Clinical Study

Do Clopidogrel Nonresponders Have an Increased Risk of Adverse Events during Supra-Aortal Angioplasty and Stenting?

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Objective. The aim of the present study was to correlate new periprocedural diffusion-weighted imaging (DWI) lesions during stenting of supra-aortal arteries with the level of platelet inhibition using point-of-care analysis. **Background.** Cardiological studies have shown that patients undergoing coronary PTA have a significantly elevated risk of severe thrombotic complications if patients show insufficient inhibition of platelet function. **Methods.** From August 2008 to June 2009, 44 patients with an indication of supra-aortal angioplasty and/or stenting were prospectively enrolled. Platelet reactivity was tested using a Multiplate device (Dynabyte). These patients underwent MRI before and after the intervention to determine the prevalence of new DWI lesions. The primary endpoint was the prevalence of DWI lesions; the secondary endpoint was clinical status until discharge from hospital. **Results.** There was no significant relationship between the primary endpoint and the degree of platelet function. Patients with high platelet reactivity showed the same amount of periprocedural complications as patients with sufficient inhibition of platelets. **Conclusions.** Clopidogrel did not have a protective effect on periprocedural complications, nor did it decrease the number of silent DWI lesions after the procedure. The prescribed strong relationship between high platelet reactivity and early post-procedural adverse events was not observed in our cohort.

1. Introduction

Several studies have shown that patients with a low response rate to clopidogrel, measured by in vitro function of platelets, have a significantly increased risk of early stent thrombosis after percutaneous transluminal coronary angioplasty (PTCA) and stenting compared to patients with sufficient inhibition of platelets [1–7]. The aim of this prospective trial was to examine if there is a relationship between the response to clopidogrel and clinical adverse events after supra-aortal percutaneous transluminal angioplasty (PTA) and stenting as well as the amount of newly occurred silent diffusion-weighted imaging (DWI) lesions.

The DWI lesion load is a known indicator of microembolic events after neurovascular interventions [8, 9], so it

was the primary target variable. Platelet reactivity was tested using a Multiplate analyzer from Dynabyte GmbH (Munich, Germany). This device is based on multiple electrode aggregometry. One study showed a correlation between a low response to clopidogrel measured by Multiplate and clinically adverse events after supraaortal stenting [2]. In the present study, we additionally used MRI to correlate the DWI lesion load with the platelet reactivity.

2. Patients and Methods

From August 2008 to June 2009, 44 patients with stenoses of supraaortal vessels and indication for treatment were prospectively enrolled (Table 1). Inclusion criteria were

TABLE 1: Vessels that underwent intervention.

Total	44
Symptomatic	33 (=75%)
Stroke	26 (=59%)
TIA	7 (=16%)
Asymptomatic	11 (=25%)
Location	
Carotid artery	
Extracranial stent	35
Intracranial stent	1
Extracranial PTA	1
Vertebral artery	
Extracranial stent	4
Intracranial stent	1
Basilar artery stent	1
Middle cerebral artery PTA	1

symptomatic stenoses of at least 50% or asymptomatic high-grade (>80%) carotid artery stenoses. Patients with contraindications for MRI were excluded. 42 patients underwent PTA and stenting, and 2 patients received PTA only. 43 patients were treated with ASS 100 mg and clopidogrel 75 mg daily at least three days before the intervention, one received a loading dose of 300 mg clopidogrel and 500 mg ASS just before the intervention because an urgent treatment was necessary. Prior to the procedure, blood samples were taken directly from the arterial sheath with sample tubes equipped for the Multiplate system, which contain hirudine as anticoagulant. The test results were available after the procedure. Afterwards patients were monitored at the Stroke Unit of our institution. They underwent clinical examination to assess if new neurological deficits had occurred.

2.1. MRI. MRI was undertaken on a 1.5-T Siemens Sonata scanner (Siemens AG, Erlangen, Germany). DWI were acquired using our standard protocol. This comprised isotropic echoplanar sequences with a repetition time of 4,100 ms; echo time of 104 ms; field of view of 210 mm; a matrix of 128 × 128; number of excitations = 2; slice thickness of 6 mm; with *b* values of 0, 500, and 1000 s/mm². Images were compared with preprocedural images by two experienced neuroradiologists unaware of the clinical outcome.

2.2. Blood Analyses. Blood samples were immediately transferred to the Department of Hemostaseology of our institution. Testing was undertaken in <3 h on the Multiplate analyzer [2, 5]. This device is based on impedance aggregometry; in particular, adenosine diphosphates- (ADP-) induced aggregometry is suitable for detecting the response to clopidogrel.

Three hundred microliters of the patients' whole blood samples, anticoagulated by hirudine, were pipetted into a test cell containing 2 × 2 electrodes, as well as 6.4 μmol/L ADP. Aggregation of platelets continuously increased the electrical resistance between the electrodes over the test period of

6 minutes per sample. This value was shown as aggregation units (AU) over time in a graph. The area under the curve, given in arbitrary units (U) represented the platelet aggregation and provided the test results.

The test cell contained two pairs of electrodes, so the results were already the mean value of two simultaneous measurements. As suggested in [10], the patients' platelet reactivity has been defined as "high on treatment" if the results exceeded 468 AU*min in response to ADP.

2.3. Statistical Analysis. Acquired data were analyzed using SPSS software (SPSS, Chicago, IL, USA).

The patients' platelet aggregation values, which were given in arbitrary units (U), were correlated with the amount of new DWI lesions by using a nonparametric test for independent values (Mann-Whitney test).

Additionally, a 2 by 2 table consisting of platelet activity status (according to the consensus [10]) and DWI lesions yes/no has been created and analyzed with a chi-square test.

3. Results

The values from the ADP-induced aggregometry ranged from 3 units to 88 AU (mean, 34.6 AU; standard deviation (SD), 20.24) (Figure 1). The distribution of ADP test values was similar in patients with and without new DWI lesions (Figure 3).

In these cases in which aggregation exceeded 468 AU*min, platelet reactivity was defined as "high." This resulted in 11 patients with high platelet reactivity out of 44 enrolled patients (25%).

After the procedure 16 out of 44 patients (36%) showed new DWI lesions. These were silent DWI lesions in 13 cases. Two patients suffered a periprocedural stroke, and one patient suffered a reperfusion trauma. The ADP-test values of these cases were 18, 24, and 64 units. That is, one of the two patients that suffered a periprocedural stroke showed high platelet reactivity whereas the other case as well as the patient with reperfusion trauma had sufficient suppression of platelets.

Of the 11 patients with insufficient platelet suppression who underwent MRI, 4 (36%) showed new DWI lesions (Figure 2). Of 33 patients with sufficient platelet inhibition, 11 (36%) had DWI lesions after the procedure (Figure 2). A statistically significant relationship between ADP-test values respectively platelet reactivity and MRI evidence of new DWI lesions ($P = 0.893$ from the Mann-Whitney test, $P = 0.635$ from the chi square test) or between outcome was not observed. However, three clinically affected patients is not sufficient for a statistical conclusion.

4. Discussion

Clopidogrel resistance is dependent upon the genetic background of the patient. Cytochrome CYP2C19 is an important enzyme that metabolizes clopidogrel. Individuals with an impaired allele (which seems to represent about one-third of the population) show ≤30% less active metabolism of

FIGURE 1: Distribution of ADP values from the study population, including three patients that received a loading dose, and those from the reference group (“Reference” in this figure means a combined reference range of healthy male and female blood donors).

FIGURE 2: Shows the number of patients with (blue) and without (red) DWI lesions among responders and non-responders.

clodipogrel in plasma. Furthermore, carriers of such an allele showed an elevated risk of death by cardiovascular causes, infarction, or stroke of 53% in the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) [11].

Studies focusing on the relationship between an inadequate response to clodipogrel and adverse events in cardiovascular or neurovascular interventions have shown a significant (or at least a considerable) connection [1–7, 11]. Most of these studies concerned cardiovascular interventions. Because of the differences in supra-aortal interventions with respect to stent types, vessel sizes, and flow characteristics, the results of these studies should not be readily transferred to other vessel territories. Furthermore, a common complication such as in-stent thrombosis shortly after PTCA is ex-

FIGURE 3: Boxplots showing the distribution of ADP values for patients with (right) and without DWI lesions (left) after the procedure.

tremely rare in supra-aortal stenting, therefore the target variables in both issues must be different. Müller-Schunk et al. [2] were the first to analyse the correlation between clodipogrel resistance and procedural complications in supra-aortal stenting. They found a significant relationship between non-response to clodipogrel and the clinical outcome.

In supra-aortal stenting, attention must be focused on periprocedural strokes or the more frequently appearing cerebral DWI lesions (which are usually clinically unremarkable). These DWI lesions could help in the highly sensitive detection of microembolic events.

If we compare a subgroup of our study population who received unprotected carotid artery stenting (CAS, $n = 35$), 11 patients (31%) showed post-procedural DWI lesions. In the literature, the percentage of DWI lesions after unprotected CAS varies from 22% to 67% [8, 9, 12].

In contrast to previous studies, a relationship between low response to clodipogrel and thromboembolic events was not observed. These thromboembolic events are represented by DWI lesions or peri- and post-procedural ischemic strokes.

Of the 16 patients who showed MRI evidence of new DWI lesions, three had clinically noticeable symptoms (as mentioned above). Studies that rely only on the patients' clinical outcomes will only detect small part of the adverse events.

If patients undergo carotid stenting or vertebral stenting with high platelet reactivity without negative consequences, the need for screening of clodipogrel non-responders before supra-aortal stenting must be questioned. Further studies should show if low response to clodipogrel leads to a higher rate of stent restenosis.

The non-response to clodipogrel has been investigated in various studies. The definition of “non-response” in the literature is inconsistent, making interstudy comparison difficult. The effect of clodipogrel responsiveness in a patient population forms a Gaussian distribution, so De Miguel [13] suggested measurement of the degree of platelet inhibition as

a nominal variable instead of dividing patients into groups of responders or non-responders. In [10], Bonello et al. suggest to focus on the absolute level of platelet reactivity instead of clopidogrel responsiveness. They present cut-off points for several platelet aggregation analyzers which help to stratify thromboembolic risks.

There are several possible alternatives for clopidogrel low-responders undergoing coronary interventions, such as increasing the loading dose from 300 mg to 600 mg, which leads to a higher and stronger ADP-induced platelet inhibition [14]. Another possibility is to try different agents such as prasugrel and ticagrelor. The latter recently showed the characteristic of significantly affecting platelet inhibition in clopidogrel non-responders in the RESPOND study [15].

5. Study Limitations

This study tries to correlate patients' platelet aggregation with the amount of new dwi lesions which is a common indicator for the safety of neurovascular interventions. The results differ from preceding studies regarding the relation to adverse events. However, 44 patients may not be enough to evaluate a statistical relation. Especially the amount of three clinically affected patients is not enough for a conclusion. Further studies with more participants are needed for verification.

6. Conclusion

In contrast to the preceding studies, we found no relationship between the patients' response to clopidogrel and adverse events represented by microembolism, detected by mri imaging. So the need for point-of-care testing of platelet function prior to angioplasty and stenting of supraaortal arteries must be questioned.

Acknowledgments

The authors state that there is no conflict of interest. The study had been approved by the ethics committee. Patients gave their informed consent prior to inclusion in the study.

References

- [1] P. A. Gurbel, K. P. Bliden, W. Samara et al., "Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST study," *Journal of the American College of Cardiology*, vol. 46, no. 10, pp. 1827–1832, 2005.
- [2] S. Müller-Schunk, J. Linn, N. Peters et al., "Monitoring of clopidogrel-related platelet inhibition: correlation of non-response with clinical outcome in supra-aortic stenting," *American Journal of Neuroradiology*, vol. 29, no. 4, pp. 786–791, 2008.
- [3] G. Patti, A. Nusca, F. Mangiacapra, L. Gatto, A. D'Ambrosio, and G. Di Sciascio, "Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention. Results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during angioplasty-platelet reactivity Predicts outcome) study," *Journal of the American College of Cardiology*, vol. 52, no. 14, pp. 1128–1133, 2008.
- [4] M. J. Price, S. Endemann, R. R. Gollapudi et al., "Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation," *European Heart Journal*, vol. 29, no. 8, pp. 992–1000, 2008.
- [5] D. Sibbing, S. Braun, T. Morath et al., "Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis," *Journal of the American College of Cardiology*, vol. 53, no. 10, pp. 849–856, 2009.
- [6] L. Tapp, E. Shantsila, and G. Y. Lip, "Role of ticagrelor in clopidogrel nonresponders: resistance is futile?" *Circulation*, vol. 121, no. 10, pp. 1169–1171, 2010.
- [7] P. Wenaweser, J. Dörffler-Melly, K. Imboden et al., "Stent thrombosis is associated with an impaired response to anti-platelet therapy," *Journal of the American College of Cardiology*, vol. 45, no. 11, pp. 1748–1752, 2005.
- [8] I. Q. Grunwald, P. Papanagiotou, C. Roth et al., "Lesion load in unprotected carotid artery stenting," *Neuroradiology*, vol. 51, no. 5, pp. 313–317, 2009.
- [9] A. Kastrup, T. Nägele, K. Gröschel et al., "Incidence of new brain lesions after carotid stenting with and without cerebral protection," *Stroke*, vol. 37, no. 9, pp. 2312–2316, 2006.
- [10] L. Bonello, U. S. Tantry, R. Marcucci et al., "Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate," *Journal of the American College of Cardiology*, vol. 56, no. 12, pp. 919–933, 2010.
- [11] J. L. Mega, S. L. Close, S. D. Wiviott et al., "Cytochrome P-450 polymorphisms and response to clopidogrel," *New England Journal of Medicine*, vol. 360, no. 4, pp. 354–362, 2009.
- [12] M. Rosenkranz, J. Fiehler, W. Niesen et al., "The amount of solid cerebral microemboli during carotid stenting does not relate to the frequency of silent ischemic lesions," *American Journal of Neuroradiology*, vol. 27, no. 1, pp. 157–161, 2006.
- [13] A. De Miguel, B. Ibanez, and J. J. Badimón, "Clinical implications of clopidogrel resistance," *Thrombosis and Haemostasis*, vol. 100, no. 2, pp. 196–203, 2008.
- [14] H. Neubauer, S. Lask, A. Engelhardt, and A. Mügge, "How to optimise clopidogrel therapy? Reducing the low-response incidence by aggregometry-guided therapy modification," *Thrombosis and Haemostasis*, vol. 99, no. 2, pp. 357–362, 2008.
- [15] P. A. Gurbel, K. P. Bliden, K. Butler et al., "Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study," *Circulation*, vol. 121, no. 10, pp. 1188–1199, 2010.