Comparison of Antiplatelet Effects of Aspirin, Ticlopidine, or Their Combination After Stent Implantation

Hans J. Rupprecht, MD; Harald Darius, MD; Ulrike Borkowski, MD; Thomas Voigtländer, MD; Bernd Nowak, MD; Sabine Genth, MD; Jürgen Meyer, MD

Background—This study was performed to analyze the influence of either aspirin, ticlopidine, or their combination on platelet activation and aggregation parameters after stent implantation.

Methods and Results—Sixty-one patients with successful implantation of a single Palmaz-Schatz stent in a native coronary artery were randomly assigned to either group A (aspirin 300 mg/d + ticlopidine 2×250 mg/d), group B (ticlopidine 2×250 mg/d), or group C (aspirin 300 mg/d). Platelet activation was evaluated on days 1, 7, and 14 by flow cytometry measurement of expression of CD62p (p-selectin) and the binding of fibrinogen to the platelet surface glycoprotein IIb/IIIa receptor. Platelet aggregation was induced by addition of ADP or collagen. Differences between treatment groups were compared by ANOVA. Between days 1 and 14, we observed a significant decrease in collagen-induced platelet aggregation in group A (62.2±2.5% versus 36.9±3.1%), whereas an increase was seen in group B (58.3±2.5% versus 67.7±3.2%) and no change was seen in group C (P<.0001). The ADP-induced aggregation declined significantly in group A (74.7±1.4% versus 55.3±2.6%), whereas a delayed reduction was seen in group B (72.0±3.0% versus 52.6±4.2%) and no change was seen in group C (P=.0017). The CD62p expression declined significantly in groups A (68.2±2.7% versus 41.3±2.7%) and B (64.8±2.9% versus 39.3±3.5%) but not in group C (P<.0001). Moreover, the fibrinogen binding decreased significantly in group A (61.0±4.3% versus 36.3±4.2%) and with delay in group B (58.3±2.2% versus 39.4±3.0%), whereas no alterations were seen in group C (P=.012).

Conclusions—Our results demonstrate synergistic and accelerated platelet inhibitory effects of ticlopidine plus aspirin in patients after stent implantation compared with a monotherapy with either ticlopidine or aspirin alone. (Circulation. 1998;97:1046-1052.)

Key Words: stents ■ platelet aggregation inhibitors ■ aspirin

Combined antiplatelet therapy with ticlopidine and aspirin has been shown to lower the risk of subacute stent thrombosis compared with conventional anticoagulant therapy.1, 2 This has enabled stenting to become a breakthrough technology in interventional cardiology, and the rate of stent implantation now amounts to 30% to 50% of all procedures in most centers.3, 5

Bearing in mind the inherent risks and side effects of ticlopidine and aspirin, especially the risk of neutropenia for the former and the risk of gastrointestinal bleeding for the latter, the question as to whether aspirin or ticlopidine alone or a combination of both might be sufficient to counteract platelet activation and aggregation after stenting deserves further investigation. Therefore we randomly assigned patients after stent implantation to a treatment with aspirin alone, ticlopidine alone, or a combination of both to compare magnitude and temporal changes of markers of platelet activation in flow cytometry and aggregation within the first 2 weeks after stent implantation.

Patient Selection

Patients with successful implantation of a single Palmaz-Schatz stent in a native coronary artery were selected for the study if there was a low risk for subacute stent thrombosis. This included a vessel diameter of at least 3.0 mm, absence of thrombus formation before and after stent placement, a TIMI grade 3 blood flow, absence of a residual dissection, and absence of a residual lesion >20% within or adjacent to the stent.

Patients with bleeding disorders, contraindications to treatment with aspirin and/or ticlopidine, abnormal blood cell count, childbearing potential, acute myocardial infarction, depressed left ventricular function, renal insufficiency, or an indication for oral anticoagulation were excluded from the study. Eligible patients adhering to the prespecified criteria were randomly assigned to the treatment groups immediately after the intervention and after written informed consent was obtained. The study was performed according to the Declaration of Helsinki and the protocol was approved by the local ethical committee.
Intervention and Adjunctive Concomitant Therapy

All patients received 10 000 IU of heparin. The first 5000 U was given after arterial puncture and another 5000 U immediately before guidewire insertion. Palmaz-Schatz stents were folded by hand on the angioplasty balloon (Europass, Cordis), and implantation was performed with a pressure of 10 to 16 atm. The arterial sheath was left in the groin for 12 to 24 hours. After sheath removal, manual compression of the groin was carried out until hemostasis occurred. Thereafter, a pressure bandage was applied for at least 12 hours.

Heparin was administered intravenously for 24 hours, when the pressure bandage was removed to maintain a partial thromboplastin time of 60 to 90 seconds.

Antiplatelet Therapy

All patients were pretreated with 100 mg aspirin/d for at least 1 week before randomization, with the last drug intake at the day of percutaneous transluminal coronary angioplasty. According to the randomization schedule, the patients were attributed to one of three antiplatelet regimens, starting immediately after the procedure for a duration of four weeks: group A: aspirin 300 mg/d + ticlopidine 2×250 mg/d, group B: ticlopidine 2×250 mg/d, and group C: aspirin 300 mg/d. After the initial 4-week treatment period, antiplatelet therapy was continued with aspirin 100 mg/d.

Laboratory Investigations

The following laboratory tests were performed on day 1, day 7, and day 14 after stent implantation.

Blood Sampling

Venous blood was withdrawn immediately after patient randomization before intake of the first dose of study medication, on day 7 and on day 14 of treatment. Twenty milliliters of blood was drawn by venipuncture and anticoagulated in acid citrate dextrose (15% vol/vol; Biostabil, Biotest). Blood was centrifuged for 12 minutes at 180g at room temperature to obtain platelet-rich plasma. Aliquots of the platelet-rich plasma were used for platelet aggregation studies, for the preparation of platelet-poor plasma (centrifugation 1500g, 10 minutes) to calibrate the platelet aggregometer, and another aliquot for flow cytometric analysis.

Platelet Aggregation Studies

Platelet aggregation was performed in platelet-rich plasma by addition of ADP or collagen and the alterations in light transmission were measured photometrically (APACT Aggregometer) and analyzed automatically. The aggregometer was calibrated for the difference in light transmission between platelet-poor and platelet-rich plasma, which was set as 100% by definition. Alterations in light transmission in response to the respective aggregating agent were expressed as percentage of light transmission. ADP (Boehringer Mannheim) was added in concentrations between 1 to 20 μmol/L to facilitate construction of a dose-response curve and calculation of ED50 values, with 1.0, 3.3, and 20.0 μmol/L used for each time point. Collagen was used as the aggregating agent in at least three concentrations of 1.0, 3.3, and 33.3 μg/mL plus additional concentrations if necessary for the evaluation of a dose-response relation.

Flow Cytometric Analysis

Platelet activation was evaluated by flow cytometry measurement of the surface membrane expression of CD62p (p-selectin, GMP140) by use of a monoclonal antibody (clone CLBI Cell Systems, dilution 1: 300) and the binding of fibrinogen to the platelet glycoprotein (GP)IIb/IIIa receptor. Aliquots of platelet-rich plasma were activated by addition of ADP (1.0, 10, 100 μmol/L), and reaction was terminated after 5 minutes by fixation of the cells with paraformaldehyde (1%) for 30 minutes.

For flow cytometric analysis, the platelet gate was identified by staining control platelets with an CD61 antibody (clone SZ21, Dianova, dilution 1:100), an epitope constitutively expressed on the platelet surface. More than 95% of all cells measured in the delineated window were CD61 positive in all treatment groups at all time points. As an isotype control, a mouse anti-human MHC II antibody (OX6) was used.

Platelet Count

Platelets were counted in venous blood samples taken in EDTA by an automatic cell counter (Coulter Instruments).

Statistics

Continuous data are expressed as mean±SEM. ANOVA for repeated measures was used for comparisons between different time points and between treatment groups as well. A value of P<.05 was considered to indicate a statistically significant difference.

Results

Platelet Aggregation Studies

Platelet aggregation ex vivo was induced by addition of collagen 1.0, 3.3, and 33.3 μg/mL. In Fig 1A, the results of collagen 3.3 μg/mL are depicted. The initial values in groups A, B, and C were not significantly different before initiation of therapy. After 7 days of therapy, a significant decrease in group A from 62.2±2.5% to 46.2±3.9% was observed. A further decline in platelet aggregation response to 36.9±3.1% occurred until the end of the observation period on day 14 (P=.0001). In contrast, in group B a significant increase in collagen-induced platelet aggregation from 58.3±2.5% to 70.9±3.5% was seen on day 7 when compared with day 1. During the second week of the observation period, the collagen-induced platelet aggregation amounted to 67.7±3.2% (P=.005). In group C there was no significant alteration in collagen-induced platelet aggregation detectable (P<.0001 for comparison of treatment groups by ANOVA (Fig 1A). The influence of different collagen concentrations on platelet aggregation in group A is shown in Fig 1B.

For the highest concentration of collagen used (33.3 μg/mL), the inhibitory effects of the platelet antagonists were surmounted by the collagen concentration used (Fig 1B). In the lower concentrations (1.0 and 3.3 μg/mL), a significant decrease in platelet aggregation response was seen during the observation period.
Comparison of Antiplatelet Effects

The ED_{50} for collagen-induced platelet aggregation increased significantly from 1.7±0.2 to 3.9±0.7 µg/mL on day 7 and 5.4±0.9 µg/mL on day 14 in group A (P=.0005; Fig 2). In group B a slight decrease of the ED_{50} was seen after withdrawal of the routine aspirin medication. In contrast, the ED_{50} was unaltered in patients receiving aspirin only (P=.0001, Fig 2).

The ADP-induced aggregation was not significantly different on day 1 between the treatment groups (Fig 3A). Aggregation declined in group A from 74.7±2.6% on day 1 to 55.3±2.6% on day 14 (P=.0001). In group B only a moderate reduction of the ADP-induced aggregation was noted (33.3%, 3.3%, or 1.0 µg/mL) in patients of group A receiving ticlopidine and aspirin. Numbers within bars represent mean±1 SEM. Probability values relate to differences between different time points in each treatment group.

Figure 1. A. Time-dependent alterations in collagen-induced platelet aggregation (collagen 3.3 µg/mL) measured as percentage of light transmittance in groups A (ticlopidine + aspirin), group B (ticlopidine), and group C (aspirin). Numbers within bars represent mean±1 SEM. Probability values relate to differences between different time points in each treatment group. Comparison of treatment groups by ANOVA revealed a value of P<.0001. B, Dose-dependent platelet stimulatory effects of collagen (33.3, 3.3, or 1.0 µg/mL) in patients of group A receiving ticlopidine and aspirin. Numbers within bars represent mean±1 SEM. Probability values relate to differences between different time points in each treatment group.

Platelet Adhesion Molecule Expression
As a marker of platelet adhesion molecule expression, the ADP-induced expression of CD62p was measured. Basal CD62p expression in the absence of stimulating agents was <5% of positive cells in all groups. Activation of platelets with ADP (100 µmol/L) resulted in an increase in CD62p-positive cells, which was not different for the three treatment groups (Fig 4A). In group A, CD62p expression declined from 68.2±2.7% to 43.7±3.1% on day 7 and to 41.3±2.7% on day 14 (P=.0001). In group B the percentage of positive cells decreased from 64.8±2.9% to 46.7±3.8% on day 7 and to 39.3±3.5% on day 14 (P=.0001). In contrast, no significant changes were noted in group C during the 2-week observation period (P>.0001 for comparison of treatment groups by ANOVA). The number of CD62p-positive cells in group A decreased significantly, independent of the ADP concentrations used (Fig 4B).

Binding of biotin-labeled fibrinogen to the platelet GPIIb/IIIa receptors was <5% in all samples measured before activation. Stimulation of fibrinogen binding by ADP (100 µmol/L) resulted in a comparable increase in all three groups on day 1 (Fig 5A). In group A fibrinogen binding decreased significantly from 61.0±4.3% on day 1 to 40.8±3.8% on day 7 and to 36.3±4.2% on day 14 (P<.0001). In group B a moderate reduction of positive cells from 58.3±2.2% on day 1 to 52.5±4.2% on day 7 was observed, with a further decrease on day 14 to 39.4±3.0% (P<.0001). In contrast, in group C there were no significant time-dependent alterations in fibrinogen binding (P=.012 for comparison of treatment groups by ANOVA). The fibrinogen binding decreased significantly in group A only when an ADP concentration of 100 µmol/L was used (Fig 5B).

Clinical Results
With regard to clinical or lesion characteristics, there were no significant differences between the three groups of patients
The patients randomized for this study did not experience any angina attacks, infarctions, subacute stent thromboses, or any other adverse cardiovascular events. One major bleeding event with a drop in hemoglobin concentration by 4 mg/dL occurred at the groin puncture site of one patient in group C; however, a transfusion of red blood cells was not required. There was no necessity for repeat interventions during the follow-up period of 2 weeks or until the medication was altered to aspirin 100 mg/d 4 weeks after stenting. As a safety measure with regard to the ticlopidine administration, white blood cell counts of all patients involved in this study were taken 2, 4, and 6 weeks after intervention. No clinically relevant alterations in white blood cell counts were detected.

**Discussion**

Since its introduction by Sigwart et al,9 coronary stent implantation has been hampered for many years by the occurrence of subacute stent thromboses and bleeding complications.6,7,10,11

Certain investigators demonstrated a reduction of the aforementioned complications by means of improved stent deployment techniques and more adequate postprocedural management.3,8,12–22

It is the merit of a group of French investigators2,5 who first demonstrated that a combination of aspirin and ticlopidine, another antiplatelet drug that acts by the inhibition of the ADP-induced platelet activation, was clearly superior to the conventional oral anticoagulation regimen with regard to a reduction of subacute stent thrombosis. A randomized single-center trial thereafter reported a reduction of major adverse cardiac events from 6.2% with oral anticoagulation to 1.5% with a combined antiplatelet treatment involving ticlopidine and aspirin.1 This correlated with a reduced stent occlusion rate of 0.8% compared with 5.4% with anticoagulation. In addition, the rate of noncardiac events, comprising mainly hemorrhagic complications, was reduced from 12.3% to 1.2%.4 Major multicenter trials (STARS, FANTASTIC) have confirmed these results.23,24
Comparison of Antiplatelet Effects

Gawaz et al. recently demonstrated that platelet activation after coronary stent implantation can be modified by selection of antithrombotic strategies. He found an increase in fibrinogen receptor activity in patients receiving oral anticoagulation compared with a decrease in patients receiving ticlopidine. Platelet surface expression of CD62p was enhanced in patients under oral anticoagulation but not in patients treated with ticlopidine. In another study, Neumann et al. were able to demonstrate that platelet fibrinogen receptor expression was an independent predictor of subacute stent occlusion, whereas prothrombin fragment F1 and F2, sensitive markers of thrombin generation, and fibrinogen, the final substrate of the coagulation cascade, did not show a strong correlation to the risk of stent occlusion.

With regard to potential side effects of either aspirin or ticlopidine, which is known to cause leukopenia in ≈1% of all patients and skin rash and diarrhea in a sizeable number of patients, the question arose as to whether a combined treat-

ment with aspirin and ticlopidine would be necessary or whether a monotherapy would be sufficient to counteract the problem of stent thrombosis. Especially in the light of improved implantation techniques with high-pressure balloon inflation and intravascular ultrasound guidance, it was suggested that the antithrombotic strategy might not be of major concern after optimal stent deployment. An observational trial with ticlopidine alone for 3 to 6 months and subcutaneous heparin for 1 week revealed a subacute stent thrombosis rate of 4.2%, a myocardial infarction rate of 1.2%, and a death rate of 2%. A randomized trial comparing a monotherapy of aspirin with a combination of ticlopidine and aspirin was prematurely terminated because 3 of 103 patients in the aspirin group died compared with none of 123 patients in the ticlopidine + aspirin group. Although the total event rate (3.9% versus 0.8%) did not reveal a statistically significant difference, the authors believed that it was not justified to withhold ticlopidine from their patients any longer. Preliminary data from the much larger STARS trial suggest a relevant reduction of clinical events through the use of a combination of ticlopidine and aspirin compared with a monotherapy with aspirin.

To determine whether monotherapy with ticlopidine, aspirin, or a combination of both agents are equivalent or whether there might be a meaningful difference, we compared these three treatment strategies in 61 randomly assigned patients and determined the collagen-induced as well as ADP-induced platelet aggregation immediately after stent implantation and 1 week and 2 weeks after stent implantation. In addition, platelet activation was determined by means of the ADP-induced CD62p expression and the ADP-induced fibrinogen binding to platelets.

In patients with aspirin monotherapy no change in collagen-induced platelet aggregation occurred during the observation period because all patients were already pretreated with aspirin before stent implantation. Although the results in the ticlopidine group on day 7 might still be contaminated by the long-lasting effects of aspirin pretreatment (Fig 1A), collagen-induced aggregation on day 14 is still higher if compared with day 1. Thus the increased aggregation response on day 7 represents an aspirin withdrawal phenomenon. There is no clear evidence for an aspirin rebound phenomenon because aggregation responses on days 7 and 14 are not strikingly different from each other. Surprisingly, the combination of aspirin and ticlopidine resulted in a significant reduction of platelet aggregation, whereas monotherapy with ticlopidine led to a marked decrease in platelet aggregation, pointing out that ticlopidine in contrast to aspirin acts by inhibition of the ADP-induced platelet activation. This effect increased over time during the observation period in the ticlopidine group. The combined treatment with aspirin and ticlopidine led to a highly significant suppression of ADP-induced platelet aggregation, which was already completely.
present 1 week after randomization. Thus the combination of both antiplatelet agents obviously caused a faster inhibition of the ADP-induced platelet aggregation compared with a mono-therapy with ticlopidine, suggesting a possible role for thromboxane A2 for the augmentation of the stimulatory effect of ADP.

The ADP-induced expression of CD62p was not altered during follow-up in the aspirin group, but a significant reduction of the percentage of CD62p-positive cells was measured in both the ticlopidine as well as the aspirin group, with a trend toward a faster effect in the latter.

The ADP-induced binding of fibrinogen to the GPIIb/IIIa receptors did not change in the aspirin group but was markedly reduced in the two ticlopidine groups. Again, the combined treatment revealed a relevant decrease of the ADP-induced fibrinogen binding already on day 7, whereas a comparable effect was seen in the ticlopidine group on day 14.

It is remarkable that the expression of the adhesion molecule CD62p being necessary for platelet adhesion is reduced to a comparable magnitude as the aggregation response. This might indicate a possible role for ticlopidine and aspirin in inhibition of platelet adhesion processes in vivo. There is recent evidence in the literature that aspirin might produce an artifact during aggregation in platelet-rich plasma that is not present if aggregation is performed in whole blood. However, because platelet aggregation in platelet-rich plasma is a widely performed test for the evaluation of platelet activity ex vivo, we used this method, for which many other clinical studies exist. This is in contrast to whole blood aggregation, which is rarely used in clinical studies. In addition, we performed flow cytometric analysis to circumvent the problems with platelet aggregation in platelet-rich plasma and to involve a second, independent method for the evaluation of platelet activity and the inhibitory effects of platelet-active drugs.

Our results demonstrate a synergistic platelet-inhibitory effect of ticlopidine plus aspirin in patients after stent implantation that might be responsible for the beneficial effects of this drug combination in patients after stent implantation.

### Table: Patient and Lesion Characteristics

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<th>Ticlopidine + Aspirin</th>
<th>Ticlopidine</th>
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<td><strong>Patient characteristics</strong></td>
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<td>Patients, n</td>
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<td>58 ± 9</td>
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<td>Previous MI</td>
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<td>72 ± 13</td>
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<td>Diameter stenosis after intervention, %</td>
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<td>12 ± 8</td>
<td>11 ± 7</td>
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<td>Maximal inflation pressure, atm</td>
<td>13 ± 4</td>
<td>12 ± 3</td>
<td>13 ± 3</td>
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MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; LAD, left anterior descending coronary artery; RCA, right coronary artery; and LCx, left circumflex artery.
combined inhibition of ADP and arachidonic acid–dependent platelet activation antagonized the two most important avenues of platelet stimulation within the coronary circulation. Whether clopidogrel, the likely successor of ticlopidine, yields equivalent platelet inhibitory effects needs to be shown in future trials. From the above data it can be concluded that the combination of aspirin and ticlopidine is clearly superior in terms of platelet aggregation parameters and platelet activation markers compared with a monotherapy with ticlopidine or aspirin and thus should be the preferred treatment strategy after stent implantation.

References
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