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ORIGINAL RESEARCH

Monitoring of Clopidogrel-Related Platelet Inhibition: Correlation of Nonresponse with Clinical Outcome in Supra-Aortic Stenting

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BACKGROUND AND PURPOSE: Clopidogrel and aspirin are antiplatelet medications used in patients intended for endovascular stent placement. Although various studies have investigated individual responsiveness to clopidogrel in patients undergoing coronary interventions, there are no studies regarding patients undergoing stent placement of supra-aortic arteries supplying the brain. We analyzed platelet function in a near-patient setting to determine the effects of antiplatelet treatment in neurologic patients and correlated the results with clinical outcome after stent placement.

MATERIALS AND METHODS: The platelet function of 50 consecutive patients scheduled for neurointerventional stent placement procedures was assessed by using point-of-care testing. All of the patients had symptomatic arteriosclerotic lesions. Clopidogrel effects were tested by impedance aggregometry. Fifty healthy blood donors without clopidogrel medication served as the control group.

RESULTS: Reference values for responders and nonresponders were established from the results of the healthy control group. Fourteen (28%) of 50 neurologic patients were stratified as clopidogrel nonresponders. Adverse events were registered in 5 (10%) of 50 patients, 1 of them with a permanent neurologic deficit (1 of 50 [2%]). All 5 of the patients with adverse events were nonresponders. There was a statistically significant correlation between adverse events and clopidogrel nonresponse (Fisher exact test, $P = .001$).

CONCLUSION: A significant rate of clopidogrel nonresponders could be identified in the treated patients. Our data strongly suggest a correlation of insufficient clopidogrel-related platelet inhibition with an increased risk of thromboembolic events in supra-aortic stent placement.

Clopidogrel is an effective and specific inhibitor of ADP-induced platelet aggregation. Clopidogrel, together with aspirin, is routinely used in patients intended for coronary stent placement, as well as extracranial and intracranial stent placement of supra-aortic vessels. Recently, considerable differences in the responsiveness to clopidogrel medication have been found in cardiology patients and control subjects.[1-4] Different studies report nonresponse rates from approximately 5%[5,6] to more than 30%.[7,8] The underlying mechanisms of this phenomenon are not well understood. Variable definitions of "resistance" and a multiplicity of different testing methods contribute to the complexity of this issue.[9] Genetic defects of the ADP receptor do not seem to play a major role in this phenomenon.[10,11] Therefore, it is probable that individual differences in clopidogrel absorption and metabolization cause the wide range in response.

Low response to antiplatelet therapy is known to be a risk factor for the development of ischemic complications in patients undergoing coronary stent placement.[12-15] Fiorella et al[16] reported in their study of intracranial stent placement that a large proportion of patients with symptomatic intracranial stenosis had antiplatelet therapy failure at the time of the pretherapeutic clinical event. However, to date there are no studies investigating the influence of clopidogrel nonresponse on complication rates in neurovascular stent placement.

We measured platelet function of 50 consecutive patients undergoing supra-aortal stent placement procedures in a near-patient setting and correlated the findings with the clinical outcome. Healthy blood donors served as control subjects.

Patients and Methods

Impedance Aggregometry

Platelet function in whole blood was measured by using impedance aggregometry (Multiplate analyzer; Dynabyte Medical, Munich, Germany).[17,18] The analysis is performed in a single-use test cell, which incorporates 2 independent impedance sensors. For the analysis, 300 μL of saline and 300 μL of patient blood (anticoagulated with direct thrombin inhibitor hirudin, 25 μg/mL, Dynabyte Medical) are pipetted into the test cell. Pipetting is performed by an attached electronic pipette. The agonist (6.4 μmol/L of ADP, ADPtest; Dynabyte Medical) is added, and real-time recording starts. During 6 minutes, the ability of platelets to adhere to the metal sensors is detected. The adhesion and aggregation of platelets are logged by measuring the impedance change. The resistance change is transformed to arbitrary aggregation units (AUs) and plotted against time. The area under the aggregation curve (AUC) is used to quantify the aggregation response and is expressed in units (U; 1 U corresponds with 10 AU*min). The results shown represent the mean value of the 2 determined AUC values.

The analysis was performed inside the angio suite. The instrument and all of the reagents are commercially available.[17]

Patients and Control Subjects

Fifty consecutive patients who were on clopidogrel medication before neurovascular intervention were prospectively tested and included in

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Table 1: Clinical and anatomic data of neurologic patients

Clinical data	Number ($N = 50$)	(%)
Stroke	31	62%
TIA	19	38%
Location of stenosis	Intracranial (*n*)	Extracranial (*n*)
ICA	2	31
VA	2	3
BA	12	0
Total	16 (32%)	36 (68)
Clopidogrel loading	[h] pre-intervention	
Mean	47 ± 88	
Minimum/maximum	6† (min)	408* (max)

Note:—TIA indicates transient ischemic attack; ICA, internal carotid artery; VA, vertebral artery; BA, basilar artery.
* The exact date of the beginning of the clopidogrel medication could not be determined in 2 patients, but was more than 14 days.
† One patient (No. 1) was loaded twice, 12 and 6 hours before the stenting.

Table 2: Demographic data, medication, and aggregation of control subjects and neurologic patients

Variable	Healthy Blood Donors	Neurologic Patients
Age, mean ± SD, y	41 ± 18	65 ± 8
Male, *n* (%)	30 (60)	36 (72)
Female, *n* (%)	20 (40)	14 (28)
Clopidogrel, *n* (%)	0	0
ASA + clopidogrel, *n* (%)	0	50 (100)
Mean aggregation, mean ± SD, AU	86 ± 23	34 ± 26
5th to 95th percentile	52–137*	1–84
Total, *n*	50	50

Note:—ASA indicates aspirin; AU, arbitrary aggregation unit.
* The fifth percentile of the aggregation results of the healthy blood donors at 52 AU was selected as a cutoff for nonresponse in patients under clopidogrel medication.

the registry. Thirty-four patients (68%) had extracranial vessel stenosis, and 16 (32%) had intracranial stenosis. All 50 of the patients were symptomatic due to their stenosis before interventional therapy. Mean modified Rankin Score (mRS) on admission was 1.2 (SD, 1.3). Forty-one patients (82%) had a score of 2 or less, and 9 (18%) had a score of 3 or 4. For details, see Tables 1 and 2.

Testing was performed in the angio suite before the procedure. All 50 of the patients received a loading dose of 300 mg of clopidogrel at least 12 hours before the intervention and after loading were treated with 75 mg/day continuously. Thirty-three patients (67%) received the loading dose on the evening before the intervention. In 7 patients (15%), clopidogrel therapy was initiated more than 48 hours before stent placement. In 2 patients, the initiation of the clopidogrel therapy preceded the intervention by more than 2 weeks but could not be determined exactly. Treatment intervals before stent placement (mean, minimum, and maximum) are given in Table 1.

All of the patients received 100 mg of aspirin per day according to the usual protocol. Stent placement was performed under activated clotting time (ACT) controlled heparinization with ACT values of 200–300 seconds. Thromboembolic complications during the intervention or transischemic attack (TIA) or stroke within the following 30 days (primary end point) were summarized as adverse events.

A control group of 50 healthy blood donors without clopidogrel medication was analyzed by using the identical procedure as the treated patients. Demographic data are shown in Table 2.

Statistical Analysis

Statistical data analysis on treated patients was done with SPSS (SPSS, Chicago, Ill) by using the Fisher exact test and logistic regression analysis.

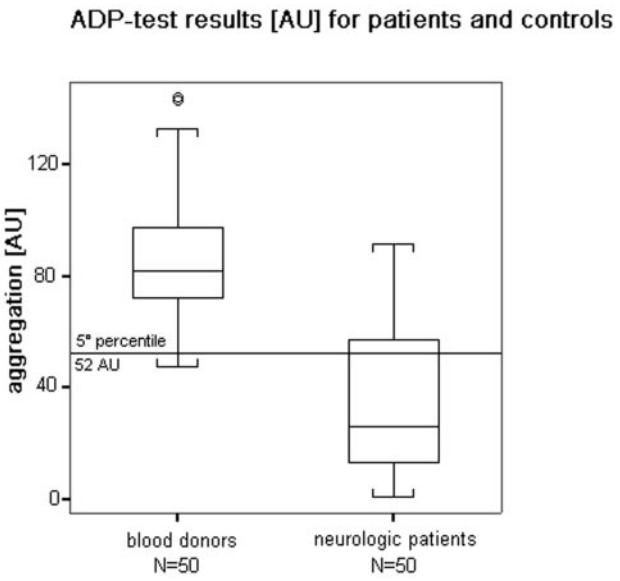

Fig 1. The fifth percentile of the results of the healthy blood donors at 52 AU is marked and used as a cutoff for nonresponsiveness in neurologic patients. Patients under clopidogrel medication show marked platelet inhibition compared with the blood donors. Neurologic patients with aggregation over 52 AU after clopidogrel medication are classified as nonresponders (also see Fig 2).

The study was approved by our institutional review board in accordance with the Declaration of Helsinki. Patients included in the study gave their written informed consent.

Results

Platelet Function Analysis

The test results for both groups are shown in Table 2. The mean aggregation in healthy blood donors as measured by the multiplate analyzer was approximately 3 times as high as in the treated patients taking clopidogrel. The fifth percentile (52 U) of the aggregation in the control group of healthy blood donors was selected as the cutoff for a nonresponse in patients taking clopidogrel. Patients under medication showing higher aggregation values than this arbitrary cutoff at 52 U were, therefore, classified as nonresponders. Results of both groups, including the cutoff for nonresponse at 52 U, are shown in Fig 1.

Fourteen (28%) of 50 patients had an aggregation activity over 52 AU and were classified as nonresponders. Ten (72%) of 14 of the nonresponders were loaded only 12 hours before stent placement, 2 (14%) of 14 nonresponders 2 days, and 2 (14%) of 14 nonresponders 9 or more days before the procedure. Individual results are shown in Fig 2.

Adverse Events

Five patients suffered from some type of adverse event: 2 developed transient intrainterventional thrombosis (Nos. 2 and 5), and 3 suffered from TIA or infarction (Nos. 3, 4, and 6). The patients marked with 2 (aggregation, 85 U) and 5 (aggregation, 69 U) in Fig 2 had adverse angiographic events without clinical deficits.

In patient 2, progressive clot formation was seen within the carotid stent at the end of the procedure (Fig 3*A*). Clotting could be dissolved by administration of a standard dose of

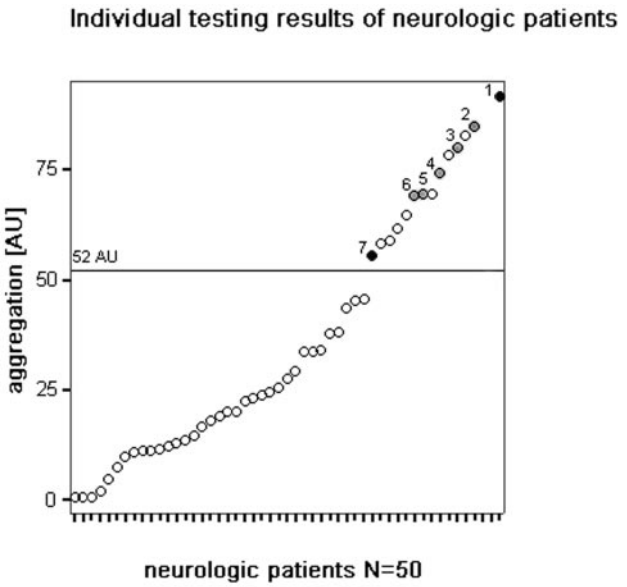

Fig 2. Fourteen (28%) of 50 patients met the criteria of nonresponse with test results of over 52 AU. Patient 1 received a second full loading dose of 300 mg of clopidogrel before treatment after the high initial test result. Patient 7 did not receive a stent due to a free-floating thrombus. The other patients marked with numbers either suffered periinterventional clinical events (3 of 50; patients 3, 4, and 6) or adverse events during the angiographic procedure without any clinical consequences (2 of 50; patients 2 and 5). All of the patients (5 of 50) with any type of adverse event qualified as clopidogrel nonresponders as measured by the multiplate analyzer.

intravenous tirofiban (30 minutes loading with 4 μg/kg of body weight, followed by the infusion of 1 μg/kg of body weight continuously for 24 hours; Fig 3*B*). No clinical complication occurred. After doubling of the clopidogrel dose to 150 mg/day, platelet function in the ADPtest decreased to 41 U, that is, to a level assigned to clopidogrel response (determined 3 days after the intervention and after cessation of the tirofiban infusion).

In patient 5, a temporary occlusion of the internal carotid artery (ICA) stenosis occurred during manipulation with the microwire. There was no neurologic deficit during or after the procedure.

Three patients suffered from clinical complications: in patient 6 (69 U), the ICA was stented 3 days after stent placement and coiling of a basilar tip aneurysm. She had received 500 mg of aspirin (ASA) intravenously and tirofiban, which was switched to clopidogrel on the day after the coiling (300 mg of loading, then 75 mg/day and 100 mg of ASA per day). On the day of the right-sided ICA stent placement, she qualified as a clopidogrel nonresponder based on an aggregation of 69 U. There was no complication during the intervention, but the patient was readmitted to the hospital 10 days later after 3 TIAs with left-sided minor hemiparesis and hemihypesthesia. Her aggregation at readmission was 56 U (nonresponse). Cerebral diffusion MR imaging and ultrasonography of the stent did not show any pathologic changes. She was heparinized and put on 2 $\times$ 75 mg of clopidogrel per day. Another test 2 days later showed a clopidogrel response with an aggregation of 27 U. There were no further events after heparin was stopped.

The second patient who suffered a clinical deficit, patient 3 (aggregation, 80 U), experienced a pontine perforator infarction with 2/5 hemiparesis 2 hours after basilar artery (BA) stent placement. He recovered to 3/5 paresis upon discharge from the hospital.

The patients with test results marked with 1 (92 U) and 4 (74 U) were included at an advanced phase of the study. To prevent complications from insufficient antiplatelet effects in these patients, who were classified as clopidogrel nonresponders, intensified platelet inhibition was performed.

In the first patient (No. 4), who was also scheduled for BA stent placement, an intravenous infusion of tirofiban (standard dosage as described above) was administered to achieve immediate platelet inhibition. There was no procedural complication. Tirofiban was stopped the day after the procedure, and heparinization with a partial thromboplastin time (PTT) of 60–80 seconds was kept up for 3 days. On day 4, when heparin was stopped, the patient suffered from an episode of vertigo, nausea, and tinnitus for 20 minutes. Heparinization was started again, but on day 5 (PTT, 40 seconds) symptoms recurred, including dysarthria and hemihypesthesia. The patient recovered completely after 45 minutes. Imaging showed 3 small lesions in diffusion MR imaging in the superior cerebellar artery territory. Unfortunately, no analysis of the antiplatelet medication was performed at that point in time. The further clinical course was asymptomatic, even without heparinization, and the patient was discharged 4 days later under aspirin at 100 mg/day and clopidogrel at 75 mg/day.

The second patient (No. 1) who was scheduled for stent placement of the BA was given another loading dose of 300 mg of clopidogrel. She was only treated 6 hours after receiving this additional medication. By then the effectiveness of clopidogrel-related platelet inhibition could be shown in the ADP test with an aggregation of 49 U compared with the initial 92 U. She did not suffer any complications. Because of the modification of treatment, she was not included in the statistical analysis.

Patient No. 7 (aggregation, 55 U) did not receive a stent. Intervention was cancelled after detection of a free-floating thrombus in diagnostic angiography. The patient was referred to surgery and received a carotid endarterectomy. He was also not included in statistical analysis.

Clinical Outcome

Mean mRS in the group of treated patients was 1.2 $\pm$ 1.3 before and 1.2 $\pm$ 1.3 after the intervention. Forty-five patients (90%) did not show a change in mRS score between admission and discharge. Five patients (10%) showed clinical improvement of their initial state due to recovery from a stroke shortly before admission. One patient (2%) deteriorated neurologically (No. 3). He dropped from mRS 0 to 4 due to a procedural complication (pontine perforator infarction) as described above.

Statistical Analysis

From the 50 patients included in the study, patients 1 and 7 were excluded from statistical analysis as explained previously. Of the 48 patients analyzed, 12 were classified as nonresponders. Five (41%) of the 12 nonresponders had some type of adverse event compared with 0 (0%) of 36 responders. Fisher exact test for association between adverse events and clopidogrel response indicates the statistically significant association ($P = .001$).

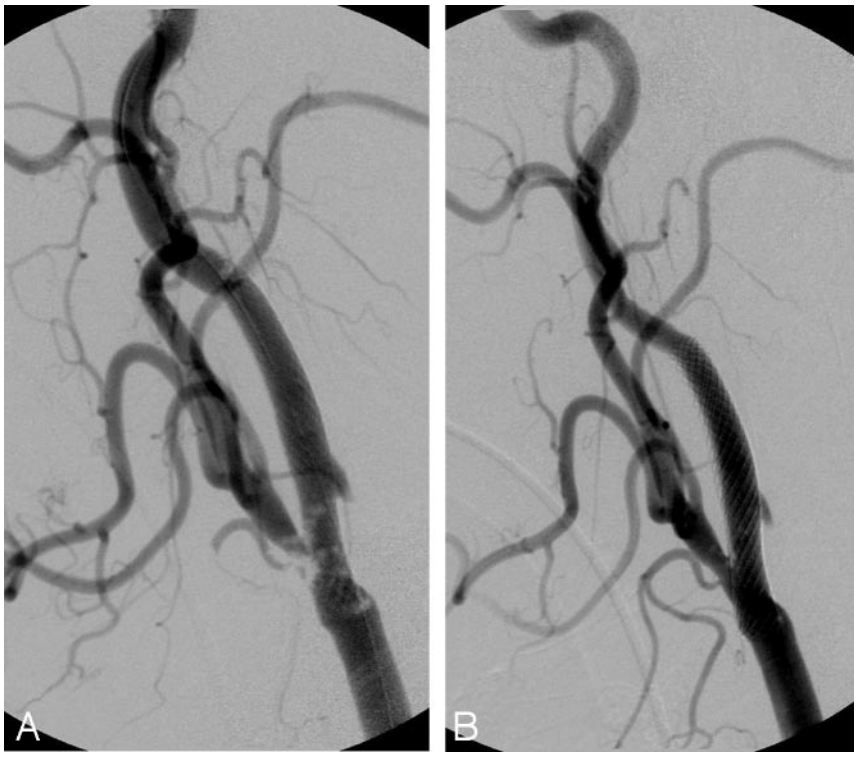

Fig 3. Patient 2 (see Fig 2) showed the second highest aggregation level of all of the patients. She developed progressive in stent clotting at the end of the procedure (*A*) that could be reversed by intravenous administration of tirofiban (*B*).

Binary logistic regression analysis of the 48 patients shows a significant correlation between aggregation (U) and the odds of having adverse events ($P = .032$). An increase of 1 U in aggregation implicated an increase in odds by 15%.

Discussion

To our knowledge the prevalence and clinical impact of clopidogrel nonresponse in patients with neuroradiologic endovascular procedures has not been investigated before. A fast and easy-to-use clopidogrel-sensitive testing method is required to address this topic. Born's aggregation[19] based on the optical detection of platelet function in platelet-rich plasma is still accepted as a "gold standard." However, this method is laborious and, therefore, not suited for on-site testing.[20] Therefore, tests suited for point-of-care analysis, such as the PFA-100 (Dade Behring, Deerfield, Ill), VerifyNow (Accumetrics, San Diego, Calif),[21] or the Multiplate Analyzer (Dynabyte Medical), which was used in this study, have been developed. The PFA-100 is not sensitive to clopidogrel.[22-24] VerifyNow has shown sensitivity to clopidogrel but was not yet being distributed in Europe when the study was started. Conventional impedance aggregometry, as used in earlier studies,[25] is usually performed with reusable electrodes, which have to be cleaned after each measurement and are less suited for near-patient testing.

We, therefore, applied a whole-blood aggregation analyzer (Multiplate) by using single-use test cells and electronic interactive pipetting. With this method, the clinical impact of nonresponse to clopidogrel as measured by the analyzer on the risk of thromboembolic complications in supra-aortic stent placement was investigated. Complication rates in extracranial ICA stent placement under clopidogrel and aspirin medication are estimated at more than 6%.[26,27] Of these complications, most events are ischemic versus only a small number of hemorrhagic complications.[26] In intracranial stent placement, the overall complication rate is estimated at approximately 6%–10%.[16,28,29] However, thromboembolic events add significantly to morbidity and mortality. Our series included no patient with procedure-related permanent morbidity or clinical worsening among the 34 extracranial stentings (0%) and 1 patient (6%) with procedure related permanent morbidity of 16 intracranial stentings. Although statistics are limited due to the small number of cases, our group does not show an overall complication rate that differs largely from those published in literature.

The dual antiplatelet premedication that we used is common practice in neurovascular stent placement. ICA stent placement with aspirin and heparin alone, resembling complete clopidogrel nonresponse, has proven to produce unacceptable high complication rates. McKevitt et al[30] encountered a neurologic complication rate of 25% compared with 0% in the dual antiplatelet group. A greater effect on platelet inhibition when administering clopidogrel in addition to aspirin has been shown.[31,32] It was even speculated that clopidogrel medication may have a greater impact on platelet inhibition in patients who are aspirin nonresponders and may, therefore, help to overcome the problem of aspirin nonresponse.[33]

The high rate of adverse events in the group of clopidogrel nonresponders in our series, compared with none in the group of clopidogrel responders (Fig 2), as defined by the analyzer results, also confirms the importance of clopidogrel-related platelet inhibition in neurovascular stent placement. All of our patients with adverse events were responsive to aspirin in impedance aggregometry. Hence, the detected effects cannot be attributed to aspirin nonresponse. A significant correlation between clopidogrel nonresponsiveness as measured by the Multiplate analyzer and

the incidence of adverse events could be statistically shown. This corresponds well with the results of cardiology studies stating that the level of platelet aggregation in coronary stent placement is correlated with outcome.[34,35] Also in our study the level of aggregation (U) had a significant impact on the odds of having adverse events.

There are numerous cardiology or angiologic studies that have reported a relation between nonresponsiveness of antiplatelet therapy and adverse clinical outcomes,[14,25,36-45] but until now these methods and findings have not been applied to interventional neuroradiology settings or validated for them. Our results show that, after an application of a 300-mg clopidogrel loading dose and a maintenance dose of 75 mg/day, platelet inhibition varies significantly with a nonresponse rate of 28% in the neurologic patients. It is known that tests performed shortly after the application of a 300-mg clopidogrel loading dose show particularly high rates of insufficient platelet inhibition.[46] Only after 24 hours is the effect of a loading dose of 300 mg fully elicited,[47] whereas a loading dose of 600 mg can achieve the maximum effect after only 4 hours.[48] The patients were mostly loaded only 12 hours before stent placement. This implies that clopidogrel loading for neurovascular stent placement, if performed with a dose of 300 mg, may have to take place at least 24 hours before the intervention. Based on the increasing evidence of a significant proportion of patients not being responsive to a clopidogrel bolus of 300 mg, a higher initial loading dose before neuroradiologic interventions can be considered. In cardiology patients it has been shown that a loading dose of 600 mg of clopidogrel cannot only achieve a more intense and rapid inhibition of platelet activation but can also increase the number of responders.[6] This corresponds well to our results in patients 1 and 6. Patient 1 showed the lowest platelet inhibition of all of the patients after the initial loading dose. Six hours after receiving another 300 mg, she was tested and qualified as a responder. Also, patient 6, an initial nonresponder, responded after a dose increase to 2 × 75 mg/day. Double-dose treatment also has been shown to achieve a more intense platelet inhibition in cardiology patients than the usually recommended 75 mg/day.[49] In primary coronary angioplasty, even a single-dose treatment with a tirofiban bolus has been proposed to overcome the time gap between clopidogrel loading and a stable and safe antiplatelet effect.[50] To optimize adjustment, however, point-of-care testing of the effectiveness of clopidogrel may be useful. With in vitro testing, patients prone to thromboembolic complications could be identified and antiplatelet regimes adapted individually with respect to the dosage and drug applied.

One limitation of our study is the relatively small number of patients examined. Another limitation is the fact that single events, like the perforator infarction in patient 3, cannot be attributed solely to the clopidogrel nonresponse. Thromboembolic complications in endovascular stent placement are multifactorial, and not all are caused by insufficient platelet inhibition. Still, statistical analysis identified clopidogrel nonresponse as measured by the analyzer as one important factor that can increase the risk of thromboembolic events.

Our results, therefore, suggest considering a dose increase or the application of an immediately acting platelet inhibitor (eg, tirofiban) in patients scheduled for neuroradiologic interventions that show an in vitro clopidogrel nonresponse to avoid an enhanced risk of adverse events. It is as unknown whether a more aggressive platelet inhibition by an enhanced dose of clopidogrel or the addition of tirofiban might increase the risk of hemorrhagic complications during the intervention. However, we did not encounter any of these in our series.

Conclusion

On-site testing of clopidogrel-related platelet inhibition by impedance aggregometry in neurointerventional radiology is feasible. It can help to identify clopidogrel nonresponsiveness, which was found in 28% of clopidogrel-treated patients in this study. A statistical relationship between nonresponsiveness to clopidogrel as defined in this study and adverse thromboembolic events could be shown. Near-patient testing of platelet inhibition before neurointerventional stent placement seems reasonable to adjust the antiplatelet protocol individually if required and has the potential to reduce the thromboembolic complications in interventional neuroradiology.

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