

Evidence Tables

PREV2 Does clopidogrel prevent vascular disease in people with type 2 diabetes compared to aspirin or in combination with aspirin?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354(16):1706-1717. (CHARISMA) Ref ID: 3368	RCT multicentre, double-blind, placebo controlled study 1++	N= 15,603 from 32 countries and 768 sites Patients with T1D/T2D N=6,556 (42%)	Inclusion criteria ¹ : Patients should be 45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease. Exclusion criteria: Patients were excluded from the trial if they were taking oral antithrombotic medications or nonsteroidal antiinflammatory drugs on a long-term basis (although cyclooxygenase-2 inhibitors were permitted).	clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) N=7,802 Diabetics N=3,304 (42.3%)	placebo plus low-dose aspirin (75 to 162 mg per day) N= 7,801 Diabetics N=3,252 (41.7%)	Median of 28 months	Primary efficacy end point: the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes Principal secondary efficacy end point: the first occurrence of myocardial infarction, stroke, death	* Composite Primary endpoint the rate of the primary event was 6.8% in the clopidogrel group and 7.3% in the placebo group (relative risk (RR), 0.93; 95% CI 0.83 to 1.05; P = 0.22) * Individual primary endpoints Death from any cause RR 0.99 95%CI (0.86 to 1.14) p= 0.90 Death from cardiovascular causes RR 1.04 95%CI (0.87 to 1.25) p= 0.68 Myocardial infarction (nonfatal) RR 0.94 95%CI (0.75 to 1.18) p=0.59 Ischemic stroke (nonfatal) RR 0.81 95%CI (0.64 to 1.02) p= 0.07 Stroke (nonfatal) RR 0.79 95%CI (0.64 to 0.98) p=0.03 * Composite Secondary endpoint	Sanofi-Aventis and Bristol-Myers Squibb

¹ To meet the criterion for enrolment on the basis of multiple risk factors, patients were required to have two major or three minor or one major and two minor atherothrombotic risk factors. **Major risk factors** Type 1 or 2 diabetes (with drug therapy), Diabetic nephropathy, Ankle-brachial index <0.9, Asymptomatic carotid stenosis ≥70% of luminal diameter, ≥1 Carotid plaque, as evidenced by intima-media thickness **Minor risk factors:** Systolic blood pressure ≥150 mm Hg, despite therapy for at least 3 months; Primary hypercholesterolemia; Current smoking >15 cigarettes/day; Male sex and age ≥65 yr or female sex and age ≥70 yr.

To meet the criterion for enrolment on the basis of established cardiovascular disease, patients were required to have one of the listed conditions: Documented coronary disease: Angina with documented multivessel coronary disease History of multivessel percutaneous coronary intervention. History of multivessel coronary-artery bypass grafting. Myocardial infarction. Documented cerebrovascular disease: Transient ischemic attack during previous 5 yr. Ischemic stroke during previous 5 yr. Documented symptomatic peripheral arterial disease: Current intermittent claudication and ankle-brachial index ≤0.85. History of intermittent claudication and previous intervention (e.g., amputation, peripheral bypass, or angioplasty)

		<p>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 enrol until the procedure had been completed; such patients were excluded if they were considered to require clopidogrel after revascularization.</p> <p>Patient characteristics: Groups were well balanced. The median age was 64 years; 29.8 percent of the patients were women. More than three quarters of the participants had established cardiovascular disease, ²as defined by the enrolment criteria, and most of the remaining patients had multiple atherothrombotic risk factors.</p>				<p>from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral).</p> <p>The primary safety end point was severe bleeding according to the GUSTO definition which includes fatal bleeding and intracranial haemorrhage, or bleeding that caused haemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention.</p>	<p>The rate of the principal secondary efficacy end point was 16.7% in the clopidogrel group, as compared with 17.9% in the placebo group (RR, 0.92; 95%CI, 0.86 to 0.995; p= 0.04)</p> <p>* Individual secondary endpoint Hospitalization for unstable angina, transient ischemic attack, or revascularization RR 0.90 95%CI (0.82–0.98) p= 0.02</p> <p>* Treatment discontinuation: 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)</p> <p>* Adverse Events A total of 4.8% of the patients in the clopidogrel group and 4.9% of those in the placebo group discontinued treatment because of an adverse event (P = 0.67).</p> <p>The rate of the primary safety end point (severe bleeding) was 1.7% in the clopidogrel group and 1.3% in the placebo group (RR, 1.25; 95%CI 0.97 to 1.61; P = 0.09)</p> <p>The rate of moderate bleeding was 2.1% in the clopidogrel group, as compared with 1.3 % in the placebo group (RR, 1.62; 95% CI 1.27 to 2.08; P<0.001). The rate of intracranial haemorrhage was similar in the two treatment groups.</p> <p>Fatal bleeding RR 1.53 95%CI (0.83 to 2.82) p= 0.17</p>	
--	--	--	--	--	--	--	--	--

						<p>Moderate bleeding according to the GUSTO criteria (bleeding that led to transfusion but did not meet the criteria for severe bleeding) was also examined, as were fatal bleeding and primary intracranial haemorrhage.</p>	<p>Subgroup analysis Patients who were enrolled because they had documented cardiovascular disease were designated "symptomatic," whereas those who were enrolled because they had multiple atherothrombotic risk factors without documented cardiovascular disease were designated "asymptomatic."</p> <p>Among the 3284 asymptomatic patients, there was an increase in the rate of primary events with clopidogrel (6.6%, vs. 5.5% with placebo; P = 0.20), whereas among the 12,153 symptomatic patients, there was a marginally significant reduction in the primary end point with clopidogrel (6.9%, vs. 7.9% with placebo; RR 0.88; 95% CI 0.77 to 0.998; P=0.046).</p> <p>In the subgroup of asymptomatic patients, there was a significant increase in the rate of death from all causes among the patients assigned to clopidogrel plus aspirin as compared with those assigned to placebo plus aspirin (5.4% vs. 3.8%, P = 0.04) as well as an increase in the rate of death from cardiovascular causes among those assigned to clopidogrel (3.9% vs. 2.2 %, respectively; P = 0.01). In contrast, clopidogrel had no significant effect on death from cardiovascular causes in the symptomatic subgroup.</p> <p>The rates of GUSTO-defined severe bleeding among the asymptomatic patients were 2.0% with clopidogrel and</p>
--	--	--	--	--	--	---	--

								1.2% with placebo (P = 0.07); the corresponding rates among the symptomatic patients were 1.6% and 1.4% (P = 0.39). Although both these differences favoured the placebo group, neither was significant. The rates of GUSTO-defined moderate bleeding among asymptomatic patients were increased (2.2% with clopidogrel and 1.4% with placebo, P = 0.08), as were the rates of moderate bleeding among symptomatic patients (2.1% and 1.3%, respectively; P<0.001). Again, both differences favoured the placebo group, but this difference was significant only among the symptomatic patients.	
Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004; 364(9431):331-337. Ref ID: 4	RCT double blind, multicentre 1++	N= 7,599 from 507 centres In 28 countries 68% with diabetes)	Inclusion criteria: Patients who had had an ischemic stroke or transient ischemic attack in the previous 3 months and had one or more of five additional risk factors (Previous ischemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease) within the previous 3 years. Exclusion criteria: Major exclusion criteria were: age younger than 40 years; severe comorbid conditions; increased risk of bleeding (clinical evidence of severe	Clopidogrel 75 mg/day + Aspirin 75 mg/day N= 3,797	Clopidogrel 75 mg/day + Placebo N= 3,802	18 months	primary endpoint: first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular death (including haemorrhagic death of any origin), or rehospitalisation for an acute ischaemic event (including	* Composite primary endpoint: Clopidogrel + aspirin n=596 (16%) Clopidogrel + placebo n=636 (17%) Relative risk reduction 6.4% 95%CI (-4.6 to 16.3) p=0.244 There were equal proportions of MI, ischaemic stroke, other vascular death and rehospitalisation for ischaemia between the groups. * Secondary endpoints There were non significant differences on the incidence of secondary endpoints between the groups * Adverse events: Adding aspirin to clopidogrel resulted in significantly more bleeding complications than in the placebo and clopidogrel arm, doubling the number of events	Sanofi-Aventis

³ defined as any fatal bleeding event; a drop in haemoglobin of ≥ 50 g/L; significant hypotension with need for inotropes [haemorrhagic shock]; symptomatic intracranial haemorrhage, or transfusion of ≥ 4 units of red-blood cells or equivalent amount of whole blood

⁴ defined as significantly disabling [with persistent sequelae]; intraocular bleeding leading to significant loss of vision; or transfusion of ≤ 3 units of red-blood cells or equivalent amount of whole blood.

MATCH			<p>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 aspirin or clopidogrel.</p> <p>Patient characteristics: In 5,994 patients whose qualifying event was ischaemic stroke, 4398 (73%) had a modified Rankin score of 0–2. According to the TOAST classification system, the principal causes of stroke were small-vessel occlusion (n=3148; 53%) and large-artery atherosclerosis (2039; 34%).</p> <p>The most prevalent risk factors at randomisation were hypertension (78%), diabetes mellitus (68%), and hypercholesterolaemia (56%). 26% of patients had previous ischaemic stroke and 19% had transient ischaemic attack.</p> <p>Most patients (n=6033; 79%) had one additional risk factor, as defined in the inclusion criteria at study entry, and 1496 (20%) had two or more.</p> <p>No imbalance in baseline characteristics was recorded between the two groups.</p>				<p>unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularisation, or transient ischaemic attack).</p> <p>Secondary endpoints included individual and various combinations of each of the outcomes forming the primary endpoint, and any death and any stroke.</p> <p>Adverse events The incidence of life-threatening bleeding³ and major bleeding⁴</p>	<p><u>Life-threatening bleeding</u> Clopidogrel + aspirin n= 96 (3%) Clopidogrel + placebo n= 49 (1%) RR 1.26 95%CI (0.64 to 1.88) p<0.0001</p> <p><u>Major bleeding</u> Clopidogrel + aspirin n= 73 (2%) Clopidogrel + placebo n= 22 (1%) RR 1.36 95%CI (0.86 to 1.86) p <0.0001</p> <p>* Follow up: At 18 months of follow-up, data were available for 7276 patients (96%), including those who died during the study and those alive at the end of the 18-month period of follow-up: 3621 in the aspirin and clopidogrel group and 3655 in the placebo and clopidogrel group. In 13 patients, vital status was not obtained.</p>	
-------	--	--	--	--	--	--	--	---	--

<p>Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001; 358(9281):527-533. Ref ID: 3372</p> <p>PCI-CURE</p>	<p>RCT (prospectively designed substudy of patients undergoing PCI) in the CURE trial</p> <p>1++</p>	<p>N=2,658</p> <p>504 were diabetics (18.9%)</p>	<p>The inclusion and exclusion criteria for the CURE trial have been described previously.</p> <p>Baseline characteristics among patients assigned placebo and clopidogrel were well balanced</p> <p>Most patients in each group received an intracoronary stent. Unfractionated heparin was used during the procedure in 2313 (87%) of patients, and low-molecular-weight heparin in about 309 (12%). Target vessels for PCI were well balanced between the placebo and clopidogrel groups (left main 24 [1.8%] vs 23 [1.8%], proximal 351 [26.1%] vs 374 [28.5%] or mid/distal 300 [22.3%] vs 308 [23.5%], left anterior descending, circumflex 393 [29.3%] vs 380 [29.0%], right coronary 440 [32.8%] vs 419 [31.9%], and saphenous vein graft 32 [2.4%] vs 43 [3.3%]).</p>	<p>Aspirin (75 to 325 mg daily) + clopidogrel (75 mg per day)⁵</p> <p>N= 1,313</p>	<p>Aspirin (75 to 325 mg daily) + Placebo</p> <p>N= 1,345</p>	<p>The average duration of follow-up after PCI was 8 months</p>	<p>The primary endpoint was a composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI⁶.</p> <p>Cardiovascular death or myocardial infarction from the time of PCI to the scheduled end of the trial was also assessed to determine the effects of continuing clopidogrel long-term after PCI.</p>	<p>* Primary composite endpoint:</p> <p>Events before PCI Before PCI, significantly fewer patients on clopidogrel than on placebo had a myocardial infarction or the composite of myocardial infarction or refractory ischaemia.</p> <p>MI or refractory ischaemia: Placebo: N= 206 (15.3%) Clopidogrel N= 159 (12.1%) RR 0.76 95%CI (0.62 to 0.93) p=0.008</p> <p>MI Placebo: N= 68 (5.1%) Clopidogrel N= 47 (3.6%) RR 0.68 95%CI (0.47 to 0.99) p=0.04</p> <p>Events from PCI to 30 days Significantly fewer patients in the clopidogrel group than the placebo group had a primary outcome of cardiovascular death, myocardial infarction, or urgent revascularisation by 30 days after PCI.</p> <p>CV death, myocardial infarction, urgent revascularisation. Placebo: N= 86 (6.4%) Clopidogrel N= 59 (4.5%) RR 0.70 95%CI (0.50 to 0.97)</p>	<p>Sanofi-Aventis and Bristol-Myers Squibb</p>
--	--	--	--	---	---	---	--	---	--

⁵ Patients were pre-treated with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. A loading dose of clopidogrel 300 mg orally or matching placebo was given immediately on a double-blind basis.

⁶ PCI was done after randomisation at the discretion of the local investigator, and clopidogrel or placebo was continued up until this point. After PCI, stented patients received an open-label thienopyridine (either clopidogrel or ticlopidine) in combination with aspirin for 2–4 weeks, after which administration of the randomly assigned study medication resumed until the end of the scheduled follow-up (3–12 months after randomisation).

			<p>1730 PCIs were done during the initial hospital stay, and 928 after discharge. During the initial hospital stay, the median number of days before PCI was 6 days in both groups and 10 days overall.</p> <p>About a quarter of patients in each group received open label thienopyridines before PCI , and more than 80% received them afterwards for a median of 30 days (IQR 19–33). The most common reason for open-label thienopyridine use after PCI was stent implantation (or expected stent implantation if started before PCI).</p>				<p>p=0.03</p> <p>- CV death, myocardial infarction Placebo: N= 59 (4.4%) Clopidogrel N= 38 (2.9%) RR 0.66 95%CI (0.44 to 0.99) p=0.04</p> <p>Events from PCI to end of follow-up From the time of PCI to the end of follow-up (mean 8 months after PCI), there were significantly fewer cardiovascular deaths or myocardial infarctions with clopidogrel than placebo</p> <p>CV death, myocardial infarction Placebo N= 108 (8.0%) Clopidogrel N= 79 (6.0%) RR 0.75 95%CI (0.56 to 1.00) p= 0.047</p> <p>CV death, myocardial infarction, any revascularisation Placebo N= 292 (21.7%) Clopidogrel N= 240 (18.3%) RR 0.83 95%CI (0.70 to 0.99) p=0.03</p> <p>Overall results: events before and after PCI Overall, when events before and after PCI were considered, there was a highly significant difference in cardiovascular death or myocardial infarction between the two groups.</p> <p>CV death, myocardial infarction Placebo N= 169 (12.6%) Clopidogrel N= 116 (8.8%) RR 0.69 95%CI (0.54 to 0.87) p=0.002</p> <p>* Adverse events</p>	
--	--	--	---	--	--	--	--	--

								<p>There was very little difference in major bleeding between the groups at 30 days and at the end of follow-up.</p> <p>Life-threatening bleeding at 30 days and at the end of follow-up was also similar between the groups (NS differences) T</p> <p>There was more minor bleeding in the clopidogrel group than the placebo group at the end of follow-up.</p> <p>Placebo N= 28 (2.1%) Clopidogrel N= 46 (3.5%) RR 1.68 95%CI (1.06 to 2.68) p=0.03</p> <p>Subgroup analysis Subanalysis of the diabetic cohort (N=504) detected 101 events (cardiovascular death or MI), with a relative risk of 0.77 (95% CI 0.52 to 1.15) for the clopidogrel group. Authors recognized that the results for the diabetes group certainly lack statistical power due to the small numbers involved.</p>	
Steinhubl SR, Berger PB, Mann JT, III, Fry ET, DeLago A, Wilmer C et al. Early and sustained dual oral antiplatelet therapy	RCT double blind, multicentre 1++	N=2,116 from 99 centres in North America	Inclusion criteria: patient who had symptomatic coronary artery disease with objective evidence of ischaemia, were referred for PCI or thought to be at high likelihood for requiring PCI with either stent	Aspirin + Clopidogrel ^{7 8} N=1,053	Aspirin + placebo N= 1,063	12 months	One-year of the composite of death, MI, or stroke in the ITT population 28-day	* One-year composite endpoint At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke. 95%CI (3.9% to 44.4%), p=0.02. Absolute reduction, 3%	Sanofi-Aventis and Bristol-Myers Squibb

⁷ Patients were randomly assigned to receive a 300-mg clopidogrel loading dose or placebo 3 to 24 hours before PCI (at this stage all the patients also received 325mg of aspirin) Thereafter, all patients received clopidogrel, 75mg/d, through day 28. from day 29 through 12 months patients in the loading-dose group received clopidogrel, 75mg/d, and those in the control group received placebo. Both groups continued to receive standard therapy including aspirin (81-325 mg/d, at the discretion of the investigator, until the end of the 12-month treatment period.

⁸ 20% of all patients could be prespecified at the time of randomization to receive a GpIIb-IIIa receptor antagonist (primarily abciximab) at the time of PCI.

<p>following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 288(19):2411-2420. Ref ID: 3371 CREDO</p>			<p>placement with or without conventional balloon angioplasty or another revascularization device; were at least 21 years old.</p> <p>Exclusion criteria: major exclusion criteria included 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: GpIIb/IIIa inhibitor within 7 days, clopidogrel within 10 days, or thrombolytics within 24 hours.</p> <p>Baseline demographics in the 2 treatment groups were well matched, although there was less use of statins and calcium channel blockers in the clopidogrel arm</p>				<p>incidence of the composite of death, MI, or urgent target vessel revascularization in the per-protocol population</p>	<p>* 28-days composite endpoint</p> <p>Clopidogrel pre-treatment did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days (p=0.23). Results were similar when the 28-day endpoint was analyzed in the ITT population (p=0.15).</p> <p>*Adverse events</p> <p>Risk of major bleeding at 1 year increased, but not significantly (8.8% clopidogrel vs 6.7% with placebo, p=0.07)</p> <p><u>Reasons for discontinuation</u></p> <p>A total of 63% of patients in the clopidogrel group and 61% of patient in the control groups completed the full 1-year course of study drug.</p> <table data-bbox="1619 914 1912 1161"> <tr> <td>Clopidogrel group:</td> <td>N=</td> </tr> <tr> <td>Total:</td> <td>411</td> </tr> <tr> <td>Patient choice</td> <td>137</td> </tr> <tr> <td>Adverse event</td> <td>142</td> </tr> <tr> <td>Outcome event</td> <td>65</td> </tr> <tr> <td>Physician decision</td> <td>33</td> </tr> <tr> <td>Require contraindicated medication</td> <td>9</td> </tr> <tr> <td>Other</td> <td>25</td> </tr> </table> <table data-bbox="1619 1190 1912 1324"> <tr> <td>Placebo group:</td> <td>N=</td> </tr> <tr> <td>Total:</td> <td>420</td> </tr> <tr> <td>Patient choice</td> <td>166</td> </tr> <tr> <td>Adverse event</td> <td>119</td> </tr> <tr> <td>Outcome event</td> <td>64</td> </tr> </table>	Clopidogrel group:	N=	Total:	411	Patient choice	137	Adverse event	142	Outcome event	65	Physician decision	33	Require contraindicated medication	9	Other	25	Placebo group:	N=	Total:	420	Patient choice	166	Adverse event	119	Outcome event	64	
Clopidogrel group:	N=																																		
Total:	411																																		
Patient choice	137																																		
Adverse event	142																																		
Outcome event	65																																		
Physician decision	33																																		
Require contraindicated medication	9																																		
Other	25																																		
Placebo group:	N=																																		
Total:	420																																		
Patient choice	166																																		
Adverse event	119																																		
Outcome event	64																																		

								Physician decision 27 Require contraindicated medication 8 Other 36	
Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.[see comment][erratum appears in N Engl J Med 2001 Dec 6;345(23):1716]. New England Journal of Medicine 2001; 345(7):494-502. Ref ID: 3346 CURE	RCT double blind multicentre 1++	N= 12,562 from 482 centres in 28 countries. 2,840 were diabetics (22.6%)	Inclusion criteria: patients who presented with acute coronary syndromes without ST-segment elevation. Patients were eligible for the study if they had been hospitalized within 24 hours after the onset of symptoms and had either electrocardiographic changes or an elevation in the serum level of cardiac enzymes or markers at entry. Exclusion criteria: We excluded patients with contraindications to antithrombotic or antiplatelet therapy, those who were at high risk for bleeding or severe heart failure, those who were taking oral anticoagulants, and those who had undergone coronary revascularization in the previous three months or had received intravenous glycoprotein IIb/IIIa receptor inhibitors in the previous three days. The groups were well balanced at baseline	Aspirin (75 to 325 mg daily) + clopidogrel (75 mg per day) ⁹ N= 6,259	Aspirin (75 to 325 mg daily) + Placebo N= 6,303	3-12 months (mean 9 months)	The first primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, the second primary outcome was the composite of the first primary outcome or refractory ischemia. The secondary outcomes were severe ischemia, heart failure, and the need for revascularization. The safety-	* Primary outcomes <u>The first primary outcome</u> occurred in 582 of the 6259 patients in the clopidogrel group (9.3%) as compared with 719 of the 6303 patients in the placebo group (11.4%) RR 0.80; 95%CI 0.72 to 0.90; P<0.001 The rate of the <u>second primary outcome</u> was also higher in the placebo group (1187 patients 18.8 %) than in the clopidogrel group (1035 patients 16.5%); RR 0.86; 95%CI 0.79 to 0.94; P<0.001 <i>The rate of each component of these composite outcomes also tended to be lower in the clopidogrel group. However, the clearest difference was observed in the rates of myocardial infarction. With respect to refractory ischemia, the difference was observed primarily in first events that occurred during the initial hospitalization (85 in the clopidogrel group as compared with 126 in the placebo group; RR 0.68; 95%CI 0.52 to 0.90; P=0.007) with little difference in the rate of rehospitalisation for unstable angina.</i> * Secondary outcomes Significantly fewer patients in the clopidogrel group than in the placebo	Sanofi-Aventis and Bristol-Myers Squibb

⁹ A loading dose of clopidogrel (300 mg orally) or matching placebo was administered immediately,

							<p>related outcomes were bleeding complications, which were categorized as life-threatening, major (requiring the transfusion of 2 or more units of blood), or minor.</p> <p>group had severe ischemia (176 patients [2.8%] vs. 237 patients [3.8%]; RR 0.74; 95%CI 0.61 to 0.90; P=0.003</p> <p>Significantly fewer patients in the clopidogrel group than in the placebo group had recurrent angina (1307 [20.9%] vs. 1442 [22.9%] RR 0.91 95%CI, 0.85 to 0.98; P=0.01</p> <p>Slightly fewer patients in the clopidogrel group underwent coronary revascularization during the study (36.% vs. 36.9%), but the difference was accounted for entirely by a difference in the rate of revascularization during the initial period of hospitalization (20.8% in the clopidogrel group vs. 22.7% in the placebo group, P=0.03).</p> <p>Radiologic evidence of heart failure was found in fewer patients in the clopidogrel group (229 [3.7%] vs. 280 [4.4%] in the placebo group; RR 0.82; 95%CI 0.69 to 0.98; P=0.03).</p> <p>* Adverse events Major bleeding was significantly more common in the clopidogrel group (3.7% in the clopidogrel group as compared with 2.7% in the placebo group. RR 1.38; 95%CI 1.13 to 1.67; P=0.001</p> <p>There was no statistical significant difference in the incidence of life-threatening bleeding episodes between the two groups</p> <p>There was no excess rate of fatal bleeding, bleeding requiring surgical</p>	
--	--	--	--	--	--	--	--	--

							<p>intervention, or hemorrhagic stroke. The excess major bleeding episodes were gastrointestinal haemorrhages and bleeding at the sites of arterial punctures.</p> <p>The number of patients who required the transfusion of 2 or more units of blood was higher in the clopidogrel group (177 [2.8%]) than in the placebo group (137 [2.2%] p=0.02).</p> <p>Overall, the risk of minor bleeding was significantly higher in the clopidogrel group than in the placebo group (322 [5.1%] vs. 153 [2.4%]) P<0.001</p> <p>Temporal trends The rate of the first primary outcome was lower in the clopidogrel group both within the first 30 days after randomization (RR 0.79; 95%CI 0.67 to 0.92) and between 30 days and the end of the study (RR 0.82; 95%CI 0.70 to 0.95). Further analysis indicated that the benefit of clopidogrel was apparent within a few hours after randomization, with the rate of death from cardiovascular causes, nonfatal MI, stroke, or refractory or severe ischemia significantly lower in the clopidogrel group by 24 hours after randomization (1.4% in the clopidogrel group vs. 2.1% in the placebo group RR 0.66; 95%CI 0.51 to 0.86).</p> <p>Subgroup analysis The diabetic subgroup (N=2,840) suffered a higher vascular even rate than</p>	
--	--	--	--	--	--	--	---	--

								their non-diabetic counterparts. Given an endpoint of cardiovascular death, non fatal MI or stroke, 14.2% of those on combined therapy suffered such an event, and 16% of the aspirin-only group suffered from a vascular event. The relative benefit failed to achieve statistical significance.	
D. L. Bhatt, S. P. Marso, A. T. Hirsch, P. A. Ringleb, W. Hacke, and E. J. Topol. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. <i>American Journal of Cardiology</i> 90 (6):625-628, 2002. CAPRI (Diabetes)	RCT 1+	N=3,866 taken from the CAPRI ¹⁰ study	Inclusion criteria: Diabetes and atherosclerosis, There were no significant differences between the groups at baseline except in hypertension (68% in the clopidogrel group and 64% in the aspirin, p=0.025)	N=1,914 clopidogrel	N=1,952 aspirin		Primary composite endpoint: Vascular death, all-cause stroke, myocardial infarction or rehospitalisation for ischaemia or bleeding ¹¹	* Primary composite endpoint: The event rate per year was 15.6% in the clopidogrel group and 17.7% in the aspirin group, with an absolute risk reduction of 2.1% (p=0.042) ¹² . Although the absolute risk reduction was larger in the diabetic patients due to their higher event rates, the relative risk reduction achieved with clopidogrel was similar in diabetics and nondiabetics (12.5% vs 6.1% NS). NNT of 48 Clopidogrel prevented 21 more events per 1000 diabetic patients treated than did ASA. In the subset of diabetic participants who received insulin at baseline (N=1,134) the end point rates were higher (17.7% with clopidogrel and 21.5% with aspirin, the absolute risk reduction was NS). NNT of 26.3. In this population clopidogrel prevented 38 additional events per 1000 insulin-treated patients than did ASA.	Not reported

¹⁰ Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events Lancet 1996. In this study clopidogrel was shown to be superior to ASA as it significantly lowered the risk of the primary endpoint by an additional 8.7% (95%CI 0.3 to 16.5) compared with ASA.

¹¹ Compared with the original CAPRI primary cluster endpoint, this is a slightly 'softer' endpoint.

¹² The event rate per year was 12.7% in the 7,594 nondiabetic patients randomized to aspirin and 11.8% in the 7,639 nondiabetic patient randomized to clopidogrel. (p=0.096)

								<p>* Number rehospitalisation for Ischaemia or bleeding events</p> <p>The incidence of rehospitalisation for any ischaemic or bleeding event was significantly lower with clopidogrel than with the aspirin group; 13.3% vs 15.6%, p=0.047 (relative risk reduction 14.5% (0.2 to 26.7, 95% CI).</p> <p>The incidence of rehospitalisation for any bleeding event was significantly lower with clopidogrel than with the aspirin group; 1.8% vs 2.8%, p=0.031 (relative risk reduction 37.0% (3.8 to 58.7, 95% CI).</p> <p>The incidence of rehospitalisation for any ischaemic event was NS.</p>	
Steinhubl SR, Berger PB, Mann JT, III, Fry ET, DeLago A, Wilmer C et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 288(19):2411-2420. Ref ID: 3371	RCT double blind, multicentre 1++	N=2,116 from 99 centres in North America	Inclusion criteria: patient who had symptomatic coronary arteria disease with objective evidence of ischaemia, 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; were at least 21 years old. Exclusion criteria: major exclusion criteria included contraindications to	Aspirin + Clopidogrel ^{13 14} N=1,053	Aspirin + placebo N= 1,063	12 months	One-year of the composite of death, MI, or stroke in the ITT population 28-day incidence of the composite of death, MI, or urgent target vessel revascularization in the per-protocol population	<p>* One-year composite endpoint</p> <p>At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke. 95%CI (3.9% to 44.4%), p=0.02. Absolute reduction, 3%</p> <p>* 28-days composite endpoint</p> <p>Clopidogrel pre-treatment did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days (p=0.23). Results were similar when the 28-day endpoint was analyzed in the ITT</p>	Sanofi-Aventis and Bristol-Myers Squibb

¹³ Patients were randomly assigned to receive a 300-mg clopidogrel loading dose or placebo 3 to 24 hours before PCI (at this stage all the patients also received 325mg of aspirin) Thereafter, all patients received clopidogrel, 75mg/d, through day 28. from day 29 through 12 months patients in the loading-dose group received clopidogrel, 75mg/d, and those in the control group received placebo. Both groups continued to receive standard therapy including aspirin (81-325 mg/d, at the discretion of the investigator, until the end of the 12-month treatment period.

¹⁴ 20% of all patients could be prespecified at the time of randomization to receive a GpIIb-IIIa receptor antagonist (primarily abciximab) at the time of PCI.

CREDO			<p>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: GpIIb-IIIa inhibitor within 7 days, clopidogrel within 10 days, or thrombolytics within 24 hours.</p> <p>Baseline demographics in the 2 treatment groups were well matched, although there was less use of statins and calcium channel blockers in the clopidogrel arm</p>					<p>population (p=0.15).</p> <p>*Adverse events</p> <p>Risk of major bleeding at 1 year increased, but not significantly (8.8% clopidogrel vs 6.7% with placebo, p=0.07)</p> <p><u>Reasons for discontinuation</u></p> <p>A total of 63% of patients in the clopidogrel group and 61% of patients in the control groups completed the full 1-year course of study drug.</p> <table data-bbox="1619 663 1912 1190"> <tr> <td>Clopidogrel group:</td> <td>N=</td> </tr> <tr> <td>Total:</td> <td>411</td> </tr> <tr> <td>Patient choice</td> <td>137</td> </tr> <tr> <td>Adverse event</td> <td>142</td> </tr> <tr> <td>Outcome event</td> <td>65</td> </tr> <tr> <td>Physician decision</td> <td>33</td> </tr> <tr> <td>Require contraindicated medication</td> <td>9</td> </tr> <tr> <td>Other</td> <td>25</td> </tr> <tr> <td>Placebo group</td> <td>N=</td> </tr> <tr> <td>Total:</td> <td>420</td> </tr> <tr> <td>Patient choice</td> <td>166</td> </tr> <tr> <td>Adverse event</td> <td>119</td> </tr> <tr> <td>Outcome event</td> <td>64</td> </tr> <tr> <td>Physician decision</td> <td>27</td> </tr> <tr> <td>Require contraindicated medication</td> <td>8</td> </tr> <tr> <td>Other</td> <td>36</td> </tr> </table>	Clopidogrel group:	N=	Total:	411	Patient choice	137	Adverse event	142	Outcome event	65	Physician decision	33	Require contraindicated medication	9	Other	25	Placebo group	N=	Total:	420	Patient choice	166	Adverse event	119	Outcome event	64	Physician decision	27	Require contraindicated medication	8	Other	36	
Clopidogrel group:	N=																																								
Total:	411																																								
Patient choice	137																																								
Adverse event	142																																								
Outcome event	65																																								
Physician decision	33																																								
Require contraindicated medication	9																																								
Other	25																																								
Placebo group	N=																																								
Total:	420																																								
Patient choice	166																																								
Adverse event	119																																								
Outcome event	64																																								
Physician decision	27																																								
Require contraindicated medication	8																																								
Other	36																																								