Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial

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Objective: **Dual antiplatelet therapy with clopidogrel plus acetylsalicylic acid (ASA) is superior to ASA alone in patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention. We sought to determine whether clopidogrel plus ASA conferred benefit on limb outcomes over ASA alone in patients undergoing below-knee bypass grafting.**
Methods: **Patients undergoing unilateral, below-knee bypass graft for atherosclerotic peripheral arterial disease (PAD) were enrolled 2 to 4 days after surgery and were randomly assigned to clopidogrel 75 mg/day plus ASA 75 to 100 mg/day or placebo plus ASA 75 to 100 mg/day for 6 to 24 months. The primary efficacy endpoint was a composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death. The primary safety endpoint was severe bleeding (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries [GUSTO] classification).**
Results: **In the overall population, the primary endpoint occurred in 149 of 425 patients in the clopidogrel group vs 151 of 426 patients in the placebo (plus ASA) group (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.78-1.23). In a prespecified subgroup analysis, the primary endpoint was significantly reduced by clopidogrel in prosthetic graft patients (HR, 0.65; 95% CI, 0.45-0.95; $P = .025$) but not in venous graft patients (HR, 1.25; 95% CI, 0.94-1.67, not significant [NS]). A significant statistical interaction between treatment effect and graft type was observed ($P_{interaction} = .008$). Although total bleeds were more frequent with clopidogrel, there was no significant difference between the rates of severe bleeding in the clopidogrel and placebo (plus ASA) groups (2.1% vs 1.2%).**
Conclusion: **The combination of clopidogrel plus ASA did not improve limb or systemic outcomes in the overall population of PAD patients requiring below-knee bypass grafting. Subgroup analysis suggests that clopidogrel plus ASA confers benefit in patients receiving prosthetic grafts without significantly increasing major bleeding risk. (J Vasc Surg 2010;52:825-33.)**

The benefit of antiplatelet therapy in patients with peripheral arterial disease (PAD) for the secondary prevention of cardiovascular (CV) events has been evaluated[1-3] and recommendations made for its use.[4-6] It should be routine practice to prescribe such agents in the absence of contraindications. An added advantage is the potential to reduce bypass graft occlusion.[7] About 10% to 15% of patients with PAD will receive bypass grafting.[4] The Antiplatelet Trialists' Collaboration[7] found that antiplatelet therapy was associated with a relative risk reduction of 43% (SD 8%; $P < .001$) in peripheral graft occlusion. A similar benefit was shown in a Cochrane meta-analysis[8] which had an overall positive effect on primary patency 12 months postoperatively (odds ratio [OR], 0.59; 95% confidence interval [CI], 0.45-0.79).

Nevertheless, despite the use of antiplatelet monotherapy, usually acetylsalicylic acid (ASA), a substantial risk of graft occlusion persists. The global incidence is reported to be 15% per year when a vein is used[9] and 20% with synthetic material (polytetrafluoroethylene)[10] rising to 45% and 75%, respectively, for below-knee grafts.

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Because these graft occlusions persist despite ASA therapy,[11] and because of the poor prognosis associated with secondary arterial reconstructions (reoperation),[12] vitamin K antagonists such as warfarin have gained popularity.[13] Although the Dutch Bypass Oral Anticoagulants study[14] reported a benefit of warfarin (target international normalized ratio 3.0-4.5) over ASA 80 mg/day for venous grafts in patients undergoing infrainguinal grafting, oral anticoagulation was associated with more bleeding.[15] Therefore, the coumadins have not been widely accepted for this indication.

Ticlopidine is a thienopyridine derivative[16] evaluated in 243 patients undergoing infrainguinal bypass grafting,[17] which showed a strong statistically significant benefit of ticlopidine vs placebo on venous bypass patency at 6, 12, and 24 months postoperatively (OR, 0.26; 95% CI, 0.11-0.63; OR, 0.38; 95% CI, 0.19-0.75; and OR, 0.37; 95% CI, 0.21-0.64, respectively).

Clopidogrel, a thienopyridine derivative, has been used successfully to decrease the risk of CV events in patients with PAD.[2] Its effects on inhibiting platelet adenosine diphosphate receptors complement the effects of ASA, and might be expected to further decrease peripheral bypass graft occlusion.

Clopidogrel was used in combination with ASA in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study,[18] in which it successfully reduced major CV endpoints. In the Clopidogrel and Metoprolol in Myocardial Infarction Trial,[19] clopidogrel plus ASA produced a highly significant reduction in death, reinfarction, or stroke ($P = .002$). Thus, in secondary prevention of CV events, a combination of ASA and clopidogrel conferred significant benefit. These trials led to the hypothesis for this trial, that a combination of ASA and clopidogrel might reduce the risk of occlusion of infrainguinal vascular grafts in patients with PAD, compared to ASA alone.

METHODS

Trial design. Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease (CASPAR) was a prospective, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of clopidogrel plus ASA as compared to ASA alone in patients undergoing unilateral below-knee arterial bypass grafting as management for PAD (Fig 1).

The locked clean database provided the source for statistical analysis. Approval for the study was obtained from regional and local ethics committees, and the trial was performed in accordance with Good Clinical Practice regulations.[20] This study is registered with ClinicalTrials.gov (NCT00174759).

Patients. Patients undergoing vascular grafting as a treatment for PAD were eligible for recruitment to the trial 2 to 4 days after bypass surgery. The postoperative lag-period of 2 days was selected by the vascular surgeons involved to allow hemostasis of the surgical wound to be complete. Patients had to satisfy inclusion criteria: age ≥40 and ≤80 years; informed consent was obtained before the conduct of any study-related procedure; chronic background treatment with daily ASA, of any dose, started at least 4 weeks before surgery (although a window of a few days without ASA before surgery was acceptable, according to local practice); a postrandomization dose of ASA between 75 and 100 mg/day; unilateral below-knee (ie, the distal anastomosis was below the level of the knee joint) bypass graft for atherosclerotic PAD; patent index graft demonstrated during bypass surgery, or between surgery and the time of randomization; and no clinical evidence of graft occlusion at randomization.

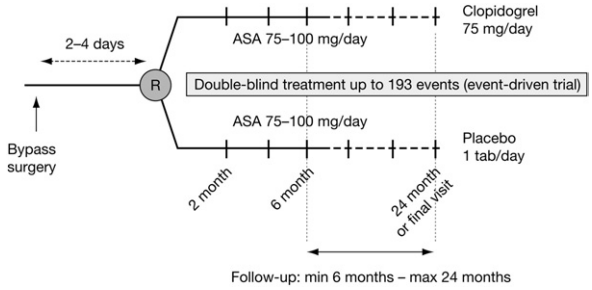

Fig 1. Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease (CASPAR) study design. R = randomization stratified by graft type (venous or prosthetic). *ASA*, Acetylsalicylic acid.

The main exclusion criteria were: onset of PAD symptoms before the age of 40 years; nonatherosclerotic vascular disease; patients receiving aortobifemoral, iliac-femoral, or crossover (femoral-femoral) grafts, or undergoing peripheral transcutaneous angioplasty during the same surgery; significant bleeding risk, such as current active bleeding at the surgical site; withdrawal of an epidural catheter less than 12 hours before randomization; peptic ulceration within 12 months of randomization; previous or current intracranial hemorrhage or hemorrhagic stroke; any history of severe spontaneous bleeding; current warfarin therapy or anticipated need for warfarin; concomitant additional antiplatelet agents or thrombolytic agents. Study drug was temporarily stopped if thrombolytic therapy became necessary during the study.

High-dose unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) was used during surgery and up to 12 hours before randomization, according to local practice, but not thereafter. From randomization day, either dextran, low-dose UFH (≤10,000 IU/day), or LMWH at a dose appropriate for prevention of deep venous thrombosis was permitted when indicated. Episodic use of cyclooxygenase-2 inhibitors (not greater than 3 weeks' continuous use) was allowed. The use of cyclooxygenase-1 nonsteroidal anti-inflammatory drugs was discouraged but, if necessary, they were allowed only at a low dose, for no longer than 7 days, and the study drug was withheld for the duration of treatment.

Procedures. After providing written informed consent, patients were randomly assigned either to clopidogrel

75 mg/day plus low-dose ASA (75 to 100 mg/day), or to placebo plus low-dose ASA. The prespecified minimum duration of treatment and follow-up was 6 months and the maximum was 24 months. Study-drug assignment was performed centrally by an interactive voice-response system using a pre-established randomization scheme, stratified according to the graft type (venous or prosthetic, with the latter class including any composite graft in which prosthetic material was used). Within each stratum, patients were randomized to clopidogrel or placebo in a 1:1 ratio. Patients were considered to be randomized as soon as the treatment allocation was given via the interactive voice-response system. Study drug was initiated on the day of randomization. All patients also received standard therapy as appropriate (eg, statins, beta-blockers, wound care) at the discretion of the investigator and other responsible clinicians. The use of appropriate background CV risk-reduction therapy according to International Guidelines was emphasized to the investigators.

Follow-up evaluations (including physical examination, duplex scan, angiography, and ankle-brachial pressure index [ABPI]) were performed at 1 month, then every 6 months thereafter until 24 months or until the end of the trial. At these visits, patients' compliance was assessed, and all interventions, outcome events, and adverse events were recorded. All patients were to be followed until a common study end date based on the prespecified target of 193 primary outcome events. Between visits, ie, 3, 9, 15, and 21 months after randomization, the site investigator contacted the patient by phone to permit earlier collection of data regarding outcome events and possible adverse events, and to encourage the patient's compliance.

Endpoints. All occurrences of the primary endpoint were adjudicated on a blinded basis by the Clinical Endpoints Committee. The primary endpoint was defined as the first occurrence, over the duration of follow-up, of the following cluster of events: occlusion of the index bypass graft documented by any imaging procedure (eg, duplex ultrasonography scan including B-mode imaging and Doppler ultrasound scan); or any surgical or endovascular revascularization procedure on the index bypass graft or para-anastomotic region; or amputation above the ankle of the index limb; or death. Secondary endpoints included the first occurrence of any individual component of the primary endpoint, and the first occurrence of the following during follow-up: CV death, or myocardial infarction, or stroke, or any amputation above the ankle.

Analysis of the primary endpoint was also prespecified in the two subgroups of graft type (venous or prosthetic) ie, where those with each type of graft were examined separately for primary endpoint occurrence between those receiving clopidogrel and those receiving placebo.

The primary safety endpoint was severe bleeding defined according to the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) classification.[21] Moderate and mild bleeding according to the GUSTO criteria were also examined.

Statistical analyses. Based on the target number of events (193) and expected relative efficacy, we planned to enroll approximately 1460 patients. The incidence of primary graft occlusion for the placebo group was projected from the ticlopidine arm of the Becquemin study,[17] in which approximately 29% of the ticlopidine-treated patients had experienced primary bypass graft occlusion/failure or death at 24 months. A similar 'failure' rate would be expected in the placebo group in the current study. There were no available results on which to base the efficacy of clopidogrel in this population. However, a 30% relative risk reduction in the incidence of primary bypass graft failure would be considered clinically important. Therefore, a total of 193 primary events were needed to detect a 30% relative reduction in the 2-year primary event rate from 28% to 19.6% with 80% power at the two-sided, .05 significance level, assuming a 21-month recruitment period and a 15% dropout rate at 2 years. All efficacy analyses were performed on an intention-to-treat basis, with the inclusion of all patients according to their randomly assigned treatment group, and the inclusion of outcomes occurring from randomization of the first patient in September 2004 to the study end date of August 2006. For the primary analysis, all 'failures' occurring after premature permanent discontinuation of the study drug were included, follow-up evaluations and study visits continued where possible, and safety outcomes (including bleeding and adverse events) were monitored throughout. The 'all treated-patients' population (used for the safety analyses) was defined as all randomized patients who received at least one dose of the study drug.

The primary efficacy of clopidogrel as compared to a placebo was assessed using a two-sided log-rank test. The treatment effect as measured by hazard ratio (HR) and 95% CI was estimated using the Cox proportional hazards model. In both these analyses, the type of graft (venous or prosthetic) was used as the stratification factor. Multivariate analyses of the potential risk factors for the primary outcome were performed, including gender, smoking habit, diabetes, medical history, and PAD stage. Cumulative incident event curves were also calculated. A statistical comparison of the safety event rates in the two groups was also performed with Pearson's χ^2 test. A preplanned subgroup analysis by graft type (venous or prosthetic) was included as part of the statistical plan document. This document was finalized, completed, and approved by the Steering Committee before initiation of data analysis.

RESULTS

Patient characteristics. A total of 851 patients were enrolled, as the requisite target event number was reached earlier than planned. Patients were enrolled in 87 sites, in 13 European countries and Australia, between September 2004 and August 2006. Of these, 425 were randomized to receive clopidogrel and ASA (venous grafts, n = 297; prosthetic grafts, n = 128), and 426 to receive placebo plus ASA (venous grafts, n = 301; prosthetic grafts, n = 125). Patient demographics and indication for bypass surgery are

Table I. Demographics of the CASPAR population

	Placebo (n = 426)	*Clopidogrel (n = 425)*
Mean age (y) (SD)	65.6 (8.5)	66.5 (8.7)
Male (%)	75.8	75.5
Mean BMI (kg/m^2) (SD)	25.7 (4.2)	25.6 (4.3)
Current smoker (%)	36.4	38.8
Hypertension (%)	70.0	70.1
Hyperlipidemia (%)	48.8	50.4
CAD and/or CRVD (%)	31.0	38.4[a]
Diabetes (%)	38.0	37.4
Mean preoperative ABPI of the index limb (SD)	0.46 (0.26)	0.44 (0.25)
PAD symptoms (%)		
Claudication only	32.6	34.1
Rest pain	26.5	26.1
Ulcers/gangrene	39.9	39.3
Distal anastomosis (%)		
Below-knee popliteal	74.8	75.5
Below-knee popliteal crural	22.1	20.7
Beyond popliteal pedal	3.1	3.8
Concomitant medication (%)		
Statins	46.8	47.8
ACE inhibitors	39.9	46.7
Beta-blockers	33.9	36.8
Diuretics	30.8	34.2

ABPI, Ankle-brachial pressure index; *ACE,* angiotensin-converting enzyme; *BMI,* body mass index; *CAD,* coronary artery disease; *CASPAR,* Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease; *CRVD,* cerebrovascular disease; *PAD,* peripheral arterial disease.
[a]$P < .05$ vs placebo.

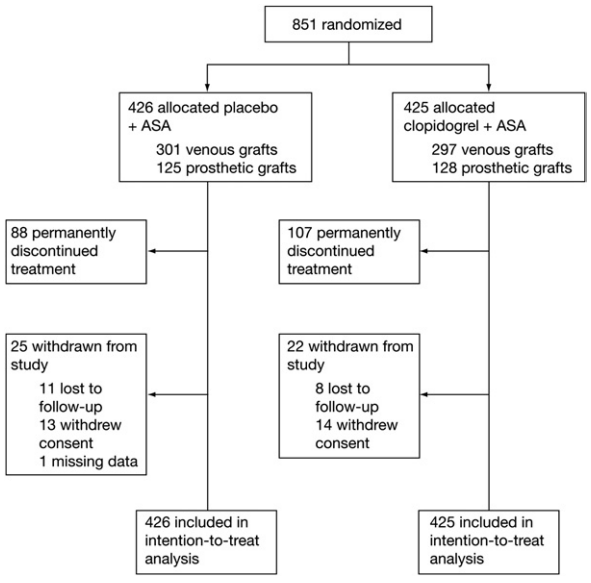

Fig 2. Distribution of patients. *ASA,* Acetylsalicylic acid.

shown in Table I; Fig 2 describes the patient flow. Similar incidences of diabetes were present in both treatment groups (39.0% and 34.8% for venous and prosthetic graft patients, respectively). Treatment was permanently discontinued by 88 patients (21.0%) in the placebo group and 107 patients (25.2%) in the clopidogrel group. However, none of the results below changed when the analyses were carried out on the on-treatment group alone. A total of 21 patients (4.9%) in the clopidogrel group and 3 patients (0.7%) in the placebo group discontinued medication because of bleeding.

Table II. Intraoperative, perioperative, and postoperative patency of grafts

	Placebo (n = 426)	*Clopidogrel (n = 425)*
Measurement of the intraoperative or perioperative graft patency (%)[a]		
Doppler	47.4	45.0
Duplex scanning	46.0	48.3
Angiography	27.9	28.5
Other	4.5	4.7
Mean postoperative ABPI of the index limb (SD)	0.89 (0.21)	0.87 (0.21)

ABPI, Ankle-brachial pressure index.
[a]Some sites used more than one method/patient.

Table III. Antithrombotic and anticoagulant therapy between surgery and randomization

	Placebo (n = 426)	*Clopidogrel (n = 425)*	*Total*
ASA (%)	69.7	76.2	73.0
Mean total ASA daily dose (mg) (SD)	94.8 (31.2)	97.0 (29.4)	96.0 (30.3)
UFH (%)	29.3	25.4	27.4
LMWH (%)	72.3	74.4	73.3
Both UFH and LMWH (%)	11.7	8.2	10.0
Dextran (%)	2.1	4.5	3.3
Others (%)	1.6	3.1	2.4

ASA, Acetylsalicylic acid; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin.

Forty-seven patients (5.5%) were withdrawn from the study: 19 patients (2.2%) were lost to follow-up, 27 patients (3.2%) withdrew consent, and 1 patient had missing data. Median duration of follow-up in the clopidogrel group was 364 days (minimum–maximum: 1-598), and 364 days (2-598) in the placebo group. The median duration of trial drug administration was 351 days (2-598) and 334 days (1-594) in the clopidogrel and placebo groups, respectively.

The means of assessment of the graft patency intraoperatively, perioperatively, or postoperatively are detailed in Table II. The study drug was initiated in both groups after a median time of 3 days (interquartile range, Q1-Q3: 2-4 days) after surgery. Seventy percent of the patients received ASA between operation and randomization in the placebo group compared with 76% in the clopidogrel group. Table III shows the antithrombotic therapy in each group between surgery and randomization.

Efficacy endpoints. Follow-up with respect to the primary efficacy endpoint was complete in 97.8% of patients

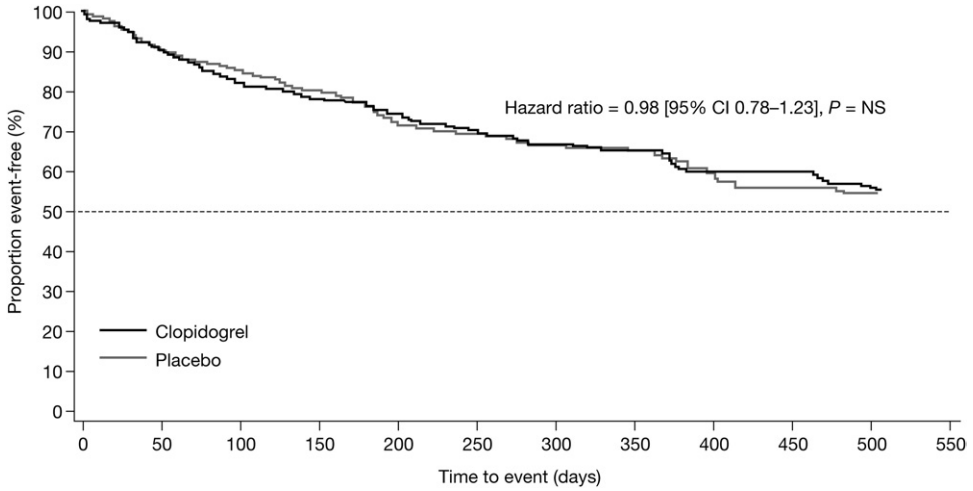

Fig 3. Kaplan-Meier curves of time to primary outcome event (graft occlusion/revascularization/replacement, amputation above ankle, death) in the total population. *CI,* Confidence interval; *NS,* not significant.

Table IV. Primary endpoint, graft occlusions, and amputations split by graft type

	Placebo (n = 426)	*Clopidogrel (n = 425)*	*Hazard ratio (95% CI)*
Primary endpoint			
All grafts	151	149	0.98 (0.78-1.23)
Venous	85	101	1.25 (0.94-1.67)
Prosthetic	66	48	0.65 (0.45-0.95)[b]
Graft occlusions[a]			
All grafts	97	93	0.94 (0.71-1.25)
Venous	38	52	1.45 (0.95-2.20)
Prosthetic	59	41	0.63 (0.42-0.93)[c]
Amputations[a]			
All grafts	45	31	0.68 (0.43-1.08)
Venous	21	19	0.93 (0.50-1.72)
Prosthetic	24	12	0.48 (0.24-0.96)[d]
Death			
All grafts	17	24	1.44 (0.77-2.68)
Venous	13	18	1.43 (0.70-2.91)
Prosthetic	4	6	1.51 (0.42-5.33)

CI, Confidence interval.
P values calculated using log-rank test.
[a]first episode.
[b]$P = .025$.
[c]$P = .021$.
[d]$P = .034$; all other *P* values were nonsignificant ($P \geq .05$).

(8 and 11 patients were lost to follow-up in the clopidogrel and placebo group, respectively).

The primary efficacy results are shown in Fig 3 and Table IV. There were 300 primary outcome events in the overall population, with no statistically significant difference between the two treatment groups (HR, 0.98; 95% CI, 0.78-1.23; $P = .87$).

However, in a prospectively defined analysis, there was a significant statistical interaction between treatment effect and type of graft used ($P = .008$ using the Wald test). There was no statistically significant difference in the incidence of primary events when a venous graft was used (HR, 1.25; 95% CI, 0.94-1.67). By contrast, in the 253 prosthetic graft patients, the addition of clopidogrel resulted in a statistically significant 35% relative risk reduction in primary outcome events (HR, 0.65; 95% CI, 0.45-0.95; $P = .025$; Fig 4; Table IV). In placebo patients receiving a prosthetic graft, the number of graft occlusions was 59 (47%) compared with 41 (32%) in the clopidogrel group (HR, 0.63; 95% CI, 0.42-0.93; $P = .021$), whereas the number of amputations above the ankle was 24 (19.2%) in the placebo group compared with 12 (9.4%) in the clopidogrel group (HR, 0.48; 95% CI, 0.24-0.96; $P = .034$). Revascularization and death incidences were similar between treatment groups (HR, 0.89; 95% CI, 0.65-1.23; and HR, 1.44; 95% CI, 0.77-2.68, respectively).

In the multivariate analysis of the primary outcome event, there was no effect of gender, smoking habit, diabetes, history of CAD or cerebrovascular disease, or PAD stage (II, III, or IV). However, there was an independent predictive effect of graft type (HR venous vs prosthetic, 0.50; 95% CI, 0.39-0.65; $P < .001$), of age (HR, <65 vs >65 years: 0.71; 95% CI, 0.56-0.91; $P = .006$) and the distal sites of anastomosis (popliteal vs crural/pedal: HR, 0.74; 95% CI, 0.56-0.97; $P = .032$). Although there was no predictive effect of the preoperative ABPI, there was an effect of postoperative ABPI (ABPI 0.5-0.9 vs <0.5: HR, 0.29; 95% CI, 0.16-0.50; and ABPI ≥0.9 vs <0.5: HR, 0.18; 95% CI, 0.10-0.32; $P < .001$). Interestingly, the presence of a statin in the concomitant medication at 1 month (visit 2) was also an independent predictor of favorable outcome (HR, 0.75; 95% CI, 0.59-0.97; $P = .028$), whereas the time from surgery to the first study drug intake, ASA dose (>100 vs ≤100 mg/day), ASA intake, and other antithrombotic treatments received from surgery to randomization were not.

Secondary outcomes included time to graft occlusion/graft intervention/amputation above the ankle of the af-

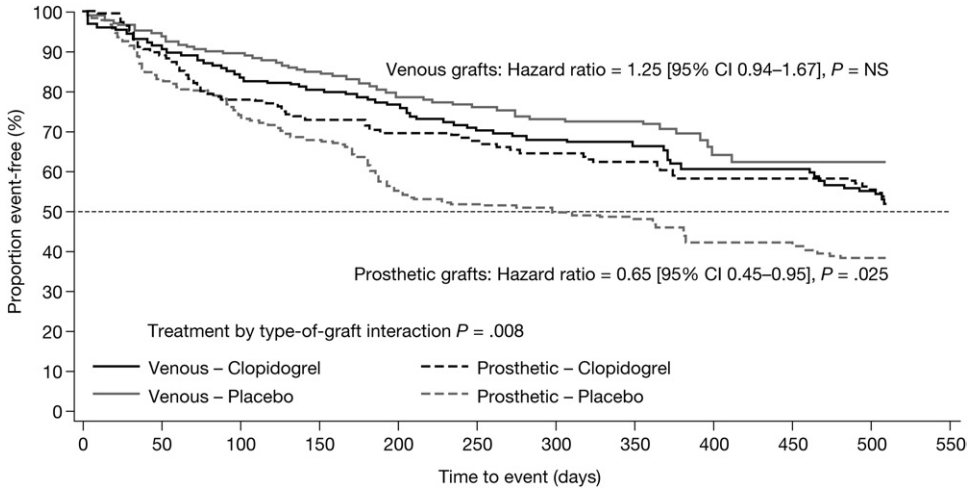

Fig 4. Kaplan-Meier curves of time to primary outcome event (graft occlusion/revascularization/replacement, amputation above ankle, death) by type of graft (intent-to-treat [ITT] population). *CI,* Confidence interval; *NS,* not significant.

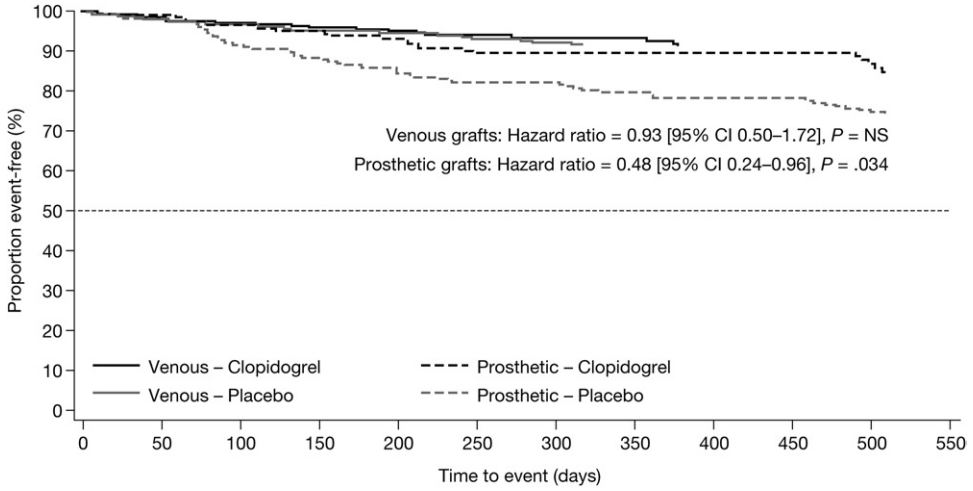

Fig 5. Kaplan-Meier curves of time to first amputation above the ankle of the affected limb: venous and prosthetic graft groups. *CI,* Confidence interval; *NS,* not significant.

fected limb in the intent-to-treat population. For all grafts, the HR (95% CI) was 0.91 (0.71-1.15). However, for patients receiving a prosthetic graft, this secondary outcome was statistically significant (HR, 0.62; 95% CI, 0.42-0.91; $P = .013$), as was amputation alone (HR, 0.48; 95% CI, 0.24-0.96; $P = .034$; Fig 5). There were no statistically significant differences in the occurrence of first myocardial infarction (HR, clopidogrel vs placebo: 0.81; 95% CI, 0.32-2.06; $P = .66$ [using the Wald test]), cardiovascular death (HR, 1.49; 95% CI, 0.73-3.01; $P = .27$), stroke (HR, 1.02; 95% CI, 0.41-2.57; $P = .96$), or amputation above the ankle (HR, 0.69; 95% CI, 0.44-1.09; $P = .11$). Overall, the HR of cardiovascular death, myocardial infarction, or stroke was 13.5% in the clopidogrel group and

Table V. Bleeding complications in the overall CASPAR population

	Placebo (n = 422)	*Clopidogrel (n = 426)*	P *value*
Total bleeding events[a]	30 (7.1%)	71 (16.7%)	< .001
Mild	21 (5.0%)	46 (10.8%)	.002
Moderate	4 (0.9%)	16 (3.8%)	.007
Severe	5 (1.2%)	9 (2.1%)	NS
Fatal	1 (0.2%)	2 (0.5%)	–

CASPAR, Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease; *NS,* nonsignificant.

[a]Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) classification definition (severe: intracranial hemorrhage, hemodynamic compromise; moderate: transfusion but no hemodynamic compromise; mild: no transfusion).

Table VI. Incidence of mild, moderate, and severe bleeding by type of graft

	Venous			*Prosthetic*		
	Placebo	*Clopidogrel*	P *value*[a]	*Placebo*	*Clopidogrel*	P *value*[a]
Mild bleeding, n (%)	16 (5.4)	36 (12.1)	.004	6 (4.8)	11 (8.6)	NS
Moderate bleeding, n (%)	2 (0.7)	11 (3.7)	.012	2 (1.6)	5 (3.9)	NS
Severe bleeding, n (%)	3 (1.0)	8 (2.7)	NS	2 (1.6)	1 (0.8)	NS

NS, Nonsignificant.
[a]Pearson χ^2 test, or when not appropriate, Fisher exact test.

10.2% in the placebo group (HR, 1.09; 95% CI, 0.65-1.82; $P = .75$).

Safety endpoints. Severe bleeding according to the GUSTO[21] definition occurred in a greater number of patients (9; 2.1%) in the clopidogrel group than the placebo group (5; 1.2%), of which 2 and 1, respectively, were fatal. This difference was not statistically significant (Table V). In contrast, a statistically significant increase in the incidence of both mild and moderate bleeding events was observed in the clopidogrel group vs placebo (Table V). The incidence of mild, moderate, and severe bleeding split by graft type (prosthetic and venous) is described in Table VI.

In the safety multivariate analysis for severe and moderate bleeding, the treatment group (clopidogrel vs placebo: HR, 2.84; 95% CI, 1.32-6.08; $P = .007$), previous heart failure (yes vs no: HR, 3.64; 95% CI, 1.50-8.84; $P = .004$), and the site of distal anastomosis (popliteal vs crural/pedal: HR, 0.33; 95% CI, 0.16-0.66; $P = .002$) were independent predictors of bleeding.

DISCUSSION

In this trial of patients requiring below-knee vascular grafting for PAD, there was no significant benefit within the whole population from dual clopidogrel and ASA therapy in terms of the primary endpoint. This is in line with the results of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, which reported that although there was a suggestion of benefit with clopidogrel in patients with symptomatic atherothrombosis, there was no significant benefit in the overall population that also included high-risk primary prevention patients.[22] In addition, a recent study reports that continuation of dual antiplatelet therapy beyond 12 to 24 months was not significantly more effective than transition to ASA monotherapy in reducing myocardial infarction or cardiac death in patients who had received a drug-eluting stent.[23] These data, however, were part of an interim analysis of two ongoing, underpowered studies in patients at low risk upon admission,[24] and require confirmation in larger randomized clinical trials.

In contrast to these reports, in this trial, when the preplanned subgroup of patients receiving prosthetic grafts was analyzed separately, a statistically significant result was seen showing that clopidogrel reduced the composite primary endpoint, and the secondary endpoints of graft occlusion and amputation. Because the study drug assignment was performed centrally using a pre-established randomization scheme, stratified according to graft type (venous or prosthetic), these results should be robust and would suggest that dual antiplatelet therapy would allow for a better outcome for prosthetic grafts to be achieved in the future. However, because these conclusions are based on secondary analyses, any clinical benefit of dual antiplatelet therapy in the subgroup of patients with prosthetic grafts would need to be confirmed.

This improvement in the composite graft/death endpoint was achieved at a slightly higher cost of increased bleeding in the mild and moderate GUSTO[21] bleeding categories, to the same level as seen in other ASA and clopidogrel combination studies, such as CURE[18] and Clopidogrel and Metoprolol in Myocardial Infarction Trial.[19] There were three fatal bleeds (one placebo and two clopidogrel), but the rates of GUSTO severe bleeding were not statistically significantly different between the treatment groups. The combined incidence of moderate, severe, and fatal bleeding was two-fold greater in the clopidogrel group than the placebo group (placebo, 10, 2.4%; clopidogrel, 27, 6.3%).

The rate of graft failure depends on the type of graft material used and the site of the distal anastomosis, with the highest failure rates for prosthetic grafts to the tibial arteries.[25] Eighty percent of all graft failures will occur within the first 2 postoperative years due to development of graft stenosis,[26] which continues to develop at a rate of approximately 5% to 7% per year causing late graft failure.[27] In the meta-analysis performed by the Cochrane Review Group,[28] the effect of postoperatively administered antiplatelet treatment was evaluated in patients with PAD receiving infrainguinal bypasses. Antiplatelet treatment had an overall positive effect on primary patency 12 months postoperatively. The size of the effect differed between patients receiving either synthetic or venous grafts. Thus, when analysis was limited to the subgroups receiving synthetic (polytetrafluoroethylene or Dacron) grafts, this effect was statistically significant 12 months postoperatively (HR, 0.22; 95% CI, 0.12-0.38). In contrast, there was less of an effect in patients receiving venous grafts (HR, 0.72; 95% CI, 0.51-1.00). The level of benefit seen brings the failure rate of these prosthetic grafts to that of their venous counterparts, and equates to the protection given in the Dutch Bypass Oral Anticoagulants trial by warfarin, without the cumbersome need for international normalized ratio monitoring

and the associated greater bleeding risk.[14] Overall, those findings and those presented here suggest that activation of the coagulation cascade may play a predominant role in patient outcomes after venous grafts, whereas the stimulation of platelets may play a more predominant role with prosthetic grafts.

In our study, the presenting severity of the disease did not affect graft outcome. In contrast, the site of the distal anastomosis did affect outcome, with the pedal/crural vessels having a worse outcome than lower popliteal, and this supports data from other studies.[25] Similarly, postoperative ABPI was linked to graft outcome, with a poorer outcome in patients with lower ABPIs. Again, these data support other published work in this area.[29]

Another intriguing result is seen with statin therapy, in which a suggestion of potential benefit to statin takers at visit two, in terms of the primary outcome, is suggested. Such a multivariate analysis is hypothesis-generating rather than confirmatory, but statins have many pleiotropic effects, in addition to lipid-lowering, per se, that could possibly explain this benefit.[30]

As with all studies, there are limitations and potential confounding factors that should be considered. The primary outcome for this study was powered with an estimated 15% discontinuation rate as a factor, but over 20% of patients in both treatment groups permanently discontinued treatment. Although this is consistent with previous clinical trials of clopidogrel, including the pivotal CURE trial (in which 21.1% of the patients permanently discontinued the study medication in the clopidogrel group),[18] there is a possibility that the higher discontinuation rates may impact the ability to detect treatment effects, although this was not the case in this study. Finally, there are factors that may influence graft patency, such as surgical techniques, runoff during procedure, target, anastomosis location, and individual patient considerations that were not prospectively recorded in this study. This is particularly important as the multicenter design of this study may increase the variation in procedures, care, and follow-up (eg, imaging). Reassuringly, however, no statistically significant regional or geographic variations were recorded.

In conclusion, the combination of clopidogrel plus ASA did not significantly reduce the primary endpoint of occlusion, revascularization procedure, above-ankle amputation, or death in the overall population of patients with PAD requiring below-knee grafting. However, in a preplanned subgroup receiving a prosthetic graft, there was a statistically significant improvement with clopidogrel for the primary outcome of graft failure or death, reducing rates of occlusion and amputation to levels that compare favorably with those seen in patients receiving venous grafts.

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REFERENCES

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
2. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.
3. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, et al. Critical issues in peripheral arterial disease detection and management: a call to action. Arch Intern Med 2003;163:884-92.
4. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(Suppl 1):S1-75.
5. Scottish Intercollegiate Guidelines Network. SIGN 89. Diagnosis and management of peripheral arterial disease. A national clinical guideline. ISBN 1 899893 54 7 2006. Available at: http://www.sign.ac.uk/pdf/sign89.pdf. Accessed March 17, 2009.
6. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to

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7. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--II: maintenance of vascular graft or arterial patency by antiplatelet therapy. BMJ 1994;308:159-68.
8. Dörffler-Melly J, Büller HR, Koopman MM, Prins MH. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. Cochrane Database Syst Rev 2003:CD000536. Review.
9. Mills JL. Mechanisms of vein graft failure: the location, distribution, and characteristics of lesions that predispose graft failure. Semin Vasc Surg 1993;6:78-91.
10. Brittenden J, Bradbury AW. The durability of iliac and femoral angioplasty. In: Greenhalgh RM, editor. The durability of vascular and endovascular surgery. WB Saunders Co, 1999.
11. Tangelder MJ, Lawson JA, Algra A, Eikelboom BC. Systematic review of randomized controlled trials of aspirin and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. J Vasc Surg 1999;30:701-9.
12. Baumgartner I, Schainfeld R, Graziani L. Management of peripheral vascular disease. Annu Rev Med 2005;56:249-72.
13. Adam DJ, Stonebridge PA, Belch JJ, Murie JA. Antiplatelet and anticoagulant therapy to prevent bypass graft thrombosis in patients with lower extremity arterial occlusive disease. Int Angiol 2001;20:90-8.
14. Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. Lancet 2000;355:346-51.
15. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993;95:315-28.
16. Savi P, Herbert JM. Clopidogrel and ticlopidine: P2Y12 adenosine diphosphate-receptor antagonists for the prevention of atherothrombosis. Semin Thromb Hemost 2005;31:174-83.
17. Becquemin JP. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. Etude de la Ticlopidine après Pontage Fémoro-Poplité and the Association Universitaire de Recherche en Chirurgie. N Engl J Med 1997;337:1726-31.
18. 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. N Engl J Med 2001;345:494-502.
19. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.
20. U.S. Food and Drug Administration. Good Clinical Practice regulations. Available at: www.fda.gov/oc/gcp/guidance.html. Accessed March 17, 2009.
21. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
22. 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;354:1706-17.
23. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med 2010;362:1374-82.
24. Berger PB. Optimal duration of clopidogrel use after stent implantation of drug-eluting stents – still in doubt. N Engl J Med 2010;362:1441-3.
25. Leng GC, Davis M, Baker D. Bypass surgery for chronic lower limb ischaemia. Cochrane Database Syst Rev 2000;(3):CD002000.
26. Stept LL, Flinn WR, McCarthy WJ 3rd, Bartlett ST, Bergan JJ, Yao JS. Technical defects as a cause of early graft failure after femorodistal bypass. Arch Surg 1987;122:599-604.
27. Szilagyi DE, Elliot JP, Hageman JH, Smith RF, Dall'olmo CA. Biologic fate of autogenous vein implants as arterial substitutes: clinical, angiographic and histopathologic observations in femoro-popliteal operations for atherosclerosis. Ann Surg 1973;178:232-46.
28. Dörffler-Melly J, Koopman MM, Prins MH, Büller HR. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. Cochrane Database Syst Rev 2005;(1):CD002071.
29. The Vascular Surgical Society of Great Britain and Ireland. Br J Surg 1997;84:562-78.
30. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7-22.

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Additional material for this article may be found online at www.jvascsurg.org (Appendices 1 and 2, online only).

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