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Clopidogrel-related platelet inhibition:

correlation with perioperative adverse events in neurointerventional procedures

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ABSTRACT

Introduction and Purpose: The measurement of the level of platelet inhibition may be useful in quantifying the risk of thromboembolic complication in subjects undergoing endovascular treatment using implantable materials. We studied the predictability of the *VerifyNow* point-of-care assay in a large sample of consecutive neurointerventional procedures. **Methods:** The percentage of P2Y₁₂-inhibition was systematically measured in a total of 271 procedures (245 patients). The incidences of poor response and adverse events within the first 48 hours were recorded. **Results:** The overall occurrence of poor response after a single loading-dose of 300 mg was 61.3% using a cut-off of 40% and 43.9% using a cut-off of 20%. In the analysis of the incidence of adverse events by P2Y₁₂-inhibition grouping, a significant association was observed between thromboembolic events and low response, with an overall incidence of 10.2% (cut-off of 40%) and 11.8% (cut-off of 20%). The assessment of predictability using different cut-offs showed that more than 90% of thromboembolic events would be in the group of poor responders using a 40% cut-off and more than 75% using 20%. **Conclusion:** The use of the *VerifyNow* assay in the neurointerventional context seems a valuable tool in the early detection of individuals at risk of perioperative thromboembolic adverse events.

Keywords: platelets, stents, stroke, hemorrhage, thrombosis

INTRODUCTION

Antiplatelet agents are routinely administered in patients undergoing neurointerventional procedures utilizing implantable material, e.g. intracranial stent placement. Insufficient platelet inhibition (PI) has been strongly associated with an increased risk of thrombus formation and embolic complications [1, 2]. As a consequence, patients are pre-operatively prepared with either a loading-dose or a period of antiplatelet treatment. This is supported by both literature to date and previous experience in the cardiology field.

Whilst Aspirin resistance seems relatively uncommon, clopidogrel resistance is much more frequent (28 to 66%) [1-3]. Since thromboembolic adverse events seem highly concentrated in the low responder group [1, 2], a level of at least 40% of platelet inhibition has consequently been recommended.

Individual response to clopidogrel may be evaluated using different techniques. Recently however, point-of-care assays have been commercially available allowing practitioners to perform prompt measurements pre or per-operatively. The level of platelet inhibition is now routinely assessed before intracranial stenting in many centers. In selected cases, antiplatelet therapy might be adapted in order to achieve the recommended levels.

Such an approach requires systematic pre-operative blood sampling, subsequent drug administration and introduces additional costs. The study of any potential benefits in achieving a level of anti-aggregation over 40% in patients undergoing intracranial procedures is imperative, as is the assessment of the risk for hemorrhagic adverse events. In the neurological field, studies up to now investigating these issues are limited.

In a sample of 271 neurointerventional procedures, we have retrospectively assessed the incidence of per- and early post-operative thromboembolic and hemorrhagic events in relation to the clopidogrel-related percentage of antiaggregation. The purpose of the present study was twofold: a) to examine a possible association between low response as measured with the

VerifyNow point-of-care assay and the incidence of thromboembolic and hemorrhagic adverse events in a large neurological sample; and b) to assess the extent to which this association is influenced by the level of antiaggregation, by analyzing the assay results using two different cut-offs of P2Y₁₂ inhibition: 20% and 40%.

METHODS

Sample

The patients included in the study fulfilled the following inclusion criteria: being aged between 18 and 90 years old and to have been treated with a non-urgent endovascular procedure intended for intracranial or supra-aortal stent placement. A *VerifyNow* System (Accumetrics, San Diego, USA) was used for measuring clopidogrel-related platelet inhibition in whole blood samples. The timing for antiplatelet effect testing was immediately after intubation for all patients.

A composite comorbidity score was attributed to each patient according to the presence of concomitant diseases at the time of endovascular treatment. A point was given for any of the following five categories: i) past history of arterial hypertension, coronary or peripheral arterial disease; ii) smoking; iii) obesity; iv) metabolic disease (e.g. diabetes mellitus) and v) known hypercoagulable state. The comorbidity score was given as the sum of accumulated points. All data was collected concurrently to treatment.

Additional information on the sample composition is provided in the Supplemental Material.

Endpoint definitions

Thromboembolic

The following critical events were considered as *thromboembolic* complications for statistical purposes and classified in one (or two) of the categories below.

Central: Partial or complete intra-stent thrombosis, perforating artery occlusion or distal thromboembolism with ischemic stroke confirmed by MRI.

Peripheral: Thrombosis or embolism at the arterial access site (e.g. femoral artery).

Severe: Any neurological thromboembolic event in which complete occlusion of the target

vessel was observed or that resulted in the necessity of ≥ 72 h of intensive care or death.

Hemorrhagic

Hemorrhagic endpoints were defined as the occurrence of one or more of the following critical events, classified in one (or two) of the categories below.

Central: Any subarachnoid hemorrhage or intracranial hematoma.

Peripheral: Any retroperitoneal, superficial or external bleeding from the arterial access point needing non-scheduled medical attention, blood derivate transfusion or any surgical or endovascular treatment.

Severe: Any hemorrhagic event necessitating surgical evacuation, external ventricular drainage, or ≥ 72 h of intensive care, or death.

Statistical analysis

Patient and treatment characteristics were presented using mean, SD and range for continuous variables and frequencies as well as proportions for categorical variables. When a single patient was treated for two lesions in two different procedures, each one was categorized and analyzed independently. The incidence of per and post-operative complications within the first 48 hours were compared between groups of procedures according to the PI range and in consideration of four categories of events: central/hemorrhagic, central/thromboembolic, peripheral/hemorrhagic and peripheral/thromboembolic. The following groups were considered: $PI \leq 20\%$, $PI > 20\%$, $PI \leq 40\%$, $PI > 40\%$ and $20\% < PI \leq 40\%$. Differences in the incidence of variables between groups were compared using the χ^2 -test, the Fisher's exact test or the Student t-test according to the specific situation, with a 95% confidence interval and a level of significance $p < 0.05$ for the whole study. The same was performed for the analysis of *severe thromboembolic* or

severe hemorrhagic endpoints. Two different samples were considered for these analyses: 1) all cases; 2) stented cases.

A *poor response* to the loading dose of clopidogrel was defined as a level of P2Y₁₂ receptor inhibition inferior or equal to the used cut-off. The correlation of the *VerifyNow* assay results with the occurrence of thromboembolic complications was further assessed using the Receiver-Operating-Characteristic (ROC) curve and the area under the curve, considering sensitivity and specificity as predictability for the occurrence or absence of *thromboembolic* endpoints respectively. The influence of the body weight on the PI after a loading-dose of clopidogrel were assessed with ANOVA (the Tukey's test) and the Pearson correlation coefficient.

RESULTS

Sample

A total of 271 procedures were performed on 245 patients. All patients were originally scheduled and prepared for intracranial or supra-aortic stent placement. The mean age at treatment was 58 ± 13.9 years old (mean \pm SD, range 20-88.5).

In a total of 185 (68.3%) cases at least one stent was deployed. In 76 others a different technique was applied and the patient did not receive a stent and in a further 10 procedures it was not possible to complete the treatment.

Supplemental Table 1 shows demographic characteristics for the 271 procedures and by range of P2Y₁₂-inhibition.

Clopidogrel related platelet-inhibition

Previous use of antiplatelet medication was recorded in 36 cases for clopidogrel and in 53 for acetyl salicylic acid (ASA). In 43 cases, both were being taken.

The mean clopidogrel P2Y₁₂ receptor inhibition at the time of the endovascular procedure was $36.4 \pm 34\%$ (mean \pm SD, range 0-100) for the whole sample, $44.5 \pm 34\%$ (range 0-98) for the subgroup of patients already taking clopidogrel 75mg daily and $33.1 \pm 33.5\%$ (range 0-100) for the subgroup with no previous use of this medication. During the procedure, the overall prevalences of poor responders were 61.3% (PI \leq 40%) and 43.9% (PI \leq 20%).

The mean P2Y₁₂-inhibition after a single loading-dose of 300 mg in patients with no previous use of clopidogrel was $33.1 \pm 33.6\%$ (n=182, range 0-100). A total of 65.4% of those cases presented with PI \leq 40% and 50% presented with PI \leq 20%. In the subgroup of patients on chronic use of clopidogrel, a total of 51.3% presented with a P2Y₁₂ ADP receptor inhibition \leq 40% and 31.3% with 20% or less.

In order to assess the effect of body weight on the platelet inhibition obtained after a single uniform loading-dose, patients with no previous use of clopidogrel were grouped in three categories according to the range of weight (Supplemental Figure 1). The percentage values of P2Y₁₂ receptor blockade was significantly lower in patients with body weight superior to 60 kilograms. A small correlation was indicated by the Pearson Coefficient, which was -0.2538 (95CI -0.39/-0.11, p=0.0006).

Incidence of perioperative thromboembolic and hemorrhagic adverse events

The rate of symptomatic neurological complications (n=12) at 48 hours after the treatment was 4.4% for the whole sample, 4% for cerebral aneurysms and 6.25% for intracranial or supra-aortic stenosis procedures. The mortality was 0.4% at 48h.

According to the previously established criteria, 72 adverse events were recorded. The frequency of the *thromboembolic* endpoints was in 17 cases *central* and in one *peripheral*. Regarding the *hemorrhagic* endpoints, eight *central* and 47 *peripheral* events were observed.

After dividing the sample into two groups using PI \leq 40% as a cut-off, a statistically significant difference was observed for the incidence of thromboembolic endpoints (p=0.002), which was 10.2% in the PI \leq 40% group and 1.0% in the PI $>$ 40% group. All of these events except one were of *central* type. If 20% is used as the cut-off, a statistically significant difference was still observed (p=0.003) with incidences of 11.8% and 2.6% (Figure 1). The mean P2Y₁₂-inhibition was 13.4% among patients presenting with *thromboembolic* endpoints and 38.1% in the others. No statistically significant difference was observed for hemorrhagic endpoints.

When considering three categories of range for P2Y₁₂-inhibition (PI \leq 20%, 20% $<$ PI \leq 40% and PI $>$ 40%) no significant difference among groups was found.

A total of nine *severe* endpoints were recorded.

Five were of *thromboembolic* type:

- An MCA occlusion due to thromboembolism early in the procedure for the treatment of a cerebral aneurysm with stenting and coiling (PI=36%);
- A fatal vertebrobasilar thrombosis following stent-assisted treatment of a superior cerebellar artery aneurysm in which per-operative aneurysm bleeding occurred (PI=0 per-operatively and 15% 23 hours later);
- Dissection, thrombosis and temporary occlusion of the internal carotid artery during a stent-assisted treatment of a brain aneurysm, resolved with thrombolytics and stenting (PI=11%);
- A vessel occlusion during stent-assisted treatment of a middle cerebral artery (MCA) aneurysm, resolved after administration of an intravenous bolus (0.25mg/Kg) of abciximab (PI=0);
- Fatal thrombosis and ischemia in the vertebrobasilar territory after a failed attempt to treat a vertebral artery stenosis in an elderly woman (PI=0).

And four were of *hemorrhagic* type:

- A fatal dissecting hematoma of the sylvian fissure after stenting of the MCA for aneurysm treatment (PI=92%);
- An intraparenchymal hematoma after angioplasty of a pre-occlusive MCA stenosis (PI=52%);
- A subarachnoid hemorrhage after treatment of an MCA stenosis with stent and angioplasty (PI=32%);
- A life-threatening retroperitoneal hematoma (PI=0).

The frequency of each type of endpoints in the whole sample or specifically among intracranial stenting procedures is shown in the Supplemental Material. Ten out of 18

thromboembolic endpoints and four out of five *severe thromboembolic* endpoints were recorded in patients presenting with a co-morbidity index ≥ 2 .

Using ROC curve analysis for the thromboembolic endpoints (Supplemental Figure 2), the point closest to the theoretical gold standard (maximal simultaneous sensitivity and specificity possible) corresponds to a cut-off of antiaggregation at 15% of P2Y₁₂-inhibition. The area under the curve is 0.735.

DISCUSSION

The present study examined the impact of a poor response to clopidogrel as measured by the *VerifyNow* point-of-care assay on the incidence of thromboembolic and hemorrhagic perioperative complications. In a sample of 271 neurointerventional procedures with implantable material, the use of a cut-off of 40% of PI resulted in an overall prevalence of 61.3% of low responders and the incidence of thromboembolic events in this subgroup was 10.2%. With a cut-off of 20% of PI, a total of 43.9% of the patients were considered poor-responders and the incidence of thromboembolic adverse events among low responders increased to 11.8%. A statistically significant difference to the good-responder group was observed using both cut-offs.

Recently it has been possible to measure the individual response to clopidogrel by different assays, such as the *VerifyNow*, *PlateletWorks* (Helena Lab., Beaumont, USA), *IMPACT-R* (with and without ADP stimulation, DiaMed AG, Cressier sur Morat, Switzerland), *DADE PFA collagen/ADP test* (Siemens Healthcare Diagnostics Products, Marburg, Germany) and others. Nonetheless, only measurements using light transmittance aggregometry tests (*VerifyNow* and *PlateletWorks*) seem to be significantly correlated to the occurrence of ischemic adverse events in patients undergoing elective coronary stenting [4].

Laboratory light transmission aggregometry is often considered as the gold standard for platelet function testing. However, this method is time consuming and requires an experienced laboratory. A point-of-care assay, such as *VerifyNow*, has the advantage of the simplicity of its utilization and fast results. Consequently, there is significant discussion on this topic. When the laboratory measurement is the gold standard, the point-of-care assay has a sensitivity of up to 55% and a specificity of up to 85% [5]. Other authors have observed a greater area under the ROC curve using the point-of-care assay, and suggest that it should be considered superior to traditional laboratory methods that may be operator-dependent [6].

Even though further studies focusing on these questions are still needed, neuroendovascular surgeons are mostly interested on how the levels of PI relates to the incidence of adverse events. The responses to that relevant question may not correspond exactly to the thresholds that have been identified in previous pharmacological studies.

Despite the data accumulated on the impact of such tests on the evolution of coronary disease, our knowledge is still very limited in the neurological field. Even though the level of platelet inhibition can be easily detected using point-of-care assays, the usefulness in measuring this in daily neurointerventional practice is still not fully understood. A small number of studies have addressed this question, yet little evidence exists on the predictability of aggregometry assays on the operative risk for neurovascular diseases.

Müller-Schunk *et al.* (2008) [2] have reported a strong association between insufficient platelet inhibition and perioperative thromboembolic complications in a sample of 34 patients undergoing stent placement for supra-aortic stenosis, and another 16 for intracranial stenosis. The five patients who experienced adverse events of a thromboembolic type were poor responders to clopidogrel. In a subgroup of 36 patients who responded well, no perioperative thromboembolic complication was observed. The global incidence of antiplatelet resistance in that series was 28%.

The same year, Lee and coworkers [1] reported their experience with 106 patients undergoing neurointerventional procedures, observing a poor response in 42.9% of patients. Three cases of per-operative thrombosis were also recorded and occurred in the poor-response group.

Clopidogrel-related platelet inhibition

As insufficient platelet inhibition has been associated with an increased risk of thrombus formation within the arterial segment exposed to the foreign material, a minimal level of

platelet inhibition has been recommended and been used for identification of patients who are poor responders to clopidogrel. The technique for measurement and cut-off are variable in neurointerventional literature and the evident corollary of this is that the prevalence of drug resistance may vary accordingly. In the original series by Müller-Shunck [2], the fiftieth percentile (52 U) of the aggregation amongst a group of healthy individuals was selected for cut-off using the Multiplate Analyzer (Dynabyte Medical). Prabakaran et al.(2008) and Lee *et al.* (2008) [1, 3] used the *VerifyNow* system with a cut-off of 40% of P2Y₁₂-inhibition, and Pandya et al. (in the same year) used it with a cut-off of 50% [7]. Those studies reported a prevalence of drug resistance varying from 28% to 66%.

Body weight is a significant influence on the level of P2Y₁₂-inhibition after a loading-dose. Lee et al. have observed a similar phenomenon in their series [1], in which a univariate analysis showed response to be significantly associated with the peripheral platelet count and inversely associated with the patient's weight. However, a multivariate analysis showed that the weight was the only independent factor affecting response. This is possibly related to pharmacokinetic phenomena such as the variation of the distribution volume for the active metabolite or to its pharmacodynamics, such as the physiological finding that insulin inhibits platelet aggregation and activation [8], an effect that has been shown to be absent in insulin-resistant obese subjects [9-11]. On this basis, we consider that the adaptation of the loading-dose for high-weight individuals may be justified. In the present study the percentage of platelet inhibition was not correlated with platelet count.

Clopidogrel is also susceptible to significant pharmacological interactions. It has been suggested that its metabolism to the active form may be impaired with the use of concomitant proton-pump inhibitors such as omeprazol. On the other hand, there is significant discussion on the fact that smoking may have a protective effect against poor response to clopidogrel. A paradoxical effect of smoking on the risk of peri-operative stroke was recently observed in the

SAMMPRIS Study (Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis) [12, 13]. Never smokers presented with higher rates of stroke after stenting, a difference that was observed in both univariate and multivariate analysis [14]. These data does not point that smoking has a protective effect per se, but rather that it may accelerate the conversion of clopidogrel to its active form. Clopidogrel is a prodrug; two consecutive cytochrome P450-dependend steps convert it to its active metabolite [15]. Cigarette smoking is an inducer of CYP1A2, which is one of the hepatic enzymes involved in the metabolism of the prodrug. There are also arguments in favor of an influence of the degree of tobacco consumption on the degree of enzymatic activation. In patients using chronic clopidogrel therapy that consumed less than a half pack per day, the effect of smoking on ADP-induced aggregation was not observed [15] and, in normal volunteers, it is known that the level of CYP1A2 activity increases in function of the 'number' of cigarettes smoked per day [16].

Incidence of perioperative thromboembolic adverse events

Considering the previous observations on the variability of the effect of clopidogrel in inducing PI, it seemed crucial to investigate the effect on the incidence of thromboembolic (and hemorrhagic) adverse events among poor responders using different cut-offs in a neurological population. Enough evidence exists to suggest that the use of stents and the treatment of symptomatic supra-aortic or intracranial stenosis are related to a significantly increased risk of ischemic adverse events [17-28]. The level of 40% of platelet inhibition, suggested in a previous study using the *VerifyNow* system [3], was based on cardiology literature [29].

In our team's experience with intracranial stenting, the combination of a loading-dose of clopidogrel the day before the procedure, a point-of-care platelet inhibition test in the interventional operating room, and a dual antiaggregation regimen after the endovascular

treatment has reduced the incidence of thromboembolic events to roughly 50%. This has been documented in previous publications [25, 26, 28, 30].

Determining the frontier between adequate antiaggregation and drug resistance has practical implications for neurointerventionists. It can help determining how vigorous antiplatelet preparation should be, the necessity of adapting doses, the implications for patients who may undergo the administration of supplementary doses, and all financial issues regarding drug administration and assay utilization. Even if point-of-care assays seem useful in measuring how efficient our treatment is, evidence on how much they can (or can not) avoid risks is absolutely necessary to understand if their routine utilization is justified.

The assessment of the predictability of the assay in the present study showed that the 40% cut-off would include 94.4% of the thromboembolic events in the poor response group and the 20% cut-off would include 77.7%. For a practitioner working with a similar population, the use of the lower cut-off would hypothetically increase the frequency of thromboembolic endpoints among good responders from 1.0% to 2.6% (Figure 1, Supplemental Table 2).

This observation has direct clinical implications. If a hypothetical candidate for an intervention presents low intermediate levels of P2Y₁₂-inhibition (e.g. 23%), one may indicate a supplementary loading-dose in order to achieve a PI level over 40%. This type of study provides information on the degree of additional benefit in terms of procedural safety.

We are assessing the predictability of the *VerifyNow* assay for events that are multifactorial. In the example of the present study, a possible limitation was the fact that the group with less than 20% of PI was slightly older, which might have contributed to an increased per-operative risk.

This multifactoriality probably contributes to the finding that the overall risk predictability of such a test is modest, as previously reported [4]. This may be assessed by the study of the form and area under the ROC curve. Since the point closest to the theoretical gold-standard (1

value in the Y axis) is relatively near to the bisector and the area under the curve is no more than 0.735, a fair but not very strong association exists between the test and the final event.

A cut-off of 15% was estimated as being the value providing the maximal simultaneous sensitivity and specificity in the studied population. The implications of such a low level were discussed by Godino et al. (2009) in a study comparing the *VerifyNow* assay and flow cytometry [31]. The authors also found through ROC curve evaluation that an inhibition $\leq 15\%$ or an absolute PRU > 213 are cut-off values that identify poor response with maximal sensibility and specificity, and that probably better reflect the physiological reality. However, we do not advocate that such values are the most appropriate in everyday clinical practice. The choice of cut-off must be based both on clinical evidence and investigations into the 'tolerable' risk for a specific type of procedure.

Incidence of perioperative hemorrhagic adverse events

This study did not demonstrate any significant increase in the incidence of intracranial perioperative hemorrhagic events in good-responders. However, it is still worth noting that only one out of four patients who presented with severe hemorrhagic endpoints had a PI under 20%. This patient, who presented with a life-threatening retroperitoneal hematoma, was a poor responder subject who had received a per-operative dose of abciximab following a thromboembolic complication. These facts lead to two interesting points. The first is that a patient presenting with a higher level of P2Y₁₂-inhibition does not seem to be under a significantly higher risk of perioperative intracranial hemorrhages. However, in cases when it occurs, this will be potentially severe, since hemostasis will be considerably affected by both efficient plaquettary antiaggregation and perioperative anticoagulants (e.g. heparin). The second point to make is that insufficient PI may correlate to an increased risk of per-procedural thrombus formation on implantable materials, and also to the consequential per-

operative utilization of rescue drugs such as rtPA or abciximab and their collateral side effects.

Interestingly, a slightly higher incidence of peripheral hemorrhage needing medical attention was observed in the low-responder group when the 20% cut-off was used ($p=0.04$). However, we consider that this data should be interpreted with caution since patients in this group were heavier, which may have predisposed these subjects to the occurrence of bleeding that was clinically important but difficult to compress.

Limitations of the present study

Our study presents limitations. Its design does not allow the assessment of the influence of tobacco consumption or the previous use of proton-pump inhibitors on the prevalence of poor response to clopidogrel. Also, the level of aspirin-related inhibition was not routinely monitored. This could potentially have led to an increased predisposition to thromboembolic adverse events related to dual drug resistance. The resistance to ASA has been reported to be considerably less frequent, ranging from 2.1 to 13% [1-3]. However, it has been suggested that poor responses to clopidogrel are more frequent amongst poor responders to ASA [10, 32].

Future perspectives need to include randomization and possibly larger, prospective studies with longer follow-up. This may help interventionists in better understanding the correlation between platelet function and the long-term evolution of patients who are treated with neuro-implantable devices.

CONCLUSIONS

The use of the light transmittance aggregometry assay *VerifyNow* in patients undergoing neurointerventional procedures seems a valuable tool in the early detection of individuals at risk of perioperative thromboembolic adverse events. The study of the predictability of this point-of care assay suggests that the adoption of a 20% cut-off may detect more than 75% of patients at risk of thromboembolism. A 40% cut-off detected more than 90% of them in the studied population, but such level of platelet inhibition seems more difficult to obtain after a single 300mg loading-dose. No significant association was observed between P2Y₁₂-inhibition levels and incidences of intracranial hemorrhage, but no definitive conclusions may be taken on its effect on the severity of those events. The level of clopidogrel-related antiaggregation after a single loading-dose seems inversely related to body weight.

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CONFLICT OF INTEREST

AB: consultant for Stryker Neurovascular (Kalamazoo, USA).

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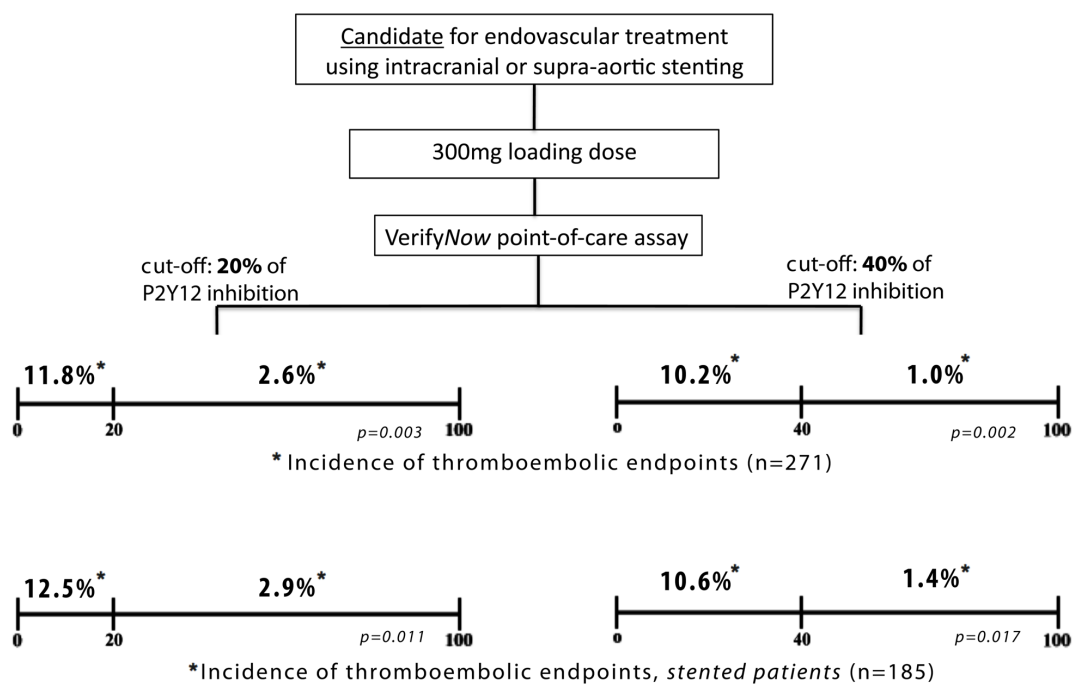
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FIGURE LEGEND

Figure 1. Incidence of thromboembolic endpoints in function of the measured P2Y₁₂ receptor inhibition at the time of the endovascular procedure, using the *VerifyNow* point-of-care assay (Accumetrics, San Diego, USA) and two different cut-offs: 20% and 40%.

Figure 1



ONLINE SUPPLEMENT

Clopidogrel-related platelet inhibition:

correlation with perioperative adverse events in neurointerventional procedures

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SUPPLEMENTAL METHODS

Sample

The following variables were retrieved: primary diagnosis, age, gender, location and indication for stent placement, weight, pre- and post-operative National Institute of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS) score, previous and ongoing co-morbidities, use of long term anti-coagulants, platelet count, administration of clopidogrel loading-dose before stenting, measured value of P2Y12 reaction units (PRUs) and reference level by light transmission aggregometry, percentage of clopidogrel-related P2Y12-inhibition and the occurrence of perioperative ischemic or hemorrhagic complications in the intracranial or cervical spaces as well as at the arterial access site and its respective management. Patients were excluded from the study if they had had a contraindication for anti-platelet treatment, a major disabling ipsilateral stroke as a first symptom, or had undergone stenting in the context of an urgent revascularization for a complete arterial occlusion. All patients who were stented for intracranial arterial stenosis had confirmed symptomatic atherosclerotic disease with lumen narrowing exceeding 50%. For those who had suffered a permanent stroke, the endovascular procedure was performed at least one week later.

Endovascular procedures

An initial neurological assessment was performed and a modified Rankin score attributed to each patient. A baseline NIHSS score was also calculated for every patient who had previously suffered from a stroke. Since this study included only potential candidates for a stent placement, a loading-dose of 300 mg of clopidogrel was administered the day before the endovascular treatment. Unfractionated heparin was infused during the procedure in order to obtain an activated clotted time (ACT) of 250s or longer.

The decision on whether to deploy an intracranial stent or not was taken after considering the feasibility of performing the treatment without it (e.g. aneurysm coiling to be safely executable using balloon remodeling techniques), or the possibility of not completing the treatment due to technical difficulties such as poor navigability. For stenting procedures, the diameter and length of each device were chosen according to the diameter of the native vessel and the extension of the pathological segment.

For cases of intracranial or supra-aortal stenosis, the degree of stenosis was estimated according to the criteria established in the WASID study using the diameter of the non-stenotic artery distal to the pathological segment as a reference. In order to avoid hemodynamic ischemic phenomena, the target mean blood pressure during the procedure was 90mmHg.

Prior to intracranial stent deployment, predilation with a Gateway Balloon (Boston Scientific Corp., Fremont, USA) was performed. It was slowly inflated to no more than 80% of the reference diameter. The appropriate length was chosen in a way that would ensure coverage of the stenotic lesion by at least 3mm beyond its proximal and distal extremities. The aim of the procedure was to obtain a residual stenosis of less than 50%. In selected cases, angioplasty and stenting were simultaneously performed using balloon-mounted stents from different manufacturers. A control DSA was performed at the end of the procedure and intravenous heparin was continued for twelve hours in order to obtain an activated cephalin time of 1.5x the baseline.

After the procedure, blood pressure control was carried out to prevent both reperfusion syndrome and secondary hemorrhagic complications. A neurological examination was performed after extubation. At post-operative day one a new mRS score was recorded (and NIHSS score if applicable), the heparin was stopped and dual

antiplatelet therapy was started. In cases of clinical deterioration, a magnetic resonance imaging (MRI) examination was immediately carried out.

Monitoring technique

A VerifyNow System (Accumetrics, San Diego, USA) was used for measuring clopidogrel-related platelet inhibition in whole blood samples. According to the original description from the manufacturer, the device contains a lyophilized preparation of human fibrinogen-coated beads, platelet activators and buffer. The assay measures platelet P2Y₁₂ receptor blockage. This measurement is based upon the ability of activated platelets to bind fibrinogen and on the aggregation of fibrinogen-coated microparticles. A special reagent containing adenosine-5-diphosphate (ADP) and prostaglandin E₁ (PGE₁) is incorporated to activate platelets without fibrin formation. This is formulated to specifically measure P2Y₁₂-mediated aggregation. Light transmittance increases as platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signals and reports results in P2Y₁₂ Reaction Units. Two different activators are incorporated into a second channel (base channel) of the assay device: a thrombin receptor activating peptide (iso-TRAP) and a PAR₄-activating peptide (PAR₄-AP). The instrument also measures the change in light transmittance in this channel and calculates the baseline platelet function for the sample. Finally, it calculates and reports the percentage P2Y₁₂-related inhibition for the patient.

The timing for antiplatelet effect testing was immediately after intubation for all patients. In a small number of patients who were already on long-term use of clopidogrel because of other indications, a previous test was also performed the day before the endovascular procedure. If this resulted in a percentage of inhibition of more than 40%, the loading-dose was not administered. In a few cases the patient received two loading-doses, either because of insufficient anti-aggregation or because of procedure postponement. Two aggregometry results were consequently available. In such circumstances, the result obtained the day of the procedure was used for statistical analysis regarding the occurrence of complications.

SUPPLEMENTAL RESULTS

Sample

Two-hundred procedures were performed for the treatment of a cerebral aneurysm, 65 for a supra-aortic or intracranial stenosis and the remaining six for an arteriovenous fistula. Of the 185 stenting procedures, the indication for endovascular treatment was a brain aneurysm in 122 (65.9%), an arterial stenosis in 59 (31.9%) and an arteriovenous fistula in six (2.2%). Only five of the cerebral aneurysms were treated with stent-assisted techniques in the acute phase of subarachnoid hemorrhage. Flow diverters (Pipeline Embolization Device; ev3 Inc., Irvine, USA) were used in three of these procedures, Neuroform (Boston Scientific, Natick, USA) stents were used in 35 (18.9%) of these procedures, Enterprise (Cordis Neurovascular, Miami Lakes, USA) in 33 (17.8%), Wingspan (Boston Scientific) stents in 30 (16.2%), XAct (Abbott Vascular, Santa Clara, USA) in 16 (8.6%), Solitaire (ev3) in 15 (8.1%), Precise (Cordis) in eight (4.3%), Multi-link Vision (Abbott) in seven (3.8%), Jostent (Abbott) in two (1.1%), Acculink (Abbott) in one (0.54%) and Pharos (Micrus Endovascular, San José, USA) in one (0.54%). Flow diverters were used in 32 procedures: Silk type (Balt Extrusion, Montmorency, France) in 18 (9.7%) and Pipeline Embolization Devices in the remaining 14 (7.6%). A combination of stents from different manufacturers was used in the remaining five cases (2.7%).

Supplemental Table 1. Demographic data of a sample of 271 neurointerventional procedures and distribution by group of P2Y12-inhibition as measured using point-of-care light transmission aggregometry (VerifyNow assay; Accumetrics, San Diego, USA).

	Overall (n=271)	PI≤20% (n=119)	20%>PI≤40% (n=47)	PI>40% (n=105)	<i>p</i>
Gender					0.503
Male	106	47	15	44	
Female	165	72	32	61	
Age	58±13.9y (20-88)	60.7±14.3y (26-85)	57.4±12.2y (34-81)	55.1±13.6y (20-88)	0.009
Weight	70.2±14.9Kg (43-130)	72.9±15.7Kg (43-130)	69.9±13.2Kg (47-102)	67.5±14.3Kg (44-124)	0.027
Platelet count (per mm³)	2.46±8.1x10 ⁵ (1.08-5.54)	2.44x10 ³ (1.23-5.09)	2.56x10 ³ (1.08-5.54)	2.42x10 ³ (1.09-4.78)	0.66
Co-morbidity Index	1.9±1 (0-5)	2±1 (0-5)	1.9±1 (1-4)	1.8±1 (0-5)	0.33
Indication of procedure					N/A
Aneurysm embolisation	200	85	34	81	
Supra-aortic or intracranial stenosis	65	34	11	20	
Arteriovenous fistula	6	-	2	4	
P2Y₁₂-inhibition	36.4±34% (0-100)	5.4±6.5% (0-20)	30.9±5.2% (21-40)	74±19.9% (41-100)	N/A

N/A, Not Applicable

Supplemental Table 2. Incidence of perioperative thromboembolic and hemorrhagic adverse events (symptomatic or asymptomatic).**Impact of a minimal level of 40% of P2Y₁₂-inhibition on the incidence of thromboembolic and hemorrhagic complications**

	PI≤40%(n=166)		PI>40%(n=105)	
Thromboembolic	17(10.2%) ^a	Hemorrhagic 37(22.3%)	Thromboembolic	1(1.0%) ^a Hemorrhagic 17(16.2%)
C	16(9.6%) ^b	C 3(1.8%)	C	1(1.0%) ^b C 5(4.8%)
P	1(0.6%)	P 34(20.5%)	P	0(0.0%) P 13(12.4%)
S	5(3.0%)	S 1(0.8%)	S	- S 2(1.9%)

^a $p=0.002$; ^b $p=0.004$ **Impact of a minimal level of 20% of P2Y₁₂-inhibition on the incidence of thromboembolic and hemorrhagic complications**

	PI≤20%(n=119)		PI>20%(n=152)	
Thromboembolic	14(11.8%) ^a	Hemorrhagic 29(24.4%)	Thromboembolic	4(2.6%) ^a Hemorrhagic 25(16.4%)
C	14(11.8%) ^b	C 2(1.7%)	C	3(2.0%) ^b C 6(3.9%)
P	-	P 27(22.7%) ^c	P	1(0.7%) P 20(13.2%) ^c
S	4(3.4%)	S 1(0.8%)	S	1(0.7%) S 3(2.0%)

^a $p=0.003$; ^b $p=0.001$; ^c $p=0.04$ **Incidence of thromboembolic and hemorrhagic events according to the level of P2Y₁₂-inhibition**

	PI≤20%(n=119)		20%<PI≤40%(n=47)		PI>40%(n=105)	
Thromboembolic	14	Hemorrhagic 29	Thromboembolic 3	Hemorrhagic 8	Thromboembolic 1	Hemorrhagic 17
	(11.8%)	(24.4%)	(6.4%)	(17.0%)	(1.0%)	(16.2%)
C	14	C 2	C 2	C 1	C 1	C 5
	(11.8%)	(1.7%)	(4.3%)	(2.1%)	(1.0%)	(4.8%)
P	-	P 27	P 1	P 7	P 0	P 13
	-	(22.7%)	(2.1%)	(14.9%)	(0.0%)	(12.4%)
S	4	S 1	S 1	S -	S -	S 2
	(3.4%)	(0.8%)	(2.1%)	-	-	(1.9%)

C, central (neurological) endpoint; **P**, peripheral (vascular access) endpoint.

Supplemental Table 3. Incidence of perioperative thromboembolic and hemorrhagic adverse events (symptomatic or asymptomatic) among patients who underwent supra-aortic or intracranial stent placement.

Impact of a minimal level of 40% of P2Y₁₂-inhibition on the incidence of thromboembolic and hemorrhagic complications

PI≤40%(n=113)				PI>40%(n=72)			
Thromboembolic	12 (10.6%) ^a	Hemorrhagic	25 (22.1%)	Thromboembolic	1 (1.4%) ^a	Hemorrhagic	13 (18.1%)
C	11 (9.7%) ^b	C	3 (2.7%)	C	1 (1.4%) ^b	C	4 (5.6%)
P	1 (0.9%)	P	22 (19.5%)	P	-	P	10 (13.9%)
S	4(3.5%)	S	2(1.8%)	S	-	S	1(1.4%)

^a $p=0.017$; ^b $p=0.03$

Impact of a minimal level of 20% of P2Y₁₂-inhibition on the incidence of thromboembolic and hemorrhagic complications

PI≤20%(n=80)				PI>20%(n=105)			
Thromboembolic	10 (12.5%) ^a	Hemorrhagic	17 (21.3%)	Thromboembolic	3 (2.9%) ^a	Hemorrhagic	21 (20.0%)
C	10 (12.5%) ^b	C	2 (2.5%)	C	2 (1.9%) ^b	C	5 (4.8%)
P	-	P	15 (18.8%)	P	1 (1.0%)	P	17 (16.2%)
S	3(3.8%)	S	1(1.3%)	S	1(1.0%)	S	2(1.9%)

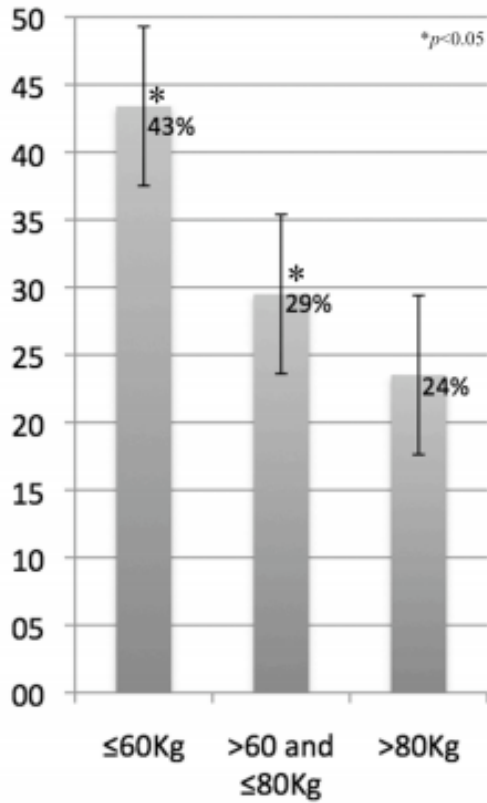
^a $p=0.011$; ^b $p=0.004$

Incidence of thromboembolic and hemorrhagic events according to the level of P2Y₁₂-inhibition

PI≤20%(n=80)				20%<PI≤40%(n=33)				PI>40%(n=72)			
Thromboembolic	10 (12.5%)	Hemorrhagic	17 (21.3%)	Thromboembolic	2 (6.1%)	Hemorrhagic	8 (24.2%)	Thromboembolic	1 (1.4%)	Hemorrhagic	13 (18.1%)
C	10 (12.5%)	C	2 (2.5%)	C	1 (3.0%)	C	1 (3.0%)	C	1 (1.4%)	C	4 (5.6%)
P	-	P	15 (18.8%)	P	1 (3.0%)	P	7 (21.2%)	P	-	P	10 (13.9%)
S	3 (3.8%)	S	1 (1.3%)	S	1 (3.0%)	S	1 (3.0%)	S	-	S	1 (1.4%)

C, central(neurological) endpoint; P, peripheral(vascular access) endpoint.

Supplemental Figure 1. Distribution by group of body weight of the results of the assays for P2Y₁₂ ADP receptor inhibition (VerifyNow, Accumetrics, San Diego, USA) in 182 cases with no on-going use of clopidogrel, and after 300mg of clopidogrel the day before the endovascular procedure.



Supplemental Figure 2. Receiver-Operator-Characteristic (ROC) curve for the sensitivity and specificity of the VerifyNow P2Y12 assay in predicting patients at risk of perioperative thromboembolic adverse events. The cut-off in which maximal sensitivity and specificity are achieved simultaneously is 15%. Area under the curve=0.735.

