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Sponsor/company:	Bristol-Myers Squibb and Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00174759
		Study Code:	C_9253
Generic drug name:	Clopidogrel	**Date:**	07/12/2007

Title of the study:	A double-blind, randomized study of clopidogrel 75 mg/day vs placebo, on a background of ASA 75-100 mg/day, in Peripheral Arterial Disease (PAD) patients receiving a unilateral below-knee bypass graft. The CASPAR 2004 study. (Clopidogrel and Acetyl salicylic acid in bypass Surgery for Peripheral ARterial disease).
Investigator(s):	Prof. Jill JF Belch, Department of Vascular Medicine & Biology, Ninewells Hospitals & Medical School, Dundee DD1 9SY, Scotland, UK; Prof. John A. Dormandy, St George's Hospital, London, UK.
Study center(s):	92 centers in 14 countries.
Study period: Date first subject enrolled: 29 Sep 2004 Date last subject completed: 24 Aug 2006	**Phase of development:** Phase III
Objectives:	The **primary objective** of this study was to evaluate whether clopidogrel 75 mg o.d. vs placebo (on a background of ASA 75–100 mg/d) led to an increased rate of primary patency, limb salvage and survival, in patients receiving a below-knee bypass graft for the treatment of PAD. The **secondary objectives** were the comparison, between the two treatment groups, of : - Primary patency, - Assisted primary patency, - Cardiovascular death, myocardial infarction, stroke, any amputation above the ankle, - Ankle Brachial Pressure Index (ABPI) changes from baseline.
Methodology:	Prospective, multicenter, double-blind, randomized, parallel-group, controlled trial of clopidogrel vs placebo, on a background of ASA. Event-driven trial (193 expected events). The randomization was not stratified according to centers but stratified according to the type of graft.
Number of subjects:	Planned: 851 Randomized: 851 Treated: 848

Diagnosis and criteria for inclusion:	Patient aged = 40 years and < 80 years; Chronic background treatment with daily ASA or Triflusal, whatever the dose, started at least 4 weeks before surgery; Unilateral below-knee bypass graft for atherosclerotic PAD within the previous 4 days; Written informed consent obtained.	
Investigational product: Dose: Administration:	Clopidogrel 75 mg tablet once daily Oral	
Duration of treatment: between 6 and 24 months		**Duration of observation:** NA
Reference therapy: Dose: Administration:	Matching Placebo Clopidogrel placebo tablet oral	

Criteria for evaluation:	**Primary criterion of efficacy:** The primary criterion was defined as the first occurrence, over the duration of follow-up, of the following: • Occlusion of the index bypass graft documented by any imaging procedure (e.g. duplex scanning , angiography), OR • Any revascularization procedure on the index bypass graft or para-anastomotic region defined as 2 cm proximal or distal to the bypass graft anastomosis (graft replacement or endovascular intervention), OR • Amputation above the ankle of the affected limb, OR • Death. **Secondary criteria of efficacy:** The secondary efficacy outcomes were as follows: - The first occurrence of any component of the following cluster of events: • Occlusion of the index bypass graft documented by an imaging procedure (e.g. Duplex scanning, angiography), OR • Any revascularization procedure of the index bypass graft (graft replacement or endovascular intervention), OR • Amputation above the ankle of the affected limb. - Each component of the above cluster was also analyzed separately. - Assisted primary patency rate. - The first occurrence of any component of the following cluster of clinical events over the duration of the follow-up: • Cardiovascular death, OR • Myocardial infarction, OR • Stroke, OR • Any amputation above the ankle. - Each category of events of the above cluster was also analyzed separately. - Change in ABPI. **Safety:** Safety outcomes, including bleeding classified as severe, moderate or mild according to the GUSTO classification, and other adverse events were examined throughout the study. The primary safety variable was severe bleeding occurring after the first intake of the study drug up to 28 days after the last dose and validated by the Adjudication Committee (fatal + non fatal severe bleeding).
Statistical methods:	The relative efficacy of clopidogrel versus placebo was assessed by comparing the survival curves for the two treatments using a two sided stratified log-rank test. Treatment effect as measured by the hazard ratio and its associated 95% confidence interval were estimated using Cox's proportional hazards model. In both of these analyses, the type of graft (venous or prosthetic) was used as the stratification factor. Statistical significance was claimed if the computed p-value was = 0.05. Covariate analyses and analyses of secondary variables were performed as supportive analyses. Safety was assessed by analysis of the incidence of bleeding events and all other reported serious and non-serious adverse events. The ITT population was the primary efficacy population and included all randomized patients. The PP population included all ITT patients who did not meet any major protocol deviation (including non compliance). The Safety population included all patients who received at least one dose (tablet) of the study drug.

Summary:	A total of 851 patients were enrolled in 92 centers from 14 countries in the CASPAR study. Of these patients, 425 were assigned to receive clopidogrel and 426 to receive placebo. The incidence of withdrawals after randomization was similar in both treatment groups (5.2% in the clopidogrel group and 5.9% in the placebo group), mainly due to consent withdrawal (3.2%) and lost to follow-up (2.2%). The ITT population comprised 851 patients and the safety population 848 patients. The PP population only comprised 761 patients, as 48 patients (11.3%) in the clopidogrel group and 42 patients (9.9%) in the placebo group had major protocol deviations; the main reasons being permanent discontinuation of study drug with less than 6 months of treatment (without primary outcome). The two treatment groups were similar with respect to demographic characteristics, medical history, hypertension, hyperlipidemia, diabetes, disease characteristics, prior and/or concomitant medication. There was a slight but significant imbalance in the proportion of patients with angina pectoris [96 patients (22.6%) in the clopidogrel group and 65 patients (15.3%) in the placebo group, p=0.007] and coronary artery disease [134 patients (31.5%) in the clopidogrel group and 103 patients (24.2%) in the placebo group p=0.017].

Results	**Efficacy** The results of the primary analysis (survival analysis) in the ITT population showed that the hazard rate of the primary outcome event was 57.3% (149 patients) in the clopidogrel group and 54.7% (151 patients) in the placebo group (HR=0.98, 95% CI = [0.78; 1.23], p=0.87). The median time to the primary outcome event was 548 days in the clopidogrel group and 560 days in the placebo group (p=0.86). Similar results were found in the PP population. When analysing the primary outcome event according to the type of graft (prosthetic or venous) in the ITT population, the results showed a statistically significant interaction between the type of graft and treatment (p=0.008). Therefore, the analysis by type of graft, which had been planned in the statistical analysis plan, appears to be justified. In patients who received prosthetic grafts, the hazard ratio in the ITT population was 0.65 (95% CI = [0.45; 0.95]), i.e. the risk of developing the primary outcome event was less likely to occur with clopidogrel than with placebo (meaning a proportional risk reduction of 35%), with a statistically significant difference between groups (p=0.027). The median time to the primary outcome event was 567 days in the clopidogrel group and 306 days in the placebo group (p=0.025). In patients who received venous grafts, the hazard ratio was 1.25 (95% CI = [0.94; 1.67]), i.e. the risk of developing the primary outcome event was more likely to occur with clopidogrel than with placebo, without a statistically significant difference between groups (p=0.13). The median time to the primary outcome event was 548 days in the clopidogrel group and not estimable in the placebo group (p=0.13). Similar results were found in the PP population. Regarding the secondary efficacy variables, no statistically significant difference was observed between the treatment groups overall. When analysing the secondary efficacy variables according to the type of graft, the results showed in patients with prosthetic grafts a statistical significant risk of developing the event which was less likely to occur with clopidogrel than with placebo for the combined secondary outcome events (HR=0.62, 95% CI = [0.42; 0.91], p=0.014; median time: 567 days with clopidogrel and 354 days with placebo, p=0.013), assisted primary patency (HR=0.61, 95% CI = [0.41; 0.91], p=0.016; median time: 567 days with clopidogrel and 383 days with placebo, p=0.015), first graft occlusion (HR=0.63, 95% CI = [0.42; 0.93], p=0.022; median time: 567 days with clopidogrel and 383 days with placebo, p=0.021) and first amputation above the ankle (of the index limb or other limb) (HR=0.48, 95% CI = [0.24; 0.96], p=0.038). In patients with venous grafts, no statistical significance was observed for any of the above criteria except for the risk of having the graft replacement which was statistically significantly more likely to occur with clopidogrel than with placebo (HR=2.16, 95% CI = [1.09; 4.31], p=0.028). Similar results were found in the PP population. Descriptive analysis of all individual outcome events showed that in patients who received prosthetic grafts the rates of outcome event were lower in the clopidogrel group than in the placebo group: 32.03% vs 47.20% for graft occlusions (p<0.05), 18.75% vs 29.60% for endovascular procedures/surgical revisions (p<0.05), 3.91% vs 6.40% for graft replacements, 9.4% vs 19.2% for amputations above the ankle of the index limb (p=0.025) and 0% vs 0.80% for amputations above the ankle of the other limb.

	In patients with venous grafts the rates of outcome event were similar in the clopidogrel group and in the placebo group: 17.51% vs 12.62% for graft occlusions, 15.49% vs 13.62% for endovascular procedures/surgical revisions, 8.42% vs 3.99% for graft replacements (p<0.05), 6.4% vs 7.0% for amputations above the ankle of the index limb and 0.34% vs 0.33% for amputations above the ankle of the other limb. Overall a total of 41 deaths occurred in the study with no statistically significant difference between groups: 6 patients (4.69%) in the clopidogrel group and 4 patients (3.20%) in the placebo group in patients with prosthetic grafts; and 18 patients (6.06%) vs 13 patients (4.32%) in patients with venous grafts, respectively. Regarding the survival analysis of the cardiovascular death, myocardial infarction or stroke in the ITT population, overall, no statistically significant difference was observed between the treatment groups (hazard ratio = 1.09, 95% CI = [0.65; 1.82], p=0.75). In patients with prosthetic grafts, the hazard ratio was 0.83 (95% CI = [0.25; 2.71]), i.e. the risk of developing a cardiovascular death, myocardial infarction or stroke was less likely to occur with clopidogrel than with placebo, with no statistically significant difference between the treatment groups (p=0.75). In patients with venous grafts, the hazard ratio was 1.16 (95% CI = [0.66; 2.06]), i.e. the risk of developing the cardiovascular death, myocardial infarction or stroke was more likely to occur with clopidogrel than with placebo, with no statistically significant difference between the treatment groups (p=0.60). The multivariate analyses of the potential risk factors for the occurrence of the primary outcome event according to the type of graft showed in the ITT population that in patients with prosthetic grafts 4 characteristics correlated significantly with the occurrence of the primary outcome event: indication for bypass graft (rest pain associated or not with claudication vs claudication, HR=1.21, 95% CI = [0.75; 1.96], p=0.019), post-operative ABPI of the index limb at V1 (<0.5 vs [0.5-0.9[, HR=1.90, 95% CI = [0.45; 8.00], p=0.033), statins at V2 (HR=0.61, 95% CI = [0.39; 0.96], p=0.033) and time from surgery to randomization (HR=1.30, 95% CI = [1.04; 1.63], p=0.023). In patients with venous grafts 2 significant risk factors were identified: age (<65 vs =65 years, p<0.001 and post-operative ABPI of the index limb at V1 (<0.5 vs [0.5-0.9[and =0.9 vs [0.5-0.9[, p<0.001). Coronary artery disease and previous cerebrovascular disease were also identified as statistically significant risk factors for death (HR=2.19, 95% CI = [1.18; 4.06], p=0.013) and for cardiovascular death, myocardial infarction, stroke or amputation above the ankle (index limb or other limb) (HR=1.48, 95% CI = [1.04; 2.11], p=0.029).

	Safety: The mean duration of treatment was lower in the clopidogrel group than in the placebo group (285.54 days and 296.74 days, respectively). Severe bleeding according to GUSTO definition occurred in 9 patients (2.7%) in the clopidogrel group and 5 patients (1.6%) in the placebo group (of which 2 and 1, respectively were fatal), with no statistically significant difference between groups. The incidences of other bleeding were statistically significantly ($p<0.001$) higher in patients who received clopidogrel compared to placebo (3.8% vs 0.9% for moderate bleeding and 10.8% vs 5.0% for mild bleeding). When analysing by type of graft, similar incidences were observed; considering the venous graft, the frequency of patients with mild bleeding was statistically significantly higher in the clopidogrel group (12.1%) than the one in the placebo group (5.4%), $p=0.004$. In the prosthetic graft population, no statistically significant difference between groups was reported (8.6% vs 4.8%, $p=0.23$). The results were similar in terms of moderate bleeding (venous graft: 3.7% in the clopidogrel group versus 0.7% in the placebo group, $p=0.012$; prosthetic graft: 3.9% vs 1.6%, $p=0.23$). No statistically significant differences between the treatment groups were observed regarding TEAEs, possibly related TEAEs, serious TEAEs, serious TEAEs possibly related, severe TEAEs, TEAEs leading to permanent study medication discontinuation and TEAEs leading to death. Overall, the incidence of TEAEs was similar between the treatment groups (47.7% in the clopidogrel group and 46.9% in the placebo group). The most frequently reported TEAEs were related to vascular disorders (12.9% in the clopidogrel group and 15.6% in the placebo group), followed by infections and infestations disorders (13.6% vs 11.6%, respectively). The incidence of SAEs was similar in both treatment groups (31.5%). Frequency of patients with at least one TEAE considered by the Investigator to be study drug-related was slightly lower in the clopidogrel group than in the placebo group (0.9% vs 1.7%, respectively); the most frequently reported TEAEs study drug-related were pertinent to cardiac disorders and nervous system disorders.
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