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Universidad Autónoma de Bucaramanga

POSGRADOS

VIGILADA MINEDUCACIÓN

Comparison of clopidogrel and ticagrelor for the dual antiplatelet therapy of patients with unruptured cerebral aneurysms undergoing endovascular treatment.

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Febrero 2022.



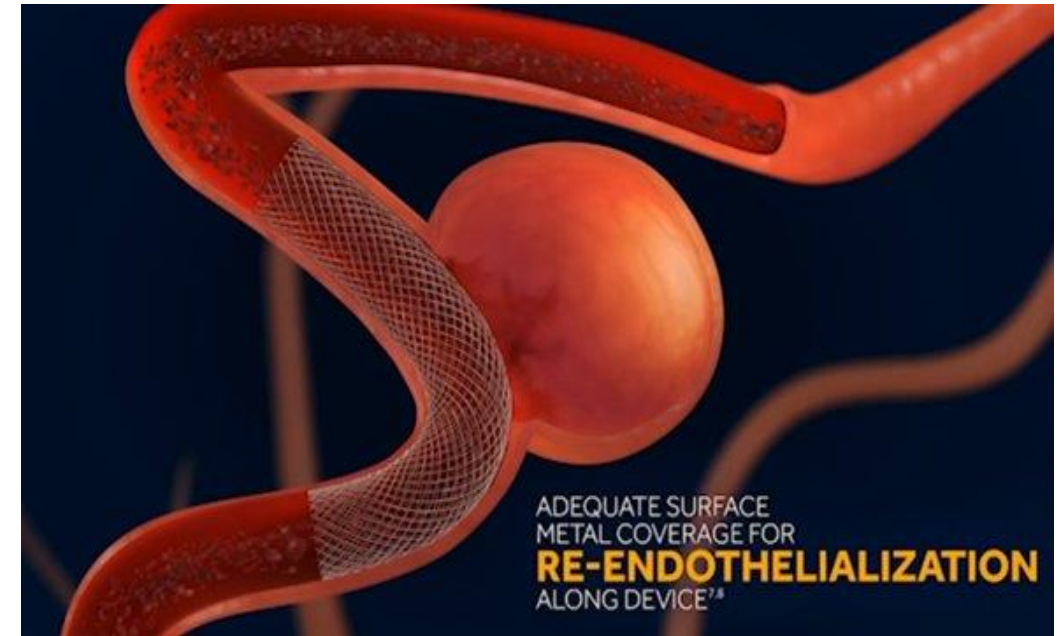
Introduction

Endovascular surgeries are the standard treatment for patients with brain aneurysms.

These surgeries, especially those using stents, require antiplatelet therapy to minimize complications before and after the procedure (1).

Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is the most common antiplatelet therapy for preventing thromboembolic events.

The use of DAPT has increased as multiple studies have shown that platelet inhibition prevents acute or subacute thrombosis in the endovascular treatment of patients with cerebral aneurysms (4,5,6), and aspirin monotherapy is insufficient (2,3).



1. Kim KS, Fraser JF, Grupke S, Cook AM. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. Journal of Neurosurgery [Internet]. 2017 Dec 1;129(4):890–905. Available from: <https://thejns.org/view/journals/j-neurosurg/129/4/article-p890.xml>
2. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, et al. Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting. Circulation. 1998 Oct 20;98(16):1597–603. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.98.16.1597>
3. Cadroy Y, Bossavy J-P, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early Potent Antithrombotic Effect With Combined Aspirin and a Loading Dose of Clopidogrel on Experimental Arterial Thrombogenesis in Humans. Circulation. 2000 Jun 20;101(24):2823–8. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.101.24.2823>
4. Suh DC, Kim SJ, Lee DH, Kim W, Choi CG, Lee JH, et al. Outcome of endovascular treatment in symptomatic intracranial vascular stenosis. Korean Journal of Radiology [Internet]. 2005 Jan 1;6(1):1–7. Available from: <https://www.kjronline.org/DOIx.php?id=10.3348/kjr.2005.6.1.1>
5. Grunwald IQ, Papanagiotou P, Politi M, Struffert T, Roth C, Reith W. Endovascular Treatment of Unruptured Intracranial Aneurysms: Occurrence of Thromboembolic Events. Neurosurgery [Internet]. 2006 Apr 1;58(4):612–8. Available from: <https://academic.oup.com/neurosurgery/article-abstract/58/4/612/2581146?redirectedFrom=fulltext>
6. Altay T, Kang HI, Woo HH, Masaryk TJ, Rasmussen PA, Fiorella DJ, et al. Thromboembolic events associated with endovascular treatment of cerebral aneurysms. Journal of NeuroInterventional Surgery [Internet]. 2011 Jun 1;3(2):147–50. Available from: <https://jn.is.bmj.com/content/3/2/147>

Comparison of clopidogrel and ticagrelor for the dual antiplatelet therapy of patients with unruptured cerebral aneurysms undergoing endovascular treatment.

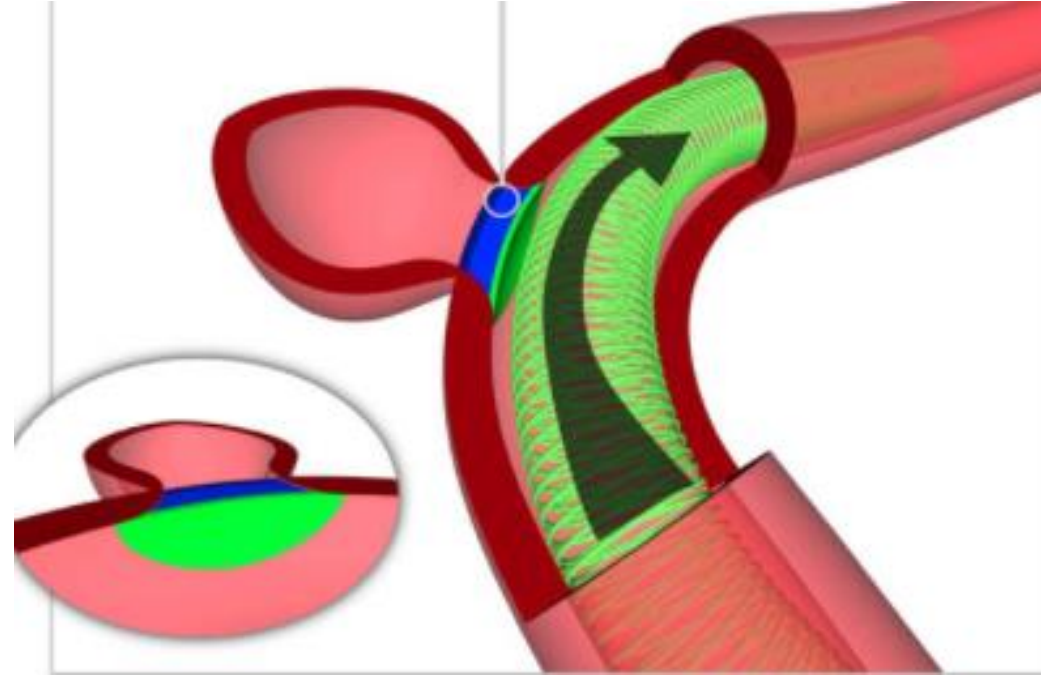


Introduction

Between 30 % and 44 % of the patients' population show variability in the therapeutic response of clopidogrel.

Drug interactions, comorbidities, genetic predisposition, race, age, among others (1,7,8).

Clopidogrel hyporesponsiveness has been associated with ischemic events, whereas clopidogrel hyperresponsiveness with hemorrhagic events during and after cerebral embolization procedures.



1. Kim KS, Fraser JF, Grupke S, Cook AM. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. Journal of Neurosurgery [Internet]. 2017 Dec 1;129(4):890–905. Available from: <https://thejns.org/view/journals/j-neurosurg/129/4/article-p890.xml>
7. Cuisset T, Quilici J, Cohen W, Fourcade L, Saut N, Pankert M, et al. Usefulness of high clopidogrel maintenance dose according to CYP2C19 genotypes in clopidogrel low responders undergoing coronary stenting for non ST elevation acute coronary syndrome. The American Journal of Cardiology [Internet]. 2011 Sep 15;108(6):760–5. Available from: [https://www.ajconline.org/article/S0002-9149\(11\)01988-6/fulltext](https://www.ajconline.org/article/S0002-9149(11)01988-6/fulltext)
8. Oliphant CS, Trevarrow BJ, Dobesh PP. Clopidogrel Response Variability. Journal of Pharmacy Practice. 2015 Nov 20;29(1):26–34. Available from: <https://journals.sagepub.com/doi/10.1177/0897190015615900>

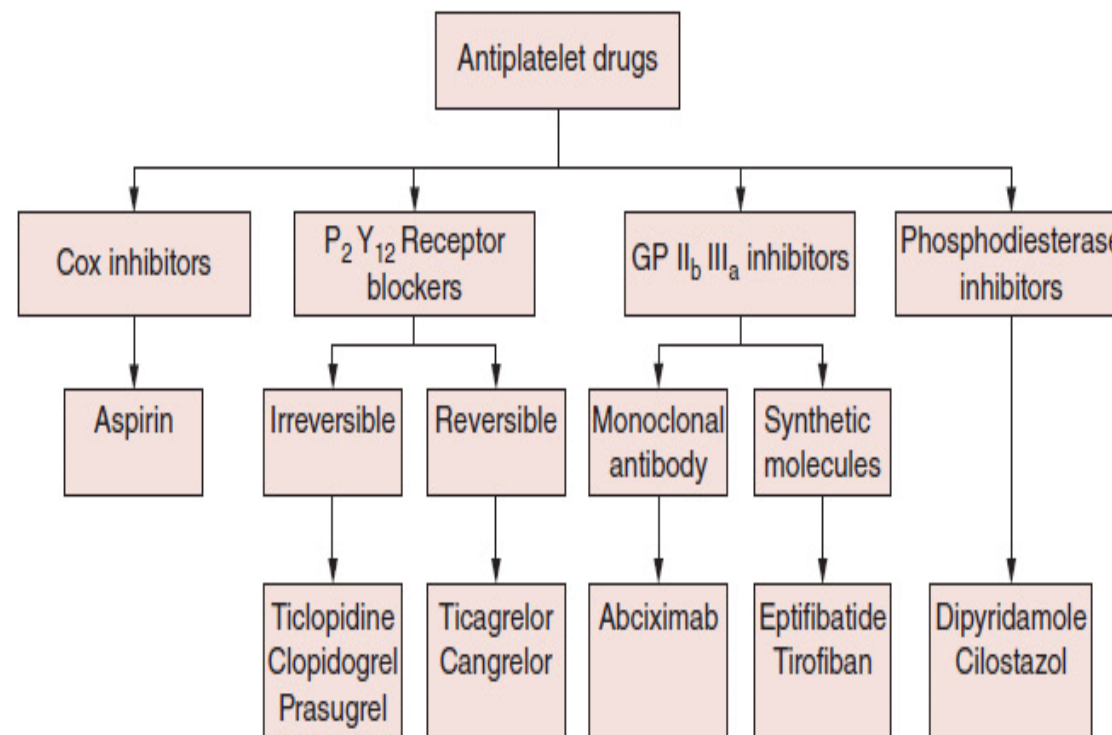
Introduction

Clopidogrel has been replaced in DAPT with other antiplatelets, such as ticagrelor.

This antiplatelet, unlike clopidogrel, is a reversible inhibitor of P2Y₁₂ and does not require metabolic activation (9,10,11,12,13).

Ticagrelor is effective and safe for preventing ischemic events in patients with the acute coronary syndrome.

Despite its advantages, the use of ticagrelor for endovascular treatment of unruptured cerebral aneurysms is rare (1,14,15,16).



9. Borchert RJ, Simonato D, R Hickman C, Fuschi M, Thibault L, Henkes H, et al. P2Y₁₂ inhibitors for the neurointerventionalist. *Interventional Neuroradiology*. 2021 May 4;159101992110150. Available from: <https://journals.sagepub.com/doi/10.1177/15910199211015042>
10. Marcucci R, Gori AM, Giusti B, Abbate R, Gensini GF, Sofi F. Clopidogrel non-responsiveness and risk of cardiovascular morbidity. *Thrombosis and Haemostasis*. 2010;103(04). Available from: <https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH09-06-0418>
11. Nordeen JD, Patel AV, Darracott RM, Johns GS, Taussky P, Tawk RG, et al. Clopidogrel Resistance by P2Y₁₂ Platelet Function Testing in Patients Undergoing Neuroendovascular Procedures: Incidence of Ischemic and Hemorrhagic Complications. *Journal of Vascular and Interventional Neurology* [Internet]. 2013 Jun 1;6(1):26–34. Available from: <https://pubmed.ncbi.nlm.nih.gov/23826440/>
12. Goh C, Churilov L, Mitchell P, Dowling R, Yan B. Clopidogrel Hyper-Response and Bleeding Risk in Neurointerventional Procedures. *American Journal of Neuroradiology* [Internet]. 2012 Dec 28;34(4):721–6. Available from: <http://www.ajnr.org/content/34/4/721>
13. Fifi JT, Brockington C, Narang J, Leesch W, Ewing SL, Bennet H, et al. Clopidogrel Resistance Is Associated with Thromboembolic Complications in Patients Undergoing Neurovascular Stenting. *American Journal of Neuroradiology* [Internet]. 2013 Apr 1;34(4):716–20. Available from: <http://www.ajnr.org/content/34/4/716>
14. Chien S-C, Chen C-C, Chen C-T, Wang AY-C, Hsieh P-C, Yeap M-C, et al. Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. *Interventional Neuroradiology*. 2021 Nov 18;159101992110549. Available from: <https://journals.sagepub.com/doi/abs/10.1177/15910199211054959>
15. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*. 2009 Sep 10;361(11):1045–57. Available from: <https://www.nejm.org/doi/full/10.1056/nejmoa0904327>
16. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *The Lancet*. 2010 Jan;375(9711):283–93. Available from:

Introduction

This study compared the effectiveness and safety of DAPT using clopidogrel and aspirin and using ticagrelor and aspirin for patients with unruptured cerebral aneurysms undergoing endovascular treatment with stents.

Also, it evaluated the development of associated thromboembolic and hemorrhagic complications in patients subjected to these two DAPT regimens.



Methodology

Retrospective cohort study of patients with endovascular treatment for unruptured cerebral aneurysms.

The study received the approval of the institutional medical ethics committee.

Although, it did not collect the patient's informed consent due to the nature of the study.

The analyzed data came from the institutional database.



Methodology

Study cohort:

Included patients from a FOSCAL reference center diagnosed with cerebral aneurysms and subjected to endovascular treatment with diverting and non-flow diverting stents between April 1, 2015, and December 30, 2020.

These patients had clopidogrel and aspirin or ticagrelor and aspirin as antiplatelet agents, and their PRU values were measured with the VerifyNow® test to assess clopidogrel response.

The cohort excluded patients with no record of VerifyNow® test, under 18 years of age, or with a history of acute treatment of subarachnoid hemorrhage.



Methodology

Study cohort:

The demographic characteristics were aneurism characteristics, type of endovascular device, whether balloons or coils were necessary, antiplatelet protocol, and VerifyNow® test results.

The study also included intraoperative and six-month complications, mortality rate, and death causality.

Methodology

Antiplatelet and anticoagulation protocol:

Patients received daily dosages of 100 mg of oral aspirin and 75 mg of oral clopidogrel for the seven days preceding and six months following the procedure.

The VerifyNow® test was performed before the surgery, and PRU values between 60 and 200 were considered as normal responses.

Patients with low antiplatelet responses (i. e., $\text{PRU} > 200$) also received a loading dose of 180 mg of oral ticagrelor the day before the procedure and maintenance doses of 90 mg of this antiplatelet every 12 hours for the following six months.



Methodology

Antiplatelet and anticoagulation protocol:

Patients with high antiplatelet responses (i.e., PRU < 60) received maintenance doses of 75 mg of oral clopidogrel every 48 hours or 72 hours or daily doses of 37.5 mg, instead of the daily 75 mg dosage.

A second VerifyNow® test was performed seven days following the procedure in these high-responder patients.

Fifty IU/kg of unfractionated heparin was administered during the endovascular procedure for anticoagulation, and subsequently an activated coagulation time test was performed.



Methodology

Statistical analysis:

The demographic and clinical characteristics of patients were analyzed using descriptive statistics.

The categorical variables were reported as counts and percentages, and continuous variables as median and 95 % confidence intervals (CI95%).

Fisher's exact test was used to evaluate differences in the complications between the two groups of patients (i.e., subjected to DAPT with clopidogrel and aspirin or with ticagrelor and aspirin), and a confidence level of 95 % was considered.

The data were gathered and cleaned in Microsoft Excel® (version 16.39).

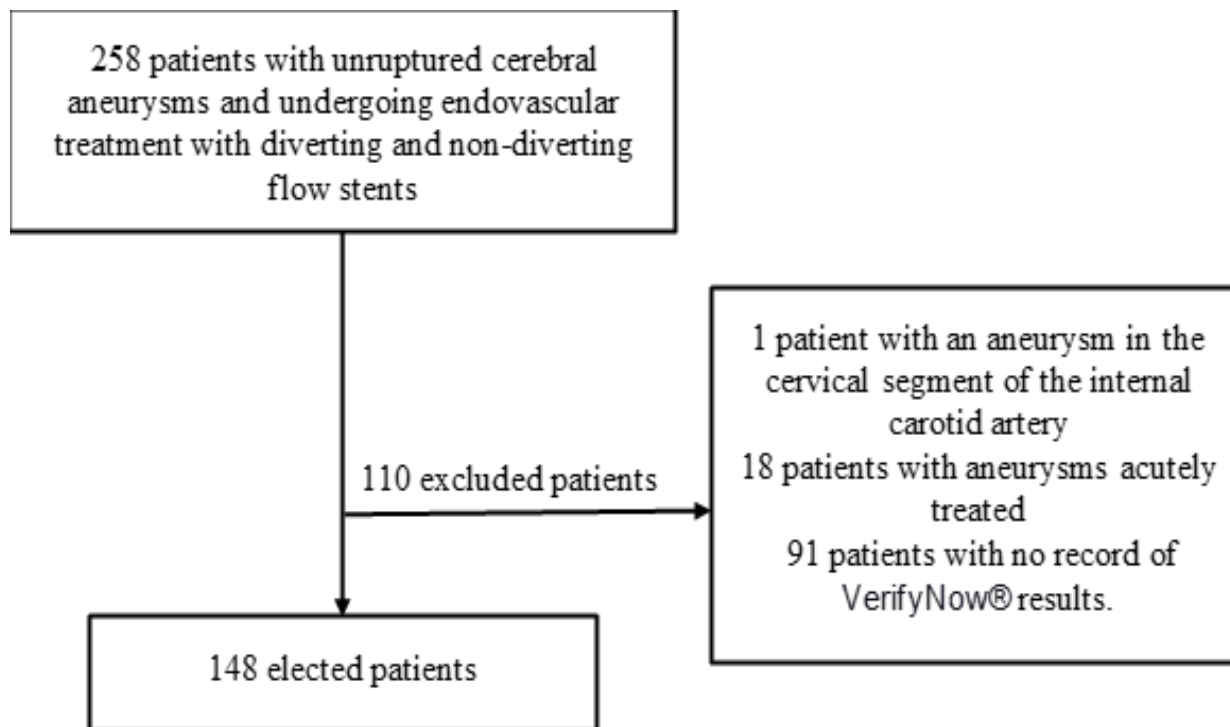
The database validation, variables processing, and analysis used the STATA/SE v 14.0 software (2003-5 Stata corp. College Station, Texas, release 9.0).



Results:

One hundred and forty-eight patients were included in the analysis.

Our evaluation excluded 110 patients, 91 lacked a VerifyNow® registry, 18 underwent acute treatment for aneurysms, and one had an aneurysm in the cervical segment of the internal carotid artery.



Results:

Patients' median age was 61.33 years, with a minimum of 24 years and a maximum of 86 years. Most patients (80.41 %) were women, and arterial hypertension was the most frequent pre-existing condition (50 %)

Variable	N (%) /median (CI95 %)
Demographic variables	
Ages in years	61.33 (59.17 – 63.49)
Sex	
Masculine	29 (19.59)
Feminine	119 (80.41)
Medical history	
Smoking	20 (13.51)
Hypertension	74 (50.00)
Family history of aneurism	23 (15.54)

Results:

Aneurysm characteristics.

The largest diameter of the aneurysm had a mean of 6.60 mm, with the shortest diameter being 1.50 mm, and the longest 55.00 mm.

Nearly half of the patients (52.03 %) had one aneurysm, while 30.41 % had two.

The most frequent aneurysm's location was the ophthalmic segment of the internal carotid artery (30.41 % of the aneurysms), and 47.30 % of the aneurysms occurred in the right hemisphere.

Seven aneurysms presented rupture and underwent a second treatment after the period of acute bleeding.

Aneurysm characteristics

Largest diameter of the aneurysm (mm)	6.60 (5.66 – 7.55)
Number of aneurysms	
1	77 (52.03)
2	45 (30.41)
3	17 (11.49)
4	4 (2.70)
5	5 (3.38)
Aneurysm localization	
Internal carotid artery (ICA)	7 (4.73)
ICA ophthalmic segment	45 (30.41)
ICA posterior communicating segment	19 (12.84)
ICA choroidal segment	6 (4.05)
ICA anterior communicating segment	18 (12.16)
ICA cavernous segment	5 (3.38)
Anterior communicating artery	8 (5.41)
Middle cerebral artery	31 (20.95)
Anterior cerebral artery	5 (3.38)
Posterior cerebral artery	1 (0.68)
Vertebral artery	2 (1.35)
Basilar artery	1 (0.68)
Laterality of the aneurysm	
Left	67 (45.27)
Right	70 (47.30)
History of ruptured aneurysm	7 (4.73)

Results:

Stent.

Also, 16.22 % of aneurysms underwent prior treatment with coils.

The most common stent type was the Pipeline (39.19 %), followed by the Leo + Baby (20.95 %).

Coils were used in 52.70 % of the patients, and balloons in 10.81 %.

The Hyperform balloon was the most used during the intra-stent balloon angioplasty (8.11 %), followed by the HyperGlide (1.35 %) and the Scepter XC (1.35 %).

Stent treatment

Previous treatment	24 (16.22)
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Used stents

1	146 (98.65)
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2	2 (1.35)
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Stent kind

Silk	6 (4.05)
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Phenox	2 (1.35)
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Solitaire	22 (14.86)
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Pipeline	58 (39.19)
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Leo + Baby	31 (20.95)
------------	------------

Leo	6 (4.05)
-----	----------

Neuroform	17 (11.49)
-----------	------------

Fred	5 (3.38)
------	----------

Fred Junior	1 (0.68)
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Concurrent use of coils and stents	78 (52.70)
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Concurrent use of balloons and stents

HyperGlide	2 (1.35)
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SCEPTER XC	2 (1.35)
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HYPERFORM	12 (8.11)
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Results:

Clopidogrel dose and VerifyNow® results.

Regarding the maximum dosage, one patient received a loading dose of 600 mg of clopidogrel the day before the procedure, followed by daily dosages of 75 mg.

Most patients (70.27 % (104 patients)) had expected Verifynow® results (i.e., PRU values between 60 and 200) prior to the procedure.

Only 12.16 % of the patients (18 patients) had PRU values above 200, and 17.57 % (26 patients) below 60.

Antiplatelet treatment and VerifyNow® tests results

Initial clopidogrel dose (mg / day)	85.64 (76.68 – 94.60)
Pre-surgical PRU	127.56 (117.06 – 138.06)
Post-surgical PRU (n = 21) *	69.76 (43.81 – 95.70)
Number of VerifyNow® tests	
1	126 (85.14)
2	20 (13.51)
3	2 (1.35)
Clopidogrel responsiveness	
Normal	104 (70.27)
Hyperresponse (PRU<60)	26 (17.57)
Hyporesponse (PRU>200)	18 (12.16)
Clopidogrel regimen modification	
Dose modification	26 (17.57)
Regimen suspension	24 (16.22)
Antiplatelet replacement for ticagrelor	24 (16.22)
No six-months follow-up	16 (8.10)

*Only 21 patients had records of post-surgical PRU as only those patients received a second VerifyNow® tests

Results:

Clopidogrel dose and VerifyNow® results.

Clopidogrel was replaced by ticagrelor in the antiplatelet protocol of 24 patients (16.22 %), which had a mean PRU of 194.

Twenty-six patients (17.57 %) had changes in their clopidogrel dosage.

Twenty four patients had their clopidogrel dose reduced in half, the mean PRU of these patients was 29.44.

The remaining two patients received a loading dose of 300 mg as they presented some level of subtherapeutic platelet inhibition and continued with 75 mg per day.

Antiplatelet treatment and VerifyNow® tests results

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Results:

Complications.

Five thrombotic (3.37 % of the patients) and six hemorrhagic (4.05 % of the patients) complications occurred during the study.

Most complications occurred during six months follow-up period.

	N (%)		P-value**
	Clopidogrel and aspirin	Ticagrelor and aspirin	
Number of patients			
During the procedure	127	21	N.A.
In the following six months	124*	24	N.A.
Complications			
Thrombotic			
During the procedure	1 (0.81)	0 (0.00)	0.838
In the following six months	4 (3.15)	0 (0.00)	1.000
Hemorrhagic			
During the procedure	1 (0.81)	0 (0.00)	0.838
In the following six months	4 (3.23)	1 (4.17)	1.000
Death	1 (0.81)	1 (4.17)	0.299

* Three of the starting 127 patients undergoing DAPT with clopidogrel and aspirin had changes in their antiplatelet therapy after having a thromboembolic complication. These patients received DAPT with ticagrelor and aspirin following the complication.

** p-value according to the Fisher's exact test.

Results:

Thrombotic and hemorrhagic complications during the procedure.

Only one patient in the group treated with clopidogrel and aspirin had a hemorrhagic and a thrombotic complication during the procedure.

The hemorrhagic complication was a subarachnoid hemorrhage (Fisher IV), and the hemorrhage resulted from the right internal carotid artery (RICA) rupture secondary to stent placement.

This patient had reconstruction of the artery during the procedure but presented thrombosis in-stent segment with subsequent refractory neurogenic shock. These complications led to patient death.

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Results:

Hemorrhagic complications in the following six months.

Five patients presenting hemorrhagic complications in the following six months, four of these patients received clopidogrel and aspirin and one ticagrelor and aspirin.

One of the patients treated with clopidogrel and aspirin presented an intraparenchymal hemorrhage (Fisher IV) in the nucleus basalis of the right hemisphere.

The hemorrhage occurred six days after the procedure and did not compromise the aneurysm area.

Another one of these patients had a hematoma in the puncture site 48 hours following the procedure. This patient required surgical intervention.

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Results:

Hemorrhagic complications in the following six months.

Regarding the other two patients receiving clopidogrel and aspirin, one presented an episode of self-limited rectal bleeding and the other self-limited gingival bleeding.

These bleedings occurred 33 days and 66 days after the procedure, respectively.

The patient treated with ticagrelor and aspirin presented hematochezia with severe anemia one month after the procedure. This patient had no abnormalities in his endoscopy and colonoscopies.

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Results:

Thromboembolic complications in the following six months.

Four patients presenting thromboembolic complications in the following six months, all in the group treated with clopidogrel and aspirin.

Three of these patients developed thrombosis within the 48 hours following the procedure.

One of these patients had an occlusion in the precentral artery secondary to thrombus migration.

Another one developed a 100 % occlusion of the anterior cerebral artery and the recurrent Heubner artery due to thrombus.

The last developed an in-stent occlusion in the anterior cerebral artery.

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Results:

Thromboembolic complications in the following six months.

The PRU values for these patients were 110, 152, and 148, respectively, and all of them underwent intravenous tirofiban infusion with successful recanalization.

These patients had their DAPT modified for one, including ticagrelor and aspirin. During follow-up, they did not present new thrombotic events.

The remaining patient presenting a thromboembolic complication in the following six months had a stroke that occurred six weeks following the procedure due to occlusion of the right anterior choroidal artery. This patient had an mRS of three at one year.

One hundred and thirty six patients in the study cohort had record of a six-month follow-up.

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Results:

Deaths.

Two patient deaths occurred.

One of these cases is the hemorrhagic complication during the procedure described above.

The other was a patient with a history of hypothyroidism, chronic atrial fibrillation managed with low molecular weight heparin, and focal epilepsy. This patient presented Fisher II-Hunt and Hess II-subarachnoid hemorrhage adjacent to a second aneurysm occurring one month after his postoperative discharge.

A second embolization was performed, but the patient presented focal epilepsy two days later. He received anticonvulsant treatment leading to the recovery and discharge of the patient. However, the patient was admitted again with a difficult-to-manage status epilepticus and septic shock refractory to vasoactive support ending in the patient's death.

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** p-value according to the Fisher's exact test.

Discussion

DAPT with clopidogrel and aspirin is typical for preventing thromboembolic events in patients undergoing neuroendovascular procedures (9,17,18).

However, previous studies have shown that nearly one-third of patients show resistance to clopidogrel and that the use of this antiplatelet is associated with a high incidence of embolic events (19,20,21,22,23,24,25).

The VerifyNow® test is the standard method for identifying high- and low-clopidogrel responders (26,27,28), but the optimal range for patients' PRU remains uncertain. The literature suggests a 240 PRU cut-off for hyporesponsive patients. However, Farrokh et al. found that several centers (44 %), like our institution, use PRU of 210 or less.

Only 16 % of centers use PRU between 230 and 240 as cut-offs for identifying hyporesponsive responders (29,30,31).

9. Borcherdt RJ, Simonato D, R Hickman C, Fuschi M, Thibault L, Henkes H, et al. P2Y12 inhibitors for the neurointerventionalist. *Interventional Neuroradiology*. 2021 May 4;159101992110150. Available from: <https://journals.sagepub.com/doi/10.1177/15910199211015042>
17. Kim KS, Fraser JF, Grupke S, Cook AM. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. *Journal of Neurosurgery* [Internet]. 2017 Dec 1;129(4):890–905. Available from: <https://thejns.org/view/journals/j-neurosurg/129/4/article-p890.xml>
18. Rosengart A, Collins MK, Hendrix P, Ueber R, Sartori M, Jain A, et al. P2Y12 inhibitors in neuroendovascular surgery: An opportunity for precision medicine. *Interventional Neuroradiology: Journal of Peritherapeutic Neuroradiology, Surgical Procedures and Related Neurosciences* [Internet]. 2021 Oct 1;27(5):682–94. Available from: <https://pubmed.ncbi.nlm.nih.gov/33541183/>
19. Altay T, Kang HI, Woo HH, Masaryk TJ, Rasmussen PA, Fiorella DJ, et al. Thromboembolic events associated with endovascular treatment of cerebral aneurysms. *Journal of NeuroInterventional Surgery* [Internet]. 2011 Jun 1;3(2):147–50. Available from: <https://jnis.bmj.com/content/3/2/147>
20. Chien S-C, Chen C-C, Chen C-T, Wang AY-C, Hsieh P-C, Yeap M-C, et al. Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. *Interventional Neuroradiology*. 2021 Nov 18;159101992110549. Available from: <https://journals.sagepub.com/doi/abs/10.1177/15910199211054959>
21. Gurbel PA, Tantry US. Aspirin and clopidogrel resistance: consideration and management. *Journal of Interventional Cardiology* [Internet]. 2006 Oct 1;19(5):439–48. Available from: <https://pubmed.ncbi.nlm.nih.gov/17020569/>
22. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *Journal of the American College of Cardiology* [Internet]. 2005 Jan 18;45(2):246–51. Available from: <https://www.sciencedirect.com/science/article/pii/S0735109704020686?via%3Dihub>
23. Kuliczowski W, Witkowski A, Polonski L, Watala C, Filipiak K, Budaj A, et al. Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. *European Heart Journal* [Internet]. 2009 Feb 1;30(4):426–35. Available from: <https://pubmed.ncbi.nlm.nih.gov/19174428/>
24. Yang H, Li Y, Jiang Y. Insufficient platelet inhibition and thromboembolic complications in patients with intracranial aneurysms after stent placement. *Journal of Neurosurgery* [Internet]. 2016 Aug 1;125(2):247–53. Available from: <https://thejns.org/view/journals/j-neurosurg/125/2/article-p247.xml>
25. Asai T, Miyachi S, Izumi T, Matsubara N, Haraguchi K, Yamanouchi T, et al. Relationship between low response to clopidogrel and periprocedural ischemic events with coil embolization for intracranial aneurysms. *Journal of NeuroInterventional Surgery* [Internet]. 2016 Jul 1;8(7):752–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/26109688/>
26. Bender MT, Zarrin DA, Campos JK, Jiang B, Chandra A, Vo CD, et al. Precision of VerifyNow P2Y12 Assessment of Clopidogrel Response in Patients Undergoing Cerebral Aneurysm Flow Diversion. *Neurosurgery* [Internet]. 2019 Oct 1;85(4):543–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/30169782/>
27. Lin S, Cui H, Chen X, Wang S, Zhou H, Du W, et al. [Clinical application of VerifyNow-P2Y12 assay in evaluation of platelet inhibition efficacy of clopidogrel]. *Zhonghua Xin Xue Guan Bing Za Zhi* [Internet]. 2012 Aug 1;40(8):662–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/23141010/>
28. Corliss BM, Polifka AJ, Harris NS, Hoh BL, Fox WC. Laboratory assessments of therapeutic platelet inhibition in endovascular neurosurgery: comparing results of the VerifyNow P2Y12 assay to thromboelastography with platelet mapping. *Journal of Neurosurgery* [Internet]. 2018 Nov 1;129(5):1160–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/29271717/>
29. Farrokh S, Owusu K, Lara LR, Nault K, Hui F, Spoelhof B. Neuro-Interventional Use of Oral Antiplatelets: A Survey of Neuro-Endovascular Centers in the United States and Review of the Literature. *Journal of Pharmacy Practice*. 2019 Jul 21;34(2):207–15.
30. Hanel RA, Taussky P, Dixon T, Miller DA, Sapin M, Nordeen JD, et al. Safety and efficacy of ticagrelor for neuroendovascular procedures. A single center initial experience. *Journal of NeuroInterventional Surgery* [Internet]. 2014 May 1;6(4):320–2. Available from: <https://jnis.bmj.com/content/6/4/320>
31. Corliss BM, Freedman R, Brennan MM, Smith J, Nerva JD, Harris NS, et al. Laboratory assessments of therapeutic platelet inhibition in endovascular neurosurgery: complication prediction using the VerifyNow P2Y12 assay and thromboelastography with platelet mapping. *Journal of Neurosurgery* [Internet]. 2020 Feb 21;134(3):884–92. Available from: <https://pubmed.ncbi.nlm.nih.gov/32084635/>



Discussion

Ticagrelor, contrasting to clopidogrel, has shown an increased rate of platelet inhibition and fewer thromboembolic complications when used in patients with coronary artery disease undergoing endovascular procedures.

Therefore, this antiplatelet seems to be an effective alternative to clopidogrel for patients treated with stents for cerebral aneurysms (32,33,34,35). Hanel et al. were the firsts to describe the ticagrelor's use for neuroendovascular treatment. In their study, 18 patients with poor response to clopidogrel showed an immediate platelet inhibition after receiving a loading dosage of 180 mg of oral ticagrelor. None of these patients presented associated complications during or after the procedure (30).

Two retrospective cohort studies also showed that DAPT with ticagrelor and aspirin is a safe alternative to prevent embolic complications in patients treated with diverting and non-diverting stents for unruptured intracranial aneurysms. These studies showed that including ticagrelor instead of clopidogrel in the DAPT of patients with an inadequate response to clopidogrel resulted in a similar antiplatelet response (34,35,36,37).

- 30. Hanel RA, Taussky P, Dixon T, Miller DA, Sapin M, Nordeen JD, et al. Safety and efficacy of ticagrelor for neuroendovascular procedures. A single center initial experience. *Journal of NeuroInterventional Surgery* [Internet]. 2014 May 1;6(4):320–2. Available from: <https://jn.is.bmj.com/content/6/4/320>
- 32. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* [Internet]. 2009 Dec 22;120(25):2577–85. Available from: <https://pubmed.ncbi.nlm.nih.gov/19923168/>
- 33. Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, et al. Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies. *Circulation*. 2010 Mar 16;121(10):1188–99. Available from: <https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.109.919456>
- 34. Wu X, You W, Wu Z, Wu Q, Jiang J, Yan H, et al. Ticagrelor versus clopidogrel for prevention of subclinical stent thrombosis detected by optical coherence tomography in patients with drug-eluting stent implantation-a multicenter and randomized study. *Platelets* [Internet]. 2021 Apr 3;32(3):404–12. Available from: <https://pubmed.ncbi.nlm.nih.gov/32326796/>
- 35. Davis K, Morrison C. Ticagrelor for Neuroendovascular Procedures: A Case Series. *Journal of Pharmacy Practice* [Internet]. 2018 Feb 1;31(1):115–9. Available from: <https://journals.sagepub.com/doi/abs/10.1177/0897190017696947?journalCode=jppa>
- 36. Cazayus M, Berge J, Marnat G, Menegon P, Gariel F, Dousset V, et al. Efficacy and safety of ticagrelor versus clopidogrel associated with aspirin for dual antiplatelet therapy in cerebral aneurysm stenting treatment: Monocentric cohort experience. *Journal of Neuroradiology* [Internet]. 2018 Mar 1;45(2):74. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S015098611730559X>
- 37. Solze S, Foussier C, Manceau P-F, Litré C-F, Backchine S, Gawlitza M, et al. Comparison of two preventive dual antiplatelet regimens for unruptured intracranial aneurysm embolization with flow diverter/disrupter: A matched-cohort study comparing clopidogrel with ticagrelor. *Journal of Neuroradiology = Journal De Neuroradiologie* [Internet]. 2019 Nov 1;46(6):378–83. Available from: <https://pubmed.ncbi.nlm.nih.gov/30731144/>



Discussion

Podlasek et al. published a meta-analysis addressing the use of dual antiplatelet regimens in patients treated with flow-diverting stents, which have a 30% to 35% higher thrombosis risk due to the increased metallic coverage resulting from the stents.

The authors found that patients undergoing DAPT with ticagrelor had a similar risk of embolic or hemorrhagic complications than patients undergoing DAPT with clopidogrel but had better survival rates (38).

A more recent study by Narata et al. described a single-center retrospective study that included 154 patients treated with diverting and non-diverting stents for unruptured intracranial aneurysms. These patients underwent DAPT with ticagrelor and aspirin and had rates of neurological complications comparable to those of previous evaluations using DAPT with ticagrelor and aspirin or with clopidogrel and aspirin (39).

38. Podlasek A, Sultan AAA, Assis Z, Kashani N, Goyal M, Almekhlafi MA. Outcome of intracranial flow diversion according to the antiplatelet regimen used: a systematic review and meta-analysis. *Journal of NeuroInterventional Surgery* [Internet]. 2020 Feb 1;12(2):148–55. Available from: <https://inis.bmj.com/content/12/2/148>

39. Narata AP, Amelot A, Bibi R, Herbreteau D, Angoulvant D, Gruel Y, 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* [Internet]. 2019 Jan 1;84(1):77–83. Available from: https://journals.lww.com/neurosurgery/Citation/2019/01000/Dual_Antiplatelet_Therapy_Combining_Aspirin_and.10.aspx



Discussion

In our study, only one patient (4.17 %) receiving DAPT with ticagrelor and aspirin presented hemorrhagic complications.

These rates of hemorrhagic complications are comparable to those reported by Shuo-Chin Chien et al. (10.00%), Narata et al. (3.9%), and Park et al. (6.5%). (14,39,40).

We evidence no thromboembolic complications in patients treated with ticagrelor and aspirin. The lack of thromboembolic complications in these patients contrasts with the thromboembolic complications rates between 2.6 % and 7.5 % observed in other evaluations (14,39,40).

Our observations and previous evaluations show that ticagrelor is an effective and safe alternative for preventing thromboembolic events in patients undergoing neuroendovascular procedures, especially in patients with an inadequate response to clopidogrel.

Using ticagrelor during the DAPT reduces thrombotic episodes without increasing hemorrhagic episodes in patients undergoing endovascular treatment with stents for unruptured intracranial aneurysms. However, ticagrelor has some disadvantages, including its increased cost and the strict dosage-administration regimen that patients must follow.

14. Chien S-C, Chen C-C, Chen C-T, Wang AY-C, Hsieh P-C, Yeap M-C, et al. Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. *Interventional Neuroradiology*. 2021 Nov 18;159101992110549. Available from: <https://journals.sagepub.com/doi/abs/10.1177/15910199211054959>

39. Narata AP, Amelot A, Bibi R, Herbreteau D, Angoulvant D, Gruel Y, 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* [Internet]. 2019 Jan 1;84(1):77–83. Available from: https://journals.lww.com/neurosurgery/Citation/2019/01000/Dual_Antiplatelet_Therapy_Combining_Aspirin_and_10.aspx

40. Park KY, Ozaki T, Kostynskyi A, Kortman H, Hilario A, Nicholson P, et al. Ticagrelor versus Clopidogrel in the Dual Antiplatelet Regimen for Intracranial Stenting or Flow-Diverter Treatment for Unruptured Cerebral Aneurysms: A Single-Center Cohort Study. *American Journal of Neuroradiology* [Internet]. 2021 Sep 1;42(9):1638–44. Available from: <http://www.ajnr.org/content/42/9/1638>



Limitations

The main limitation of our observations is that they originated from a single-center, retrospective, and non-randomized study, which might have led to a biased comparison of the groups studied.

Another limitation is that not all patients treated with ticagrelor and aspirin had the control Verifynow® test.

Finally, the number of adverse events observed during our evaluations was low, and the sample size was not enough for the analysis as we lacked statistical power.

All of the above considered, we recommend realizing further evaluations, including prospective, randomized, controlled, and multicenter studies.



Conclusion

Our study showed that DAPT with ticagrelor and aspirin is a safe and effective alternative to DAPT with clopidogrel and aspirin for patients with an inadequate response to clopidogrel.

Using ticagrelor during DAPT reduced thromboembolic complications without increasing hemorrhagic complications in patients undergoing endovascular treatment with diverting and non-diverting stents.



Declaration of conflict of interest

The authors declare no potential conflict of interest exists concerning this article's research, authorship, or publication.

Funds

The authors received no financial support for this article's research, authorship, or publication.

Ethical approval

The medical ethics committee of the FOSCAL clinic approved this study, and the approval number was 003902.



References.

- Kim KS, Fraser JF, Grupke S, Cook AM. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. Journal of Neurosurgery [Internet]. 2017 Dec 1;129(4):890–905. Available from: <https://thejns.org/view/journals/j-neurosurg/129/4/article-p890.xml>
- Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, et al. Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting. Circulation. 1998 Oct 20;98(16):1597–603. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.98.16.1597>
- Cadroy Y, Bossavy J-P, Thalarnas C, Sagnard L, Sakariassen K, Boneu B. Early Potent Antithrombotic Effect With Combined Aspirin and a Loading Dose of Clopidogrel on Experimental Arterial Thrombogenesis in Humans. Circulation. 2000 Jun 20;101(24):2823–8. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.101.24.2823>
- Suh DC, Kim SJ, Lee DH, Kim W, Choi CG, Lee JH, et al. Outcome of endovascular treatment in symptomatic intracranial vascular stenosis. Korean Journal of Radiology [Internet]. 2005 Jan 1;6(1):1–7. Available from: <https://www.kjronline.org/DOIx.php?id=10.3348/kjr.2005.6.1.1>
- Grunwald IQ, Papanagiotou P, Politi M, Struffert T, Roth C, Reith W. Endovascular Treatment of Unruptured Intracranial Aneurysms: Occurrence of Thromboembolic Events. Neurosurgery [Internet]. 2006 Apr 1;58(4):612–8. Available from: <https://academic.oup.com/neurosurgery/article-abstract/58/4/612/2581146?redirectedFrom=fulltext>
- Altay T, Kang HI, Woo HH, Masaryk TJ, Rasmussen PA, Fiorella DJ, et al. Thromboembolic events associated with endovascular treatment of cerebral aneurysms. Journal of NeuroInterventional Surgery [Internet]. 2011 Jun 1;3(2):147–50. Available from: <https://jnis.bmj.com/content/3/2/147>
- Cuisset T, Quilici J, Cohen W, Fourcade L, Saut N, Pankert M, et al. Usefulness of high clopidogrel maintenance dose according to CYP2C19 genotypes in clopidogrel low responders undergoing coronary stenting for non ST elevation acute coronary syndrome. The American Journal of Cardiology [Internet]. 2011 Sep 15;108(6):760–5. Available from: [https://www.ajconline.org/article/S0002-9149\(11\)01988-6/fulltext](https://www.ajconline.org/article/S0002-9149(11)01988-6/fulltext)
- Oliphant CS, Trevarrow BJ, Dobesh PP. Clopidogrel Response Variability. Journal of Pharmacy Practice. 2015 Nov 20;29(11):26–34. Available from: <https://journals.sagepub.com/doi/10.1177/0897190015615900>
- Borchert RJ, Simonato D, R Hickman C, Fuschi M, Thibault L, Henkes H, et al. P2Y12 inhibitors for the neurointerventionalist. Interventional Neuroradiology. 2021 May 4;159101992110150. Available from: <https://journals.sagepub.com/doi/10.1177/15910199211015042>
- Marcucci R, Gori AM, Giusti B, Abbate R, Gensini GF, Sofi F. Clopidogrel non-responsiveness and risk of cardiovascular morbidity. Thrombosis and Haemostasis. 2010;103(04). Available from: <https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH09-06-0418>
- Nordeen JD, Patel AV, Darracott RM, Johns GS, Taussky P, Tawk RG, et al. Clopidogrel Resistance by P2Y12 Platelet Function Testing in Patients Undergoing Neuroendovascular Procedures: Incidence of Ischemic and Hemorrhagic Complications. Journal of Vascular and Interventional Neurology [Internet]. 2013 Jun 1;6(1):26–34. Available from: <https://pubmed.ncbi.nlm.nih.gov/23826440/>
- Goh C, Churilov L, Mitchell P, Dowling R, Yan B. Clopidogrel Hyper-Response and Bleeding Risk in Neurointerventional Procedures. American Journal of Neuroradiology [Internet]. 2012 Dec 28;34(4):721–6. Available from: <http://www.ajnr.org/content/34/4/721>
- Fifi JT, Brockington C, Narang J, Leesch W, Ewing SL, Bennet H, et al. Clopidogrel Resistance Is Associated with Thromboembolic Complications in Patients Undergoing Neurovascular Stenting. American Journal of Neuroradiology [Internet]. 2013 Apr 1;34(4):716–20. Available from: <http://www.ajnr.org/content/34/4/716>
- Chien S-C, Chen C-C, Chen C-T, Wang AY-C, Hsieh P-C, Yeap M-C, et al. Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. Interventional Neuroradiology. 2021 Nov 18;159101992110549. Available from: <https://journals.sagepub.com/doi/abs/10.1177/15910199211054959>
- Wallentin L, Becker RC, Budaj A, Cannon CP, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine. 2009 Sep 10;361(11):1045–57. Available from: <https://www.nejm.org/doi/full/10.1056/nejmoa0904327>
- Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. The Lancet. 2010 Jan;375(9711):283–93. Available from: <https://www.thelancet.com/journals/lancet/article/PIIS0140673609621917/fulltext>
- Kim KS, Fraser JF, Grupke S, Cook AM. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. Journal of Neurosurgery [Internet]. 2017 Dec 1;129(4):890–905. Available from: <https://thejns.org/view/journals/j-neurosurg/129/4/article-p890.xml>
- Rosengart A, Collins MK, Hendrix P, Uber R, Sartori M, Jain A, et al. P2Y12 inhibitors in neuroendovascular surgery: An opportunity for precision medicine. Interventional Neuroradiology: Journal of Peritherapeutic Neuroradiology, Surgical Procedures and Related Neurosciences [Internet]. 2021 Oct 1;27(5):682–94. Available from: <https://pubmed.ncbi.nlm.nih.gov/33541183/>
- Altay T, Kang HI, Woo HH, Masaryk TJ, Rasmussen PA, Fiorella DJ, et al. Thromboembolic events associated with endovascular treatment of cerebral aneurysms. Journal of NeuroInterventional Surgery [Internet]. 2011 Jun 1;3(2):147–50. Available from: <https://jnis.bmj.com/content/3/2/147>
- Chien S-C, Chen C-C, Chen C-T, Wang AY-C, Hsieh P-C, Yeap M-C, et al. Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. Interventional Neuroradiology. 2021 Nov 18;159101992110549. Available from: <https://journals.sagepub.com/doi/abs/10.1177/15910199211054959>
- Gurbel PA, Tantry US. Aspirin and clopidogrel resistance: consideration and management. Journal of Interventional Cardiology [Internet]. 2006 Oct 1;19(5):439–48. Available from: <https://pubmed.ncbi.nlm.nih.gov/17020569/>
- Serebruany VL, Steinhilb SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. Journal of the American College of Cardiology [Internet]. 2005 Jan 18;45(2):246–51. Available from: <https://www.sciencedirect.com/science/article/pii/S0735109704020686?via%3Dihub>
- Kuliczowski W, Witkowski A, Polonski L, Watala C, Filipiak K, Budaj A, et al. Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. European Heart Journal [Internet]. 2009 Feb 1;30(4):426–35. Available from: <https://pubmed.ncbi.nlm.nih.gov/19174428/>
- Yang H, Li Y, Jiang Y. Insufficient platelet inhibition and thromboembolic complications in patients with intracranial aneurysms after stent placement. Journal of Neurosurgery [Internet]. 2016 Aug 1;125(2):247–53. Available from: <https://thejns.org/view/journals/j-neurosurg/125/2/article-p247.xml>
- Asai T, Miyachi S, Izumi T, Matsubara N, Haraguchi K, Yamanouchi T, et al. Relationship between low response to clopidogrel and periprocedural ischemic events with coil embolization for intracranial aneurysms. Journal of NeuroInterventional Surgery [Internet]. 2016 Jul 1;8(7):752–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/26109688/>
- Bender MT, Zarrin DA, Campos JK, Jiang B, Chandra A, Vo CD, et al. Precision of VerifyNow P2Y12 Assessment of Clopidogrel Response in Patients Undergoing Cerebral Aneurysm Flow Diversion. Neurosurgery [Internet]. 2019 Oct 1;85(4):543–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/30169782/>
- Lin S, Cui H, Chen X, Wang S, Zhou H, Du W, et al. [Clinical application of VerifyNow-P2Y12 assay in evaluation of platelet inhibition efficacy of clopidogrel]. Zhonghua Xin Xue Guan Bing Za Zhi [Internet]. 2012 Aug 1;40(8):662–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/23141010/>
- Corliss BM, Polifka AJ, Harris NS, Hoh BL, Fox WC. Laboratory assessments of therapeutic platelet inhibition in endovascular neurosurgery: comparing results of the VerifyNow P2Y12 assay to thromboelastography with platelet mapping. Journal of Neurosurgery [Internet]. 2018 Nov 1;129(5):1160–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/29271717/>
- Farrokh S, Owusu K, Lara LR, Nault K, Hui F, Spoelhof B. Neuro-Interventional Use of Oral Antiplatelets: A Survey of Neuro-Endovascular Centers in the United States and Review of the Literature. Journal of Pharmacy Practice. 2019 Jul 21;34(2):207–15.
- Hanel RA, Taussky P, Dixon T, Miller DA, Sapin M, Nordeen JD, et al. Safety and efficacy of ticagrelor for neuroendovascular procedures. A single center initial experience. Journal of NeuroInterventional Surgery [Internet]. 2014 May 1;6(4):320–2. Available from: <https://jnis.bmj.com/content/6/4/320>
- Corliss BM, Freedman R, Brennan MM, Smith J, Nerva JD, Harris NS, et al. Laboratory assessments of therapeutic platelet inhibition in endovascular neurosurgery: complication prediction using the VerifyNow P2Y12 assay and thromboelastography with platelet mapping. Journal of Neurosurgery [Internet]. 2020 Feb 21;134(3):884–92. Available from: <https://pubmed.ncbi.nlm.nih.gov/32084635/>
- Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation [Internet]. 2009 Dec 22;120(25):2577–85. Available from: <https://pubmed.ncbi.nlm.nih.gov/19923168/>
- Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, et al. Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies. Circulation. 2010 Mar 16;121(10):1188–99. Available from: <https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.109.919456>
- Wu X, You W, Wu Z, Wu Q, Jiang J, Yan H, et al. Ticagrelor versus clopidogrel for prevention of subclinical stent thrombosis detected by optical coherence tomography in patients with drug-eluting stent implantation—a multicenter and randomized study. Platelets [Internet]. 2021 Apr 3;32(3):404–12. Available from: https://journals.lww.com/neurosurgery/Citation/2019/01000/Dual_Antiplatelet_Therapy_Combining_Aspirin_and_10.aspx
- Davis K, Morrison C. Ticagrelor for Neuroendovascular Procedures: A Case Series. Journal of Pharmacy Practice [Internet]. 2018 Feb 1;31(1):115–9. Available from: <https://journals.sagepub.com/doi/abs/10.1177/0897190017696947?journalCode=jppa>
- Cazayus M, Berge J, Marnat G, Menegon P, Garieff F, Dousset V, et al. Efficacy and safety of ticagrelor versus clopidogrel associated with aspirin for dual antiplatelet therapy in cerebral aneurysm stenting treatment: Monocentric cohort experience. Journal of Neuroradiology [Internet]. 2018 Mar 1;45(2):74. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S015098611730559X>
- Soize S, Fousseier C, Manceau P-F, Litré C-F, Backchine S, Gawlitza M, et al. Comparison of two preventive dual antiplatelet regimens for unruptured intracranial aneurysm embolization with flow diverter/disrupter: A matched-cohort study comparing clopidogrel with ticagrelor. Journal of Neuroradiology = Journal De Neuroradiologie [Internet]. 2019 Nov 1;46(6):378–83. Available from: <https://pubmed.ncbi.nlm.nih.gov/30731144/>
- Podlasek A, Sultan AAA, Assis Z, Kashani N, Goyal M, Almekhlafi MA. Outcome of intracranial flow diversion according to the antiplatelet regimen used: a systematic review and meta-analysis. Journal of NeuroInterventional Surgery [Internet]. 2020 Feb 1;12(2):148–55. Available from: <https://jnis.bmj.com/content/12/2/148>
- Narata AP, Amelot A, Bibi R, Herbreteau D, Angoulvant D, Gruel Y, 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 [Internet]. 2019 Jan 1;84(1):77–83. Available from: https://journals.lww.com/neurosurgery/Citation/2019/01000/Dual_Antiplatelet_Therapy_Combining_Aspirin_and_10.aspx
- Park KY, Ozaki T, Kostynskyy A, Kortman H, Hilaria A, Nicholson P, et al. Ticagrelor versus Clopidogrel in the Dual Antiplatelet Regimen for Intracranial Stenting or Flow-Diverter Treatment for Unruptured Cerebral Aneurysms: A Single-Center Cohort Study. American Journal of Neuroradiology [Internet]. 2021 Sep 1;42(9):1638–44. Available from: <http://www.ajnr.org/content/42/9/1638>



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