and benefit (no. events = 36)	Undetected	HR 0.49 (0.26-0.93)	48 per 1,000	24 fewer per 1,000 (from 35 fewer to 3 fewer)	Low due to imprecision

Bibliography: Belch JJ, Dormandy J, Biasi GM, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg.* 2010;52(4):825-833. HR = hazard ratio. See Table S1, S2, S5, and S14 legends for expansion of other abbreviations.

<sup>a</sup>Control group risk estimates obtained from event rates in aspirin arm of BOA study, normalized to 1 y.

<sup>b</sup>Unclear whether any of severe bleeds were fatal.

**Table S16—[Section 8.1-8.3] Evidence Profile: Warfarin vs Aspirin for Patients With PAD Postsurgical Revascularization**

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin <sup>a</sup>	Risk Difference With OAC (95% CI)	Quality of Evidence
2 650 (1 RCT) 21 mo	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events <400)	Undetected	RR 1.03 (0.86-1.23)	90 per 1,000	2 more per 1,000 (from 22 fewer to 20 more)	Moderate due to imprecision
	All-cause mortality (critical outcome)								
2 650 (1 RCT) 21 mo	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events <400)	Undetected	RR 0.69 (0.43-1.1)	18 per 1,000	5 fewer per 1,000 (from 10 fewer to 1 more)	Moderate due to imprecision
	MI (critical outcome), including fatal strokes								
2 650 (1 RCT) 21 mo	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events <400)	Undetected	RR 0.74 (0.48-1.14)	21 per 1,000	5 fewer per 1,000 (from 11 fewer to 2 more)	Moderate due to imprecision
	Stroke (critical outcome); <sup>c</sup> including ischemic, hemorrhagic, and other stroke types; includes fatal strokes								
Extracranial major bleeding (critical outcome) <sup>d</sup> ; nonfatal bleeding requiring hospitalization, excluding all reports of intracranial hemorrhage or postsurgical bleeding									
2 650 (1 RCT) 21 mo	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events <400)	Undetected	RR 1.90 (1.33-2.73)	19 per 1,000	17 more per 1,000 (from 6 more to 32 more)	Moderate due to imprecision
	Limb loss (critical outcome); all amputation (ipsilateral and contralateral)								
2 650 (1 RCT) 21 mo	No serious risk of bias <sup>b</sup>	No serious inconsistency	No serious indirectness	Serious imprecision CIs include significant harm and benefit (no. events <400)	Undetected	RR 0.91 (0.7-1.18)	48 per 1,000	4 fewer per 1,000 (from 14 fewer to 8 more)	Moderate due to imprecision

**Bibliography:** Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet*. 2000;355(9201):346-351. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>Control group risk estimates obtained from event rates in aspirin arm of study, normalized to 1 y.

<sup>b</sup>Thirteen and 27 patients withdrew from the warfarin and aspirin arms, respectively. Not included in analysis. Sixteen and 13 patients were lost to follow-up, respectively; included in the analysis.

<sup>c</sup>Hemorrhagic strokes: 14 of 1,326 in the intervention (OAC) group and four of 1,324 in the comparison (antiplatelet agent) group.

<sup>d</sup>Fatal bleeding events: 16 of 1,326 in the intervention group (OAC group) and 12 of 1,324 in the comparison group (antiplatelet agent group).