Platelet Function Under Aspirin, Clopidogrel, and Both After Ischemic Stroke
A Case-Crossover Study
Armin J. Grau, MD, PhD; Sven Reiners, Cand Med; Christoph Lichy, MD; Florian Buggle, MD; Andreas Ruf, MD, PhD

Background and Purpose—Combined antiplatelet agents may offer additive protection over single drugs after stroke. We investigated whether platelet activation is reduced under combined aspirin and clopidogrel compared with each drug alone.

Methods—In a case-crossover study, 31 patients with previous atherothrombotic or lacunar stroke who were treated with aspirin (100 to 300 mg/d) received clopidogrel (75 mg/d) and both aspirin and clopidogrel for 4 weeks. Platelet function in whole blood was studied after each treatment period and in healthy control subjects to assess activation-dependent antigens CD62p and CD63 by flow cytometry and collagen/epinephrine (CEPI-CT) and collagen/ADP (CADP-CT) closure times with the platelet function analyzer PFA-100, which investigates platelet-related function under shear stress.

Results—CD62p expression and CD63 expression were not different under the 3 treatment regimens. CD63 but not CD62p expression was lower in control subjects than in stroke patients regardless of the antiplatelet treatment (p < 0.05). CEPI-CT was prolonged under aspirin and aspirin plus clopidogrel compared with clopidogrel monotherapy (p < 0.0001). CADP-CT was longer under combination therapy than under aspirin (p = 0.0009) or clopidogrel (p = 0.0074) or in control subjects (p = 0.0010), mainly because of strong prolongation in a patient subgroup (28%).

Conclusions—CD63 expression reflecting the release of platelet lysosomes is consistently increased after stroke and incompletely suppressed by treatment with aspirin, clopidogrel, or both. The strong prolongation of CADP-CT under combined aspirin and clopidogrel in a patient subgroup may indicate a lower risk of thrombosis but also a higher risk of hemorrhage. The predictive value of platelet activation parameters requires investigation in prospective studies.

Key Words: inflammation ■ platelet aggregation inhibitors ■ platelets ■ secondary prevention

Antiplatelet drugs are the treatment of choice for secondary prevention after cerebral ischemia of noncardioembolic origin. However, the efficacy of presently available drugs is limited. Compared with placebo, aspirin reduced the relative risk of vascular events by 13% according to two meta-analyses1,2 and stroke risk by 18% in the European Stroke Prevention Study 2.3 Under clopidogrel, the relative risk of a compound outcome cluster of stroke, myocardial infarction, and vascular death was marginally, although significantly, lower than under aspirin (8.4%), whereas the risk reduction for stroke alone was not significant.4 Aspirin inhibits platelet aggregation by inhibition of cyclooxygenase, whereas clopidogrel reduces platelet activation via ADP receptor-dependent pathways. On the basis of these different modes of action, it is an attractive concept that the combination of both drugs may have additive effects on platelet inhibition. The combination of aspirin and clopidogrel or ticlopidine was shown to be a successful treatment strategy after coronary stenting and in unstable angina pectoris5,6 and is currently being tested in a large, randomized, placebo-controlled study on secondary prevention after stroke. However, it is unknown at present whether the combination of aspirin and clopidogrel leads to reduced platelet activation in patients at high risk for ischemic stroke or other vascular events.

We performed a case-crossover study to test the hypothesis that in patients with a history of stroke, platelet activation parameters are reduced under combination therapy with aspirin and clopidogrel compared with either therapy alone. We also investigated inflammatory parameters under treat-
ment with aspirin, clopidogrel, and both because aspirin but not clopidogrel possesses anti-inflammatory potential and inflammatory indexes were shown to predict the risk of vascular events.8 Furthermore, we compared platelet activation and inflammatory parameters in patients with previous stroke and healthy control subjects. Platelet function in whole blood was assessed by flow cytometry and by the platelet function analyzer (PFA-100).

**Subjects and Methods**

In the present study, patients who had suffered ischemic stroke and were treated with aspirin for secondary prevention received clopidogrel alone or a combination of clopidogrel and aspirin for 4 weeks. Platelet function was determined at the end of each treatment period and included flow cytometric assessment of the expression of p-selectin (CD62p) or lysosome-associated membrane protein (CD63) and studies with the PFA-100 (Dade Behring) assessing collagen/epinephrine (CEPI) and collagen/ADP (CADP) closure time (CT).

Patients between 18 and 80 years of age were eligible for study participation if they had suffered ischemic stroke between 6 months and 2 years ago, if the index stroke was caused by large-artery atherosclerosis or cerebral microangiography, and if they had received aspirin (100 to 300 mg/d) for at least 3 months. Large-artery atherosclerosis was diagnosed by duplex studies or angiography showing stenoses of brain-supplying arteries of ≥50% diameter reduction and a typical morphology for atherosclerotic lesions. Cerebral microangiopathy was diagnosed if neuroimaging showed ischemic lesions of <1.5 cm and clinical symptoms in accordance with typical lacunar syndromes (pure motor stroke, pure sensory stroke, sensorimotor stroke, dysarthria clumsy hand syndrome, ataxic hemiparesis).

Exclusion criteria included the presence of concurrent stroke etiologies, operation or angioplasty for symptomatic stenosis performed within 3 months or planned for the future, pregnancy or childbirth, known allergy against or previous treatment with clopidogrel, hemorrhagic diathesis, history of gastrointestinal or other bleedings, history of drug-induced disorders, poorly controlled hypertension (≥180/110 mm Hg), trauma or surgery within the last 3 months or any surgery planned for the next 3 months, cancer, rheumatic diseases, intake of anticoagulants or nonsteroidal antiinflammatory drugs, severe liver (international normalized ratio ≥1.5) or renal (creatinine ≥1.5 mg/dL) insufficiency, drug or alcohol abuse, any blood cell abnormalities (anemia, leukopenia, thrombocytopenia, or thrombocytosis), and epileptic seizures.

Thirty-five patients were identified by chart review and were willing to participate. Of these, 4 had to be excluded because of anemia, thrombocytosis, severe hepatic disturbance and suspected alcohol abuse, and recent pretreatment with clopidogrel (n=1, respectively). Therefore, 31 patients were entered into the study, 20 with stroke caused by large-artery atherosclerosis and 11 with lacunar strokes. The patients took 300 (n=26), 250 (n=3), 200 (n=1), and 100 (n=1) mg/d aspirin. Demographic data of the patients are given in Table 1. All patients gave written, informed consent. The study protocol was approved by the local Human Subjects Committee. According to legal requirements, patients received special insurance.

Patients were asked to take clopidogrel (75 mg/d) instead of aspirin for 4 weeks and both aspirin (300 mg/d) and clopidogrel (75 mg/d) for another 4 weeks. In the first part of the study, clopidogrel was administered, followed by the combination therapy. In the second part, 6 patients were randomly assigned to first receive the combination therapy and then the clopidogrel monotherapy. After each treatment phase, the patients visited the clinic, were asked about potential side effects, and received a physical examination. Laboratory examinations—including whole blood count, liver enzymes, electrolytes, urea, creatinine, C-reactive protein (CRP), fibrinogen, and partial thromboplastin time—were performed at study entry and after both treatment periods. Clopidogrel was made available by Sanofi-Synthelabo Inc. Intake of study drugs was controlled by counting of delivered tablets.

For the control group, we investigated 21 presumably healthy subjects who had none of the above exclusion criteria and no vascular risk factor or arterial vascular disease. None of the control subjects took aspirin, clopidogrel, or other platelet-inhibiting drugs. Control subjects were matched to patients for age and sex distribution.

**Assessment of Platelet Function**

Venipuncture of forearm veins was performed under minimal stasis, with the first few milliliters rejected. Flow cytometry was done according to the consensus protocol for flow cytometric characterization of platelet function as reported recently.6 Briefly, peripheral venous blood was collected into an aldehyde-based fixation solution that blocks metabolic processes within milliseconds and preserves CD62p and CD63 for at least 24 hours at room temperature. The samples were incubated with saturating concentrations of FITC-labeled antibodies (Beckman Coulter) against CD62p (clone CLBThromb6) or CD63 (Clone CLBGran12) and with PE-labeled antibodies against CD41a (clone P2) for 15 minutes at room temperature in the dark. As control experiments, platelets were incubated with FITC-coupled unspecific mouse IgG1 (Beckman Coulter) with the same fluorochrome-to-protein ratio and concentration as the specific IgG. These controls yielded the same fluorescence as platelets whose binding of FITC-labeled specific antibodies was blocked by an excess of unlabeled antibodies of the same clone. After immunolabeling, the samples were analyzed by FACScan (Becton Dickinson). Forward light scatter and expression of CD41a were used for platelet identification. Platelet-bound anti-CD62p or anti-CD63 antibodies were then determined by analyzing 5000 platelets for FITC fluorescence. Results were expressed as a percentage of antibody-positive platelets, defined as those with a fluorescence intensity exceeding that of 98% to 99% of the control platelets. The intra-test variability was low (mean coefficient of variation, 0.023 for CD62p; 0.039 for CD63).

For PFA-100 studies, blood was collected into tubes containing 3.2% buffered citrate (Sarstedt), kept at room temperature, and analyzed within 3 hours after venipuncture. The PFA-100 simulates an injured blood vessel by aspirating blood through disposable test cartridges coated with collagen and either ADP (50 μg) or epinephrine (10 μg). Whole blood (900 μL) flows under constant high shear rates (5000 to 6000/s) through a capillary and a microscopic aperture (147 μm) cut into the coated membrane. When blood comes into contact with the membrane, platelets adhere, aggregate, and form a plug that occludes the aperture with consecutive cessation of blood flow. The time required to occlude the aperture is automatically reported as the CT. Measurements are terminated after a maximum of 300 seconds. Aspirin usually prolongs the CEPI-CT but does not extend the CDP-CT. CDP cartridges detect platelet dysfunction not mediated by aspirin.9 On the basis of a recent review10 and our own control group, CEP-CEI >193 seconds and CDP-CT >133 seconds were considered prolonged. Measurements were performed in duplicate. The intratest variability was 0.050 for CEPI and 0.085

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (n=31)</th>
<th>Control Subjects (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>63.0±9.4</td>
<td>62.8±10.4</td>
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<tr>
<td>Female sex</td>
<td>11 (35.5%)</td>
<td>7 (33.3%)</td>
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<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
<td>8 (25.8%)</td>
<td>...</td>
</tr>
<tr>
<td>Current smoking</td>
<td>12 (38.7%)</td>
<td>...</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>21 (67.7%)</td>
<td>...</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5 (16.1%)</td>
<td>...</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4 (12.9%)</td>
<td>...</td>
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**TABLE 1. Demographic Data in Patients and Control Subjects**
for CADP cartridges. CRP was determined by immunoturbidimetric assay (Aeroset; threshold of detectability: 3 mg/L). Fibrinogen was measured by functional coagulation testing (derived fibrinogen) with Recombiplastin (Instrumentation Laboratory) as reagent. Leukocyte counts were assessed by Coulter counter analysis.

Data are presented as mean and SD or median and percentiles as appropriate. We used the Friedman test for intraindividual comparisons between the 3 treatment regimens. For comparisons of the 4 platelet function parameters between treatment groups, differences were considered significant at $P < 0.0125$. The Wilcoxon signed-rank test was applied for further analyses of treatment regimens if the Friedman test yielded significant results. The Mann-Whitney U test was used to compare patients and control subjects; the Spearman rank correlation coefficient was used to correlate parameters; and Fisher’s exact test was used for analyses of categorical variables. Analysis of variance (ANOVA) was applied to analyze the influence of various factors on a parameter. Variables without normal distribution received logarithmic transformation before ANOVA. We used the software package SAS (version 8.02) for the analyses.

Results

None of the 31 stroke patients had symptoms attributable to cerebral ischemia or developed any cerebral or systemic bleeding during the study. One patient withdrew from the study during therapy with aspirin plus clopidogrel because of sudden severe shoulder pain. Bleeding into the shoulder joint was excluded by MRI. One patient was excluded shortly after initiation of the combination therapy because of a first epileptic seizure. Therefore, 29 patients completed the entire study.

Under the 3 treatment regimens, the expression of CD62p and CD63 was not significantly different (Table 2). In contrast, CEPI-CT and CADP-CT showed significant differences between treatments ($P < 0.0001$, respectively; Table 2, Figures 1 and 2). Regarding CEPI-CT, differences were due to prolonged clot formation under aspirin ($P < 0.0001$) and aspirin plus clopidogrel ($P < 0.0001$) compared with clopidogrel monotherapy. The CEPI-CT was maximally inhibited (>300 seconds) in 23 of 31 patients (74.2%) under aspirin and in 26 of 29 patients (89.7%) under both aspirin and clopidogrel ($P = 0.18$). Normal values ($≤ 193$ seconds) were found in 5 of 31 patients (16.1%) despite medication with aspirin and in 1 of 29 patients under the combination therapy (3.4%; $P = 0.20$). The CADP-CT was prolonged under the combination therapy compared with monotherapy with either aspirin ($P = 0.0009$) or clopidogrel ($P = 0.0074$). Results under aspirin and clopidogrel were not different ($P = 0.51$). The CADP-CT was outside the normal range (>133 seconds) in 2 patients (6.5%) under clopidogrel but in 8 patients (27.6%) under the combination therapy ($P = 0.039$). Complete inhibi-
tion of CADP-CT (>300 seconds) occurred in 7 patients under the combination therapy but in 0 of the patients under clopidogrel (P<0.004). CEPI-CT and CADP-CT were correlated with each other under clopidogrel (R=0.32, P=0.006) and the combination therapy (R=0.54, P<0.001) but not under aspirin monotherapy (R=0.17, P=0.15). CD62p and CD63 expression showed significant correlations under all medications (R=0.53, P<0.001). CEPI-CT and CADP-CT on one side and CD62p and CD63 expression on the other side were not significantly correlated with each other.

Platelet activation parameters did not differ between patients who took 300 mg of aspirin and those who took a smaller doses (P>0.30) or between patients with lacunar stroke and patients with stroke resulting from large-artery atherosclerosis (P>0.25). Smoking, hypertension, hypercholesterolemia, diabetes mellitus, and the presence of coronary heart disease and/or peripheral arterial disease did neither influence CEPI-CT, CADP-CT, or CD63 expression. Diabetes mellitus (P=0.003) and hypercholesterolemia (P=0.010) were associated with higher CD62p expression (ANOVA).

Leukocyte counts, platelet counts, and CRP and fibrinogen levels were not different under the 3 treatment regimens (P>0.10).

Control subjects had lower CD63 expression (median, 1.0%; 25th and 75th quartiles, 0.2% and 2.8%) than patients under all 3 therapeutic regimen (P<0.05). In contrast, there was no difference regarding CD62p expression (control subjects; median, 2.3%; 25th and 75th quartiles, 0.7% and 3.6%). The CEPI-CT was similar in patients under treatment with clopidogrel and control subjects (median, 117 seconds; 25th and 75th quartiles, 108 and 127 seconds). The CADP-CT (median, 83; 25th and 75th quartiles, 81 and 93 seconds) was not different from patients treated with aspirin or clopidogrel; however, it was shorter than in patients under aspirin plus clopidogrel (P=0.001). Leukocyte counts were 5.17±1.40x10^9/L compared with 6.77±1.70x10^9/L (P=0.003), and fibrinogen levels tended to be lower in control subjects than in patients under therapy with aspirin (2.97±0.65 versus 3.50±1.06 g/L; P=0.069), whereas no difference existed regarding platelet counts and CRP levels.

Discussion

Combination therapy with aspirin and clopidogrel was well tolerated and safe in our patients during the short treatment period of 4 weeks. Both serious adverse events that occurred were not causally related to the study medication. The main hypothesis of the present investigation was that in patients after stroke, aspirin plus clopidogrel may reduce platelet activation to below the level reached with each single agent alone. This study shows that the CADP-CT assessed with the PFA-100 was prolonged under combination therapy, whereas the 3 other platelet activation markers were not significantly changed.

We chose flow cytometry and the PFA-100 because both methods allow platelet function analysis in whole blood. Aggregometry with platelet-rich plasma and measurement of platelet release products have the problem of potential artifactual platelet activation during blood sampling, and release products may lack sensitivity because of dilution effects in plasma. Flow cytometric analysis of platelets is a relatively new and powerful technique that has been developing into a useful clinical tool. It has the advantage of little artifactual in vitro activation, particularly because blood fixation was used in our study. Previous studies showed that CD62p and CD63 expression by platelets is increased in acute ischemic stroke. CD62p (p-selectin) is a glycoprotein localized on the a-granule membrane that is rapidly translocated to the cell surface after stimulation and mediates the adhesion of platelets to leukocytes. P-selectin upregulates tissue factor in monocytes, promotes fibrin deposition, and leads to leukocyte accumulation in areas of vascular injury associated with thrombosis and inflammation. CD63 is expressed on the platelet surface after the release of lysosomes. It may protect the plasma membrane against degradation by lysosomal proteins; however, its biological function is not sufficiently understood. In a baboon model, degranulated platelets shed CD62p from the cell surface but continued to circulate and function. Such shedding after cell activation may explain why CD62p expression was not increased in our patients in the chronic stage after stroke. In contrast, CD63, for which shedding is not known to occur, was expressed more strongly in patients than control subjects.
In our study, neither clopidogrel nor the combination of aspirin and clopidogrel led to lower CD63 expression than therapy with aspirin. These results indicate that currently available antiplatelet drugs, even if combined, do not inhibit the release of platelet lysosomes in vivo, a mechanism that requires strong platelet activation. In patients with previous myocardial infarction, clopidogrel with and without aspirin suppressed CD62p and CD63 expression after stimulation with ADP or thrombin. Assessment of drug effects on platelet reactivity in vitro was not performed in our study but may be a meritorious focus of future research.

The PFA-100 assesses platelet-related function, in particular adhesion and aggregation, under shear stress. Its advantages are ease of operation, rapidity, and comparability between different laboratories. It was shown to reliably monitor platelet function under treatment with aspirin and GPIIb/IIIa receptor antagonists and to be useful in screening for congenital and acquired platelet dysfunction. It is not sensitive to heparin or defects in coagulation proteins, e.g., hemophilia A. To the best of our knowledge, the PFA-100 has not been applied in clinical stroke. As expected, the CEPI-CT was strongly prolonged under treatment with aspirin compared with clopidogrel or the control group. Despite intake of aspirin, 16.1% of our stroke patients had normal CEPI-CT values. In a PFA-100-based study using the same cutoff value, the rate of “aspirin resistance” was 9.5% in patients with stable cardiovascular disease receiving 325 mg/d aspirin. Measuring platelet aggregation in platelet-rich plasma, Helgason et al detected aspirin resistance in 20.6% of their stroke patients taking ≥325 mg/d aspirin. Aspirin resistance defined by in vivo thromboxane biosynthesis was recently shown to predict ischemic events. Patients with normal CEPI-CT values despite aspirin medication may be at increased risk of ischemic events; however, prospective data based on the PFA-100 are not yet available.

Clopidogrel acts via inhibition of ADP-induced platelet activation. In accordance with previous studies, treatment with clopidogrel was not reflected by prolonged CADP-CT. This shows that the current setup of the PFA-100, mainly the high ADP concentration in CADP cartridges, is not suitable for monitoring therapy with clopidogrel or ticlopidine. Most interestingly, CADP-CT was longer under combined aspirin and clopidogrel than under either monotherapy. In patients undergoing percutaneous transluminal coronary angioplasty, the combination of ticlopidine and aspirin led to a nonsignificant increase in CADP-CT compared with aspirin alone or was associated with normal CADP-CT; however, ticlopidine medication was shorter than in our study. The combination therapy was associated with a heterogeneous response among our patients. About one fourth of the subjects showed a very strong inhibitory effect, whereas in the other patients, the difference from both monotherapies was not significant. In the subjects who showed a strong inhibition, the combination therapy could be associated with good protection against ischemic events but also with an increased bleeding risk. It is unknown why some individuals react with a strong response to combined aspirin and clopidogrel and others do not. It was recently shown that closure times in the PFA-100 are highly dependent on the von Willebrand factor. Differences in von Willebrand factor levels could possibly explain variations between patients. It is a limitation of our study that the von Willebrand factor was not assessed. Furthermore, the nonrandomized, non–placebo-controlled sequential treatment design could be regarded as a limitation, but it is unlikely that it affects the data interpretation. Similarly, it is unlikely that effects seen under the combination therapy represent late treatment effects of clopidogrel rather than effects of the combination therapy.

Aspirin but not clopidogrel possesses an anti-inflammatory mode of action; however, the 3 inflammatory parameters assessed were not different under the medication with or without aspirin. In accordance with previous studies, leukocyte counts and fibrinogen levels were higher after stroke than in healthy control subjects, although the difference was not significant for fibrinogen. We did not use a highsensitivity test for CRP assessment and may therefore have overlooked small differences in CRP.

From the results of this study, it appears meritorious to investigate in larger studies whether the CADP-CT is a predictor of ischemic events or bleeding complications under treatment with combined aspirin and clopidogrel and whether normal CEPI-CT predicts an increased rate of ischemic events under monotherapy with aspirin. CD62p and CD63 expression may not be suitable for monitoring therapy with aspirin, clopidogrel, or both after stroke. Although not influenced by the antiplatelet agents studied here, CD63 expression could still be a predictor of the risk of ischemic events, an issue that requires investigation in a larger prospective study.

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References

Synergistic Antiplatelet Effects of Clopidogrel and Aspirin Detected With the PFA-100 in Stroke Patients

Currently, it is neither standard nor clinical practice to measure platelet function under treatment with antiplatelet drugs. This practice follows a “one size fits all” principle, which is not likely to be correct. Historically, platelet function tests, mainly aggregometry, have been cumbersome and time consuming and may have lacked reproducibility if they were not carried out by highly trained personnel. Aggregometric measurements have another major disadvantage: they evaluate platelet function at low shear rates, which is in stark contrast to the high shear rates prevailing at sites of arterial stenosis. Thus, their relevance for predicting platelet behavior in stenotic arteries remains to be determined.

A number of point-of-care platelet function tests have recently become available. One of these novel test systems is the PFA-100 platelet function analyzer, which is designed to overcome many of the drawbacks of aggregometry. In particular, the PFA-100 is a high-shear system that has successfully been applied to detect and monitor the effects of various antiplatelet drugs.

Until recently, the PFA-100 was considered insensitive to the effects of thienopyridines such as clopidogrel, whereas the in vivo bleeding time could detect clopidogrel effects.

In this issue of Stroke, Grau et al report a nonrandomized, crossover trial in which 31 patients with previous stroke received aspirin, clopidogrel, and both in a sequential manner. Consistent with previous reports, aspirin maximally prolonged collagen/epinephrine-induced closure times (CEPI-CT >300 seconds) in 74% of patients, while one fourth of patients were more or less resistant to aspirin treatment. However, the study is underpowered to allow any conclusions on dose-effect relationships because most patients received 300 mg aspirin. Although the authors conclude that the CEPI-CT was insensitive to clopidogrel effects, a subgroup of 4 to 6 patients appeared to have prolonged CEPI-CT values under clopidogrel. Along similar lines, combination of both drugs enhanced “aspirin” responder rates to 90%.

Neither aspirin nor clopidogrel alone prolonged collagen/ADP-induced closure time (CADP-CT), whereas the combination of both significantly prolonged CADP-CT in 25% of patients; most patients displayed even maximal CADP-CT values (>300 seconds). This degree of platelet dysfunction is typically observed only in patients with severe thrombocytopenia, von Willebrand disease, or a congenital deficiency in
platelet glycoprotein GPIb or GPIIb/IIIa or in those under treatment with infusable GPIIb/IIIa antagonists. Thus, CADP-CT values >300 seconds can be regarded as clinically relevant, and it is conceivable that this degree of platelet inhibition translates into greater clinical benefit in terms of reduction of vascular accidents but also poses a greater risk for bleeding complications. However, response patterns were not continuous over the range of possible CADP-CT values but rather appeared to follow an “all or none” principle (normal or >300 seconds). Hence, it is tempting to speculate that 1 single hereditary or environmental factor could largely determine the response to combined treatment with aspirin and clopidogrel in this test system.

Although provocative, the small sample size and nonrandomized design are evident limitations of the present trial. Thus, confirmation of these interesting findings in larger randomized trials and other patient populations is desirable. Such trials should ideally try to identify the predictive value of the PFA-100 for either vascular or bleeding complications in these patients and provide some mechanistic insight into or explanations for the variability in response.

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References
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