Drug Class Review
on
Newer Antiplatelet Agents

Final Report Update 1 Evidence Tables

January 2007

Original Report Date: November 2005
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	RCT, unblinded, multicenter	Consecutive pts. with successful stent implantation
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	DB, prospective randomized study	Consecutive pts. from March 1998 to January 2001 undergoing elective single vessel PTCA with stenting. Pt with Canadian Cardiac society Class-II stable angina pectoris and de novo lesions in large native coronary arteries.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	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	None	ASA 100mg every day for life. 86% on statins, Glycoprotein 2B/3A antagonist C 11%, T 7%, p 0.07
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	C 300mg loading dose (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	None	ASA 300mg daily. Study stated that all pts were on the standard treatment of stable angina but exact therapy not listed

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	Scheduled f/u visits at 6 mos and whenever clinically indicated thereafter. All pts were contacted by questionnaire to assess vital and functional status as well as major adverse cardiac events 2 yrs after enrollment of the last patient. If pts did not return a signed questionnaire or any uncertainties remained, a MD interviewed the patients and their family MD over the phone. All information derived from contingent hospital re-admission records or provided by the referring MD or by the output. clinic was reviewed. Definition of Outcome: Primary- CV death (any death for which there was no clearly documented non-cardiac cause. Secondary- composite of cardiac death and MI (typical CP at rest followed by an increase in CK and CK-MB 2XULN and 5X ULN after CABG OR new Q waves in the ECG.	C (65 ± 11); T (64±10) ; C 27% female and 73% male, T 26% female and 74% male; ethnicity not reported
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	Coronary angiography made by Judkins technique from right femoral artery, Coronary lesions were assessed by multiple orthogonal views with coronary angiography and visually evaluated for morphologic features similar to those reported by the ACC/AHA. Ballon angioplasty and stent implantation was performed by 3 different invasive cardiologists. 12 lead ECG just before and immediately after coronary stenting for exclusion of an acute ischemia. A significant ST-segment depression was defined as horizontal/down sloping depression of ST segment >0.1 mV and 0.08 s after the J point that persisted more than 1 min., blood sampling for cTnT--drawn from an antecubital vein just before and 12 h after the procedure and put in a heparinzed collection vial. --measure by "Cardiac T Quantitative" equipment (Boehriner Mannheim, Germany and evaluated within 20 min by "Cardiac Reader". Clinical f/u during the hospital stay with respect to procedure related MMI and major clinical events. Pts were observed during hospitalization period. Definition of primary end point was the procedure-related MMI (minor myocardial injury) assessed by cardiac troponin T (cTnT) at 12 h after procedure. Secondary end-point was major clinical events (death, AMI and repeat revascularization via either by-pass surgery or PTCA.)- followed during hospital stay as well as major or minor bleeding (not defined). Deaths = cardiac origin if associated with CHF, AMI or sudden cardiac death (<1 hr after symptom onset). AMI= new Q wave or the evaluation of a current injury (ST elevation) lasting >1 day and the development of a T wave change; new specific ST elevation or depression ≥1 mV and increase in serum CK, CK-MB activity.	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 not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	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	Number screened NR/ number eligible NR/ -see Muller original paper/ 700 enrolled and randomized	None
Atmaca et al., 2002 (38), Ankara, 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 hx for CAD: C group 30.1%, T group 26.6%, p=NS	Number screened not reported but assume it is 168 (consecutive pts); Number eligible168/number enrolled 168/158 randomized	10

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	**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)
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	**No outcome data reported.**

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	Monitored; Elicited by investigator Reported spontaneously by patient----f/u visits at 6 mos and whenever clinically indicated thereafter. Pts were contacted by questionnaire to assess vital and functional status as well as major adverse cardiac events 2 yrs after enrollment of the last patient. If questionnaire or any uncertainties remained, a MD interviewed pts and their family MD over the phone. All information derived from contingent hospital re-admission records or provided by the referring MD or by the outpatient clinic was reviewed. CK and CK-MB and ECG (along with pt's symptoms) were done to define if a MI after CABG occurred.	no adverse events reported
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	Monitored--ECG, blood sampling, clinical f/u, cTnT, angiography	Ticlopidine vs Clopidogrel Bleeding: 0.0% (0/75) vs 0.0% (0/83)

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Mueller C et al., 2003 (40), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	This was not a safety study	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 glybproprotein 2B/3A inhibition and reported a higher incidence of TSO (thrombotic stent ocllusion) 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 atorvastatn and simvastatin, which are also metabolized by the CYP-450 3A4 system.) This inhibitory effect has not been reported for T.
Atmaca et al., 2002 (38), Ankara, Turkey (fair)	0	

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Taniuchi et al., 2001 (41), USA (fair)	RCT per protocol, Prospective, single site, open-label administration of drugs--comprised of cases from 4 operators	Btw 9/9/98 and 11/14/99, 1,367 consecutive pts 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.
Muller C et al., 2000 (39), Germany (fair)	RCT, (using prespecified randomization sequence); single site; unblinded (all endpoints were adjudicated by a clinical-events committee whose members were unaware of the pt tx assignment	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

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Taniuchi et al., 2001 (41), USA (fair)	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.	None	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)
Muller C et al., 2000 (39), Germany (fair)	250mg twice a day T + 100mg ASA X 4 wks vs. 75mg C + 100mg ASA x 4 wks	None	GP 2B/3A-11 % in C vs. 7% in T; p=0.07

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Taniuchi et al., 2001 (41), USA (fair)	clinical f/u, blood test, angiography performed if stent closure occurred, pt reported	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
Muller C et al., 2000 (39), Germany (fair)	Clinical follow-up complete in 99.9% of the patients. Baseline angiograph and repeated to document TSO (thrombus stent occlusion). Surgery or prolonged U-guided compression and femoral artery dissection or occlusion requiring urgent Percutaneous or surgical tx was defined as a severe peripheral vascular event. For quantitative coronary angiography analysis, the CAAS II system (Pie Medical, The Netherlands) was used.	C group 65±11 years old, 26% female, 74% male; T group 64± 10 years, 26% female, 74% male. Ethnicity not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Taniuchi et al., 2001 (41), USA (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)	Number screened not reported/ number eligible not reported although had to have successful stent implantation (i.e. screened) to be randomized/number enrolled not reported/ 1016 randomized (522 T and 494 C).	2 pts stopped medication without an identified clinical reason; 1 from each arm of tx. 2 T pts stopped med due to reported rash-(not confirmed by PE). Additional pts had rash but were confirmed on PE ? stopped med
Muller C et al., 2000 (39), 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	Number screened not reported/ number eligible not reported/793 underwent stents (enrolled); 700 randomized; clinic f/u was complete for 699	Not Reported

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Taniuchi et al., 2001 (41), USA (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)
Muller C et al., 2000 (39), 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 occulsion: 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Taniuchi et al., 2001 (41), USA (fair)	
Muller C et al., 2000 (39), Germany (fair)	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

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Taniuchi et al., 2001 (41), USA (fair)	Monitored and Reported spontaneously by patient---clinical follow-up; self-reported; surgery in one case for major access site bleeding, blood counts; probably angiography if stent closure occurred	Ticlopidine vs Clopidogrel Bleeding: 0.4% (2/522) vs 0.4% (2/494) Gastrointestinal: 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)
Muller C et al., 2000 (39), Germany (fair)	Monitored and Reported spontaneously by patient-Clinical follow-up, blood test, observation, pt reporting, quantitative coronary angiography analysis, CAAS II system was used	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)

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Taniuchi et al., 2001 (41), USA (fair)		Occurrence of both acute closure (within 24 hrs of implantation) and subacute stent thrombosis (day 1-30) were essentially equal for the 2 tx 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.
Muller C et al., 2000 (39), Germany (fair)		

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Leon et al., 1998 (45), USA (fair)	RCT, Multicenter; un-blinded. Also had a parallel arm registry within the study	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.
Bertrand et al., 2000 (14), USA, CLASSICS (good)	RCT, DB, Multicenter, parallel-group	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

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Leon et al., 1998 (45), USA (fair)	All pts received nongeneric, 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.	Pts who did not meet the criteria for successful stenting were enrolled in a prospective trial that was identical to the randomized trial in terms of data collection and f/u except pts were not assigned to a specific drug-tx strategy	Not reported
Bertrand et al., 2000 (14), USA, CLASSICS (good)	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)	None	See Exclusion Criteria

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Leon et al., 1998 (45), USA (fair)	Detailed case-report forms completed by clinical coordinator at each site; monitored by independent study monitors and submitted to the data-coordinating centers. Angiograms, assessed for AE at discharge and then 4 wks post stenting. All events were classified by an independent clinical events committee whose members were unaware of the pts' tx assignments.	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 not reported
Bertrand et al., 2000 (14), USA, CLASSICS (good)	A Critical Event Adjudication Committee validated all potential outcome events --only validated events were analyzed. The primary end point was the incidence of any one of the following validated events occurring during the study drug treatment period between visits 1 and 4 or until discontinuation of study drug 1. major peripheral or bleeding complications including false aneurysms, surgical repair of puncture site complications, blood transfusion (≥2 U of blood), intracranial bleeding, retroperitoneal bleeding, overt hemorrhage with a decrease of Hgb ≥ 3 g/dL compared with BL) 2. neutropenia -(< 1.5 x 109/L) 3. thrombocytopenia-plt < 100 x 109/L 4. early discontinuation of study drug because of noncardiac adverse event (including death of noncardiac origin)	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.

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Leon et al., 1998 (45), USA (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	1965 pts with 2147 lesions were enrolled (screened) between 2/96 and 11/96.1653pts with 1772 lesions eligible and were randomized. The remaining 312 pts with 375 lesion s were enrolled in a parallel registry.	0
Bertrand et al., 2000 (14), USA, CLASSICS (good)	Overall: HTN 49.9%; DM (11.3%); former or current smoker 69%, tx for hypercholesterolemia (57%);previous stable angina (55.8%)	Number of patients screened not reported/number eligible not reported/1021 enrolled/1020 randomized	1

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Leon et al., 1998 (45), USA (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)
Bertrand et al., 2000 (14), USA, 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Leon et al., 1998 (45), USA (fair)	
Bertrand et al., 2000 (14), USA, CLASSICS (good)	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)

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Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Leon et al., 1998 (45), USA (fair)	Monitored-detailed case-report by the clinical coordinator at each site, monitored by independent study monitors, angiograms were submitted to the angiographic core lab and analyzed with a computer-based system. pts assess at discard and 4 wks after stenting. All events were classified by an independent clinical events committee, blood tests, EC, procedure-related bleeding episode requiring transfusion	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)
Bertrand et al., 2000 (14), USA, CLASSICS (good)	Monitored at weekly visits	Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg Allergy: 1.2% (4/340) vs 0.00% (0/335) vs 0.00% (0/345) Gastrointestinal 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Leon et al., 1998 (45), USA (fair)		No significant difference in the risk of neutropenia or thrombocytopenia btw the groups
Bertrand et al., 2000 (14), USA, CLASSICS (good)	T: 28, C: 17, C (LD): 7	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Hall, 1996 (43), Japan, Italy (poor)	randomized, single-center conducted between Jan 1994 and Mar. 1995. parallel univariate risk analysis of the CAPRIE trial	Coronary artery disease 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 stensosis >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 appostion to the vessel wall with good plaque compression. The quantitative criterion for stent expansion used was the achievement of an intrastent 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 Cariodlogy Cook), Wiktor (Medtronic, Inc), Micro (Applied Vascular Engineering) Wall (Schneider Inc), and the Cordis (Cordis Corp) stents.
Diener, 2004 (19), Europe, USA (good)	DB, RCT, centers (stroke units and neurology departments) in 28 countries (507 centers). Study conducted between Dec. 2000 and Apr. 2002.	ischemic stroke or TIA in the previous 3 months and had one or more 5 additional risk factors-previous ischemic stroke, previous MI, angina pectoris, DM or symptomatic PAD-within the previous 3 years.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Hall, 1996 (43), Japan, Italy (poor)	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)	None	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.
Diener, 2004 (19), Europe, USA (good)	ASA 75mg per day + clopidogrel 75mg daily vs. placebo and clopidogrel 75mg daily x 18 months. (patients were already taking clopidogrel prior to entering into the study)	None	80% of pts were receiving ASA

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Hall, 1996 (43), Japan, Italy (poor)	Clinical f/u was performed by telephone contact of all pts within 1-4 mos of hospital discharge. Short term complications (stent thrombosis) were assessed continually through regular and uniform contact of all pts within 4 wks of hospital discharge and 2 mos later. Comparison of clinical events and medication side effects within the first month after a successful stent procedure was performed. Angiographic data were obtained for all lesions at 1 month and quantitative intravascular US measurements performed for all lesions. Coronary angiograms were analyzed without knowledge of the intravascular ultrasound data by experienced angiographers not involved in the stenting procedure. a central validation committee was blinded to tx assignment adjudicated all outcomes	ASA group 58 years old ±10; 89% male and 11% female. T + ASA group 57 years old ± 9; 88% male and 12% female. Ethnicity not reported
Diener, 2004 (19), Europe, USA (good)	f/u visits were scheduled at 1,3,6,12,and 18 months. Visits were supplemented by monthly follow-up telephone calls to pts.	ASA + C group: 66.5 years old ± 9.9; 37% women and 63% men. Placebo + C group: 66.1 years old ± 9.9; 37% women and 63% men Ethnicity not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Hall, 1996 (43), 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	Number screened not reported/number eligible not reported/number enrolled not reported although stated stent deployment attempted in 358/226 randomized	
Diener, 2004 (19), Europe, USA (good)	27% (ASA + C) vs. 26% (P + C) previous ischemic stroke before qualifying event; 5% in both group previous MI; 10% in each group with PAD, 68% in both groups with DM, 48 and 47% past or current smoker. The most prevalent risk factor at randomization were HTN (78%); DM (68%); and hypercholesterolemia (56%). 26% had previous ischemic stroke and 19% had TIA. Most patients (79%) had one additional risk factor and 20% had two or more. Most pts had lacunar strokes due to microangiopathy, which might not be of pure atherothrombotic origin.	Number screened not reported/number eligible not reported/ number enrolled not reported/ 7599 randomized. At 18 months of f/u- data was available for 7276 pts (96%)	4 lost to f/u- ASA + C group; 9 lost to f/u in P + C group. 270 pts in both group discontinued treatment for a reason other than endpoint or adverse event

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Hall, 1996 (43), 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)
Diener, 2004 (19), Europe, USA (good)	**Clopidogrel + Aspirin vs Clopidogrel + Placebo** *Outcomes at 18 months* MI (fatal or not): 1.6% (59/3797) vs 1.6% (62/3802) RR = 0.95 (0.67, 1.36) Ischemic stroke (fatal or not): 7.9% (299/3797) vs 8.4% (319/3802) RR = 0.94 (0.81, 1.09) Other vascular death: 1.8% (69/3797) vs 1.9% (74/3802) RR = 0.93 (0.67, 1.29) Rehospitalization for acute ischemic event: 4.5% (169/3797) vs 4.8% (181/3802) RR = 0.93 (0.76, 1.15)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Hall, 1996 (43), Japan, Italy (poor)	
Diener, 2004 (19), Europe, USA (good)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Hall, 1996 (43), Japan, Italy (poor)	Monitored	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)
Diener, 2004 (19), Europe, USA (good)	Monitored	Clopidogrel + Aspirin vs Clopidogrel + Placebo Life-threatening bleeding: 2.6% (96/3759) vs 1.3% (49/3781) Fatal-bleeding: <1.0% (16/3759) vs <1.0% (11/3781) Non-fatal bleeding: 1.0% (38/3781) vs 2.0% (81/3759) Symptomatic intracranial: 1.0% (25/3781) vs 1.0% (40/3759) Primary intracranial hemorrhage: 1.0% (32/3759) vs <1.0% (17/3781) Major bleeding: 1.9% (73/3759) vs 0.6% (22/3781)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Hall, 1996 (43), Japan, Italy (poor)		
Diener, 2004 (19), Europe, USA (good)		Ongoing trials: CHARISMA -C + ASA along in primary and secondary prevention (Cerbrovasc Dis 2004; 17(suppl 3): 11-16. FASTER pts with CV disease of different causes : acute TIA and minor ischemic stroke; SPS3-lacunar strokes in Secondary Prevention of Small Subcortical Strokes and ischemic strokes arising from aortic arch plaques in ARCH. (no references for these last trials were provided)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Gorelick et al., 2003 (52), USA (fair/good)	RCT, DB, multicenter between Dec. 1992 and Oct 2001 with 2 year f/u	African American race; 29-85 years of age with a noncardioembolic 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 tx program.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Gorelick et al., 2003 (52), USA (fair/good)	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	None	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Gorelick et al., 2003 (52), USA (fair/good)	Laboratory studies: BUN, plt ct, CBC, serum Cr, lipid panel, bilirubin, ALT, AST, LDH, alkaline phosphatase; serum glucose, electrolytes, and UA. before entry, at 12 and 24 mos, and at any time a pt experienced an outcome event or terminated from the trial. CBC and plt count were performed every 2 wks during the first 3 mos of the study or at any unscheduled time the local investigative team deemed it was indicated. Study participants were examined in person at baseline, every 2 wks during the first 3 months, and at 6, 10, 12, 16, 20 and 24 months; and at any unscheduled time the investigative team deemed it was indicated for pt safety, medication compliance, or the occurrence of outcome events or SAEs. Telephone contact was made during study months for which pts did not have an in-person exam to screen for med compliance, outcome events, and SAEs. A predetermined lab "panic value" system whereby the main lab noticed the local investigative team and the clinical safety monitor of a critical value; an internal in house safety committee; and an external data safety and monitoring board appointed by the NIH.	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

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Gorelick et al., 2003 (52), USA (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.	Number screened not reported/number eligible not reported/number enrolled not reported/1809 randomized	15.2% in ticlopidine treatment group and 13.3% ASA group

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Gorelick et al., 2003 (52), USA (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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Gorelick et al., 2003 (52), USA (fair/good)	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Gorelick et al., 2003 (52), USA (fair/good)	Monitored	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Gorelick et al., 2003 (52), USA (fair/good)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
CAPRIE Steering Committee, 1996 (22), International (good)	RCT, blinded; multicenter conducted btw Mar. 1992 and Feb. 1995.	dx 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.
Diener et al., 1996 (18), *I*nternational, ESPS-2 (good)	RCT, 2x2 factorial, DB, PC, multicenter trial at 59 sties in 13 countries between 2/89 and March 1995	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
CAPRIE Steering Committee, 1996 (22), International (good)	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)	use of anticoagulants or antiplatelet drugs were discontinued before randomization and thrombolytic treatment should not have been received within the previous 48 hours.	Not reported
Diener et al., 1996 (18), *I*nternational, ESPS-2 (good)	ASA 50mg; dipyridamole SR (Persantine Retard) 200mg twice a day; ASA/DP, placebo x 2 years	None	Not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
CAPRIE Steering Committee, 1996 (22), International (good)	F/u visit was monthly for the first 4 months and every 4 mos thereafter. Information on AE, use of study drug and concomitant meds, blood for hematological and biochemical assessment made by 1 of 3 central laboratories. Compliance was assessed by counting returned tablets. Human safety data on clopidogrel--weekly assessment of blood counts and 2-wkly assessments of biochemistry during the first 3 mos. After 500 pts were entered, a blinded review of these data by steering committee did not show any cause for concern, so the frequency of these assessment was halved. Alert values of <1.2 x 10 9/L for neutrophils and <100x 109/L for platelets were established whereby investigators were to begin daily complete blood counts. If cts < 0.45 x 10 9/L or 80 x 10 9/L for neutrophils and platelets respectively the study drug was to be permanently DCs.	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.
Diener et al., 1996 (18), *I*nternational, ESPS-2 (good)	General medical examination was performed and included BP measurement and electrocardiogram.	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%

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
CAPRIE Steering Committee, 1996 (22), International (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	Number screened not reported/ number eligible not reported/ number enrolled/not reported/19185 randomized	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
Diener et al., 1996 (18), *I*nternational, ESPS-2 (good)	Diabetes: 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%	#screened-not reported, # eligible-unknown; 7054 enrolled and randomized; 6602 pts analyzed (438 pts omitted- 1 center excluded due to serious inconsistencies). Statistical analyses were performed for the original 7054 data base as well as the 6,602 patient data base.	see above

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
CAPRIE Steering Committee, 1996 (22), International (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)
Diener et al., 1996 (18), *I*nternational, 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
CAPRIE Steering Committee, 1996 (22), International (good)	
Diener et al., 1996 (18), International, ESPS-2 (good)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
CAPRIE Steering Committee, 1996 (22), International (good)	Monitored	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)
Diener et al., 1996 (18), International, ESPS-2 (good)	Monitored	same adverse events as 268

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
CAPRIE Steering Committee, 1996 (22), International (good)		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%.
Diener et al., 1996 (18), *I*nternational, ESPS-2 (good)		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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
ESPS-2 authors, 1997(55), International, ESPS-2 (good)	Randomized, 59 clinical centers in 13 European between 2/89 and 3/95	All pts had experienced a recent (within the preceding 3 months) ischemic CVA episode as a qualifying event

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
ESPS-2 authors, 1997(55), International, ESPS-2 (good)	Placebo, ASA 50mg; modified release dipyridamole 400mg used alone or in combination x 2 years	None	Not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
ESPS-2 authors, 1997(55), International, ESPS-2 (good)	Patient reporting; all adverse events were recorded by the investigator at each follow-up visit. Patient compliance--measurement of plasma salicylic acid (SA) and DP concentrations in randomly selected pt (15%); pt questioning as to taking the prescribed drug regularly; counting of residual capsules in the packages used by the pt. laboratory: leucocytes, erythrocytes, plt, HCT, HG, SR, BUN, Cr, Uric acid, FBS, TC, LDL and fibrinogen were measure at entry, after 12 months and 24 months.	< 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 not reported. Report does provide breakdown of those between 50-59, 60-69 and 70-79.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
ESPS-2 authors, 1997(55), International, ESPS-2 (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	# screened/eligible not reported. 7054 were randomized. 6602 pts data were analyzed for final report	138 cases (2.1%) were either misdiagnosed or not included into the study--4 tx 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. Tx cessations were 7.2% more frequent in the 2 DP groups 29.2% than in the non-DP groups (22.0%).

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
ESPS-2 authors, 1997(55), International, ESPS-2 (good)	**Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo** (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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
ESPS-2 authors, 1997(55), International, ESPS-2 (good)	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
ESPS-2 authors, 1997(55), International, ESPS-2 (good)	Monitored; Reported spontaneously by patient	Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
ESPS-2 authors, 1997(55), International, ESPS-2 (good)		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 tx 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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Juergens et al., 2004 (37), Australia (poor)	RCT, not blinded	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.
Mehta, 2001 (15), International, PCI-CURE (good)	RCT then 2-4 week open-label following PCI and then resumed double blind treatment for a mean of 8 months	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Juergens et al., 2004 (37), Australia (poor)	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	None	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.
Mehta, 2001 (15), International, PCI-CURE (good)	clopidogrel 300mg x 1 loading dose and then 75mg daily + ASA 75mg-325mg daily vs. matching placebo + ASA 75mg-325mg daily x 3-12 months (mean of 8 months)	None	Glycoprotein 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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Juergens et al., 2004 (37), Australia (poor)	30 day MACE, clinical f/u	Ticlopidine group: mean age 60 ± 10; male%/female% 80/20. In clopidogrel group: mean age 60± 12; male% female% 71/29. Ethnicity not reported
Mehta, 2001 (15), International, PCI-CURE (good)	MI defined as the presence of at least 2 of the 3 following: ischemic symptoms; cardiac enzyme concentration at least 3X ULN if within 48 h of PCI, and 2X ULN thereafter; or new ECG changes compatible with MI. Urgent target-vessel revascularization within 30 d of PCI was defined as a second PCI or any coronary artery bypass graft procedure done on a non-elective basis in the target vessel because of recurrent myocardial ischemia. Death, MI, refractory ischemia, and major and life-threatening bleeding were adjudicated by a committee blinded to treatment. Mean follow-up = 8 mos post-PCI. Follow-up assessments will occur at baseline, hospital discharge, and at 1 month and 3 mos (with additional f/u visits at 6, 9, and 12 mos for pts randomized early in the study per CURE Study Investigators (see Eur Heart J 2000; 21: 2033-2041) Of note, (information provided in the rationale, design and baseline characteristic article for CURE trial (Eur Heart J 2000; 21: 2033-2041), and independent Data and Safety Monitoring Board (DSMB) monitored the progress of all aspects of the study. For efficacy, the co-primary outcomes will be monitored us	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 not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Juergens et al., 2004 (37), 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	Number of pts screened not reported/number eligible not reported/number/enrolled and randomized 307	0
Mehta, 2001 (15), 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	Number screened not reported /(12562 pts were randomized into CURE) 2658 pts of the CURE population underwent PCI and were eligible/2658 were enrolled/randomized-N/A	0 drop-outs/0 lost to f/u/analyzed

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Juergens et al., 2004 (37), 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)
Mehta, 2001 (15), International, PCI-CURE (good)	**Clopidogrel vs Placebo** *Outcomes at 30 days* CV death, myocardial infarction, 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Juergens et al., 2004 (37), Australia (poor)	
Mehta, 2001 (15), International, PCI-CURE (good)	*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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Juergens et al., 2004 (37), Australia (poor)	Monitored, Reported spontaneously by patient. dx of recurrent MI- increase of >30% in the CK concentration above baseline. CK and CK-MB measurements were performed routinely on all pts the morning after the procedure and more frequently if there was a clinical suspicion of an adverse cardiac event. Occurrences of thrombotic stent occlusion (TSO), defined angiographically as total occlusion of the stented segment, were also note. Routine blood count analysis was not performed as part of the trial after hospital discharge, but when incidental blood tests were performed, results were ascertained. Pt were contacted by telephone at 2 wks and 4 wks to assess the presence of any adverse events.	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) Gastrointestinal: 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)
Mehta, 2001 (15), International, PCI-CURE (good)	Monitored- Major bleeding was defined as bleeding that was significantly disabling, intraocular, or requiring at least 2 units of blood. Major bleeding was subclassified as life threatening if it was fatal, if it led to a decrease in hemoglobin concentration of 50 g/L, if it caused significant hypotension requiring IV inotropes or surgical intervention, if it resulted in symptomatic intracranial hemorrhage, or if it necessitated transfusion of 4 or more units of blood. Monitor bleeding was defined as other bleeding that led to interruption of study medication. Major and life-threatening bleeding (as well as death, Mi, refractory ischemia) were adjudicated by a committee that were blinded to treatment.	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Juergens et al., 2004 (37), Australia (poor)		
Mehta, 2001 (15), International, PCI-CURE (good)		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 glycoprotein 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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)	RCT,one-center	June 1999-December 2000-symptomatic coronary artery disease 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
Cure Trial Investigators, 2001 (15), International, CURE (good)	RCT, DB, PC between Dec. 1998 and Sept. 2000, multicenter, international. See #117 for rationale, design and baseline characteristics	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)	Clopidogrel 300mg loading dose 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.	None	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.
Cure Trial Investigators, 2001 (15), International, CURE (good)	clopidogrel 300mg loading dose 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.	None	Medications at time of randomization: 66% on ASA, 37% ACE inhibitor, 58.6% BB, 28.3% calcium-channel blockers, 25.4% lipid-lowering agents

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)	An on-line quantitative angiographic analysis system was used to analyze the coronary artery pre and post-procedure. Follow-up with referring physician at 4 weeks after procedure for clinical assessment and completed blood count.	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 not reported
Cure Trial Investigators, 2001 (15), International, CURE (good)	Follow-up assessments occurred at discharge, at one or three months, and then every 3 months until the end of the study.	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 not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Piamsomboon et al., 2001 (35), Bangkok, 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	Number screened not reported/ number eligible not reported/ 68 enrolled/ 68 randomized	0 withdrawn or lost to f/u
Cure Trial Investigators, 2001 (15), 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	Number screened not reported/number eligible not reported/number enrolled not reported/12,562 randomized	6 pts in the clopidogrel and 7 pts in the placebo lost to follow-up

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)	**Ticlopidine + Aspirin vs Clopidogrel + Aspirin** *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)
Cure Trial Investigators, 2001 (15), International, CURE (good)	**Clopidogrel vs Placebo** *Outcomes at a 12 months* Nonfatal MI, stroke, or death from cardiovascular cause: 9.3% (582/6259) vs 11.4% (719/6303) RR = 0.82 (0.73, 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 = 0.88 (0.81, 0.95); NNT = 40 (28, 104) Death from cardiovascular causes: 5.1% (318/6259) vs 5.5% (345/6303) RR = 0.93 (0.80, 1.10) MI: 5.2% (324/6259) vs 6.7% (419/6303) RR = 0.78 (0.68, 0.90); NNT = 68 (44, 155) Q-wave MI: 1.9% (116/6259) vs 3.1% (193/6303) RR = 0.61 (0.48, 0.76); NNT = 83 (57, 150) MI non-q-wave: 3.5% (216/6259) vs 3.8% (242/6303) RR = 0.90 (0.75, 1.08)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)	
Cure Trial Investigators, 2001 (15), International, CURE (good)	Stroke: 1.2% (75/6259) vs 1.4% (87/6303) RR = 0.87 (0.64, 1.18) Refractory ischemia: 8.7% (544/6259) vs 9.3% (587/6303) RR = 0.93 (0.83, 1.04) Refractory ischemia during initial hospitalization: 1.4% (85/6259) vs 2.0% (126/6303) RR = 0.68 (0.52, 0.89); NNT = 156 (92, 521) Refractory ischemia after discharge: 7.6% (459/6259) vs 7.6% (461/6303) RR = 1.00 (0.89, 1.14) Death from noncardiovascular causes: 0.7% (41/6259) vs 0.7% (45/6303) RR = 0.92 (0.60, 1.40)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)	Monitored- Patients were instructed to attend f/u with their referring MD at 4 weeks after the procedure for clinical assessment and complete blood count. Clinical assessment was done ever 8 weeks. Acute stent thrombosis-thrombotic stent closure within 24 hours after the stent implantation. Subacute stent thrombosis was defined as thrombotic stent closure more than 24 hours after the stent implantation. Major CV events were defined as CV death, stroke, acute nonfatal MI and unstable angina. Acute MI was diagnosed when there were two of the following: characteristic ischemic pain for ≥ 20 minutes, elevation of C, CK-MB more than twice the upper limit, and new electrocardiographic change. Mj bleeding was defined as bleeding which required blood transfusion. Restenosis was defined as a diameter stenosis more than 50%	Ticlopidine + Aspirin vs Clopidogrel + Aspirin At 1 month follow-up 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)
Cure Trial Investigators, 2001 (15), International, CURE (good)	Monitored-Data were periodically reviewed by an independent data and safety monitoring board. All primary outcomes and life-threatening and mj bleeding complications were adjudicated	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Piamsomboon et al., 2001 (35), Bangkok, Thailand (poor)		
Cure Trial Investigators, 2001 (15), International, CURE (good)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Steinhuble et al., 2002 (16) North America, CREDO (good)	RCT, DB, PC between June 1999 through April 2001	symptomatic coronary artery disease 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
Hass et al., 1989 (20), North America, TASS (good)	RCT, MC	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Steinhuble et al., 2002 (16) North America, CREDO (good)	3-24 hrs before PCI: 300mg loading dose 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	None	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
Hass et al., 1989 (20), North America, TASS (good)	Ticlopidine 250mg twice a day or ASA 1300mg daily x2-6 years	None	Not reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Steinhuble et al., 2002 (16) North America, CREDO (good)	Follow-up assessment was performed on days 2, 28, 60, 180, 270 and 365 following randomization	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
Hass et al., 1989 (20), North America, TASS (good)	Follow-up one month after randomization and then at 4 month intervals throughout the trial. Patients were questioned about new symptoms, new medical problems, ADR, compliance. Blodd and urine samples were obtained. During the first three months, CBC were done every 2 weeks	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Steinhuble et al., 2002 (16) 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	17898 screened/2116 eligible/2116 enrolled/2116 randomized	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)
Hass et al., 1989 (20), 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	8814 screened/3069 eligible/3069 enrolled/3069 randomized	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

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Steinhuble et al., 2002 (16) 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)
Hass et al., 1989 (20), 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Steinhuble et al., 2002 (16) North America, CREDO (good)	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)
Hass et al., 1989 (20), North America, TASS (good)	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 myocardial infarction: 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Steinhuble et al., 2002 (16) North America, CREDO (good)	Monitored: All potential events were identified by site investigators or through screening of protocol-specified ECGs and laboratory test, blinded to treatment assignments. An independent clinical events committee, also blinded to treatment assignment, adjudicated all outcome events, and all analyses were based on the committee's classification of the end points.	Clopidogrel vs Placebo Major bleeding: 8.8% (93/1053) vs 6.7% (71/1063) 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) nvs 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)
Hass et al., 1989 (20), North America, TASS (good)	Not reported	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) Gastrointestinal pain: 7.2% (110/1518) vs 10.0% (153/1527) Gastritis: 0.9% (13/1518) vs 1.7% (26/1527) Gastrointestinal 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Steinhuble et al., 2002 (16) North America, CREDO (good)		
Hass et al., 1989 (20), North America, TASS (good)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Rupprecht et al., 1998 (44), Germany (poor)	R, single center	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

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Rupprecht et al., 1998 (44), Germany (poor)	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	None	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Rupprecht et al., 1998 (44), Germany (poor)	Laboratory studies immediately after randomization, on day 7 and on day 14 of treatment. Platelet aggregation, platelet cont and platelet activation (evaluated by flow cytometry measurement) were done as well as fibrinogen binding.	Age Group A: 59 ±8; 76% male, 24% female, Ethnicity, not reported. Group B: 59±10; 70% male, 30% female, Ethnicity not reported. Group C: 59±9; 75% male, 25% female, Ethnitic not reported.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Rupprecht et al., 1998 (44), Germany (poor)	Group A: 19% diabetes; 48% hypercholesterolemia, 33% smoker, 19% previous MI, 19% previous PTCA, 10% unstable angina, 38% unstable angina. Group B: 20% diabetes, 40% HTN, 45% hypercholesterolemia,40% smoker, 25% previous MI, 15% previous PTCA, 5% previous CABG, 45% unstable angina. Group C:15% diabetes, 45% hypertension, 40% hypercholesterolemia, 35% smoking, 20% previous MI, 15% previous PTCA, 10% previous CABG	Unknown/unknown/unknown/61	Unknown

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Rupprecht et al., 1998 (44), Germany (poor)	**No outcome data reported.**

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Rupprecht et al., 1998 (44), Germany (poor)	**No outcome data reported.**

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Rupprecht et al., 1998 (44), Germany (poor)	Monitored	one major bleeding event with a drop in Hgb concentration by 4mg/dL at groin puncture site of one patient in group C

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Rupprecht et al., 1998 (44), Germany (poor)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
ESPRIT Study Group, 2006(21) International, ESPRIT (fair)	RCT, MC, open, non-blinded between July 1, 1997 and Dec 31, 2005	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
ESPRIT Study Group, 2006(21) International, ESPRIT (fair)	Combination therapy of ASA and dipyridamole and ASA alone. Dose of dipryridamole 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)	None	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
ESPRIT Study Group, 2006(21) International, ESPRIT (fair)	Patients returned every 6 months for a consultation with their randomizing MDs or a trained trial nurse. If not possible, follow-up information was obtained by telephone contact with the patient or caregiver or from the family MD. At each contact, the occurrence of possible outcome events, hospital admissions and adverse events was recorded as well as current handicap (modified Rankin scale) changes in trial medication.	ASA + Dipyridamole: mean age 63 ± 11; 66% males, 44% females, Ethnicity was not reported although the study was conducted in Europe and Australia. ASA alone group: median Age 63 ±11, 65% males, 45% females,

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
ESPRIT Study Group, 2006(21) International, 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.	Unkown/unknown/unknown/2739 randomized	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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
ESPRIT Study Group, 2006(21) International, ESPRIT (fair)	**ASA + Dipyridamole vs ASA** *Outcomes at 3.5 years* Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
ESPRIT Study Group, 2006(21) International, ESPRIT (fair)	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 myocardial infarction: 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
ESPRIT Study Group, 2006(21) International, ESPRIT (fair)	Monitored	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
ESPRIT Study Group, 2006(21) International, 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.	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Bhatt et al., 2006; (13) International, CHARISMA (good)	RCT, MC, DB, PC between October 1 2002, and November 2003	45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerbrovascular 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 diabetes (with drug therapy), diabetic nephropathy, ABI <0.9, asymptomatic carodtd stenosis ≥70% luminal diameter, ≥1 carotid plaque, as evidence by intima=media thickness. Minor risk factors could include systolc 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 cebreovascular 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Bhatt et al., 2006; (13) International, CHARISMA (good)	clopiogrel 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	None	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 clopiogrel, 47.1% diuretics, 24.1% nitrates, 36.9% calcium antagonists, 55.7% beta-blockers, 25.9% angiotensin II-receptor blockers, 18.3% rampiril, 46.3% other angiotensin-converting -enzyme inhibitors, 76.9% statins, 41.5% antidiabetic medications

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Bhatt et al., 2006; (13) International, CHARISMA (good)	Follow-up evaluations were performed at one month, 3 months, and 6 months and every 6 months thereafter until the end of the trial. At these visits, patients' compliance was assessed, standard medication was adjusted as appropriate, and all interventions, outcome events, and AE were recorded.	Clopiogrel + 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

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Bhatt et al., 2006; (13) 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% diabetes, 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% Hypercholesteroemia, 5.9% CHF, 34.9% prior MI, 3.7% atrial fibrillation, 24.3% prior stroke, 11.9% prior TIA, 41.7% diabetes, 22.7% peripheral arterial disease, 23.1% prior PCI, 19.9% prior CABG, 5.2% prior carotid endarterectomy, 11.0% prior peripheral angioplasty or bypass, 12.9% diabetic nephropathy	Unknown/ unknown/15603 enrolled/15603	treatment was permanently discontinued by 20.4% of the patients in the clopiogrel 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Bhatt et al., 2006; (13) International, CHARISMA (good)	**Clopidogrel + ASA vs. Placebo + ASA** *Outcomes at 28 months* First occurrence of myocardial infarction, 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) Myocardial infarction (nonfatal): 1.9% (146/7802) vs 2.0% (155/7801) RR = 0.94 (0.75, 1.18)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Bhatt et al., 2006; (13) International, CHARISMA (good)	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 myocardial infarction, 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Bhatt et al., 2006; (13) International, CHARISMA (good)	Monitored	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Bhatt et al., 2006; (13) 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 clopiogrel group and 4.9% of those in the placebo group discontinued treatment because of an adverse event p=0.67)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	RCT, MC, BP performed at 2 Italian institutions. Patients were enrolled by March 2004	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 acute coronary syndrome who were scheduled to undergo coronary angiography

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	Clopidogrel 600mg X1 (loading dose) + ASA 100mg/d vs. Clopidogrel 300mg x1 (loading dose 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	None	Before intervention, patients received weight-adjusted IV heparin (target activated clotting times of >300 seconds in the absence of glycoprotein Iib/IIIa receptor antagonist was used). Use of glycoprotein 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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	Randomization blocks were created and distributed to the 2 centers. MDs performing the procedure and the follow-up assessment were not aware of the randomization assignment. One-month clinical follow-up was obtained by office visit in all study patients	High loading dose: age 63± 10; 78% males, 22% females; Ethnicity: Not stated. Conventional Loading Dose: age 65 ±10; 76% males,24% females; Ethnicity: Not stated.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	High Loading Dose: 31% diabetes mellitus, 64% systemic hypertension, 70% hypercholesterolemia, 16% smokers, 33% previous MI, 13% previous coronary intervention, 5% previous bypass surgery, 25% Non-ST-elevation acute coronary syndrome, 75% stable angina, 30% multivessel coronary artery disease. Conventional Loading Dose: 32% Diabetes mellitus, 64% Systemic hypertension, 62% hypercholesterolemia, 16% current smokers, 37% previous MI, 16% previous coronary intervention, 5% previous bypass surgery, 25% Non-ST elevation acute coronary syndrome, 75% stable angina, 23% multivessel coronary artery disease	Unknown/329/329/255	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).

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Patti et al., 2005; (17), 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 Myocardial infarction: 4.0% (5/126) vs 11.6% (15/129) RR = 0.34 (0.13, 0.91), NNT = 13 (7, 86)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	Monitored	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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Patti et al., 2005; (17), Italy, ARMYDA-2 (good)	0	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
Di Pasquale et al., 2005;(42), Italy	RCT, DB, single center study in Italy between May 2002 to December 2003.	>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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period	(6) Allowed other medications/ interventions
Di Pasquale et al., 2005;(42), Italy	clopidogrel 75mg/day + ASA 160mg or ticlopidine 500mg/day + ASA 160mg X 6 months	None	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 continous 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. Paitents 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.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
Di Pasquale et al., 2005;(42), Italy	Regularly followed up as outpatients. 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: Not reported. Clopidogrel group: 61.3± 11.8; 68.2% males, 31.8% females; Ethnicity: Not reported.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/eligible/ enrolled/randomized	(11) Number withdrawn/ lost to fu/analyzed
Di Pasquale et al., 2005;(42), Italy	Ticlopidine group: 38% diabetes, 46% HTN, 28% Current smoker; 36% Hypercholesterol; 48% + family history; EF, % 53.4 ± 14. Clopidogrel group: 40% diabetes, 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."	Unknown/428/428/428	Not Reported

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12a) Results
Di Pasquale et al., 2005;(42), Italy	**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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Di Pasquale et al., 2005;(42), Italy	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Di Pasquale et al., 2005;(42), Italy	Monitored	Ticlopidine + ASA vs Clopidogrel + ASA At least one side effect: 9.3% (20/214) vs 6.5% (14/214) Gastrointestinal: 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)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Di Pasquale et al., 2005;(42), Italy	unknown	All patients received GPIIb/IIIA prior to randomization. All patients were high-risk NSTEMI with 1st coronary event.

MI=Myocardial Infarction

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Mueller C. et al., 2003 (40), Germany and Switzerland	Yes-pre-specified randomization sequence	Yes	Yes	Yes- "consecutive pts with successful stent implantation" were randomized
Atmaca et al., 2002 (38), Ankara, 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 ejection fraction <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.
Taniuchi et al., 2001 (41), 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)
Mueller C. et al., 2000 (39), 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)

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Mueller C. et al., 2003 (40), 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 pts' treatment assignments.
Atmaca et al., 2002 (38), Ankara, Turkey	Yes-but methods not described
Taniuchi et al., 2001 (41), USA	No
Mueller C. et al., 2000 (39), Germany	Yes-endpoints were adjudicated by a clinical-events committee whose members were unaware of the pts tx assignments

Evidence Table A2. Quality Assessment for Controlled Trials

			Internal Validity		
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Mueller C. et al., 2003 (40), Germany and Switzerland	No	No	Yes/Not applicable/Not reported/Not reported	No-	Yes
Atmaca et al., 2002 (38), Ankara, Turkey	Yes	Yes	yes/not applicable/Yes/not reported	No	No
Taniuchi et al., 2001 (41), USA	No	No	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-	Yes
Mueller C. et al., 2000 (39), Germany	No	Not reported	Yes/Not applicable/Not reported/No	No	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Mueller C. et al., 2003 (40), Germany and Switzerland	Unable to determine	fair/poor-not blinded
Atmaca et al., 2002 (38), Ankara, Turkey	See #3 answer-BL characteristics were shown after 10 patients were excluded	fair
Taniuchi et al., 2001 (41), 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.	fair
Mueller C. et al., 2000 (39), Germany	No	fair-unblinded and not powered to show SS difference in cardiac events

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Mueller C. et al., 2003 (40), Germany and Switzerland	Number screened not reported/number eligible not reported/700 enrolled	unsuccessful stent placement was all that was reported but would suspect that the exclusions study would be similar to Mueller 2000 et al. study	None	Not reported
Atmaca et al., 2002 (38), Ankara, Turkey	168 screened, number eligible not reported/ 158 enrolled	unstable angina, AMI within 2 wks, 12 lead resting ECK with R or L BBB, paced rhythm or complete atrioventricular block, CABG within 2 wks, renal dysfunction, pericardial disease, cardiomyopathy, recent myocarditis. Pts who received a stent as a bailout indication, and pts who were given tirofian during the procedure	None	No (unsure)
Taniuchi et al., 2001 (41), USA	1367 screened/Number eligible not reported/number enrolled not reported/1016 randomized	1. prior intolerance to ASA, T or C, 2. a comorbidity with expected survival of < 6 months and 3. prior enrollment in a separate research protocol	None	Yes
Mueller C. et al., 2000 (39), Germany	793 screened/Number eligible not reported/ 700 enrolled (699 completed clinical f/u)	Cardiogenic shock, mechanical ventilation; known allergy to ASA, T, or C; long-treatment with T, C, or warfarin; and stenting intended primarily as a bridge to CABG	None	No

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Mueller C. et al., 2003 (40), Germany and Switzerland	Yes-although C was initiated without a LD	Not reported	The study is the first presentation of extended f/u data from a randomized trial. The mean f/u as 28 months in the T group and 27 months in the C group
Atmaca et al., 2002 (38), Ankara, Turkey	Yes-T 500mg every day + 300mg ASA d	Not reported	No10/168 enrolled were excluded for receiving a stent as a bailout indication and tirofiban treatment during the procedure
Taniuchi et al., 2001 (41), USA	Yes	Sanofi/Bristol-Meyers Squibb	Yes-broad population included AMI and those with adjunctive 2b/3A inhibitors. States that the population more representative of pts receiving intracoronary stents in the US. Diabetics constituted 29% of the population vs. 21-23 in Muller study(2000) and 10-12 in CLASSICS.
Mueller C. et al., 2000 (39), Germany	Yes in regards to T but note: C was used without a LD	Not reported	No-the study was not performed to show a statistical significant difference in cardiac events. However, there was a higher TSO incidence in pts assigned to C group.

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Leon et al., 1998 (45), 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
Bertrand et al., 2000 (14), Europe CLASSICS	Yes	Yes	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Leon et al., 1998 (45), 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.
Bertrand et al., 2000 (14), Europe CLASSICS	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

			Internal Validity		
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Leon et al., 1998 (45), USA	No	No	Not reported/Not applicable/ Not reported/Not reported	No	Yes
Bertrand et al., 2000 (14), Europe CLASSICS	yes	Yes	Yes/ (1 withdrew consent before taking his first study med--not included in data) Not applicable/Not reported/Not reported	No	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Leon et al., 1998 (45), 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.	fair
Bertrand et al., 2000 (14), Europe CLASSICS	Yes-except for the one that withdrew consent	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Leon et al., 1998 (45), USA	1965 screened;1653 eligible; 1653 enrolled. (Of the 312 enrolled in the parallel registry-298 were eligible)	unsuccessful stent placement -they were then enrolled in a prospective registry trial. Presence of additional stenosis within the target vessel; recent (within 7 days before enrollment) AMI; known contraindications to the use of ASA, T or warfarin; a hx of bleeding diathesis; current treatment with abciximab; and planned angioplasty of another lesion within 30 days after enrollment.	Not-applicable	Yes
Bertrand et al., 2000 (14), Europe CLASSICS	Number screened not reported/1021 eligible/ 1020 enrolled	1. stenting procedure involving ≥stents or >1 vessel, involving the left main coronary artery or a major bifurcation, or involving vein grafts; primary angioplasty for ongoing MI with documented ST elevation and/or CPK-MP levels >2XULN and CPK MB levels greater than normal; persistent objective ischemia determined by 12 lead ECG between stenting and randomization; administration of oral anticoagulants. GP 2b/3A receptor antagonists and other antiplatelet agents, except for ASA within 1month before randomization; administration of thrombolytics 2 wks before randomization; need for anticoagulants, thrombolytic agents, or GP 2b/3a receptor antagonists after the procedure; PTCA, CABG within 2 months before the procedure; hx of allergy or intolerance or contraindication to ASA< T, or C.	None	Yes-pt had hx of allergy or intolerance/contraindication to ASA, T or C--excluded

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Leon et al., 1998 (45), USA	Yes	Supported by a grant from Cordis, a Johnson and Johnson Company	high rate of stent thrombosis in group assigned to ASA alone contradicts previous reports stating that it was similar to A + T; death rate is low which may be contribute to the fact that there were differences in selection factors used or improved diagnosis and tx strategies for stent thrombosis. It did have a high percentage of Q wave which indicates that the clinical consequences of stent thrombosis remain severe. Lower incidence of stent thrombosis in ASA and T group is offset by sl but SS increased risk of hemorrhagic and vascular surgical complications. Although the incidence of hemorrhagic complications in the group assigned to ASA and W was lower than previous studies which might indicate that femoral-artery puncture and sheath-removal techniques have improved over the years.
Bertrand et al., 2000 (14), Europe CLASSICS	Yes	Funded by Sanofi and BMS	Yes-compare the relative safety of C with and without LD compared with T + ASA in pt who had undergoing successful intracoronary stenting. Secondary objective--evaluate the incidence occurrence of cardiac events during the period of study drug administration. Population was low-risk--pts tat had successful stent. This study was underpowered to show efficacy differences

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Hall et al., 1996 (43), Milan, Italy and Tokyo, 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
Diener et al., 2004 (19), 28 countries including multiple ones in Europe, USA, Spain	Yes	Yes-centrally with an interactive voice-response system (by phone) and was based on a computer-generated list of treatment numbers.	Yes	Yes-

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Hall et al., 1996 (43), Milan, Italy and Tokyo, Japan	Not reported
Diener et al., 2004 (19), 28 countries including multiple ones in Europe, USA, Spain	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

			Internal Validity		
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Hall et al., 1996 (43), Milan, Italy and Tokyo, Japan	No	No	Yes/Yes/No/No=	No	yes
Diener et al., 2004 (19), 28 countries including multiple ones in Europe, USA, Spain	Yes	Yes	Yes/Yes/Yes/No	No	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Hall et al., 1996 (43), Milan, Italy and Tokyo, Japan	No	Poor
Diener et al., 2004 (19), 28 countries including multiple ones in Europe, USA, Spain	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Hall et al., 1996 (43), Milan, Italy and Tokyo, Japan	Number screened 358 (stent deployment)/Number eligible not reported/ 226 enrolled	allergic to ASA, taking T or other non-aspirin antiplatelet agents before the procedure, or required warfarin for other medical reasons were excluded. Pt with suboptimal results at the end of the stent procedure were excluded	No	Yes
Diener et al., 2004 (19), 28 countries including multiple ones in Europe, USA, Spain	Number screened not reported/number eligible not reported/ 7599 enrolled.	are younger than 40 years; severe comorbid conditions; increased risk of bleeding (clinical evidence of severe hepatic insufficiency, current peptic ulceration, history of systemic bleeding, or other history of bleeding diathesis or coagulopathy); scheduled for major surgery or vascular surgery; and contraindications for ASA or clopidogrel.	None	No

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Hall et al., 1996 (43), Milan, Italy and Tokyo, Japan	Yes	Not reported	relevant to some extent, however pts had to have a successful intravascular US-guided stenting in order to be randomized--pt selection bias but eliminates some of the issue that stent thrombosis was due to a mechanical reason vs. pharmacological. Unclear whether a population that stent was performed in pt for emergency reasons or those with small vessels or long vessels would be different. A larger cohort of pt would be necessary for assessment of any significant difference between the antiplatelet regimens due to the low incidence of thrombosis events or other clinical end points between the two poststent antiplatelet regimens. There was a sl imbalance in the # of pts in each group (ASA- 103 and T-123) owing to premature termination of the study before the expected target of 450 pt after the 3 deaths in the ASA group.
Diener et al., 2004 (19), 28 countries including multiple ones in Europe, USA, Spain	yes	MATCH steering committee had overall responsibility for the implementation of the trial. Sanofi-Synthelabo contracted Parexel International (Paris, France) to undertake site monitoring and data management. Sanofi-Synthelabo provided input into the study through 3 of its employees, who represented the sponsor on the steering committee (representing only 1 vote of 10) and paid study-related expenses to the other members of the committee. The data safety monitoring board had full access to the database throughout the trial. The steering committee had full access after closure of the database, and final key analyses were done separately and in parallel by sponsor and by statisticians who worked independently from sponsor	high-risk patients (majority of pts already on ASA) with mainly lacunar strokes included were included

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Gorelick et al., 2003 (52), 62 academic and community hospitals in 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
CAPRIE Steering Committee, 1996 (22), International	Yes	Yes	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Gorelick et al., 2003 (52), 62 academic and community hospitals in USA	Yes-except of 1 statistician who developed the randomization algorithm
CAPRIE Steering Committee, 1996 (22), International	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

			Internal Validity		
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Gorelick et al., 2003 (52), 62 academic and community hospitals in USA	yes-	yes	Yes/Yes/No/Not reported-	yes--15.2% in the Ticlopidine group and 13.3% ASA group lost to f/u or voluntary withdrawal	Yes
CAPRIE Steering Committee, 1996 (22), International	Yes	Yes	Yes/Yes/Yes/No	No	yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Gorelick et al., 2003 (52), 62 academic and community hospitals in USA	No	fair/Good
CAPRIE Steering Committee, 1996 (22), International	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Gorelick et al., 2003 (52), 62 academic and community hospitals in USA	Number screened not reported/number eligible not reported/ 1809 enrolled. (902 in Ticlopidine were included in analysis vs. 907 in the ASA group)	TIA, subarachnoid hemorrhage, cardiac source embolism, iatrogenic or nonatherosclerotic strokes, postoperative stroke occurring within 30 days of operation, or carotid endarterectomy as primary treatment measure for entry cerebral infarct; mean arterial blood pressure >130 mmHg on 3 consecutive days; modified Barthel index <10; hx of dementia or neurodegenerative disease; severe comorbid condition (eg cancer) judged to limit survival during 2 yr f/u; enrollment in another clinical trial; allergy or sensitivity to study drugs; woman of childbearing potential; GI bleeding; bleeding diathesis, or plt or other hematologic abnormality curently active or clinically active in the past year; hematuria or positve tool guaiac test related to mj bleeding source; and prolonged prothrombin time or partial thromboplastin time. BUN >40mg/dL, serum Cr >2.0mg/dL, thrombocytopenia or neutropenia, LFT >=2X ULN, a.fib, cardiac sources of embolism requiring warfarin therapy, large artery carotid occlusive disease treated by CEA, which would serve to increase the likelihood of enrolling lacunar infarction	None	Undetermined
CAPRIE Steering Committee, 1996 (22), International	Number screened not reported/number eligible not reported/ 19185 patients enrolled	Age <21 years; severe cerebral deficit likely to lead to pt being bedridden or demented, carotid endartectomy after qualifying stroke; qualifying stroke induced by carotid endarterectomy or angiography; pt unlikely to be discharged alive after qualifiying event; severe co-morbidity likely to limit pt's life expectancy to <3 y, uncontrolled hypertension, scheduled for major surgery, contraindications to study drugs: severe renal or hepatic insufficiency, haemostatic disorder or systemic bleeding, hx of haemostatic disorder of systemic bleeding, hx of thrombocytopenia or neutropenia, hx of drug-induced haematologic or hepatic abnormalities, known to have abnormal WBC, differential, or platelet count, anticipated requirement for long-term anticoagulants, non-study antiplatelet drugs or NSAIDs affecting plt. function; Hx of ASA sensitivity; Women of childbearing age not using reliable contraception, currently receiving investigation drug, previously entered in other clopidogrel studies, geographic or other factors making study partipciation impractical.	use of anticoagulants or antiplatelet drugs were discontinued before randomization and thrombolytic treatment should not have been received within the previous 48 hours.	No

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Gorelick et al., 2003 (52), 62 academic and community hospitals in USA	yes	None	All African American pts-at the time the study was developed there was uncertainty about the referred ASA dose for recurrent stroke prevention
CAPRIE Steering Committee, 1996 (22), International	Yes	Study was funded by Sanofi and Bristol-Myers Squibb	first study of an antiplatelet drug to include pts from the clinical subgroups of ischemic cerebrovasclar, cardiac and PAD..Study was powered to detect a realistic treatment effect in the whole study cohort but not in each of the 3 clinical subgroups.

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Diener et al., 1996 (18), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes	Yes	Yes	Yes
ESPS-2 Authors, 1997 (55), multicenter-59 sites in 13 countries	Yes-randomized to tx 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
Juergens C et al., 2004 (37), single center, Australia	Yes-sealed envelope system	No-sealed envelope	Yes	Yes
Mehta et al., 2001 (15), International, (PCI-CURE) (good)	Yes	Yes	Yes-although of note, before PCI, fewer pts on clopidogrel than on placebo had MI or refractory ischemia, p=0.008.	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Diener et al., 1996 (18), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes
ESPS-2 Authors, 1997 (55), multicenter-59 sites in 13 countries	Yes
Juergens C et al., 2004 (37), single center, Australia	No
Mehta et al., 2001 (15), International, (PCI-CURE) (good)	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.

Evidence Table A2. Quality Assessment for Controlled Trials

				Internal Validity	
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Diener et al., 1996 (18), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes	Yes	Yes/Yes/Yes/No	No	Yes
ESPS-2 Authors, 1997 (55), multicenter-59 sites in 13 countries	Yes	Yes	Yes/Yes/Yes/No	Yes-see comments	Yes
Juergens C et al., 2004 (37), single center, Australia	No	No	Yes/Not reported/Not reported/No	No	yes
Mehta et al., 2001 (15), International, (PCI-CURE) (good)	yes, except during the open-label time after the PCI procedure	Yes	Yes/No/No/No	No	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Diener et al., 1996 (18), multicenter-59 sites in 13 countries between 2/89 and 3/95	unsure	Good
ESPS-2 Authors, 1997 (55), multicenter-59 sites in 13 countries	Unsure	fair/good
Juergens C et al., 2004 (37), single center, Australia	Unable to determine-- drug discontinuation occurred more often in the Ticlopidine group--including the composite of drug discontinuation, hemorrhage and vascular complications	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
Mehta et al., 2001 (15), International, (PCI-CURE) (good)	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Diener et al., 1996 (18), multicenter-59 sites in 13 countries between 2/89 and 3/95	see above	See above	None	Undetermined
ESPS-2 Authors, 1997 (55), multicenter-59 sites in 13 countries	Number screened not reported/number eligible not reported/ 6602 enrolled	Not specified in this article	None	Undetermined
Juergens C et al., 2004 (37), single center, Australia	Number screened not reported/number eligible not reported/307 enrolled	Cardiogenic shock, unsuccessful stent deployment; known allergy to ASA, ticlopidine, or clopidogrel; recurrent treatment with C or T and need to anticoagulants after the procedure .	None	No
Mehta et al., 2001 (15), International, (PCI-CURE) (good)	Number screened not reported /number eligible (had PCI) 2658/2658 enrolled	contraindications to antithrombotic/antiplatelet therapy, those at high risk of bleeding, New York Heart Association Class IV heart failure, ongoing long-term need for oral anticoagulants, undergone PCI (PTCA/stent) or coronary-artery bypass grafting in the previous 3 months prior to randomization, or received a glycoprotein 2b/3a inhibitor fewer than 3 days before randomization.	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Diener et al., 1996 (18), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes	supported by a grant from Boehringer Ingelheim	
ESPS-2 Authors, 1997 (55), multicenter-59 sites in 13 countries	Yes	Not reported	# treatment interruptions: Placebo group n= 1649: 127 (adverse events), 148 (other medical reason), 81 (non-medical reason), 4 unknown reason, Lost to follow-up or endpoint 358 (21.7%) ; ASA group n= 1649: 141 (adverse events, 149 (other medical reason), 72 (non-medical reason), 4 unknown reason, Lost to follow-up or endpoint 302 (18.3%); DP group n= 1654: 249 (adverse events), 136 (other medical reason), 95 (non-medical reason); 5 unknown reason) Lost to follow-up or endpoints 279 (16.9%); DP-ASA n= 1650: 262 adverse events, 136 (other medical reason). 79 (non-medical reason), 2 unknown reason, Lost to follow-up or endpoints 248 (15%)
Juergens C et al., 2004 (37), single center, Australia	Yes-except for the low LD of clopidogrel	Not reported	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
Mehta et al., 2001 (15), International, (PCI-CURE) (good)	Yes	Supported by a research grant from Sanofi-Synthelabo and Bristol-Myers-Squibb	Patients were consider "moderate risk" group of patients with ACS--may not be generalizable to high-risk group of patients

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Piamsomboon et al., 2001 (35), Bangkok, Thailand, single center (poor)	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
Cure Investigators et al., 2001 (12), International	Yes	Yes	Yes	Yes
Fiotti et al., 2003 (60), Italy, single-centered (fair-poor)	No-method not reported	No-sealed envelope	No	Yes
Steinhuble et al., 2002 (16), North America, CREDO (good)	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

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Piamsomboon et al., 2001 (35), Bangkok, Thailand, single center (poor)	Not reported
Cure Investigators et al., 2001 (12), International	Yes-although ?success of blinding
Fiotti et al., 2003 (60), Italy, single-centered (fair-poor)	No
Steinhuble et al., 2002 (16), North America, CREDO (good)	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

				Internal Validity	
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Piamsomboon et al., 2001 (35), Bangkok, Thailand, single center (poor)	Not reported	Not reported	Not reported/No/Not reported/ Not reported	No	Yes
Cure Investigators et al., 2001 (12), International	Yes	Yes	Yes/not applicable/Yes/unsure--reasons for withdrawal not reported	No	Yes
Fiotti et al., 2003 (60), Italy, single-centered (fair-poor)	No	No	Yes/Not applicable/Not reported/ Not reported	No	No
Steinhuble et al., 2002 (16), North America, CREDO (good)	yes	Yes	Yes/Not applicable/Yes/Yes	No	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Piamsomboon et al., 2001 (35), Bangkok, Thailand, single center (poor)	No	Poor
Cure Investigators et al., 2001 (12), International	No	Good
Fiotti et al., 2003 (60), Italy, single-centered (fair-poor)	No	fair-poor--not randomized, open-labeled, single centered,
Steinhuble et al., 2002 (16), North America, CREDO (good)	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Piamsomboon et al., 2001 (35), Bangkok, Thailand, single center (poor)	Number screened not reported/number eligible not reported/ 68 patients enrolled	contraindication to antiplatelet stents, left main coronary artery disease, hemostatic disorder or systemic bleeding, history of thrombocytopenia or neutropenia, presence of abnormal white blood cell, differential or platelet count, requirement of long-term anticoagulant or non-steroidal anti-inflammatory drugs, childbearing age women, and severe hepatic or renal dysfunction	No	No
Cure Investigators et al., 2001 (12), International	Number screened not reported/number eligible not reported/ number enrolled not reported/12,562randomized	contraindications to antithrombotic/antiplatelet therapy, those at high risk of bleeding, New York Heart Association Class IV heart failure, ongoing long-term need for oral anticoagulants, undergone PCI (PTCA/stent) or coronary-artery bypass grafting in the previous 3 months or had received IV GYP 2b/3a receptor inhibitors in the previous 3 days	None	No
Fiotti et al., 2003 (60), Italy, single-centered (fair-poor)	Number screened not reported; Number eligible not reported/numbers enrolled 223/numbers randomized 223. For the match control group: 8% of all putative controls contacted refused to enter into study. 446 matched controls living in the same area was enrolled during the same time period	Symptoms did not meet WHO criteria for intermittent claudication i.e. leg pain on walking disappearing in less than 10 min on standing, and ankle/brachial pressure index less than 0.80 in either leg at rest (two assessment on separate days). From the match group- same family name of on of the pts were excluded.	No	Not reported
Steinhuble et al., 2002 (16), North America, CREDO (good)	17898 screened/2116 eligible/2116 enrolled/ 2116 randomized	contraindications to antithrombotic/antiplatelet therapy; greater than 50% stenosis of the left main coronary artery; failed coronary intervention in the previous 2 weeks; coronary anatomy not amenable to stent placement; persistent ST elevation within 24 hours prior to randomization; planned staged interventional procedure; and administration of the following medications prior to randomization; GP 2b/3a inhibitor within 7 days, clopidogrel within 10 days, or thrombolytics within 24 hours.	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Piamsomboon et al., 2001 (35), Bangkok, Thailand, single center (poor)	No-would not use as high of dose of ASA any longer	Not reported	Small sample size limits generalizability of results; dose of ASA is no longer being utilized; 4 different types of stent used
Cure Investigators et al., 2001 (12), International	Yes	Supported by Sanofi-Synthelabo and Bristol-Myers Squibb	Patients were consider "moderate risk" group of patients with ACS--may not be generalizable to high-risk group of patients
Fiotti et al., 2003 (60), Italy, single-centered (fair-poor)	No	Not reported	No-pts could select drug therapy, population was from northern Italy-perhaps not generalizable; medications taken by match control group was not stated
Steinhuble et al., 2002 (16), North America, CREDO (good)	Yes	supported from Bristo-Meyers Squibb/Sanofi-Synthelabo partnership.	high proportion of pts discontinued study med prior to the completion of the full year of follow-up so that the risk reduction associated with long-term clopidogrel may be underestimated. Unknown whether pretreatment therapy contributed any to the benefit of the long-term therapy. (63% in clopidogrel group and 61% of control patients completed 1 year). (45% clopidogrel and placebo patients DC study drug after PCI)

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Hass et al., 1989 (20), North America, TASS (good)	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
Juergens C et al., 2004 (37), Australia (poor)	Yes-sealed envelope system	No	Yes	Yes-not in detail (successful stent deployed)
Rupprecht et al., 1998 (44), Germany (poor)	Not reported	Not reported	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Hass et al., 1989 (20), North America, TASS (good)	Yes
Juergens C et al., 2004 (37), Australia (poor)	No
Rupprecht et al., 1998 (44), Germany (poor)	No

Evidence Table A2. Quality Assessment for Controlled Trials

				Internal Validity	
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Hass et al., 1989 (20), North America, TASS (good)	Yes	Yes	Yes/Not applicable/Yes/Yes	3% ticlopidine (n=46) and 2% assigned to the ASA group, (n=38)	yes
Juergens C et al., 2004 (37), Australia (poor)	No	No	Yes/Not applicable/Yes/Unsure	No	Yes
Rupprecht et al., 1998 (44), Germany (poor)	No	No	Not reported/Not applicable/ Not reported/Not reported	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Hass et al., 1989 (20), North America, TASS (good)	Yes	Good
Juergens C et al., 2004 (37), Australia (poor)	No	poor
Rupprecht et al., 1998 (44), Germany (poor)	Unable to determine	poor

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Hass et al., 1989 (20), North America, TASS (good)	8814/3069/3069/3069	Patient less than 40 years of age, women with childbearing potential, symptoms were due to migraine, carcinogenic embolism, or hematological disorders were ineligible as were those with a history of peptic ulcer disease, upper GI bleeding, ,or life-threatening diseases such s cancer. Those with previous hypersensitivity or intolerance to ASA and those with a need for the continued use of ASA or anticoagulants.	None	No
Juergens C et al., 2004 (37), Australia (poor)	307/307/307/307	Cardiogenic shock; unsuccessful stent deployment; known allergy to aspirin, ticlopidine, or clopidogrel; recent treatment with clopidogrel or ticlopidine; and need for anticoagulants after the procedure	None	No
Rupprecht et al., 1998 (44), Germany (poor)	not reported/not reported/not reported/61	bleeding disorders, contraindications to treatment with aspirin and/or ticlopidine, abnormal blood cell count, childbearing potential, acute MI, depressed LV fx, renal insufficiency, or an indication for oral anticoagulation	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Hass et al., 1989 (20), North America, TASS (good)	No-standard of care would no longer be 1300mg daily	Supported by Syntex Research	yes
Juergens C et al., 2004 (37), Australia (poor)	N0-ASA dose was 300mg the day before and then a minimum of 100mg per day after that. Clopidogrel 150 was given after the procedure. Both ticlopidine and clopidogrel was given x 14 days	Not reported	No-treatment arms are not utilized in practice any longer
Rupprecht et al., 1998 (44), Germany (poor)	No-Asa dose with ticlopidine is higher (300mg) than what would be used in practice	Not reported	No-outcomes were reported was primarily a comparison of the antiplatelet effects .

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
ESPRIT Study Group 2006;(21) 14 countries-Europe/Australia (fair)	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
Bhatt et al., 2006,(13) International, CHARISMA (good)	Study drug assignment was performed centrally by an interactive voice-response system on the basis of a preestablished randomization scheme, stratified according to site.	Yes	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
ESPRIT Study Group 2006;(21) 14 countries-Europe/Australia (fair)	Treatment was not blinded. None of the investigators had any knowledge of event rates or complication rates according to treatment allocation.
Bhatt et al., 2006,(13) International, CHARISMA (good)	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

			Internal Validity		
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
ESPRIT Study Group 2006;(21) 14 countries-Europe/Australia (fair)	No	No	Yes/Not applicable/Yes/Yes	No	Yes as well as on-treatment
Bhatt et al., 2006,(13) International, CHARISMA (good)	Yes	Yes	Yes/Not applicable/Yes/Yes	No..f/u 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.	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
ESPRIT Study Group 2006;(21) 14 countries-Europe/Australia (fair)	Yes--see #11 under Table A1	Fair
Bhatt et al., 2006,(13) International, CHARISMA (good)	NO	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
ESPRIT Study Group 2006;(21) 14 countries-Europe/Australia (fair)	Number screened not reported/ Number eligible not reported/number enrolled 2763/ 2763 randomized	possible cardiac source of embolism (atrial fibrillation on ECG, valvular heart disease, or recent MI), cerebral ischemic associated with high-grade carotid stenosis for which carotid endarterectomy or endovascular treatment was planned, any blood coagulation disorder, any contraindication for ASA or dipyridamole, and a limited life expectancy.	No	No
Bhatt et al., 2006,(13) International, CHARISMA (good)	Number screened not reported/number eligible not reported/15603/15603	taking oral antithrombotic medications or NSAIDS on a long-term basis (COX-2 were permitted). Patients were also excluded if, in the judgment of the investigator, they had established indications for clopidogrel therapy (such as a recent acute coronary syndrome). Patients who were scheduled to undergo a revascularization were not allowed to enroll until the procedure had been completed; such patients were excluded if they were considered to require clopidogrel after revascularization.	No--those patients already taking oral antithrombotic medications were excluded	No-~10% were taking open-label clopidogrel

Evidence Table A2. Quality Assessment for Controlled Trials

		External Validity	
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
ESPRIT Study Group 2006;(21) 14 countries-Europe/Australia (fair)	Yes--although varying dose of ASA were used..median dose was 75mg . The majority (46%) of the patients were on 30mg ASA which is lower than typically used in standard practice. (not available in US)	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	Dosage forms of extended dipyridamole not available in US. Only 8% of the population was taking Aggrenox formulation.
Bhatt et al., 2006,(13) International, CHARISMA (good)	Yes	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.	The results for in the asymptomatic (multiple atherothrombotic risk factors) and symptomatic (established cardiovascular disease) will need to be further clarified based on the definitions that were used for each of these groups before broad recommendation for or against the use of clopidogrel can be made in these patient populations.

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Patti et al., 2006,(17),Italy,ARMY DA-2,(good)	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
Di-Pasquale et al., 2005; (42), Italy, fair	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 physician.	Yes	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity
Author, Year Country	**(5) Outcome assessors masked?**
Patti et al., 2006,(17),Italy,ARMYDA-2,(good)	Yes
Di-Pasquale et al., 2005; (42), Italy, fair	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

Evidence Table A2. Quality Assessment for Controlled Trials

				Internal Validity	
Author, Year Country	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**
Patti et al., 2006,(17),Italy,ARMY DA-2,(good)	Yes	Yes	Yes/Not applicable/Yes/Yes	No	No
Di-Pasquale et al., 2005; (42), Italy, fair	Yes	Yes	Not reported/Not applicable/ Not reported/Not reported	Not reported-other than no one died	Not stated

Evidence Table A2. Quality Assessment for Controlled Trials

Author, Year Country	(11) Post-randomization exclusions?	(12) Quality Rating
Patti et al., 2006,(17),Italy,ARMY DA-2,(good)	No	Good
Di-Pasquale et al., 2005; (42), Italy, fair	No	Fair

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			*External Validity*
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Patti et al., 2006,(17),Italy,ARMY DA-2,(good)	Number screened not reported/number eligible 329/329/255	primary intervention for acute MI, baseline levels of creating kinase MB (CK-MB) above the upper normal limit, contraindications to antithrombotic or antiplatelet therapy (including platelet count <70 x 10 9/L). High risk of bleeding, coronary artery bypass grafting in the previous 3 months, and treatment with clopidogrel within 10 days from randomization.	No	No
Di-Pasquale et al., 2005; (42), Italy, fair	not reported other than is was "consecutive patients"/Not reported/428/428	Patients with previous NSTEMI/STEMI, with left bundle branch block, a history of cardiomyopathy or heart failure, previous PCI and coronary artery bypass grafting were excluded.	NO	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

			External Validity
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Patti et al., 2006,(17),Italy,ARMY DA-2,(good)	Yes	No external funding	Sample size was calculated on assumptions related to any post procedural increase of CK-MB levels, instead of the primary end point. Fewer patients were enrolled at the cost of a reduced power with regard to the primary end point. Although no significant complications related to the higher loading dose were observed, the study may also be under powered to draw definitive conclusions about its safety.
Di-Pasquale et al., 2005; (42), Italy, fair	Yes	Not reported	Sample size was calculated assuming an incidence of clopidogrel and ticlopidine discontinuation (3 and 9%)…although the majority of tables never indicate the total amount of patients that were included when evaluated for non-cardiac side effects or cardiac events at 180 days. No data was provided regarding discontinuation other than stating it was "low." Study population consisted of only high-risk patients with a first episode of ACE and all patients received IV GP 2b/3a treatment. Baseline platelets and units were not provided

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Mueller et al., 2003 (40)	Yes	Yes	Yes-Primary endpoint-CV death during the entire f/u period--(defined as any death for which there was no clearly documented non-cardiac cause. Secondary end point-composite of cardiac death and MI (typical CP at rest followed by an increase in CK and CK-MB beyond 2X ULN and 5X ULN after CABG, new Q waves. No bleeding monitoring were included
Atmaca et al., 2003 (38)	Yes	yes-6%	Yes-procedure related MMI and major clinical events (death, AMI, and PTCA or bypass surgery). Also, major or minor bleeding complications during hospitalization period--not defined. Deaths-cardiac origin if associated with CHF, AMI or sudden cardiac death (<1 hr after symptom onset). AMI= new Q wave or the ST elevation lasting more than 1 day and the development of T wave change; new specific ST segment elevation or depression ≥0.1 mV; and increase in CK, CK-MB activity
Taniuchi et al., 2001 (41)	Yes	Yes	Yes
Muller et al., 2000 (39)	Yes	Yes	Yes
Moussa et al., 1999 (36)	Yes	Not clear-1.1% (16 pts) in TA group (n=1406) vs. 0.7% (2 pts) in CA group (n=283) were lost to follow-up	No

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Mueller et al., 2003 (40)	Yes-f/u visits at "our" institution at 6 months and whenever clinically indicated thereafter. All pts were contacted by questionnaire to assess vital and functional status as well as MACE 2 years after enrollment of the last pt. If pt did not return a signed questionnaire or any uncertainties remained, a MD interviewed the pts and their family MD over the phone. Information from contingent hospital re-admission records or provided by referring MD or by the outpt clinic was reviewed.	No	Yes
Atmaca et al., 2003 (38)	No	No-were blinded but ascertainment techniques specifically to address bleeding complications were not included	Yes
Taniuchi et al., 2001 (41)	No	No-	Yes
Muller et al., 2000 (39)	Yes	no	Yes
Moussa et al., 1999 (36)	No	No--pts were instructed to f/u with their referring MD in 2 wks for clinical assessment and blood count analysis (all different). NP performed telephonic f/u eval at 1 month on an ongoing basis. A quantitative angiography was done pre and post procedure	No-Quantitative angiography- the minimum lumen diameter in mm was 0.90 ± 0.45 vs. 0.84 ± 0.47 in the TA group, p= 0.02 preprocedure but postprocedure the diameter was similar, p=1.

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
Mueller et al., 2003 (40)	Yes	Fair/poor-not blinded, multiple providers, questionnaires used but data not reported
Atmaca et al., 2003 (38)	Yes-study was intended to evaluate during hospitalization	fair-ascertainment methods were not detailed
Taniuchi et al., 2001 (41)	Yes-for the tolerability portion of the study. i.e. drugs given x 2 wks which was the length of time for primary safety end point. Secondary cardiac end points were documented throughout a 30 day after stent implementation	fair-done at single-site, open-label administration of drugs, with twice dosing of T and single dosing of C
Muller et al., 2000 (39)	yes	fair-unblinded
Moussa et al., 1999 (36)	Yes- BUT incidence of stent thrombosis, MACE and drug SE was reported at 1 month f/u but T was given for only 2 weeks	Poor--not randomized, pts were assessed by their own referring MD in 2 wks, study was a chronologically consecutive manner (all the pts btw 96-98 received T and those btw Mar. 98 and Jun. 98 received C. The incidence of stent thrombosis with antiplatelet therapy is low (1.5% TA group vs. 1.4% in CA group, p = NS), a large randomized trial is needed to establish validity of these data

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Mueller et al., 2003 (40)	no adverse events reported
Atmaca et al., 2003 (38)	Ticlopidine vs Clopidogrel Bleeding: 0.0% (0/75) vs 0.0% (0/83)
Taniuchi et al., 2001 (41)	
Muller et al., 2000 (39)	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)
Moussa et al., 1999 (36)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Diarrhea: 4.4% (61/1390) vs 3.2% (5/281) Neutropenia: 0.3% (4/1390) vs 0.0% (0/281) Rash: 5.9% (82/1390) vs 2.1% (6/281)

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Leon et al., 1998 (45)	Yes	Yes	Yes
Bertrand et al., 2000 (14)	Yes	Yes	Yes
Hall et al., 1996 (43)	Yes	Yes	Yes
Diener et al., 2004 (19)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Leon et al., 1998 (45)	Yes	Yes	Yes
Bertrand et al., 2000 (14)	No	Unsure-pts and assessors were blinded but ascertainment techniques were not stated	Yes
Hall et al., 1996 (43)	Yes	Yes-Coronary angiograms were analyzed without knowledge of the intravascular ultrasound data by experienced angiographers not involved in the stenting procedure.	Yes
Diener et al., 2004 (19)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
Leon et al., 1998 (45)	Yes	good
Bertrand et al., 2000 (14)	Yes	good
Hall et al., 1996 (43)	Yes	Poor-unblinded randomized-open label, not same qty of pts in each group;
Diener et al., 2004 (19)	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Leon et al., 1998 (45)	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)
Bertrand et al., 2000 (14)	Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg Allergy: 1.2% (4/340) vs 0.00% (0/335) vs 0.00% (0/345) Gastrointestinal 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)
Hall et al., 1996 (43)	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% (0/123)
Diener et al., 2004 (19)	Clopidogrel + Aspirin vs Clopidogrel + Placebo Life-threatening bleeding: 2.6% (96/3759) vs 1.3% (49/3781) Fatal-bleeding: <1.0% (16/3759) vs <1.0% (11/3781) Non-fatal bleeding: 1.0% (38/3781) vs 2.0% (81/3759) Symptomatic intracranial: 1.0% (25/3781) vs 1.0% (40/3759) Primary intracranial hemorrhage: 1.0% (32/3759) vs <1.0% (17/3781) Major bleeding: 1.9% (73/3759) vs 0.6% (22/3781)

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Gorelick et al., 2003 (52)	Yes	No the drop-out rate or voluntary withdrawal were 15.2% in Ticlopidine tx group and 13.3% for those receiving ASA	Yes
CAPRIE Investigators et al., 1996 (22)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Gorelick et al., 2003 (52)	yes	yes	Yes
CAPRIE Investigators et al., 1996 (22)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
Gorelick et al., 2003 (52)	Yes	fair/good-high drop out rate
CAPRIE Investigators et al., 1996 (22)	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Gorelick et al., 2003 (52)	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)
CAPRIE Investigators et al., 1996 (22)	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)

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
ESPS-2 authors, 1997 (55)	yes	No	yes
Juergens et al., 2004 (37)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
ESPS-2 authors, 1997 (55)	yes	Yes	Yes
Juergens et al., 2004 (37)	Yes	No	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
ESPS-2 authors, 1997 (55)	Yes	fair/good-high drop out rate
Juergens et al., 2004 (37)	Yes	Poor

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
ESPS-2 authors, 1997 (55)	Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo GI event: 30.5% (505/1654) vs 32.8% (541/1650) vs 30.4% (502/1649) vs 13.3% (219/1649) 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)
Juergens et al., 2004 (37)	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) Gastrointestinal: 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) 16 pts in TA group (1.1%) and 2 pts in the CA group (0.7%) were lost to f/u. 46 pt (3.3%) in the TA group and 8 pts (2.8%) in the CA group p=0.85) DC the study drug early for reasons other than the occurrence of an outcome events. Reasons for stopping T: rash in 30 pts; Diarrhea in 6 pts; rash and diarrhea in 5 pts, neutropenia in 4 pts and noncompliance in 1 pt. Reasons for DC C were rash in 4 pts, diarrhea in 3 pts and noncompliance in 1 pt. The incidence of stent thrombosis, cardiac events, and med side effects at 1 month f/u was reported for 1671pts

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Quilliam et al., 2001 (80)	No-case-control design	N/A-case control design	No
Rupprecht et al., 1998 (44)	Yes	Yes	Yes-although those that were prespecified were not outcomes of interest to this report i.e. platelet Aggregation Studies, Flow Cytometric Analysis, Platelet Count
Mehta et al., 2001(15) (PCI-CURE)	Yes	Yes	Yes
Piamsomboon et al., 2001 (35)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Quilliam et al., 2001 (80)	No	No	Yes
Rupprecht et al., 1998 (44)	Yes	Unsure	Yes
Mehta et al., 2001(15) (PCI-CURE)	No	Yes although pts/providers were not during the open-label section of the study although there was central adjudication done by a committee of clinicians who were blinded to treatment allocation	Yes
Piamsomboon et al., 2001 (35)	Yes	Unsure-randomized pts unclear whether patients and assessors were blinded to intervention, and whether ascertainment techniques were valid	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
Quilliam et al., 2001 (80)	yes	Poor--not randomized but case-control with data derived from SAGE-Systematic Assessment of Geriatric Drug use Via Epidemiology from 1992-1997. Studied the likelihood of hospitalization for bleeding among elderly nursing home stroke survivors from 5 states. Hospitalization claims for outcome identification were used--possibly missing less severe cases for inclusion. Potential for misclassification of bleeds i.e. GI bleeds may range from minor to life threatening. No information on the actual indication for use of these agents and presumed that they are being used for secondary stroke prevention. By design, residents were excluded with a known hospitalization for bleeding from the sample of potential controls. The first recorded hospitalization for a bleeding event within the study was used among the cases as the event of interest.....possible that pts were hospitalized for bleeding before the claims data were available
Rupprecht et al., 1998 (44)	No-lab investigations were performed on days 1,7 and day 14 after stent implantation although therapy was x 4 weeks	
Mehta et al., 2001(15) (PCI-CURE)	Yes	good
Piamsomboon et al., 2001 (35)	yes	Poor-ascertainment methods were not detailed, randomization was done by "research nurse" with no other details, questionable whether patients/providers were blinded, multiple providers were involved

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Quilliam et al., 2001 (80)	no adverse events reported
Rupprecht et al., 1998 (44)	Ticlopidine vs Ticlopidine + Aspirin vs Aspirin Major bleeding: 0% (0/20) vs 0% (0/21) vs 5.0% (1/20)
Mehta et al., 2001(15) (PCI-CURE)	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)
Piamsomboon et al., 2001 (35)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin 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% (0.0/37)

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
CURE Investigators et al., 2001 (12)	Yes	Yes	Yes
Fiotti et al., 2003 (60)	No-match case control	Yes	Yes
Steinhuble et al., 2002 (16) (CREDO)	Yes	Yes	yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
CURE Investigators et al., 2001 (12)	Yes	Yes	Yes
Fiotti et al., 2003 (60)	Yes	No	Yes
Steinhuble et al., 2002 (16) (CREDO)	Yes	Yes although pts/providers were not during the open-label section of the study although there was central adjudication done by a committee of clinicians who were blinded to treatment allocation	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
CURE Investigators et al., 2001 (12)	Yes	Good
Fiotti et al., 2003 (60)	Yes	Fair/poor-pt selected own therapy; match-control for age and gender and not disease states; used Regional Health Service Data Base to select controls
Steinhuble et al., 2002 (16) (CREDO)	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
CURE Investigators et al., 2001 (12)	Clopidogrel vs Placebo Major bleeding: 3.7% (231/6259) vs 2.7% (169/6303) 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)
Fiotti et al., 2003 (60)	Ticlopidine vs Aspirin Minor bleeding: 6% (6/92) vs 1.5% (20/131) Upper GI discomfort: 15.2% (14/92) vs 6.1% (8/131)
Steinhuble et al., 2002 (16) (CREDO)	Clopidogrel vs Placebo Major bleeding: 8.8% (93/1053) vs 6.7% (71/1063) 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: 5.3% (56/1053) vs 5.6% (59/1063) 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 A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Hass et al., 1989 (20), North America	yes	No-higher than other studies but less than 5%	yes
Patti et al. 2005 (17) (ARMYDA-2)	Yes	Yes	Yes
ESPRIT Study group 2006 (21) ESPRIT	Yes	4.1% in ASA + dipyridamole group; 3.6% in ASA group	Yes
Bhatt et al., 2006 (13) (CHARISMA)	Yes	Yes	Yes
Pasquale et al, 2005 (42)	Yes	Not stated	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Hass et al., 1989 (20), North America	yes-pts were evaluated one month after randomization and then 4 month interval throughout the trial.	Yes	Yes
Patti et al. 2005 (17) (ARMYDA-2)	Yes	Yes	Yes
ESPRIT Study group 2006 (21) ESPRIT	Yes	Unsure	Yes
Bhatt et al., 2006 (13) (CHARISMA)	Yes	Yes	Yes
Pasquale et al, 2005 (42)	Yes-pts were evaluated with 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.	Yes	Unsure

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8) Overall adverse event assessment quality
Hass et al., 1989 (20), North America	Yes	good
Patti et al. 2005 (17) (ARMYDA-2)	Yes	Good
ESPRIT Study group 2006 (21) ESPRIT	Yes	Good
Bhatt et al., 2006 (13) (CHARISMA)	Yes	Good
Pasquale et al, 2005 (42)	Yes	Good

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Hass et al., 1989 (20), North America	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) Gastrointestinal pain: 7.2% (110/1518) vs 10.0% (153/1527) Gastritis: 0.9% (13/1518) vs 1.7% (26/1527) Gastrointestinal 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)
Patti et al. 2005 (17) (ARMYDA-2)	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)
ESPRIT Study group 2006 (21) ESPRIT	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)
Bhatt et al., 2006 (13) (CHARISMA)	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)
Pasquale et al, 2005 (42)	Ticlopidine + ASA vs Clopidogrel + ASA At least one side effect: 9.3% (20/214) vs 6.5% (14/214) Gastrointestinal: 1.9% (4/214) vs 0% (0/214)

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Casella et al. 2003 (34)	Compare the clinical efficacy of C + ASA vs. T+ ASA (standard therapy) after coronary stenting via formal meta-analysis.	studies/abstracts included up to Dec. 2001
Robless et al. 2001 (52)	To provide evidence-based recommendations on the use of antiplatelet treatment for the prevention of CV events and stroke in PVD pts.	Databases used Medline 1/66-1/99; Embase 1/80-1/99; register of trials held by the APTC; Cochrane Controlled Trials Register; Proceeding from vascular surgical society mgt, pharmaceutical companies that market antiplatelet agents (T C)
Bhatt et al. 2002 (33)	Determine whether clopidogrel plus ASA is at least as efficacious as ticlopidine plus ASA in reducing ischemic events in pts receiving coronary stents	through 12/00

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Casella et al. 2003 (34)	Medline (+ manual search of the references) search: , English-language 1. direct comparison of combination therapy with C and ASA vs. T + ASA combination after coronary stenting; 2. clear description of the study methods; 3. ability to extract data for different endpoints. The key words used were C, T and coronary stenting and their various combinations
Robless et al. 2001 (52)	Studies: DB, RCT by 1/99 of antiplatelet tx (ASA, dipyridamole, indubufen, sulphinpryaozone, picotamide, suloctidil, T and C) vs. placebo, or vs. other antiplatelet agents, in pts with stable intermittent claudication or critical ischemia (Fontaine stages II-IV) or undergoing vascular surgical intervention (surgery or PTA) were included. Search strategy included NLM Medline database from 1/66-1/99; Embase from 1/80-1/99 using the same terms, register of trials held by the APTC(1994), Cochran Controlled Trials Register in the Cochrane Library (including Medical Editors' Trial Amnesty Database, Proceedings from vascular surgical society mg, and pharmaceutical companies that market antiplatelet agents (T and C)
Bhatt et al. 2002 (33)	Medline search, English language that compared C +ASA vs. T + ASA. Medical subject headings and key words used were C, T and stents. Relevant abstracts and presentation from 1999 and 2000 AHA, ACC, European Soc. Of Cardiology and Transcather CV Therapeutics were identified. If results were published only in abstract form or presented orally or in a poster, data were verified with primary investigator.

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Casella et al. 2003 (34)	2736 in the randomized trials and 8952 pts in the registries trials. 11,688-efficacy analysis; 7165 for safety analysis	3 randomized trials and 7 registries were included. The 3 randomized trials were CLASSICS (the only double-blind study), TOPPS, and Mueller et al (1999)
Robless et al. 2001 (52)	6452 pts with IC, ABPI < 0.85, IC with previous leg amputation, bypass or angioplasty from the CAPRIE Trial would be the only one of interest	systematic review of 39 randomized controlled trials of antiplatelet therapy. 24 trials of antiplatelet tx v P in IC and 10 trials o antiplatelet tx vs. P in pts undergoing lower limb bypass surer. 2 trials antiplatelet tx vs. P in PVD pt undergoing PTA. 5 trials of ASA vs. a second antiplatelet tx in pts with PVD. 2 trials comparing antiplatelet tx vs. P as well as ASA vs. a second antiplatelet tx-- as both of these trials had 3 study arms involving 2 antiplatelet tx and placebo. Only one study (CAPRIE-RCT. DB, AC, MC) meets the criteria for this drug class review
Bhatt et al. 2002 (33)	13955	meta-analysis; 3 randomized trials (CLASSICS), (TOPPS), and Muller 200-CIrculation 2000) and 7 single-center registries

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
		6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophr 10mg to 30mg/day.
Casella et al. 2003 (34)	All were stent pts. Of the randomized trials, all differed in their inclusion and exclusion criteria: CLASSICS study enrolled a very low risk population. The registries overall included a higher risk population.	The randomized and registries all differed in mode and length of therapy. The randomized trials intervention included 300mg C x1 (LD) or no loading dose+ 75mg/day x 3.73 wks; 300mg X1 (LD) + 75mg/day x 2 wks and 75mg C daily x 4 wks. 1 registry trial included in meta-analysis mode to therapy was not reported. 2 registries trials were 300mg C X1 + 75mg/day x 4 wks. 1 registry trial was 75mg/day for 2 or 4 wks; 1 registry trial was 300mg x 1 + 75mg/day x 2 wks; 1 registry trial was 150mg x 2 + 75mg/day x 4 wks; 1 registry trial was 300mg C X 1 or no loading dose + 75mg/day x 4 wks. Dose/duration of T and ASA were not indicated for any of the studies
Robless et al. 2001 (52)	Participants: All pts with stable PVD (Fontaine stage II) for more than 6 months or pts undergoing vascular surgical intervention (surgery or PTA) for PVD were included in the analysis. 6452 pts with IC, ABPI < 0.85, IC with previous leg amputation, bypass or angioplasty from the CAPRIE Trial would be the only one of interest	ASA 325mg vs. C 75mg x 12 months from CAPRIE
Bhatt et al. 2002 (33)	all were stent pts. Of the randomized trials, all differed in their inclusion and exclusion criteria:	All studies were C + ASA or T + ASA. Different among the registries and sometimes within the registries) as to whether pts were pretreated with thienopyridine before the procedure, whether LD were administered and whether the length of therapy was 14 or 28 days. CLASSICS--LD of C in one arm and therapy was administered within 6 h of completion of the procedure x 3.73 weeks; TOPPS used LD of both T and C, given after the procedure x 2 wks, Muller et al used a 500mg LD for T are only x 3.73 wks.

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Casella et al. 2003 (34)	Study Endpoints: Efficacy Evaluation and Safety Evaluation: Efficacy: composite of death and non-fatal MI. (pre-specified outset of the analysis). The secondary endpoint was a composite of MACE (mg adverse cardiac events, according to the definition used in the single studies. The def. differed although it was mostly a combination of death, non-fatal MI, TVR (target vessel revascularization or subacute stent thrombosis). Rates were pooled and analyzed as individual endpoints. At 30 days, C was associated with a significant decrease in the occurrence of death or non-fatal MI from 3.4 to 1.6% (OR 0.63, 95% CI 0.47 to 0.85, p=0.003). There was a trend (OR 0.83, 95% CI 0.66 to 1.03, p=0.1) toward less MACE in pts receiving C (2.7%) instead of T (3.8%), less mortality (OR 0.70, 95% CI 0.40 to 1.25, p = 0.2), and less non-fatal MI (OR 0.76, 95% CI 0.54 to 1.07, p = 0.1).
Robless et al. 2001 (52)	5 trials comparing one antiplatelet regimen against ASA in pts with PVD. 292 (8.4%) of 3467 pts in the ASA group suffered a vascular event. In the seconds antiplatelet regimen (T500mg, C 75mgor dipyridamole/ASA [in doses of 330mg/75mg; 600mg/225mg;990mg/225 respectively] 227 (6.6%) of 3461 pts suffered a vascular event.
Bhatt et al. 2002 (33)	30 day major adverse cardiac events (MACE), as defined in each trial, was the prespecified primary endpoint. MACE+ death, MI, TVR or subacute stent thrombosis (SAST) in all studies except CLASSICS and 2 registries. Secondary end point was all-cause mortality. Pooled data: OR 0.51 (95% CI 0.42 to 0.63). 50% RR in the MACE in C + ASA vs T + ASA (2.10% vs. 4.04%) was SS p=0.001). The reduction in the MACE was seen in randomized and registry data but was only substantial and SS in the registries. The OR in favor of C in the randomized trials was 0.90 (95% CI 0.57 to 1.44) The OR in favor of C in the larger numbers of pt in the registries was 0.45 (95% CI 0.36 to 0.57, p=0.001). MORTALITY: OR in favor of C was 0.44 (95% CI 0.29 to 0.67)--56% reduction in mortality in those pt treated with C and ASA vs T and AA 90.48 vs 1.09%, p=0.001). If look at just the randomized trials, the OR in favor of C was 0.47 (95% CI 0.17 to 1.30, p=0.14). The registry data produced an OR of 0.45 in favor of C (95% CI 0.28 to 0.70, p=0.001). Meta-analysis (adjust for heterogeneity) for both MACE C 0.72 (0.59 to 0.89, p=0.002) compared with T. OR for rate of mortality was 0.55 in favor of C (0.37 to 0.82, p=0.003)

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Casella et al. 2003 (34)	When the analysis was limited to 3 randomized trials, the % of pts who reached the primary endpoint in the C group (19/1529; 1.2%) was similar to that of the T group (15/1207; 1.2%) (OR 1.05, 95% CI 0.52 to 2.12, p= 0.9). However there was a trend toward a lower death rate for pts treated with C (6/1529, 0.4%) than those treated with T (9/1207; 0.7%) (OR 0.60, 95% CI 0.21 to 1.70, p=0.3). This datum was consistent with the death rate reported in the registries.C *Loading dose (7 studies) vs. no loading C dose (4 studies)* : a significant advantage for all endpoints was seen. (ODDS RATIO PLOTS ON PG 681--blurred-unable to read it. CLASSICS trial--when each arm was analyzed, no difference in the rate of death or non-fatal MI of C compared to T (1.1 vs 0.6% for the no loading dose, p=0.7, and 0.9 vs 0.6% , p =0.9 for the LD C arm vs. T. The group that had AMI tended to be slighlty older, more men, high rate of prior cardiac surgery and CHF (data not shown)More DM, histoty of angia pectoris, AMI or ischemic stroke also had a higher prevalence in the group with AMI and a BL CR in the upper quartile > 1.3 mg/dL)
Robless et al. 2001 (52)	CAPRIE--215 (6.7%) of 3223 pts in C suffered a vascular event compared with 277 (8.6%) of 3229 pts in the ASA group. In this CAPRIE subgroup the odds ratio for vascular events was 0.77 (95% CI 0.64-0.92) favoring clopidogrel p= 0.0028)
Bhatt et al. 2002 (33)	None reported

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Casella et al. 2003 (34)	Safety analysis: At 30 days there was a 47% reduction in the occurrence of major adverse SE (OR 0.53, 95% CI 0.42 to 0.66, p < 0.00001) in pts treated with C + ASA. Incidence of drug intolerance was significantly reduced a month pts on C + ASA (OR 0.51, 95% CI 0.36 to 0.72, p < 0.0001). Fewer C pts developed neutropenia or thrombocytopenia (OR 0.58, 95% CI 0.71 to 1.99, p = 0.5)	CLASSICS study was a safety study involving 3 arms comparing a LD vs. no LD of clopidogrel vs. T. The published trial pooled both C arms, but for this analysis, each arm was considered independently. Randomized vs. registry studies and LD vs. no LD data were analyzed. TOPSS study did not report the rate of non-fatal MI, leaving only 2 randomized trials suitable for the combined endpont analysis. Unable to read Figure 1 and 2 (Odds ratio plots)---blurred. I
Robless et al. 2001 (52)	In the 5 trials of ASA compared to other antiplatelet agents (see I for description)68 (2%) of 3467 pts in the ASA group had mj bleed vs. 50 (1.4%) of 3561 pt. NS	Study was supported by BJS Research Bursary 1997
Bhatt et al. 2002 (33)	None reported	Nice OR plots comparing each study for the rate of 30 day MACE as well as for the pooled data AND for the 30 day mortality

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Hankey et al. 2000 (20)	Establish how the thienopyridines (T and C) compare with ASA in terms of effectiveness and safety in the prevention of vascular events among pts at high risk of vascular disease	No date was reported although the paper was received March 10, 2000; final revision received April 21, 2000. The range of years that studies were included were 1983-2000 per reference section.
Tran et al. 2004 (18)	Summarize the current state of evidence regarding antiplatelet treatment in pts with CV disease, CAD, and PAD, and to provide reasonable recommendations for clinical practice	1960-8/2004
Serebruany et al. 2004 (55)	Determine the frequency of bleeding complications dependent on the class and dose of antiplatelet agent used observed in recently published mj RC trials	1988-2002

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Hankey et al. 2000 (20)	all unconfounded randomized trials comparing either T or C with ASA for pts at high risk of vascular disease (symptoms of ischemia of the cerebral, coronary, or peripheral circulations) who were followed up for at least 1 month for the occurrence of vascular events
Tran et al. 2004 (18)	Studies 1. randomized; 2. recruited pts with established vascular disease (TIA, ischemic stroke, CAD and PAD), 3. compare an antiplatelet regimen with P or one antiplatelet regimen with another; and 4. assessed tx for at least 10 days. Key words related to antiplatelet agents (ASA, T, dipyridamole, C) and vascular disease (ACS, atherothrombosis, ischemic stroke, MI, PAD, TIA, unstable again) were used to search the MEDLINE database and trial registers of the Cochrane Groups. Journal and abstracts--manually searched and reference lists of trials and review articles were scrutinized. Meta-analysis and scientific statement of guidelines from official societies were also reviewed.
Serebruany et al. 2004 (55)	English; were retrieved from MEDLINE, OVID and CARDIOSOURCE. Only studies had f/u for at least 1 month and in which a full description of hemorrhagic complications were reported

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Hankey et al. 2000 (20)	22656 (9840-recent TIA or ischemic stroke; 6302 recent MI; 6514 symptomatic peripheral arterial disease)	specialized search trial registers (Cochrane Stroke Group and ATC, Medline, and Embase) and Sanofi was contacted. 4 trials- 3 trials with ASA vs. T (n=3471); and one trial with clopidogrel -CAPRIE (n=19185). CAPRIE and TASS (N Engl J Med 1989;321:501-7)- centralize, computer generated scheme with good preconcelment of tx allocation. Tohgi et al (Jpn J med 1987;26:117-119) and Schoop (Sanofi internal report)-said to be randomized but method not stated
Tran et al. 2004 (18)	30619-23000 (ACT) since it had primarily ASA = ~7619	111 trials, all were "randomized (see criteria)
Serebruany et al. 2004 (55)	~23232 (338,191 pts in meta-analysis)	72 trials were identified; 50 were eligible (see criteria). Most of the studies used TIMI criteria to assess bleeding severity. Criteria from GUSTO was also present--less common.

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Hankey et al. 2000 (20)	CAPRIE-recent ischemic stroke, recent MI, or PAD; Tohgi-pts with recent TIA; Schoop-men with PAD and TASS-pts with recent TIA or minor ischemic stroke. Average age ~63 years, approximately 2/3 were male, and most were white	6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophr 10mg to 30mg/day. CAPRIE-C 75mg daily vs. ASA 325mg daily x 23 months; Tohgi-T 200mg daily vs. ASA 1500mg daily X 12 months; Schoop T 500mg daily vs. ASA 1500mg daily X 24 months and TASS T 500mg daily vs. ASA 1300mg daily x 40 months
Tran et al. 2004 (18)	22 trials with TIA or stroke (n=30619), 47 trials with CAD pts (n=59821) and 42 trials with PAD (n=9214). One table indicated n= 19302 for MI, previous MI n=20006; unstable angina n=5031; stable angina/CAD n=2920	21 trials ASA ,T, dipyridamole, ASA + dipyridamole in TIA/stroke trials; 46 trials included ASA, T, dipyridamole, ASA + dipyridamole in CAD; 42 trials ASA, T, dipyridamole, ASA + Dipyridamole, picotamide in PAD. No specific data was provided for dose; duration etc. All the trials were vs. P or one antiplatelet regimen with another
Serebruany et al. 2004 (55)	(In all 50 trials) Most had AVS (unstable angina and acute MI). A few trials involved HTN pt, and about 40% were PTCA. About 85% of pts were enrolled in US.	ASA < 100mg (6 listed on table which includes ESPS2; 3 trials mentioned in text; ASA ≥ 100mg (9 trials) ; dipyridamole (including Aggrenox) ESPS -2 listed twice on table; # trials not mentioned in text, ADP receptor blockers (10 trials) ; IV GP 2b/3A (18 trials) and oral GP 2b/3a inhibitors(7 trials)

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Hankey et al. 2000 (20)	OR of a serious vascular disease (stroke, MI or vascular death) 12.0% for theinopyridine vs. 13% for ASA; OR 0.91, 95% CI 0.84 to 0.98; 2p=0.01 which corresponds to the prevention or delay of 11 (95% CI 2 to 19) vascular events per 1000 pt treated for 2 years. Reduction in the odds of any stroke (5.7% vs. 6.4% for ASA; or 0.88, 95% CI 0.79 to 0.98, corresponding to the prevention or delay of 7 (95% CI 1 to 13) strokes per 1000 pts treated for 2 years. There was a NS trend toward a reduction in ischemic stroke (OR, 0.90, 95% CI 0.81 to 1.01), MI infarction (OR 0.88, 95% CI 0.76 to 1.01), vascular or unknown cause of death (OR 0.93, 95% CI 0.82 to 1.06), and death from any cause (OR 0.95, 95% CI 0.85 to 1.05)
Tran et al. 2004 (18)	TIA or STROKE; ASA-ATC (meta-analysis) provided most of the data-23,000 pts with antiplatelet therapy (usually ASA) compared with P or untreated control OR 22 (15.2 to 27.5) p<.001 in ischemic stroke, MI or vascular death. ATC was for mean 29 months--was associated with 22% reduction in recurrent ischemic stroke, MI or vascular death (17.6% vs. 21.4%, p <.001) TICLOPIDINE and CLOPIDOGREL: T Studies: CATS-1072 pts, T 500mg/day compared with P or untreated control reduced the risk of stroke, MI or vascular death by 23% (11.3% vs. 14.0%, p=.02) after 2 years of f/u.TASS-3069 pts with TIA or minor stroke (1300mg/day) reduced the risk of nonfatal stroke or death by 12% (17% vs. 19%), p=.02 after 3 years of follow-up. Diarrhea and rash (25%) and serious hematologic adverse effects, including neutropenia (1-2%) and TTP (0.025%-0.05%) have been reported in other studies (Hankey, Bennett, Hass). C study: CAPRIE: For all pts: reduction of stroke, MI or vascular death by 8,7% (95% CI 0.3 to 6.5; p=.04) For specifically ischemic stroke, RRR was similar and NS different from overall results. MATCH: ASA 75mg + C 75mg vs. C in 7599 pt with recent TIA or ischemic stroke. Combination of ASA and C did not significa
Serebruany et al. 2004 (55)	low-dose ASA and dipyridamole was associated with lowest risk (3.6 and 6.7% respectively) . TOTAL Rates of Bleeding (includes mj, minor, stroke, GI) Dipyridamole: 2 trials, N= 3,304 6.7% rate; 95% CI 5.8%, 8.5%); Plavix (7 trials) n= 19,191; 8.5% rate and 95% CI 8.1, 8.8%

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Hankey et al. 2000 (20)	Among the 9840 TIA/ischemic stroke, vascular events (16.8% for theinopyridine vs. 18.3% for ASA; OR 0.90, 95% CI 0.81 to 1.00); stroke (10.4% thienopyridine vs. 12.0% for ASA; OR 0.86, 95% CI 0.75 to 0.97). Absolute reduction of 14 (95% CI -1 to 29) vascular events/1000 pts treated for ~2 years was similar to that observed among all high-risk pts. risk of stroke among pts with a previous TIA or ischemic stroke in the ASA group (12.0%) was almost twice as high as that for all high-risk pts (6.4%) Absolute reduction of 16 strokes (95% CI 3 to 28) per 1000 pts was approximately twice as large as that for all high-risk pts combined.
Tran et al. 2004 (18)	open-label: n=652 pt with unstable angina: T compared with control reduced the risk of death or Mi by 46% at 6 months p = .009 Balsano: Circulation 1990;336:827-830. There is a section in article specifically addressing STEMI--go back and review if needed
Serebruany et al. 2004 (55)	

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Hankey et al. 2000 (20)	No clear difference btw the theinopyridines and ASA in the odds of experiencing an intracranial hemorrhage (0.3% vs. 0.4% ASA); (OR 0.82, 95% CI 0.53 to 1.27) or an extracranial hemorrhage (8.8% vs 8.9% ASA; OR 1.00, 95% CI 0.91 to 1.09). C and T were associated with a significant reduction in the odds of GI hemorrhage (1.8% vs 2.5%; OR 0.71, 95% CI 0.59 to 0.86) and of indigestion/N/V (14.8% for T or C vs 17.1% for ASA, OR 0.84, 95% CI 0.78 to 0.90) but with and increased odds of diarrhea and or skin rash. Compared to ASA, T produced an 2 fold increase in the odds of skin rash 11.8% for T vs 5.5% for ASA; OR 2.2 95% CI 1.7-2.9) and diarrhea (20.4% for T vs 9.9% for ASA; OR 2.3, 95% CI 1.9 to 2.8) whereas C produced a smaller increase of approx 1/3 in the odds of skin rash (6.0% for C vs 4.6% for ASA; OR 1.3, 95% CI 1.2 to 1.5) and of diarrhea (4.5% for C vs 3.4% for ASA, OR 1.3, 95% CI 1.2.to 1.6). Neutropenia (<1.2x 109/L 2.3% T vs. 0.8% ASA; OR 2.7, 95% CI 1.5 to 4.8) C 0.1% vs 0.2 ASA; OR 0.63, 95% CI 0.29 to 1.36; Thrombocytopenia < 100x 109 pts/L 0.26% vs 0.26%; OR 1.00; 95% CI 0.57 to 1.74) No published tria available for the frequency of thrombocytopenia associated with T compared with ASA	Most of the data were from the 2 largest trials-CAPRIE, TASS. Conclusion per article 1. theinopyridine provide sl. More protection than does ASA against vasc events among high-risk pts, but the extent of added benefit is uncertain, both overall and especially for individual pts. 2. C appears to be safer than T. 3. C is at least as safe as ASA.
Tran et al. 2004 (18)	NSTEMI ACE: CURE trial: C + ASA -mj bleeding (3.7% vs. 2.7%; RRR, 1.38;95% CI 1.13 to 1.67; p=.001) but no significant excess in life-threatening bleeding (2.1% vs. 1.8%; p=.13) Incidence of bleeding with C was lower in pts receiving ASA ,100mg.d vs. higher dose	ER form of dipyridamole was used in ESPS-2 vs. short-acting dipyridamole in other studies. ESPIRT (European/Australian Stroke Prevention in Reversible Ischemia Trial, n=4500, ER-DP 400mg/d + ASA (30-325mg/d) vs. ASA alone in pt s/p TIA or minor ischemic stroke a and ProFESS trial-Prevention Regimen for Effectively Avoiding Second Strokes n=15500l C + ASA vs. ER-DP + ASA in pt with ischemic TIA or stroke--no effervescences were provided. No studies have compared C with P/control (in the absence of ASA) in pt with NSTEMI ACS. References for PTCA: PCI-CURE Lancet 2001358:527-533 and CREDO-JAMA 2002:288:2411-2420. There is a section in this article about STEMI that was not extracted---GO BACK IF NEEDED
Serebruany et al. 2004 (55)	Major Bleeding: Dipyridamole 2 trials:, 3,304 pts, 1.0% rate (f) (95% CI 0.7%, 1.3%). Thienopyridines- 8 trials; 18,574 pts; rate 2.1%; (1.9%, 2.3%). MINOR Thienopyridine (1 trial, n= 6259) 5.1% rate (4.6, 5.7) Stroke (bleeding) Thienopyridine 2 trials, 15,858 pts; 0.3% rate and 95% CI 0.2%,0.3) GI bleeding: Thienopyridine 5 trials, N= 17,824; 1.6% rate; 95% CI, 1.4%, 1.8%).	

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Antithrombotic Trialists' Collaboration 2002 (44)	Determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events	All trials, published or otherwise that were available by Sept 1997
Hankey et al. 2000 (20)	Determine the effectiveness and safety of thienopyridine derivative (ticlopidine and clopidogrel) vs ASA for the prevention of serious vascular events (stroke, MI or vascular death) in pts at high-risk, specifically pts with previous TIA or ischemic stroke	All unconfounded, DB, R trials directly comparing ticlopidine or clopidogrel with ASA in high vascular risk pts. All trials were done within the last 20 years.
Wilterdink and Easton 1999 (45)	Review and compare the results of ESPS-2 and previous studies of dipyridamole + ASA and aggregate them in a meta-analysis	1994 ATC trial + 1996 ESPS-2 trial
Bennett et al. 1999 (60)	Review ticlopidine-associated hematologic toxic effects	Clinical trials, MedWatch database from 1992 through 1997, published phase 3 clinical trials and case reports, hematologists, and plasmapheresis centers.

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Antithrombotic Trialists' Collaboration 2002 (44)	randomized trials of an antiplatelet regimen vs control or of one antiplatelet regimen vs another in high risk patients.
Hankey et al. 2000 (20)	Al truly randomized trials in which a thienopyridine derivative (ticlopidine or clopidogrel) was compared directly with ASA, and in which pts were followed up prospectively and systematically for the occurrence of serious vascular events for at least one month were included.
Wilterdink and Easton 1999 (45)	2 trials (see previous entry)
Bennett et al. 1999 (60)	Not stated

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Antithrombotic Trialists' Collaboration 2002 (44)	o (trial was mainly ASA, the combination of ASA and dipyridamole is not of the same formulation as the drug of interest	Not applicable
Hankey et al. 2000 (20)	4 trials involving a total of 22,656 high vascular risk pts. ASA vs ticlopidine in 3 trials (3471 pts) and clopidogrel in one trial (19,185)	4 trials involving a total of 22,656 high vascular risk pts. ASA vs ticlopidine in 3 trials (3471 pts) and clopidogrel in one trial (19,185)
Wilterdink and Easton 1999 (45)	6602	ATC-meta-analysis, ESPS-2 RCT
Bennett et al. 1999 (60)	98 cases of ticlopidine-associated TTP	2 large stroke preventions studies (Phase 3)-CATS, TASS; 2 large phase 3 clinical Stent trial

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable	6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophr 10mg to 30mg/day. Not applicable
Hankey et al. 2000 (20)	Patients were on average about 63 years of age, and about 2/3 were men.43% -TIA or ischemic stroke, 28% MI, 29% PAD	1 trial-(CAPRIE)-19,185 pts with ischemic stroke 6431, recent MI 6302, PAD 6452) and3 trials with ticlopidine
Wilterdink and Easton 1999 (45)	6602 pts with cerebral ischemia dn recorded 824 strokes.	1 trial and 1 meta-analysis that contained 14 trials that compared the combination of dipyridamole and ASA (different agent than what was used in ESPS-2 vs ASA
Bennett et al. 1999 (60)	56 cases in stroke prevention-mean age 66.9±11.8).42 cases in stent setting--mean age 62.4±11.5	stent/cva populations. Ticlopidine has been used less than 2 weeks in 5.4% and 2.4%, between 2 and 3 weeks in 17.9% and 21.4%, between 3 and 4 weeks in 30.4% and 38.1% and between 4 and 12 weeks in 46.4% and 38.1%.

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable
Hankey et al. 2000 (20)	High vascular risk pts: composite outcome stroke, MI OR vascular death, 12% vs. 13% [OR0.91, 95% CI:0.84 to 0.98)-NNT 11/1000 (95% CI 2-19), Fatal and non-fatal stroke 5.7% vs 6.4%, (OR 0.88, 95% CI:0.79 to 0.98)-NNT7(95% CI 1-13 strokes per 1000.
Wilterdink and Easton 1999 (45)	ESPS-2 + 14 trials of dipyridamole + ASA vs ASA alone, the combination reduces the risk of stroke by 23% over ASA alone.
Bennett et al. 1999 (60)	Death in 60% not receiving plasmapheresis compared with 21.9% of patients receiving plasmapheresis for stroke prevention and 14.3% of patients receiving plasmapheresis in the stent setting.

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable
Hankey et al. 2000 (20)	TIA or ischemic stroke pt: several vascular events (from 3 trials)16.8 vs 18.3% with ASA; (OR:0.90, 95% CI 0.81 to 1.00, corresponding to the avoidance of 14 per 1000 pts treated for 2 years
Wilterdink and Easton 1999 (45)	Non-fatal stroke (ESPS-2 trial + 9/14 meta-analysis trials:)-p=.005 in favor of dipyridamole + ASA.
Bennett et al. 1999 (60)	ticlopidine-associated TTP in the stroke prevention setting were more likely to be women 62.5% vs 28.6%, p=.01

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable	
Hankey et al. 2000 (20)	Neutropenia-2 trials--ticlopidine 2.3% vs 0.8% with ASA(2.7, 95% CI 1.5 to 4.8)Rash: clopidogrel6.0% vs 4.6% (OR 1.3, 95% CI: 1.2 to 1.5) and ticlopidine 11.8% vs 5.5% [OR 2.2, 95% CI 1.7 to 2.9)	
Wilterdink and Easton 1999 (45)	Not stated	ATC trial did not have the same formulation as the agent used in ESPS-2 trial
Bennett et al. 1999 (60)	Normal platelet counts within 2 weeks of the onset of Top were documented in most patients in both groups. Ticlopidine had been used < 2 weeks in 5.4% and 2.4% in stroke prevention and stent placement respectively; between 3-4 weeks in 30.4 and 38.1% and between 4-12 weeks in 46.4 and 38.1 respectively.	

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Hankey et al. 2001 (43)	Review effectiveness and safety of the thienopyridines compared with aspirin for the prevention of vascular events among patients at high risk of vascular disease	"last 20 years"
ESPRIT et al. 2006{ID#2314}	The incidence for the composite outcome of vascular death, non-fatal stroke, or non-fatal MI in patients with cerebral ischemic of presumed arterial origin	Previous meta-analysis published by the authors with the addition of ESPRIT data. The meta-analysis is based on the data of 6 trials, including 3888 patients allocated to ASA and dipyridamole and 3907 to ASA alone; the total number of outcome events is 1158.
Purkayastha et al. 2006{ID#2197)	Assessing the effect of clopidogrel on postoperative outcome after coronary surgery by comparing patients who were taking clopidogrel at the time of surgery with patients who stopped clopidogrel at least seven days before surgery (control group)	Medline and the Cochrane database. 11 comparative studies published between 1999 and 2004 of patients undergoing coronary surgery while taking clopidogrel and a control group were used.
Biondi-Zoccai et al. 2003{ID#2260}	Perform an updated systematic review of randomized trials comparing clopidogrel vs. ticlopidine in patients undergoing coronary stenting, with specific emphasis on the role of front-loaded clopidogrel treatment	Medline 1/1986-1/2003), BioMedCentral, CENTRAL, ISI Current Contents, LILACS and mRCT were searched by a trained investigator. Major pertinent reviews were also systematically sought. Cross-references and quoted papers were checked and experts contacted to identify other relevant trials.

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Hankey et al. 2001 (43)	All confounded randomized trials comparing either ticlopidine or clopidogrel with ASA among patients at high risk of vascular disease (those with symptoms of ischemia of the cerebral, coronary, or peripheral circulations) who were followed for at least one month for the recurrence of vascular events. Specialize trial registers of the Cochrane Stroke Group and the Antithrombotic Trialist's Collaboration, MEDLINE, and Embase were searched. Additional unpublished information and data was sought from Sanofi as well as the principal investigators of the CAPRIE trial.
ESPRIT et al. 2006{ID#2314}	
Purkayastha et al. 2006{ID#2197)	Not stated..although the studies are listed which included 4 studies pre-ESPS 2 time, ESPS-2 and then ESPRIT
Biondi-Zoccai et al. 2003{ID#2260}	Not stated although the studies had to include coronary artery bypass grafting procedure and clopidogrel
	a. controlled comparison of ticlopidine vs. clopidogrel treatment in addition to aspirin in patients undergoing coronary stent implantation; b. randomized treatment allocation; c. intention-to-treat analysis.

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Hankey et al. 2001 (43)	22656	4 randomized trials
ESPRIT et al. 2006{ID#2314}		
Purkayastha et al. 2006{ID#2197)	3888	Not stated
Biondi-Zoccai et al. 2003{ID#2260}	4002 of whom 605 (15.1%) underwent cardiac surgery while taking clopidogrel and 3397 (84.9%) while not taking clopidogrel	No further details provided
	2962 patients (average follow-up 7.4 months) (1649 to clopidogrel and 1313 to ticlopidine)	5 studies. All studies have been included in the paper. Primary end-points of the studies included were: minor myocardial injury, stent thrombosis, cardiovascular death, safety, tolerability. Studies were from 1998-2001. One study was from USA, 2 studies conducted in Europe, 1 study from Turkey , 1 study from Thailand. Various antiplatelet regimens of included studies were listed

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
		6 trials of expophor 5 mg to 20 mg/day; 4 studies of zenophr 10mg to 30mg/day.
Hankey et al. 2001 (43)	ASA vs ticlopidine in 3 trials (n=3,471) and with clopidogrel in 1 trial (n=19,185 pts). Recent TIA or ischemic stroke was the qualifying event in 9840 pts, a recent MI in 6,302 pts, and symptomatic PAD in 6,514 pts. Average age was approx. 63, with approx. 2/3 of the pts being male and white.	ASA vs ticlopidine in 3 trials (n=3,471) and with clopidogrel in 1 trial (n=19,185 pts).
ESPRIT et al. 2006{ID#2314}	ASA + Dipyridamole vs. ASA studies in patients with cerebral ischemic of presumed arterial origin	ASA + Dipyridamole vs. ASA. Aggrenox used in ESPS-2 study and in 8% of the population in the ESPRIT trial
Purkayastha et al. 2006{ID#2197)	Not stated--except that the included trials were not randomized trials. The studies were not matched for the clopidogrel and control groups either.	Not stated in detail
Biondi-Zoccai et al. 2003{ID#2260}	Ages ranged from 59-65, % males range 61-78, % HTN 43-73, % Dyslipidemia 27-57% (not available in 2 studies), % smoking 45-69 (not available in 2 studies), Previous MI 17-46% (not available in one study), %previous revascularization 12-21% (not available in 2 studies), % ACS 0-59%, Gp IIb/IIIa% 0-48% (not available in one study) . No studies reported implantation of new-generation drug-eluting or radiation-emitting intracoronary devices	Quality score range: 7-11 (best 12). Clopidogrel loading dose was administered in three of the studies; absent in one study; and included in one of the three study arms in one study.

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Hankey et al. 2001 (43)	pts at high risk of vascular disease: odds of a serious vascular events with thienopyridine compared with ASA, 12 vs 13, OR 0.91, 95% CI 0.84-.98, p=.01--NNT 11/1000 tx for 2 years (95% CI 2-19). Odds of suffering any stroke were reduced in favor of thienopyridine group (5.7% vs. 6.4%; OR 0.88, 95% CI 0.79-0.98) compared with ASA,,NNT 7 strokes/1000 patients. Reduction in ischemic stroke (OR 0.90, (0.81-1.01), MINOR 0.88, (0.76-1.01), vascular or unknown cause of death (OR 0.93, 0.82-1.06) and death from any cause (OR, 0.85-1.05)
ESPRIT et al. 2006{ID#2314}	Total number of events for the composite outcome of vascular death, non-fatal stroke, or non-fatal MI was 1158. The overall risk ratio was 0.82 (95% CI 0.74-0.91) favoring Aspirin+ dipyridamole vs. ASA alone
Purkayastha et al. 2006{ID#2197)	Clopidogrel vs. Non-clopidogrel: Adverse Events: Weighted Mean Difference (WMD) 1.53, 95% CI 1.02-2.32), with no significant heterogeneity between the studies. Patients in the clopidogrel group had a small, significantly increased length of stay in hospital (WMD 1.18, 95% CI 0.24 to 2.12) but with significant heterogeneity between the studies. Overall transfusion requirement were significant for the clopidogrel group (WMD 1.36, 95% CI 0.80-1.92), although all these results were associated with significant heterogeneity. Mortality did not differ significantly.
Biondi-Zoccai et al. 2003{ID#2260}	non-significant trend toward increased mortality in patients treated with clopidogrel 2.3% vs. ticlopidine 1.7%,RR 1.64 (95% CI 0.94-2.86, p=0.080). After stratification for loading regimen, clopidogrel with loading was associated with non-significantly lower mortality rates than ticlopidine 0.9% vs. 1.6% RR 0.68 (95% CI 0.29-1.63). Clopidogrel without any loading regimen yielded a highly significantly 3-fold increased risk of death than ticlopidine 4.2% vs. 1.7%, RR 2.9 (95% CI 1.45-6.1). Cumulative risk of death or MI was similar in the overall analysis comparing clopidogrel vs. ticlopidine after stenting 4% vs. 3.7% (RR 1.31, 95% CI 0.91-1.91). Clopidogrel without loading had an unfavorable impact on the rate of death or MI in comparison to ticlopidine 6.4% vs. 4.1%, RR 1.89, (95% CI 1.15-3.1) while clopidogrel with a loading dose yielded non-significantly better results than ticlopidine 2.3% vs. 3.4%, RR 0.83 (95% CI 0.47-1.45). The rate of MI was similar in the overall analysis in patients treated with clopidogrel vs. ticlopidine. Even after stratification for loading vs. non-loading tx, clopidogrel appeared equivalent to ticlopidine, despite a trend toward increased risk of MI in patients treated with clopidogrel without loading vs. ticlopidine.

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Hankey et al. 2001 (43)	pts restricted presenting with stroke or TIA--thienopyridine and ASA produced similar benefits for the composite of all vascular events (16.8% vs 18.3% for ASA, or0.90, 95% CI0.81-1.00) corresponding to the NNH 14 serious vascular events per 1000 pts treated x 2 years. The risk of any stroke was decreased in the thienopyridine group compared with ASA (10.4% vs 12.%, OR 0.86, 95% CI 0.75-0.97) corresponding to 16 (95% CI3-28) strokes avoided per 1000 pts treated.
ESPRIT et al. 2006{ID#2314}	
	RR and 95% CI was reported for each of the study included in the meta-analysis
Purkayastha et al. 2006{ID#2197)	
Biondi-Zoccai et al. 2003{ID#2260}	
	Secondary endpoints: similar rates of clinical revascularization and non-cardiac safety profile (major bleeding, severe hematologic adverse effects) for the two drugs.

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Hankey et al. 2001 (43)	intracranial hemorrhage (0.3 vs. 0.4%l OR 95% CI 0.53-1.27) Extracranial hemorrhage (8.8% vs 8.9% for ASA; OR 1.00, 95% CI 0.91-1.09. gastrointestinal hemorrhage 1.8% vs 2.5% for ASA; OR 0.71, 95% CI 0.59-0.86) and indigestion/n/v 14.8% vs. 17.1%, OR 0.84, 95% CI 0.78-0.90. The odds of diarrhea or skin rash were increased in the thienopyridine A vs. C skin rash 6.0% vs. 4.6%; OR 1.3, 95% CI 1.2-1.5) and diarrhea (4.5% vs. 3.4%, OR 1.3, 95% CI 1.2-1.6). A vs. T: skin rash (11.8% vs. 5.5%, OR 2.2,95%CI 1.7-2.9) diarrhea (20.4% vs. 9.9%, r 2.3, 95CI 1.9-2.8). Neutropenia with ticlopidine was 2.3% vs. 0.8% with ASA; OR ,95% CI 1.5-4.8. No increased risk was observed with C compared with ASA (0.1% vs. 0.2%; OR 0.63, 95% CI 0.29-1.36)	
ESPRIT et al. 2006{ID#2314}	Not stated	Different formulations of ASA + dipyridamole were included
Purkayastha et al. 2006{ID#2197)	See under Main Results	This meta-analysis had several limitations including combining retrospective and prospective studies. Studies were not randomized. Inadequate description of the studies as well as the citations of the studies not included. Patient characteristics were not described. Due to these limitations, no conclusions can be drawn from this meta-analysis.
Biondi-Zoccai et al. 2003{ID#2260}	clopidogrel vs. ticlopidine: major bleeding, severe hematologic adverse effects 0.5% vs. 0.7%, RR=0.94, 0.36-2.5	This meta-analysis had several limitations including small number of studies of different quality, small number of overall events as well as varying degrees of glycoprotein IIB/IIIA inhibitors utilized (0-48%). The standard of practice now recommends a loading dose of clopidogrel so these findings are of interest but are not of practical importance.