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for the CLASSICS Investigators

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Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared With Ticlopidine in Combination With Aspirin After Coronary Stenting

The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)

Michel E. Bertrand, MD; Hans-Jürgen Rupprecht, MD; Philip Urban, MD; Anthony H. Gershlick, MD;
for the CLASSICS Investigators

Background—Combination therapy with the ADP receptor antagonist ticlopidine plus aspirin has emerged as standard care after coronary stenting. Clopidogrel, a new ADP receptor antagonist, has greater molar potency than ticlopidine and better safety/tolerability.

Methods and Results—Patients (n=1020) were randomized after successful stent placement and initiated on a 28-day regimen of either (1) 300-mg clopidogrel loading dose and 325 mg/d aspirin on day 1, followed by 75 mg/d clopidogrel and 325 mg/d aspirin; (2) 75 mg/d clopidogrel and 325 mg/d aspirin; or (3) 250 mg BID ticlopidine and 325 mg/d aspirin. The primary end point consisted of major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug as the result of a noncardiac adverse event during the study-drug treatment period. The primary end point occurred in 9.1% of patients (n=31) in the ticlopidine group and 4.6% of patients (n=31) in the combined clopidogrel group (relative risk 0.50; 95% CI 0.31 to 0.81; $P=0.005$). Overall rates of major adverse cardiac events (cardiac death, myocardial infarction, target lesion revascularization) were low and comparable between treatment groups (0.9% with ticlopidine, 1.5% with 75 mg/d clopidogrel, 1.2% with the clopidogrel loading dose; $P=NS$ for all comparisons).

Conclusions—The safety/tolerability of clopidogrel (plus aspirin) is superior to that of ticlopidine (plus aspirin) ($P=0.005$). The 300-mg loading dose was well tolerated, notably with no increased risk of bleeding. Secondary end point data are consistent with the hypothesis that clopidogrel and ticlopidine have comparable efficacy with regard to cardiac events after successful stenting. (*Circulation*. 2000;102:624-629.)

Key Words: aspirin ■ receptors ■ stents ■ thrombosis ■ ticlopidine

Intracoronary stenting is widely used to treat vessel closure after PTCA or electively during angioplasty to decrease the rate of restenosis.¹ Current stents are metallic and thrombogenic, resulting in a risk of acute and subacute thrombosis within the first month after stent placement.² Such thrombotic events result in serious clinical consequences, including death, myocardial infarction (MI) or emergency CABG. Initial attempts to reduce stent thrombosis involved regimens combining heparin, oral anticoagulant, and aspirin, but these were hampered by a high rate of complications, especially bleeding requiring blood transfusion and puncture site complications requiring surgical repair.³⁻⁵

Several randomized trials have shown that combination therapy with aspirin plus ticlopidine is superior to heparin and coumarin in preventing subacute stent occlusion.⁶⁻⁹ These benefits have been demonstrated prospectively in low-risk,⁸ mixed-risk or intermediate-risk,^{6,7} and high-risk patients.⁹ The ticlopidine-aspirin combination leads to fewer hemorrhagic or peripheral complications than the conventional regimen combining oral anticoagulant with aspirin (0% to 2% versus 3% to 7%). Moreover, the dual antiplatelet approach shows better efficacy than aspirin alone.^{8,10} Thus, the combination of 250 mg BID ticlopidine and aspirin has become the reference antithrombotic therapy after coronary stenting,

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A list of all CLASSICS participants is given in the Appendix.

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although full antiplatelet effect requires a few days because of the delayed onset of action by ticlopidine.¹¹

Clopidogrel (Plavix/Iscover), a new platelet ADP receptor antagonist, has a more potent platelet antiaggregant effect than ticlopidine,¹² a faster onset of action, and does not cause the adverse events that limit ticlopidine therapy.¹³ A loading dose of clopidogrel produces rapid and pronounced diminution of 5 $\mu\text{mol/L}$ ADP-induced platelet aggregation in human volunteers.¹⁴ This suggests the potential for an earlier therapeutic benefit in the prevention of stent thrombosis. A preclinical study showed that when aspirin is combined with acute high-dose or chronic low-dose clopidogrel, graft and stent thrombosis is significantly reduced in a synergistic manner.¹⁵ Makkar et al¹⁶ have provided further preclinical evidence for synergism between clopidogrel and aspirin. These findings predict that concurrent inhibition of the ADP and thromboxane A₂ pathways of platelet recruitment will produce additive and/or synergistic decreases in thromboocclusive events. We therefore evaluated the safety of clopidogrel (with or without a loading dose) in combination with aspirin compared with ticlopidine in combination with aspirin in patients who had undergone successful coronary stenting.

Methods

Objectives

The primary objective was to evaluate, for the treatment period, the relative safety of clopidogrel (with or without an initial loading dose) plus aspirin compared with ticlopidine plus aspirin in patients who had undergone successful intracoronary stenting. The secondary objective was to evaluate the incidence occurrence of cardiac events during the period of study drug administration.

Study Design

Forty-eight centers in 8 European countries enrolled patients between May and November 1998. The study was designed as a multicenter, randomized, controlled, double-blind, parallel-group trial. Written informed consent was obtained from each patient, and the study was performed according to local regulations, the principles of the Helsinki Declaration, and the *European Guidelines for Good Clinical Practice*.

Randomization

After coronary stenting, and on receipt of informed consent and satisfactory documentation of all inclusion and exclusion criteria, eligible patients were randomized into 1 of 3 treatment groups.

Inclusion and Exclusion Criteria

Randomized patients satisfied the following criteria: successful planned or unplanned coronary stenting (1 or 2 stents) in a single vessel (reference vessel diameter >2.8 mm) with the use of any commercially available non-heparin-coated stents; $<10\%$ adjacent residual stenosis; no angiographic evidence of thrombus formation or dissection within the treated vessel; blood flow of TIMI grade 3 in each stented segment and associated major side branches; preoperative creatine phosphokinase (CPK) levels less than twice the upper limit of normal (ULN); and eligibility to commence study drug within 6 hours after stent implantation. Principal exclusion criteria were stenting procedure involving \geq stents or >1 vessel, involving the left main coronary artery or a major bifurcation, or involving vein grafts; primary angioplasty for ongoing myocardial infarction with documented ST-segment elevation and/or elevated CPK-MB levels $>2\times$ ULN and CPK MB levels greater than normal; persistent objective ischemia determined by 12-lead ECG between stenting and randomization; administration of oral anticoagulants, GP IIb/IIIa receptor antagonists and other antiplatelet agents, except for aspirin,

within 1 month before randomization; administration of thrombolytics 2 weeks before randomization; need for anticoagulants, thrombolytic agents, or GP IIb/IIIa receptor antagonists after the procedure; percutaneous or surgical revascularization (PTCA, CABG) within 2 months before the procedure; history of allergy or intolerance or contraindication to aspirin, ticlopidine, or clopidogrel.

Study Drugs and Procedures

All study drugs (including aspirin) were administered on a blinded basis (double-dummy) and were to be initiated within 6 hours of completion of stenting. Patients were to receive 28 days of treatment with either (1) 300 mg clopidogrel (loading dose) and 325 mg/d aspirin on day 1, followed by 75 mg/d clopidogrel and 325 mg/d aspirin (days 2 to 28); (2) 75 mg/d clopidogrel and 325 mg/d aspirin (days 1 to 28); (3) 250 mg BID ticlopidine and 325 mg/d aspirin (days 1 to 28).

Heparin was discontinued at the end of the procedure and 4 hours before sheath removal. In cases in which stent placement was performed in the late afternoon, intravenous heparin could be continued for a few hours to avoid sheath removal during the night, provided that the total duration of administration did not exceed 36 hours.

End Points

A Critical Event Adjudication Committee validated all potential outcome events; only validated events were analyzed. The primary end point was the incidence of any one of the following validated events occurring during the study drug treatment period between visits 1 and 4 or until discontinuation of study drug: (1) major peripheral or bleeding complications (including false aneurysms, surgical repair of puncture site complications, blood transfusion [≥ 2 U of blood], intracranial bleeding, retroperitoneal bleeding, overt hemorrhage with a decrease of hemoglobin ≥ 3 g/dL compared with baseline); (2) neutropenia (neutrophil count $<1.5\times 10^9/\text{L}$); (3) thrombocytopenia (platelet count $<100\times 10^9/\text{L}$); (4) early discontinuation of study drug because of a noncardiac adverse event (including death of noncardiac origin).

Secondary evaluation criteria for safety were incidence of the specific adverse events rash or urticaria, pruritus, and diarrhea; incidence of any adverse event or other specific groups of adverse events; change from baseline to visit 4 in laboratory parameters.

The secondary (efficacy) end points were the incidence of the following events during the treatment period: (1) cardiac events (combined and separately): cardiovascular death (including all deaths not definitively ascribed to a specific noncardiac cause); MI (spontaneously or in association with angioplasty or CABG); or target vessel revascularization (performed because of recurrent ischemia, arrhythmia, or hemodynamic failure).

MI occurring in the absence of angioplasty or CABG was diagnosed by new abnormal Q waves not present at baseline or CPK levels increased beyond $2\times$ ULN, together with a CPK-MB increase above the ULN and/or measurements of troponin T >0.2 $\mu\text{g/L}$. After angioplasty, CPK and CPK-MB had to be $>3\times$ ULN and/or troponin T >1.0 $\mu\text{g/L}$. After CABG, CPK and CPK-MB had to be $>5\times$ ULN and/or troponin T had to be >2.0 $\mu\text{g/L}$.

Statistical Methods

Study Power

The incidence of the primary event cluster for the clopidogrel arm was projected from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study,¹³ in which the incidence of discontinuations of study drug as the result of noncardiac adverse events during the first 28 days of treatment was 2.5% and the incidence of neutropenia and thrombocytopenia were each $<0.1\%$. On the basis of data available for ticlopidine in stent patients, it was reasonable to predict that the primary event rate including bleeding would be between 2.5% and 5% in the clopidogrel group. Power calculations were based on the assumption that the event rate for ticlopidine would be 5% greater than for clopidogrel with the use of a sample size of 335 per group (670 for the pooled clopidogrel

TABLE 1. Baseline Clinical Characteristics

	Total (n=1020)	Ticlopidine 250 mg BID (n=340)	Clopidogrel 75 mg QD (n=335)	Clopidogrel 300/75 mg QD (n=345)	P
Mean age \pm SD, y	60 \pm 10.1	61 \pm 9.9	60 \pm 10.4	60 \pm 10.1	0.757
Sex, M/F, %	77/23	75/25	78/22	77/23	0.557
Previous unstable angina, n (%)	441 (43.2)	154 (45.3)	132 (39.4)	155 (44.9)	0.224
Previous stable angina, n (%)	569 (55.8)	177 (52.1)	201 (60.0)	191 (55.4)	0.114
Silent ischemia, n (%)	75 (7.4)	27 (7.9)	30 (9.0)	18 (5.2)	0.154
Previous MI, n (%)	370 (36.3)	123 (36.2)	121 (36.1)	126 (36.5)	0.993
Treatment for diabetes, n (%)	115 (11.3)	41 (12.1)	35 (10.4)	39 (11.3)	0.803
Hypertension, n (%)	509 (49.9)	165 (48.5)	173 (51.6)	171 (49.6)	0.713
Treatment for hypercholesterolemia, n (%)	581 (57.0)	199 (58.5)	187 (55.8)	195 (56.5)	0.761
Former or current smoker, n (%)	704 (69.0)	225 (66.2)	237 (70.7)	242 (70.1)	0.396

groups). For an event rate of 2.5% in the clopidogrel group, the study would have 92% power to detect a significant difference between clopidogrel and ticlopidine at the 5% significance level (for the pooled clopidogrel groups) and would have 74% power to detect a significant difference at the 2.5% level (for the separate clopidogrel groups). For a clopidogrel event rate of 5%, the corresponding values were 79% and 54%.

Primary End Point

Assessment of relative safety was based on a comparison between treatment groups of the proportions of patients who had a primary end point event(s). Proportions were compared between treatment groups by means of Fisher's exact test (2-sided). On the basis of prospective decision rules given in the study protocol, the 2 clopidogrel groups were pooled and compared with ticlopidine at the 5% significance level. The 2 clopidogrel groups were also compared at the 5% level. Because there was a significant difference between the clopidogrel groups, separate comparisons of each clopidogrel regimen to ticlopidine were also performed, based on prospective decision rules. Bonferroni adjustment was performed when testing of each clopidogrel group to ticlopidine was indicated. Estimates and 95% confidence intervals for the relative risk of an event were calculated for pairs of treatments.

Secondary End Points

Assessments of efficacy, based on the cardiac and death end points, were carried out in the same manner as for the primary end point.

Additional safety assessments were based on the proportion of patients with ≥ 1 episodes of a specific adverse event or groups of events and the change from baseline to day 28 for each laboratory parameter. The same testing strategy as used for the primary end point was applied. The proportions of events in the treatment groups were compared by means of Fisher's exact test (2-sided), and laboratory changes from baseline were compared between treatments with the use of a 1-way ANOVA.

Only events occurring during the treatment period (from randomization to the day after the last dose of study drug) were included in the primary analysis.

Results

One thousand twenty-one patients were enrolled in 48 centers from 8 European countries (see the Appendix). One randomized patient withdrew consent immediately before taking his first study medication. Baseline characteristics for the 1020 patients who received study drug are given in Table 1; Table

TABLE 2. Stent Procedural Details

Parameter	Total (n=1020)	Ticlopidine 250 mg BID (n=340)	Clopidogrel 75 mg QD (n=335)	Clopidogrel 300/75 mg QD (n=345)
Balloon angioplasty, %	95.2	95.9	96.4	93.3
Stented segment, %*				
LAD	45.6	46.9	43.0	47.0
LCx	19.6	16.2	23.9	18.8
RCA	33.4	35.7	31.9	32.5
Stents implanted, %†				
1	87.5	84.4	89.3	88.7
2	12.3	15	10.5	11.3
Time from stent to start of dosing, mean \pm SD, h‡	2.4 \pm 1.5	2.4 \pm 1.5	2.3 \pm 1.5	2.4 \pm 1.6

LAD indicates left anterior descending; LCx, left circumflex; and RCA, right coronary artery.

Several patients were protocol deviators with respect to the stent procedure: *13 patients (1.3%) were stented in the left main stem, and 1 patient (0.1%) received stents in more than 1 vessel; †3 patients (0.3%) received ≥ 3 stents; ‡10 patients (1.0%) had stent-dosing times that exceeded 6 hours. Data for time from stent to start of dosing were available for 337 of 340 patients in the ticlopidine group, 331 of 335 patients in the clopidogrel 75 mg QD group, and 344 of 345 patients in the clopidogrel 300/75 mg QD group.

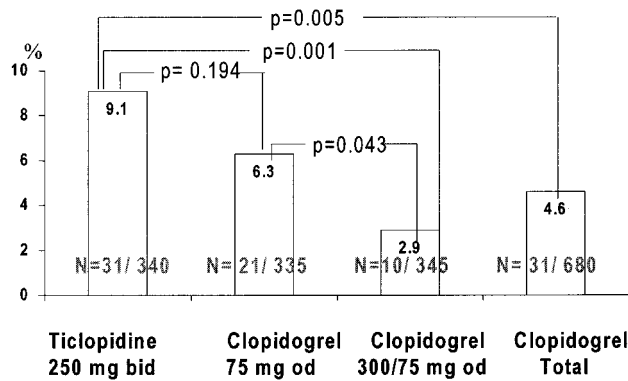


Figure 1. Occurrence of primary end point by treatment.

2 gives details on stent implantation. There were no significant differences between treatment groups.

Primary Study End Point

Figure 1 summarizes data on the primary end point at 28 days, which occurred in 9.1% (31 of 340) of patients in the ticlopidine group and in 4.6% (31 of 680) of patients in the combined clopidogrel group—a relative risk reduction of 50% (95% CI 31% to 81%; $P=0.005$) in favor of clopidogrel. The incidence of the primary end point at 28 days was 6.3% (21 patients) in the 75 mg QD clopidogrel group and 2.9% (10 patients) in the clopidogrel loading-dose group ($P=0.043$).

Table 3 provides a breakdown of primary end point data. The incidence of major peripheral or bleeding complications was low and similar in the 3 groups (1.2% for ticlopidine, 1.2% for 75 mg QD clopidogrel, and 1.5% for clopidogrel loading dose) during the treatment period. The risk of an event in the clopidogrel loading-dose group was approximately a third of that for ticlopidine patients (2.9% versus

9.1%). This was primarily due to a higher frequency of discontinuations as the result of noncardiac adverse events (8.2% with ticlopidine versus 2.0% with the clopidogrel loading dose), which, in turn, was due to an increased frequency of discontinuations because of skin disorders (mostly rash) (2.6% with ticlopidine versus 0.6% with the clopidogrel loading dose), gastrointestinal disturbances (2.6% versus 0.3%), and allergic adverse events (1.2% versus 0%).

One (0.3%) ticlopidine patient developed neutropenia (neutrophil count $<0.1 \times 10^9/L$) 28 days after randomization and recovered without sequelae 7 days after the end of treatment. Two patients (0.6%) in each clopidogrel group had mild thrombocytopenia (70 to $100 \times 10^9/L$), although these cases were transient and without clinical significance. In 3 of the cases, heparin was given concomitantly and there was no premature treatment cessation.

Secondary End Points

There was a low and comparable overall rate of major adverse clinical events (MACE) in the 3 groups: 0.9% with ticlopidine, 1.2% with the clopidogrel loading dose, and 1.5% with 75 mg QD clopidogrel. There were no statistically significant differences between the combined clopidogrel group and ticlopidine ($P \geq 0.555$) or between the 2 clopidogrel groups ($P \geq 0.058$) for any of the secondary end points (see Table 4).

Analyses of the primary and secondary end points with all the validated outcome events recorded in the study, including those occurring during the follow-up period, did not change the overall conclusion.

Discussion

The CLOpidogrel ASpirin Stent International Cooperative Study (CLASSICS) is the first randomized trial of clopidogrel in coronary stenting and the first to evaluate

TABLE 3. Summary of Data on Primary (Safety) End Point

Outcome Event	Ticlopidine (n=340)	Clopidogrel 75 mg QD (n=335)	Clopidogrel 300/75 mg QD (n=345)	Clopidogrel Total (n=680)
Composite (any of the below)*	31 (9.1%)	21 (6.3%)	10 (2.9%)	31 (4.6%)
Major peripheral or bleeding complication	4 (1.2%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Neutropenia $<1.5 \times 10^9/L$	1 (0.3%)	0	0	0
Thrombocytopenia 70– $100 \times 10^9/L$	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Early discontinuation due to noncardiac event	28 (8.2%)	17 (5.1%)	7 (2%)	24 (3.5%)
Skin disorder	9 (2.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Gastrointestinal disorder	9 (2.6%)	8 (2.4%)	1 (0.3%)	9 (1.3%)
Allergy	4 (1.2%)	0	0	0
Others	6 (1.8%)	6 (1.8%)	4 (1.2%)	10 (1.5%)

*Patients may have had >1 of the events included in the end point. Breakdown of discontinuations is based on the primary reason, for example, if a patient had multiple reasons for early discontinuation, they were included in one of the specific categories if possible rather than “other” or the specific category and other. If they did not have a reason that fell into one of the specific categories, they were included under “other.” No patient had reasons that fell into 2 specific categories.

For frequency of composite outcome events: $P=0.005$ for ticlopidine vs clopidogrel combined; $P=0.001$ for ticlopidine vs 300/75 mg QD clopidogrel; $P=0.194$ for ticlopidine vs 75 mg QD clopidogrel; $P=0.043$ for 300/75 mg QD clopidogrel vs 75 mg QD clopidogrel.

TABLE 4. Summary of Data on Secondary (Efficacy) End Point

	Ticlopidine (n=340)	Clopidogrel 75 mg QD (n=335)	Clopidogrel 300/75 QD (n=345)
No. of patients with ≥1 cardiac event*	3 (0.9%)	5 (1.5%)	4 (1.2%)
Details	1 MI 1 MI+TLR 1 TLR	1 MI 3 MI+TLR 1 TLR	2 MI 1 Fatal MI 1 SD

TLR indicates target lesion revascularization; SD, sudden death.

*P=NS for all comparisons.

clopidogrel-aspirin combination therapy and a loading dose of clopidogrel. The rationale for CLASSICS stemmed from (1) clear evidence from the Intracoronary Stenting and Antithrombotic Regimen trial (ISAR), the Full Anticoagulation Versus Aspirin and Ticlopidine trial (FANTASTIC), the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS), and the Stent Anti-thrombotic Regimen Study (STARS) that the ticlopidine-aspirin combination improves clinical outcome after stent implantation, compared with aspirin alone or aspirin plus full anticoagulation with heparin and coumarin⁶⁻⁹; (2) the safety profile of ticlopidine, which may result in early discontinuation of the drug; (3) the superior safety profile of clopidogrel compared with ticlopidine; and (4) the comparable clinical efficacy of these 2 ADP receptor antagonists.^{13,17} The decision to test a clopidogrel loading dose was based on data from healthy volunteers,¹⁸ which showed that a loading dose produced a faster onset of platelet inhibition. The 300-mg loading dose was chosen to provide an optimal benefit/risk ratio.

Because of limited information on the use of clopidogrel and aspirin in combination, CLASSICS was primarily a safety study, with a primary end point consisting of major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of the study drug for noncardiac adverse events. The primary end point occurred in a higher percentage of patients in the ticlopidine group (9.1%) than in the combined clopidogrel group (4.6%) ($P=0.005$), demonstrating a superior safety profile for clopidogrel. The safety advantage of clopidogrel is derived from a lower frequency of noncardiac adverse events, with significantly fewer cases of skin disorders (0.7% versus 2.6%), gastrointestinal disorders (1.3% versus 2.6%), and allergy (0% versus 1.2%). These differences indicate that with clopidogrel, more patients will be able to benefit from a full course of therapy with an effective combination antiplatelet regimen, and thus the risk of subacute stent thrombosis caused by early discontinuation of ticlopidine should be reduced.

Data from CLASSICS are supported by findings from a nonrandomized comparison of combination therapy in coronary stent patients. Moussa et al¹⁹ compared the safety and effectiveness of clopidogrel and aspirin with those of ticlopidine and aspirin in a consecutive series of patients ($n=1406$ for ticlopidine; $n=238$ for clopidogrel). At 1-month follow-up, no difference was found in the rates of stent thrombosis or MACE between the 2 groups. No clopidogrel-treated patient had neutropenia, and there was a significantly lower overall

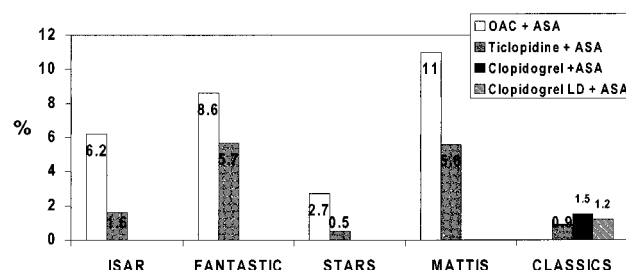


Figure 2. Comparison of MACE rates (%) in CLASSICS with those of ISAR,⁶ FANTASTIC,⁷ STARS,⁸ and MATTIS⁹ trials. OAC indicates oral anticoagulants; ASA, acetylsalicylic acid (aspirin); and LD, loading dose.

incidence of medication side effects (neutropenia, diarrhea, rash) with clopidogrel compared with ticlopidine.

Comparison of incidence rates for MACE (death, MI, revascularization) in CLASSICS with those in the ISAR, FANTASTIC, MATTIS, and STARS trials reveals that the event rates in all 3 arms of CLASSICS were lower than those in the ticlopidine-aspirin arms of FANTASTIC and MATTIS and comparable to those reported for ticlopidine plus aspirin in ISAR and STARS (Figure 2). These data reinforce the superiority of the ADP receptor antagonist-aspirin combination in improving clinical outcome after coronary stent placement.

No rebound phenomenon was observed in this study, as in the previous trials. This could be potentially of interest in special situations such as after brachytherapy, in which cases of late stent occlusion have been described.

Results from CLASSICS should be viewed in the context of the study design. First, patients were randomized after successful stenting and were therefore a relatively low-risk population. Second, although the incidence of MACE was low and similar in the 3 treatment arms, this trial was underpowered to show efficacy differences. Third, administration of GP IIb/IIIa receptor antagonists in the month before randomization or after stenting were exclusion criteria; therefore, CLASSICS does not provide information on concomitant use of clopidogrel with these agents.

Conclusions

The safety/tolerability of clopidogrel (plus aspirin) is superior to that of ticlopidine (plus aspirin). The 300-mg loading dose was well tolerated, notably with no increased risk of bleeding. Secondary end point data are consistent with the hypothesis that clopidogrel and ticlopidine have comparable efficacy regarding cardiac events after successful stent placement; however, the study was not powered to draw definitive conclusions on efficacy. The favorable benefit/risk ratio of clopidogrel and aspirin, including the use of a loading dose, supports their combined use in coronary stent patients.

Appendix

Steering Committee

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