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# Antiplatelet Effect of Ticlopidine After Coronary Stenting

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***Objectives.*** **This study sought to investigate the contribution of ticlopidine to the inhibition of platelet activation after coronary stent placement.**

***Background.*** **After coronary stenting, antiplatelet therapy with aspirin and ticlopidine improves stent patency compared with anticoagulation. However, the specific role of ticlopidine has not been elucidated.**

***Methods.*** **After successful coronary stent placement, we randomized 22 patients to receive ticlopidine and aspirin (ticlopidine group) and 25 to receive aspirin alone (aspirin group). Surface expression on platelets of the activated fibrinogen receptor and of P-selectin was assessed by flow cytometry.**

***Results.*** **In the aspirin group the percent of platelets with activated fibrinogen receptors increased between days 1 and 5 ($p = 0.001$), whereas there were no substantial changes in the ticlopidine group. The percent of P-selectin–positive platelets did not change significantly in the aspirin group but decreased in the ticlopidine group ($p = 0.019$). At day 5 after the intervention, the percent of platelets with activated fibrinogen receptors in the ticlopidine group was significantly lower (median [interquartile range]: 8.5 [3.1 to 17.8] vs. 18.1 [8.5 to 35.5], $p = 0.025$), and there was a trend to fewer P-selectin–positive platelets than in the aspirin group (5.8 [3.4 to 9.5] vs. 8.8 [4.0 to 15.8], $p = 0.073$).**

***Conclusions.*** **Combined antiplatelet therapy with ticlopidine plus aspirin is superior to treatment with aspirin alone in suppressing platelet activation after coronary stenting.**

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After coronary stent placement, platelet function is a major determinant of the risk of subacute stent thrombosis (1,2). In patients treated with coumarin, overlapping heparin and aspirin, we found progressive platelet activation within the first week after coronary stenting (3). This activation was shown by increased surface expression of the activated fibrinogen receptor and P-selectin, a marker of alpha-degranulation (3). In contrast, combined antiplatelet therapy with ticlopidine and aspirin reduced the surface expression of the activated fibrinogen receptor and prevented further alpha-degranulation after stenting (3). Consistent with these functional studies, we showed (4) that combined antiplatelet therapy improves stent patency compared with anticoagulation.

It is unclear whether the differential effect of the two antithrombotic regimens is due to the antiplatelet effects of ticlopidine or is caused by platelet activation through unfractionated heparin (3–9). No previous study has specifically addressed the role of ticlopidine in combined antiplatelet therapy. However, treatment with ticlopidine is costly and can exert rare but potentially life-threatening side effects, such as neutropenia (10,11).

In the present randomized study we investigated the contribution of ticlopidine to the inhibition of platelet activation by combined antiplatelet therapy after coronary stenting.

## Methods

**Patient selection and study protocol.** The study included patients with successful intracoronary stent placement after percutaneous transluminal coronary angioplasty (PTCA) at our institution. Indications for stenting were extensive coronary dissections after PTCA, complete vessel closure, residual stenosis ≥30% and lesions in venous bypass grafts. Exclusion criteria were contraindications for aspirin or ticlopidine, absolute indication for anticoagulation, stents primarily intended as a bridge to aortocoronary bypass grafting, acute myocardial infarction and antecedent treatment with ticlopidine.

Immediately after stenting, patients were randomized by means of sealed envelopes to the ticlopidine group receiving ticlopidine (Tiklyd, Sanofi-Winthrop), 250 mg twice daily, plus aspirin (Bayer), 100 mg twice daily, or to the aspirin group receiving aspirin, 100 mg twice daily, alone. Peripheral venous blood samples were obtained immediately after completion of the procedure and daily thereafter until day 5. All patients gave written informed consent. The study was approved by our institutional ethics committee.

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**Abbreviations and Acronyms**

CD = cluster of differentiation
FITC = fluorescein isothiocyanate
GP = glycoprotein
LIBS1 = ligand-induced binding site 1
PTCA = percutaneous transluminal coronary angioplasty

**Stent procedure and poststenting management of patients.** Stent implantation was performed as previously described (4,12). Before PTCA, heparin 15,000 U, and aspirin, 500 mg, were given intravenously. The 7-mm or the articulated 15-mm standard Palmaz-Schatz stent (Johnson & Johnson) was hand-crimped on conventional angioplasty balloons. We slightly oversized the balloons and optimized stent apposition by higher pressure dilations (>12 atm). If necessary, we implanted multiple stents for complete coverage of the dissection. We did not use intravascular ultrasound but routinely performed off-line quantitative coronary angiography (AWOS, Siemens).

After sheath removal and local hemostasis by manual compression, we applied a pressure bandage for 12 h. Patients did not receive additional heparin after the intervention, and the concomitant postinterventional therapy did not differ between the two treatment groups.

**Immunologic detection of platelet activation.** Preparation and immunolabeling of platelets with fluorescein isothiocyanate (FITC)–conjugated monoclonal antibodies were performed immediately after blood was drawn, as described earlier (1,3,13). By use of a fluorescence-activated cell scanner-Calibur flow cytometer (Becton-Dickinson), the platelet population was identified by size and granularity (>98% positive for cluster of differentiation [CD]41). Antibody binding of anti–ligand-induced binding site 1 (LIBS1) and anti-CD62P was measured as the percent of platelets positive for both epitopes after subtracting nonspecific fluorescence, determined by use of an irrelevant isotype-matched FITC-conjugated immunoglobulin G (Dianova). Anti-CD41 antibody binding was determined as the relative change in fluorescence intensity per platelet. To ensure reproducibility of flow cytometry, a sample from a healthy control subject was always analyzed in conjunction with patient samples.

Monoclonal antibodies anti-CD41 and anti-CD62P were commercially obtained as FITC conjugates (Dianova). Anti-CD41 is directed against the glycoprotein complex IIb/IIIa (GPIIb/IIIa) and detects the receptor regardless of whether it is in its rest or activated form. Anti-LIBS1 monoclonal antibody recognizes a cryptic epitope on GPIIIa that becomes exposed only on the activated and ligand-occupied GPIIb–IIIa complexes (3). Thus, anti-LIBS1 binding indicates fibrinogen receptor activity. Anti-CD62P recognizes P-selectin that is expressed on the activated platelet surface as a consequence of alpha-degranulation (3).

**Statistical analysis.** The study primarily sought to test the hypothesis that by day 5 after stenting, the surface expression of LIBS1 and P-selectin on platelets differed between the two treatment groups. This hypothesis was derived from our previous study comparing combined antiplatelet therapy with anticoagulation (3). Secondarily, we tested the differences in LIBS1 and P-selectin surface expression between immediately after stenting and day 5. We terminated the study prematurely after the second cardiac event had occurred in the aspirin group.

Cytometric data that were not normally distributed were reported as median (interquartile range), and differences were tested by the Wilcoxon matched-pairs signed-rank or the Mann-Whitney *U* test, as appropriate. Otherwise, we report continuous variables as mean value ± SD and tested differences by the *t* test. Frequencies were tested by the Fisher exact test. A p value <0.05 in the two-tailed test was regarded as significant.

**Table 1.** Baseline Characteristics

| | Aspirin Group (n = 25) | Ticlopidine Group (n = 22) | p Value |
|---|---|---|---|
| Age (yr) | 62.1 ± 11.4 | 66.3 ± 10.4 | 0.21 |
| Women | 10 (40.0) | 1 (4.5) | 0.005 |
| Smokers | 5 (20.0) | 10 (45.5) | 0.12 |
| Hypercholesterolemia | 2 (7.1) | 8 (36.4) | 0.08 |
| Arterial hypertension | 17 (68.0) | 16 (72.7) | 0.76 |
| Diabetes mellitus | 6 (24.0) | 4 (18.2) | 0.73 |
| Multivessel disease | 14 (46.7) | 16 (53.3) | 0.38 |
| Previous MI | 0 (0) | 1 (4.5) | 0.47 |
| Previous CABG | 1 (4.0) | 5 (22.7) | 0.08 |
| Previous PTCA | 5 (20.0) | 3 (13.6) | 0.71 |

Data presented are mean value ± SD or percent of patients. CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

## Results

Twenty-five patients were randomized to the aspirin group and 22 to the ticlopidine group. The two groups were homogeneous with respect to major baseline clinical and angiographic characteristics except for a higher number of women and a slightly larger target vessel diameter in the aspirin group (Tables 1 and 2). The two groups did not differ significantly with respect to the prevalence of cardiovascular risk factors or previous cardiac events (Table 1). Two patients in the aspirin group sustained subacute stent occlusion on days 4 and 5, respectively, which was fatal in one. Access site or bleeding complications were not encountered in either study group.

At the end of the procedure, platelet variables did not show significant differences between the two treatment groups (Table 3). At day 5 after the intervention, the percent of LIBS1-positive platelets in the ticlopidine group was significantly lower and the percent of P-selectin–positive platelets tended to be lower than that in the aspirin group (Table 3, Fig. 1 and 2). These differences could be attributed to a differential effect of the two treatment regimens on the time course of the percent of LIBS1-positive and P-selectin–positive platelets. In the

**Table 2.** Angiographic and Procedural Characteristics

| | Aspirin Group | Ticlopidine Group | p Value |
|---|---|---|---|
| Target vessel* | | | 0.49 |
| LAD | 8 (28.6) | 13 (48.3) | |
| LCx | 4 (14.3) | 4 (13.8) | |
| RCA | 14 (50.0) | 10 (34.5) | |
| Venous bypass graft | 2 (7.1) | 2 (6.9) | |
| Indication for stenting* | | | 0.75 |
| Abrupt closure | 0 | 0 | |
| Dissection | 8 (28.6) | 11 (37.9) | |
| Residual stenosis | 18 (64.3) | 16 (55.2) | |
| Venous bypass graft | 2 (7.1) | 2 (6.9) | |
| Before PTCA | | | |
| Ref diam (mm) | 3.30 ± 0.48 | 3.00 ± 0.48 | 0.01 |
| MLD (mm) | 1.12 ± 0.58 | 0.90 ± 0.55 | 0.18 |
| % diam stenosis | 66.9 ± 14.8 | 70.2 ± 17.5 | 0.48 |
| Immediately after stenting | | | |
| Ref diam (mm) | 3.41 ± 0.45 | 3.12 ± 0.45 | 0.02 |
| MLD (mm) | 3.08 ± 0.51 | 2.93 ± 0.45 | 0.27 |
| % diam stenosis | 9.8 ± 12.3 | 6.2 ± 9.5 | 0.24 |
| Balloon/vessel ratio | 1.03 ± 0.14 | 1.08 ± 0.14 | 0.24 |
| No. of 7-mm stent segments/vessel | 2.0 ± 1.5 | 2.4 ± 1.6 | 0.32 |
| Length of stented segment (mm) | 14.5 ± 10.4 | 16.9 ± 11.1 | 0.41 |

*Three patients in the aspirin group and seven in the ticlopidine group had two vessels stented. Data presented are mean value ± SD or number (%) of vessels. diam = diameter; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MLD = minimal lumen diameter; RCA = right coronary artery; Ref = reference.

aspirin group, the percent of LIBS1-positive platelets significantly increased between days 1 and 5, whereas there were no substantial changes in the ticlopidine group (Fig. 1 and 3). However, the percent of P-selectin–positive platelets did not change significantly in the aspirin group but decreased significantly in the ticlopidine group (Fig. 2). Expressed as differences between days 5 and 1, the changes in the percent of LIBS1-positive platelets as well as those in P-selectin–positive platelets differed significantly between the two treatment groups ($p = 0.002$ for LIBS1, $p = 0.014$ for P-selectin).

At days 2 to 4, the surface expression of LIBS1 (Fig. 3) and

**Table 3.** Platelet Counts and Glycoprotein Surface Expression

| | Aspirin Group (n = 25) | Ticlopidine Group (n = 22) | p Value |
|---|---|---|---|
| End of stenting procedure | | | |
| Platelet count ($nl^{-1}$) | 191 (176–224) | 219 (182–262) | 0.28 |
| LIBS1-positive platelets (%) | 6.5 (2.9–13.8) | 8.0 (4.3–16.7) | 0.56 |
| P-selectin–positive platelets (%) | 8.5 (5.1–12.9) | 8.1 (5.4–16.3) | 0.65 |
| Anti-CD41 binding (arb U) | 672 (662–703) | 685 (649–711) | 0.72 |
| Day 5 | | | |
| Platelet count ($nl^{-1}$) | 216 (173–277) | 222 (192–265) | 0.50 |
| LIBS1-positive platelets (%) | 18.1 (8.5–35.5) | 8.5 (3.1–17.8) | 0.025 |
| P-selectin–positive platelets (%) | 8.8 (4.0–15.8) | 5.8 (3.4–9.5) | 0.073 |
| Anti-CD41 binding (arb U) | 654 (627–679) | 671 (630–704) | 0.41 |

Data presented are median (interquartile range). arb U = arbitrary units; LIBS1 = ligand-induced binding site 1.

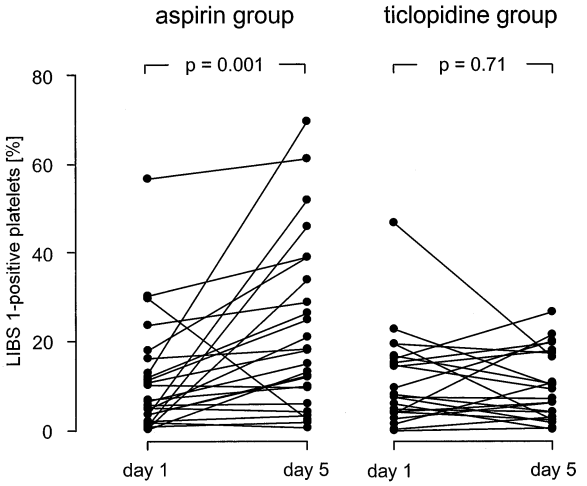
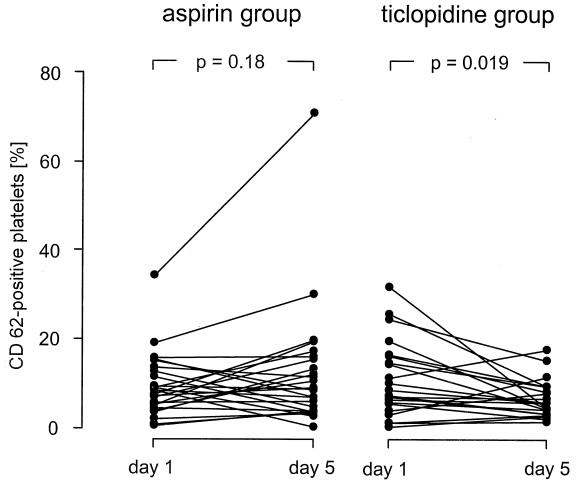



**Figure 1.** Individual values of surface expression of activated platelet fibrinogen receptor (LIBS1) immediately after (day 1) and at day 5 after coronary stent placement in patients treated with aspirin and with aspirin plus ticlopidine. In patients with stent occlusion, the last values before the event are depicted (18% and 29%).

P-selectin (data not shown) on platelets did not show significant differences between the two treatment groups. Platelet count and anti-CD41 immunofluorescence essentially remained at the same level throughout the study period (Table 3).

The two patients with subacute stent occlusion had elevated levels of LIBS1 surface expression before the event, representing the 66th and 87th percentiles of the entire study cohort. Moreover, their platelet anti-CD41 immunofluorescence ranged within the highest tercile of the entire study population (68th and 94th percentiles of the entire study cohort). However, P-selectin surface expression before stent occlusion cor-

**Figure 2.** Individual values of surface expression of P-selectin immediately after (day 1) and at day 5 after coronary stent placement in patients treated with aspirin and with ticlopidine plus aspirin. In patients with stent occlusion, the last values before the event are depicted (6.2% and 8.8%).



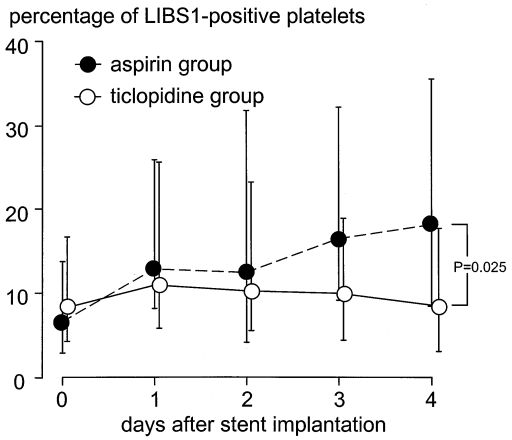



**Figure 3.** Time course of changes in LIBS1 surface expression on circulating platelets in the ticlopidine and aspirin groups. Median and interquartile ranges are shown.

responded to the 47th and 61st percentiles of the entire study cohort.

## Discussion

The present study shows that in suppressing platelet activation after coronary stenting, combined antiplatelet therapy with ticlopidine plus aspirin is superior to treatment with aspirin alone. Ticlopidine plus aspirin, but not aspirin alone, significantly decreased the surface expression of P-selectin within 5 days of treatment and prevented the fibrinogen receptor activation that was found in patients treated with aspirin alone. By day 5 after stenting, surface expression on platelets of the activated fibrinogen receptor was significantly lower in patients treated with than without ticlopidine, and there was a trend to lower P-selectin surface expression.

The platelet membrane glycoproteins that we analyzed by flow cytometry are not mere markers of platelet activation but play important functional roles. P-selectin mediates the interaction of platelets with endothelial cells and myeloid leukocytes and signals a variety of inflammatory and procoagulant responses in these cells (13,14). The GP IIb/IIIa complex constitutes the central receptor of platelet aggregation and is the most abundant constitutively expressed protein on the platelet surface (15). On platelets at rest, GP IIb/IIIa is present in an inactivated state (15). Stimulation of platelets converts GP IIb/IIIa to its activated state, which binds fibrinogen (15). This conversion represents the key mechanisms of platelet aggregation (15). With the use of anti-LIBS1 antibodies, we were able to detect this event on circulating platelets in our patients (2,3). Thus, immunologic characterization of platelet function enabled us to show that ticlopidine treatment after stenting interferes with key mechanisms of platelet function.

The importance of the platelet membrane markers that we examined is further supported by our findings in the two patients in the aspirin group who had subacute stent occlusion. Similar to our previous data (1), these patients showed surface expression of GP IIb/IIIa in the highest tercile of study cohort. Moreover, the proportions of their platelets circulating with activated fibrinogen receptors represented the 66th and 87th percentiles of the study cohort. In concert with our previous investigations (1,2,4), these findings underscore that the number and functional status of platelet fibrinogen receptors are of major pathophysiologic relevance regarding the risk of subacute stent occlusion. Nevertheless, the level of platelet activation, assessed by immunologic markers, does not suffice to fully explain subacute stent thrombosis in the two patients in the aspirin group. This is consistent with the notion that apart from changes in platelet function, vessel- and procedure-related mechanisms play a pivotal role in stent thrombosis (1,12,16–19).

The findings in the ticlopidine group concur with our earlier study comparing the effect on platelet function of combined antiplatelet therapy with that of anticoagulation (3). They suggest that the differential effect of these two antithrombotic regimens described earlier is predominantly due to the action of ticlopidine and not to heparin-induced platelet activation.

Blockage of the cyclo-oxygenase pathway by aspirin only inhibits platelet activation by weak agonists (8). Synergistically to this effect, ticlopidine interferes with platelet activation by strong agonists (5). Ticlopidine irreversibly inhibits the binding of the potent agonist adenosine diphosphate to its receptor on platelets and thus prevents exposure of fibrinogen receptors and platelet aggregation (20). Consistent with the known delay in the onset of action of ticlopidine (5), we were unable to detect an effect on platelet function before day 5 after stenting. Moreover, because GP IIb/IIIa is constitutively expressed on the platelet membrane (15), ticlopidine did not affect the total number of surface-expressed GP IIb/IIIa complexes, regardless of their activation status.

**Limitations of the study.** After two cardiac events in the aspirin group, we terminated the study prematurely. This may have interfered with our ability to detect significant differences in P-selectin surface expression between the two treatment groups. Nevertheless, even with a sample size below that projected, we verified differences in fibrinogen receptor activation at day 5. Moreover, unequivocal differences in the time course of P-selectin expression confirmed a differential effect of the two treatment regimens on this glycoprotein, as well.

Inhomogeneities between the study groups in gender distribution and target vessel diameter may have had an influence on the study results. However, we were unable to demonstrate a relation between gender or target vessel diameter and platelet markers (data not shown). We therefore have no reason to assume that these factors had an effect on the outcome of the study.

**Clinical implications.** We recently showed (4) that combined antiplatelet therapy is superior to anticoagulation in preventing stent thrombosis. Our present study suggests that the beneficial effect of combined antiplatelet therapy can be attributed to the action of ticlopidine. Withholding ticlopidine after coronary stenting may thus have deleterious effects. This implication of our present study is supported by published

clinical experience. Our present study and two others (21,22) found an excess of cardiac events when ticlopidine was withheld after stenting, even though statistical significance was only reported in one study (22). While this report was in preparation, results from the Stent Anticoagulation Regimen Study (STARS) (23) were reported that indicated that combined antiplatelet therapy with ticlopidine and aspirin more effectively prevents adverse cardiac events after stenting than therapy with aspirin alone. The platelet function data that we report strongly support the use of combined antiplatelet therapy with ticlopidine and aspirin after coronary stenting, particularly for those patients at high risk for subacute stent occlusion.

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