Platelet Function Under Aspirin, Clopidogrel, and Both After Ischemic Stroke: A Case-Crossover Study

To the Editor:

We read with great interest the articles by Grau et al1 and Marquardt et al,2 which were from the same institute, concerning the platelet function under antiplatelet therapy and the course of platelet activation markers after acute ischemic stroke. Many studies have shown that activated platelets can be detected in the systemic circulation in patients with stroke, undergoing cardiopulmonary bypass surgery, peripheral artery occlusive disease, acute myocardial infarction, and other thrombotic disorders. However, which marker for activated platelets can most precisely reflect in vivo platelet activation remains uncertain. Besides, it is of great importance whether the marker is useful to predict the recurrence of vascular event and to monitor the antiplatelet therapy. We would like to compare their recent 2 studies1,2 with previous ones including our study,3 their previous study4 and others.5–10

Platelet activation in patients with chronic phase of stroke has been observed using CD62p expression as a marker of platelet activation.3–5 In the previous study by Grau et al,1 the proportion of platelets expressing activation-dependent antigens (CD62p and CD63) was higher in patients with both acute and previous cerebrovascular ischemia as compared with age- and sex-matched control subjects. In addition, relatively more platelets expressed CD62p than CD63 in most patients in that study. They explained it was because the secretion of lysosomes usually require stronger stimulation than the release of α-granules. On the contrary, in the recent study by Marquardt et al,2 CD62p expression was not significantly different on days 14 and 90 after stroke compared with control groups. We wonder why platelet activation detected by CD62p expression was not observed when compared serially. On the other hand, increased CD63 expression was observed on days 14 and 90 after stroke, which indicates continuously ongoing platelet activation. They explained that in the subacute stage after ischemic stroke, CD63 is a more sensitive marker of platelet activation than CD62p, most likely because of shedding of CD62p.5 If so, it may be possible to detect the elevation of soluble p-selectin. Then, we would like to know if soluble p-selectin in plasma rather than CD62p on the platelet surface can be a marker of platelet activation in the subacute stage after stroke. Another question is about the course of platelet activation markers in their study.2 It is considered that platelets are activated more strongly in the acute phase of stroke than in the chronic phase of stroke.2,5 In the study by Marquardt et al,2 CD62p expression declined over time after stroke, and 60% of patients showed a decrease in CD62p. However, the percentage of CD63-expressing platelets did not change between days 1 and 90 after stroke, and only 36% of patients showed a decrease in CD63 over time. Moreover, 30% of patients showed an increase in CD63, and in 34% of patients, CD63 expression did not change. If CD63 is a more sensitive marker of platelet activation than CD62p, we wonder why CD63 did not reflect the difference of platelet activation among the different phases of stroke.

In the chronic phase of stroke, CD62p and CD63 expression did not differ between patients treated with aspirin, clopidogrel, both of them, or anticogulants in the recent articles by Grau et al1 and Marquardt et al.2 Other recent studies have consistently shown that aspirin does not affect the flow cytometric detection of platelet activation, neither expression of CD62p6–9 nor CD63.7,8 In contrast, reduction of CD62p expression has been found for the thienopyridine derivatives, clopidogrel9 and ticlopidine.10 Although CD62p expression stimulated with various agonists was decreased in these studies,9,10 the expression of CD62p without stimulation was also significantly lower in patients with atherothrombotic stroke but not in those with lacunar stroke, who were treated with ticlopidine in our study.1 It is possible that the significant difference was not detected because CD62p expression was not increased in patients with chronic phase of stroke in the study by Marquardt et al,2 because they included patients with both subtypes of ischemic stroke. Also in the study by Grau et al,1 CD63 expression treated with aspirin plus clopidogrel seemed slightly low, and the difference might be significant when it was assessed in a larger number of patients or in patients with a specific subtype, that is, atherothrombotic stroke, in whom stronger platelet activation occurs than in those with lacunar stroke as reported by us.2

Masako Yamazaki, MD
Shinichiro Uchiyama, MD
Department of Neurology
Tokyo Women’s Medical University
Tokyo, Japan


Response

We wish to thank Drs Yamazaki and Uchiyama for their interest in our studies. The authors correctly hint to the fact that CD62p expression by platelets was increased in the subacute stage after stroke in our first study but not in our recently published study.2 In contrast, both studies consistently showed that CD62p and CD63 are significantly increased over control values in the acute stage after stroke. We think that our more recent study that included serial measurements in 50 patients at 10 time points after stroke contains the more valid data. Furthermore, these results were confirmed by our case-crossover study on platelet function under aspirin, clopidogrel, and both after stroke, where we again found that CD63 but not CD62p was increased over values in control subjects in the subacute stage after stroke.3 The first study was a pilot study and had the disadvantage that different subjects were
investigated in the acute and the chronic stage after stroke and therefore does not allow good comparability between both periods. Given our new results, it is certainly an important question whether soluble p-selectin is a marker of platelet activation in the subacute stage after stroke.

Drs Yamazaki and Uchiyama correctly state that, in fact, CD63 expression by platelets did not follow the somewhat expected course of declining values but remained elevated on an increased level for at least 3 months after stroke. We had concluded that “in the subacute stage after ischemic stroke CD63 is a more sensitive marker of platelet activation than CD62p” because CD63 but not CD62p remain increased during that period. Certainly, we must be careful when we apply our hypothetical models to empirical data. We do not sufficiently know how platelet activation “really” behaves in different stages after acute cerebral ischemia and, in particular, we cannot expect that each feature of platelet activation as a complex scenario follows the same dynamic over time. At least, we should not expect that all of these features “reflect the difference of platelet activation among the different phases of stroke” as long as we are still on our way to characterize these phases after stroke regarding platelet activation.

We agree with Yamazaki and Uchiyama that different stroke subtypes may be reflected by differences in platelet activation parameters. In our subgroup analyses, we did not find differences between lacunar and atherothrombotic stroke regarding neither CD62p nor CD63 and we found differences only with respect to CD63 and cardioembolism.2 However, as we mention in the discussion, the focus of our study was the longitudinal assessment of platelet markers, and studies with larger numbers of patients are required to study differences between etiologic subgroups.

In our recent case-crossover study on platelet function under aspirin, clopidogrel, and both after stroke, we found barely any difference regarding CD63 expression among the 3 treatments.3 As most of our patients had atherothrombotic stroke, we do not think that the combination therapy will be able to suppress CD63 expression efficiently. However, larger studies may be required to finally solve this issue. We feel that the most important issue in platelet function and stroke is to identify a platelet marker that is easily and reliably assessable in clinical practice and that turns out to predict recurrent events after stroke and may thus be helpful to guide therapeutic decisions.

Armin J. Grau, MD, PhD
Lars Marquardt, MD
Neurology Department
Städtisches Klinikum Ludwigshafen
Ludwigshafen, Germany

Andreas Ruf, MD, PhD
Department of Clinical Chemistry
Städtisches Klinikum Karlsruhe
Karlsruhe, Germany

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Masako Yamazaki and Shinichiro Uchiyama

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