Platelet Function Testing in Patients with Acute Ischemic Stroke: An Observational Study

Francesca Rosafio, MD,* Nicoletta Lelli, MD,† Stefano Mimmi, PhD,‡ Laura Vandelli, MD,* Guido Bigiardi, MD,* Maria Luisa Dell’Acqua, MD,* Livio Picchetto, MD, PhD,* Roberta Pentore, MD,* Diana Ferraro, MD, PhD,* Tommaso Trenti, MD,† Paolo Nichelli, MD, PhD,* and Andrea Zini, MD*

Background: The measurement of platelet reactivity in patients with stroke undergoing antiplatelet therapies is not commonly performed in clinical practice. We assessed the prevalence of therapy responsiveness in patients with stroke and further investigated differences between patients on prevention therapy at stroke onset and patients naive to antiplatelet medications. We also sought differences in responsiveness between etiological subtypes and correlations between Clopidogrel responsiveness and genetic polymorphisms. Methods: A total of 624 stroke patients on antiplatelet therapy were included. Two different groups were identified: “non-naive patients” and “naive patients”. Platelet function was measured with multiple electrode aggregometry, and genotyping assays were used to determine CYP2C19 polymorphisms. Results: Aspirin (ASA) responsiveness was significantly more frequent in naive patients compared with non-naive patients (94.9% versus 82.6%, \(P < .0010\)). A better responsiveness to ASA compared with Clopidogrel or combination therapy was found in the entire population (\(P < .0010\)), in non-naive patients (\(P < .0253\)), and in naive patients (\(P < .0010\)). Multivariate analysis revealed a strong effect of Clopidogrel as a possible “risk factor” for unresponsiveness (odds ratio 3.652, \(P < .0001\)). No difference between etiological subgroups and no correlations between responsiveness and CYP2C19 polymorphisms were found. Conclusion: In our opinion, platelet function testing could be potentially useful in monitoring the biological effect of antiplatelet agents. A substantial proportion of patients with stroke on ASA were “resistant”, and the treatment with...
Clopidogrel was accompanied by even higher rates of unresponsiveness. Longitudinal studies are needed to assess whether aggregresponsiveness might supply individualized prognostic information and whether it can be considered a valid tool for future prevention strategies. **Key Words:** Ischemic stroke—platelet inhibitor—secondary prevention—aggregometry.

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**Introduction**

Control of cerebrovascular risk factors and therapeutic secondary prevention are fundamental to prevent ischemic cerebrovascular events (transient ischemic attack [TIA]/stroke). Treatment of noncardiogenic strokes (atherosclerotic, lacunar, or cryptogenic infarcts) is based on antiplatelet agents, which reduce the relative risk of stroke or death on average by about 22%.12 Regarding their mechanism of action, antiplatelet agents are classified in 3 groups: thienopyridines, aspirin, and glycoprotein IIb/IIIa inhibitors. Oral antiplatelet therapy, with ASA, works by inhibiting cyclooxygenase-1 (COX-1), a key enzyme in the production of thromboxane A2 from arachidonic acid, resulting in reduced platelet aggregation.13

The intensified therapy has been associated with a diminished pharmacodynamic response to Clopidogrel.14 Recently, a systematic review and meta-analysis of randomized clinical trials was performed to evaluate the clinical efficacy and safety of intensified antiplatelet therapy versus Clopidogrel at a standard dosage, on the basis of the laboratory tests used to monitor the intake of antiplatelet drugs.15,16

A greater risk of recurrence of cardiovascular events has been demonstrated in patients with resistance to ASA or Clopidogrel.15-17 Furthermore, pharmacological interactions with other drugs (e.g., proton-pump inhibitor) have been associated with a diminished pharmacodynamic response to Clopidogrel.18 Recently, a systematic review and meta-analysis of randomized clinical trials was performed to evaluate the clinical efficacy and safety of intensified antiplatelet therapy versus Clopidogrel at a standard dosage, on the basis of the laboratory tests used to monitor the intake of antiplatelet drugs.15,16

The intensified therapy protocol was associated with a significant reduction in cardiovascular mortality, stent thrombosis, and myocardial infarction, with no difference in the rate of major bleeding between the 2 groups, although the net clinical benefit significantly depended on the risk of stent thrombosis with standard Clopidogrel dose. Similarly, another systematic review and meta-analysis of randomized trials, concerning tailored antiplatelet therapy in patients with acute coronary syndrome, showed a minor occurrence of death or clinical adverse events in personalized antiplatelet therapy compared with conventional treatment.20

Although several data are available on cardiovascular diseases, there are a small number of studies regarding monitoring of antiplatelet therapy in patients with ischemic stroke. In most of them, the evaluation of antiplatelet effect has been performed mainly with Platelet Function Assay-100, with evidence of a low responsiveness to low-dose ASA and enteric-coated ASA in a significant proportion of patients (37%) in Alberts et al’s study.21 Other data pointed to limitations of platelet aggregation monitoring, particularly in terms of reliability of results.22-24

The Trinity Antiplatelet Responsiveness study investigated the prevalence of ex vivo nonresponsiveness in patients with ischemic stroke/patients with TIA evaluated with a “longitudinal definition of HTPR” by comparing responsiveness to antiplatelet therapy at follow-up with patients’ baseline values.25 Payne et al reported a significant clinical impact of monitoring the intake of a single dose of Clopidogrel with flow cytometry and aggregometry before carotid endarterectomy to reduce postoperative embolization.26 Recently, some studies evaluated...
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