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Dual Antiplatelet Therapy Regimens and Duration for Intracranial Stenting Procedures: Literature Review

Suggested Protocol for Neuro-interventional Procedure in Lithuania

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Abstract. *Objectives of the study.* Our aim was to analyse different antithrombotic drug regimens and duration in intracranial stenting procedures (stent assisted coiling, flow diverter) for unruptured aneurysms and based on the literature review from 2017–2023 to implement dual antiplatelet therapy algorithm for neuro-interventional procedures in Lithuania. *Research methods and methodology.* A comprehensive literature search of PubMed, BioMed Central, BMJ Journals, EBSCO Publishing, SAGE Journals Online, ScienceDirect, SpringerLink was conducted by two independent readers (MP, GŠ) for studies published from January 2017 to April 2023. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. 23 studies: 6 retrospective cohort, 11 retrospective case-control, 1 prospective cohort, 1 prospective randomized-control, 1 systemic literature review, 3 metanalysis observational studies were identified. *Results and conclusions.* We found widespread variation in practices even among the same country centres, lending credence to the importance of a future prospective studies of dual antiplatelet drug therapy (DAPT) regimens and duration for the purpose of deriving optimal methods and streamlining tactics. Our suggested algorithm for DAPT in neuro-interventional procedures in Lithuania is provided in Graph 1.

Key words: antiplatelet therapy, aspirin, clopidogrel, dual antiplatelet therapy, flow diverter, pipeline embolization device, prasugrel, PRU – P2Y212 reaction units, stent-assisted coiling, ticagrelol, unruptured aneurysms.

Introduction

Endovascular stent – assisted coiling embolization (SACE) or flow diverter (FD) embolization is regarded an effective treatment method for unruptured intracranial aneurysms (UIAs) [1]. FD has been shown to be safe and effective in a number of studies, with a positive safety and efficacy profile in terms of procedure-related complications and aneurysm occlusion rates across different types of aneurysm [2]. The 2.82% risk of thromboembolism during endovascular repair, which can lead to stent occlusion, can be reduced by using antiplatelet (AP) drugs, which work by preventing platelets from aggregating and forming thrombi in the arterial circulation. Aspirin (ASA) and P2Y12 antagonists (clopidogrel (CP), prasugrel (PS), and ticagrelor (TS)) are the discussed examples of AP drugs. There are a number of large-scale randomized control trials on the use of APs after cardiovascular procedures, but for neuro-interventional procedures, there is less data and no established consensus. DAPT consisting of ASA and CP is the most widely used AP regimen [3]. To become effective, CP must first be converted from a prodrug by the hepatic cytochrome enzyme CYP2C19.

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The effectiveness of medications may be affected by genetic variations in this enzyme or by interactions between different medications. Whilst ASA resistance appears to be 2.1–13.5%, CP resistance is 28–66% and is associated with an increase in thromboembolic events: stent thrombosis, brain ischemia [4]. Since PS and TC are just as effective without this enzyme, there is less individual variation in their dosages. The danger of haemorrhage is another problem associated with AP use, and it can be fatal. Therefore, AP treatments must strike a compromise between avoiding thromboembolic (TE) events associated with FD stents and increasing the risk of bleeding [5].

Results

Table 1 (in page 134) provides a synopsis of the research done between 2017 and 2023 on the optimal AP drug regimen and duration in neuro-interventional radiology.

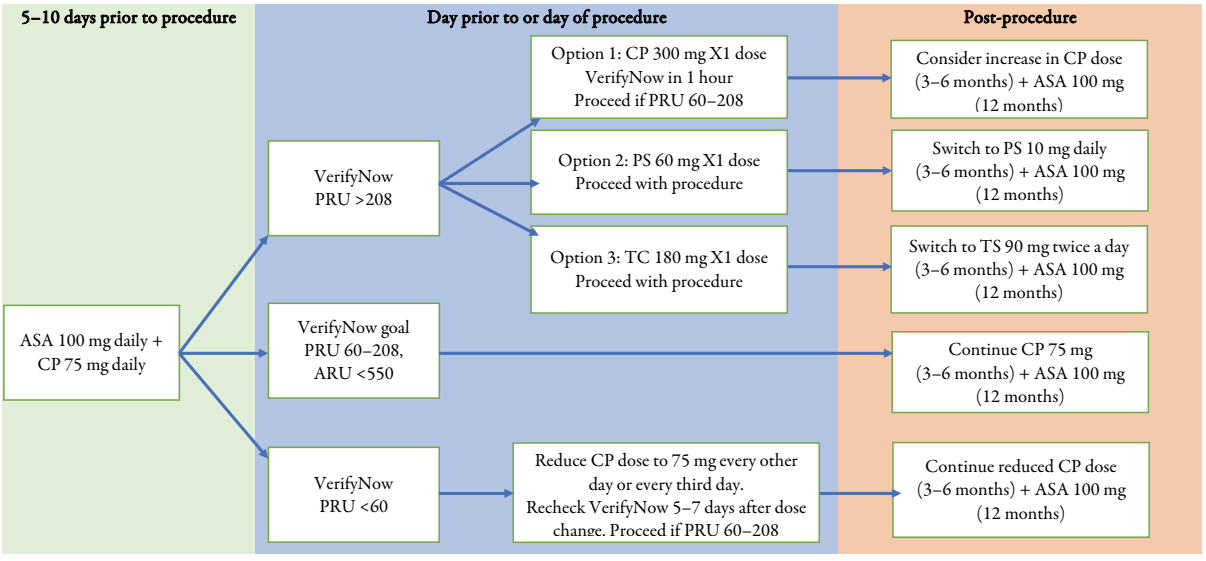
Discussion

We find widespread variation in practices even among the same country centres, lending credence to the importance of a future prospective studies of drug regimens for the purpose of deriving optimal methods and streamlining tactics.

One possible explanation for these results is the scarcity of randomized controlled trials in the field of neuro-interventional radiology. Even though the degree of evidence is generally poor, certain insights can be extracted from the current literature. Care must also be taken when extrapolating results from cardiology studies as the populations discussed are not equivalent.

Conclusions/recommendations

Taking into consideration the acceptability, DAPT drug prices (CP ≈4 EUR, TC ≈60 EUR, PS ≈500 EUR), dosages (ASA available in 100 mg and 500 mg in Lithuanian market) and common practices of laboratory tests in neuro-interventional radiology in Lithuania as well as summarising the variety of regimens presented in Table 1, we provide recommendations on pre-procedural and post-procedural DAPT regimen and duration in Graph 1.



Graph 1. Suggested protocol for DAPT in intracranial stenting procedures of scheduled unruptured aneurysms in Lithuania

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Table 1. Summary of recent research findings regarding the use of antiplatelet for neuro-interventions

Author (year); study type	Type of procedure	Number of participants (Number of unruptured aneurysms)	Pathology	Antiplatelet regime		Platelet function testing	Otcomes	
				Pre-operation	Post-operation		Efficacy	Safety
Prasugrel + AS								
Pressman et al. [6] (2021); retrospective cohort study	PED	201	Unruptured and ruptured intracranial aneurysms.	Various regimens: ASA 325 mg + CP 75 mg a day, ASA 325 mg + PS 10 mg a day, ASA 325 mg + TC 90 mg a day.	DAPT for 6 months, single ASA long-term.	VerifyNow: PRU and ARU were assesed; PRU 60–200.	1 pt with TIA; 1 pt with in-stent thrombosis; 1 pt with acute stroke.	69 pts with nuisance bleeds (e.g. easy bruising, bleeding from small cuts, petechiae, ecchymosis).
Xia et al. [7] (2019); metanalysis of observational studies	Neurointerventional procedures	1 394	Unruptured intracranial aneurysms.	CP *vs* PS with heterogeneous doses with ASA.		VerifyNow: PRU and percentage inhibition of platelet.	Lower rate of TE events with PS compared with CP (relative risk [RR] = 0.19, $P = 0.0001$).	Equal rates of HH complications (OR = 1.00, $p = 1.00$).
Cagnazzo et al. [8] (2019); metanalysis of observational studies	Neurointerventional procedures	1 354 (672)	Unruptured intracranial aneurysms.	The influence of the intraprocedural UFH administration was not evaluated. Various combinations: PS loading dose: 20 mg *vs* 30 mg *vs* 40–60 mg *vs* 60 mg + ASA 325 mg 1 day before treatment; PS maintenance: 5 mg/day *vs* 5–10 mg/day *vs* 10 mg/day. CP loading dose: 75 mg + ASA 100 mg or ASA 325 mg *vs* 300 mg 5 days before treatment; CP maintenance: 75 mg/day + ASA, 75–100 mg/day *vs* 75 mg/day + ASA, 325 mg/day.		VerifyNow P2Y12 assay.	Low dose PS reduced ischemic events compared with clopidogrel.	Lower complications rates of low dose PS (20 mg/5 mg) compared with CP (odds ratio [OR] = 0.36, $p = 0.006$). Acceptable rate of HH complications.

Ticagrelor + ASA								
Yi et al. [9] (2023); retrospective cohort study	SACE	194 (210)	Unruptured intracranial aneurysms.	DAPT with CP 75 mg + ASA 100 mg per day was for at least 5 days. Patients with CP resistance were replaced with TC 90 mg + ASA 100 mg, and the concentration of TC was ensured to reach steady state (about 3 days).	ASA 100 mg per day + TC 90 mg twice per day or ASA 100 mg + CP 75 mg per day for 6 months, and then shifted to ASA alone for long-term use.	Thromboelastography: resistance to ASA was defined as AA inhibition rate <50%, and resistance to CP as ADP inhibition rate <30%.	TC seemed to be as effective and safe as CP for SACE in unruptured intracranial aneurysms. Hematocrit and fibrinogen levels were independent risk factors for the incidence of major adverse cardiovascular and cerebrovascular events.	
Caroff et al. [10] (2021); french comprehensive national survey of 40 neurointerventional surgery centers/ retrospective case-control study	SACE, Y-configuration stenting, FD	Unknown, survey to the centers provided	Unruptured and ruptured intracranial aneurysms.	The most common intravenous (IV) UFH bolus dose was 50 IU/kg – in 59% of centers, 70 IU/kg – in 19%, 60 IU/kg – in 8%, <50 IU/kg – in 8%, 100 IU/kg – in 3% and 80 IU/kg in 3% of centers; followed by a continuous infusion in 72% of centers. UFH was stopped by the end of the procedure in 73% of centers and was prolonged for 24–48 hours in 27%. Only 35% of centers monitored UFH treatment during embolization (with ACT test). DAPT is commonly prescribed, of the centers, 56%, 39%, and 5% used a daily dose of ASA of 75 mg, 160 mg, and 300 mg, respectively. ASA was associated with CP, TC, or PS in 43%, 51%, and 6% of centers. CP resistance was tested for in 94% of the centers using this drug as first-line therapy. When insufficient PUR was found, most centers switched to using TC (87%).	In cases of SACE, DAPT for 3 or 6 months in 62% and 38% of centers; ASA was prescribed for 6, 12, or 12–24 months in 16%, 57%, and 11% of centers; lifelong ASA – in 16% of centers. In cases of Y-configuration stenting, DAPT for 3 or 6 months in 48% and 52% of centers. ASA for 6, 12, or 12–24 months in 11%, 56%, and 9% of centers; lifelong ASA – in 24% of centers. In cases of FD, DAPT for 3, 6, or 12 months in 39%, 53%, and 8% of centers. ASA for 6, 12, or 12–24 months in 11%, 63%,	The vasodilator-stimulated phosphoprotein (VASP) test – 43% of centers; VerifyNow – 36% of centers.	Not mentioned.	Not mentioned.

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Author (year); study type	Type of procedure	Number of participants (Number of unruptured aneurysms)	Pathology	Antiplatelet regime		Platelet function testing	Otcomes	
				Pre-operation	Post-operation		Efficacy	Safety
				All centers using CP reported initiating DAPT at least 5 days before treatment. In contrast, only 26% of centers using TC reported initiating DAPT at least 5 days before treatment; indeed, in 63% of centers it was given the day before.	and 8% of centers; lifelong aspirin was prescribed in 18% of centers.			
Park et al. [11] (2021); retrospective cohort study	FD, SACE	201 (233)	Unruptured intracranial aneurysms.	Systematic UFH 500–1000 IU/10 kg of body weight of UFH IV following placement of the femoral/radial sheath, followed by a 1000 IU hourly during the procedure. For the CP group, ASA 81 mg + CP 75 mg once daily for at least 3 days. For the TC group ASA 81 mg once daily + TC 90 mg twice daily for at least 3 days. For patients without any DAPT premedication, a loading dose of ASA 325 mg + CP 300 mg or TC 180 mg was also administered on the day of the procedure.	DAPT was maintained for 3–6 months, followed by discontinuation of CP or TC treatment. ASA monotherapy was maintained indefinitely.	Not performed.	TC appears to be as effective and safe as CP in SACE or FD treatment for unruptured cerebral aneurysms.	
Charbonnier et al. [12] (2021); prospective cohort studies	FD	413	Unruptured and ruptured intracranial aneurysms.	ASA + CP; if PRU >208, CP was changed for TC.	DAPT for 3 months and then only ASA for 3 additional months.	Resistance with PRU.	Neurological complications after FD implantation were overrepresented by cerebrovascular ischemic events occurring during the peri-operative period, but also in a delayed manner after 1 year. Long-term follow-up is relevant after aneurysm intervention using FD.	

Li et al. [1] (2021); prospective randomised control study	PED, FD, SACE	157	Unruptured intracranial aneurysms.	DAPT: CP 75 mg + ASA 100 mg; for patients with HPR on CP, CP 75 mg was switched to 1 dose of TC 180 mg before the procedure, followed by 2 daily doses of 90 mg of TC after the procedure. For patients with HPR on ASA, the ASA dose was increased to 200 mg. The treatment adjustment was administered at least 1 day before stenting.		Light transmittance aggregometry: HPR was defined as >50% response to ADP and >20% response to AA. Assessed 1 day prior the procedure and 14 days after, and futher adjustment in DAPT was made.	Patients who underwent platelet function monitoring – guided AP therapy before stent placement exhibited an increased clinical benefit related to fewer thromboembolic complications, especially ischemic stroke.	Although a significant increase in bleeding events was observed in patients with antiplatelet therapy adjustment.
Mohammaden et al. [13] (2020); retrospective control-case study	PED	24	Unruptured and ruptured intracranial aneurysms.	During the procedure, an intravenous bolus dose of intravenous UFH 5000 units was administered. Patients who underwent elective FD received 3 days of TC 90 mg twice daily before the procedure followed by the same dose after the procedure.		Not specified.	No TE complications.	1 episode of ruptured aneurysm rebleeding.
Podlasek et al. [14] (2020); metanalysis of observational studies	FD	1 005	Unruptured and ruptured intracranial aneurysms.	CP, PS or TC with ASA. Total of 832 (82.8%) patients received CP + ASA, while 137 (13.6%) patients received TC + ASA, and 36 (3.6%) patients received PS + ASA. Atallah et al. defined clopidogrel hyporesponders as those with platelet inhibition <30% and switched to TC, and to PS if the response was again not satisfactory. Moore et al. defined clopidogrel hyporesponders as those <50% platelet inhibition or PRU >208, and those patients were switched to TC. Adeeb et al. used three different methods to obtain platelet inhibition rate and either switched hyporesponders to TC or gave a loading dose of CP before the procedure.		VerifyNow was performed for all patients only in 3 studies; 2 other studies included selective antiplatelet testing at the discretion of the institution involved.	Equal TE complications across all 3 groups.	TC and PS had lower mortality than CP. Equal HH complications across all 3 groups.

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Author (year); study type	Type of procedure	Number of participants (Number of unruptured aneurysms)	Pathology	Antiplatelet regime		Platelet function testing	Otcomes	
				Pre-operation	Post-operation		Efficacy	Safety
Soize et al. [4] (2019); retrospective cohort study	PED FRED	80 (80) (40 pts in CP and 40 pts in TC group)		UFH bolus of 50 IU/kg followed by a UFH perfusion at 600 IU/kg/day in the perioperative period. 5 days of DAPT (ASA 75 mg + CP 75 mg or TC 90 mg twice a day) (pts enrolled from March 2013 to October 2015 received CP *vs* pts enrolled from November 2015 to March 2017 were given TC).	DAPT for 3 months.	Not performed.	CP group: 3 pts with territorial infarction; 10 pts with >6 small DWI lesions. TC group: 1 pt territorial infarction; 20 pts with >6 small DWI lesions. No stenosis or occlusion of parent vessels noted in either group at 3 months.	CP group: 2 pts with groin haematomas without active bleeding. No mortality in both groups.
Narata et al. [3] (2019); retrospective cohort study	FD (113), SACE (41)	113 (113)	Unruptured intracranial aneurysm.	2 × loading dose TC 180 mg given evening before and morning of procedure. 2 groups following perioperative UFH dose: group I = 70 U/kg; group II = 50 U/kg.	TC 90 mg given evening after intervention DAPT (ASA 160 mg + TC 90 mg twice a day) for 3 months, then ASA for 1 year.	Not performed.	1.9% ischemic complications.	3.9% intracranial HH complications.
DeGrote et al. [5] (2018); retrospective case-control study	PED	29	Unruptured and ruptured intracranial aneurysms.	TC 90 mg twice daily + ASA 81 mg daily.	DAPT (TC + ASA) was continued until a follow-up at 6 months, when angiography was performed. If no complications (e.g., continued aneurysm filling or incomplete endothelialization) were identified, the TC was discontinued.	VerifyNow: if PRU <70 and/or the patient was not appropriately tolerating dual antiplatelet therapy reduce the TC to 60 mg twice daily.	Only one ischemic event was observed during the 1-year follow up, and this event occurred after DAPT had been discontinued.	No intracranial haemorrhage events were observed.

Clopidogrel + ASA								
Al Kasab et al. [15] (2020); retrospective case-control study	PED	29 (29)	Unruptured and ruptured intracranial aneurysms.	For unruptured aneurysms, patients were bolused with 3,000 units of UFH at procedure onset. Patients with ruptured aneurysms did not receive an UFH bolus. Loaded pre-procedure: DAPT (ASA 325 mg + CP 600 mg).	DAPT (ASA 325 mg + 75 mg). 2 pts with ischaemic strokes switched to TC.	Not performed.	4 pts with ischaemic strokes.	1 pt with groin haematoma (minor haemorrhage).
Neyens et al. [16] (2020); retrospective case-control study	PED	243 (243)	Unruptured and ruptured intracranial aneurysms.	Anticoagulation was maintained with intermittent UFH bolus fixed at 3000–5000 units, ≈50–100 units/kg to achieve ACT of 200–300 seconds (1.5–2.5 times baseline) for all PED procedures. 24–48 h of loading dose ASA 325–650 mg + CP 600 mg.	DAPT (ASA and CP) for minimum 6 months. Changed to TC if hyporesponder to CP (48 pts).	VerifyNow: compared groups who received personalised antiplatelet therapy according to test results to those who didn't.	7 pts with intraoperative thrombus; 6 pts with non-occlusive thrombus; 3 pts with complete occlusion at day 10, 24 and 20.	No difference in pts with HH complications.
Peret et al. [17] (2020), retrospective case-control study	FD, SACE	362 (419)	Unruptured intracranial aneurysms.	The UFH bolus of 5000 IU was followed by a continuous drip (2000 to 2500 IU/h), with the purpose of doubling the baseline ACT. Systemic UFH was prolonged for 12–24 h in all patients. Patients with a weight ≤80 kg received a loading dose of ASA 320 mg + CP 300 mg the day before and on the morning of the procedure. For patients >80 kg, 480 mg of ASA + 450 mg CP.	DAPT for 3 months (ASA 80 mg + CP 75 mg) and was then seen by a senior neurointerventionalist. ASA 80–100 mg for life after the 3 month appointment. In selected cases, CP 75 mg was also prescribed for 3 extra months.	Not performed.	Comparing standard *vs* high dosing of AP premedication, TE complications rate is low and most of them were clinically silent.	HH complications rate was substantial and a significant proportion of them were associated with mortality.
Bender et al. [18] (2019); retrospective case-control study	PED	53 (53)	Unruptured intracranial aneurysms.	7 days of DAPT (ASA 325 mg + CP 75 mg).	DAPT for life.	P2Y12 Reaction unit levels.	4 pts with Major ischaemic stroke.	Nil pts with intracranial haemorrhages; 1 pt with groin haematoma.

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Author (year); study type	Type of procedure	Number of participants (Number of unruptured aneurysms)	Pathology	Antiplatelet regime		Platelet function testing	Otcomes	
				Pre-operation	Post-operation		Efficacy	Safety
Kim et al. [19] (2018); retrospective cohort study	SACE	507	Unruptured intracranial aneurysms.	DAPT (100 mg ASA + 75 mg CP) was administered for 5 days before the scheduled SACE procedures. On the day of the procedure, DAPT was administered in the morning and systemic UFH was administered after femoral sheath placement in the operating room.	DAPT duration (short-term, <9 months; long-term, ≥9 months) to evaluate delayed TE events.	P2Y12 response testing routinely only starting from 2015.	Compared with short-term DAPT, long-term DAPT can delay the occurrence of delayed TEs but does not lower their incidence. Most events occurred within 1 month of switching from DAPT to single-antiplatelet therapy, regardless of DAPT duration.	
Cagnazzo et al. [20] (2018); retrospective case-control study	12 aneurysms with PED; 3 aneurysms with Silk; 2 aneurysms with FRED	15 (17)	Unruptured and ruptured intracranial aneurysms.	Concurrent with the procedure, intravenous UFH was performed (activated clotting time maintained above 250 seconds). Minimum 5 days of DAPT (ASA 75 mg + CP 75 mg). If non responder (<40% platelet inhibition), given additional loading dose CP 300 mg or PSl 10–20 mg.	DAPT for minimum 6 months, after clinical and radiological evaluation switched to ASA for 1 year.	VerifyNow	2 pts with stent thrombosis (1 occurring 12 h post intervention, 1 occurring 10 days after due to discontinuation of DAPT); 1 pt with small basal ganglia infarct due to insufficient platelet inhibition 24 h after treatment.	Nil HH complications.
Patel et al. [21] (2017); retrospective case-control study	PED	100 (100)		Following groin puncture, patients received boluses of IV UFH with a goal ACT of 2–2.5 times the baseline value for the duration of the procedure. 1–4 weeks of DAPT (ASA 325 mg + CP 75 mg). CP dose is adjusted depending on assay.	DAPT for 6–12 months.	P2Y12 assay; a goal P2Y12 reaction unit value 60–230.	5 pts developed acute thrombus formation intraoperatively, requiring Abcximab loading dose. 3 month follow-up showed gross patency of PED in all patients.	1 pt with small intraparenchymal haemorrhage.

Peschillo et al. [22] (2017); retrospective case-control study	PED, Silk	26 (26)	Unruptured and ruptured intracranial aneurysms.	3–10 days of DAPT (ASA 100–300 mg + CP 75 mg).	DAPT for 3–12 months. 5 groups used ASA + CP; 1 group used ASA + TC; 1 group used ASA + tirofiban + CP.	Not performed.	1 pt with intraoperative TE; 1 pt with stent occlusion at 3 months; 4 pts had FD deploy complication causing stenoocclusion intra-operatively; 1 pt with TE intraoperatively.	2 pts died, 1 due to cardiac complications and the other unknown cause.
Texakalidis et al. [23] (2017); systemic literature review	PED	1 556 (1 382)	Unruptured and ruptured intracranial aneurysms.	ASA 300–325 mg (2–14 days) + CP 75 mg (3 to more than 10 days) before elective PED in 61.7% of patients. ASA 81 mg + CP 75 mg for 5–10 days were used in 27% of patients. In 6.3% of them, ASA 100–150 mg + CP 75 mg for 5 days was used.	ASA >6 months and CP 3–12 months was the regimen of choice for 93% of patients.	The VerifyNow: PRU in 9 out of 13 studies; PRU + ARU in 4 out of 13.	There was no statistically demonstrable relationship between TE events in patients who received low dose (81–150 mg) pre-PED ASA versus high dose (300–325 mg) pre-PED ASA (9.4% *vs* 8.1%, $p = 0.32$).	In patients who received low versus high dose of pre-PED ASA, HH events occurred at 0.7% and 3.3% respectively; however, no statistical significance was achieved ($p = 0.053$).
Adeeb et al. [24] (2017); retrospective case-control study	PED	402	Unruptured and ruptured intracranial aneurysms.	UFH 3000–5000 U bolus at the beginning of the procedure, with hourly dosing of 1000 U, ACT target 250–300. ASA 325 mg + CP 75 mg daily for 3–14 days before the intervention to achieve 50–60% platelet inhibition. The last dose of CP was given the morning of platelet function testing. If a patient was a CPl non-responder: to continue on same dose CP *vs* one-time 600 mg CP boost within 24 hours pre-procedure *vs* switch to TC.	DAPT for at least 3 months and ASA indefinitely thereafter.	The VerifyNow: PRU >208 CP non-responders.	CP non-responders experienced a significantly higher rate of TE complications when compared with CP responders (17.4% *vs* 5.6%; $p = 0.0002$).	There was no significant difference in the HH complications between groups.

AA – arachidonic acid, ACT – activated clotting time, AP – antiplatelet, ARU – Aspirin Reaction Units, ASA – acetylsalicylic acid (aspirin), CP – clopidogrel, DAPT – dual antiplatelet therapy, DWI – diffusion weighted imaging, FD – flow diverter, FRED – Flow Re-direction Endoluminal Device, HH – haemorrhagic, HPR – high on treatment platelet reactivity, PED – Pipeline Embolization Device, PRU – P2Y212 ReactionUnits, PS – prasugrel, SACE – Stent-assisted coil embolization, TC – ticagrelol, TIA – transient ischaemic attack, TE – thromboembolic, UFH – unfractioned heparin.

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