Drug Class Review

Newer Antiplatelet Agents

Final Update 2 Evidence Tables

June 2011

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in evidence tables

Abbreviation	Term
ABPI	Ankle-brachial pressure index
ACS	Acute coronary syndrome
ACT	Active-control trial
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASA	Acetylsalicylic acid
bid	Twice daily
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CASPAR	Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease
CCT	Controlled clinical trial
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CR	Controlled release
CTVT	clinical target vessel thrombosis
CV	Cardiovascular
CVD	cerebrovascular disease
CVS	Cardiovascular system
CYP3A4-MET	Cytochrome P450 3A4-metabolized statin
d	Day
DB	Double-blind
dL	Deciliter
DM	Deabetes Mellitus
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ER	Extended release
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram
GI	Gastrointestinal
GP	Glycoprotein
GP	General practitioner

Abbreviation	Term
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
h	Hour
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICAD	Ischemic coronary artery disease
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IR	Immediate release
ITT	Intent-to-treat
L	Liter
LA	Long acting
LD	loading dose
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
MD	maintenance dose
mg	Milligram
MI	Myocardial Infarction
min	Minute
mL	Milliliter
mo	Month
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NIHSS	National Institutes of Health Stroke Scale
NR	Not reported
NS	Not significant
NSD	No significant difference
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
P	*P* value
P	Placebo
PAD	Peripheral arterial disease
PAOD	Peripheral arterial obstructive disease
PCI	Percutaneous coronary intervention

Abbreviation	Term
PCT	Placebo-controlled trial
PPY	Per person year
PTCA	percutaneous transluminal coronary angioplasty
qd	Once daily
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SB	Single-blind
SD	Standard deviation
SE	Standard error
SR	Sustained release
TIA	Transient ischemic attack
tid	Three times daily
TIMI	Thrombolysis in Myocardial Infarction
TTP	Thrombotic thrombocytopenic purpura
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Akbulut, 2004 Turkey Fair	Patients with typical stable angina pectoris or documented myocardial ischemia, and with only one angiographic lesion in one native coronary artery undergoing successful stent implantation without pre-dilatation with C-reactive protein levels ≤5 mg/l at 72 hours after the procedure.	A: Clopidogrel 75 mg/d + aspirin 300 mg/d B: Placebo + aspirin 300 mg/d (received clopidogrel 75 mg/d for 4 weeks, then were switched to placebo) Dosing schedule: All patients received dual antiplatelet therapy with 75 mg/day clopidogrel and 300 mg/day aspirin for at least four weeks. At the end of the fourth week, clopidogrel was switched with placebo in the placebo group, with a follow-up of 20 weeks.	All patients received aspirin 300 mg/d, otherwise NR	Age: 59.5 years (SD 5) Male: 78.2% Ethnicity NR
Aronow, 2009/Brener, 2007 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002
Atmaca, 2002 Turkey Fair	Consecutive patients from March 1998 to January 2001 undergoing elective single vessel PTCA with stenting. Patients with Canadian Cardiac society Class-II stable angina pectoris and de novo lesions in large native coronary arteries.	C 300mg LD and then 75mg per day thereafter vs T 2 x 250mg daily. Both started on the same day as stent placement. All pts received 300mg ASA daily concomitantly	ASA 300mg daily. Study stated that all pts were on the standard treatment of stable angina but exact therapy not listed	C group: age: 63.1 ± 8.2, 60% male, 40% female, T group: 62.1±7.4; 64% male and 46% female. All NS. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Akbulut, 2004 Turkey Fair	BMI: 22.3 kg/m2 (SD 2.5) Hypertension: 30.8% Current smoker: 24.4% Family history: 26.9% Clinical indications: Asymptomatic: 19.2% Stable angina pectoris: 60.3% Unstable angina pectoris: 20.5%	78	0/0/78
Aronow, 2009/Brener, 2007 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002
Atmaca, 2002 Turkey Fair	Smokers: C group 45.7%, T group 43%, p=NS; DM C 21.6%, T 15%,p= NS; Hyperlipidemia: C group 28.9%, T group 25.4%, p=NS. Family history for CAD: C group 30.1%, T group 26.6%, p=NS	158	10

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Akbulut, 2004 Turkey Fair	Clopidogrel vs Placebo (during 20 week follow-up period) CV death, stroke or heart failure: 0 (0%) vs 0 (0%) Non-Q-wave MI: 1 (2.56%) vs 2 (5.12%) Q-wave MI: 0 (0%) vs 1 (2.56%) Refractory ischemia: 0 (0%) vs 1 (2.56%) Since all patients that developed ischemia were revascularized, the revascularization rate was higher in the placebo group (10.25% versus 2.56% in the clopidogrel group, P=0.01). One patient experienced a non-Q-wave MI (1.25%) during the first four-week period when all patients received clopidogrel+aspirin therapy; however, investigators did not include these events in the study since they occurred before formation of the study groups.	Clopidogrel vs Placebo Rash: 2 (5.12%) vs 1 (2.5%); P=0.001 One patient (1.28%) developed non-life-threatening GI bleeding during the first four-week period when all patients received clopidogrel+aspirin therapy; however, investigators did not include this in the study since it occurred before formation of the study groups. No life-threatening or non-life-threatening, major or minor bleeding, or hematological abnormality were seen after formation of the study groups.
Aronow, 2009/Brener, 2007 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	Clopidogrel vs Placebo Major bleeding: Overall=8.8% (93/1053) vs 6.7% (71/1063); subgroup of patients who underwent treatment for 1-year=49/902 (5.6%) vs 34/914 (3.9%), P=0.09, HR 1.04 (95% CI, 0.75-1.44)
Atmaca, 2002 Turkey Fair	NR	Ticlopidine vs Clopidogrel Bleeding: 0.0% (0/75) vs 0.0% (0/83)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Akbulut, 2004 Turkey Fair	Clopidogrel vs Placebo Total withdrawals: 0 (0%) vs 0 (0%) Due to AE: 0 (0%) vs 0 (0%) One patient (1.28%) developed a minor hemorrhage leading to discontinuation of the study during the first four-week dual-therapy lead-in period; however, investigators did not include this in the study since it occurred before formation of the study groups.	NR	
Aronow, 2009/Brener, 2007 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002
Atmaca, 2002 Turkey Fair	0	NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Belch, 2010 13 European countries and Australia CASPAR Fair	Patients ≥40 and ≤80 undergoing vascular grafting as a treatment for atherosclerotic PAD were enrolled 2 to 4 days after bypass surgery. Patients had chronic background treatment with daily ASA of any dose, started at least 4 weeks before surgery; a post-randomization dose of ASA between 75 and 100 mg/day; unilateral below-knee bypass graft for atherosclerotic PAD; patent index graft demonstrated during bypass surgery, or between surgery and the time of randomization; and no clinical evidence of graft occlusion at randomization.	A: Clopidogrel 75 mg/day + ASA 75-100 mg/d B: Placebo + ASA 75-100 mg/d For 6 to 24 months	Either dextran, low-dose unfractionated heparin (≤10,000 IU/day), or low-molecular-weight heparin at a dose appropriate for prevention of deep venous thrombosis was permitted when indicated. Episodic use of cyclooxygenase-2 inhibitors (not greater than 3 weeks' continuous use) was allowed. The use of cyclooxygenase-1 nonsteroidal anti-inflammatory drugs was discouraged but, if necessary, they were allowed only at a low dose for ≤7 days, and the study drug was withheld for the duration of treatment. Study drug was temporarily stopped if thrombolytic therapy became necessary during the study. All patients also received standard therapy as appropriate (e.g., statins, beta-blockers, wound care). The use of appropriate background CV risk-reduction therapy according to International Guidelines was emphasized.	Age: 66.0 years (SD 8.6) Male: 75.8% Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Belch, 2010 13 European countries and Australia CASPAR Fair	Mean BMI: 25.7 kg/m2 Current smoker: 37.6% Hypertension: 70.0% Hyperlipidemia: 49.6% CAD and/or cerebrovascular disease: 34.7% DM: 37.7% Mean preoperative ankle-brachial pressure index of the index limb: 0.45 PAD symptoms: Claudication only: 33.3% Rest pain: 26.3% Ulcers/gangrene: 39.6 Concomitant medication (%) Statins: 47.3% ACE inhibitors: 43.3% Beta-blockers: 35.3% Diuretics: 32.5%	451	113/19/451

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Belch, 2010 13 European countries and Australia CASPAR Fair	<u>Placebo vs Clopidogrel:</u> Graft occlusion, revascularization, amputation, or death: All grafts: 151 vs 149; HR: 0.98 (95% CI, 0.78 to 1.23) Venous: 85 vs 101; HR: 1.25 (95% CI, 0.94 to 1.67) Prosthetic 66 vs 48; HR: 0.65 (95% CI, 0.45 to 0.95); P=0.025 Graft occlusions (first episode): All grafts 97 vs 93; HR: 0.94 (95% CI, 0.71 to 1.25) Venous: 38 vs 52; HR: 1.45 (95% CI, 0.95 to 2.20) Prosthetic: 59 vs 41; HR: 0.63 (95% CI, 0.42 to 0.93); P=0.021 Amputations (first episode): All grafts: 45 vs 31; HR: 0.68 (95% CI, 0.43 to 1.08) Venous: 21 vs 19; HR: 0.93 (95% CI, 0.50 to 1.72) Prosthetic: 24 vs 12; HR: 0.48 (95% CI, 0.24 to 0.96); P=0.034 Death: All grafts: 17 vs 24; HR: 1.44 (95% CI, 0.77 to 2.68) Venous: 13 vs 18; HR: 1.43 (95% CI, 0.70 to 2.91) Prosthetic: 4 vs 6; HR: 1.51 (95% CI, 0.42 to 5.33) Time to graft occlusion/graft intervention/amputation above the ankle of the affected limb: All grafts: HR 0.91 (95% CI, 0.71 to 1.15) Prosthetic grafts: HR 0.62 (95% CI, 0.42 to 0.91); P=0.013 Time to first occurrence, HR clopidogrel vs placebo: MI: 0.81: 95% CI, 0.32 to 2.06; P=0.66 CV death: 1.49; 95% CI, 0.73 to 3.01; P=0.27 Stroke: 1.02; 95% CI, 0.41 to 2.57; P=0.96 Amputation above the ankle: 0.69; 95% CI, 0.44 to 1.09; P=0.11 HR of cardiovascular death, MI, or stroke: 10.7% vs 13.5%; HR: 1.09; 95% CI, 0.65 to1.82; P=0.75 Median duration of follow-up, days: 364 vs 364 Median duration of trial drug administration, days: 334 vs 351	<u>Placebo vs Clopidogrel:</u> Total bleeding events: 30 (7.1%) vs 71 (16.7%); P<0.001 Mild: 21 (5.0%) vs 46 (10.8%); P=0.002 Moderate: 4 (0.9%) vs 16 (3.8%); P=0.007 Severe: 5 (1.2%) vs 9 (2.1%) Fatal: 1 (0.2%) vs 2 (0.5%)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Belch, 2010 13 European countries and Australia CASPAR Fair	Placebo vs Clopidogrel: Total withdrawals: 113 (26.5%) vs 129 (30.6%) Due to bleeding: 3 (0.7%) vs 21 (4.9%) Withdrawals due to overall AEs NR	Sanofi-Aventis and Bristol-Myers Squibb	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Berger, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
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Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Berger, 2009 Companion to Bhatt, 2006 CHARISMA	Placebo vs Clopidogrel Subgroup: All-cause death: P=0.018 for current smoking; P=0.308 for former smoking Overall: 306 (5.0%) vs 278 (4.6%); HR 0.912 (95% CI, 0.776 to 1.073) Current smoker: 88 (7.2%) vs 59 (4.9%); HR 0.676 (95% CI, 0.486 to 0.941) Former smoker: 149 (4.8%) vs 140 (4.5%); HR 0.945 (95% CI, 0.750 to 1.190) Never smoker: 69 (4.0%) vs 79 (4.5%); HR 1.142 (95% CI, 0.827 to 1.577) CV death: P=0.037 for current smoking; P=0.080 for former smoking Overall: 191 (3.1%) vs 172 (2.8%); HR 0.904 (95% CI, 0.736 to 1.111) Current smoker: 50 (4.1%) vs 35 (2.9%); HR 0.708 (95% CI, 0.459 to 1.090) Former smoker: 96 (3.1%) to 80 (2.6%); HR 0.838 (95% CI, 0.623 to 1.128) Never smoker: 45 (2.6%) to 57 (3.3%); HR 1.262 (95% CI, 0.854 to 1.865) Cancer death: P=0.437 for current smoking; P=0.392 for former smoking Overall: 60 (1.0%) vs 51 (0.8%); HR 0.854 (95% CI, 0.588 to 1.240) Current smoker: 15 (1.2%) to 14 (1.2%); HR 0.938 (95% CI, 0.453 to 1.943) Former smoker: 33 (1.1%) to 30 (1.0%); HR 0.915 (95% CI, 0.558 to 1.499) Never smoker: 12 (0.7%) to 7 (0.4%); HR 0.584 (95% CI, 0.230 to 1.483)	Clopidogrel vs Placebo Risk of severe or moderate bleeding according to smoking status: Current smoker: 3.9% vs 2.4; P=0.04; HR 1.62 vs 1.0; increase in risk of bleeding associated with use of clopidogrel was 62% Former smoker: 3.5% vs 2.5%; P=0.02; HR 1.43 vs 1.0; increase in risk of bleeding associated with use of clopidogrel was 43% Never smoker: 3.7% vs 2.8%; P=0.15; HR 1.43 vs 1.0; increase in risk of bleeding associated with use of clopidogrel was 31% (P=NS)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Berger, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Bernardi, 2007 Argentina RACS Fair	Patients ≥18 years of age with symptomatic CAD with objective evidence of ischemia, a target lesion with ≥50% stenosis by visual estimation in a native coronary artery ≥2.5 mm, and had undergone a successful PCI procedure with placement of ≥1 stent without evident complications in the previous 24 hours.	A: Clopidogrel for 30 days B: Clopidogrel for 180 days	All patients received aspirin (75 to 325 mg). A GP IIb/IIIa inhibitor was administered to 17% of patients by physician preference, in 90% as a bailout only after thrombus had formed or a complication had occurred.	Age: 60.5 years (SD 11) Male: 80% Ethnicity NR
Bertrand, 2000 Europe CLASSICS Good	Successful planned or unplanned coronary stenting (1 or 2 stents) in a single vessel (reference vessel diameter >2.8 mm) with the use of any commercially available non-heparin-coated stents; <10% adjacent residual stenosis; no angiographic evidence of thrombus formation or dissection within the treated vessel; blood flow of TIMI grade 3 in each stented segment and associated major side branches; preoperative CPK less than 2x ULN; and eligibility to commence study drug within 6 hours after stent implantation	Initiated within 6 hrs of completion of stenting. 1. 300mg C (LD) and 325mg/day ASA on day 1, followed by 75mg daily C and 325 mg/day ASA (days 2-28) 2. 75mg/day C and 325mg/day ASA (days 1-28); 3. 250mg twice a day T and 325mg/day ASA (days 1-28). (ASA was given in a blinded fashion in all arms)	ASA within 1 month before randomization	T group 61 ± 9.9 years old; 75% male and 25% female; C group (without LD) 60 ± 10.4 years old; 78% male and 22% female; C group with LD: 60 ± 10.1 years old; 77% male and 23% female. Ethnicity not stated.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	
Bernardi, 2007 Argentina RACS Fair	Age >70 years: 26.7% Weight: 78.4 kg (SD 11.2) Hypertension: 68.1% Obesity: 24.2% Current smoker: 28.3% Previous vascularization: 20.2% Previous MI: 25.3% Previous cardiac heart failure: 3.5% Previous stroke: 1.6% Previous PVD: 3.8% Mean duration of clopidogrel pretreatment before the PCI procedure: 3.3 hours (SD 2.1) DM: Type 1: 1.5% Type 2: 12.8% Indication for PCI: ACS: 72% MI: 15%	1004	NR/25/NR	
Bertrand, 2000 Europe CLASSICS Good	Overall: HTN 49.9%; DM (11.3%); former or current smoker 69%, treatment for hypercholesterolemia (57%);previous stable angina (55.8%)	1020		1

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Bernardi, 2007 Argentina RACS Fair	Clopidogrel treatment for 30 days vs Clopidogrel treatment for 180 days Event rates from 30 days through 180 days: Patients lost to follow-up: 14 (3%) vs 11 (2.4%); P=0.54 Death: 12 (2.6%) vs 4 (0.87%); P=0.047 MI: 13 (2.8%) vs 7 (1.5%); P=0.18 Stroke: 1 (0.21%) vs 0 (0%); P=0.32 Target vessel revascularization: 26 (5.6%) vs 18 (3.98%); P=0.22 Cardiovascular death: 8 (1.7%) vs 4 (0.87%); P=0.25 Death, MI, stroke: 23 (5.0%) vs 8 (1.7%); P=0.010, relative risk decrease 65% Major adverse cardiac events (death, MI stroke, or target vessel revascularization): 40 (8.7%) vs 25 (5.4%); P=0.054	Clopidogrel treatment for 30 days vs Clopidogrel treatment for 180 days Total bleeding: 0.64% vs 1.52%; P=0.34
Bertrand, 2000 Europe CLASSICS Good	Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg *Outcomes at 28 days* (*All RRs based on T vs C75mg) MI: 0.3% (1/340) vs 0.3% (1/335) vs 0.6% (2/345) RR = 0.99 (0.06, 15.69) MI + Target lesion revascularization: 0.3% (1/340) vs 0.9% (3/335) vs 0% (0/345) RR = 0.33 (0.03, 3.14) Fatal MI: 0% (0/340) vs 0% (0/335) vs 0.3% (1/345) RR = NC Sudden death: 0% (0/340) vs 0% (0/335) vs 0.3% (1/345) RR = NC Target lesion revascularization: 0.3% (1/340) vs 0.3% (1/335) vs 0% (0/345) RR = 0.99 (0.06, 15.69) ≥ 1 cardiac event : 0.9% (3/340) vs 1.5% (5/335) vs 1.2% (4/345) RR = 0.59 (0.14, 2.45)	Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg Allergy: 1.2% (4/340) vs 0.00% (0/335) vs 0.00% (0/345) GI disorder: 2.6% (9/340) vs 2.4% (8/335) vs 0.3% (1/345) Major peripheral or bleeding complication: 1.2% (4/340) vs 1.2% (4/335) vs 1.5% (5/345) Neutropenia <1.5 x 10to9/L: 0.3% (1/340) vs 0.00% (0/335) vs 0.00% (0/345) Skin disorder: 2.6% (9/340) vs 0.9% (3/335) vs 0.6% (2/345) Thrombocytopenia 70-100x10to0/L: 0.3% (1/340) vs 0.00% (0/335) vs 0.00% (0/345)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bernardi, 2007 Argentina RACS Fair	Clopidogrel treatment for 30 days vs Clopidogrel treatment for 180 days Total withdrawals: NR Due to AE: 1.1% vs 2.4%	NR	The trial was neither blinded nor placebo controlled. A 300-mg LD of clopidogrel was administrated orally in the 2 arms before coronary angioplasty or immediately afterward.
Bertrand, 2000 Europe CLASSICS Good	T: 28, C: 17, C (LD): 7	Funded by Sanofi and BMS	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Best, 2008 Companion to Steinhuble, 2002 CREDO	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Best, 2008 Companion to Steinhuble, 2002 CREDO	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Best, 2008 Companion to Steinhuble, 2002 CREDO	Clopidogrel vs Placebo Multivariate model for the composite endpoint of death, MI, and stroke at 1 year: Use of clopidogrel: Normal renal function: HR 0.47 (P=0.003) Moderate chronic kidney disease: HR 0.84 (P=0.485) Moderate chronic kidney disease: HR 1.7 (P=0.073) Creatine clearance <60 mL/min and clopidogrel interaction: HR 2.45 (95% CI, 1.28 to 4.70); P=0.007	Relative risk of major bleeding with clopidogrel at 1 year (patients who received clopidogrel vs those who did not based on creatinine clearance): Creatinine clearance ≥90: HR 1.168 (95% CI, 0.741 to 1.841) Creatinine clearance 60-89: HR 1.595 (95% CI, 0.970 to 2.621) Creatinine clearance <60: HR 1.124 (95% CI, 0.511 to 2.476)

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Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Best, 2008 Companion to Steinhuble, 2002 CREDO	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)	Steinhuble 2002 (CREDO)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Bhatt, 2006 International CHARISMA Good	45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic PAD. To meet the criterion for enrollment on the basis of multiple risk factors (asymptomatic groups), patients were required to have 2 major or 3 minor or one major and 2 minor atherothrombotic risk factors. Major risk factors could include type 1 or 2 DM (with drug therapy), diabetic nephropathy, ABI <0.9, asymptomatic carotid stenosis ≥70% luminal diameter, ≥1 carotid plaque, as evidence by intima-media thickness. Minor risk factors could include systolic BP ≥150 mm Hg (despite therapy for at least 3 months), primary hypercholesterolemia, current smoking > 15 cigarettes/day, Males sex and age ≥65 yr or female and age ≥70 years. To meet the criterion for enrollment on the basis of established CV disease (symptomatic group), patients had to have documented coronary disease (e.g., anginal with documented multivessel coronary disease, history of multivessel PCI, history of multivessel CABG, MI during the previous 5 years, documented cerebrovascular disease e.g., TIA during previous 5 yr, ischemic stroke during previous 5 year), or documented symptomatic PAD (e.g., current intermittent claudication and ABI ≤0.85, history of intermittent claudication and previous intervention such as amputation, peripheral bypass, or angioplasty).	Clopidogrel 75mg per day plus low-dose ASA (75-162 mg/day) or placebo plus low-dose ASA and followed for a median of 28 months	All patients also received standard therapy as appropriate at the discretion of the investigator and other responsible clinicians. In the C + ASA group: 99.7 ASA, 9.9% open-label clopidogrel, 48.2% diuretics, 23.2% nitrates, 36.7% calcium antagonists, 55% BB, 25.5% angiotensin 2-receptor blockers, 17.8% ramipril, 46.2% other ACE inhibitors, 76.8% statins, 41.8% antidiabetic medications. In the P + ASA group: 99.7% ASA, 10.4% open-label clopidogrel, 47.1% diuretics, 24.1% nitrates, 36.9% calcium antagonists, 55.7% beta-blockers, 25.9% angiotensin II-receptor blockers, 18.3% ramipril, 46.3% other angiotensin-converting -enzyme inhibitors, 76.9% statins, 41.5% antidiabetic medications	Clopidogrel + ASA: Median age 64 (range 39-95); 29.7% females, 70.3% males, 80.4% white, 9.9% Hispanic, 5.0% Asian, 3.2% Black, 1.5% Other. Placebo + ASA group: median age 64 (range 45-93),29.8% females, 70.2% males, 80% white, 10.7% Hispanic, 5.0% Asian, 3.0% Black, 1.4% Other

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Bhatt, 2006 International CHARISMA Good	C + ASA group: 77.7% Documented vascular disease, 21.3% Multiple risk factors, 1.0% neither subgroup, 20.1% current smokers, 48.9% former smokers, 73.3 HTN, 73.7% hypercholesterolemia, 6.0% CHF, 34.2% prior MI, 3.8% AF, 12.0% prior TIA, 42.3% DM, 22.6% PAD, 22.4% prior PCI, 19.5% priori CABG, 5.4% prior carotid endarterectomy, 11.3% prior peripheral angioplasty or bypass, 12.9% diabetic nephropathy. P + ASA group: 78.1% documented vascular disease, 20.8% multiple risk factors, 1.1% neither subgroup, 20.3% current smokers, 48.7% former smokers, 73.9% HTN, 74.2% Hypercholesteremia, 5.9% CHF, 34.9% prior MI, 3.7% atrial fibrillation, 24.3% prior stroke, 11.9% prior TIA, 41.7% DM, 22.7% PAD, 23.1% prior PCI, 19.9% prior CABG, 5.2% prior carotid endarterectomy, 11.0% prior peripheral angioplasty or bypass, 12.9% diabetic nephropathy	15603	treatment was permanently discontinued by 20.4% of the patients in the clopidogrel group, as compared with 18.2% in the placebo group (p<0.001). A total of 4.8% of the clopidogrel patients and 4.9% of those in the placebo group discontinued treatment because of an adverse event (p=0.67)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Bhatt, 2006 International CHARISMA Good	Clopidogrel + ASA vs. Placebo + ASA *Outcomes at 28 months* First occurrence of MI, stroke, or death from cardiovascular cause: 6.8% (534/7802) vs 7.3% (573/7801) RR = 0.93 (0.83, 1.04) Death from any cause: 4.8% (371/7802) vs 4.8% (374/7801) RR = 0.99 (0.86, 1.14) Death from cardiovascular causes: 3.1% (238/7802) vs 2.9% (229/7801) RR = 1.04 (0.87, 1.24) MI (nonfatal): 1.9% (146/7802) vs 2.0% (155/7801) RR = 0.94 (0.75, 1.18) Ischemic stroke (nonfatal): 1.7% (132/7802) vs 2.1% (163/7801) RR = 0.81 (0.65, 1.02) Stroke (nonfatal): 1.9% (150/7802) vs 2.4% (189/7801) RR = 0.79 (0.64, 0.98), NNT = 200 (104, 2340) First occurrence of MI, stroke, or death from cardiovascular causes, or hospitalization for unstable angina, transient ischemic attack, or a revascularization procedure: 16.7% (1303/7802) vs 17.9% (1396/7801) RR = 0.93 (0.87, 1.00) Hospitalization for unstable angina, transient ischemic: 11.1% (866/7802) vs 12.3% (957/7801) RR = 0.90 (0.83, 0.99), NNT = 86 (46, 625)	Clopidogrel + ASA vs Placebo + ASA Severe bleeding: 1.7% (130/7802) vs 1.3% (104/7801) Fatal bleeding: 0.3% (26/7802) vs 0.2% (17/7801) Intracranial hemorrhage: 0.3% (26/7802) vs 0.3% (27/7801) Moderate bleeding: 2.1 (164/7802) vs 1.3% (101/7801) Thrombotic thrombocytopenic purpura: 0.01% (1/7802) vs 0% (0/7801)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bhatt, 2006 International CHARISMA Good	Treatment was permanently discontinued by 20.4% of the patients in the clopidogrel group, as compared with 18.2% in the placebo group (p,0.001). A total of 4.8% of the patients in the clopidogrel group and 4.9% of those in the placebo group discontinued treatment because of an adverse event p=0.67). Average delay from randomization to discontinuation was 287 days (95% CI, 277 to 296)	Sanofi-Aventis and Bristol-Myers Squibb. The sponsor and cosponsor had advisory input in the design of the study, had nonvoting input in the executive committee, and were responsible for auditing at individual study sites. The executive committee bears complete responsibility for the analysis of the results, the veracity and completeness of the reporting, and the writing of the manuscript; the sponsors did have the opportunity to review the manuscript.	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Boehringer Ingelheim, 2010 (unpublished study NCT00311402) Japan JASAP Fair	Patients 50 years and older with a diagnosis of cerebral infarction (excluding cardiogenic cerebral embolism) who meet the diagnostic criteria based on the National Institute of Neurological Disorders and Stroke (NINDS) ad hoc committee's classification of cerebrovascular disease III, occurring between 1 week and 6 months before the time of enrollment (including first and recurrent cerebral infarctions).	A: Aggrenox (extended-release dipyridamole 200 mg plus ASA 50 mg), 1 capsule bid (dosing information provided by Boehringer Ingelheim public comment) B: ASA 81 mg qd for up to 124 weeks	NR	Age: 66.1 years Female: 28.5% Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Boehringer Ingelheim, 2010 (unpublished study NCT00311402) Japan JASAP Fair	NR	1294	387/3/1291

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Boehringer Ingelheim, 2010 (unpublished study NCT00311402) Japan JASAP Fair	<u>Aggrenox vs ASA</u> Patients with first recurrent cerebral infarction (fatal or nonfatal): 45 (6.9%) vs 32 (5.0%); P=0.97; HR 1.47; 95% CI, 0.93 to 2.31 Patients with TIA: 3 (0.5%) vs 3 (0.5%); P=0.977; HR 1.02; 95% CI, 0.21 to 5.07 Patients with ACS: 9 (1.4%) vs 16 (2.5%); P=0.192; HR 0.58; 95% CI, 0.26 to 1.31 Patients with other vascular events: 11 (1.7%) vs 6 (0.9%); P=0.215; HR 1.88; 95% CI, 0.69 to 5.07 Patients with ischemic vascular event composite: 57 (8.7%) vs 51 (8.0%); P=0.443; HR 1.16; 95% CI, 0.79 to 1.69 Number of patients with stroke: 57 (8.7%) vs 39 (6.1%); P=0.043; HR 1.52; 95% CI, 1.01 vs 2.29 Number of patients with composite endpoint of stroke or major bleeding: 71 (10.9%) vs 55 (8.6%); P=0.101; HR 1.34; 95% CI, 0.94 to 1.91	<u>Aggrenox vs ASA</u> Total patients with serious AEs: 178 (27.2%) vs 167 (26.1%) Total patients with other (not including serious) AEs: 634 (96.8%) vs 604 (94.5%) Cerebral hemorrhage: 12 (1.8%) vs 7 (1.1%); P=0.223; HR 1.79; 95% CI, 0.70 vs 4.54 Subarachnoid hemorrhage: 0 (0%) vs 1 (0.2%); P=0.998 Intracranial hemorrhage (post-hoc): 13 (2.0%) vs 13 (2.0%); P=0.919; HR 1.04; 95% CI, 0.48 to 2.25 Headache: 293 (44.7%) vs 187 (29.3%) Neutropenia: 0 (0%) vs 1 (0.2%)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Boehringer Ingelheim, 2010 (unpublished study NCT00311402) Japan JASAP Fair	Aggrenox vs ASA Total withdrawals: 210 (32.1%) vs 177 (27.7%) Due to AE: 118 (18.0%) vs 105 (16.4%)	Boehringer Ingelheim Pharmaceuticals	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
CAPRIE Steering Committee, 1996 International CAPRIE Good	Diagnosis of ischemic stroke, (including retinal and lacunar infarction) was defined as ● focal neurological deficit likely to be of atherothrombotic origin, ● Onset >1 wk and ≤6 mos before randomization, ● Neurological signs persisting ≥1 wk from stroke onset ● CT or MRI ruling out hemorrhage or non-relevant disease. MI defined as ● Onset ≤35 d before randomization ●2 of the following: -characteristic ischemic pain for ≥ 20 min,-elevation of CK, CK-MB, LDH, or AST to 2x upper limit of laboratory normal with no other explanation, -development of new ≥40 Q waves in at least two adjacent ECG leads or new dominant R wave in V1 (R≥1 mm > S in V1) or symptomatic atherosclerotic PAD defined as ●Intermittent claudication (WHO: leg pain on walking, disappearing in <10 min or standing) or presumed atherosclerotic origin; and ankle/arm systolic BP ratio ≤0.85 in either leg at rest (2 assessments on separate days); or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty with no persisting complications from intervention had to be established.	Blister packs containing either 75mg of clopidogrel + ASA placebo OR 325mg ASA plus clopidogrel placebo to take with morning meal x 1-3 years (mean 1.9 years)	NR	mean age 62.5 ± 11.1 in the clopidogrel and 62.5 ± 11.1 in the ASA group. Both groups had 72 % male, 28% female and 95% white.
Collet, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
CAPRIE Steering Committee, 1996 International CAPRIE Good	20% DM, 52% HTN, 22% stable angina, 9% unstable angina, 17% MI (not including the qualifying event), 29% current smokers, 49% ex smokers in both groups	19185	42 (0.22%) were lost to f/u-22 in the clopidogrel and 20 in the ASA group. 21.2% had study drug permanently discontinued early for reasons other than the occurrence of an outcome event; 21.3% in the clopidogrel and 21.1% in the ASA group. 46 pts did not receive clopidogrel as allocated vs. 40 in the ASA group although they were included in the analysis
Collet, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
CAPRIE Steering Committee, 1996 International CAPRIE Good	Clopidogrel vs Aspirin *Outcomes at 36 months* Ischemic stroke, MI, or vascular death: 9.8% (939/9553) vs 10.7% (1021/9546) RR = 0.92 (0.84, 1.00) Ischemic stroke, MI, amputation, or vascular death: 10.2% (979/9553) vs 11.0% (1051/9546) RR = 0.93 (0.86, 1.01) Vascular death: 3.7% (350/9553) vs 4.0% (378/9546) RR = 0.93 (0.80, 1.07) Any stroke, MI or death from any cause: 11.9% (1133/9553) vs 12.6% (1207/9546) RR = 0.94 (0.87, 1.01) Death from any cause: 5.9% (560/9553) vs 6.0% (571/9546) RR = 0.98 (0.88, 1.10)	Clopidogrel vs Aspirin Abnormal liver function: 3.0% (285/9599) vs 3.2% (302/9586) Any bleeding disorder: 9.3% (890/9599) vs 9.3% (890/9586) Diarrhea: 4.5% (428/9599) vs 3.4% (322/9586) GI hemorrhage: 2.0% (191/9599) vs 2.7% (255/9586) Indigestion/nausea/vomiting: 15.0% (1441/9599) vs 17.6% (1686/9586) Intracranial hemorrhage: 0.4% (34/9599) vs 0.5% (47/9586) Rash: 6.0% (578/9599) vs 4.6% (442/9586)
Collet, 2009 Companion to Bhatt, 2006 CHARISMA	Clopidogrel + ASA vs. Placebo + ASA Patients who did not discontinue study drug vs patients who permanently discontinued study drug, from randomization to end of follow-up: Death: 424 (3.4%) vs 321 (10.7%); adjusted HR 5.23 (95% CI, 5.08 vs 5.38), P<0.001 CV death: 313 (2.5%) vs 154 (5.1%); adjusted HR 3.53 (95% CI 3.33-3.73), P<0.001 MI: 241 (1.9%) vs 145 (4.8%); HR 3.04 (2.82 to 3.27), P<0.001 Independent correlates of CV death in the global population: Permanently discontinued study drug: HR 4.318, P<0.001	Clopidogrel + ASA vs. Placebo + ASA Patients who did not discontinue study drug vs patients who permanently discontinued study drug: Severe bleed: 87 (0.7%) vs 147 (4.9%); HR 7.42 (95% CI 5.67 to 9.70), P<0.001

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
CAPRIE Steering Committee, 1996 International CAPRIE Good		Study was funded by Sanofi and Bristol-Myers Squibb	The plans were to recruit 15000 pts, 5000 in each of the clinical subgroups, over 3 years and to terminate the study after 1 further year of follow-up. If the recruitment over time was uniform, this sample would have resulted in a mean duration of potential f/u of 2.33 years/pt and 35000 pt/years at risk. Assumed expected 3 year event rates would be 25% for the primary outcome cluster for pts entering the study with recent stroke or MI and 14% for pts entering with PAD. Study expected to have 90% power to detect an overall relative-risk reduction of 11.6%. The expected width of the corresponding 95% CI would be about 8%. Pt recruitment was achieved well ahead of schedule and 15000 had been randomized after only 2 years and 3 months. A blinded review of overall outcome event rates showed them to be lower than initial expectation. So, pt recruitment was continued but staggered closing dates and hence, completion dates, 1 year later: PAD would finish 2 months before pts with MI who would finish 2 months before pts with stroke. Revised estimate of RRR would be 12-13%.
Collet, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
CURE Trial Investigators, 2001 International CURE Good	Hospitalized within 24 hours after onset of symptoms and did not have ST-segment elevation. Initially pts >60 yrs with no new ECG changes but with a history of CAD were included But after a review of the overall rates of events among the first 3000 patients, it was recommended that only pts who had either ECG changes or an elevation in the serum level of cardiac enzymes or markers at entry would be included.	Clopidogrel 300mg LD followed by 75 mg/day plus ASA 75 to 325 mg daily) or matching placebo plus ASA, 75 to 325mg daily x 3-12 months (mean duration of treatment, 9 months.	Medications at time of randomization: 66% on ASA, 37% ACE inhibitor, 58.6% BB, 28.3% calcium-channel blockers, 25.4% lipid-lowering agents	Clopidogrel group: 64.2± 11.3 years; 38.7% female, 61.3% males. Placebo group: 64.2 ± 11.3 years; 38.3% females, 61.7% females. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
CURE Trial Investigators, 2001 International CURE Good	32.4% MI, 17.7% CABG or PTCA, 4% stroke, 7.6% heart failure, 59.9% HTN; 22.4% DM; 60.6% current or former smoker in Clopidogrel group In Placebo: 32% MI, 18.1% CABG or PTCA, 3.7% stroke, 7.8% heart failure, 57.8% HTN; 22.8% DM; 60.9% current or former smoker	12,562	6 pts in the clopidogrel and 7 pts in the placebo lost to follow-up

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
CURE Trial Investigators, 2001 International CURE Good	Clopidogrel vs. placebo *Outcomes at 12 months* Nonfatal MI, stroke, or death from cardiovascular cause: 9.3% (582/6259) vs 11.4% (719/6303) RR = 0.80 (0.72, 0.90); NNT = 47 (32, 96) Nonfatal MI, stroke, death from cardiovascular causes, or refractory ischemia: 16.5% (1035/6259) vs 18.8% (1187/6303) RR = 0.86 (0.79, 0.94); NNT = 40 (28, 104) Death from cardiovascular causes: 5.1% (318/6259) vs 5.5% (345/6303) RR = 0.93 (0.79, 1.08) MI: 5.2% (324/6259) vs 6.7% (419/6303) RR = 0.77 (0.67, 0.89); NNT = 68 (44, 155) Q-wave MI: 1.9% (116/6259) vs 3.1% (193/6303) RR = 0.60 (0.48, 0.76); NNT = 83 (57, 150) MI non-q-wave: 3.5% (216/6259) vs 3.8% (242/6303) RR = 0.89(0.74, 1.07) Stroke: 1.2% (75/6259) vs 1.4% (87/6303) RR = 0.86 (0.63, 1.18) Refractory ischemia: 8.7% (544/6259) vs 9.3% (587/6303) RR = 0.93 (0.82, 1.04) Refractory ischemia during initial hospitalization: 1.4% (85/6259) vs 2.0% (126/6303) RR = 0.68 (0.52, 0.90); NNT = 156 (92, 521) Refractory ischemia after discharge: 7.6% (459/6259) vs 7.6% (461/6303) RR = 0.99 (0.87, 1.13) Death from non-CV causes: 0.7% (41/6259) vs 0.7% (45/6303) RR = 0.91 (0.60, 1.39)	Clopidogrel vs Placebo Major bleeding: 3.7% (232/6259) vs 2.7% (170/6303) Life-threatening bleeding: 2.2% (135/6259) vs 1.8% (112/6303) Transfusion of 2 or more units of blood: 2.8% (177/6259) vs 2.2% (137/6303) Early major bleeding: 2.0% (125/6259) vs 1.5% (95/6303) Late major bleeding: 1.7% (106/6259) vs 1.1% (69/6303) Major bleeding after CABG: 1.3% (81/6259) vs 1.1% (69/6303) Minor bleeding: 5.1% (322/6259) vs 2.4% (153/6303) Vascular complication: 1.3% (2/154) vs 1.3% (2/153) Thrombocytopenia: 0.4% (26/6259) vs 0.4% (28/6303) Neutropenia: 0.1% (8/6259) vs 0.1% (5/6303)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
CURE Trial Investigators, 2001 International CURE Good		Supported by Sanofi-Synthelabo and Bristol-Myers Squibb	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Dasgupta, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Dasgupta, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Dasgupta, 2009 Companion to Bhatt, 2006 CHARISMA	Clopidogrel + ASA vs. Placebo + ASA Patients with diabetic nephropathy: Overall death: 73 (7.3%) vs 45 (4.5%); P=0.008; HR 1.8 (95% CI, 1.2 to 2.7) CV death: 51 (5.1%) vs 31 (3.1%); P=0.023; HR 1.7 (95% CI, 1.1 to 2.9) Overall CV death/MI/stroke: 85 (8.4%) vs 75 (7.5%); P=0.405; HR 1.1 (95% CI, 0.8 to 1.6) Nonfatal MI: 22 (2.2%) vs 29 (2.9%); P=0.347; HR 0.8 (95% CI, 0.4-1.3) Nonfatal stroke: 20 (2.0%) vs 22 (2.2%); P=0.766; HR 0.9 (95% CI, 0.5 to 1.7) Overall CV death/MI/stroke/hospitalization: 166 (16.5%) vs 161 (16.1%); P=0.784; HR 1.0 (95% CI, 0.8 to 1.3) Hospitalization: 97 (9.6%) vs 104 (10.4%); P=0.634; HR 0.9 (95% CI, 0.7 to 1.2)	Clopidogrel + ASA vs. Placebo + ASA Patients with diabetic nephropathy: GUSTO severe bleeding: 26 (2.6%) Vs 15 (1.5%); P=0.075; HR 1.8 (95% CI 0.9 to 3.3) GUSTO moderate bleeding: 28 (2.8%) vs 24 (2.4%); P=0.543; HR 1.2 (95% CI, 0.7 to 2.0)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Dasgupta, 2009 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Di Pasquale, 2005 Italy Fair	>18 and < 75 years of age; were hospitalized with an admission diagnosis of first episode of ACS. All patients had to have a 1st episode of NSTEMI, Killip class I-II and an acceptable echocardiograph window. The echocardiogram performed at entry had to show alterations of the segmentary kinetics. The basal creatine kinase and troponin had to be within the normal range at entry (0.5-0.1 pg/ml). All patients had to show an increase in TNI plasma levels in the samples obtained after hospitalization.	Clopidogrel 75mg/day + ASA 160mg or ticlopidine 500mg/day + ASA 160mg X 6 months	All NSTEMI patients received a standard tirofiban infusion 0.4ug/kg/min for 30 min, followed by an infusion of 0.1 ug/kg/min for 72 hours. All patients received standard treatment of nitrates (5-100 ug/ml), aspirin (160mg/day), heparin (5000 IU as bolus and subsequent 1000 IU/h continuous infusion), statin (simvastatin/pravastatin 40mg), angiotensin-converting enzyme inhibitors and, where possible, B-blockers) IV doses of metoprolol and subsequent oral administration) Additional heparin was given in the cathlab depending on the activating clotting time, with a target of 250s. Post PCI--ASA, statins and the usual post-NSTEMI treatment (B-blockers, nitrates and angiotensin-converting enzyme). Both groups underwent PCI within 72 hours from admission. Patients had echocardiographic examination before discharge and 1 month after treatment when, as part of the PCI protocol, they were also submitted to exercise testing, as well as after 3 and 6 months.	Range 35-7; Ticlopidine group: 60.7±10.5; 70% males; 30% females Ethnicity NR Clopidogrel group: 61.3± 11.8; 68.2% males, 31.8% females Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Di Pasquale, 2005 Italy Fair	Ticlopidine group: 38% DM, 46% HTN, 28% Current smoker; 36% Hyper-cholesterol; 48% + family history; EF, % 53.4± 14. Clopidogrel group: 40% DM, 50% HTN, 26% current smoker; 34% hypercholesterolemia; 50% + family history; EF,% 55.8± 13."Both groups were similar in regard to clinical data and risk factors. Both groups were similar in diseased vessels and number of implanted stents."	428	NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Di Pasquale, 2005 Italy Fair	Ticlopidine + ASA vs Clopidogrel + ASA *Outcomes at 180 days* Total cardiac events (reocclusions): 20.6% (44/214) vs 22.4% (48/214) RR = 0.92 (0.64, 1.32) *Outcomes at first 90 days* Ischemic events: 18.7% (40/214) vs 20.6% (44/214) RR = 0.91 (0.62, 1.33) *Outcomes at last 90 days* Ischemic events: 1.9% (4/210) vs 1.9% (4/210) RR = 1.00 (0.25, 3.95)	Ticlopidine + ASA vs Clopidogrel + ASA At least one side effect: 9.3% (20/214) vs 6.5% (14/214) GI: 1.9% (4/214) vs 0% (0/214) Dermatological: 1.9% (4/214) vs 0.9% (2/214) Major bleeding: 0.9% (2/214) vs 0.9% (2/214) Minor bleeding: 2.8% (6/214) vs 2.8% (6/214) Platelet reduction: 1.9% (4/214) vs 1.9% (4/214)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Di Pasquale, 2005 Italy Fair	Unknown	NR	All patients received GPIIb/IIIA prior to randomization. All patients were high-risk NSTEMI with 1st coronary event.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Diener, 1996 International ESPS-2 Good	older than 18 years old and had experienced a TIA (clinical neurological symptoms persisting for less than 24 h) or a completed ischemic stroke (clinical neurological deficit lasting more than 24 h) within the preceding 3 months. Diagnosis based on clinical neurological examination only was acceptable but CT or MRI were recommended to confirm the diagnosis.	ASA 50mg; dipyridamole SR (Persantine Retard) 200mg twice a day; ASA/DP, placebo x 2 years	NR	Mean age: Placebo: 66.6, ASA: 66.8, DP: 66.7, DP-ASA: 66.8 Sex M/F: Placebo: 57.7%/42.3%; ASA 58%/42%; DP 58.3%/41.7%; DP-ASA; 57.9%/42.1%

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Diener, 1996 International ESPS-2 Good	DM: placebo 14.5%; ASA 14.6%; DP 16.8%; DP-ASA 15.4% HTN: placebo 62%; ASA 59.6%; DP 61.2%; DP-ASA 59.4% Current Smoker: placebo 23.5%; ASA 23.5%; DP 23.9%; DP-ASA 25.6% PVD: placebo 22%; ASA 22%; DP 22.4%;DP-ASA 21.7%	7054	NR/NR/6602

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Diener, 1996 International ESPS-2 Good	Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo *Outcomes at 24 months* (RR based on D+A vs A) Death: 11.4% (188/1654) vs 11.2% (185/1650) vs 11.0% (182/1649) vs 12.2% (202/1649) RR = 1.02 (0.84, 1.23)	See ESPS-2 1997

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Diener, 1996 International ESPS-2 Good		supported by a grant from Boehringer Ingelheim	Prior to unblinding of the data, the data quality control unit identified 2 issues that required investigation: 1. 14 randomization numbers were issued that did not correspond to existing pts 2. Serious inconsistencies in pt case record from and compliance assay determinations led the Steering Committee to question the reliability of data from one centre which had randomized 438 pts. total. The data from this centre were excluded before unblinding the data. The results presented are based on 6,602 pts and not the total 7054.On the side note, the excluded patients had no impact on the results reported in this paper.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
ESPRIT Study Group, 2006 Europe and Australia ESPRIT Fair	Patients were referred within 6 months of a TI (including transient monocular blindness) or minor ischemic stroke (grade less than or equal to 3 on the modified Rankin scale) or presumed arterial origin.	Combination therapy of ASA and dipyridamole and ASA alone. Dose of dipyridamole was 200mg bid, either as a fixed dose combination of ASA and dipyridamole or as a free combination. Dipyridamole was preferably used as an extended-release formulation. 83% of the patients allocated to dipyridamole and ASA used extended-release dipyridamole. 8% of the patients were on the same formulation as Aggrenox. If no fixed-dose combination was prescribed, the ASA dose was left to the discretion of MD provided it was between 30mg and 325mg per day. The median ASA dose was 75mg. The trial also addressed the efficacy of mild anticoagulation therapy (target INR 2-3) vs. aspirin (results of that aspect of the trial are not included in table)	If no fixed dose combination of dipyridamole and ASA was prescribed, the aspirin dose was left to the discretion of local MDs provided it was between 30mg and 325mg per day, as was the case for patients allocated to aspirin alone.	ASA + Dipyridamole: mean age 63 ± 11; 66% males, 44% females, Ethnicity was NR although the study was conducted in Europe and Australia. ASA alone group: median Age 63 ±11, 65% males, 45% females

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
ESPRIT Study Group, 2006 Europe and Australia ESPRIT Fair	ASA + dipyridamole vs. ASA: 12% vs 11% history of stroke; 7% vs. 7% history of MI; 19% vs. 18% diabetics;60% vs. 59% history of HTN; 10% vs. 9% a history of angina; 47% vs. 46% hyperlipidemia; 36% vs. 37% current smokers; 43% vs. 42% no symptoms on Rankin grade; 33% vs. 34% Rankin grade 1 (minor symptoms; no limitations); 18% vs. 18% Rankin grade 2 (some restrictions; no help needed); 6% vs. 6% Rankin grade 3 (help needed; still independent). Qualifying event: 5% vs. 6% (transient monocular blindness); 30% vs. 27% TIA; 66% vs. 67% minor ischemic stroke. Time from longest event to randomization: 11% vs. 11% < 1 week; 23% vs. 20% 1 wk to 1 month' 66% vs. 69% 1-6 months.	2739	12 pts (4 in ASA monotherapy) were inappropriately enrolled, 39 pts were enrolled more than 6 months after their last ischemic CV event--but were included in all analyses. Of patients allocated to ASA alone, 13% (n=184) discontinued their medication, mainly because of a medical reason, such as a new TIA or stroke or an indication for oral anticoagulant therapy. Before unblinding of the data, the executive committee reviewed all baseline and follow-up data obtained at the central trial office. Because of incomplete data, patients from one hospital (n=24) were excluded from all analyses. From four other hospitals, follow-up data were incomplete. From these hospitals (n=11), follow-up was closed at the time all data were complete. In the ASA and dipyridamole group 57 patients (4.1%) were lost to follow-up and 470 patients (35%) discontinued treatment.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
ESPRIT Study Group, 2006 Europe and Australia ESPRIT Fair	ASA + Dipyridamole vs ASA *Outcomes at 3.5 years* Death from all vascular causes, non-fatal stroke, non-fatal MI, non-fatal major bleeding complications: 12.7% (173/1363) vs 15.7% (216/1376) RR = 0.81 (0.67, 0.97), NNT = 33 (18, 254) Death from all causes: 6.8% (93/1363) vs 7.8% (107/1376) RR = 0.88 (0.67, 1.15) Death from all vascular causes: 3.2% (44/1363) vs 4.4% (60/1376) RR = 0.74 (0.51, 1.08) Death from all vascular causes, non-fatal stroke: 9.7% (132/1363) vs 12.4% (171/1376) RR = 0.78 (0.63, 0.97), NNT = 36 (20, 253) All major ischemic events: 10.3% (140/1363) vs 12.6% (174/1376) RR = 0.81 (0.66, 1.00) Death from all vascular causes, non-fatal stroke, non-fatal MI: 10.9% (149/1363) vs 14.0% (192/1376) RR = 0.78 (0.64, 0.96), NNT = 33 (18, 181) First ischemic stroke: 7.0% (96/1363) vs 8.4% (116/1376) RR = 0.84 (0.64, 1.08) First cardiac event: 3.2% (43/1363) vs 4.4% (60/1376) RR = 0.72 (0.49, 1.06)	ASA + Dipyridamole vs ASA Major bleeding complication: 2.6% (35/1363) vs 3.9% (53/1376) Non-fatal extracranial bleeding: 1.5% (21/1363) vs 2.3% (32/1376) Fatal extracranial bleeding: 0.1% (2/1363) vs 0% (0/1376) Non-fatal intracranial bleeding: 0.7% (9/1363) vs 1.2% (17/1376) Fatal intracranial bleeding: 0.2% (3/1363) vs 0.3% (4/1376) Minor bleeding complication: 12.5% (171/1363) vs 12.2% (168/1376)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
ESPRIT Study Group, 2006 Europe and Australia ESPRIT Fair	19% (n=255) allocated to the combination therapy discontinued the medication due to AE whereas 2.5% (n=35) in the aspirin group discontinued due to AE . 26% (n=123) reported HA as at least one of the reasons in the combination group.	None of the sponsors had a commercial interest in the outcome of the study. Sponsors had no role in study design, data collection, data analysis, data interpretation or writing of the report. The study was sponsored by: The Council of Singapore; European Commission anivo Foundation, Netherlands' The French Ministry of Health, Netherlands, The Netherlands Heart Foundation; Thrombosis Foundation, Netherlands; UK Stroke Association; University Medical Center Utrecht, Netherlands	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
ESPS-2 authors, 1997 International ESPS-2 Fair/Good	All pts had experienced a recent (within the preceding 3 months) ischemic CVA episode as a qualifying event	Placebo, ASA 50mg; modified release dipyridamole 400mg used alone or in combination x 2 years	NR	< 60 years and male with TIA -322 pts; < 60, years and female with TIA-169 pts; (Total TIA pt = 1562) < 60 years and female with stroke 327 pts; ≥ 60 years and male with TIA- 554 pts; (Total # stroke pts-5038) ≥ 60 years and female with TIA-517 pts. Ethnicity NR. Report does provide breakdown of those between 50-59, 60-69 and 70-79.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
ESPS-2 authors, 1997 International ESPS-2 Fair/Good	76.3% had stroke and 23.7% had TIA as ischemic CVA episode as the qualifying events. Article provides breakdown of # of pts with multiple other conditions	7054	138 cases (2.1%) were either misdiagnosed or not included into the study--4 treatment groups each contained approx 1/4 of these pts, so that misdiagnosis or not included is not expected to change significantly the results in the intention-to-treat analysis. Loss to f/u-42 pt (0.6%) of trial population. These subjects were also equally distributed over the 4 treatment groups. 1/4 of all pts stopped treatment for a reason (medical or non-medical) other than reaching an endpoint. Treatment cessations were 7.2% more frequent in the 2 DP groups 29.2% than in the non-DP groups (22.0%).

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
ESPS-2 authors, 1997 International ESPS-2 Fair/Good	<u>Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo</u> (All RRs based on D+A vs A) *Outcomes at 24 months* All strokes: 12.8% (211/1654) vs 9.5% (157/1650) vs 12.5% (206/1649) vs 15.2% (250/1649) RR = 0.76 (0.63, 0.93); NNT = 34 (20, 118) Non-fatal strokes: 11.1% (183/1654) vs 8.3% (137/1650) vs 11.3% (186/1649) vs 13.8% (228/1649) RR = 0.74 (0.60, 0.91); NNT = 32 (19, 90) Fatal strokes: 3.4% (56/1654) vs 2.3% (38/1650) vs 2.4% (39/1649) vs 2.6% (43/1649) RR = 0.97 (0.63, 1.51) At least one TIA: 13.0% (215/1654) vs 10.4% (172/1650) vs 12.5% (206/1649) vs 16.2% (267/1649) RR = 0.83 (0.69, 1.00) Stroke or TIA: 23.1% (382/1654) vs 18.1% (299/1650) vs 22.6% (372/1649) vs 28.7% (473/1649) RR = 0.80 (0.70, 0.92); NNT = 23 (14, 59) MI: 2.9% (48/1654) vs 2.1% (35/1650) vs 2.4% (39/1649) vs 2.7% (45/1649) RR = 0.90 (0.57, 1.41) Fatal MI: 0.9% (15/1654) vs 1.0% (17/1650) vs 1.3% (22/1649) vs 1.0% (16/1649) RR = 0.77 (0.41, 1.45) Non-fatal MI: 2.0% (33/1654) vs 1.1% (18/1650) vs 1.0% (17/1649) vs 1.8% (29/1649) RR = 1.06 (0.55, 2.05) Other vascular events: 2.1% (35/1654) vs 1.3% (21/1650) vs 2.3% (38/1649) vs 3.3% (54/1649) RR = 0.55 (0.33, 0.94); NNT = 100 (53, 919) All ischemic events: 16.4% (271/1654) vs 12.5% (206/1650) vs 16.1% (266/1649) vs 18.6% (307/1649) RR = 0.77 (0.65, 0.92); NNT = 27 (17, 79) Non-fatal ischemic events: 12.8% (212/1654) vs 9.3% (153/1650) vs 12.3% (203/1649) vs 15.1% (249/1649) RR = 0.75 (0.62, 0.92); NNT = 33 (19, 108) Fatal ischemic events: 5.7% (95/1654) vs 4.8% (80/1650) vs 5.3% (88/1649) vs 5.5% (90/1649) RR = 0.91 (0.68, 1.22) Vascular death: 7.6% (125/1654) vs 7.1% (117/1650) vs 7.2% (118/1649) vs 7.5% (124/1649) RR = 0.99 (0.77, 1.27) Vascular events: 19.6% (324/1654) vs 14.9% (246/1650) vs 19.0% (314/1649) vs 21.9% (361/1649) RR = 0.78 (0.67, 0.91); NNT = 24 (15, 64)	<u>Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo</u> GI event: 30.5% (505/1654) vs 32.8% (541/1650) vs 30.4% (502/1649) vs 28.2% (465/1649) Nausea: 14.8% (245/1654) vs 15.4% (254/1650) vs 12.4% (204/1649) vs 13.7% (226/1649) Dyspepsia: 16.6% (274/1654) vs 17.6% (290/1650) vs 17.2% (283/1649) vs 16.1% (266/1649) Vomiting: 7.2% (119/1654) vs 8.1% (133/1650) vs 5.6% (93/1649) vs 6.6% (109/1649) Gastric pain: 14.5% (240/1654) vs 16.6% (274/1650) vs 14.7% (242/1649) vs 13.3% (219/1649) Diarrhea: 15.4% (254/1654) vs 12.1% (199/1650) vs 6.6% (109/1649) vs 9.3% (154/1649) Headache: 37.2% (615/1654) vs 38.2% (630/1650) vs 33.1% (546/1649) vs 32.4% (534/1649) Bleeding any site (total): 4.7% (77/1654) vs 8.7% (144/1650) vs 8.2% (135/1649) vs 4.5% (74/1649) Dizziness: 30.1% (498/1654) vs 29.5% (486/1650) vs 29.2% (481/1649) vs 30.9% (509/1649)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
ESPS-2 authors, 1997 International ESPS-2 Fair/Good		NR	External audit was brought in --which also failed to establish guilt or innocence. A definitive decision could only be made by the Steering Committee once the compliance assays had been conducted. The initial power study for ESPS-, fixed to 80% for a risk reduction of 30% at the alpha level - 0.05, led to a total sample size of 5000 pts (1250/group) based on the best estimations available at the time. An interim analysis was done per protocol and the estimates were changed, characterized by a lower drop out rate and a lower risk reduction (25%). Rerunning the simulation led to a new sample size of about 7000 pts (1750/group). ESPS 2 was designed to have sufficient statistical power only for the whole group and not for subgroup analysis. Data in this report is analyzed for the overall treatment groups, the only exception benign a few subgroups which were defined a priori as baseline risk factors for stroke and which were confirmed by the Cox's model to be independent risk variables for stroke occurrence.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Fukuuchi, 2008 Japan Phase IIIb Fair	Patients 20-80 years old with a history of cerebral infarctions (excluding cardiogenic cerebral embolism), with most recent stroke >8 days before inclusion with a well-documented clinical course, and computed tomography or magnetic resonance imaging to document brain infarct at initial screening.	A: Clopidogrel 5 mg/d after a meal B: Ticlopidine 200 mg/d after a meal For 52 weeks	NR	Age: 64.5 years (SD 9.3) Male: 73.1% Ethnicity NR (trial conducted in Japan

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Fukuuchi, 2008 Japan Phase IIIb Fair	Age ≥65 years: 56.3% Current or ex-smoker: 63.2% Time from most recent onset of cerebral infarction: <4 weeks: 18.9% 4-12 weeks: 18.4% >12 weeks: 62.6% Type of most recent infarction: Atherothrombotic: 29.7% Lacunar: 68.1% Unknown: 2% Size of infarct: Minor: 75.7% Intermediate: 22.8% Major: 1.3% Unknown: 0.2% Comorbidities: Hypertension: 67.8% DM: 19.3% Hyperlipidemia: 38.8% Angina (nonserious): 2.3% Obesity: 1.8% Chronic arterial obstruction: 0.9% CHF (nonserious): 0.3%	1172	389/NR/1151 for efficacy, 1155 for safety

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Fukuuchi, 2008 Japan Phase IIIb Fair	Clopidogrel vs Ticlopidine Efficacy endpoint event: 17 (3%) vs 15 (2.6%); HR 0.977; 95% CI, 0.488 to 1.957; P=0.948 Cerebral infarction: 17 (3%) vs 15 (2.6%) MI: 0 (0%) vs 0 (0%) Vascular death: 0 (0%) vs 0 (0%) Other vascular events: 8 (1.4%) vs 9 (1.6%) TIA: 2 (0.3%) vs 4 (0.7%) Angina: 3 (0.5%) vs 4 (0.7%) Peripheral arterial obstruction: 1 (0.2%) vs 1 (0.2%) Other: 2 (0.3%) vs 1 (0.2%) Any vascular event: 25 (4.4%) vs 24 (4.2%); HR 0.898; 95% CI, 0.513 to 1.573; P=0.708	Clopidogrel vs Ticlopidine Any primary safety event: 40 (7%) vs 87 (15.1%); HR 0.401; 95% CI 0.276 to 0.583; P<0.001 Cumulative incidence of patients experiencing at least one safety event: 7.9% vs 17.6%; P<0.001 Hematologic disorders: 6 (1%) vs 14 (2.4%); HR 0.386; 95% CI, 0.148 to 1.005; P=0.043 Leukopenia: 0 (0%) vs 4 (0.7%) Neutropenia: 5 (0.9%) vs 14 (2.4%) Thrombocytopenia: 1 (0.2%) vs 0 (0%) Atraumatic serious hemorrhage: 8 (1.4%) vs 5 (0.9%); HR 1.342; 95% CI, 0.439 to 4.104; P=0.604 Cerebral hemorrhage: 3 (0.5%) vs 1 (0.2%) Intracranial: 1 (0.2%) vs 0 (0%) Gastric hemorrhage: 1 (0.2%) vs 0 (0%) Hepatic dysfunction: 24 (4.2%) vs 69 (11.9%); HR 0.305; 95% CI, 0.192 to 0.486; P<0.001 Other serious adverse events: 5 (0.9%) vs 1 (0.2%); HR 4.432; 95% CI 0.517 to 37.965; P=0.137

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Fukuuchi, 2008 Japan Phase IIIb Fair	Clopidogrel vs Ticlopidine Total withdrawals: 156 (27.2%) vs 233 (40.3%) Due to AE: 97 (17%) vs 154 (27%); P<0.001	Daiichi Pharmaceutical Co. and sanofi-aventis	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Gorelick, 2003 U.S. Fair/Good	African American race; 29-85 years of age with a non-cardioembolic ischemic stroke (confirmed by cranial computed tomographic scan or magnetic resonance image of the brain consistent with occurrence of the entry cerebral infarct; measurable neurological deficit that correlates at onset with entry cerebral infarct with onset at least 7 days but not more than 90 days; pts needed to be available to be follow up in an outpatient treatment program.	250mg twice a day Ticlopidine + Placebo twice a day with meals vs. 325mg ASA twice a day+ placebo twice a day with meals x 2 years	At the time the blinded phase of the study was halted by the data and safety monitoring board on 7/15/02 - [recruitment and f/u had been ongoing for about 6.5 yrs] because futility analyses indicated a <1% chance of ticlopidine being significantly better than ASA therapy in the prevention of primary outcome if the trial were to continue to completion. 47.1% of the pts had not completed the 2-yr f/u period; the patients were given the option of remaining in the study taking study-sponsored open-label aspirin or transition into the community for stroke prevention therapy according to their community physician. 307 (41%) in the ticlopidine group and 403 (44.4%) in the ASA group completed the 24 month examination.	T group: 60.9 years old ± 10.7, 54.5% women, 45.5% male and 61.6± 10.4 years old, 52.4% female and 47.6% male in the ASA group. 100% African American

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gorelick, 2003 U.S. Fair/Good	Patients in the ticlopidine group had ≤ 73.8% in Ticlopidine and 74.5% in the ASA group had high school or less education; 44% were making less than 14999 household income vs. 44.4% in ASA group. 85% had HTN vs. 86.3% in ASA group, 40% DM vs. 42.1% in ASA, 62% past/current smoking vs. 61.9% in ASA.; 40.6% in Ticlopidine group vs. 43.6% in ASA group had hypercholesterolemia.	1809	15.2% in ticlopidine treatment group and 13.3% ASA group

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Gorelick, 2003 U.S. Fair/Good	Ticlopidine vs Aspirin: *Outcomes at 2 years* Fatal recurrent stroke: 0.4% (4/902) vs 0.2% (2/907) RR = 2.01 (0.37, 10.95) Nonfatal recurrent stroke: 11.3% (102/902) vs 9.3% (84/907) RR = 1.22 (0.93, 1.61) Fatal MI: 0.1% (1/902) vs 0% (0/907) RR = NC Nonfatal MI: 0.9% (8/902) vs 0.9% (8/907) RR = 1.01 (0.38, 2.67) Major vascular death: 0.8% (7/902) vs 0.4% (4/907) RR = 1.76 (0.52, 5.99) Other vascular death: 1.2% (11/902) vs 1.5% (14/907) RR = 0.79 (0.36, 1.73) Any recurrent stroke: 11.9% (107/902) vs 9.5% (86/907) RR = 1.25 (0.96, 1.64) All cause death: 5.0% (45/902) vs 4.4% (40/907) RR = 1.13 (0.75, 1.71) Vascular death: 2.5% (23/902) vs 2.1% (19/907) RR = 1.22 (0.67, 2.22) Recurrent stroke or All cause death: 15.3% (138/902) vs 12.9% (117/907) RR = 1.19 (0.94, 1.49) Recurrent stroke, MI or All cause death: 16.1% (145/902) vs 13.8% (125/907) RR = 1.16 (0.94, 1.45)	Ticlopidine vs Aspirin: Cardiovascular system: 7.3% (66/902) vs 8.4% (76/907) Diarrhea: 0.3% (3/902) vs 0.2% (2/907) Digestive system: 4.2% (38/902) vs 4.7% (43/907) Endocrine system: 1.2% (11/902) vs 1.1% (10/907) Hemic & lymphatic system: 4.2% (38/902) vs 3.2% (29/907) Major GI tract hemorrhage: 0.4% (4/902) vs 2.2% (20/907) Musculoskeletal system: 1.9% (17/902) vs 1.2% (11/907) Nervous system: 7.3% (66/902) vs 6.6% (60/907) Neutropenia: 3.4% (31/902) vs 0.9% (8/907) Other bleeding : 0.7% (6/902) vs 1.2% (11/907) Psychiatric system: 1.1% (10/902) vs 0.6% (5/907) Respiratory system: 4.2% (38/902) vs 4.1% (37/907) Skin & appendages: 1.7% (15/902) vs 1.7% (15/907) Special senses: 0.3% (3/902) vs 0.7% (6/907) Thrombocytopenia: 0.3% (3/902) vs 0.2% (2/907) Urogenital system: 2.7% (24/902) vs 1.9% (17/907)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gorelick, 2003 U.S. Fair/Good		None	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Hall, 1996 Japan, Italy Poor	CAD manifested by clinical symptoms or objective evidence of MI either on exercise test or by nuclear scintigraphy and angiographic evidence of single-vessel or multivessel coronary disease with target lesion stenosis >70% by visual estimate. The study required completion of a successful intravascular US guided stent implantation procedure--included qualitative evaluation of the stent site involving the achievement of good stent apposition to the vessel wall with good plaque compression. The quantitative criterion for stent expansion used was the achievement of an intra-stent lumen CSA (at the tightest measured point) that was 80% of the distal reference lumen CSA. In smaller vessels in which the lesions had a measured CSA of <7.5mm, the quantitative criterion was modified so that it was the achievement of stent lumen greater than the distal lumen CSA. 6 different types of stents used: Palmaz-Schatz (Johnson and Johnson Interventional Systems CO), Gianturco-Roubin (Cook Cardiology, Cook, Inc), Gianturco-Roubin (Cook Cardiology Cook), Wiktor (Medtronic, Inc), Micro (Applied Vascular Engineering) Wall (Schneider Inc), and the Cordis (Cordis Corp) stents.	T 250mg twice a day x 1 month with short-term ASA 325mg x 5 days OR ASA 325mg/day. T not administered before or during the stent procedure but only after successful procedure (intravascular US criteria for optimal stent expansion were met and the angiographic result was acceptable)	Intracoronary NTG before baseline and final angiograms. Pts received ASA 325mg and calcium channel antagonists before stent deployment. A bolus of 10000 U heparin was given after sheath insertion with an additional bolus of 5000U given as needed to maintain the activated clotted time to >250 seconds.	ASA group 58 years old ±10; 89% male and 11% female. T + ASA group 57 years old ± 9; 88% male and 12% female. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Hall, 1996 Japan, Italy Poor	Previous MI in the ASA vs. T + ASA group - 48% and 50% respectively. 10% in both groups had had an angioplasty before. % of CABG in each group-already reported. In the ASA group 39% currently smoking vs. 29% in the T + ASA group-p= NS. 40% in both groups had HTN p = .01. 6% DM in ASA group vs. 16% in the T + ASA group ; p=0.9. Unstable angina- 28% in ASA group vs. 33% in T + ASA group p=0.5	226	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Hall, 1996 Japan, Italy Poor	Ticlopidine + Aspirin vs Aspirin *Outcomes at 1 month* Stent thrombosis: 0.8% (1/123) vs 2.9% (3/103) RR = 0.28 (0.29, 2.64) MI: 0.8% (1/123) vs 3.9% (4/103) RR = 0.21 (0.02, 1.84) Emergency bypass: 0% (0/123) vs 0% (0/103) RR = NC Elective bypass: 0% (0/123) vs 0% (0/103) RR = NC Death: 0% (0/123) vs 2.9% (3/103) RR = NC Repeat PTCA: 0.8% (1/123) vs 1.9% (2/103) RR = 0.42 (0.04, 4.55) Any major event: 0.8% (1/123) vs 3.9% (4/103) RR = 0.21 (0.02, 1.90)	Ticlopidine + Aspirin vs Aspirin Vascular complication: 0% (0/123) vs 1% (1/103) Leukopenia: 0.8% (1/123) vs 0.0% (0/103) Skin rash: 1.6% (2/123) vs 0.0% (0/103)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hall, 1996 Japan, Italy Poor		NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Hass, 1989 North America TASS Good	3 months before entry into the study they had ad 1 or more of the following: TIA lasting less than 24 hours and followed by completely recovery); amaurosis fugax; reversible ischemic neurologic deficit; or minor stroke between 2/82-5/86.	Ticlopidine 250mg twice a day or ASA 1300mg daily x2-6 years	NR	Ticlopidine group: mean age 62.7 ± 9.4; male%/female% 64/36, 80% white. In aspirin group: mean age 63.2± 9.3; male% female% 65/35, 81% white.
Juergens, 2004 Australia Poor	Intracoronary stents were successfully deployed (<30% residual stenosis without acute complications in the catheterization laboratory resulting in death or emergency bypass surgery) from July 1999 until January 2001.	Ticlopidine 500mg (LD) immediately after procedure and then 250mg twice a day+ ASA or clopidogrel 150mg (LD) immediately after procedure and then 75mg every day+ ASA x 14 days. All pts received >=300mg ASA in the 24 hrs before the procedure and a minimum of 100mg/day for duration of the study	Heparin was administered as boluses to maintain an activated clotting time > 250 seconds, and GP 2B/3A could be used at the operator's discretion and in fact was used in 23% of the pts receiving ticlopidine and 25% of pts in the clopidogrel group. Heparin could be restarted after sheath removal at the operator's discretion.	Ticlopidine group: mean age 60 ± 10; male%/female% 80/20. In clopidogrel group: mean age 60± 12; male% female% 71/29. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Hass, 1989 North America TASS Good	T vs. ASA group: 41% vs. 42% smokers; 18% stable angina in both groups; 1% unstable angina in both groups; 16% and 17% MI, 19% and 20% DM, 14% and 15% PVD. 40 and 41% hypercholesterolemia	3069	46 (3%) ticlopidine group and 38 (2%) ASA group lost to follow-up. 51.6% patients in the ticlopidine and 47% in the ASA groups prematurely terminated study medication primarily AE (20.9% T group and 14.5% ASA group ($p<0.05$) and noncompliance 13.6 vs. 13.3
Juergens, 2004 Australia Poor	T group: 58% HTN, 23% DM, 17% current smoker, 72% hypercholesterolemia, 12% Previous CABG, 10% recent MI, 47% unstable angina. Clopidogrel group: 56% HTN, 19% DM, 21% current smoker, 79% hypercholesterolemia, 7% previous CABG, 14% recent MI and 44% Unstable angina	307	0

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Hass, 1989 North America TASS Good	Ticlopidine vs Aspirin *Outcomes at 60 months* Death from all causes or nonfatal stroke: 20.0% (306/1529) vs 22.7% (349/1540) RR = 0.88 (0.77, 1.01) Nonfatal stroke: 10.2% (156/1529) vs 12.3% (189/1540) RR = 0.83 (0.68, 1.02) Fatal stroke: 1.0% (16/1529) vs 1.5% (23/1540) RR = 0.70 (0.37, 1.32) Death from other causes: 8.8% (134/1529) vs 8.9% (137/1540) RR = 0.99 (0.78, 1.24) Fatal or nonfatal stroke: 11.2% (172/1529) vs 13.8% (212/1540) RR = 0.84 (0.69, 1.01); NNT = 40 (21, 561) Death from all causes: 11.4% (175/1529) vs 12.7% (196/1540) RR = 0.90 (0.74, 1.08) Cerebrovascular: 1.4% (22/1529) vs 1.8% (28/1540) RR = 0.79 (0.45, 1.38) Cardiovascular: 5.8% (89/1529) vs 5.1% (78/1540) RR = 1.15 (0.86, 1.54) Acute MI: 1.4% (21/1529) vs 0.9% (14/1540) RR = 1.51 (0.77, 2.96) Sudden death: 2.9% (44/1529) vs 2.7% (41/1540) RR = 1.08 (0.71, 1.64) Other cardiovascular: 1.6% (24/1529) vs 1.5% (23/1540) RR = 1.05 (0.60, 1.85)	Ticlopidine vs Aspirin Diarrhea: 20.4% (310/1518) vs 9.8% (150/1527) Dyspepsia: 12.6% (191/1518) vs 13.8% (210/1527) Nausea: 11.1% (169/1518) vs 10.2% (156/1527) GI pain: 7.2% (110/1518) vs 10.0% (153/1527) Gastritis: 0.9% (13/1518) vs 1.7% (26/1527) GI hemorrhage: 0.5% (7/1518) vs 1.4% (21/1527) Peptic ulcer: 0.8% (12/1518) vs 2.9% (45/1527) Rash: 11.9% (180/1518) vs 5.2% (80/1527) Urticaria: 2.0% (30/1518) vs 0.3% (5/1527) All hemorrhagic: 9.0% (137/1518) vs 10.0% (152/1527) Severe neutropenia: 0.9% (13/1518) vs 0.0% (0/1527)
Juergens, 2004 Australia Poor	Ticlopidine + Aspirin vs Clopidogrel + Aspirin *Outcomes at 30 days* Cardiovascular death: 0.7% (1/153) vs 0% (0/154) RR = NC Non-fatal MI: 1.3% (2/153) vs 1.3% (2/154) RR = 1.0 (0.14, 7.00) Urgent target vessel revascularization: 0.7% (1/153) vs 1.9% (3/154) RR = 0.34 (0.04, 3.19) MACE: 2.0% (3/153) vs 1.9% (3/154) RR = 1.0 (0.21, 4.91) Thrombotic stent occlusion: 0.7% (1/153) vs 1.9% (3/154) RR = 0.34 (0.04, 3.19)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Any non-cardiac event: 3.9% (6/153) vs 1.9% (3/154) Bleeding: 0.7% (1/153) vs 0.6% (1/154) Dermatological:1.3% (2/153) vs 0% (0/154) GI: 1.3% (2/153) vs 0.0% (0/154) Hemorrhagic complications: 0.0% (0/153) vs 0.6% (1/154) Vascular complication: 1.3% (2/153) vs 1.3% (2/154)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hass, 1989 North America TASS Good		Supported by Syntex Research	
Juergens, 2004 Australia Poor		NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Kayacioglu, 2008 Turkey Poor	Patients who underwent CABG operation. NOTE: The study included a control group who had not developed reactive thrombocytosis after CABG surgery, but our review only focused on the patients who did develop reactive thrombocytosis.	A: ASA 300 mg/d B: ASA 300 mg/d + Clopidogrel 75 mg/d	NR	Age: 57 years (SD 9.4) Male: 90% Ethnicity NR
Kelly, 2006 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Kayacioglu, 2008 Turkey Poor	Hypertension: 55% DM: 23.3% Hyperlipidemia: 45% Cigarette smokers: 76.7% EF: 0.53	60	NR/NR/60
Kelly, 2006 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Kayacioglu, 2008 Turkey Poor	ASA 300 mg/d vs ASA 300 mg/d + Clopidogrel 75 mg/d 6-month graft occlusion: 4 (20%) vs 0; P<0.01; 3 had occlusion of the venous graft, and 1 had occlusion of the left internal mammary artery	NR
Kelly, 2006 Companion to Steinhuble, 2002 CREDO	Clopidogrel vs Placebo Effect of clopidogrel on 1 year death, MI, stroke according to BMI category: Low-normal (<25): 14% vs 10% Overweight (25-29.9): 9% vs 11% Obese (30-39.9): 6% vs 13% Severely obese (≥40): 5% vs 11% Risk of the 1-year combined endpoint of death, MI or stroke associated with randomization to clopidogrel was reduced by 25% (OR 0.748; 95% CI, 0.901 to 0.930; P=0.009) for every 5-unit increase in BMI. There was no significant relationship between BMI and the incidence of the 1-year composite endpoint in patients who received placebo therapy.	Clopidogrel vs Placebo Any bleeding: Low-normal (<25): 67 (41%) vs 58 (33%) Overweight (25-29.9): 145 (34%) vs 117 (28%) Obese (30-39.9): 138 (35%) vs 115 (28%) Severely obese (≥40): 15 (25%) vs 12 (23%) P=0.07 for clopidogrel (based on BMI); P=0.17 for placebo

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kayacioglu, 2008 Turkey Poor	NR	NR	ASA therapy was started in all groups on the first postoperative day. The platelet count was measured 1 hour after the operation and on the first, third, and seventh postoperative days. Investigators randomized the patients on the seventh postoperative day if platelet counts had not exceeded 450 × 10^3/mm^3 during the previous days.
Kelly, 2006 Companion to Steinhuble, 2002 CREDO	See Steinhuble, 2002	See Steinhuble, 2002	See Steinhuble, 2002

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Keltai, 2007 Companion to CURE Trial Investigators, 2001 CURE	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Keltai, 2007 Companion to CURE Trial Investigators, 2001 CURE	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Keltai, 2007 Companion to CURE Trial Investigators, 2001 CURE	Placebo vs Clopidogrel CV Death, non-fatal MI, or stroke: Lower eGFR tertile (<64 ml/min): 14.9% vs 13.4%; RR clopidogrel/placebo: 0.89 (95% CI, 0.76 to 1.05) Medium eGFR tertile (64-81.2 ml/min): 10.8% vs 7.5%; RR clopidogrel/placebo: 0.68 (95% CI, 0.56 to 0.84); P<0.05 Upper eGFR tertile (>81.3 ml/min): 8.8% vs 6.6%; RR clopidogrel/placebo: 0.74 (95% CI, 0.60 to 0.93); P<0.05 Death: Lower eGFR tertile (<64 ml/min): 10.0% vs 9.6%; RR clopidogrel/placebo: 0.95 (95% CI, 0.78 to 1.16) Medium eGFR tertile (64-81.2 ml/min): 4.7% vs 4.3%; RR clopidogrel/placebo: 0.91 (95% CI, 0.68 to 1.21) Upper eGFR tertile (>81.3 ml/min): 3.6% vs 3.4%; RR clopidogrel/placebo: 0.94 (95% CI, 0.67 to 1.30) CV death: Lower eGFR tertile (<64 ml/min): 8.7% vs 8.3%; RR clopidogrel/placebo: 0.95 (95% CI, 0.77 to 1.17) Medium eGFR tertile (64-81.2 ml/min): 4.3% vs 3.7%; RR clopidogrel/placebo: 0.85 (95% CI, 0.63 to 1.16) Upper eGFR tertile (>81.3 ml/min): 3.1% vs 2.9%; RR clopidogrel/placebo: 0.93 (95% CI, 0.65 to 1.32)	Placebo vs Clopidogrel Bleeding - life threatening: Lower eGFR tertile (<64 ml/min): 2.5% vs 2.3%; RR clopidogrel/placebo: 0.89 (95% CI, 0.60 to 1.31) Medium eGFR tertile (64-81.2 ml/min): 1.6% vs 2.0%; RR clopidogrel/placebo: 1.23 (95% CI, 0.78 to 1.93) Upper eGFR tertile (>81.3 ml/min): 1.2% vs 2.0%; RR clopidogrel/placebo: 1.65 (95% CI, 1.01 to 2.70); P<0.05 Bleeding - major: Lower eGFR tertile (<64 ml/min): 1.7% vs 2.3%; RR clopidogrel/placebo: 1.37 (95% CI, 0.89 to 2.12) Medium eGFR tertile (64-81.2 ml/min): 0.7% vs 1.3%; RR clopidogrel/placebo: 1.78 (95% CI, 0.95 to 3.34) Upper eGFR tertile (>81.3 ml/min): 0.6% vs 1.2%; RR clopidogrel/placebo: 2.05 (95% CI, 1.03 to 4.07); P<0.05 Bleeding - minor: Lower eGFR tertile (<64 ml/min): 2.4% vs 5.2%; RR clopidogrel/placebo: 1.50 (95% CI, 1.21 to 1.86); P<0.05 Medium eGFR tertile (64-81.2 ml/min): 2.5% vs 4.8%; RR clopidogrel/placebo: 1.61 (95% CI, 1.27 to 2.06); P<0.05 Upper eGFR tertile (>81.3 ml/min): 2.3% vs 5.2%; RR clopidogrel/placebo: 2.26 (95% CI, 1.56 to 2.61); P<0.05

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Keltai, 2007 Companion to CURE Trial Investigators, 2001 CURE	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)	See CURE Trial Investigators 2001 (CURE)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Kennedy, 2007 Canada, U.S. FASTER Fair	Patients aged ≥40 years with a minor stroke as defined by a National Institutes of Health Stroke Scale score of ≤3 at the time of randomization, or TIA within 24 hours of onset. In addition, weakness or speech disturbance, dysarthria or dysphasia, had to be part of the symptom complex for greater than 5 min for patients to be eligible.	A: Clopidogrel 300 mg LD then 75 mg QD; and Simvastatin 40 mg QD B: Clopidogrel 300 mg LD then 75 mg QD only C: Simvastatin 40 mg QD only D: Double placebo For 90 days Factorial design	All patients were given 81 mg aspirin daily for the study duration, with a LD of 162 mg if they were naïve to aspirin before study enrollment.	Age: 68.1 years Female: 47.2% White: 91.8%

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Kennedy, 2007 Canada, U.S. FASTER Fair	Mechanism of event: Cardioembolic: 6.8% Lacunar: 29.6% Large artery: 24.5% Other: 1.3% Unknown: 37.7% Medical history: Hypertension: 50.5% DM: 10.7% Hypercholesterolemia: 7.1% PVD: 2% Known carotid disease at baseline: 2% Smoking within the past year: 26% Previous stroke: 7.4% Previous TIA: 16.1% Previous MI: 4.8% Previous CAD: 6.1% Known atrial fibrillation/flutter: 1.3% Other cardiac arrhythmias: 4.6% CHF: 0.7% Valvular heart disease: 0.8% Surgical history: CABG/PTCA: 1.8% Peripheral vascular surgery: 1.3% Radiotherapy to neck: 0.8% Carotid endarterectomy: 0.3%	396	160/7/392

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Kennedy, 2007 Canada, U.S. FASTER Fair	Clopidogrel vs Placebo 90 day risk of stroke: 5 (5.1%) vs 9 (9.5%); Risk difference -3.8% (95% CI, -9.4 to 1.9); RR 0.7 (95% CI, 0.3 to 1.2); P=0.19 90 day risk of stroke, MI, and vascular death: 6 (6.1%) vs 11 (11.6%); Risk difference -3.3% (95% CI, -9.3 to 2.7); RR 0.7 (95% CI, 0.4 to 1.3); P=0.28 90 day risk of stroke, TIA, ACS, and all-cause death: 12 (12.2%) vs 21 (22.1%); Risk difference -7.0% (95% CI, -14.6 to 0.6); RR 0.7 (95% CI, 0.4 to 1.2); P=0.07	No Clopidogrel vs Clopidogrel Intracranial hemorrhage: 0 (0%) vs 2 (1%); P=0.5; 95% CI (-0.4 to 2.4) Severe extracranial hemorrhage: 0 (0%) vs 1 (0.5%); P=1.0; 95% CI, -0.5 to 1.5 Moderate extracranial hemorrhage: 0 (0%) vs 2 (1%); P=0.5; 95% CI, -0.4 to 2.4 Mild extracranial hemorrhage: 0 (0%) vs 1 (0.5%); P=1.0; 95% CI, -0.5 to 1.5 Total symptomatic: 0 (0%) vs 6 (3%); P=0.03; 95% CI, 0.6 to 5.4 Total asymptomatic: 27 (13.9%) vs 61 (30.8%); P=0.0001; 95% CI, 8.8 to 25.0

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kennedy, 2007 Canada, U.S. FASTER Fair	Clopidogrel vs Placebo Total withdrawals: 40 (2.2%) vs 45 (23.2%); P=0.47 Due to AE: 17 (8.6%) vs 20 (10.3%); P=0.56	Canadian Institutes of Health Research, the Canadian Stroke Network, the Canadian Stroke Consortium, and the Ministry of Health and Long-Term Care of Ontario	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Leon, 1998 U.S. Fair	1 or two target lesions with more than 60% stenosis in a 3-to-4 mm native coronary artery, not involving the left main coronary artery or a major coronary bifurcation. The implantation of the stent was considered successful if the final degree of stenosis within the stent was less than 10% (by visual estimate), there was no evidence of thrombus or of dissections (more than grade B according to the NHLB Institute criteria, there was grade 3 flow according to TIMI criteria, and no more than 2 stents were needed to treat one long (≤ 25 mm) lesion or two focal (≤ 12 mm) lesions in 1 or two native coronary arteries. If successful, then pt was eligible to be randomized.	All pts received non-generic, non-enteric coated ASA 325mg and IV heparin (10,000-15,000 U) to maintain an activated clotting time of 250-300 s during stents prior to randomization. 3 antithrombotic drug regimens used: ASA 325mg/day (non-enteric) x 4 wks; 325 mg of non-enteric ASA+ IV heparin to achieve APTT of 40-60 s and DC once an INR of 2-2.5 s was reached with oral warfarin x 4 wks; and 325mg non-enteric/day and 250mg T bid x 4 wks. First dose of T or warfarin was administered at the conclusion of the stenting procedure.	NR	ASA alone: 61±11 years old; 28% female and 72% male; ASA and warfarin: 62 years old ±11; 30% female and 70% male; ASA and T 61±12 years old, 29% female and 71% male. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Leon, 1998 U.S. Fair	DM (18, 20, 18%); Smoking (27,29, 29%), single-vessel disease (67,67,68%); Previous MI (32,39,36%) in the ASA, ASA + warfarin and ASA and T groups respectively. Not all data were available for all the pts for previous restenosis, lesion grade B2 or C, ostial location of lesion, bifurcation or target vessel LAD	1653	0

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Leon, 1998 U.S. Fair	Ticlopidine + Aspirin vs Aspirin *Outcomes at 30 days* Death: 0% (0/546) vs 0.2% (1/557) RR = NC Revascularization of target lesion: 0.5% (3/546) vs 3.4% (19/557) RR = 0.05 (0.01, 0.39); NNT = 30 (21, 60) Angiographically evident thrombosis: 0.5% (3/546) vs 2.9% (16/557) RR = 0.19 (0.06, 0.65); NNT = 43 (26, 124) Recurrent MI: 0.5% (3/546) vs 2.7% (15/557) RR = 0.20 (0.59, 0.70); NNT = 47 (28, 151)	Ticlopidine + Aspirin vs Aspirin Cerebrovascular: 0.0% (0/546) vs 0.4% (2/557) Hemorrhagic complications: 5.5% (30/546) vs 1.8% (10/557) Neutropenia or thrombocytopenia: 0.5% (3/546) vs0.2% (1/557) Vascular surgical complications: 2.0% (11/546) vs 4.0% (2/557)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Leon, 1998 U.S. Fair		Supported by a grant from Cordis, a Johnson and Johnson Company	No significant difference in the risk of neutropenia or thrombocytopenia btw the groups

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Mehta, 2001 International PCI-CURE Good	See CURE trial--symptoms indicative of ACS within the past 24 hours and no ST-segment elevation >1 mm on ECG. Other ECG evidence of new ischemia or concentrations of cardiac enzymes (including troponin) at least 2x the upper limit of normal was required. Of note, initially patients above the age of 60 with no new ECG changes but with objective evidence of ischemia were included in the trial. However, after a review of the overall event rates among the first 3000 pts, the steering committee recommended that all pts have either ECG changes or a cardiac enzyme rise at entry.	Clopidogrel 300mg x 1 LD and then 75mg daily + ASA 75mg-325mg daily vs. matching placebo + ASA 75mg-325mg daily x 3-12 months (mean of 8 months)	GP 2b/3a during PCI . (About 25% of pts in each group received open-label thienopyridines before PCI and more than 80% received them afterwards for a median of 30 days.	PCI population: Mean age 61.6 ± 11.2 in the clopidogrel group and 61.4 ± 10.9 in the placebo group. 30% in both groups were women; 70% males. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Mehta, 2001 International PCI-CURE Good	19% were diabetics; 26% vs. 27.3% in the placebo and clopidogrel groups respectively had a previous MI; 13.8% in the placebo and 13.4% in the clopidogrel group had a previous PCI. 13% and 12% in the placebo and clopidogrel group had a previous CABG, respectively; ~30 were smokers in both groups	2658	0 drop-outs/0 lost to f/u/analyzed

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Mehta, 2001 International PCI-CURE Good	Clopidogrel vs Placebo *Outcomes at 30 days* CV death, MI, urgent revascularization: 4.5% (59/1313) vs 6.4% (86/1345) RR = 0.70 (0.50, 0.97); NNT = 53 (28, 560) CV death, MI: 2.9% (38/1313) vs 4.4% (59/1345) RR = 0.66 (0.44, 0.99); NNT = 67 (34, 1405) CV death: 1.1% (14/1313) vs 1.0% (13/1345) RR = 1.10 (0.52, 2.34) MI: 2.1%(28/1313) vs 3.8% (51/1345) RR = 0.56 (0.35, 0.89); NNT = 60 (34, 268) Q-wave MI: 0.8% (11/1313) vs 2.4% (32/1345) RR = 0.35 (0.18, 0.70); NNT = 65 (40, 170) Urgent revascularization: 1.9% (25/1313) vs 2.8% (38/1345) RR = 0.67 (0.41, 1.11) *Outcomes at 12 months* CV death, MI: 6.0% (79/1313) vs 8.0% (108/1345) RR = 0.75 (0.56, 1.00) CV death, MI, any revascularization: 18.3% (240/1313) vs 21.7% (292/1345) RR = 0.83 (0.70, 0.99); NNT = 29 (15, 254) CV death: 2.4% (32/1313) vs 2.3% (31/1345) RR = 1.07 (0.65, 1.75) MI: 4.5% (59/1313) vs 6.4% (85/1345) RR = 0.71 (0.51, 0.99); NNT = 55 (28, 912) Q-wave MI:1.5% (20/1313) vs 3.5% (47/1345) RR = 0.43 (0.26, 0.73); NNT = 51 (32, 127) Any revascularization: 14.2% (186/1313) vs 17.1% (230/1345) RR = 0.82 (0.68, 1.00)	Clopidogrel vs Placebo Major bleeding: 2.7% (36/1313) vs 2.5% (33/1345) Life-threatening bleeding: 1.2% (16/1313) vs 1.3% (18/1345) Non-life-threatening bleeding: 1.5% (20/1313) vs 1.1% (15/1345) Minor bleeding: 3.5% (46/1313) vs 2.1% (28/1345) Blood transfusions of 2 or more units: 2.1% (28/1313) vs 2.0% (27/1345)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Mehta, 2001 International PCI-CURE Good		Supported by a research grant from Sanofi-Synthelabo and Bristol-Myers-Squibb	334/1313 took open-label thienopyridine before PCI and 969/1313 received study drug up to PCI per protocol analysis in the clopidogrel group. 329/1345 took open-label thienopyridine before PCI (mean of 10 days) while 1016/1345 received study drug up to PCI per protocol analysis in the placebo group. Benefit seen at 30 days after PCI may be an underestimate of the true treatment effect, since ~25% of pts in both groups also received open-label thienopyridine before the procedure--although analysis was also done excluding those pts that had open-label thienopyridine--42% reduction in the primary outcome was seen. Investigators did not routinely screen for symptomless increases in periprocedural cardiac enzyme concentrations, and so some smaller, non-Q wave Mi might not have been documented. However, the study was randomized and DB so authors stated that this approach should still lead to an unbiased estimate of the effect of clopidogrel. There was a reduction in the use of IV GP 2b/3a antagonist during PCI in the clopidogrel group. Baseline characteristics of the study population are consistent with at least a moderate risk group of patients with ACS per authors.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Mueller, 2003 Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3 Fair/Poor	Consecutive patients with successful stent implantation	T 250mg bid vs. C 75mg/day x 4 wks. The first dose of T (500mg) or C (75mg) was given immediately after stent implantation. All pts. received 100mg ASA daily	ASA 100mg every day for life. 86% on statins, GP 2B/3A antagonist C 11%, T 7%, p 0.07	C (65 ± 11); T (64±10) ; C 27% female and 73% male, T 26% female and 74% male Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Mueller, 2003 Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3 Fair/Poor	smokers: C 28%, T: 32%, p=0.32; Previous CABG: C 15%, T: 12%, p=0.25; Previous AMI: C 48%, T: 44%, p=0.29; Unstable angina: C 40%. T: 38%; p=0.59	700	None

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Mueller, 2003 Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3 Fair/Poor	Ticlopidine + Aspirin vs Clopidogrel + Aspirin *Outcomes at 28 and 27 months* Cardiovascular mortality: 2.3% (8/345) vs 7.3% (26/355) RR = 0.32 (0.15, 0.69); NNT = 20 (12, 54) Cardiovascular death or non-fatal MI: 5.5% (19/345) vs 11.3% (40/355) RR = 0.73 (0.46, 1.14) Nonfatal MI: 3.5% (12/345) vs 4.8% (17/355) RR = 0.73 (0.35, 1.50) Death from all causes: 2.6% (9/345) vs 8.2% (29/355) RR = 0.32 (0.15, 0.66); NNT = 18 (11, 44)	NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Mueller, 2003 Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3 Fair/Poor	This was not a safety study	NR	This is a f/u study of Circulation 2000;11:590-3.Because 2 studies (CAPRIE-Lancet 1996;348:1329-39 and Mueller et al. Circulation 2000; 101: 90-3 restricted the usage of GP 2B/3A inhibition and reported a higher incidence of TSO (thrombotic stent occlusion) with C at 30 days (1.4% vs. 0.6%, p= 0.13), NS, it raised some concern about long-term survival. Authors extended the f/u study of the previous study to a median of 28 months. Frequent use of statins in this study was suggested that that may have induced or exaggerated differences in antiplatelet efficacy between T or C (previous reports that C activation requires the CYP-450 3A4 system and that antiplatelet activity of C is inhibited by atorvastatin and simvastatin, which are also metabolized by the CYP-450 3A4 system.) This inhibitory effect has not been reported for T.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Muller, 2000 Germany Fair	Sept 98-April 99 underwent successful (<50% residual stenosis without acute complications in the catheter lab resulting in death or emergency bypass grafting) stent implantation	250mg twice a day T + 100mg ASA X 4 wks vs. 75mg C + 100mg ASA x 4 wks	GP 2B/3A-11 % in C vs. 7% in T; p=0.07	C group 65±11 years old, 26% female, 74% male; T group 64± 10 years, 26% female, 74% male. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Muller, 2000 Germany Fair	Approx. 50% of the stent procedures were performed in ACS. C group: 23% DM, 15% previous CABG, 48% previous MI, 40% unstable angina. In T group: 21 % DM, 12 % previous CABG; 44% previous MI; 38% unstable angina--none SS	700	NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Muller, 2000 Germany Fair	Ticlopidine + Aspirin vs Clopidogrel + Aspirin *Outcomes at 30 days* Cardiac events: 1.7% (6/345) vs 3.1% (11/355) RR = 0.56 (0.21, 1.50) Cardiac death: 0.3% (1/345) vs 0.3% (1/355) RR = 1.03 (0.06, 16.39) Thrombotic stent occlusion: 0.6% (2/345) vs 2% (7/355) RR = 0.29 (0.06, 1.41) Urgent target vessel revascularization: 0.6% (2/345) vs 1.7% (6/355) RR = 0.34 (0.07, 1.69) Nonfatal MI: 1.2% (4/345) vs 2% (7/355) RR = 0.59 (0.17, 2.00) Noncardiac events: 9.6% (33/345) vs 4.5% (16/355) RR = 2.12 (1.19, 3.78) Noncardiac death: 0.3% (1/345) vs 0% (0/355) RR = NC Hemorrhagic complication: 0.9% (3/345) vs 0.6% (2/355) RR = 1.54 (0.26, 9.18) Vascular complication: 1.7% (6/345) vs 2% (7/355) RR = 0.88 (0.30, 2.60) Stroke: 0% (0/345) vs 0% (0/355) RR = NC	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Hemorrhagic complications: 0.9% (3/345) vs 0.6% (2/355) Neutropenia or thrombocytopenia: 0.9% (3/345) vs 0% (0/355) Vascular surgical complications: 1.7% (6/345) vs 2% (7/355)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Muller, 2000 Germany Fair		NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Patti, 2005 Italy ARMYDA-2 Good	1. Patients with typical effort angina, positive stress test (ECG, nuclear scan, or stress echo), and indication for coronary angiography; or 2. patients with a non-ST segment-elevation ACS who were scheduled to undergo coronary angiography	Clopidogrel 600mg X1 (LD) + ASA 100mg/d vs. Clopidogrel 300mg x1 (LD administered 4-8 prior to procedure) + ASA 100mg/d. Post-PCI: C 75mg daily for up to 1 month (6 months in pts receiving drug-eluting stents and 9 months for ACS) + ASA 100mg daily	Before intervention, patients received weight-adjusted IV heparin (target activated clotting times of >300 seconds in the absence of GP IIB/IIIa receptor antagonist was used). Use of GP IIB/IIIa receptor antagonist was allowed at the operator's discretion. All patients without contraindications were pretreated before intervention with ASA 100mg/d; they received ASA 100mg indefinitely.	High LD: age 63± 10; 78% males, 22% females; Ethnicity: Not stated. Conventional LD: age 65 ±10; 76% males,24% females; Ethnicity: Not stated.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Patti, 2005 Italy ARMYDA-2 Good	High LD: 31% DM, 64% systemic hypertension, 70% hypercholesterolemia, 16% smokers, 33% previous MI, 13% previous coronary intervention, 5% previous bypass surgery, 25% Non-ST-elevation ACS, 75% stable angina, 30% multivessel CAD. Conventional LD: 32% DM, 64% Systemic hypertension, 62% hypercholesterolemia, 16% current smokers, 37% previous MI, 16% previous coronary intervention, 5% previous bypass surgery, 25% Non-ST elevation ACS, 75% stable angina, 23% multivessel CAD	255	After coronary angiography, 74 patients (37 in each randomization arm) who did not receive angioplasty were excluded from the study (44 were treated medically and 30 with elective bypass surgery).

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Patti, 2005 Italy ARMYDA-2 Good	Clopidogrel 600-mg vs Clopidogrel 300-mg *Outcomes at 30 days* Death: 0% (0/126) vs 0% (0/129) RR = NC Target vessel revascularization: 0.8% (1/126) vs 0% (0/129) RR = NC MI: 4.0% (5/126) vs 11.6% (15/129) RR = 0.34 (0.13, 0.91), NNT = 13 (7, 86)	Clopidogrel 600-mg vs Clopidogrel 300-mg Major bleeding: 0% (0/126) vs 0% (0/129) Minor bleeding: 0.8% (1/126) vs 0.8% (1/129) Groin hematoma: 7.1% (9/126) vs 4.7% (6/129) Local vascular complications requiring surgery: 0% (0/126) vs 0% (0/129) Thrombocytopenia: 0% (0/126) vs 0% (0/129)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Patti, 2005 Italy ARMYDA-2 Good	0	No external funding	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pekdemir, 2003 Turkey Fair	Patients undergoing elective percutaneous coronary revascularization and had a successful stent-placement procedure.	A: Clopidogrel 75 mg for 1 month B: Clopidogrel 75 mg for 6 months All patients were preloaded with 300 mg of clopidogrel orally 24 hours prior to the procedure.	300 mg aspirin and 10,000 IU heparin were administered intraoperatively, then replaced by low molecular weight heparin on day 2. Tirofiban was administered routinely for patients with ACSs and with visible intracoronary thrombi during the procedure (n=58). Where appropriate, adjustments were made to the regimen if patients were receiving other medications, such as beta-blockers, calcium antagonists, nitrates, and statins. All patients received aspirin 100 mg throughout the study.	Age: 56.5 years (SD 10.5) Female: 42.8% Ethnicity NR
Piamsomboon, 2001 Thailand Poor	June 1999-December 2000-symptomatic CAD or documented myocardial ischemia by treadmill exercise test or myocardial perfusion scan and coronary angiographic evidence of ≥ 70 % stenosis in diameter. Pts underwent coronary stenting	Clopidogrel 300mg LD 4 hrs prior to procedure, followed by 75mg once daily x 4 wks + ASA 300mg twice a day x 4 wks vs. ticlopidine 250 mg twice a day starting 2 d prior to stent and continued x 4 wks + ASA 300mg twice a day x 4 wks. At 4 wks follow-up, ASA was decreased to 300mg once daily if there was no contraindication.	100 U/kg bolus dose of heparin was given initially, a repeated dose was given as needed to keep the activated clotting time ≥ 250 seconds.	60 ± 9 years ; 84% male and 16% female in ticlopidine + ASA group; 61 ± 10 years; 73% male and 27% female in clopidogrel + ASA group. Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Pekdemir, 2003 Turkey Fair	Arterial hypertension: 51.1% DM: 14.7% Hypercholesterolemia: 41.7% Smoking: 60.8% Heredity: 22.7% Previous MI: 30.2% Previous coronary artery bypass graft: 9.4% Left ventricular function, EF: 57.4% (SD 16.7) After thrombolysis: 10.4% Admission to clinic: Unstable angina: 30.2% Stable angina: 39.6% Silent ischemia: 5.8% MI: 12.9% Heart failure: 11.5%	278	17/0/278
Piamsomboon, 2001 Thailand Poor	Ticlopidine + ASA group: 29% (n=9) acute MI, 32% (n= 10) unstable angina, 48% (n= 15) HTN; 39% (12) hypercholesterolemia, 45% (n=14) smoking; 29% DM (n=9), 19% (n=6) previous MI, 6% (n= 2) previous revascularization. Clopidogrel + ASA group: 30% (n=11) acute MI, 27% (n= 10) unstable angina, 38% (n= 14) HTN; 27% (10) hypercholesterolemia, 27% (n=10) smoking; 38 % (n=14) DM, 14% (n= 5) previous MI,11% (n= 4) previous revascularization	68	0 withdrawn or lost to f/u

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Pekdemir, 2003 Turkey Fair	<u>Clopidogrel for 1 month vs Clopidogrel for 6 months</u> Pseudoaneurysm: 2 (1.4%) vs 1 (0.7%); χ^2 value: 0.285; Observed power: 0.080; P=NS Major adverse coronary events: 18 (12.9%) vs 19 (13.8%); χ^2 value: 0.125; Observed power: 0.064; P=NS Death: 2 (1.4%) vs 1 (0.7%); χ^2 value: 0.285; Observed power: 0.080; P=NS Acute MI: 3 (2.1%) vs 3 (2.2%); χ^2 value: 0.004; Observed power: 0.050; P=NS CABG: 3 (2.1%) vs 2 (1.4%); χ^2 value: 0.157; Observed power: 0.068; P=NS Re-PTCA: 13 (9.3%) vs 15 (10.9%); χ^2 value: 0.297; Observed power: 0.081; P=NS Target vessel revascularization: 16 (11.4%) vs 17 (12.3%); χ^2 value: 0.024; Observed power: 0.052; P=NS Subacute stent occlusion: 5 (3.6%) vs 3 (2.2%); χ^2 value: 1.849; Observed power: 0.027; P=NS Late stent occlusion: 3 (2.2%) vs 2 (1.6%); χ^2 value: 0.024; Observed power: 0.067; P=NS In-stent restenosis: 29 (20.7%) vs 33 (23.9%); P=NS In-stent restenosis-Positive vs In-stent restenosis-Negative DM: 19 (30.6%) vs 18 (9.04%); OR 4.44 (95% CI, 2.15 to 9.18); P=0.001 Elderly: 18 (29%) vs 54 (27.1%); OR 1.10 (95% CI, 0.58 to 2.01); P=NS Smoking: 37 (59.7%) vs 124 (62.3%); OR 0.90 (95% CI, 0.50 to 1.60); P=NS Male sex: 36 (58.1%) vs 115 (57.8%); OR 1.01 (95% CI, 0.57 to 1.80); P=NS	<u>Clopidogrel for 1 month vs Clopidogrel for 6 months</u> Hemorrhagic complication: 8 (5.7%) vs 4 (2.9%); χ^2 value: 1.183; Observed power: 0.192; P=NS
Piamsomboon, 2001 Thailand Poor	<u>Ticlopidine + Aspirin vs Clopidogrel + Aspirin</u> *Outcomes at a 1 month* Major cardiovascular event: 0% (0/31) vs 0% (0/37) RR = NC Death: 6.5% (2/31) vs 0% (0/37) RR = NC *Outcomes at 6 months* Major cardiovascular events: 3.6% (1/31) vs 2.7% (1/37) RR = 1.19 (0.08, 18.31) Recurrent angina pectoris: 3.6% (1/31) vs 16.5% (5/37) RR = 0.24 (0.03, 1.94) In-stent restenosis: 3.6% (1/31) vs 13.3% (4/37) RR = 0.30 (0.04, 2.53)	<u>Ticlopidine + Aspirin vs Clopidogrel + Aspirin At 1 month follow-up</u> Major bleeding: 3.2% (1/31) vs 5.4% (2/37) Minor bleeding: 0.0% (0/31) vs 5.4% (2/37) Rash: 3.2% (1/31) vs 0% (0/37)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pekdemir, 2003 Turkey Fair	NR by treatment group (17 total)	NR	
Piamsomboon, 2001 Thailand Poor		NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Rupprecht, 1998 Germany Poor	Successful implantation of a single Palmaz-Schatz stent if they were at low risk for subacute stent thrombosis. This included a vessel diameter of the stented segment of ≥ 3.0 mm, absence of thrombus formation before and after stent placement, a TIMI grade 3 blood flow, absence of a residual dissection, and absence of a residual lesion >20% within or adjacent to the stent	pretreated with 100mg aspirin/day for at least 1 wk before randomization; then randomized to either: Group A: ASA 300 mg/day plus ticlopidine 2 X 250mg/day; Group B: ticlopidine 2 x 250 mg/day; Group C: aspirin 300 mg/day x 4 wks. After initial 4 wk treatment period, ASA 100mg/day was continued	All received heparin 10 000 IU during PCI procedure and then continued x 24 hours to maintain a aPTT of 60 to 90 seconds. All patients were pretreated with 100mg ASA per day for at least 1 week before randomization.	Age Group A: 59 ±8; 76% male, 24% female, Ethnicity NR. Group B: 59±10; 70% male, 30% female, Ethnicity NR. Group C: 59±9; 75% male, 25% female, Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Rupprecht, 1998 Germany Poor	Group A: 19% DM; 48% hypercholesterolemia, 33% smoker, 19% previous MI, 19% previous PTCA, 10% unstable angina, 38% unstable angina. Group B: 20% DM, 40% HTN, 45% hypercholesterolemia,40% smoker, 25% previous MI, 15% previous PTCA, 5% previous CABG, 45% unstable angina. Group C:15% DM, 45% hypertension, 40% hypercholesterolemia, 35% smoking, 20% previous MI, 15% previous PTCA, 10% previous CABG	61	Unknown

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Rupprecht, 1998 Germany Poor	NR	One major bleeding event with a drop in Hgb concentration by 4mg/dL at groin puncture site of one patient in group C

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rupprecht, 1998 Germany Poor		NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Sacco, 2008 35 countries (Asia, Europe, Israel, Australia, Latin America, South Africa, U.S., Canada) PRoFESS Study Group Good	Recent ischemic stroke (within <90 days after randomization), defined by symptoms persisting for more than 24 hours or symptoms of a shorter duration but with evidence of a recent brain infarction on a computed tomographic scan or magnetic resonance imaging; clinical and neurologic stability before randomization; and an average age of 55 years or older.	A: Aspirin 25 mg + ER Dipyridamole 200 mg BID B: Clopidogrel 75 mg QD and C. Telmisartan 80 mg QD D. Placebo for a mean of 2.5 years	NR	Age: 66.1 years Female: 36% White: 57.5% African American: 4% Chinese: 18% South Asian: 8.4% Other Asian: 6.3% Native Latin: 4.9% Other: 0.8%
Saw, 2007 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Sacco, 2008 35 countries (Asia, Europe, Israel, Australia, Latin America, South Africa, U.S., Canada) PRoFESS Study Group Good	Previous stroke or TIA: 24.5% Hypertension: 74% Hyperlipidemia: 46.7% DM: 28.2% Atrial fibrillation: 2.6% Valvular disease: 1.7% Deep-vein thrombosis: 1.5% Ischemic CAD: 16.3% MI: 6.7% Peripheral arterial obstructive disease: 2.9% TOAST classification of qualifying stroke % of patients with small artery occlusion:52% % of patients with large artery arthrosclerosis: 28.6% Cardio-embolism: 1.8% Acute stroke of other determined cause: 2.0% Stroke of undetermined cause: 15.5% Region Asia: 31.7% Europe, Israel, or Australia: 38.2% Latin America or South Africa: 5.6% U.S. or Canada: 24.4%	20333	5251/125/20332
Saw, 2007 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Sacco, 2008 35 countries (Asia, Europe, Israel, Australia, Latin America, South Africa, U.S., Canada) PRoFESS Study Group Good	<u>Aspirin + ER dipyridamole vs clopidogrel</u> Recurrent stroke: 9.0% vs 8.8%, HR, (95% CI) 1.01 (0.92 to 1.11) Composite of vascular events (stroke, MI or death from vascular causes): 13.1% vs 13.1%, HR, (95% CI) 0.99 (0.92 to 1.07) MI: 1.7% vs 1.9%, HR (95% CI) 0.90 (0.73 to 1.10) Death from vascular causes: 4.3% vs 4.5% , HR (95% CI) 0.94 (0.73 to 1.10) Death from any cause: 7.3% vs 7.4%, HR (95% CI) 0.97 (0.87 to 1.07) New or worsening CHF: 1.4% vs 1.8%, HR (95% CI): 0.78 (0.62 to 0.96), p=0.02 Other vascular event: 5.2% vs 5.1%, HR (95% CI): 1.03 (0.91 to 1.16) First ischemic stroke: 7.7% vs 7.9%, HR (95% CI) 0.97 (0.88 to 1.07) First recurrence of stroke or major hemorrhagic event: 11.7% vs 11.4%, HR (95% CI) 1.03 (0.95 to 1.11)	<u>Aspirin + ER dipyridamole vs clopidogrel</u> Major hemorrhagic event: 4.1% vs 3.6%, HR (95% CI), 1.15 (1.00 to 1.32) Hemorrhagic event (major or minor): 5.3% vs 4.9%, HR (95% CI) 1.08 (0.96 to 1.22) Intracranial hemorrhage: 1.4% vs 1.0% , HR (95% CI): 1.42 (1.11 to 1.83), p=0.006 Thrombotic thrombocytopenic purpura or neutropenia: 0.1% vs 0.1%, HR (95% CI): 0.89 (0.32 to 2.44) Any serious adverse event: 27.0% vs 26.8% Serious blood and lymphatic system disorders: 0.9% vs 0.7% Serious skin and subcutaneous tissue disorders: 0.4% vs 0.4%
Saw, 2007 Companion to Bhatt, 2006 CHARISMA	<u>Clopidogrel vs Placebo</u> CV death, MI, and stroke at a median of 28 months according to statin administration: All patients: 6.8% to 7.3%; HR 0.93; P=0.23 No statins: 8.7% vs 8.5%; HR 1.02; P=0.87 Statins: 5.9% vs 6.7%; HR 0.87; P=0.08 CYP3A4-MET: 5.9% vs 6.6%; HR 0.89; P=0.18 Non-CYP3A4-MET: 5.7% vs 7.2%; HR 0.78; P=0.19 Atorvastatin: 5.7% vs 7.1%; HR 0.80; P=0.06 Pravastatin: 5.1% vs 7.0%; HR 0.72; P=0.13	<u>Clopidogrel vs Placebo</u> Major bleeding: All patients: 1.6% to 1.3%; OR 1.24; P=0.11 No statin: 2.1% vs 1.7%; OR 1.29; P=0.20 Any statin: 1.4% vs 1.2%; OR 1.19; P=0.33 CYP3A4-MET: 1.4% vs 1.2%; OR 1.19; P=0.39 Non-CYP3A4-MET: 1.3% vs 1.2%; OR 1.14; P=0.76 Atorvastatin: 1.2% vs 1.3%; OR 0.87; P=0.61 Pravastatin: 1.3% vs 1.3%; OR 1.04; P=0.93

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sacco, 2008 35 countries (Asia, Europe, Israel, Australia, Latin America, South Africa, U.S., Canada) PRoFESS Study Group Good	<u>Aspirin + ER dipyridamole vs clopidogrel</u> Total withdrawals:29.1% vs 22.6%, p<0.001 Withdrawals due to AE: 16.4% vs 10.6% *Proportion of commonly reported AE leading to permanent discontinuation* Headache: 5.90% vs 0.87% GI disorders: 4.76% vs 2.27% GI hemorrhage: 0.11% vs 0.07% Rash: 0.26% vs 0.35% Pruritus: 0.09%vs 0.10%	Boehringer Ingelheim, Bayer Schering Pharma and Glaxo Smithkline	This trial used a non-inferiority design. Telmisartan and placebo arms not discussed in this article. Patients assigned to clopidogrel group received clopidogrel +aspirin for 8 months. Following protocol amendment, 18305 patients were subsequently randomized to receive aspirin + ER dipyridamole or clopidogrel alone. Inclusion criteria modified at a later time to include patients 50-54 years or those with strokes within 90 to 120 days before randomization.
Saw, 2007 Companion to Bhatt, 2006 CHARISMA	See Bhatt 2006	See Bhatt 2006	See Bhatt 2006

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Steinhuble, 2002 North America CREDO Good	symptomatic CAD with objective evidence of ischemia (i.e. symptoms of angina pectoris, positive stress test results, or dynamic electrocardiographic [ECG changes); were referred for PCI or thought to be at high likelihood for requiring PCI with either stent placement with or without conventional balloon angioplasty or another revascularization device; at least 21 years old; provided informed consent before randomization; and agreed to comply with all protocol-specified procedures	3-24 hrs before PCI: 300mg LD of clopidogrel + ASA 325mg (pretreatment group) or matching placebo + ASA 325mg. After PCI: both groups received 75mg/day of clopidogrel and 325mg/day of ASA through day 28. After 28 days: (pretreatment group) 75mg daily of clopidogrel + ASA 81- 325mg/day (at discretion of the investigator) vs. matching placebo + ASA 81 -325mg/day (at discretion of the invest.) x 12 mos	20% of all pts could be prespecified at the time of randomization to receive a Gp2b/3a receptor antagonist (primarily abciximab) at the time of PCI. Bail-out GP 2b/3a inhibitor use was allowed for all pts at the discretion of the MD performing Pick	Clopidogrel Group: 61.5± 11.2, 29.3% female; 70.7% male, 88.2% white; Placebo Group: 61.8± 11.0, 27.9% female, 72.1% male, 89.5% white

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Steinhuble, 2002 North America CREDO Good	34% previous MI,6.7 % previous stroke, 26.45% DM, 10% PVD, 68.5% HTN, 30.8% smoking (within past year); 74.7% hyperlipidemia	2116	Clopidogrel group: 50 discontinued study drug prior to day 28; 411 permanently discontinued study drug, 38 no f/u at 1 y(28 withdrew consent, 8 lost-to f/u, 2 other). Placebo group: 44 discontinued study drug prior to day 28; 420 permanently discontinued study drug, 48 no f/u at 1 y (31 withdrew consent, 15 lost-to f/u, 2 other)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Steinhuble, 2002 North America CREDO Good	Clopidogrel vs Placebo *Outcomes at 12 months* Death, MI, stroke: 8.5% (89/1053) vs 11.5% (122/1063) RR = 0.73 (0.57, 0.95); NNT = 33 (18, 210) Death, MI: 8.0% (84/1053) vs 10.4% (111/1063) RR = 0.76 (0.58, 1.00) Death: 1.7% (18/1053) vs 2.3% (24/1063) RR = 0.76 (0.41, 1.39) MI: 6.6% (70/1053) vs 8.5% (90/1063) RR = 0.79 (0.58, 1.06) Stroke: 0.9% (9/1053) vs 1.1% (12/1063) RR = 0.76 (0.32, 1.79) Revascularization any tvr: 13.2% (139/1053) vs 13.5% (144/1063) RR = 0.97 (0.78, 1.21) Revascularization urgent tvr: 2.0% (21/1053) vs 2.2% (23/1063) RR = 0.92 (0.51, 1.66) Any revascularization: 21.4% (225/1053) vs 21.0% (223/1063) RR = 1.01 (0.86, 1.20)	Clopidogrel vs Placebo Non-procedural major bleeding: 1.2% (13/1053) vs 0.8% (8/1063) Procedural major bleeding: 7.7% (81/1053) vs 5.9% (63/1063) Major bleeding from CABG: 6.0% (63/1053) vs 5.2% (55/1063) Major bleeding from non-CABG: 1.7% (18/1053) vs 0.8% (8/1063) Minor bleeding: 5.3% (56/1053) vs 5.6% (59/1063) Non-procedural minor bleeding:0.7% (7/1053) vs 0.8%(8/1063) Procedural minor bleeding:4.7% (50/1053) vs 4.9% (52/1063) Minor bleeding from CABG: 2.3% (24/1053) vs 2.8% (30/1063) Minor bleeding from non-CABG: 2.5% (26/1053) vs 2.1% (22/1063)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Steinhuble, 2002 North America CREDO Good		supported from Bristol-Meyers Squibb/Sanofi-Synthelabo partnership.	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Taniuchi, 2001 U.S. Fair	Btw 9/9/98 and 11/14/99, 1,367 consecutive patients with successful implantation (defined as <20% residual stenosis, with TIMI 2 or TIMI 3 flow) of an FDA-approved stent in a native coronary artery or in a CABG graft were screened.	T 500mg LD or C 300mg LD administered within 1 hr of stent implantation. Drugs were administered x 2 wks but the exact dose was not stated although it was stated that T was given BID (assume 250mg bid) and C daily dose (assume 300mg qd). All pts received 325mg AS daily.	ASA 325mg every day; 2B/3A-50.2% T group and 46.1% C group p = 0.198; Post-procedural anticoagulation was up to the discretion of the operator--not stated if they were used. The majority of stents used were Boston Scientific NIR and ACS Duet stents (71% and 11.5%, respectively)	T group:63.1 years old; 60.2% males and 39.8% females in T group; C group: 63.6 years old; 61.5% males and 38.5% females; Ethnicity not-reported

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Taniuchi, 2001 U.S. Fair	AMI (41.4% of the pts were within 1 wk of MI) accounts for high incidence of angiographically evident thrombus (20.9% overall) and cardiogenic shock were not excluded. (T 18.2% vs. C 24.3% ; p=0.009) DM -29% of the population (vs. 21-23 in Mueller study (Circ.2000) and 10-12% in CLASSICS). Also, 21% overall had previous bypass grafting (include saphenous vein graft stents; stents were placed in vein grafts in 9.5% of the total population)	1016	2 pts stopped medication without an identified clinical reason; 1 from each arm of treatment. 2 T pts stopped med due to reported rash-(not confirmed by PE). Additional pts had rash but were confirmed on PE ? stopped med

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Taniuchi, 2001 U.S. Fair	Ticlopidine vs Clopidogrel *Outcomes at 30 days* Acute closure: 0.57% (3/522) vs 0.61% (3/494) RR = 0.95 (0.19, 4.67) Subacute thrombosis: 1.3% (7/522) vs 1.4% (7/494) RR = 0.95 (0.33, 2.68) Target vessel revascularization: 2.3% (12/522) vs 2.4% (12/494) RR = 0.95 (0.43, 2.09) 30-d closure: 1.9% (10/522) vs 2.0% (10/494) RR = 0.95 (0.40, 2.25) Cardiac death: 1.5% (8/522) vs 0.6% (3/494) RR = 2.52 (0.67, 9.46) Major adverse cardiac events: 4.6% (24/522) vs 3.9% (19/494) RR = 1.20 (0.66, 2.15)	Ticlopidine vs Clopidogrel Bleeding: 0.4% (2/522) vs 0.4% (2/494) GI: 0.4% (2/522) vs 0% (0/494) Neutropenia: 0.4% (2/522) vs 0% (0/494) Occurrence of thrombocytopenia: 0.6% (3/522) vs 1% (5/494) Rash: 1% (5/522) vs 0.2% (1/494)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Taniuchi, 2001 U.S. Fair		Sanofi/Bristol-Meyers Squibb	Occurrence of both acute closure (within 24 hrs of implantation) and subacute stent thrombosis (day 1-30) were essentially equal for the 2 treatment arms. 30 d rate of stent closure 1.92% for T and 2.02% for C are similar to the 2.0% rate reported by Muller (2000). and sl higher than the range of 0.9% T to 1.5% for C in CLASSICS. (possibly due to higher risk pts enrolled in this study-AMI, cardiogenic shock, lesions with thrombus and cases in which multiple stents were placed). 30 d rate of Major adverse stents was 4.23% overall...between Muller and CLASSICS 0.9% to 3.1%). When the occurrence of 30 d stent thrombosis of Muller, CLASSICS and TOPPS are combined, the rate associated with T is 1.16% (14/1207) and C 1.77% (24/1529) p=0.355. The combined 30 d major adverse cardiac event rate is 2.73% (33/1207) for T and 2.62 (41/1529) for C; p=8.50.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Uchiyama, 2009 Japan Phase IIIa (deduced from pooled data) Fair	Patients 20-80 years old with a history of cerebral infarctions (excluding cardiogenic cerebral embolism), with most recent stroke >8 days before inclusion with a well-documented clinical course, and computed tomography or magnetic resonance imaging to document brain infarct within 1 month of the start of treatment	A: Clopidogrel 5 mg/d after a meal B: Ticlopidine 200 mg/d after a meal For 26 weeks	NR	Age: 64.9 years (SD 8.9) Male: 68.5% Ethnicity NR (trial conducted in Japan

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Uchiyama, 2009 Japan Phase IIIa (deduced from pooled data) Fair	Age ≥65 years: 58% Current or ex-smoker: 37% Time from most recent onset of cerebral infarction: <4 weeks: 39.9% 4-12 weeks: 26.2% >12 weeks: 32.9% Type of most recent infarction: Atherothrombotic: 20.2% Lacunar: 77.6% Comorbidities: Hypertension: 70% DM: 24.5% Hyperlipidemia: 29.8%	749	173/NR/711 for efficacy, 714 for safety

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Uchiyama, 2009 Japan Phase IIIa (deduced from pooled data) Fair	Clopidogrel vs Ticlopidine Primary vascular endpoints: 7 (1.9%) vs 8 (2.3%) Cerebral infarction: 7 (1.9%) vs 8 (2.3%) MI: 0 (0%) vs 0 (0%) Vascular death: 0 (0%) vs 0 (0%) Other vascular events: 2 (0.5%) vs 2 (0.6%) TIA: 1 (0.3%) vs 2 (0.6%) Angina pectoris: 0 (0%) vs 0 (0%) Peripheral arterial occlusion: 1 (0.3%) vs 0 (0%) Others: 0 (0%) vs 0 (0%) All vascular event: 9 (2.5%) vs 10 (2.9%)	Clopidogrel vs Ticlopidine (estimated from a graph) Leukopenia: 18 (4.9%) vs 38 (10.9%) Neutropenia: 0 (0%) vs 8 (2.3%) Thrombocytopenia: 3 (0.8%) vs 9 (2.5%) Major hemorrhagic adverse drug reactions: 5 (1.4%) vs 3 (0.8%)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Uchiyama, 2009 Japan Phase IIIa (deduced from pooled data) Fair	Clopidogrel vs Ticlopidine Total withdrawals: 84 (22.9%) vs 89 (25.6%) Due to AE: 37 (10.1%) vs 31 (8.9%)	Sanofi-aventis K.K	Patients were given both the active drug and an indistinguishable placebo

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Wiviott, 2005 U.S., Canada JUMBO–TIMI 26 Fair	Men and nonpregnant woman 18 to 75 years of age, who were a candidate for elective or urgent PCI with intended coronary stenting, and had a native target coronary artery stenosis >60% (by visual estimation) that was thought by the operator to be amenable to stenting with ≥2 approved coronary stents per lesion (multilesion or multivessel stenting was acceptable if all lesions were treated in a single non-staged procedure).	A: Prasugrel 40 mg LD followed by 7.5 mg QD (low-dose) B: Prasugrel 60 mg LD followed by 10 mg QD (intermediate dose) C: Prasugrel 60 mg LD followed by 15 mg QD (high dose) D: Clopidogrel 300 mg LD followed by 75 mg QD For 29 to 34 days	All subjects received aspirin 325 mg/d for the duration of the study. The use of GP IIb/IIIa inhibitors was at the discretion of the treating physician (who elected to use in 71% of patients). All subjects received unfractionated heparin therapy with target activated clotting times of 200 to 250 seconds for patients receiving an intravenous GP IIb/IIIa inhibitor and 250 to 300 seconds for those not receiving a GP IIb/IIIa inhibitor.	Median age: 60 years Female: 23% White: 91.1%

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wiviott, 2005 U.S., Canada JUMBO–TIMI 26 Fair	Age ≥65 years: 73.4% Median BMI: 29.5 kg/m2 DM: 26.4% Smoker: 25.2% Prior aspirin: 77% ST-segment depression: 12% GP IIb/IIIa use: 69% Mean TIMI risk score: 2.3 (SD 1.1) TIMI risk score ≥2: 54%	905	57/3/904

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Wiviott, 2005 U.S., Canada JUMBO–TIMI 26 Fair	<u>Prasugrel vs Clopidogrel</u> Major adverse cardiac event: 47 (7.2%) vs 24 (9.4%); P=0.260; HR 0.76 (95% CI, 0.46 to 1.2) Death: 3 (0.5%) vs 0 (0%); P=0.278 Stroke: 3 (0.5%) vs 0 (0%); P=0.278 MI: 37 (5.7%) vs 20 (7.9%); P=0.226; HR 0.72 (95% CI, 0.42 to 1.24) Recurrent ischemia: 6 (0.9%) vs 4 (1.6%); P=0.391; HR 0.58 (95% CI, 0.16 to 2.05) Severe ischemia: 9 (1.7%) vs 11 (3.5%); P=0.086; HR 0.47 (95% CI, 0.2 to 1.14) Clinical target vessel thrombosis: 4 (0.6%) vs 6 (2.4%); P=0.024; HR 0.26 (95% CI, 0.07 to 0.92) Death/MI: 40 (6.2%) vs 20 (7.9%); P=0.349; HR 0.78 (95% CI, 0.46 to 1.33) Death/MI/clinical target vessel thrombosis: 41 (6.3%) vs 24 (9.4%); P=0.101; HR 0.66 (95% CI, 0.40 to 1.10) Significant non-CABG bleeding (TIMI major + minor) at 30 days: 11 (1.7%) vs 3 (1.2%) Within Prasugrel group, low-dose vs intermediate-dose vs high-dose: 3 (1.5%) vs 4 (2.0%) vs 4 (1.6%) TIMI major non-CABG bleeding at 30 days: 3 (0.5%) vs 2 (0.8%) Within Prasugrel: Within Prasugrel group, low-dose vs intermediate-dose vs high-dose: 1 (0.5%) vs 1 (0.5%) vs 1 (0.4%)	<u>Prasugrel vs Clopidogrel</u> Bleeding: Non-CABG TIMI major+minor: 11 (1.7%) vs 3 (1.2%); P=0.590; HR 1.42 (95% CI, 0.40 to 5.08) Non-CABG TIMI major: 3 (0.5%) vs 2 (0.8%); P=0.544; HR 0.58 (95% CI, 0.10 to 3.46) Non-CABG TIMI major+minor+minimal: 27 (4.2%) vs 9 (3.5%); P=0.685; HR 1.17 (95% CI, 0.55 to 2.48) Transfusion rates: 0.9% vs 1.1% Intracranial hemorrhage (subdural hematoma): 1 (0.2%) vs 0 (0%) Intra-prasugrel group comparisons, low-dose vs intermediate-dose vs high-dose: Minimal bleeding: 2% vs 1.5% vs 3.6% Post-discharge minimal bleeding episodes: 0.5% vs 0.5% vs 1.2%

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wiviott, 2005 U.S., Canada JUMBO–TIMI 26 Fair	Total withdrawals: 57 (6.3%); NR by group Due to AE: NR	Eli Lilly and Sankyo Co., Ltd.	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Wiviott, 2007a/Wiviott, 2008/O'Donoghue, 2009 30 countries TRITON–TIMI 38 Good	Patients with ACSs (representative of the entire spectrum of those syndromes, namely moderate-to-high-risk unstable angina, NSTEMI, or STEMI) with scheduled PCI.	A: Prasugrel 60 mg LD and 10 mg/d maintenance dose B: Clopidogrel 300 mg LD and 75 mg/d maintenance dose) For 6 to 15 months (median 14.5 months)	Use of aspirin was required, and a daily dose of 75 to 162 mg was recommended	Median age: 61 years Female: 26% White: 92.5%

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wiviott, 2007a/Wiviott, 2008/O'Donoghue, 2009 30 countries TRITON–TIMI 38 Good	Unstable angina or NSTEMI: 74% STEMI: 26% ≥75 years: 13% Median BMI: 28 Region of enrollment: North America: 32% Western Europe: 26% Eastern Europe: 24.5% Middle East, Africa, or Asia–Pacific region: 14% South America: 4% Medical history: Hypertension: 64% Hypercholesterolemia: 56% DM: 23% Tobacco use: 38% Previous MI: 18% Previous CABG: 7.5% Index procedure: PCI: 99% CABG: 1% Stent: 94.5% Bare-metal stent only: 47.5% ≥1 Drug-eluting stent: 47% Multivessel PCI: 14%	13,608	NR/14/13608 for efficacy endpoints, 13457 for safety endpoints

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Wiviott, 2007a/Wiviott, 2008/O'Donoghue, 2009 30 countries TRITON–TIMI 38 Good	Prasugrel vs Clopidogrel (HR values reported for prasugrel) Death from cardiovascular causes, nonfatal MI, or nonfatal stroke: At 15 months: 643 (9.9%) vs 781 (12.1%); HR 0.81; 95% CI, 0.73 to 0.90; P <0.001 At days 1-3 after randomization: 4.7% vs 5.6%; HR 0.82; 95% CI, 0.71 to 0.96;P=0.01 At Day 3 to 15 months: 5.6% vs 6.9%; HR 0.80; 95% CI, 0.70 to 0.93; P=0.003 Death from cardiovascular causes at 15 months: 133 (2.1%) vs 150 (2.4%); HR 0.89; 95% CI, 0.70 to 1.12; P=0.31 Nonfatal MI at 15 months: 475 (7.3%) vs 620 (9.5%); HR 0.76; 95% CI, 0.67 to 0.85; P <0.001 Nonfatal stroke at 15 months: 61 (1.0%) vs 60 (1.0%); HR 1.02; 95% CI, 0.71 to 1.45; P=0.93 Death from any cause at 15 months: 188 (3.0%) vs 197 (3.2%); HR 0.95; 95% CI, 0.78 to 1.16; P=0.64 Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization at 15 months: 652 (10.0%) vs 798 (12.3%); HR 0.81; 95% CI, 0.73 to 0.89; P<0.001 Death from any cause, nonfatal MI, or nonfatal stroke at 15 months: 692 (10.7%) vs 822 (12.7%); HR 0.83; 95% CI, 0.75 to 0.92; P<0.001 Urgent target-vessel revascularization at 15 months: 156 (2.5%) vs 233 (3.7%); HR 0.66; 95% CI, 0.54 to 0.81; P<0.001 Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia at 15 months: 797 (12.3%) vs 938 (14.6%); HR 0.84; 95% CI, 0.76 to 0.92; P<0.001 Stent thrombosis at 15 months: 68 (1.1%) vs 142 (2.4%); HR 0.48; 95% CI, 0.36 to 0.64; P<0.001 Clopidogrel vs Prasugrel Clinical events by DM status: Subjects without DM: CV death/MI/CV accident: 10.6% vs 9.2%; HR 0.86 (95% CI, 0.76–0.98); P=0.02 CV death/MI: 10.0% vs 8.5%; HR 0.85 (95% CI, 0.75–0.97); P=0.01 MI: 8.7% vs 7.2%; HR 0.82 (95% CI, 0.72–0.95); P=0.006 CV death: 1.9% vs 1.7%; HR 0.91 (95% CI, 0.68–1.23); P=0.53 Stent thrombosis: 2.0% vs 0.9%; HR 0.45 (95% CI, 0.31–0.65); P<0.001 All DM: CV death/MI/CV accident: 17.0% vs 12.2%; HR 0.70 (95% CI, 0.58–0.85); P<0.001; P=0.09 vs no DM CV death /MI: 15.4% vs 10.8%; HR 0.68 (95% CI, 0.56–0.84); P<0.001; P=0.08 vs no DM MI: 13.2% vs 8.2%; HR 0.60 (95% CI, 0.48–0.76); P<0.001; P=0.02 vs no DM CV death: 4.2% vs 3.4%; HR 0.85 (95% CI, 0.58–1.24); P=0.40; P=0.78 vs no DM Stent thrombosis: 3.6% vs 2.0%; HR 0.52 (95% CI, 0.33–0.84); P=0.007; P=0.63 vs no DM	Prasugrel vs Clopidogrel Non–CABG-related TIMI major bleeding: 146 (2.4%) vs 111 (1.8%); HR 1.32; 95% CI, 1.03 to 1.68; P=0.03 Related to instrumentation: 45 (0.7%) vs 38 (0.6%); HR 1.18; 95% CI, 0.77 to 1.82; P=0.45 Spontaneous: 92 (1.6%) vs 61 (1.1%); HR 1.51; 95% CI, 1.09 to 2.08; P=0.01 Related to trauma: 9 (0.2%) vs 12 (0.2%); HR 0.75; 95% CI, 0.32 to 1.78; P=0.51 Life-threatening: 85 (1.4%) vs 56 (0.9%); HR 1.52; 95% CI, 1.08 to 2.13; P=0.01 Related to instrumentation: 28 (0.5%) vs 18 (0.3%); HR 1.55; 95% CI, 0.86 to 2.81; P=0.14 Spontaneous: 50 (0.9%) vs 28 (0.5%); HR 1.78; 95% CI, 1.12 to 2.83; P=0.01 Related to trauma: 7 (0.1%) vs 10 (0.2%); HR 0.70; 95% CI, 0.27 to 1.84; P=0.47 Fatal: 21 (0.4%) vs 5 (0.1%); HR 4.19; 95% CI, 1.58 to 11.11; P=0.002 Nonfatal: 64 (1.1%) vs 51 (0.9%); HR 1.25; 95% CI, 0.87 to 1.81; P=0.23 Intracranial: 19 (0.3%) vs 17 (0.3%); HR 1.12; 95% CI, 0.58 to 2.15; P=0.74 Major or minor TIMI bleeding: 303 (5.0%) vs 231 (3.8%); HR 1.31; 95% CI, 1.11 to 1.56; P=0.002 Bleeding requiring transfusion: 244 (4.0%) vs 182 (3.0%); HR 1.34; 95% CI, 1.11 to 1.63; P<0.001 CABG-related TIMI major bleeding: 24 (13.4%) vs 6 (3.2%); HR 4.73; 95% CI, 1.90 to 11.82; P<0.001 Serious AEs not related to hemorrhage: 22.5% vs 22.8%; P=0.52 Severe thrombocytopenia: 17 (0.3%) vs 18 (0.3%); P=0.86 Neutropenia: 2 (<0.1%) vs 10 (0.2%); P=0.02 Colonic neoplasms: 13 (0.2%) vs 4 (0.1%); P=0.03 Known GI bleeding preceded the diagnosis of colonic neoplasms: 7 vs 2

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Wiviott, 2007a/Wiviott, 2008/O'Donoghue, 2009 Continued	Clopidogrel vs Prasugrel Clinical events by DM subtype: Subjects with DM on insulin: CV death/MI/CV accident: 22.2% vs 14.3%; HR 0.63 (95% CI, 0.44 to 0.89); P=0.009 CV death/MI: 19.3% vs 13.1%; HR 0.64 (95% CI, 0.44 to 0.93); P=0.02 MI: 17.3% vs 9.9%; HR 0.56 (95% CI, 0.37 to 0.84); P=0.005 Stent thrombosis 5.7% vs 1.8%; HR 0.31 (95% CI, 0.12 to 0.77); P=0.008 DM not on insulin: CV death/MI/CV accident: 15.3% vs 11.5%; HR 0.74 (95% CI, 0.59 to 0.93); P=0.009 CV death/MI: 14.0% vs 10.1%; HR 0.70 (95% CI, 0.55 to 0.89); P=0.004 MI: 11.9% vs 7.7%; HR 0.62 (95% CI, 0.47 to 0.82); P<0.001 Stent thrombosis: 3.0% vs 2.0%; HR 0.66 (95% CI, 0.37 to 1.15); P=0.14 Treated with a PPI vs Not treated with a PPI CV death, MI, or stroke: Clopidogrel: 11.8% (255/2257) vs 12.2% (526/4538); Adjusted HR 0.94 (95% CI, 0.80 to 1.11) Prasugrel: 10.2% (220/2272) vs 9.7% (423/4541); Adjusted HR 1.00 (95% CI, 0.84 to 1.20) All-cause death: Clopidogrel: 2.9% (58/2257) vs 3.3% (139/4538); Adjusted HR 0.68 (95% CI, 0.47 to 0.96) Prasugrel: 3.1% (65/2272) vs 3.0% (123/4541); Adjusted HR 1.00 (95% CI, 0.71 to 1.41) CV death: Clopidogrel: 2.2% (44/2257) vs 2.5% (106/4538); Adjusted HR 0.71 (95% CI, 0.47 to 1.07) Prasugrel: 2.2% (46/2272) vs 2.0% (87/4541); Adjusted HR 1.06 (95% CI, 0.70 to 1.62) MI: Clopidogrel: 9.5% (209/2257) vs 9.8% (424/4538); Adjusted HR 0.98 (95% CI, 0.82 to 1.17) Prasugrel: 7.7% (166/2272) vs 7.3% (319/4541); Adjusted HR 1.02 (95% CI, 0.84 to 1.25) Stent thrombosis (ARC definite or probable): Clopidogrel: 2.4% (50/2150) vs 2.3% (92/4272); Adjusted HR 1.08 (95% CI, 0.75 to 1.55) Prasugrel: 1.1% (22/2159) vs 1.1% (46/4263); Adjusted HR 1.03 (95% CI, 0.60 to 1.76) Net clinical outcome (death, MI, stroke, or TIMI major non-CABG bleeding): Clopidogrel: 13.9% (299/2257) vs 13.8% (594/4538); Adjusted HR 0.96 (95% CI, 0.83 to 1.12) Prasugrel: 12.6% (268/2272) vs 12.1% (516/4541); Adjusted HR 0.99 (95% CI, 0.85 to 1.17) Patients with a single reduced-function CYP2C19 allele: CV death, MI, or stroke: Clopidogrel: 10.2% (12/120) vs 13.0% (30/237); HR 0.76 (95% CI, 0.39 to 1.48) Prasugrel: 7.4% (9/122) vs (9.9%, 24/250); HR 0.81 (95% CI, 0.35 to 1.85) Patients who did not have a reduced-function CYP2C19 allele (wild-type carriers): CV death, MI, or stroke: Clopidogrel: 7.2% (23/333) vs 8.4% (60/731); HR 0.90 (95% CI, 0.55 to 1.48) Prasugrel: 9.1% (27/323) vs 10.2% (72/725); HR 0.89 (95% CI, 0.57 to 1.39)	Clopidogrel vs Prasugrel (bleeding not related to CABG) *Subjects without DM:* Major hemorrhage: 1.6% vs 2.4%; HR 1.43 (95% CI, 1.07–1.91); P=0.02 Major or minor: 3.6% vs 4.9%; HR 1.32 (95% CI, 1.08–1.61); P=0.006 Death/MI/CV accident/major bleed: 12.3% vs 11.5%; HR 0.92 (95% CI, 0.82–1.03); P=0.16 All DM: Major hemorrhage: 2.6% vs 2.5%; HR 1.06 (95% CI, 0.66–1.69); P=0.81; P=0.29 vs no DM Major or minor: 4.3% vs 5.3%; HR 1.30 (95% CI, 0.92–1.82); P=0.13; P=0.93 vs no DM Death/MI/CV accident/major bleed: 19.2% vs 14.6%; HR 0.74 (95% CI, 0.62–0.89); P=0.001; P=0.05 vs no DM *Subjects with DM on insulin:* Major hemorrhage: 2.3% vs 1.9%; HR 0.87 (95% CI, 0.31 to 2.39); P=0.78 Major or minor: 4.5% vs 4.4%; HR 0.93 (95% CI, 0.46 to 1.88); P=0.84 Death/MI/CV accident/major bleed: 24.1% vs 16.8%; HR 0.66 (95% CI, 0.47 to 0.92); P=0.01 DM not on insulin: Major hemorrhage: 2.7% vs 2.7%; HR 1.11 (95% CI, 0.65 to 1.89); P=0.70 Major or minor: 4.2% vs 5.6%; HR 1.42 (95% CI, 0.96 to 2.10); P=0.08 Death/MI/CV accident/major bleed: 17.7% vs 13.9%; HR 0.78 (95% CI, 0.63 to 0.96); P=0.02 Treated with a PPI vs Not treated with a PPI TIMI major or minor bleeding (non-CABG): Clopidogrel: 4.6% (92/2234) vs 3.4% (139/4482); Adjusted HR 1.13 (95% CI, 0.85 to 1.49) Prasugrel: 4.8% (98/2253) vs 5.0% (205/4488); Adjusted HR 0.92 (95% CI, 0.71 to 1.18) TIMI major bleeding (non-CABG): Clopidogrel: 2.4% (46/2234) vs 1.6% (65/4482); Adjusted HR 1.20 (95% CI, 0.80 to 1.79) Prasugrel: 2.5% (51/2253) vs 2.4% (95/4488); Adjusted HR 0.97 (95% CI, 0.67 to 1.39)

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wiviott, 2007a/Wiviott, 2008/O'Donoghue, 2009 30 countries TRITON–TIMI 38 Good	Prasugrel vs Clopidogrel Total withdrawals: NR Due to AE: NR (7.2%) vs NR (6.4%) Due to AE related to hemorrhage: 2.5% vs 1.4%; P<0.001	Daiichi Sankyo and Eli Lilly	

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Wiviott, 2007b/O'Donoghue, 2009 France, Germany, Israel, U.S. PRINCIPLE-TIMI 44 Fair	Patients ≥18 years of age and were scheduled to undergo cardiac catheterization with planned PCI for angina and at least one of the following: coronary angiography within 14 days with at least 1 lesion amenable to PCI, a functional study within 8 weeks with objective findings of ischemia, or prior PCI or coronary artery bypass graft surgery. Excluded patients with planned PCI for immediate treatment of MI.	A: Clopidogrel 600 mg LD before PCI; after PCI, 150 mg QD maintenance dose B: Prasugrel 60 mg LD before PCI; after PCI, 10 mg QD maintenance dose For 2 phases (crossover design) of 14 ± 2 days for each drug	GP IIb/IIIa inhibitor bailout was permitted. Actual GP IIb/IIIa inhibitor use, prasugrel vs clopidogrel: 3 (2.9%) vs 1 (1%)	Age: 63.9 years Female: 25.3% Ethnicity NR

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wiviott, 2007b/O'Donoghue, 2009 France, Germany, Israel, U.S. PRINCIPLE-TIMI 44 Fair	Age ≥65 years: 53.7% Mean BMI: 29 kg/m2 Prior MI: 29.4% Hypertension: 81.6% Prior CABG: 19.4% Dyslipidemia: 88.6% DM: 30.9% Current smoker: 16.9% Angina, Canadian Cardiovascular Society III or IV: 37.8% Prior aspirin: 87.6% β-Blocker: 80.1% Statin: 89.5% PCI for index event: 55.7%	201	4/0/201

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Efficacy/Effectiveness Outcomes	Harms
Wiviott, 2007b/O'Donoghue, 2009 France, Germany, Israel, U.S. PRINCIPLE-TIMI 44 Fair	Prasugrel vs Clopidogrel Stroke: 0 (0%) vs 0 (0%) Death: 0 (0%) vs 0 (0%)	Prasugrel vs Clopidogrel TIMI major bleeds: 0 (0%) vs 0 (0%) TIMI minor bleeding episodes: 2 (2%) vs 0 (0%) TIMI major or minor bleeding events after LD phase: 0 (0%) vs 0 (0%) All hemorrhagic events during LD and pre-crossover maintenance dose period: 19 (18.6%) vs 14 (14.1%); P=MS Hemorrhagic events after crossover, clopidogrel followed by prasugrel group vs prasugrel followed by clopidogrel group: 4 (4%) vs 0 (0%) Major adverse cardiac events: One subject in the clopidogrel group had acute stent thrombosis resulting in a MI and required urgent target vessel revascularization, and 2 subjects in the prasugrel group had periprocedural MIs. One subject in the prasugrel followed by clopidogrel group experienced a MI after the crossover.

Evidence Table 1. Data abstraction of randomized controlled trials

Author, Year Country Trial Name (Quality Rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wiviott, 2007b/O'Donoghue, 2009 France, Germany, Israel, U.S. PRINCIPLE-TIMI 44 Fair	Prasugrel vs Clopidogrel Total withdrawals: 2 (2%) vs 2 (2%) Due to AE: 0 (0%) vs 0 (0%)	Daiichi Sankyo Co., Ltd., and Eli Lilly	

Evidence Table 2. Quality assessment of randomized controlled trials (update 2)

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Akbulut 2004	Unclear; no description at all about allocation method	Unclear	Yes	Yes	Unclear	Unclear; "isochronous placebo" but nothing about blinding or matching placebo.	Unclear; "isochronous placebo" but nothing about blinding or matching placebo.
Belch 2010 (CASPAR)	Probably yes, given IVRS	Yes	Higher rate of CAD and/or cerebrovascular disease in clopidogrel group (38.4% vs 31.0%; $P < 0.05$)	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind
Bernardi 2007	Yes	Yes- central internet-based computerized randomization service	Mostly; Previous history of CV events were slightly more prevalent in 30-day group	Yes	No - open label	No - open label	No - open label
Fukuuchi 2008/Uchiyama 2009	Unclear	Unclear	Unclear; some imbalances noted for site of infarct ($P = 0.084$), basal nucleus infarction site ($P = 0.094$), and smoking status ($P = 0.071$)	Yes	Unclear, described as double-blind	Yes	Yes
Kayacioglu 2008	Unclear	Unclear	Control group generally healthier and more female; intervention groups are similar	Limited	NR; assume NO	NR; assume NO	NR; assume NO
Kennedy 2007 (FASTER)	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials (update 2)

Author, Year	Intent-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating	
Akbulut 2004	Yes	Yes	NR/NR/NR	Unclear/Unclear	Fair	
Belch 2010 (CASPAR)	Yes	Yes	Unclear, Unclear, Unclear	No: 28% overall Yes: clopidogrel=30%, placebo=26.5%	Fair	
Bernardi 2007	Yes	Yes	NR/Yes/NR	Yes/Yes: 30-day LTF = 3.0%, non-adherence 1.1%; 180-day LTF = 2.4%, non-adherence 2.4%	Fair	
Fukuuchi 2008/Uchiyama 2009	Yes, only excluded 21/1172 (1.8%)	Yes	Unclear, Unclear, Unclear	No: 34% overall No: clopidogrel=27%, ticlopidine=40%	Fair	
Kayacioglu 2008	Unclear, but data available for ITT	Unclear	Unclear	Unclear	Poor	
Kennedy 2007 (FASTER)	Yes, only excluded 4/396 (1%) who withdrew consent	Yes	Unclear, Unclear, Unclear	Unclear, not reported for clopidogrel-only and double-placebo groups	Fair	Trial stopped early due to slow enrollment

Evidence Table 2. Quality assessment of randomized controlled trials (update 2)

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Pekdemir 2003	Yes; randomly assigned in equal proportions with the use of a prespecified randomization sequence	Unclear	Mostly; smokers higher in the 6 month group.	Yes	Yes	No	No
Sacco 2008	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Uchiyama 2009 (Phase IIIa study only)	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Yes	Yes
Unpublished Boehringer Ingelheim Trial #9.178, NCT00311402 (JASAP)	Unclear	Unclear	Yes for age and sex, others NR	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind
Wiviott SD 2005 JUMBO-TIMI 26	Unclear	Unclear	Unclear - 10% higher smokers in comparator	Yes	Yes	Yes	Yes
Wiviott SD 2007 PRINCIPLE-TIMI 44	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes
Wiviott SD 2007 TRITON-TIMI 38	Unclear; probably Yes given IVRS	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials (update 2)

Author, Year	Intent-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Pekdemir 2003	Yes	Yes	NR/NR/NR	Unclear/Unclear	Fair
Sacco 2008	Yes	Yes	Crossovers=Unclear Adherence=No: medication compliance of more than 75% was 76.8% for clopidogrel and 69.6% for ERDP/ASA Contamination=Unclear	Yes Yes	Good
Uchiyama 2009 (Phase IIIa study only)	Yes, only excluded 38/749 (5.1%)	Yes	Unclear, Unclear, Unclear	Yes: 24% overall Yes: clopidogrel=23%, ticlopidine=24%	Fair
Unpublished Boehringer Ingelheim Trial #9.178, NCT00311402 (JASAP)	Yes, only excluded 3/1294 (0.02%)	Yes	Unclear, Unclear, Unclear	No: 30% overall Yes for between-groups	Fair
Wiviott SD 2005 JUMBO-TIMI 26	Yes	Yes	Unclear	Yes (6.3% lost) Yes	Fair
Wiviott SD 2007 PRINCIPLE-TIMI 44	Yes	Yes	Unclear	Yes (2% lost) Yes	Fair
Wiviott SD 2007 TRITON-TIMI 38	Yes	Yes	Unclear	Yes Yes	Good

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Atmaca, 2002 Turkey	Yes, closed envelope system without patient stratification	Yes-closed envelope system without patient stratification	C Group had higher frequency lesion in the RCA p= <0.02, and T Group had a higher EF <0.04	Yes-undergoing elective single vessel PTCA. Inclusion criteria pts with Canadian Cardiac Society Class-II stable angina pectoris and de novo lesions in large native coronary arteries.
Bertrand, 2000 Europe CLASSICS	Yes	Yes	Yes	Yes
Bhatt, 2006 International CHARISMA	Study drug assignment was performed centrally by an interactive voice-response system on the basis of a pre-established randomization scheme, stratified according to site.	Yes	Yes	Yes
CAPRIE Steering Committee, 1996 International	Yes	Yes	Yes	Yes
Cure Investigators, 2001 International	Yes	Yes	Yes	Yes
Di Pasquale, 2005 Italy	Randomization was performed at entry before starting any treatment and carried out using a preliminary computer algorithm, and the assignment of patients was decided at the time of admission by an independent	Yes	Yes	Yes

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat (ITT) analysis?
Atmaca, 2002 Turkey	Yes-but methods not described	Yes	Yes	No
Bertrand, 2000 Europe CLASSICS	Yes	Yes	Yes	Yes
Bhatt, 2006 International CHARISMA	Yes	Yes	Yes	Yes
CAPRIE Steering Committee, 1996 International	Yes	Yes	Yes	Yes
Cure Investigators, 2001 International	Yes-although unclear success of blinding	Yes	Yes	Yes
Di Pasquale, 2005 Italy	ECG and angiographic data were assessed and revised by 2 independent observers in order to reduce bias in the assessment of reperfusion and the result of PCI	Yes	Yes	Not stated

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Post-randomization exclusions?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Quality Rating
Atmaca, 2002 Turkey	See #3 answer- baseline characteristics were shown after 10 patients were excluded	Yes/not applicable/yes/not reported	No	Fair
Bertrand, 2000 Europe CLASSICS	Yes-except for the one that withdrew consent	Yes/ (1 withdrew consent before taking his first study med--not included in data) Not applicable/Not reported/Not reported	No	Good
Bhatt, 2006 International CHARISMA	No	Yes/not applicable/yes/yes	No. Follow-up with respect to the primary efficacy end points was complete in 99.5% of the C + ASA group and 99.6% of patients in the P + ASA group.	Good
CAPRIE Steering Committee, 1996 International	No	Yes/Yes/Yes/No	No	Good
Cure Investigators, 2001 International	No	Yes/not applicable/yes/unsure--reasons for withdrawal not reported	No	Good
Di Pasquale, 2005 Italy	No	Not reported/Not applicable/ Not reported/Not reported	Not reported-other than no one died	Fair

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Diener, 1996 13 countries	Yes	Yes	Yes	Yes
ESPRIT Study Group, 2006 14 countries-Europe/Australia	Telephone call, fax, or email to the central trial office.	Yes- computer-generated randomization codes stratified by hospital before the start of the trial. The randomization codes and randomization program were generated by a clinical epidemiologist at the Academic Medical Center of the University of Amsterdam who was not otherwise involved in the trial.	Yes	Yes
ESPS-2 Authors, 1997 13 countries	Yes-randomized to treatment groups according to a minimization technique which took into account the initial diagnosis	Yes-randomization was performed by a central computer, accessible to the centers day and night, and requiring the entry by the trialist of inclusion and exclusion criteria before allocating a randomization number to the pt.	Yes	Yes
Fiotti, 2003 Italy	No-method not reported	No-sealed envelope	No	Yes

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat (ITT) analysis?
Diener, 1996 13 countries	Yes	Yes	Yes	Yes
ESPRIT Study Group, 2006 14 countries-Europe/Australia	Treatment was not blinded. None of the investigators had any knowledge of event rates or complication rates according to treatment allocation.	No	No	Yes as well as on-treatment
ESPS-2 Authors, 1997 13 countries	Yes	Yes	Yes	Yes
Fiotti, 2003 Italy	No	No	No	No

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Post-randomization exclusions?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Quality Rating
Diener, 1996 13 countries	Unsure	Yes/Yes/Yes/No	No	Good
ESPRIT Study Group, 2006 14 countries-Europe/Australia	Yes--see #11 under Table A1	Yes/Not applicable/Yes/Yes	No	Fair
ESPS-2 Authors, 1997 13 countries	Unsure	Yes/Yes/Yes/No	Yes-see comments	Fair/good
Fiotti, 2003 Italy	No	Yes/Not applicable/Not reported/ Not reported	No	Fair/poor--not randomized, open-labeled, single centered,

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Gorelick, 2003 USA	Yes -1:1 and the sequence was stratified by site to balance the treatment groups. Local study site personnel called a automated telephone registration system to register a study participant	Yes	Yes	Yes
Hall, 1996 Italy and Japan	Yes-using a standard list of random numbers	Method not reported-did not indicate whether the standard list of random numbers were unreadable till allocation	No, incidence of total occlusions at baseline angiography was higher in the ASA group (15%) than in the T-ASA group 8%, p<.05. A higher percentage of pts had previous CABG or DM in T+ASA group (11%, 16% respectively) compared with ASA only group (3%, 6%) p= .02 and .01	Yes
Hass, 1989 North America TASS	Randomized by a private independent, nonprofit organization--randomization within each center was stratified on the basis of 3 factors: history of ischemic CV disease, occurrence of a moderate or major stroke >3 months before entry, and the pt's sex.	Not reported	Yes	Yes

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat (ITT) analysis?
Gorelick, 2003 USA	Yes-except of 1 statistician who developed the randomization algorithm	Yes	Yes	Yes
Hall, 1996 Italy and Japan	Not reported	No	No	Yes
Hass, 1989 North America TASS	Yes	Yes	Yes	Yes

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Post-randomization exclusions?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Quality Rating
Gorelick, 2003 USA	No	Yes/Yes/No/Not reported	Yes-15.2% in the Ticlopidine group and 13.3% ASA group lost to f/u or voluntary withdrawal	Fair/good
Hall, 1996 Italy and Japan	No	Yes/Yes/No/No=	No	Poor
Hass, 1989 North America TASS	Yes	Yes/Not applicable/Yes/Yes	3% ticlopidine (n=46) and 2% assigned to the ASA group, (n=38)	Good

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Juergens, 2004 Australia	Yes-sealed envelope system	No-sealed envelope	Yes	Yes-not in detail (successful stent deployed)
Leon, 1998 USA	Yes-used a prespecified randomization sequence to one of the 3 antithrombotic-drug regimens, according to clinical site and history of DM	Yes	Yes	Yes
Mehta, 2001 International PCI-CURE	Yes	Yes	Yes-although of note, before PCI, fewer pts on clopidogrel than on placebo had MI or refractory ischemia, p=0.008.	Yes
Mueller, 2003 Germany and Switzerland	Yes-pre-specified randomization sequence	Yes	Yes	Yes- "consecutive pts with successful stent implantation" were randomized

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat (ITT) analysis?
Juergens, 2004 Australia	No	No	No	Yes
Leon, 1998 USA	Yes-treatment was not blinded, but all end points were adjudicated by a clinical events committee whose members were unaware of the pts' treatment assignments.	No	No	Yes
Mehta, 2001 International PCI-CURE	344/1313 PC pts in the clopidogrel group and 329/1345 PCI patients in the placebo group took open label thienopyridine before PCI. Following PCI, open label continued for 2-4 weeks and then the double-blind therapy was resumed.	Yes, except during the open-label time after the PCI procedure	Yes	Yes
Mueller, 2003 Germany and Switzerland	Yes-treatment was not blinded, but all end points were adjudicated by a clinical events committee whose members were unaware of the patients' treatment assignments	No	No	Yes

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Post-randomization exclusions?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Quality Rating
Juergens, 2004 Australia	Unable to determine-- drug discontinuation occurred more often in the Ticlopidine group--including the composite of drug discontinuation, hemorrhage and vascular complications	Yes/Not reported/Not reported/No	No	Poor-not randomized, open-labeled, single centered, ? Allocation method, use of GP 2B/3An varied not only the agents but the frequency. LD of clopidogrel was 150mg instead of 300mg
Leon, 1998 USA	Yes-3 components were primarily responsible for the differences seen in the incidence of primary event: revascularization of the target lesion (p=0.002), angiographically evident thrombosis (p=0.004), and recurrent MI (p=0.01), there was also significant difference in the incidence of revascularization of the target lesion and angiographically evident thrombosis between the group assigned to ASA and T and either the group assigned to ASA only or the group assigned to ASA and W.	Not reported/Not applicable/ Not reported/Not reported	No	Fair
Mehta, 2001 International PCI-CURE	No	Yes/No/No/No	No	Good
Mueller, 2003 Germany and Switzerland	Unable to determine	Yes/Not applicable/Not reported/Not reported	No-	Fair/poor-not blinded

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Muller, 2000 Germany	No-unblinded	Yes-prespecified randomization sequence	Yes	Yes-successful implantation (<50% residual stenosis without acute complications in the catheter lab resulting in death or emergency CABG)
Patti, 2006 Italy ARMYDA-2	Randomization blocks were created and distributed to the 2 centers	Not reported	Age was significantly higher in the conventional loading dose vs. high loading dose p=0.027	Yes
Piamsomboon, 2001 Thailand	No- unblinded	Not reported	Mean lumen diameter in the ticlopidine groups was smaller than the clopidogrel group 2.75 ± 0.33 vs. 3.00 ±0.52, p= 0.01)	Yes
Rupprecht, 1998 Germany	Not reported	Not reported	Yes	Yes
Steinhuble, 2002 North America CREDO	Yes	Yes	Less use of statins and calcium channel blockers in the clopidogrel arm 53.5 vs. 57.3, p=.08; 25.5 vs. 29.4, p=.05 respectively	Yes
Taniuchi, 2001 USA	Method not reported other than it stated it used a randomized protocol	Method not reported	Yes except the C group had more thrombus on angiography than the T group p= 0.009	Yes-successful implantation (<20% residual stenosis, with TIMI2 or TIMI 3 flow) of an FDA-approved stent in a native coronary artery or in a CABG)

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat (ITT) analysis?
Muller, 2000 Germany	Yes-endpoints were adjudicated by a clinical-events committee whose members were unaware of the pts treatment assignments	No	Not reported	Yes
Patti, 2006 Italy ARMYDA-2	Yes	Yes	Yes	No
Piamsomboon, 2001 Thailand	Not reported	Not reported	Not reported	Yes
Rupprecht, 1998 Germany	No	No	No	No
Steinhuble, 2002 North America CREDO	Yes	Yes	Yes	Yes
Taniuchi, 2001 USA	No	No	No	Yes

Evidence Table 3. Quality assessment of randomized controlled trials (original and update 1 only)

Author, Year Country	Post-randomization exclusions?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Quality Rating
Muller, 2000 Germany	No	Yes/Not applicable/Not reported/No	No	Fair-unblinded and not powered to show SS difference in cardiac events
Patti, 2006 Italy ARMYDA-2	No	Yes/Not applicable/Yes/Yes	No	Good
Piamsomboon, 2001 Thailand	No	Not reported/No/Not reported/ Not reported	No	Poor
Rupprecht, 1998 Germany	Unable to determine	Not reported/Not applicable/ Not reported/Not reported	No	Poor
Steinhuble, 2002 North America CREDO	No	Yes/Not applicable/Yes/Yes	No	Good
Taniuchi, 2001 USA	Cardiac death occurred more frequently in the T group (1.53% vs. 0.61%) resulting in a higher overall rate of major adverse cardiac events (4.60% vs. 3.85%) at 30 day but neither differences reached SS.	Yes-1367 screened/1016 randomized; the primary end point, failure to complete 2 weeks of concurrent therapy with ASA was reached in 3.64% (19 pts) in the T group and in 1.62% (8 pts) in C group (p=0.043).	No	Fair

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Banerjee, 2008 U.S. Fair	Retrospective cohort	Clopidogrel Dosage: NR Median duration of exposure: 526 days	January 2004 to July 2006 Unclear (reported patients who underwent PCI at "our institution")	530
Berger, 2008 U.S. Fair	Retrospective cohort	Clopidogrel Exposure period: Jan 2004 to December 2006	November 2006-December 2007 Patient records at 14 U.S. hospitals	596

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Banerjee, 2008 U.S. Fair	Age: 65 (SD 9 years) Men: 98% Caucasian: 78% African American: 13% Other: 9% Hypertension: 89% Hyperlipidemia: 87% Tobacco use: 70% DM: 47% Renal failure: 16% Previous coronary artery disease: 49% Previous MI: 27% Previous heart failure: 20% Stable angina pectoris: 42% Acute coronary syndromes: 57% DES: 85% Bare metal stent: 10%	Clopidogrel use<1 yr vs clopidogrel use>1 yr Incidence of major bleeding: 5% vs 3.2%, p=0.24	NR	
Berger, 2008 U.S. Fair	Age: 64 years Male: 68.3% Caucasian: 87.8% DM: 36.1% Hypertension: 77.9% Congestive heart failure: 9.1% Previous CABG: 5% Previous MI: 23.8% Previous PCI: 24.2% COPD: 12.2% CVA:9.2% Current tobacco smoker: 27% Alcohol abuse: 5.0%	Group A vs Group B Patients with excessive or major bleeding: 34.5% vs 25.6%, p=0.049 Combined endpoint of major bleeding or reoperation: Clopidogrel exposure associated with significantly increased risk OR 1.55, (95% CI 1.00 to 2.41), p=0.048 Control for confounding -increased risk for major bleeding: OR 1.82 , 95% CI 1.11 to 3.01, p=0.02 Reoperation for bleeding complication: 4.7% vs 1.3% , p=0.049 CURE major bleeding: 53.8% vs 34.9%, p<0.001 TIMI major bleeding: 54.3% vs 46.9%, p=0.130	Astra Zeneca, LP	Group A: Exposure to clopidogrel within 5 days of surgical incision Group B: Clopidogrel naïve or exposure to Clopidogrel > 5 days prior to surgical incision

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Brulotte, 2007 Canada Poor	Retrospective cohort	A. Aspirin + Clopidogrel B. Aspirin + Warfarin C. Aspirin + Clopidogrel + Warfarin (CTT) Dosage: Aspirin max dose 325 mg, others NR	2002 to 2005 Medical charts of patients discharged from Quebec Heart Hospital	183

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Brulotte, 2007 Canada Poor	Age: mean 70.7 years (SD 11) Male: 70% Hypertension: 58% Congestive heart failure: 32% Coronary angiography: 80% Radial access: 90% Femoral access: 10% PCI with bare metal stent: 74% ASA dosage ≤81 mg 93%, 160mg 0.5% and 325 mg 6% PPI: 46% Mean (SD) duration of follow-up: 346 (403) days	Aspirin + Warfarin vs CTT Overall bleeding: 16% vs 3 %, p=0.03 Minor bleeding: 9% vs 0%, p=0.015 Major bleeding: 7% vs 3%, p=NS (Data from Aspirin + CTT), p=NS	NR	

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Charlot, 2010 Good	Retrospective cohort	Clopidogrel, PPI Dosage : NR Duration of exposure: 1 yr	2000-2006 National Patient Registry, Denmark	60393 (56406 patients claimed prescription of clopidogrel within 30 days of discharge and were included in the primary analysis)

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Charlot, 2010 Good	Patients receiving clopidogrel vs Propensity Score-matched Patients Receiving Clopidogrel (propensity score matched baseline covariates) Mean age: 65 years vs 67.4 years Male: 59% vs 61.7% Income group 1: 9.1% vs 11.8% Income group 2: 20.5% vs 17% Income group 3: 23.2% vs 24.1% Income group 4: 33.9% vs 25% Shock: 0.6% vs 0.9% Diabetes with complications: 4.3% vs 5.4% Peptic ulcer: 1% vs 0.6% PCI: 67% vs 61.1% Pulmonary edema: 0.7% vs 0.9% Cerebral vascular disease: 3.3% vs 4.1% Cancer: 0.3% vs 0.5% Cardiac dysrhythmias: 7.4% vs 8.9% Acute renal failure: 0.5% vs 0.7% Chronic renal failure: 1% vs 1.4% Loop diuretic: 28.2% vs 38.8% Spironolactone: 7.9% vs 11% Aspirin: 70.8% vs 66.2% Statin: 87.8% vs 85% Beta Blocker:86.6% vs 83.8% ACE Inhibitor: 52% vs 55.6% Diabetes medication: 11.5% vs 13.3%	Clopidogrel + PPI vs no PPI Risk reduction for gastrointestinal bleeding : 0.82 (95% CI 0.63 to 1.07) , p=0.140	Danish Medical research Council (grant 271-06-0572) and Danish Heart Foundation (Grant 10-04-R78-A2865-22586)	

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Gurbuz, 2006 Fair	Prospective cohort	A. Aspirin 81mg + Clopidogrel 75 mg B. Aspirin 325 mg Duration of exposure: Clopidogrel for 30 days in 186 patients and a mean of 33.6(SD12.0) mo in 139 patients. Follow-up period 37.7 (13.4)mo	NR	591
Hayashi, 2010 Japan Fair	Retrospective cohort	A. 75 mg clopidogrel QD + aspirin B. 200mg ticlopidine QD + aspirin Duration : 12 mo	Patients undergoing first PCI between January 2007 to April 2009 Patients database ,Ohashi Medical Center, Toho University	311

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Gurbuz, 2006 Fair	Age: 67.6 yrs (SD 10.7) Female: 36% End stage renal disease: 2.4% Unstable angina: 5.8% PVD: 3.4% Prior CABG: 5.9% Diabetes: 24.7% Hyperlipidemia: 55% EF<30%: 17.4% COPD: 6.6% Prior MI<1 wk: 29% Prior MI>1wk: 17.3% AHA Class III and IV: 17.8% Preoperative aspirin: 97.5% Preoperative clopidogrel: 2.9% Preoperative Canadian Cardiovascular Society angina classes I and II: 63.6% Preoperative Canadian Cardiovascular Society angina classes III and IV: 29.1%	Total 17 bleeding complications in 15 (2.5%) patients Clopidogrel Aspirin vs aspirin bleeding complications: 6(1.8%) vs 9 (3.3%) major: 2(0.62%) vs2(0.75%), p=NR minor: 5 (1.5%) vs 8(3%),p=NR	NR	
Hayashi, 2010 Japan Fair	Mean age: 69 years Women: 28% Region: 100% Japanese Unstable angina pectoris: 37% Stable angina: 63% DM: 39% Hypertension: 78.1% Hypercholesteremia: 60.5% Prior MI: 19% Prior coronary artery bypass surgery: 7.4% Hemoglobin, g/dl: Mean left ventricular EF: 64.5	Clopidogrel + Aspirin vs Ticlopidine + Aspirin Incidence of major bleeding at 30 days: 4.4% vs 3.9%, OR 1.12, 95% CI 0.31 to 4.14), p=0.94	NR	

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Hsiao 2009 Taiwan Good	Retrospective cohort	A. Clopidogrel with PPI B. Clopidogrel without PPI Duration (mean days): A=572.8, B=611.1	1/1/01 to 12/31/06, Taiwanese National Health Insurance database	A=590 B=2036
Karjalainen, 2007 Finland Poor	Retrospective cohort	A. Aspirin + clopidogrel B. (No Suggestions) C. Warfarin Aspirin D. Warfarin clopidogrel E. Warfarin monotherapy F. Clopidogrel monotherapy G. Aspirin monotherapy Dosage NR Duration: 12 mo	2003-2004 Computerized PCI databases	478
Leong, 2005 Australia Poor	Prospective cohort	A. Clopidogrel 75mg QD B. Clopidogrel 75 mg QD + Aspirin 150mg QD C. Aspirin 150mg QD Duration : NR	July 1, 2000 to June 30, 2003 Cardiac surgery database of patients undergoing CABG at the Flinders Medical Center	919

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Hsiao 2009 Taiwan Good	Mean age=71.6 years Men=59.6% Diabetes=41.8% Stroke=35.3% Myocardial infarction=19.3% PTCA=13.6% CABG=1.3% GI-related hospitalizations=0.63 Time from most recent GI hospitalization to initiation of antiplatelet therapy (mean days): 447.7	Recurrent major GI complications: A=141/590 (23.9%), B=438/2036 (21.5%) Hospitalization for major GI complications (HR adjusted for propensity score, with vs without PPI): 1.08 (0.89 to 1.33)	NR, but authors reported no conflicts of interest	
Karjalainen, 2007 Finland Poor	Mean age: 70 years Men: 74% Diabetes: 25% Current smoking: 26.2% Hypertension: 62% Previous heart failure: 14.6% Previous stroke: 13% Previous MI: 35.1% Previous PCI: 14.2% Previous CABG: 14.4% Acute STEMI: 11.5% Acute NSTEMI: 24.1% Unstable angina: 18.2%	(No Suggestions) vs Warfarin + aspirin vs Warfarin + clopidogrel vs Aspirin + clopidogrel % of major bleeding: 6.6% vs 6.1% vs 11.1% vs 11.8%, p=NS between groups	Finnish Foundation for Cardiovascular Research, Helsinki, Finland	
Leong, 2005 Australia Poor	Age: 63.6 years male: 76.2% DM: 30.7%	Clopidogrel vs aspirin vs both vs neither % reopening for bleeding (OPCABG): 0% vs 0% vs 0% vs 0% % reopening for bleeding (CABG): 0.0% vs 1.5% vs 3.4% vs 0.5%, p=0.33	NR	

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Petersen, 2010 U.S. Fair	Retrospective cohort	A. Clopidogrel high use≥344 days supply B. Clopidogrel medium use≥264 and ≤343 days supply C. ≥90 days supply and ≤264 days supply	Patients receiving drug eluting stent between January 1, 2003 to August 31, 2006 Administrative claims data, Healthcare Integrated Research Database	18939 9256 (alive and eligible at 12 mo follow-up-primary analysis cohort)

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Petersen, 2010 U.S. Fair	Baseline characteristics of patients weighted by the level of clopidogrel use Age: 57.7 years Male: 77% Prior procedures CABG: 1.3% PCI: 2.7% Comorbid conditions and risks Angina: 20.9% Cerebrovascular disease: 7.5% COPD: 7.3% Congestive heart failure: 6.5% DM: 24.9% Dialysis: 0.6% Dyslipidemia: 66% Hypertension: 45.7% Ischemic heart disease: 47.5% Malignancy: 5.4% Peripheral artery disease: 5.2% Prior MI: 8.3% Renal disease: 2.2% Medications at baseline ACE inhibitor: 25.0% Beta blocker: 32.4% Clopidogrel: 12.1% Statin: 39%	Risk of bleeding at 12 mo for low clopidogrel use: HR 0.77 (95% CI 0.65 to 0.90), p= 0.002 vs high clopidogrel use for medium clopidogrel use: HR 0.84 (95% CI 0.71 to 0.94), p=0.03 vs high clopidogrel use for high clopidogrel use: HR 1.00 Bleeding events during exposure were associated with bleeding events during follow-up at 12 mo: HR 2.79 , 95% CI 2.23 to 8.45, p<0.001 Use of statins during exposure period was associated with a lower rate of bleeding event HR 0.82 (95% CI 0.71 to 0.94), p=0.004 Use of beta blocker during exposure period and association with bleeding event: HR 0.88, 95% CI (0.77 to 1.01), p=0.08 Use of ACE inhibitor during exposure period and association with bleeding event: HR 1.01 (95% CI 0.88 to 1.17), p=0.84 Risk of bleeding at 6 mo Low clopidogrel use associated with low risk of bleeding events: HR 1.56, 95% CI 0.71 to 0.92, p=0.002 Risk of bleeding at 18 mo Medium clopidogrel use and its association with low risk of bleeding HR 0.74 (95% CI, 0.60 to 0.92), p=0.007 Low clopidogrel use and its association with low risk of bleeding HR 0.75 (95% CI 0.60 to 0.93), p=0.01	Duke University School of Medicine	

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Ray, 2010 U.S. Good	Retrospective cohort	Clopidogrel with or without PPIs including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole. Drug doses: NR Exposure period: 199 through 2005	NR Automated data of Tennessee Medicaid Program	20,596

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Ray, 2010 U.S. Good	Mean age: 60.5 years Male: 50.3% White: 78.1% AMI: 30.2% PCI with stent: 52.8% Non-drug-eluting stent: 47.1% Drug-eluting stent: 17.8% CABG: 12.6% <u>Previous GI or bleeding disease or medications associated with increased risk of bleeding</u> Peptic ulcer hospitalization: 3.7% Gastritis: 2.4% Esophageal disease: 15.9% Other upper GI disease: 1.7% Diverticulitis or diverticulosis: 1.6% Other lower GI disease: 4.3% GI bleeding: 11.5% Other bleeding: 2.3% Nonselective NSAID: 67.7% COX-2 selective NSAID: 20.5% Systemic corticosteroid: 28% Anticoagulant: 11.6%	Non-PPI vs PPI Bleeding hospitalization: Site of bleeding Gastroduodenal, events (%): 117 (12.2%) vs 63 (8.2%), HR 0.50 (95% CI, 0.39 to 0.65) Other GI, events (%): 76 (7.9%) vs 81 (10.5%), HR 0.99 (95% CI, 0.67 to 1.47) Other non-GI events, events (%): 32 (3.3%) vs 36 (4.7%) , HR 1.26(95% CI 0.68 to 2.34) <u>Gastroduodenal bleeding: PPI dose</u> Low: person-Years (Events) 974 (45) HR 0.48 (0.36 to 0.64) High: person-years (Events) 490 (14) HR 0.53 (95% CI, 0.32 to 0.89) <u>Gastroduodenal bleeding: Individual PPIs</u> Esomeprazole, Person-Years (events): 747 (5), HR: 0.43,(95% CI 0.18 to 1.07) Omeprazole, Person-Years (events): 704 (5), HR 0.43 (0.16 to 1.13) Pantoprazole, Person-Years (events): 4629 (34), 0.46 (0.33 to 0.63) Rabeprazole, Person-years (events): 288 (1), 0.25 (0.03 to 2.01) Lansoprazole, Person-years (events): 1096 (14), HR 0.71 (0.43 to 1.18)	Agency for Healthcare Research and Quality and National Heart, Lung and Blood Institute	

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Sibbing, 2010 U.S. Fair	Prospective cohort	600mg clopidogrel LD Dual antiplatelet regimen: 75mg clopidogrel QD and 100mg aspirin BID Duration : NR	February 2007 to April 2008 Patients recruited from Deutsches Herzzentrum (Munich, Germany)	1524
Sorensen, 2009 Denmark Good	Retrospective cohort	A. Aspirin B. Clopidogrel C. Vitamin K antagonist D. Aspirin + Clopidogrel E. Aspirin + Vitamin K antagonist F. Vitamin K antagonist + clopidogrel G. Triple therapy Dosage: NR Duration of exposure : 476.5 (SD 142.0) d	2000-2005 Nationwide registers from Denmark	40812

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Sibbing, 2010 U.S. Fair	Age: 67.4 years Female: 22.6% BMI: 27.5kg/m2 EF: 54.7 Serum creatinine: 1.02mg/dL Diabetes Mellitus: 28.2% Active smoker: 13.6% Arterial hypertension: 91.3% Hypercholesterolemia: 70.1% Family history of CAD: 42.1% Previous MI: 31.9% Previous bypass surgery: 14.6% Multivessel disease: 84.8% Non-STEMI/STEMI: 11.1%	CYP2C19wt/wt vs CYP2C19 wt/*17 vs CYP2C19*17/*17 Proportion of patients with 30-day incidence of TIMI bleedings (major or minor) : 2.5% vs 4% vs 7.8%, p=0.01 wt/*17 and *17/*17 versus wt/wt: OR, 1.80; 95% CI, 1.03 to 3.14 Proportion of patients with TIMI major bleeding : 0.6% vs 1.1% vs 1.3%, p=0.22 *17/*17 versus wt/wt: OR 2.04, 95% CI 0.68 to 6.12 wt/wt vs *17/*17: OR 2.39; , 95% CI 0.95 to 2.10 Results of a multivariable regression model combining TIMI major and minor bleeding as dependant variable CYP2C19*17 allele carriage: OR 1.85 (95% CI 1.19 to 2.86), p=0.006. Unadjusted OR for CYP2C19*17 allele carriage OR 1.80, 95% CI 1.03 to 3.14) Age (per 10-y increment): OR 1.57 (1.13 to 2.17), p=0.006 Sex: OR 1.31 (95% CI, 0.68 to 2.54),p= 0.42 Use of PPIs OR 1.21 (0.60 to 2.45), p=0.59 Clopidogrel loading interval (per 1-h increment) OR 1.00 (95% CI 0.99 to 1.02), p=0.70	Deutsches Herzzentrum, Munich, Germany (grant F 1.1-0.5, 984323	
Sorensen, 2009 Denmark Good	(Baseline represented by first drug exposure group) Age: 68 years % male: 63% Cerebrovascular disease: 5% Diabetes with complication: 5% Cardiac dysrhythmias: 10% Acute renal failure: 1% Chronic renal failure: 1% Malignant disease: 2% Shock 1% Pulmonary edema: 1% Previous bleeding: 5% PCI: 37%	Vitamin K antagonist alone vs Aspirin Vitamin K antagonist vs Clopidogrel + Vitamin K antagonist Incidence of non fatal and fatal bleeding (% per-person -year): 4.3% vs 5.1% vs 12.3% Adjusted NNH for fatal and non fatal bleeding : 165.9 vs 45.4 vs 15.2 Adjusted risk of non fatal and fatal bleeding: HR, (95% CI) 1.23 (95% CI 0.94 to 1.61) vs 1.84 (95% CI 1.51 to 2.23) vs 3.52 (95% CI 2.42 to 5.11)	Danish Heart Foundation (08-4-R64-A1885-B641-22470) and the Danish Medical Research Council (271-06-0572)	Harms data for only 3 treatment arms reported here. Please see publication for harms data on other treatment arms

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Yasuda, 2009 Japan Poor	Retrospective cohort	A. Aspirin 100mg/d + ticlopidine 100-200mg/d B. Aspirin 100mg/d + clopidogrel 50-75mg/d B. Aspirin + cilostazol 200-300mg/d mean duration of follow-up 15.8 mo	January 2006 to December 2007, Hospital records	243
Zeymer, 2008 Germany Poor	Prospective cohort	A. Aspirin B. Aspirin + Clopidogrel Dosage NR for 12 mo	2002-2004 The Acute Coronary Syndromes Registry	4290

Evidence Table 4. Data abstraction of observational studies

Author, year Country	Population characteristics	Harms	Funder	Comments
Yasuda, 2009 Japan Poor	Mean age: 68 years (range 36-88) Male: 75.3%	Aspirin + ticlopidine vs aspirin + clopidogrel vs aspirin + cilostazol % of patients with UGI bleeding events: 4% vs 0% vs 0%	NR	
Zeymer, 2008 Germany Poor	Age: 69.2% Women: 35% Prior MI: 24.5% Prior PCI or CABG: 18% Prior stroke: 10.1% DM: 46.4%	Clopidogrel Aspirin vs aspirin % increase in major bleeding complications: 5.4% vs 3.3, p<0.05	NR	

Evidence Table 5. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Banerjee, 2008 U.S.	Yes	No, No	Yes	Yes	Unclear; manual abstraction by trained abstractors, using standardized electronic data reporting form	Not for major bleeding; significantly more patients with diabetes at baseline in use ≥ 1 year (54% vs 35%; $P < 0.001$)	Yes	Fair
Berger, 2008 U.S.	No, patients in clopidogrel group had greater prevalence of prior CVA, MI, PCI	No, No	Yes	No	Unclear	Probably, but data not shown for logistic regression model for major bleeding	Unclear	Fair
Brulotte, 2007 Canada	No, 60% (277/460) were excluded for "main reasons" of inability to be reached by phone, drug regimen not fitting one of the groups when verified by pharmacist; significant baseline differences in prevalence of hypertension, history of coronary angiography, and follow-up duration	No, No	Yes	Yes	No; patients were contacted by phone to document bleeding and recall bias may have influenced this assessment	No	Yes	Poor
Charlot, 2010	Unclear: groups differed but did adjust	No, No	Yes	Yes	Unclear, don't know reliability of the database	Yes	Yes, 1 year	Good

Evidence Table 5. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Gurbuz, 2006	Only difference was longer follow-up for the no clopidogrel group (42.72 months vs 33.64 months; *P*= 0.001)	No, No	No for major bleeding	No	Unclear	No	Yes	Fair
Hayashi, 2010 Japan	Yes, no differences at baseline	No, No	Yes	No	Unclear	No	Unclear; 30 days	Fair
Hsiao 2009	Unclear, groups differed but did adjust	No, No	Yes	No	Unclear	Yes	Yes	Good
Karjalainen, 2007 Finland	Unclear, control group matched for age, sex, and disease, but more comorbidities in warfarin group	No, No	Yes	No	Unclear; potential for recall bias due to using patient phone calls to supplement outcomes not retrievable by chart	Not for subgroup comparisons of interest	Yes, 1 year	Poor
Leong, 2005 Australia	Unclear, groups differed	No, No	Yes	No	Unclear	No	Unclear; within 30 days of operation	Poor
Petersen, 2010 U.S.	Unclear: groups differed but did adjust	No, No	Yes	No	Unclear	Yes	Yes	Fair
Ray, 2010 U.S.	Unclear: groups differed but did adjust	No, No	Yes	Yes	Unclear, don't know reliability of the database	Yes	Unclear, "current use" of ≥ 1 day	Good

Evidence Table 5. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Sibbing, 2010 U.S.	Unclear; more active smokers in homozygous group	No, No	Yes	No	Unclear; data gathered from many sources by "specialized personnel", including phone follow-up to patient	Yes	Unclear, 30-day incidence	Fair
Sorensen, 2009 Denmark	Unclear; groups differed but did adjust	No, No	Yes	Yes	Unclear	Yes	Yes	Good
Yasuda, 2009 Japan	Unclear; 90 (17%) excluded because of being transferred to another hospital; 24 (5%) of exclusions unaccounted for; groups differed and no adjustment	No, No	Yes	No	Unclear	No	Unclear	Poor
Zeymer, 2008 Germany	Unclear; groups differed	No, No	No	Yes	Yes	No for major bleeding	No, in-hospital bleeding only	Poor

Evidence Tables 6. Data abstraction of systematic reviews

Author Year Country	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Berger, 2009 U.S.	To assess the efficacy of clopidogrel in men and women	1999 to May 2007	Prospective, randomized, placebo controlled, open or blinded trials. Assignment of participants to clopidogrel treatment and a placebo group. Data on all-cause mortality, cardiovascular death, MI, stroke and major bleeding.	79613	Randomized placebo controlled trials

Evidence Tables 6. Data abstraction of systematic reviews

Author Year Country	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Berger, 2009 U.S.	Age (range): 56.4 to 66.5 Caucasians: 81.8% to 91% % women: 20% to 39% BMI (kg/m2): 27.4 to 30.1 Current smoker: 14.4% to 52% Diabetes: 16.0 % to 45.6% Previous MI: 5.7% to 39.7% Cerebrovascular disease: 5.2 to 59.4 PVD: 4.1 to 9.8 Previous CABG: 7.4 to 23.2 Previous PCI: 2.0 to 31.1	Clopidogrel : 75 mg+ Aspirin 75mg to 325mg QD Placebo Duration: 2 weeks to 35 mo	Clopidogrel vs placebo All-cause mortality: Proportion, OR, 95% CI Men CREDO: 1.5% vs 2%, 0.75, (0.34 to 1.65) CURE: 5.6% vs 6.4%, 0.86, (0.71 to 1.04) CHARISMA: 4.9% vs 4.9%, 0.99, (0.84 to 1.18) Total men: Proportion NR, 0.91,(0.84 to 0.97) Women CREDO: 2.3% vs 3.0%, 0.74 (0.27 to 2.02) CURE: 6% vs 5.8%, 1.04 (0.82 to 1.32) CHARISMA: 4.5% vs 4.6% (0.75 to 1.30) Total women: Proportion NR, 0.99 (0.90 to 1.08) MI (Men) CREDO: 7% vs 8.6% 0.80 (0.55 to 1.16) CURE: 5.4% vs 6.8%, 0.76 (0.63 to 0.91) CHARISMA: 2.6% vs 2.8% 0.92 (0.73 to 1.16) MI(Women) CREDO: 5.8% vs 8.1%,0.70 (0.37 to 1.33) CURE: 4.9% vs 6.1%,0.79 (0.61 to 1.01) CHARISMA 1.8% vs 1.9%, 0.94 (0.61 to 1.43) Total women: Proportion NR, 0.81 (0.70 to 0.93)

Evidence Tables 6. Data abstraction of systematic reviews

Author Year Country	Subgroups	Adverse events	Comments
Berger, 2009 U.S.	NA	Clopidogrel vs placebo Major bleeding (Men) CREDO: 8.7% vs 6.9%, 1.29 (0.88 to 1.88) CURE: 3.5% vs 2.9%, 1.24 (0.96 to 1.60) CHARISMA: 1.7% vs 2.9%, 1.29 (0.95 to 1.75) Total men: Proportion NR, 1.22 (1.05 to 1.42) Major bleeding (Women) CREDO: 9.1% vs 6.1%, 1.54 (0.84 to 2.86) CURE: 4% vs 2.4%, 1.68 (1.21 to 2.34) CHARISMA: 1.5% vs 1.3%, 1.18 (0.72 to 1.92) Total women: Proportion NR, 1.43 (1.15 to 1.79)	This systematic review answers the 4th key question on subgroups. No other subgroup information discussed in the publication is relevant. Results from CLARITY and COMMIT studies not abstracted as the are not included in the report

Evidence Table 7. Quality assessment of systematic reviews

Author Year	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?
Berger 2009	Partly, no details provided about decision-making process	Yes	Partly, yes for assessment of blinding of outcome assessors, no for others	Yes	Yes