Journal of Neuroradiology 46 (2019) 378–383

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original Article

Comparison of two preventive dual antiplatelet regimens for unruptured intracranial aneurysm embolization with flow diverter/disrupter: A matched-cohort study comparing Cclopidogrel with ticagrelor>

Sébastien Soize[a,b], Cédric Foussier[a], Pierre-François Manceau[a], Claude-Fabien Litré[c], Serge Backchine[d], Matthias Gawlitza[a], Laurent Pierot[a,*]

[a] Department of neuroradiology, CHU de Reims, hôpital Maison Blanche, Université Reims-Champagne Ardenne, Reims, France
[b] UNICAEN, Inserm, UMR-S 1237 physiopathology and imaging of neurological disorders, Cyceron, 14000 Caen, France
[c] Department of neurosurgery, CHU de Reims, hôpital Maison Blanche, Université Reims-Champagne Ardenne, Reims, France
[d] Department of neurology, CHU de Reims, hôpital Maison Blanche, Université Reims-Champagne Ardenne, Reims, France

ARTICLE INFO

Article history:
Available online 5 February 2019

Keywords:
Unruptured aneurysm
Flow diverter
Flow disrupter
Dual antiplatelet regimen
Clopidogrel
Ticagrelor

ABSTRACT

Purpose. – Standard dual antiplatelet therapy (DAPT) for complex aneurysms treated with flow diversion and flow disruption is acetylsalicylic acid (ASA) plus clopidogrel. However, clopidogrel resistance frequently occurs and can lead to thromboembolic events. Ticagrelor is an alternative not requiring platelet inhibition testing. We compared two DAPT regimens (ASA with clopidogrel or ticagrelor) on morbi-mortality, safety and efficacy of unruptured aneurysm embolization with flow diverter/disrupter.
Materials and methods. – This retrospective analysis of a 1:1 matched cohort compares patients treated with ASA + clopidogrel (March 2013–December 2015) vs. ASA + ticagrelor (January 2016–March 2017). No platelet inhibition testing was conducted. Patients matched for age (±10 years), type of treatment and aneurysm sac size (±2 mm). Primary outcome measures were morbidity and mortality at 1-month; secondary outcomes were thromboembolic and hemorrhagic complications [on angiography and magnetic resonance imaging (MRI)] and groin complications. Outcomes were compared using bivariate analyses.
Results. – Ninety patients fulfilled inclusion criteria, of which 80 remained after matching (40 per group). There was no statistical difference in 1-month morbidity between the ticagrelor and clopidogrel groups (2.5% vs. 10%, $P = 0.36$) and no deaths reported. We observed no significant differences between ticagrelor and clopidogrel groups in terms of angiographic thromboembolic complications (5% vs. 12.5%, $P = 0.43$), territorial infarction on DWI (2.5% vs. 7.5%, $P = 0.61$), angiographic (0% vs. 0%, $P = 1$) and MRI (5% vs 5%, $P = 1$) hemorrhagic complications, new microbleeds (57.5% vs. 40%, $P = 0.12$) and groin puncture complications (2.5% vs. 0%, $P = 1$). At three months, there was no delayed territorial infarction or hemorrhage in either group.
Conclusions. – Ticagrelor is safe and effective in replacing clopidogrel as DAPT for unruptured aneurysms.

Introduction

Endovascular treatment (EVT) is the first line treatment in the majority of patients suffering from ruptured and unruptured cerebral aneurysms [1–3]. Improved endovascular techniques such as balloon-assisted coiling, stent-assisted coiling (SAC) and more recently flow diversion and flow disruption have facilitated treatment of an increased number of aneurysms including complex aneurysms with unfavorable anatomy [4,5]. Additionally, flow diversion help to reduce the rate of aneurysm recurrence, which remains the primary weakness of endovascular EVT [4]. Intraoperative rupture and thromboembolic events (TE) are the main concerns during EVT because of potential disastrous outcomes. To prevent thromboembolism, some EVT techniques (SAC and flow diversion) are performed under dual antiplatelet therapy (DAPT). By extension, the treatment of complex wide-neck bifurcation aneurysms by flow disruption often occurs under DAPT [5].

* Corresponding author at: Department of neuroradiology, hôpital Maison Blanche, 45, rue Cognacq-Jay, 51092 Reims, France.
E-mail address: lpierot@gmail.com (L. Pierot).

https://doi.org/10.1016/j.neurad.2019.01.094
0150-9861/

Acetylsalicylic acid (ASA) plus clopidogrel is the DAPT of reference used for preventing thrombosis in such procedures [5–7].However, unlike ASA resistance which seems relatively uncommon, clopidogrel resistance occurs frequently (28 to 66%) [8] and is known to induce additional thromboembolic complications [8,9]. Evaluating the biological activity of this medication in vivo is complex and unreliable, and no standardized platelet function test exists. Furthermore, major bleeds are more common with double-dose than with standard-dose of clopidogrel [10,11]. Consequently, the benefit of assessing clopidogrel resistance remains unclear and increases time and burden of care [12,13], and, as a result, other P2Y12 inhibitors (e.g., ticagrelor and prasugrel) which are less subject to resistance are usually indicated in patients with acute coronary syndrome [10,11]. The above data has led some clinicians to explore the usefulness of ticagrelor for neurointerventional procedures [10,11,14]. In contrast to clopidogrel, ticagrelor produces greater platelet inhibition, has faster onset action and exhibits fewer inter-individual variations with respect to drug side effects [14].

Currently, little data regarding safety and efficacy of ticagrelor in neurointerventional procedures is available [15,16] and only one study compared ticagrelor with clopidogrel in patients treated with flow diverters [15] One major concern with ticagrelor remains its safety, especially in regard to the PLATO trial results, which compared ticagrelor to clopidogrel in acute coronary syndrome settings and found a significantly increased risk of intracranial hemorrhage in patients receiving ticagrelor [11]. In our institution, patients were treated with ASA plus clopidogrel without systematic testing for resistance up to December 2015. At that point, we switched from clopidogrel to ticagrelor in order to avoid the issue of clopidogrel resistance testing. The present study compares the impact of two DAPT (ASA + clopidogrel vs. ASA + ticagrelor) on the morbidity, mortality, safety (hemorrhagic complications) and efficacy (prevention of thromboembolism) of unruptured aneurysm embolization with flow diverter/disrupter.

Materials and methods

Study setting

This retrospective study analyzed our institution's prospectively collected registry of consecutive patients treated by endovascular means of intracranial aneurysms. In line with French law, ethics committee approval is waived for retrospective studies. The manuscript follows reporting guidelines (STROBE) for observational study reports [17]. For the purpose of this study, we included patients who fulfilled the following inclusion criteria:

- unruptured intracranial aneurysm treated by embolization between March 2013 and March 2017;
- embolization realized with a flow diverter or flow disrupter and;
- 24–48 hour MRI follow-up. Patients were dichotomized according to antiplatelet regimen: ASA + clopidogrel (Group 1: March 2013 to December 2015) and ASA + ticagrelor (Group 2: January 2016 to March 2017).

Patients of both groups were matched for age (±10 years), type of treatment (intrasaccular or intravascular) and aneurysm sac size (±2 mm), creating a 1:1 matched cohort.

Antiplatelet therapy

During the study period, patients treated for unruptured aneurysms with flow diverter and flow disrupters received loading of DAPT over 5 days (clopidogrel) and 2 days (ticagrelor) before embolization. From March 2013 to October 2015, patients received 75 mg of ASA + once per day 75 mg of clopidogrel (Group 1); between November 2015 and March 2017, patients received 75 mg ASA + 90 mg of ticagrelor twice per day (Group 2). Both groups received heparin bolus of 50 IU/kg followed by a heparin perfusion at 600 IU/kg/day in the perioperative period. Both groups received DAPT over the next 3 months. Importantly, no patient underwent clopidogrel resistance testing because it was not part of the institutional protocol at that time. Consequently, there was no selection for clopidogrel responsiveness in either group.

Primary outcome measures were morbidity and mortality. Morbidity at 1 month was defined as any worsening of the modified Rankin Scale (mRS) compared to pre-therapeutic mRS. Secondary outcome measures were thromboembolic complications (per-procedure and on 24–48 hour follow-up MRI), hemorrhagic complications (per-procedure and on 24–48 hour follow-up MRI) and groin puncture hemorrhagic complications (hematoma >2 cm or false aneurysm, with or without need for a treatment (transfusion, surgery or ultrasound-guided compression).

Endovascular treatment

All patients eligible for endovascular aneurysmal treatment were discussed in a multidisciplinary meeting (neurosurgeons, neurologists and neuroradiologists) to determine the safest and most effective treatment method. Treatments were performed with a biplane angiographic system (Axiom Artis, Siemens, Erlangen, Germany). After transfemoral access, a triaxial system reached the targeted aneurysm. Intrasaccular treatment was completed with the Woven EndoBridge (WEB device, Sequent Medical/Microvention, Tustin, CA, USA) flow disruption device, and intravascular treatment with two different flow diverters: the Pipeline Embolization Device: (PED), (Covidien, Irvine, CA, USA), or the Flow Re-Direction Endoluminal Device (FRED), (MicroVention, Tustin, CA, USA). Vascular closing systems were used in all procedures (Angioseal or Femoseal Systems, St Jude Medical, St. Paul, MN, USA).

Recorded data

Baseline patient characteristics (sex, age and pretreatment mRS), the aneurysm status (first treatment or remnant) and aneurysms characteristics (location, maximum sac diameter and neck size) were collected. Aneurysm location was categorized as follows: supraclinoid internal carotid artery (ICA), cavernous ICA, anterior cerebral artery (ACA) or anterior communicating artery (ACom), middle cerebral artery (MCA) and basilar artery (BA). Treatment types were also recorded and dichotomized into intrasaccular device (flow disrupter) or intravascular device (flow diverter).

We recorded all complications occurring during aneurysm treatment and hospital stay. During treatment we also recorded thromboembolic events (i.e., clot visible on angiography), aneurysm rupture and vessel dissection. After treatment, we observed hemorrhagic complications at puncture site and any ischemic or hemorrhagic complication on MRI realized 24–48 hours after treatment (see "image analysis" for description). At 1-month post-treatment, the treating physician evaluated neurological outcome using the mRS. Finally, at 3-months post-treatment, patients underwent another MRI examination and clopidogrel or ticagrelor was stopped. Any new ischemic or hemorrhagic complication at 3-months was recorded and classified according to their clinical impact (silent or symptomatic). Also, parent vessel patency was evaluated. Then, in absence of ischemic event or vessel stenosis/thrombosis, clopidogrel or ticagrelor was stopped and ASA was pursued for 1-year post-treatment.

Image analysis

All follow-up examinations were performed on a 3-Tesla MR Unit (Achieva, Philips Healthcare, Best, The Netherlands or Skyra, Siemens, Erlangen, Germany) with a protocol including at least diffusion weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR) T2* and time-of-flight (TOF)-MRA sequences. Gadolinium-enhanced sequences were optional. An independent analysis of the post-treatment DWI and T2* maps was performed by two neuroradiologists (3 and 6-years' experience, respectively) separately and blinded to patient characteristics and treatment strategies. Readers determined if there was a territorial infarction, defined as a DWI positive lesion > 15 mm diameter according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria, as well as the presence and number of small DWI(+) lesions, hereafter defined as a high signal intensity lesion of ≤ 15 mm diameter [18]. Patients were categorized in two groups according to the number of small DWI(+) lesions: either 0 to 5 lesions or > 6 DWI(+) lesions [19].

Additionally, readers noted any major hemorrhagic complication, defined by the appearance of a subarachnoid hemorrhage or a parenchymal hematoma on FLAIR and/or T2* sequences. The appearance of minor hemorrhage (microbleeds) and their burden were also reported. Microbleeds were defined as small areas (≤ 10 mm) of signal void on T2* sequence with associated blooming [20]. All available MR sequences were analyzed to exclude potential microbleeds mimics (vascular structures, thrombus, calcifications, iron deposits, cavernous malformation or hemorrhagic metastases). Almost all patients (36/40 for Group 1 and 36/40 for Group 2) had a recent pre-therapeutic MRI to rule out pre-existing ischemia or hemorrhage. Disagreements were solved by a third reader (9 years of experience).

Statistical analyses

Inter-reader agreement for detection of territorial infarction, small artery infarction, > 6 DWI(+) lesions and major and minor hemorrhagic complications were assessed using Cohen's kappa coefficient (κ). Inter-reader agreement for counting small artery infarction (DWI + lesions) and microbleeds burden were assessed using intra-class correlation coefficients (ICC) and their 95% confidence intervals (CI). Distribution normality was assessed with the Kolmogorv-Smirnov test. Continuous variables were described as median and interquartile range and categorical variables as proportions. Bivariate comparisons of primary and secondary outcome measures between Groups 1 and 2 were tested using χ^2 tests for categorical variables (Fisher's exact test was used when the expected cell frequency was < 5), Student's *t*-test for continuous variables and Mann–Whitney U-test for ordinal variables and continuous variables that had skewed distributions. As flow diverters and flow disrupters have different mechanism of action, we also conducted a sub-group analysis according to the treatment type. All statistical tests were 2-sided and $P < 0.05$ was considered statistically significant. Analyses were performed using Medcalc software (Release 18.2, Ostend, Belgium).

Results

Patients

We treated 354 intracranial aneurysms with 167 unruptured aneurysms and 197 ruptured aneurysms during the study period. Ninety patients fulfilled the inclusion criteria (45 in each group). After matching age, type of treatment and aneurysm sac size, 80 patients (40 in each group) were included in the final 1:1 matched cohort. In the cohort, 46 patients (57.5%) were treated with a flow disrupter and 34 (42.5%) with a flow diverter. Baseline characteristics did not differ between groups (Table 1).

Table 1
Patients and aneurysms baseline characteristics.

	Clopidogrel ($n = 40$)	Ticagrelor ($n = 40$)	*P*-value
Demographics			
Female	30 (75.0%)	26 (65.0%)	.33
Age (years)	56 (47–61)	54.5 (44–61)	.67
Aneurysms			
Aneurysm remnant	7 (17.5%)	7 (17.5%)	.99
Size (max. diameter, mm)	6.5 (5.0–9.5)	6.5 (5.0–7.9)	.39
Neck (mm)	5.0 (4.0–5.5)	4.0 (3 .5–5.0)	.21
Location			
Supraclinoidal ICA	14 (35.0%)	13 (32.5%)	.81
Cavernous ICA	3 (7.5%)	2 (5.0%)	.99
ACA/ACom	6 (15.0%)	6 (15.0%)	.99
MCA	12 (30.0%)	14 (35.0%)	.63
BA	5 (12.5%)	5 (12.5%)	.99
Treatment type			
Flow-diverter	17 (42.5%)	17 (42.5%)	.99
Flow-disrupter	23 (57.5%)	23 (57.5%)	.99

Continuous variables are described as median and interquartile range and categorical variables as number and percentage. ICA: internal carotid artery; ACA: anterior communicating artery; ACom: anterior communicating artery; MCA: middle cerebral artery; BA: basilar artery.

Inter-reader agreements

Inter-reader agreement for the detection of territorial infarction [K (95% CI) = 1 (1–1)], small DWI (+) lesion > 6 [K (95% CI) = 0.83 (0.71–0.95)], major [K (95% CI) = 1 (1–1)] and minor hemorrhagic complications [K (95% CI) = 0.82 (0.68–0.96)] was excellent.

Inter-reader agreement for counting small DWI (+) lesions [ICC (95% CI) = 0.97 (0.96–0.98)] and microbleeds burden [ICC (95% CI) = 0.86 (0.79–0.91)] was also excellent.

Primary outcome measures (morbidity and mortality)

At 1 month, morbidity was 1/40 patients (2.5%) with ticagrelor, and 4/40 patients (10%) with clopidogrel (not tested for responsiveness), without statistically significant difference ($P = 0.36$). Complications in the clopidogrel group were 2 parenchymal hematomas (mRS 1 and 4 at 1 month), 1 territorial infarction (mRS 3) and 1 patient with 27 small DWI(+) lesions (mRS 1). The single complication in the ticagrelor group was a territorial infarction (mRS 2). Mortality was zero in both groups ($P = 1$). Consequently, combined morbi-mortality was 2.5% vs. 10% ($P = 0.36$). Comparisons between primary and secondary outcome measures are detailed in Table 2.

Secondary outcome measures

Thromboembolic complications

During the procedure, thromboembolic complications (any visible clot) occurred in 2/40 patients (5%) with ticagrelor and 5/40 patients (12.5%) with clopidogrel ($P = 0.43$). Post-procedure, early MRI imaging showed territorial infarction on DWI in 1/40 (2.5%) patients with ticagrelor and 3/40 (7.5%) patients with clopidogrel ($P = 0.61$). In contrast, patients with >6 small DWI lesions were more frequent with ticagrelor than with clopidogrel (20/40 patients (50%) vs. 10/40 patients (25%), $P = 0.02$).

Hemorrhagic complications

During the procedure, no hemorrhagic complication (sac perforation, dissection) was observed in both groups. However,

Table 2
Comparison of safety and efficacy of dual antiplatelet therapy with clopidogrel or ticagrelor.

	Clopidogrel ($n=40$)	Ticagrelor ($n=40$)	*P*-value
1-month morbidity and mortality			
Mortality	0 (0.0%)	0 (0.0%)	1
Morbidity	4 (10%)	1 (2.5%)	.36
Thrombo-embolic complications			
Per-procedure[a]	5 (12.5%)	2 (5.0%)	.43
Territorial infarction[b]	3 (7.5%)	1 (2.5%)	.61
>6 DWI(+) lesions[b]	10 (25%)	20 (50%)	.02
Hemorragic complications			
Per-procedure[a]	0 (0.0%)	0 (0.0%)	1
Major bleeding (SHA or PH)[b]	2 (5.0%)	2 (5.0%)	1
Patients with new microbleed(s)[b]	16 (40%)	23 (57.5%)	.12
Number of new microbleed(s)[b]	1 (0–2)	2 (1–2)	.01
Groin puncture complication	0 (0%)	1 (2.5%)	1

Note: Continuous variables are described as median and interquartile range and categorical variables as number and percentage.
DWI: diffusion weighted imaging; SHA: subarachnoid hemorrhage; PH: parenchymal hematoma.
[a] Seen on angiography.
[b] Seen on 24–48 hours follow-up MRI.

post-procedural MRI imaging showed major hemorrhagic complications in 2/40 (5%) patients given ticagrelor and 2/40 (5%) patients given clopidogrel ($P=1$). These complications involved two limited subarachnoid hemorrhages in the cistern surrounding the aneurysm dome in patients treated with flow disruptors (1 in each group) and two parenchymal hematomas (1 in each group), one at the aneurysm site probably because of sac perforation undetected during the procedure and one probably related to distal vessel perforation caused by microwire manipulations. Interestingly, early MRI revealed that patients under ticagrelor seemed to develop more microbleeds. Indeed, the appearance of at least one microbleed was observed in 23/40 (57.5%) patients given ticagrelor and 16/40 (40%) patients given clopidogrel ($P=0.12$). The burden of microbleeds was also higher with ticagrelor than clopidogrel [2 (1–2) vs. 1 (0–2), $P=0.01$].

Groin puncture complications

Groin complications occurred in 1/40 (2.5%) patients given ticagrelor and 0/40 (0%) given clopidogrel ($P=1$). The complication corresponded to a false aneurysm closed by surgery in a patient given ticagrelor. Additionally, we observed hematomas <2 cm diameter without active bleeding in 2 patient given clopidogrel.

Delayed ischemic and hemorrhagic complications (at 3-months)

At 3-months MRI follow-up, there was no territorial infarction and no major bleeding in both groups [0 (0%) vs. 0 (0%), $P=1$, respectively]. There was no difference in terms of patients with new microbleeds [9 (22.5%) vs. 16 (40%), $P=0.15$] and patients with >6 small DWI (+) lesions (1 (2.5%) vs. 0 (0%), $P=1$) between Ticagrelor and Clopidogrel groups. Also, no stenosis or occlusion of parent vessels was noted in either group.

Analysis by type of treatment

In the subgroups of patients treated with flow-diverters and flow-disrupters, there was no statistical differences in terms of per-procedure thromboembolic and hemorrhagic complications, ischemic and hemorrhagic complications on 24–48 h MRI follow-up, morbidity and mortality at 1-months (Table 3).

Discussion

The development of advanced techniques has ushered in a new aneurysm treatment era. However, SAC and flow diversion carries an increased risk of thromboembolic complications which lead to the routine use of DAPT [7,8,12–21]. Although not mandatory, patients treated with flow disruptors are also treated with DAPT as a precaution [22–24] DAPT may also be useful when flow disruption requires the use of a stent (device protrusion) or is replaced by SAC (technical failure). ASA plus clopidogrel is the standard DAPT for such procedures; [4–9,12,13,21–24] however, platelet function testing to detect clopidogrel resistance remains debatable [12,13]. A number of alternate antiplatelet agents - most frequently involving ticagrelor for neurovascular field- have become available, with theoretical advantages when compared to clopidogrel in regard to bioavailability and consistency of antiplatelet effects. Little data is available in the neurovascular literature to support the use of one agent over another. As ticagrelor reaches greater platelet inhibition compared with clopidogrel, one major concern is its safety for neurointerventional procedures. Our study found no difference in terms of morbidity and mortality between patients under DAPT with ticagrelor or clopidogrel. Still, although not significant, some differences cannot be underestimated. Indeed, morbidity looked lower with ticagrelor (2.5%) compared to clopidogrel (10%). This result was sustained in flow-diverter and also flow-disrupter subgroups. We also did not find any statistical difference in terms of major hemorrhagic complications (aneurysm rupture, subarachnoid hemorrhage and parenchymal hematoma) between patients under clopidogrel or ticagrelor. These results are reassuring regarding the safety of ticagrelor for neurointerventional procedures and

Table 3
Analysis by type of treatment.

	Flow-disrupters			Flow-diverters		
	Clopidogrel ($n=23$)	Ticagrelor ($n=23$)	*P*-value	Clopidogrel ($n=17$)	Ticagrelor ($n=17$)	*P*-value
Thromboembolic complications						
Per-procedure[a]	1 (4.3%)	1(4.3%)	1	4 (23.5%)	1 (5.9%)	0.33
Territorial infarction[b]	0 (0%)	2 (8.6%)	0.49	1 (5.9%)	1 (5.9%)	1
>6 DWI(+) lesions[b]	8 (34.7%)	2 (8.6%)	0.07	8 (47.1%)	12 (70.6%)	0.30
Hemorragic complications						
Per-procedure[a]	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	1
Major bleeding (SHA or PH)[b]	0 (0%)	1 (4.3%)	1	1 (5.9%)	2 (11.8%)	1
Patients with new microbleed(s)[b]	13 (56.5%)	6 (26.1%)	0.07	10 (58.8%)	10 (58.8%)	1
Number of new microbleed(s)[b]	0 (0-0)	0 (0-1)	0.42	0 (0-1)	1 (0-1)	0.33
Groin puncture complication	0 (0%)	1 (4.3%)	1	0 (0%)	0 (0%)	1
Morbidity at 1 month	1 (4.3%)	0 (0%)	1	3 (17.6%)	1 (5.9%)	0.60
Mortality at 1 month	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	1

Note: Continuous variables are described as median and interquartile range and categorical variables as number and percentage.
DWI: diffusion weighted imaging; SHA: subarachnoid hemorrhage; PH: parenchymal hematoma.
[a] Seen on angiography.
[b] Seen on 24–48 hours follow-up MRI.

are in line with previous series [15,16]. In addition, it is important to remind that in case of sac perforation during the procedure, the use of platelet transfusion can reverse the effects of clopidogrel but not of ticagrelor [25,26]. However, this disadvantage may be not for long as recent pre-clinical studies demonstrated the efficacy of specific ticagrelor antidote [27,28].

Interestingly, we found that patients receiving ticagrelor were prone to a higher burden of new microbleeds (on 24–48 hour follow-up MRI) compared to patients under clopidogrel ($P = 0.01$). This finding may be important and needs further exploration. Indeed, even if microbleeds are most often asymptomatic, they may, at times, cause neurological deficit and increase the risk of hemorrhagic stroke, death and cognitive impairment [29]. Previous studies have shown that the use of platelet aggregation inhibitors is related to the presence of cerebral microbleeds [30] and that the appearance of cerebral microbleeds after neurointerventional procedures for acute ischemic stroke has been reported in around 20% of patients [31]. Our study found new microbleeds in 57.5% of patients given ticagrelor and 40% of patients given clopidogrel ($P = 0.12$). However, the number of new microbleeds per patient was very low and may be asymptomatic (median of 2 microbleeds for patients under ticagrelor and median of 1 under clopidogrel).

Another concern is the efficacy of DAPT in preventing thromboembolic complications. In line with another study comparing ticagrelor with clopidogrel, [15] we found no difference in terms of thromboembolic complications (either on angiography or MRI). Despite non-significant results, per-procedure thromboembolic events appeared to be lower with ticagrelor (5%) than clopidogrel (12.5%). This difference may be accounted for by the absence of platelet function testing in our series. Indeed, Moore et al. found thromboembolic complications in 4.2% of patients given ticagrelor (patients tested as non-responders to clopidogrel) and 6% given clopidogrel (patients tested as responders to clopidogrel) [15]. Moore et al. compared the safety and efficacy of DAPT with ticagrelor versus clopidogrel in the best possible conditions for clopidogrel efficacy (patients selected according to clopidogrel level of resistance), whereas our evaluation was done with the worst possible conditions (clopidogrel resistance was not evaluated). Our study, as well as that of Moore et al, was undoubtedly underpowered due to the low patient numbers, limiting our ability to identify and draw conclusions of any differences between groups. However, the incidence of thromboembolic events reported in these two studies may help determine appropriate sample sizes for future prospective trials. Indeed, with a thromboembolic complication difference between 2.2% (tested patients) and 7.5% (untested patients), the number of subjects necessary to detect a significant difference with ticagrelor will require sample sizes of 100 (for untested patient) and 1100 (for tested patient), assuming a type I error (α) of 0.05 and a type II error (β) of 0.20. Regardless, no significance difference in terms of safety and efficacy between DAPT with ticagrelor or clopidogrel exists. Consequently, with systematic platelet function testing prior to embolization, ticagrelor is a suitable alternative for patients hyporesponsive to clopidogrel. Nonetheless, in institutions where platelet function testing cannot be done routinely, the most pragmatic and safe option is to use ticagrelor instead of clopidogrel.

Approximately 50% of patients experience small DWI(+) lesions after embolization, [32] which is consistent with our results. Surprisingly, we observed a higher proportion of patients who had >6 small DWI(+) lesions under ticagrelor compared to clopidogrel (50% vs. 25%, $P = 0.02$). Because this result is likely related to a variety of non-identifiable operating conditions when collecting data, it is difficult to offer a clear explanation to this difference.

Currently, DAPT for complex embolization of unruptured aneurysms is no more limited to clopidogrel. Ticagrelor, which directly and reversibly antagonizes ADP binding to the P2Y12 receptor, appears to be as safe and efficacious as clopidogrel. Also, according to Sedat et al., prasugrel seems to be a safe alternative to clopidogrel for coiling and stenting procedures and can potentially decrease the clinical consequences of intraoperative and postoperative thromboembolic complications without increasing the rate of hemorrhagic events [33].

Our study has several limitations. First, the study's retrospective nature and small sample size reveals inherent biases related to such design, which we attempted to reduce by using a 1:1 matching-cohort design. Notably, we matched patients according to their type of treatment to ensure not comparing flow-diverters with flow-disrupters as they have very different devices with different rates of ischemic complications. Additionally, we performed a subgroup analysis according to types of treatment. Second, our procedures were completed under determined heparin doses; therefore, extrapolation of findings from our population to other heparin regimens may be limited. Larger studies are needed to confirm the clinical utility of ticagrelor in neurointerventions. Third, neither procedure length nor mean arterial pressure during the procedures was reported, which potentially could have been confounding variables. Fourth, as we do not test platelet resistance, we could not stratify patients given clopidogrel according to responsiveness level; however, as shown above, such conditions may have required a very large number of patients. Finally, taking ticagrelor twice a day may theoretically reduce its compliance compared to clopidogrel; yet, its rapid action mechanism provides a shorter loading delay (2 days vs. 5 days) that may compensate for this weakness.

Conclusion

Ticagrelor appears to be safe and effective in replacing clopidogrel in DAPT settings for unruptured aneurysms. Future randomized controlled trials comparing ticagrelor and clopidogrel would be ethically and clinically sound.

Funding

None

Disclosure of interest

LP consults for Microvention-Terumo, Balt, Penumbra and Neuravi-Cerenovus.

The other authors declare that they have no competing interest.

Acknowledgement

This work was supported by grants from French Society for Childhood Cancer (SFCE), the Federative Research Structure No. 1 (SFR1) and the Hospital Clinical Research Program (PHRC) of France, the Vietnamese ministry of education and training. We acknowledge the support of the MRI facility UMS IRMaGe of Grenoble, and the precious help of Mr. Patrice Jousse† for artwork.

References

[1] Molyneux AJ, Kerr RSC, Yu L-M, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809–17.

[2] Cognard C, Pierot L, Anxionnat R, et al. Clarity Study Group. Results of embolization used as the first treatment choice in a consecutive nonselected population of ruptured aneurysms: clinical results of the Clarity GDC study. Neurosurgery 2011;69:837–41.

[3] Pierot L, Spelle L, Vitry F. ATENA Investigators. Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach: results of the ATENA study. Stroke 2008;39:2497–504.
[4] Pierot L, Biondi A. Endovascular techniques for the management of wide-neck intracranial bifurcation aneurysms: a critical review of the literature. J Neuroradiol 2016;43:167–75.
[5] Pierot L, Wakhloo AK. Endovascular treatment of intracranial aneurysms: current status. Stroke 2013;44:2046–54.
[6] Soize S, Gawlitza M, Pierot L. Complications du traitement endovasculaire des anévrismes cérébraux : incidences, analyses en sous-groupes et facteurs de risques issus de l'étude ARETA. J Neuroradiol 2018;45:70.
[7] Faught RWF, Satti SR, Hurst RW, et al. Heterogeneous practice patterns regarding antiplatelet medications for neuroendovascular stenting in the USA: a multicenter survey. J Neurointerv Surg 2014;6:774–9.
[8] 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.
[9] Tan LA, Keigher KM, Munich SA, et al. Thromboembolic complications with Pipeline Embolization Device placement: impact of procedure time, number of stents and pre-procedure P2Y12 reaction unit (PRU) value. J NeuroInterv Surg 2015;7:217–21.
[10] Mehta SR, Tanguay J-F, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233–43.
[11] Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory Effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATelet inhibition and patient outcomes) PLATELET substudy. J Am Coll Cardiol 2010;56:1456–62.
[12] Nordeen JD, Patel AV, Darracott RM, et al. Clopidogrel resistance by P2Y12 platelet function testing in patients undergoing neuroendovascular procedures: incidence of ischemic and hemorrhagic complications., clopidogrel resistance by P2Y12 platelet function testing in patients undergoing neuroendovascular procedures: incidence of ischemic and hemorrhagic complications. J Vasc Interv Neurol 2013;6(26):26–34.
[13] Skukalek SL, Winkler AM, Kang J, et al. Effect of antiplatelet therapy and platelet function testing on hemorrhagic and thrombotic complications in patients with cerebral aneurysms treated with the pipeline embolization device: a review and meta-analysis. J Neurointerv Surg 2016;8:58–65.
[14] Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009;361:1045–57.
[15] Moore JM, Adeeb N, Shallwani H, et al. A multicenter cohort comparison study of the safety, efficacy, and cost of ticagrelor compared to clopidogrel in aneurysm flow diverter procedures. Neurosurgery 2017;81:665–71.
[16] Narata AP, Amelot A, Bibi R, et al. Dual antiplatelet therapy combining aspirin and ticagrelor for intracranial stenting procedures: a retrospective single center study of 154 consecutive patients with unruptured aneurysms. Neurosurgery 2018.
[17] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
[18] Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
[19] Kang D-H, Kim BM, Kim DJ, et al. MR-DWI-positive lesions and symptomatic ischemic complications after coiling of unruptured intracranial aneurysms. Stroke 2013;44:789–91.
[20] Gregoire SM, Chaudhary UJ, Brown MM, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology 2009;73:1759–66.
[21] Pierot L, Spelle L, Berge J, et al. Feasibility, complications, morbidity, and mortality results at 6 months for aneurysm treatment with the flow re-direction endoluminal device: report of SAFE study. J Neurointerv Surg 2018;10:765–70, http://dx.doi.org/10.1136/neurintsurg-2017-013559 [Epub 2018 Jan 19].
[22] Pierot L, Moret J, Barreau X, et al. Safety and efficacy of aneurysm treatment with WEB in the cumulative population of three prospective, multicenter series. J Neurointerv Surg 2018;10:553–9.
[23] Gawlitza M, Soize S, Januel AC, et al. Treatment of recurrent aneurysms using the Woven EndoBridge (WEB): anatomical and clinical results. J Neurointerv Surg 2018;10:629–33.
[24] Pierot L, Gubucz I, Buhk JH, et al. Safety and efficacy of aneurysm treatment with the WEB: results of the WEBCAST 2 study. AJNR Am J Neuroradiol 2017;38:1151–5.
[25] Godier A, Taylor G, Gaussem P. Inefficacy of platelet transfusion to reverse ticagrelor. N Engl J Med 2015;372:196–7.
[26] Teng R, Carlson GF, Nylander S, Andersson TL. Effects of autologous platelet transfusion on platelet inhibition in ticagrelor-treated and clopidogrel-treated subjects. J Thromb Haemost 2016;14:2342–52.
[27] Buchanan A, Newton P, Pehrsson S, et al. Structural and functional characterization of a specific antidote for ticagrelor. Blood 2015;125:3484–90.
[28] Pehrsson S, Johansson KJ, Janefeldt A, et al. Hemostatic effects of the ticagrelor antidote MEDI2452 in pigs treated with ticagrelor on a background of aspirin. J Thromb Haemost 2017;15:1213–22.
[29] Charidimou A, Shams S, Romero JR, et al. Clinical significance of cerebral microbleeds on MRI: a comprehensive meta-analysis of risk of intracerebral hemorrhage, ischemic stroke, mortality, and dementia in cohort studies (v1). Int J Stroke 2018;13:454–68.
[30] Vernooij MW, Haag MDM, van der Lugt A, et al. Use of antithrombotic drugs and the presence of cerebral microbleeds: the Rotterdam Scan Study. Arch Neurol 2009;66:714–20.
[31] Shi Z-S, Duckwiler GR, Jahan R, et al. New Cerebral Microbleeds After Mechanical Thrombectomy for Large-Vessel Occlusion Strokes. Medicine (Baltimore) 2015;94:e2180.
[32] Bond KM, Brinjikji W, Murad MH, et al. Diffusion-weighted imaging-detected ischemic lesions following endovascular treatment of cerebral aneurysms: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2017;38:304–9.
[33] Sedat J, Chau Y, Gaudart J, et al. Prasugrel versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. Interv Neuroradiol 2017;23:52–9.