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ABSTRACT

BACKGROUND AND PURPOSE: The optimal antiplatelet regimen after flow diverter treatment of cerebral aneurysms is still a matter of debate. A single antiplatelet therapy might be advantageous in determined clinical scenarios. This study evaluated the efficacy and safety of prasugrel single antiplatelet therapy versus aspirin and clopidogrel dual antiplatelet therapy.

MATERIALS AND METHODS: We performed a post hoc analysis of 4 retrospective multicenter studies including ruptured and unruptured aneurysms treated with flow diversion using either prasugrel single antiplatelet therapy or dual antiplatelet therapy. Primary end points were the occurrence of any kind of procedure- or device-related thromboembolic complications and complete aneurysm occlusion at the latest radiologic follow-up (mean, 18 months). Dichotomized comparisons of outcomes were performed between single antiplatelet therapy and dual antiplatelet therapy. Additionally, the influence of various patient- and aneurysm-related variables on the occurrence of thromboembolic complications was investigated using multivariable backward logistic regression.

RESULTS: A total of 222 patients with 251 aneurysms were included, 90 (40.5%) in the single antiplatelet therapy and 132 (59.5%) in the dual antiplatelet therapy group. The primary outcome–procedure- or device-related thromboembolic complications–occurred in 6 patients (6.6%) of the single antiplatelet therapy and in 12 patients (9.0%) of the dual antiplatelet therapy group ($P = .62$; OR, 0.712; 95% CI, 0.260–1.930). The primary treatment efficacy end point was reached in 82 patients (80.4%) of the single antiplatelet therapy and in 115 patients (78.2%) of the dual antiplatelet therapy group ($P = .752$; OR, 1.141; 95% CI, 0.599–2.101). Logistic regression showed that non-surface-modified flow diverters ($P = .014$) and fusiform aneurysm morphology ($P = .004$) significantly increased the probability of thromboembolic complications.

CONCLUSIONS: Prasugrel single antiplatelet therapy after flow diverter treatment may be as safe and effective as dual antiplatelet therapy and could, therefore, be a valid alternative in selected patients. Further prospective comparative studies are required to validate our findings.

ABBREVIATIONS: AIT = acute in-stent thrombosis; ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; FD = flow diverter; PTA = percutaneous transluminal angioplasty; RROC = Raymond-Roy occlusion classification; SAPT = single antiplatelet therapy; TE = thromboembolic complications

Endovascular treatment of intracranial aneurysms still involves procedural complications. Despite multiple risk-reduction strategies, such as antiplatelet therapy and platelet reactivity testing, thromboembolic complications (TE) remain the leading cause of death and morbidity.[1] Especially, flow diverters (FDs) carry a relatively high risk of TE, and manufacturers usually recommend a dual antiplatelet therapy (DAPT).[2,3] The most commonly used DAPT regimen is acetylsalicylic acid (ASA) in combination with clopidogrel; however, there is no standardized dose or duration.[4] Recently, surface-modified FDs have been developed to reduce thrombogenicity, which could enable the use of single antiplatelet therapy (SAPT). Preliminary results of flow diversion with SAPT seem promising; however, it still remains unclear which drug is best suited for SAPT and whether it can be safely applied in conventional, non-surface-modified FDs.[5-8] Resistance to ASA and clopidogrel has been described, which remarkably increases the risk of TE.[9] Other potent P2Y12 inhibitors with a high level of platelet inhibition and a less frequent drug resistance, such as prasugrel, can be an alternative antiplatelet therapy option for patients treated with FDs.[10-12]

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This retrospective multicentric study evaluated the efficacy and safety of prasugrel SAPT versus ASA and clopidogrel DAPT for aneurysm treatment with FDs. Both surface-modified and conventional FDs have been included.

MATERIALS AND METHODS

Patient Selection

We performed a post hoc analysis of 4 retrospective multicenter studies of flow diversion,[13-16] including all patients who underwent FD treatment of ≥1 intracranial aneurysm between 2013 and 2021. Anterior and posterior circulation and ruptured and unruptured aneurysms were included. These studies evaluated both FDs with surface modification and non-surface-modified FDs. If prior implants were present in the target vessel (eg, intraluminal stent or FD), these patients were excluded. Of these patients, we further selected those treated with either SAPT with prasugrel or DAPT consisting of ASA and clopidogrel. Follow-up data had to be available for at least 3 months after the index procedure. If a patient receiving either prasugrel SAPT or ASA and clopidogrel DAPT died, he or she was included regardless of the duration of the follow-up.

The analysis was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies (Online Supplemental Data).

Medication Protocols

We compared 2 different medication regimens: either SAPT with prasugrel or DAPT consisting of ASA and clopidogrel. Patients were assigned to the respective treatment arms according to the standard medication protocol of each participating site.

In the SAPT group, patients were loaded with prasugrel the day before the procedure with a standard loading dose of 30 mg, with possible adjustment according to the patient's weight (20 mg for patients weighting <60 kg; 40 mg for overweight patients). The postprocedural medication included 5 mg (low dose in patients younger than 75 years of age or <60 kg) or 10 mg of prasugrel once daily for 6–12 months, after which the patient either continued with reduced doses of prasugrel or was switched to 100 mg of ASA once daily for an additional 6 months or life-long based on a case-by-case decision.

Patients in the DAPT group were treated with 100 mg of ASA and 75 mg of clopidogrel (loading dose, 300 mg), starting no less than 5 days before the procedure, which was then maintained for a minimum of 3 months after the procedure. Thereafter, patients were switched to ASA-only according to the in-house protocols of each site.

Platelet inhibition was routinely tested before elective procedures and was managed according to the local standards of the respective institutions.

Patients with acutely ruptured aneurysms, who were treated in an emergency setting or if stent placement was unplanned, received an IV bolus of tirofiban immediately before stent deployment, followed by a maintenance dose for 6–24 hours (dosage adapted to the patient's weight according to the instructions for use), followed by either prasugrel or the above-described DAPT medication scheme.

In case of acute in-stent thrombosis (AIT) during the procedure, patients were also given an IV or intra-arterial bolus (depending on the respective institutional protocol) of a glycoprotein IIb/IIIa inhibitor (ie, tirofiban) as soon as possible. Likewise, the maintenance dosage was given for 6–24 hours, followed by the intended oral antiplatelet drugs.

Data Collection

We performed a post hoc analysis of 4 retrospective multicenter studies.[13-16] We reviewed data on patient demographics, clinical and aneurysm characteristics, procedure-related data, FD specifications, antiplatelet regimens according to the 2 options mentioned above, as well as follow-up data including the degree of aneurysm occlusion, the degree of intimal hyperplasia, and clinical outcome (Online Supplemental Data).

Aneurysmal occlusion rates were assessed using the O'Kelly Marotta Scale[17] or the Raymond-Roy occlusion classification (RROC),[18] respectively, for invasive catheter angiographies and contrast-enhanced MR imaging scans. To enhance clarity and comparability for the follow-up assessments of aneurysm occlusion, we referred to the RROC scale only.

The clinical evaluation was performed by a certified neurologist using the mRS before treatment in the immediate postoperative period (<24 hours), at discharge, and then at subsequent clinical appointments scheduled for the same time as the respective imaging follow-up. Scores of 0 and 1 were assumed to indicate good functional outcome.

End Points

The primary safety end point was the occurrence of any kind of TE (symptomatic and asymptomatic documented by imaging alone). Secondary safety end points were the occurrence of permanently disabling TE, defined as those that led to a permanent shift of the preprocedural mRS score, hemorrhagic complications of any kind, the occurrence of intimal hyperplasia, and a good functional outcome at the latest clinical follow-up.

The primary efficacy end point was complete aneurysm occlusion (RROC I) at the latest radiologic follow-up according to the RROC. The secondary efficacy end point was adequate aneurysm occlusion (RROC I + II) at the latest radiologic follow-up according to the RROC. End point evaluation was site-assessed.

Statistics

SPSS Statistics, Version 25.0 (IBM) was used for statistical analysis. Quantitative data are presented as number (relative frequency) or mean (SD). Patients were divided into 2 groups according to periprocedural antiplatelet treatment (SAPT or DAPT). Between-group comparisons were performed with the Fisher exact test for categoric variables. To investigate the influence of patient- and procedure-related factors on the occurrence of TE, we analyzed all selected variables with clinical importance using univariate logistic regression models, with "thromboembolic complications" as the outcome variable. Subsequently, only the significant variables ($P < .05$) of these analyses were used in an interim multivariable logistic regression model. This model was adjusted with a variable selection on the basis of the P value with a backward stepwise approach based on the Wald test, resulting in the final multivariable logistic regression model. P values of .05 were defined as the threshold for statistical significance and were not adjusted for multiple testing due to the hypothesis-generating approach of the

Table 1: Main characteristics of the 2 medication groups including patients, aneurysms, and procedure-related characteristics[a]

	SAPT	DAPT	*P* Value
Patient characteristics			
No. of patients	90	132	
Patient age (yr)	52 (SD, 11.8) (10–74)	56 (SD, 12.9) (14–92)	.555
Sex (female)	59 (65.6%)	101 (76.5%)	<.001[b]
Aneurysm characteristics			
No. of aneurysms	102	149	
Aneurysm size	7.5 (SD, 6.1) (1–32)	6.7 (SD, 5.3) (1–28)	.099
SAH	13 (12.8%)	27 (18.1%)	.020[b]
Saccular morphology	81 (81.4%)	109 (75.2%)	.021[b]
Anterior circulation	91 (89.2%)	128 (85.9%)	.120[b]
Procedural details			
No. of procedures	91	133	–
No. of implanted FD (total)	105	148	0.306
No. of implanted FD (with surface-modification)	29 (27.6%)	71 (47.9%)	<.001[b]
Additional coiling	14 (13.7%)	29 (19.4%)	.016[b]
PTA	–	14 (9.4%)	<.001[b]
Previously treated aneurysms	20 (19.6%)	18 (12.1%)	.001[b]

Note:—The en dash indicates 0 (0%).
[a] Data are mean (SD) (minimum–maximum) or absolute number of cases (relative frequency in percentages).
[b] Statistically significant.

Table 2: Comparison of study end points between SAPT and DAPT[a]

	SAPT ($n = 90$)	DAPT ($n = 132$)	*P* Value
Complications			
Thromboembolic (all)	6	12	.188
Thromboembolic (permanently disabling)	0	5	<.001[b]
Hemorrhagic	0	3	.003[b]
Intimal hyperplasia/asymptomatic parent artery occlusion	3 (2.9%) mild/3 (2.9%)	6 (4.0%) mild/2 (1.3%)	.768
Radiologic and clinical follow-up			
Follow-up duration	18 (SD, 12.3) (3–60)	18 (SD, 12.6) (6–74)	.553
Complete occlusion (RROC I) at latest follow-up	82 (80.4%)	115 (78.2%)	.367
Good clinical outcome at latest clinical follow-up (mRS 0-1)	90 (100%)	116 (87.8%)	<.001[b]

[a] Data are mean (SD) (minimum-maximum) or absolute number of cases (relative frequency in percentages).
[b] Statistically significant.

study. Hence, the *P* values should be interpreted descriptively. For ORs, 95% confidence intervals were calculated.

RESULTS

Patient and Aneurysm Characteristics and Procedural Details

A total of 222 consecutive patients (72.1% women; mean age, 54 [SD, 12.6] years) with 251 aneurysms who were treated in 224 procedures with FDs were included in this study. A flow chart (Online Supplemental Data) depicts how many patients were excluded from the respective studies and the reasons.

Forty patients had a history of SAH (18.0%); of these, 21 were treated in the acute stage within 3 days after aneurysm rupture. Thirty-eight aneurysms (15.1%) were secondarily treated due to residual aneurysm filling or regrowth after previous treatment with either coils or surgical clipping.

Most aneurysms (82.9%) were treated with flow diversion only, while 17.1% received adjunctive coiling. The rationale for adjunctive coiling was a maximum size of >10 mm, an irregular shape, or an acute aneurysm rupture. In-stent percutaneous transluminal angioplasty (PTA) to enhance vessel wall apposition of the FD was necessary in 14 cases (5.9%).

We used 4 different types of FDs with and without surface modification for the reduction of thrombogenicity: The Flow-Redirection Endoluminal Device (FRED/FRED Jr; MicroVention) ($n = 153$, 56.9%) and its variant with an antithrombotic surface modification FRED X (MicroVention) ($n = 49$, 18.2%); and the Pipeline Vantage Embolization Device with Shield Technology (PED Vantage; Medtronic), which also has a surface modification ($n = 67$, 24.9%). The number of implanted FDs per treatment was 1 in 212 treatments (94.6%), 2 in 10 treatments (4.5%), and ≥3 in 2 treatments (0.9%).

The main patient and aneurysm characteristics as well as procedural details are summarized in the Online Supplemental Data.

Medication Subgroups

The SAPT group consisted of a total of 90 patients (40.5%) (65.6% women; mean age, 52 [SD, 11.8] years) with 102 aneurysms treated in 91 procedures with a total of 105 implanted devices. In this cohort, 13 patients (12.7%) had a history of SAH. Of these, 5 were treated in an acute setting within 3 days after the bleeding.

The DAPT group consisted of 132 patients (59.5%) (76.5% women; 56 [SD 12.9] years), who had 149 aneurysms treated in 133 interventions using 148 FDs. Twenty-seven patients (18.2%) had a history of SAH, and 16 of them were treated in an emergency setting.

More detailed data for both groups as well as between-group comparison results are reported in Table 1. Study end points are reported in Table 2.

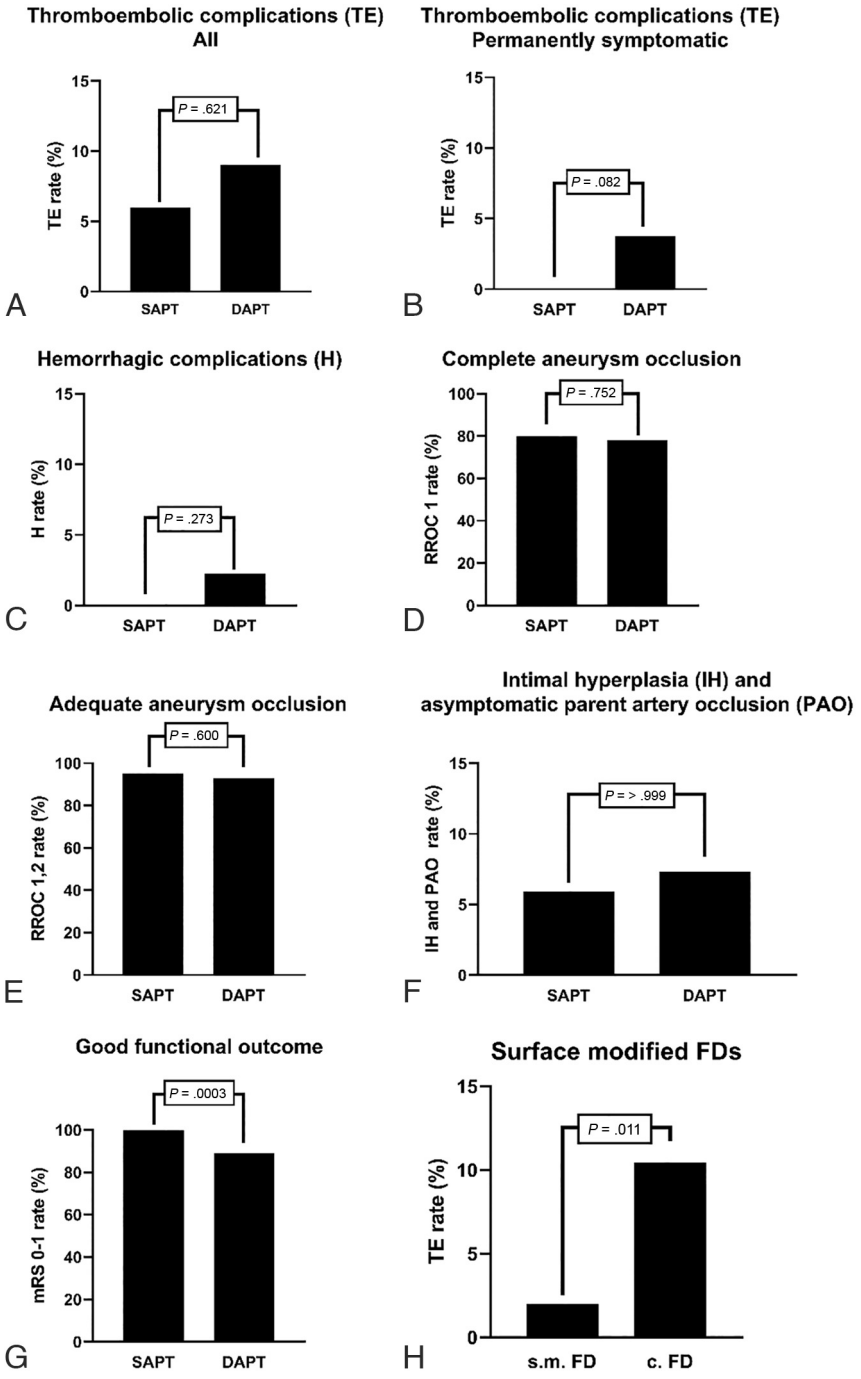

FIGURE. *A*, Rate of all observed thromboembolic procedure- or device-related complications in the SAPT with prasugrel and in the DAPT. *B*, Rate of permanently disabling thromboembolic procedure- or device-related complications in the SAPT and DAPT groups. *C*, Rate of hemorrhagic procedure-related complications in the SAPT and DAPT groups. *D*, Rate of complete aneurysm occlusion at latest follow-up in the SAPT and DAPT groups. *E*, Rate of adequate aneurysm occlusion at latest follow-up in the SAPT and DAPT groups. *F*, Rate of intimal hyperplasia and asymptomatic parent artery occlusion in the SAPT and DAPT groups. *G*, Rate of good functional outcome at the latest follow-up in the SAPT and DAPT groups. *H*, Thromboembolic complications in surface-modified or conventional FDs.

Procedural Complications

A total of 18 TE (8.1%) were observed in the peri- and postinterventional period. Twelve of these complications were observed in the DAPT group (66.7%), while the remaining 6 (33.3%) occurred in the SAPT group (Fig 1*A*). The medication regimen had no significant effect on the occurrence of thromboembolic events in the Fisher exact test ($P = .621$; OR, 0.712; 95% CI, 0.260–1.930). We observed AIT in 8 cases, with the thrombus being detected either in the stent itself or in a covered side branch (5 in the DAPT group and 3 in the SAPT group); asymptomatic parent artery occlusion was noted in the follow-up of 5 cases (2 in the DAPT group and 3 in the SAPT group), and symptomatic peri- or postprocedural ischemic strokes led to a permanent mRS shift in 5 patients (all occurred in the DAPT group).

All cases of AIT were acutely treated with intraoperative administration of tirofiban. The thrombus dissolved in all instances, and the affected patients did not develop any clinical sequelae.

The permanently disabling TE ($n = 5$), all occurring in the DAPT group, are summarized in the Online Supplemental Data. The Fisher exact test showed only a trend without reaching statistical significance for the influence of the medication regimen on the occurrence of permanently disabling thromboembolic events ($P = .082$; OR, 0.000; 95% CI, 0.000–1.096) (Fig 1*B*).

Regarding the correlation of the FD type and the incidence of TE, regardless of the medication, we found a lower incidence of 2% in surface-modified FDs compared with 10.5% for conventional stents ($P = .011$; OR, 0.175; 95% CI, 0.039– 0.739) (Fig 1*H*). Considering the TE ($n = 6$) only in the SAPT group, they all occurred in the patients using the FRED Jr, a non-surface-modified FD, dedicated to small vessels.

The analysis of the influence of patient- and procedure-related factors on the occurrence of TE is reported in the Online Supplemental Data. The results of the final multivariable logistic regression model are presented in Table 3. FDs without surface modification ($P = .014$; OR, 7.119; 95% CI, 1.492– 33.960) and fusiform aneurysm morphology ($P = .004$; OR, 6.563; 95% CI, 1.835–23.472) were the 2 parameters that showed a significant relation to the occurrence of TE in the multivariable model.

A total of 3 hemorrhagic complications (1.3%), which were severe groin hematomas, occurred in the DAPT group, leading to a prolonged hospital stay. One necessitated a surgical intervention,

Table 3: Influence of patient and procedure-related factors on the occurrence of thromboembolic complications: final multivariable logistic regression model

	P Value	OR (95% CI)
Non-surface-modified FD	.014	7.119 (1.492–33.960)
Fusiform morphology	.004	6.563 (1.835–23.472)

while the remaining 2 were managed conservatively. No severe hemorrhagic complications were observed in the SAPT group (Fig 1*C*).

Other procedure-related complications included 1 case of fatal hospital-acquired pneumonia, 3 cases of SAH sequelae (vasospasms and consequent infarctions), 1 case of anaphylaxis due to iodinated contrast media, and 1 case of worsening of a pre-existing stroke.

Radiologic and Clinical Follow-Up

The 251 aneurysms had a mean follow-up period of 18 (SD, 12.5) months (range, 3–74 months). Two patients, both of the DAPT group, had no follow-up due to periprocedural death. Both presented with acute SAH, and their conditions deteriorated during hospitalization with acquired pneumonia. One additionally had a postoperative in-stent thrombosis with progressive infarctions.

In the SAPT group, 82 aneurysms (80.4%) were completely occluded (RROC I), 15 aneurysms (14.7%) had a residual neck filling (RROC II), and 5 aneurysms (4.9%) had an aneurysmal filling at the last available follow-up. In the DAPT group, complete aneurysm occlusion (RROC I) was observed in 115 aneurysms (78.2%); residual neck filling (RROC II), in 23 (15.7%) aneurysms; and aneurysmal filling (RROC III), in 9 (6.1%) aneurysms. Therefore, the primary treatment efficacy end point was similarly reached in 80.4% of cases for the SAPT group ($n = 82$ aneurysms) and in 78.2% of cases in the DAPT group ($n = 115$ aneurysms) (Fig 1*E*). Adequate aneurysm occlusion, defined as RROC I and RROC II, was reached in 97 cases (95.1%) in the SAPT group and in 138 cases (92.6%) in the DAPT group (Fig 1*F*). The Fisher exact test showed no statistical significance of the influence of the medication regimen on the complete occlusion or on the adequate occlusion at latest follow-up ($P = .752$; OR, 1.141; 95% CI, 0.599–2.101 and $P = .600$; OR, 1.546; 95% CI, 0.508– 4.109, respectively).

When we considered only aneurysms that were not additionally coiled, the primary treatment efficacy end point was reached in 79.6% ($n = 70$ aneurysms after excluding the $n = 14$ coiled aneurysms) in the SAPT group and in 76.5% % ($n = 120$ aneurysms after excluding the $n = 29$ coiled aneurysms) in the DAPT group. Both groups had a mean follow-up of 18 months, in the SAPT group with an SD of 12.3 months (range, 3–60 months) and in the DAPT group with an SD of 12.6 months (range, 6–74 months) (Table 2).

Mild intimal hyperplasia (<50%) was observed in 3 (2.9%) parent arteries in the SAPT group and in 6 (4.0%) parent arteries in the DAPT group. There were no cases of moderate or severe intimal hyperplasia recorded. However, during follow-up, 5 cases of asymptomatic parent artery occlusion were assessed, 3 in the SAPT and 2 in the DAPT group (Fig 1*D*).

A good functional outcome, defined as an mRS of 0–1 at the latest clinical follow-up, was observed in all 90 patients (100%) in the SAPT group and in 116 patients (87.9%) in the DAPT group (Fig 1*G*). The influence of the medication regimen on the good functional outcome at the latest follow-up showed statistical significance in the Fisher exact test ($P = .001$; OR, +infinity; 95% CI, 3.275–+infinity). Because radiologic and clinical follow-ups occurred simultaneously, the latest clinical follow-up coincided with the latest radiologic follow-up.

DISCUSSION

In the present study, we demonstrated that SAPT with prasugrel is comparable with conventional DAPT with ASA and clopidogrel, both in terms of safety and efficacy. Thromboembolic and hemorrhagic events tended to be less frequent in terms of numeric values in the SAPT group, however, without reaching statistical significance. Occlusion rates at the latest available follow-up were similar in the 2 groups, while a good functional outcome was significantly better in the SAPT group.

The rate of symptomatic TE was 3.6% in our study, which is similar to that reported in the literature.[3] The encountered TE are discussed in more detail in the respective publications.[13-16] Prophylactic DAPT consisting of ASA and clopidogrel is commonly used to reduce the risk of TE after FD treatment for at least 3–6 months; however, there is no standardized antiplatelet treatment protocol.[4] Despite this precaution, TE are still common and resistance to both ASA, and especially clopidogrel is thought to be among the main contributing factors to these adverse events. Emerging data suggest that ASA, which acts through inhibition of platelet cyclooxygenase leading to an irreversible inhibition of platelet-dependent thromboxane, may have an unpredictable antiplatelet response.[19,20] Clopidogrel is a prodrug that is converted to its active form via an isoenzyme of cytochrome P450. Decreased plasma levels of the active clopidogrel metabolite can be influenced by genetic polymorphisms, diet, smoking, alcohol, and demographics,[21] and clopidogrel resistance in the setting of neurointerventions has been reported to have a prevalence as high as 36.5%.[9] Other potent antiplatelet agents, P2Y12 inhibitors, are becoming increasingly used in neurointerventional procedures, supported by evidence from the cardiac literature that showed a high level of platelet inhibition and less resistance.[10]

Prasugrel, a third-generation oral thienopyridine, has a similar mechanism of action to clopidogrel with the advantage of having a faster onset of action, more efficient platelet inhibition due to less variability in the patient response, and faster restoration of platelet activity after cessation.[21] Prasugrel is a prodrug that is converted by liver enzymes into its active metabolite and binds irreversibly to P2Y12 receptors. Genetic polymorphisms do not (or only minimally) influence the metabolism of prasugrel, so there is no or little resistance to the drug. Prasugrel has been shown to be safe and effective in a broad variety of neurointerventions.[21,22] Also in the setting of flow diversion, prasugrel is considered a safe alternative for clopidogrel-resistant patients because it seems to be associated with a lower incidence of thromboembolic and hemorrhagic complications, as well as mortality.[13,23] Different meta-analyses of prospective and retrospective studies highlighted the potential benefits of alternative P2Y12

inhibitors such as prasugrel in reducing treatment-related complications.[24-26] In the present study, we also observed a lower incidence of thromboembolic and hemorrhagic complication rates in the prasugrel-treated subgroup. Both in terms of absolute values and the severity of the complication, the prasugrel group was superior to the DAPT group, however without reaching statistical significance.

A type of TE that was observed homogeneously in both drug regimen groups was the occurrence of AIT. This observation suggests that AIT can occur independent of the medication used and could be best detected using an active surveillance strategy that enables fast counteracting.[27]

In our study, we compared prasugrel, given as monotherapy, with a DAPT medication scheme. Which drug is most suitable for SAPT in the setting of flow diversion is still unclear. Different drugs have been used for SAPT, including ASA, prasugrel, or ticagrelor, another P2Y12 inhibitor.[5-7,28] In 2 prospective trials investigating 2 different SAPT alternatives, in unruptured intracranial aneurysms using a surface-modified FD, ASA monotherapy was linked to a significantly higher incidence of ischemic complications (42.8%), while prasugrel monotherapy appeared to be safe in a comparable population.[8,29]

Most data about SAPT in the setting of flow diversion rely on surface-modified FDs designed to have a less thrombogenic coating, allowing the use of SAPT. Indeed, the drawback of SAPT could be a potentially increased risk of TE, which, however, we did not observe in our study, as mentioned above. A small retrospective study found SAPT with ticagrelor to be safe after PED placement, a non-surface-modified FD.[28] In the present study, we included not only FDs with surface modification (FRED X and PED Vantage with Shield Technology) but also conventional FDs (FRED and FRED Jr). In the SAPT group, all TE ($n = 6$) occurred with the FRED Jr, which is a non-surface-modified FD. This FD is designed to be specifically used for smaller, distal vessels. This design might bias this observation because thromboembolism is suspected to be higher in the distal vascular areas.[30] Nevertheless, non-surface-modified FDs were linked to an increased risk of the occurrence of TE in the multivariate logistic regression analysis. This link might justify a more cautious use of SAPT with this kind of FD; however, further dedicated studies are required. Fusiform aneurysm morphology was also unsurprisingly linked with an increased risk of the occurrence of TE. Prior studies have already demonstrated that fusiform aneurysms are at higher risk of TE.[31]

In terms of efficacy, the present study suggests comparable results between the 2 medication groups, with slightly higher RROC I occlusion rates at the latest available follow-up (80% versus 78%, respectively, in the SAPT versus DAPT group) and a similar incidence of in-stent stenosis (3% versus 4%, mild in all cases) and retreatment ($n = 2$ versus $n = 3$). The efficacy results were confirmed to be slightly higher in the SAPT group, also when considering only aneurysms that were not additionally coiled (80% versus 77%, respectively, in the SAPT versus DAPT group), because previous results are partially biased by the higher rate of adjunctive coiling in the DAPT group, which lightly augments the treatment efficacy in those patients.

The acceptance of prasugrel as the antiplatelet of choice for patients undergoing FD treatment does depend not only on the balance between thrombotic and bleeding events but also on the economic implications. Because the newer antiplatelet agents are more expensive than clopidogrel, prasugrel is likely to increase overall outpatient pharmacy expenditures. Nevertheless, data from the cardiology field suggest that prasugrel and ticagrelor are economically attractive treatment strategies as an alternative to clopidogrel because they might reduce other medical expenses.[32,33] Yet, dedicated comparative studies about the cost-effectiveness of these therapies in neurointerventions are still lacking and required.

The main limitation of this study is its retrospective and observational design, with no randomization to the respective medication groups attributed to the site standard. Furthermore, the imaging and clinical data were not analyzed by an independent core lab, and end points were evaluated by the treating interventionalists themselves, possibly leading to an intrinsic reporting bias. Another important limitation is the inconsistency of the medication conversion both in terms of timing and in terms of the drug that was given according to in-house protocols at each site. The tests used for assessing antiplatelet reactivity differed among the participating centers and included VerifyNow (Werfen), light transmission aggregometry, and Multiplate (Roche Diagnostics). Moreover, there were discrepancies in the classification of what constituted normal levels in the platelet inhibition tests, which were based on different in-house standards. Furthermore, PTA rates were significantly higher in the DAPT group, which might eventually have biased the TE complication rates.

Larger studies are required to overcome the limitation of our small sample size, which might have prevented us from reaching statistical significance showing better outcomes for the prasugrel group. Nevertheless, to date, this is the largest study to directly compare the efficacy and safety of prasugrel SAPT with conventional ASA and clopidogrel DAPT in flow diversion.

CONCLUSIONS

When comparing prasugrel SAPT with ASA and clopidogrel DAPT after FD aneurysm treatment, we found no statistically significant difference regarding the occurrence of TE. Permanently disabling TE complications and hemorrhagic complications were more frequent in the DAPT group, however, without reaching statistical significance. TE were significantly more frequent in non-surface-modified FDs in distal, small vessels regardless of the medication. Occlusion rates at the latest available follow-up were comparable between groups. We conclude that the monotherapy with prasugrel may be at least as safe and effective as DAPT with ASA and clopidogrel and could, therefore, be a valid alternative in selected patients. Further prospective comparative studies are required to validate our findings and to better determine which patient subgroups would benefit the most from SAPT.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES

1. Fiehler J, Ries T. **Prevention and treatment of thromboembolism during endovascular aneurysm therapy.** *Klin Neuroradiol* 2009;19:73–81 CrossRef Medline
2. Zhou G, Su M, Yin YL, et al. **Complications associated with the use of flow-diverting devices for cerebral aneurysms: a systematic review and meta-analysis.** *Neurosurg Focus* 2017;42:E17 CrossRef Medline
3. Al-Mufti F, Cohen ER, Amuluru K, et al. **Bailout strategies and complications associated with the use of flow-diverting stents for treating intracranial aneurysms.** *Interv Neurol* 2020;8:38–54 CrossRef Medline
4. Tonetti DA, Jankowitz BT, Gross BA. **Antiplatelet therapy in flow diversion.** *Neurosurgery* 2020;86:S47–52 CrossRef Medline
5. Lobsien D, Clajus C, Behme D, et al. **Aneurysm treatment in acute SAH with hydrophilic-coated flow diverters under single-antiplatelet therapy: a 3-center experience.** *AJNR Am J Neuroradiol* 2021;42:508–15 CrossRef Medline
6. Hellstern V, Aguilar Perez M, Henkes E, et al. **Use of a p64 MW flow diverter with hydrophilic polymer coating (HPC) and prasugrel single antiplatelet therapy for the treatment of unruptured anterior circulation aneurysms: safety data and short-term occlusion rates.** *Cardiovasc Intervent Radiol* 2022;45:1364–74 CrossRef Medline
7. Bhogal P, Petrov A, Rentsenkhu G, et al. **Early clinical experience with the p48MW HPC and p64MW HPC flow diverters in the anterior circulation aneurysm using single anti-platelet treatment.** *Interv Neuroradiol* 2022;28:266–76 CrossRef Medline
8. de Castro-Afonso LH, Nakiri GS, Abud TG, et al. **Treatment of distal unruptured intracranial aneurysms using a surface-modified flow diverter under prasugrel monotherapy: a pilot safety trial.** *J Neurointerv Surg* 2021;13:647–51 CrossRef Medline
9. Fifi JT, Brockington C, Narang J, et al. **Clopidogrel resistance is associated with thromboembolic complications in patients undergoing neurovascular stenting.** *AJNR Am J Neuroradiol* 2013;34:716–20 CrossRef Medline
10. Warlo EM, Arnesen H, Seljeflot I. **A brief review on resistance to P2Y(12) receptor antagonism in coronary artery disease.** *Thromb J* 2019;17:11 CrossRef Medline
11. Pearce S, Maingard JT, Kuan Kok H, et al. **Antiplatelet drugs for neurointerventions, Part 2: clinical applications.** *Clin Neuroradiol* 2021;31:545–58 CrossRef Medline
12. Pearce S, Maingard JT, Li K, et al. **Antiplatelet drugs for neurointerventions, Part 1: clinical pharmacology.** *Clin Neuroradiol* 2020;30:425–33 CrossRef Medline
13. Jesser J, Alberalar ND, Kizilkilic O, et al. **Safety and efficacy of the FRED Jr flow re-direction endoluminal device for intracranial aneurysms: retrospective multicenter experience with emphasis on midterm results.** *Front Neurol* 2021;12:722183 CrossRef Medline
14. Vollherbst DF, Lucking H, DuPlessis J, et al. **The FRESH study: treatment of intracranial aneurysms with the new FRED X flow diverter with antithrombotic surface treatment technology: first multicenter experience in 161 patients.** *AJNR Am J Neuroradiol* 2023;44:474–80 CrossRef Medline
15. Vollherbst DF, Cekirge HS, Saatci I, et al. **First clinical multicenter experience with the new Pipeline Vantage flow diverter.** *J Neurointerv Surg* 2023;15:63–69 CrossRef Medline
16. Mohlenbruch MA, Seker F, Ozluk E, et al. **Treatment of ruptured blister-like aneurysms with the FRED flow diverter: a multicenter experience.** *AJNR Am J Neuroradiol* 2020;41:2280–84 CrossRef Medline
17. O'Kelly CJ, Krings T, Fiorella D, et al. **A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents.** *Interv Neuroradiol* 2010;16:133–37 CrossRef Medline
18. Roy D, Milot G, Raymond J. **Endovascular treatment of unruptured aneurysms.** *Stroke* 2001;32:1998–2004 CrossRef Medline
19. Schror K. **Aspirin and platelets: the antiplatelet action of aspirin and its role in thrombosis treatment and prophylaxis.** *Semin Thromb Hemost* 1997;23:349–56 CrossRef
20. Ferreira M, Freitas-Silva M, Assis J, et al. **The emergent phenomenon of aspirin resistance: insights from genetic association studies.** *Pharmacogenomics* 2020;21:125–40 CrossRef Medline
21. Borchert RJ, Simonato D, Hickman CR, et al. **P2Y12 inhibitors for the neurointerventionalist.** *Interv Neuroradiol* 2022;28:92–103 CrossRef Medline
22. Stetler WR, Chaudhary N, Thompson BG, et al. **Prasugrel is effective and safe for neurointerventional procedures.** *J Neurointerv Surg* 2013;5:332–36 CrossRef Medline
23. Atallah E, Saad H, Bekelis K, et al. **The use of alternatives to clopidogrel in flow-diversion treatment with the Pipeline Embolization Device.** *J Neurosurg* 2018;129:1130–35 CrossRef Medline
24. Podlasek A, Al Sultan AA, Assis Z, et al. **Outcome of intracranial flow diversion according to the antiplatelet regimen used: a systematic review and meta-analysis.** *J Neurointerv Surg* 2020;12:148–55 CrossRef Medline
25. Xia P, He C, Chen L, et al. **Efficacy and safety of prasugrel therapy for intracranial aneurysms with endovascular treatment: a meta-analysis.** *J Neurol Sci* 2019;397:174–78 CrossRef Medline
26. Cagnazzo F, Perrini P, Lefevre PH, et al. **Comparison of prasugrel and clopidogrel used as antiplatelet medication for endovascular treatment of unruptured intracranial aneurysms: a meta- analysis.** *AJNR Am J Neuroradiol* 2019;40:681–86 CrossRef Medline
27. Hohenstatt S, Ulfert C, Herweh C, et al. **Acute intraprocedural thrombosis after flow diverter stent implantation: risk factors and relevance of standard observation time for early detection and management.** *Clin Neuroradiol* 2022;33:343–51 CrossRef Medline
28. Mohammaden MH, English SW, Stapleton CJ, et al. **Safety and efficacy of ticagrelor as single antiplatelet therapy in prevention of thromboembolic complications associated with the Pipeline Embolization Device (PED): multicenter experience.** *J Neurointerv Surg* 2020;12:1113–16 CrossRef Medline
29. de Castro-Afonso LH, Nakiri GS, Abud TG, et al. **Aspirin monotherapy in the treatment of distal intracranial aneurysms with a surface modified flow diverter: a pilot study.** *J Neurointerv Surg* 2021;13:336–41 CrossRef Medline
30. Cagnazzo F, Perrini P, Dargazanli C, et al. **Treatment of unruptured distal anterior circulation aneurysms with flow-diverter stents: a meta-analysis.** *AJNR Am J Neuroradiol* 2019;40:687–93 CrossRef Medline
31. Brinjikji W, Lanzino G, Cloft HJ, et al. **Risk factors for ischemic complications following Pipeline Embolization Device treatment of intracranial aneurysms: results from the IntrePED Study.** *AJNR Am J Neuroradiol* 2016;37:1673–78 CrossRef Medline
32. Mahoney EM, Wang K, Arnold SV, et al. **Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction TRITON-TIMI 38.** *Circulation* 2010;121:71–79 CrossRef Medline
33. Kim K, Lee TA, Touchette DR, et al. **Comparison of 6-month costs between oral antiplatelet agents following acute coronary syndrome.** *J Manag Care Spec Pharm* 2018;24:800–12 CrossRef Medline