CHEST Online Data Supplement

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

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Table S1—*[Section 2.1] Aspirin (75-100 mg) Compared With No Aspirin in the Primary Prevention of Cardiovascular Disease*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 10 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Without Aspirin	With Aspirin (95% CI)	Quality of Evidence
Overall mortality (critical outcome), including cancer mortality, vascular mortality, and fatal bleeds[a]									
100,076 (9), 3.8-10 y	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision CI includes no benefit	Undetected	RR 0.94 (0.88-1.00)	60-y-old man[c]		Moderate due to imprecision
							100 deaths per 1,000	6 fewer deaths per 1,000 (from 12 fewer to 0 fewer)	
Nonfatal MI (critical outcome)									
95,000 (6), 3.8-10 y	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 0.77 (0.69-0.86)	Low-risk population[e]		High
							27 MI per 1,000[d]	6 fewer MI per 1,000 (from 8 fewer to 4 fewer)	
							Moderate-risk population[e]		
							83 MI per 1,000[d]	19 fewer MI per 1,000 (from 26 fewer to 12 fewer)	
							High-risk population[e]		
							136 MI per 1,000[d]	31 fewer MI per 1,000 (from 42 fewer to 19 fewer)	

(Continued)

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Table S1—*Continued*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 10 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Without Aspirin	With Aspirin (95% CI)	Quality of Evidence
Nonfatal stroke (critical outcome), including ischemic, hemorrhagic, and unknown cause[f]									
95,000 (6), 3.8-10 y	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 0.95 (0.85-1.06)	Low-risk population[e]		High
							23 strokes per 1,000[d]	1 fewer stroke per 1,000 (from 3 fewer to 1 more)	
							Moderate-risk population[e]		
							65 strokes per 1,000[d]	3 fewer strokes per 1,000 (from 10 fewer to 4 more)	
							High-risk population[e]		
							108 strokes per 1,000[d]	5 fewer strokes per 1,000 (from 16 fewer to 6 more)	

(Continued)

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Table S1—*Continued*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 10 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Without Aspirin	With Aspirin (95% CI)	Quality of Evidence
Major extracranial bleed (important outcome), mainly GI and usually defined as bleed requiring transfusion or resulting in death[e]									
95,000 (6), 3.8-10 y	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 1.54 (1.30-1.82)	Low-risk population[g]		High
							8 bleeds per 1,000[d]	4 more bleeds per 1,000 (from 2 more to 7 more)	
							Moderate-risk population[g]		
							24 bleeds per 1,000[d]	16 more bleeds per 1,000 (from 7 more to 20 more)	
							High-risk population[g]		
							40 bleeds per 1,000[d]	22 more bleeds per 1,000 (from 12 more to 33 more)	

Bibliography: Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' Collaboration. 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 et al. Effect of aspirin on cardiovascular and all-cause mortality in primary prevention of cardiovascular disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2011;24(7):621-629.[a] MI = myocardial infarction; RR = risk ratio.

[a]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).

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

[e]Control group risk estimate for 10-y mortality applies to a 60-y-old man and comes 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).

[d]Control group risk estimates in low-, moderate-, and high-cardiovascular-risk groups are based on the Framingham score. As explained in the article, we used data from an individual patient data 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.

[e]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.

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

[g]In the individual patient data 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 for future major bleeding events, respectively.

Table S2—*[Sections 3.1.1-3.1.5, 3.2.1] Aspirin vs No Aspirin in Patients With Established CAD*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 5 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk Without Aspirin	Risk Difference With Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome), including sudden death, pulmonary embolism, hemorrhage, and unknown cause (proportion not reported)									
17,000 (16 RCTs), 27mo	No serious limitations	No serious limitations	No serious limitations	Imprecise[a] CI includes benefit and no effect	Undetected	RR 0.90 (0.82-0.99)	133 per 1,000[b]	13 fewer per 1,000 (from 21 fewer to 1 fewer)	Moderate due to imprecision[a]
Nonfatal MI (critical outcome)									
17,000 (16 RCTs), 27 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.69 (0.60-0.80)	117 per 1,000[b]	37 fewer per 1,000 (from 47 fewer to 23 fewer)	High
Nonfatal stroke (critical outcome), including ischemic, hemorrhagic, and unknown cause[c]									
17 000 (16 RCTs), 27 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.81 (0.71-0.92)	135 per 1,000[b]	26 fewer per 1,000 (from 39 fewer to 11 fewer)	High
Major extracranial bleed (important outcome)									
17,000 (16 RCTs), 27 mo	No serious limitations	No serious limitations	Indirectness only reported in stroke/TIA trials[d]	No serious limitations	Undetected	RR 2.69 (1.25-5.76)	15 per 1,000[e]	25 more per 1,000 (from 44 more to 71 more)	Moderate due to indirectness

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

[a] Rated down for imprecision because the 95% CI suggests possible benefit and no effect on total mortality.

[b] Control group risk estimates (without aspirin) for MI and stroke come from observed yearly event rates in 16 RCTs reported in the meta-analysis, adjusted to a 5-y time frame. The control group rate 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 the control group rate estimate without aspirin.

[c] Of the strokes in the meta-analysis, 0.8% with aspirin were intracranial hemorrhages, and 0.4% of strokes without aspirin were intracranial hemorrhages.

[d] Rated down for indirectness because bleeding events were only reported in a subset of trials with stroke and TIA populations.

[e] To estimate control group risks for major bleeds, we have used major bleed event rates from the aspirin arm in the CAPRIE trial adjusted to a 5-y time frame as the starting point (to ensure consistency across evidence profiles). We then used the RR of 2.69 for the comparison of aspirin to no aspirin observed in the meta-analysis to derive the control group rate estimate without aspirin.

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Table S3—*[Sections 3.1.1-3.1.5] Clopidogrel vs Aspirin for Patients With Established CAD*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 5 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin	Risk Difference With Clopidogrel (95% CI)	Quality of Evidence
Total mortality (critical outcome), including fatal MI, fatal ischemic stroke, fatal hemorrhagic stroke, and other vascular death[a]									
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[b]	No serious indirectness	Serious imprecision CI includes harm with clopidogrel	Undetected	RR 0.98 (0.87-1.10)	120 per 1,000[c]	2 fewer per 1,000 (from 16 fewer to 12 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes no benefit with clopidogrel	Undetected	RR 0.85 (0.72-1.0)	80 per 1,000[c]	12 fewer per 1,000 (from 22 fewer to 0 more)	Moderate due to imprecision
Nonfatal stroke (critical outcome), including ischemic and hemorrhagic stroke[d]									
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes harm with clopidogrel	Undetected	RR 0.94 (0.83-1.06)	110 per 1,000[c]	7 fewer per 1,000 (from 19 fewer to 7 more)	Moderate due to imprecision
Major extracranial bleed (important outcome), including any bleeding disorder, severe[e]									
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes harm with clopidogrel	Undetected	RR 0.88 (0.7-1.12)	40 per 1,000[f]	5 fewer per 1,000 (from 12 fewer to 5 more)	Moderate due to imprecision

Bibliography: 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. See Table S1 and S2 legends for expansion of abbreviations.

[a] Of the deaths in CAPRIE, 27 of 571 (4.7%) with aspirin were fatal bleeding events, and 23 of 560 (4.1%) with clopidogrel were fatal bleeding events.

[b] Subgroup analysis of composite end point reported relative risk reduction of 7.3% for patients with stroke and 23.8% for patients with peripheral arterial disease and a 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; therefore, we did not rate down for inconsistency.

[c] Control group risk estimates for total mortality come from the aspirin arm of the CHARISMA trial. Estimates for MI and stroke come from observed events in the aspirin arm of a meta-analysis of 16 RCTs in secondary prevention (Baigent et al[9]), adjusted to a 5-y time frame.

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

[e] 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 ($P = .05$).

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

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Table S4—*[Sections 3.1.1-3.1.6] Resource Implications: Clopidogrel vs Aspirin for Secondary Prevention of Vascular Disease*

Author/Year	Patient Population	Conclusion	ICER	Effectiveness Unit	Year of Cost Basis	Type of Analysis	Type of Model	Time Frame
Sarasin et al[1]/2000	Aged 65 y with prior stroke or TIA	Cost-effective	$ 26,580	QALY	1998	Cost utility	Markov	Lifetime
Schleinitz et al[2]/2004	Aged 63 y in the CAPRIE trial population[a] with PAD	Cost-effective	$ 25,100	QALY	2002	Cost utility	Markov	Lifetime
Schleinitz et al[2]/2004	Aged 63 y in the CAPRIE trial population[a] with PAD with stroke past 6 mo	Cost-effective	$ 31,200	QALY	2002	Cost utility	Markov	Lifetime
Schleinitz et al[2]/2004	CAPRIE population with MI in the past 35 d	Dominated	Dominated		2002	Cost utility	Markov	Lifetime
Karnon et al[3]/2005	Men aged 60 y in the CAPRIE trial	Cost-effective	£ 21,489	QALY	2003	Cost utility	Markov	Lifetime
Durand-Zaleski and Bertrand[4]/2004	CAPRIE base case population	Cost-effective	£ 13,390	LYG	2003	Cost-effectiveness	Markov	2 y
Durand-Zaleski and Bertrand[4]/2004	CAPRIE subgroup with prior stroke or MI	Cost-effective	£ 6,310.00	LYG	2003			

LYG = life year gained; PAD = peripheral arterial disease; QALY = quality-adjusted life year. See Table S1 and S2 legends for expansion of other abbreviations.

[a] LYG.

Table S5—*[Sections 3.1.1-3.1.5] Aspirin Plus Clopidogrel vs Aspirin in the Secondary Prevention of Cardiovascular Events*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time frame: 5 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin	Risk Difference With Aspirin + Clopidogrel (95% CI)	Quality of Evidence
Total mortality (critical outcome), including deaths from cardiovascular cause and hemorrhage[a]									
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	Undetected	RR 0.99 (0.86-1.14)	120 per 1,000[d]	1 fewer per 1,000 (from 17 fewer to 17 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	RR 0.94 (0.75-1.18)	80 per 1,000[d]	5 fewer per 1,000 (from 20 fewer to 14 more)	Moderate due to imprecision
Nonfatal stroke (critical outcome), including ischemic, hemorrhagic, and unknown cause[e]									
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	RR 0.81 (0.64-1.02)	110 per 1,000[d]	21 fewer per 1,000 (from 40 fewer to 2 more)	Moderate due to imprecision
Major extracranial bleed (critical outcome), including severe bleeding as defined by the GUSTO criteria but excluding fatal and intracranial bleeds[f]									
15,603 (1 RCT), 28 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	RR 1.25 (0.97-1.61)	40 per 1,000[h]	10 more per 1,000 (from 1 fewer to 24 more	Moderate due to imprecision

Bibliography: Bhatt DL, Fox KA, Hacke W, 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. Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: colllaborative meta-analysis of individual participant data from randomized trials. *Lancet*. 2009;373(9678):1849-1860. GUSTO = Global Use of Strategies To Open Occluded Arteries. See Table S1, S2, and S4 legends for expansion of other abbreviations.

[a] Of the deaths in the CHARISMA trial, 17 of 571 (3%) with aspirin were fatal bleeding events, and 26 of 574 (4.5%) with clopidogrel and aspirin were fatal bleeding events.

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

[c] CI includes important benefit and harm (for mortality) and no benefit (for stroke).

[d] 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, *Lancet* 2009), adjusted to 5-y time frame.

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

[f] 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).

[g] CI includes no benefit and important harm.

[h] Control group risk estimates come from observed major bleeding events in the CAPRIE trial, adjusted to a 5-y time frame, and not from the 16 RCTs included in the meta-analysis or from CHARISMA because these studies did not report major bleeds consistently.

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Table S6—*[Sections 3.1.1-3.1.6] Aspirin Plus Clopidogrel vs Clopidogrel in the Secondary Prevention of Cardiovascular Events*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time frame: 1 y Post-ACS		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	With Clopidogrel	Difference With Aspirin + Clopidogrel (95% CI)	Quality of Evidence
Total mortality (critical outcome), including fatal bleeds[a]									
7,599 (1 RCT), 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected	RR 1.06 (0.84-1.34)	119 per 1,000[c]	7 more per 1,000 (from 19 fewer to 40 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
7,599 (1 RCT), 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected	RR 0.85 (0.57-1.26)	68 per 1,000[d]	10 fewer per 1,000 (from 29 fewer to 18 more)	Moderate due to imprecision
Nonfatal stroke (critical outcome), including ischemic, hemorrhagic, and unknown cause[e]									
7,599 (1 RCT), 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected	RR 0.90 (0.77-1.04)	103 per 1,000[d]	10 fewer per 1,000 (from 24 fewer to 4 more)	Moderate due to imprecision
Major extracranial bleed (critical outcome), including life-threatening and major bleeding[f]									
7,599 (1 RCT), 18 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 2.44 (1.83-3.24)	35 per 1,000[g]	60 more per 1,000 (from 29 to 78 more)	High

Bibliography: 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. 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. ACS = acute coronary syndrome. See Table S1, S2, and S4 legends for expansion of other abbreviations.

[a] Risk of fatal bleeding was 0.43% (16 events) and 0.29 (11 events) in the treatment and control groups, respectively.

[b] CIs include possible benefit and possible harm and low number of events.

[c] Control group risk estimates for total mortality were derived by applying relative risk ratio for clopidogrel vs aspirin to the total mortality rate observed in the aspirin arm of the CHARISMA trial.

[d] Control group risk estimates for nonfatal MI and nonfatal stroke were derived by applying relative risk ratio for clopidogrel vs aspirin to the observed event rates in the aspirin arm of a meta-analysis of 16 RCTs in secondary prevention (Baigent et al), adjusted to a 5-y time frame.

[e] In nonfatal ischemic stroke, the rates of primary intracranial hemorrhage were 0.7% (27) and 0.4% (15) in the treatment and control groups, respectively.

[f] Control group risk estimates for extracranial bleeding from observed major bleeding events in the CAPRIE trial, adjusted to a 5-y time frame, and not from the 16 RCTs included in the meta-analysis because these studies did not report major bleeds consistently.

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Table S7—*[Sections 3.1.1-3.1.6] Moderate-Intensity Warfarin Plus Aspirin vs Aspirin Alone in Patients With Established CAD*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 5 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin[a]	Risk Difference With Warfarin Plus Aspirin (95% CI)	Quality of Evidence
Total mortality									
7,835 (10 RCTs), 3-60 mo	No serious limitations	No serious limitations	Serious[b]	Imprecise CI includes benefit and harm	Undetected	RR 1.0 (0.82-1.22)	120 per 1,000[a]	0 more per 1,000 (from 22 fewer to 26 more)	Low due to indirectness and imprecision
Nonfatal MI (critical outcome)									
7,835 (10 RCTs), 3-60 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.69 (0.54-0.88)	80 per 1,000[a]	25 fewer per 1,000 (from 37 fewer to 10 fewer)	Moderate due to imprecision
Nonfatal stroke (critical outcome), including ischemic and hemorrhagic									
7,073 (5 RCTs), 3-60 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.56 (0.37-0.86)	110 per 1,000[a]	48 fewer per 1,000 (from 69 fewer to 15 fewer)	Moderate due to imprecision
Major extracranial bleed (critical outcome)[c]									
7,835 (10 RCTs), 3-60 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 2.37 (1.62-3.47)	40 per 1,000[d]	55 more per 1,000 (from 25 more to 99 more)	High
Burden of treatment (important outcome)[e]									
N/A[e]						Warfarin > aspirin	Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/monitoring, increased hospital/clinic visits		High
							Aspirin: daily medication only		

Bibliography: Johnson WC, Williford WO. 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;35:413-421. 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;28:446-457. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357:217-227. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. *Ann Intern Med*. 2005;143(4):241-250. 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):184-1860. N/A = not applicable; OASIS = Optimal Antiplatelet Strategy for Interventions. See Table S1, S2, and S4 legends for expansion of other abbreviations.

[a]Control group risk estimates for vascular mortality, MI, and strokes (ischemic, hemorrhagic, and unknown cause) come from observed events in a meta-analysis of 16 RCTs in secondary prevention (Baigent et al).

[b]Cannot determine cardiovascular mortality, only total mortality. Imbalance in one study for cancer deaths.

[c]In the OASIS trial, there may be double counting of hemorrhagic strokes as major bleeding and death.

[d]Control group risk estimates for major bleeds come from the aspirin-alone arm of the CAPRIE trial.

[e]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.

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Table S8—*[Sections 3.2.1-3.2.5] Clopidogrel vs Aspirin for Patients With Recent ACS*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 1 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin	Risk Difference With Clopidogrel (95% CI)	Quality of Evidence
Vascular mortality (critical outcome), including fatal MI, fatal ischemic stroke, fatal hemorrhagic stroke, and other vascular death[a]									
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[b]	No serious indirectness	No serious imprecision	Undetected	RR 0.92 (0.80-1.07)	60 per 1,000[c]	5 fewer per 1,000 (from 12 fewer to 5 more)	High
Nonfatal MI (critical outcome)									
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency[b]	No serious indirectness	Serious imprecision CI includes no benefit with clopidogrel	Undetected	RR 0.85 (0.72-1.0)	70 per 1,000[c]	10 fewer per 1,000 (from 22 fewer to 0 more)	Moderate due to imprecision
Nonfatal stroke (critical outcome), including ischemic and hemorrhagic stroke[d]									
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency[b]	No serious indirectness	No serious imprecision[e]	Undetected	RR 0.94 (0.83-1.06)	20 per 1,000[c]	1 fewer per 1,000 (from 3 fewer to 1 more)	High
Major extracranial bleed (important outcome), including any bleeding disorder, severe[f]									
19,185 (1 RCT), 1.9 y	No serious risk of bias	No serious inconsistency[b]	No serious indirectness	No serious imprecision[e]	Undetected	RR 0.88 (0.70-1.12)	30 per 1,000[c]	3 fewer per 1,000 (from 9 fewer to 3 more)	High

Bibliography: 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. CURE = Clopidogrel in Unstable Angina To Prevent Recurrent Events. See Table S1, S2, S4, and S6 legends for expansion of other abbreviations.

[a] Of the deaths in CAPRIE, 27 of 405 (6.7%) with aspirin were fatal bleeding events, and 23 of 372 (6.2%) with clopidogrel were fatal bleeding events.

[b] Subgroup analysis of composite end point reported relative risk reduction of 7.3% for patients with stroke and 23.8% for patients with peripheral arterial disease patients 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 subgroup analysis; therefore, we did not rate down for inconsistency.

[c] Control group risk estimates for death, MI, stroke, and bleeds come from the CURE trial (9-mo follow-up slightly adjusted to fit 1-y time frame).

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

[e] Our decision not to rate down for imprecision is due to the low control group risk for strokes and major bleeds that result in no important harm of clopidogrel (as judged by the upper limit of the 95% CI for the absolute effect).

[f] 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.

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Table S9—*[Sections 3.2.1-3.2.5] Aspirin Plus Clopidogrel vs Aspirin in Patients With a Recent ACS*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 1 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin	Risk Difference With Aspirin + Clopidogrel (95% CI)	Quality of Evidence
Vascular mortality (critical outcome)[a]									
12,562 (1 RCT), 9 mo	No serious limitations	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 0.93 (0.79-1.08)	60 per 1,000[b]	4 fewer per 1,000 (from 13 fewer to 5 more)	Moderate due to imprecision
Nonfatal MI (important outcome)									
12,562 (1 RCT), 9 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.77 (0.67-0.89)	70 per 1,000[b]	16 fewer per 1,000 (from 23 fewer to 8 fewer)	High
Nonfatal stroke (important outcome)[c]									
12,562 (1 RCT), 9 mo	No serious limitations	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 0.86 (0.63-1.18)	20 per 1,000[b]	3 fewer per 1,000 (from 7 fewer to 4 more)	Moderate due to imprecision
Major bleed (important outcome)[d,e]									
12,562 (1 RCT), 9 mo	No serious limitations	No serious limitations	No serious limitations	Imprecise CI includes no substantial harm	Undetected	RR 1.38 (1.13-1.67)	30 per 1,000[b]	11 more per 1,000 (from 4 more to 20 more)	Moderate due to imprecision

Bibliography: Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502. See Table S1, S2, and S6 legends for expansion of abbreviations.

[a] Of the total deaths in the CURE (Clopidogrel in Unstable Angina To Prevent Recurrent Events) trial, 15 of 390 (3.8%) with aspirin were fatal bleeding events, and 11 of 359 (3.1%) with clopidogrel were fatal bleeding events.

[b] Control group risk estimates come from the CURE trial (9-mo follow-up adjusted to fit 1-y time frame).

[c] Of the strokes in CURE, five of 87 (5.7%) with aspirin were hemorrhagic, and seven of 75 (9.3%) with clopidogrel were hemorrhagic.

[d] Major bleed defined as substantially disabling bleed, intraocular bleed leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood.

[e] Of the major extracranial bleeds in CURE, 47 of 169 (27.8%) with aspirin were GI and 83 of 231 (35.9%) with clopidogrel were GI.

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Table S10—*[Sections 3.2.1-3.2.5] Ticagrelor Plus Aspirin vs Clopidogrel Plus Aspirin in Patients With a Recent ACS*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects, Time Frame: 1 y[a]		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Clopidogrel and Aspirin	Risk Difference With Ticagrelor and Aspirin (95% CI)	Quality of Evidence
Vascular mortality (critical outcome)[a]									
18,624 (1 RCT), 6-12 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.79 (0.69-0.91)	50 per 1,000[b]	10 fewer per 1,000 (from 15 fewer to 4 fewer)	High
Nonfatal MI (critical outcome)									
18,624 (1 RCT), 6-12 mo	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	RR 0.84 (0.75-0.95)	70 per 1,000[b]	11 fewer per 1,000 (from 17 fewer to 3 fewer)	High
Nonfatal stroke (critical outcome)[c]									
18,624 (1 RCT), 6-12 mo	No serious limitations	No serious limitations	No serious limitations	Imprecise CI includes important harm	Undetected	RR 1.17 (0.91-1.52)	13 per 1,000[b]	2 more per 1,000 (from 1 fewer to 7 more)	Moderate due to imprecision
Major bleed (critical outcome), including major non-CABG-related bleeding TIMI criteria									
18,624 (1 RCT), 6-12 mo	No serious limitations	No serious limitations	No serious limitations	Imprecise CI includes important harm	Undetected	RR 1.25 (1.01-1.53)	22 per 1,000[b]	6 more per 1,000 (from 0 more to 11 more)	Moderate due to imprecision

Bibliography: Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
CABG = coronary artery bypass graft; TIMI = Thrombolysis in Myocardial Infarction. See Table S1, S2, and S6 legends for expansion of other abbreviations.
[a] Of the total deaths in PLATO (Platelet Inhibition and Patient Outcomes), 20 of 399 (5.0%) with ticagrelor were fatal bleeding events, and 23 of 506 (4.5%) with clopidogrel were fatal bleeding events.
[b] One-year control group risk estimates come from PLATO, with events reported at 12 mo.
[c] Of the total strokes in PLATO, 23 of 125 (18.4%) with ticagrelor were hemorrhagic, and 13 of 106 (12.3%) with clopidogrel were hemorrhagic.

Table S11—*[Sections 3.2.1-3.2.5] Prasugrel Plus Aspirin vs Clopidogrel Plus Aspirin in Patients With a Recent ACS and PCI*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects, Time Frame: 1 y[a]		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Clopidogrel and Aspirin	Risk Difference With Prasugrel and Aspirin (95% CI)	Quality of Evidence
Vascular mortality (critical outcome), including fatal bleeds 0.4% with prasugrel and 0.1% with clopidogrel									
13,608 (1 RCT), 14.5 mo	No serious limitations	Serious limitations[b]	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 0.89 (0.70-1.12)	50 per 1,000[a]	5 fewer per 1,000 (from 15 fewer to 6 more)	Low due to inconsistency and imprecision
Nonfatal MI (critical outcome)									
13,608 (1 RCT), 14.5 mo	No serious limitations	Serious limitations[b]	No serious limitations	No serious imprecision	Undetected	RR 0.76 (0.67-0.85)	70 per 1,000[a]	17 fewer per 1,000 (from 23 fewer to 10 fewer)	Moderate due to inconsistency
Nonfatal stroke (critical outcome), including hemorrhagic (0.3%) in both groups									
13,608 (1 RCT), 14.5 mo	No serious limitations	Serious limitations[b]	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 1.02 (0.71-1.45)	13 per 1,000[a]	0 fewer per 1,000 (from 2 fewer to 6 more)	Low due to inconsistency and imprecision
Major bleed (critical outcome), including major non-CABG-related bleeding TIMI criteria									
13,608 (1 RCT), 14.5 mo	No serious limitations	Serious limitations[b]	No serious limitations	Imprecise CI includes negligible and substantial harm	Undetected	RR 1.32 (1.03-1.68)	22 per 1,000[a]	7 more per 1,000 (from 0 more to 18 more)	Low due to inconsistency and imprecision

Bibliography: Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20): 2001-2015. PCI = percutaneous coronary intervention. PLATO = Platelet Inhibition and Patient Outcomes. See Table S1, S2, S6, and S10 legends for expansion of other abbreviations.

[a] Control group risk estimates come from the PLATO study, adjusted to a 1-y time frame.

[b] Rated down for inconsistency for all outcomes because of credible subgroup analyses showing net harm for composite end point in certain subgroups.

Table S12—*[Sections 3.2.6-3.2.7] Triple Therapy (Warfarin, Aspirin, Clopidogrel) vs Dual Antiplatelet Therapy in Patients With Acute Large Anterior MI at Risk for or With LV Thrombus Who Undergo PCI With Stent Placement*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 3 mo		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Clopidogrel + Aspirin	Risk Difference With Warfarin + Clopidogrel and Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome)									
10,883 (10 RCT), 3-60 mo	No serious limitations	No serious limitations	Very serious indirectness[a]	Imprecise confidence interval includes benefit and harm	Undetected	RR 1.00 (0.82-1.22)	25 per 1,000[b]	0 more per 1,000 (from 4 fewer to 6 more)	Low due to indirectness and imprecision
Nonfatal MI (critical outcome)									
10,883 (10 RCTs), 3-60 mo	No serious limitations	No serious limitations	Very serious indirectness[a]	No serious imprecision	Undetected	RR 0.69 (0.54-0.88)	35 per 1,000[b]	11 fewer per 1,000 (from 16 fewer to 4 fewer)	Low due to indirectness
Nonfatal stroke (critical outcome), including ischemic and hemorrhagic									
6,709 (1 RCT), 1.3 y	No serious limitations	No serious limitations	Very serious indirectness[c]	Serious imprecision Baseline risk estimates imprecise[d]	Undetected	RR 0.56 (0.39-0.82)	Anteroapical MI without LV thrombus		Low due to indirectness and imprecision
							15 per 1,000[d]	7 fewer per 1,000 (from 9 fewer to 3 fewer)	
							Anteroapical MI with LV thrombus		
							100 per 1,000[d]	44 fewer per 1,000 (from 18 fewer to 61 fewer)	
Major extracranial bleed (critical outcome)									
10,883 (10 RCTs), 3-60 mo	No serious limitations	No serious limitations	Very serious indirectness[a]	No serious limitations	Undetected	RR 2.37 (1.62-3.47)	11 per 1,000[c]	15 more per 1,000 (from 7 more to 27 more)	Low due to indirectness

(Continued)

Table S12—*Continued*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 3 mo		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Clopidogrel + Aspirin	Risk Difference With Warfarin + Clopidogrel and Aspirin (95% CI)	Quality of Evidence
Burden of treatment (important outcome)[e]									
N/A[e]						Warfarin > aspirin	Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/ monitoring, increased hospital/clinic visits Aspirin: daily medication only		High

Bibliography: Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. *Ann Intern Med.* 2005;143(4):241-250. ACTIVE-W = Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; LV = left ventricular. See Table S1, S2, S6, and S11 legends for expansion of other abbreviations.

[a] Relative risk for warfarin, aspirin, and clopidogrel vs dual antiplatelet therapy derived from meta-analysis of studies comparing warfarin plus aspirin to aspirin alone in patients following ACS.

[b] Three-month risk estimates for control (aspirin + clopidogrel) event rates come from PLATO study. Assumed that one half of total events at 1 y occurred in first 3 mo based on the PLATO study.

[c] We assumed that the relative risk for the outcome of nonfatal stroke (ischemic and hemorrhagic) would be the same as observed in ACTIVE-W, which compared warfarin to dual antiplatelet therapy (aspirin + clopidogrel). We calculated the RR and 95% CI after extracting the number of nonfatal strokes (ischemic and hemorrhagic) in each group from the published report because it did not directly report RR in the article.

[d] Control group risk estimates for nonfatal stroke is based on ~1.5% rate/3 mo (see text) with clopidogrel and aspirin following anterior MI and 10% rate/3 mo in patients with anterior MI and LV thrombus. There is considerable imprecision in these estimates.

[e] 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.

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Table S13—*[Sections 4.1.1-4.3.5] Thienopyidine Plus Aspirin vs Warfarin Plus Aspirin in the First Month Following PCI*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects, Time Frame: 30 d		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Warfarin and Aspirin	Risk Difference With Thienopyidine and Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome)									
2,436 (4 RCTs), 4-6 wk	No serious limitations	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 0.73 (0.25-2.18)	7 per 1,000[a]	2 fewer per 1,000 (from 5 fewer to 8 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
2,436 (4 RCTs), 4-6 wk	Serious risk of bias Lack of blinding	No serious limitations	No serious limitations	No serious imprecision	Undetected	RR 0.50 (0.29-0.83)	39 per 1,000[a]	19 fewer per 1,000 (from 28 fewer to 7 fewer)	Moderate due to risk of bias
Stroke (critical outcome); not reported in meta-analysis									
Major bleed[b] (critical outcome)									
2,436 (4 RCTs), 4-6 wk	Serious risk of bias Lack of blinding	Serious inconsistency $I^2 = 72\%$	No serious limitations	Serious imprecision CI includes no benefit	Undetected	RR 0.38 (0.14-1.02)	64 per 1,000[a]	40 fewer per 1,000 (from 55 fewer to 1 more)	Low due to imprecision, heterogeneity, and study limitations

Bibliography: Cosmi B, Rubboli A, Castelvetri C, Milandri M. Ticlopidine versus oral anticoagulation for coronary stenting. *Cochrane Database Syst Rev*. 2001;(4):CD002133. See Table S1, S2, and S11 legends for expansion of abbreviations.

[a] Control group risk estimates come from the meta-analysis.

[b] Bleeding definitions varied greatly across studies.

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Table S14—*[Sections 4.1.1-4.3.5] Triple Therapy With Cilostazol vs Clopidogrel Plus Aspirin Following Elective PCI With Stenting*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 6-9 mo		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Clopidogrel + Aspirin	Risk Difference with Cilostazol + Clopidogrel + Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome); vascular mortality not reported									
2,809 (10 RCTs), 6-9 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	RR 0.73 (0.25-2.12)	20 per 1,000[a]	5 fewer per 1,000 (from 15 fewer to 22 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
2,689 (9 RCTs), 6-9 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and harm	Undetected	RR 1.12 (0.57-2.24)	50 per 1,000[a]	6 more per 1,000 (from 21 fewer to 62 more)	Moderate due to imprecision
Nonfatal stroke (critical outcome); not reported in meta-analysis									
Major extracranial bleed (important outcome); not clearly defined									
19,185 (1 RCTs), 6-9 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and harm	Undetected	RR 0.87 (0.44-1.74)	50 per 1,000[a]	6 fewer per 1,000 (from 28 fewer to 37 more)	Moderate due to imprecision

Bibliography: Tamhane U, Meier P, Chetcuti S, et al. Efficacy of cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials. *EuroIntervention*. 2009;5(3):384-393. See Table S1, S2, and S11 legends for expansion of abbreviations.

[a]Control group risk estimates come from the meta-analysis performed for dual antiplatelet therapy following PCI with stent placement (Tamhane et al).

Table S15—*[Sections 4.1.1-4.3.5] Cilostazol Plus Aspirin vs Clopidogrel Plus Aspirin Following Elective PCI With Stenting*

Quality Assessment							Summary of Findings		
							Estimation of Absolute Event Rates and Risk Differences Time Frame: 6-9 mo		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Event Rate With Clopidogrel + Aspirin	Risk Difference With Cilostazol + Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome); not reported									
Nonfatal MI (critical outcome); not reported									
Nonfatal stroke (critical outcome); not reported									
Major adverse cardiac events (important outcome); the only vascular event outcome reported in meta-analysis, but not specified further									
3,437 (13 RCTs), 6 mo	Serious risk of bias variable blinding, loss to follow-up	No serious inconsistency	Serious indirectness Composite outcome	Serious imprecision CI includes benefit and harm	Publication bias detected	RR 0.56 (0.25-1.27)	75 per 1,000[a]	33 fewer per 1,000 (from 56 fewer to 20 more)	Low due to risk of bias, indirectness, imprecision, and publication bias
Major extracranial bleed (important outcome) Not clearly defined									
3,437 (13 RCTs), 6 mo	Serious risk of bias variable blinding, loss to follow-up	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and harm	Publication bias detected	RR 0.66 (0.32-1.39)	50 per 1,000[a]	17 fewer per 1,000 (from 34 fewer to 20 more)	Low due to risk of bias, imprecision, and publication bias

Bibliography: Biondi-Zoccai GG, Lotrionte M, Anselmino M, et al. Systematic review and meta-analysis of randomized clinical trials appraising the impact of cilostazol after percutaneous coronary intervention. *Am Heart J*. 2008;155(6):1081-1089. See Table S1, S2, and S11 legends for expansion of abbreviations.

[a]Control group risk estimates come from the meta-analysis (Biondi-Zoccai et al).

Table S16—*[Sections 4.1.1-4.3.5] High-Dose Aspirin vs Low-Dose Aspirin for 30 d Post-PCI*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 30 d		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	HR (95% CI)	Risk With Aspirin 75-100 mg	Risk Difference With Aspirin 300-325 mg (95% CI)	Quality of Evidence
Total mortality (critical outcome)[a]									
17,236 (1 RCT), 30 d	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision CI included important benefit and no benefit[c]	Undetected	HR 0.87 (0.74-1.03)	25 per 1,000[d]	3 fewer per 1,000 (from 7 fewer to 1 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
17,236 (1 RCT), 30 d	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision CI included benefit and harm[c]	Undetected	HR 0.97 (0.82-1.16)	21 per 1,000[d]	1 fewer per 1,000 (from 4 fewer to 3 more)	Moderate due to imprecision
Stroke (critical outcome)[e]									
17,236 (1 RCT), 30 d	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision CI included benefit and harm[c]	Undetected	HR 1.19 (0.84-1.68)	5 per 1,000[d]	1 more per 1,000 (from 1 fewer to 3 more)	Moderate due to imprecision
Major bleed (important outcome)[f]									
17,236 (1 RCT), 30 d	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision CI included benefit and harm[c]	Undetected	HR 1.09 (0.89-1.34)	14 per 1,000[d]	1 more per 1,000 (from 2 fewer to 5 more)	Moderate due to imprecision

Bibliography: Mehta SR, Tanguay JF, Eikelboom JW, et al; CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376(9748):1233-1243. CURRENT-OASIS = Clopidogrel Optimal Loading Dose Usage To Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions; HR = hazard ratio. See Table S1, S10, and S11 legends for expansion of other abbreviations.

[a] Of the total deaths in CURRENT-OASIS 7, 15 of 314 (4.8%) occurred with low-dose aspirin, and 16 of 273 (5.9%) were fatal bleeding events.

[b] OASIS aspirin dose was not blinded.

[c] Borderline decision to rate down for imprecision. Although CIs for absolute effects are fairly narrow, the 30-d time frame suggests imprecise effect estimates (eg, three more strokes and bleeds per 1,000 treated for 30 d).

[d] Control group risk estimates come from event rates in patients allocated to low-dose aspirin undergoing PCI in CURRENT-OASIS 7.

[e] Unclear from the article whether hemorrhagic and fatal strokes were included in total strokes.

[f] TIMI criteria used. It is unclear from the article whether hemorrhagic and fatal bleeding were included in total major bleeding.

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Table S17—*[Sections 4.1.1-4.3.5] Six to Twelve Months vs One Month of Clopidogrel Plus Aspirin Following PCI With Placement of Bare Metal Stent*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 6-9 mo		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With 1 mo Clopidogrel + Aspirin	Risk Difference With 6-12 mo Clopidogrel + Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome)									
3,390 (3 RCTs), 6-12 mo	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI included important benefit and harm	Undetected	RR 0.73 (0.48-1.13)	28 per 1,000[b]	8 fewer per 1,000 (from 15 fewer to 4 more)	Low due to risk of bias and imprecision
Nonfatal MI (critical outcome)									
4,852 (3 RCTs), 6-12 mo	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	RR 0.66 (0.50-0.86)	28 per 1,000[b]	9 fewer per 1,000 (from 14 fewer to 4 fewer)	Moderate due to risk of bias
Nonfatal stroke (critical outcome)									
2,194 (2 RCTs), 6-12 mo	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI included important benefit and harm	Undetected	RR 0.46 (0.16-1.32)	10 per 1,000[b]	5 fewer per 1,000 (from 8 fewer to 3 more)	Low due to risk of bias and imprecision
Major extracranial bleed (important outcome); not clearly defined[c]									
5,052 (3 RCTs), 6-12 mo	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI includes important benefit and harm	Undetected	RR 1.17 (0.86-1.6)	50 per 1,000[b]	8 more per 1,000 (from 7 fewer to 30 more)	Low due to risk of bias and imprecision

Bibliography: Data for meta-analysis extracted from following studies: Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-533. Pekdemir H, Cin VG, Camsari A, et al. A comparison of 1-mo and 6-mo clopidogrel therapy on clinical and angiographic outcome after stent implantation. *Heart Vessels*. 2003;18(3):123-129. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288(19):2411-2420. Bernardi V, Szarfer J, Summay G, et al. Long-term vs short-term clopidogrel therapy in patients undergoing coronary stenting (from the Randomized Argentine Clopidogrel Stent [RACS] trial). *Am J Cardiol*. 2007;99(3):349-352. Akbulut M, Ozbay Y, Karaca I, Ilkay E, Gundogdu O, Arslan N. The effect of long-term clopidogrel use on neointimal formation after percutaneous coronary intervention. *Coron Artery Dis*. 2004;15(6):347-352. See Table S1, S2, and S11 legends for expansion of abbreviations.

[a] Bernardi et al and Pekdemir et al were not blinded, and there was no placebo control; Bernardi et al stopped early for benefit. Akbulut et al design was unclear (no mention of randomization, but the Health Technology Assessment report refers to it as randomized); Mehta et al had variable follow-up.

[b] Control group risk estimates were derived from rates in subjects treated with dual antiplatelet therapy for 1 mo in included trials.

[c] Major bleeding not stratified by type of bleed; unclear whether major bleeding included any fatalities.

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Table S18—*[Sections 4.1.1-4.3.5] Extended Duration of Clopidogrel Plus Aspirin Following PCI With Placement of Drug-Eluting Stent*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time frame: 19 mo		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With 12 mo Clopidogrel + Aspirin	Risk Difference With 19 mo Clopidogrel + Aspirin (95% CI)	Quality of Evidence
Total mortality (critical outcome)									
2,701 (2 RCTs), 19 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI included no benefit and important harm	Undetected	RR 1.65 (0.80-3.36)	6 per 1,000[b]	4 more per 1,000 (from 1 fewer to 14 more)	Moderate due to imprecision
Nonfatal MI (critical outcome)									
2,701 (2 RCTs), 19 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI includes no benefit and important harm	Undetected	RR 1.73 (0.54-5.53)	3 per 1,000[b]	2 more per 1,000 (from 1 fewer to 13 more)	Moderate due to imprecision
Nonfatal stroke (critical outcome)									
2,701 (2 RCTs), 19 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI includes no benefit and important harm	Undetected	RR 2.64 (0.76-9.16)	2 per 1,000[b]	3 more per 1,000 (from 1 fewer to 16 more)	Moderate due to imprecision
Major extracranial bleed (important outcome) Not clearly defined[c]									
2,701 (2 RCTs), 19 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision CI includes no benefit and important harm	Undetected	RR 2.97 (0.43-20.72)	1 per 1,000[b]	2 more per 1,000 (from 1 fewer to 19 more)	Moderate due to imprecision

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[a] Open-label study, although study end points were adjudicated by blinded assessors.

[b] Control group risk estimates come from subjects receiving dual antiplatelet therapy for 1 y in the merged trials.

[c] Major bleeding defined by TIMI criteria; no information was provided on the type of major bleeding events in either group. No fatal bleeding was reported.

Table S19—*[Sections 5.1-5.3] Warfarin vs Aspirin in Patients With Systolic LV Dysfunction (Ischemic and Nonischemic)*

Quality Assessment							Summary of Findings		
							Anticipated Absolute Effects Time Frame: 5 y		
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	Risk With Aspirin[a]	Risk Difference With Warfarin (95% CI)	Quality of Evidence
Total mortality (critical outcome)									
1,357 (3 RCTs), 23-27 mo	Serious[b] limitations	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 0.95 (0.76-1.19)	193 per 1,000[a]	10 fewer per 1,000 (from 46 fewer to 36 more)	Low due to risk of bias and imprecision
MI (critical outcome)[c]									
1,358 (3 RCTs), 23-27 mo	Serious[b] limitations	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RR 0.99 (0.35-2.84)	33 per 1,000[a]	0 fewer per 1,000 (from 21 fewer to 60 more)	Low due to risk of bias and imprecision
Stroke (critical outcome)[d]									
1,358 (3 RCTs), 23-27 mo	Serious[b] limitations	No serious limitations	No serious limitations	Imprecise CI includes no benefit	Undetected	RR 0.34 (0.13-0.97)	24 per 1,000[a]	16 fewer per 1,000 (from 21 fewer to 1 fewer)	Low due to risk of bias and imprecision
Major bleed (critical outcome)[e]									
1,358 (3 RCTs), 23-27 mo	Serious[b] limitations	No serious limitations	No serious limitations	Imprecise CI includes important harm	Undetected	RR 1.97 (0.89-4.3)	30 per 1,000[a]	29 more per 1,000 (from 3 fewer to 99 more)	Low due to risk of bias and imprecision
Burden of treatment (important outcome)									
						Warfarin > aspirin	Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/monitoring, increased hospital/clinic visits		High
							Aspirin: daily medication only		

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[a] Control group risk estimates were derived from event rates from the aspirin arm of the pooled studies.

[b] Two of three trials were stopped early (one for benefit, one for slow enrollment); problems with blinding.

[c] Fatal and nonfatal MIs not reported separately in all studies.

[d] Fatal and nonfatal strokes not reported separately in all studies; types of strokes (ischemic/hemorrhagic) not reported.

[e] Definition of major hemorrhage varied.

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