Neuroradiology (2021) 63:925–934
https://doi.org/10.1007/s00234-020-02599-2

INTERVENTIONAL NEURORADIOLOGY

The use of cangrelor in neurovascular interventions: a multicenter experience

Gustavo M. Cortez[1,2] · André Monteiro[1] · Nader Sourour[3] · Frédéric Clarençon[3] · Mahmoud Elhorany[3] · Mikayel Grigoryan[4] · Soz Mirza[4] · Guilherme Dabus[5] · Italo Linfante[5] · Pedro Aguilar-Salinas[6] · Yasmeen Murtaza[1] · Amin Aghaebrahim[1] · Eric Sauvageau[1] · Ricardo A. Hanel[1]

Received: 7 September 2020 / Accepted: 3 November 2020 / Published online: 11 November 2020

Abstract

Purpose Thromboembolic events represent the most common procedure-related complication associated with neurointerventions. Cangrelor is a potent, intravenous (IV), P2Y12-receptor antagonist with a rapid onset and offset presented as an alternative antiplatelet agent. We aim to evaluate the safety and effectiveness of IV cangrelor in neurovascular intervention.

Methods This is a retrospective analysis of data from four cerebrovascular interventional centers. We identified patients who underwent acute neurovascular intervention and received cangrelor as part of their optimum care. Patients were divided into 2 groups: ischemic and aneurysm. Periprocedural thromboembolic events, hemorrhagic complications, and outcomes were analyzed.

Results Sixty-six patients were included, 42 allocated into the ischemic group (IG), and 24 into aneurysm group (AG). The IG periprocedural symptomatic complication rate was 9.5%, represented by 3 postoperative intracranial hemorrhages and 1 retroperitoneal hematoma. At discharge, 47.6% had a favorable outcome and the mortality rate was 2.4%, related to clinical deterioration of a large infarct. In the AG, 4.2% had a periprocedural complication during or after cangrelor infusion, represented by an intracranial hemorrhage in an initially ruptured aneurysm. Favorable clinical outcome was seen in 56.2% and 87.7% of ruptured and unruptured aneurysms, respectively, upon discharge.

Conclusions Cangrelor may be a feasible alternative for patients requiring immediate intervention with the use of endoluminal devices. It allows the possibility for a secure transition to long-term ticagrelor and progression to surgery in the setting of unexpected complications.

Keywords Cangrelor · Stroke · Aneurysm · Thromboembolism · Intracranial hemorrhage

✉ Ricardo A. Hanel
rhanel@lyerlyneuro.com

[1] Lyerly Neurosurgery, Baptist Neurological Institute, 800 Prudential drive, Weaver tower, 11th floor, Jacksonville, FL, USA

[2] Research Department, Jacksonville University, Jacksonville, FL, USA

[3] Department of Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France

[4] Adventist Health Glendale Comprehensive Stroke Center, Los Angeles, CA, USA

[5] Miami Neuroscience, Cardiac, and Vascular Institute, Baptist Hospital, Miami, FL, USA

[6] Department of Neurosurgery, University of Arizona, Tucson, AZ, USA

Introduction

Thromboembolic events (TE) may lead to catastrophic complications in patients undergoing endovascular treatment for cerebrovascular diseases. In cases of endoluminal prosthesis utilization, dual-antiplatelet therapy (DAPT), most commonly aspirin and clopidogrel, has become the standard of care in order to prevent such undesirable outcomes [1]. When such devices utilization is deemed imminent, rapid onset of antiplatelet effect without increasing the risk of major bleeding is desired [2].

Although clopidogrel platelet inhibition onset is expected within 2 h in a healthy individual, studies with patients undergoing percutaneous coronary intervention (PCI) revealed significant inadequate platelet inhibition [3]. Further analysis depicted that clopidogrel resistance is estimated to occur in

as many as 30% of the patients [4]. Genetic polymorphisms, drug-drug interactions, and clinical factors may increase platelet reactivity and prevent adequate efficacy of clopidogrel [5]. The necessity of newer and efficacious antiplatelet drugs that fulfill the expectations for patient safety must be warranted.

Prasugrel and ticagrelor have shown to be more potent P2Y12-receptor antagonists, associated with less interpatient variability and a significant reduction of thromboembolic events in PCI patients [6, 7]. Glycoprotein IIB/IIIA inhibitors (GPI) are also recognized as an alternative, but hemorrhagic complications are a concern [8]. While these agents were developed to overcome the risks of clopidogrel resistance, there are some caveats that could not be completely solved: (1) in the setting of acute neurological intervention, delayed onset of the effect could predispose to early device thrombosis; (2) in the presence of unexpected case evolution, a tardy and erratic offset could result in devasting complications in patients requiring surgery; and (3) none of currently used antiplatelet agents, enteral (clopidogrel, prasugrel, ticagrelor), or parenteral options (tirofiban, eptifibatide, abciximab) can be readily reversed in cases of hemorrhagic complications. The pharmacokinetic and pharmacodynamic parameters of the available IV antiplatelet agents are depicted in Table 1.

Cangrelor (Kengreal, Chiesi, USA) is a potent, IV, P2Y12-receptor antagonist presented as an alternative to other antiplatelet agents. It is a nonthienopyridine adenosine analog that reversibly and directly antagonizes the platelet receptor [6]. It does not require metabolic activation with an immediate onset warranted when given as a bolus and infusion, reaching a sustained and profound platelet inhibition. The plasma half-life is 3–6 min, and platelet activity gets back to normal within 60 min after discontinuation of the infusion, ensuring a rapid offset [6]. Cangrelor was approved by the US Food and Drug Administration and European Medicines Agency as an adjunct therapy for patients undergoing PCI. Interventional cardiology trials showed its efficacy in preventing periprocedural ischemic event without an increase in severe bleeding [9].

Single-center case series have recently described the potential of this novel therapy in the management of acute cerebrovascular pathologies [10–14]. They have addressed the feasibility of cangrelor use in patients undergoing acute intervention for stroke and aneurysm management. To bolster their findings, we present the first multicenter experience with the aim of elucidating the safety and efficacy of cangrelor in neurovascular interventions.

Methods

A retrospective review was performed at 4 centers (three in the USA and one in France) between 2016 and 2019. The cohort consisted of all consecutive adult patients (≥ 18 years old) who underwent neurovascular intervention and received cangrelor as part of their optimum care. Local ethics committees and/or Institutional Review Boards at each institution approved the retrospective analysis of de-identified data, which did not require informed consent. Each center collected its data, which was entered into a standardized data form. Patients were divided into two subpopulations: ischemic group (IG) and aneurysm group (AG), including ruptured and unruptured.

Study treatments, exposure, and interventions

Indications for endovascular therapy in the IG were based on current guidelines. Patients received intravenous thrombolytic therapy (tissue plasminogen activator, t-PA) if they met criteria. Mechanical thrombectomy (using stent-retriever and/or aspiration) was performed when intracranial large vessel occlusion (LVO) due to local thrombus was present. Additionally, stents were deployed in the setting of atherosclerotic disease (intracranial and/or extracranial) at the operator's discretion. The indication relied on the degree of stenosis, acute neurologic presentation, and refractoriness to primary

Table 1 Overview of intravenous antiplatelet therapy protocols for neurovascular intervention

	Cangrelor (Kengreal)	Tirofiban (Aggrastat)	Eptifibatide (Integrillin)	Abciximab (Reopro)
Class	ATP analog	GP IIb/IIIa inhibitor	GP IIb/IIIa inhibitor	GP IIb/IIIa inhibitor
Reversibility	Reversible	Irreversible	Irreversible	Irreversible
Prodrug	No	Non-peptide	Peptide	Monoclonal antibody
Administration route	Intravenous	Intravenous	Intravenous	Intravenous
Neurovascular dose				
Loading dose (bolus)	15–30 μg/kg	None-0.4 μg/kg	90–180 μg/kg	0.125–0.25 mg/kg
Maintenance dose	2–4 μg/kg/min	0.10 μg/kg/min	0.5–2 μg/kg/min	0.125 μg/kg/min
Onset of effect	0–2 min	5–30 min	5–15 min	10 min
Restoration of platelet activity	30–60 min	4–8 h	4–8 h	12–48 h
Half-Life	2–5 min	1–2 h	1–3 h	1–4 h

intervention. Aneurysms were secured according to their location, morphology, size, and operator's preference.

The decision to use IV cangrelor was made by experienced interventionalists based on the necessity of immediate potent antiplatelet effect. Aspirin (75–325 mg) was started either during or just after the procedure. In hemorrhagic cases, 1–50 units per kilogram of heparin was used, but no heparin was routinely used in the setting of ischemic disease. Patients received a cangrelor loading dose of 15–30 μg/kg, followed by a 2–4-μg/kg/min maintenance dose. The infusion was maintained until the index procedure's conclusion or until judged necessary by the treating physician. Transition to ticagrelor (AstraZeneca, Cambridge, UK) occurred before or immediately after stopping cangrelor infusion, and patients were discharged in dual-antiplatelet therapy. Table 2 summarizes median infusion duration and preferred dosages in each institution. VerifyNow P2Y12 (Accumetrics, San Diego, California) assay was used to quantify the antiplatelet therapy's response. When available, the results were reported as platelet reactivity unit (PRU), in which values between 60 and 200 were considered ideal.

Study outcomes

The safety outcome was defined by symptomatic complications related to the intervention (procedure-related) and/or cangrelor use (drug-related) that occurred during or up to 72 h of the index procedure (periprocedural). All complications and outcomes were collected from chart review and defined by each site treating physician. A complication was adjudicated as drug-related according to specific questions asked about the possible relationship to cangrelor use. Symptomatic intracranial hemorrhage was defined according to ECASS II criteria (European Cooperative Acute Stroke Study) and symptomatic TE by radiological evidence of vessel occlusion associated with neurological deterioration. Additional information about successfully managed minor events was also retrieved.

Patients modified Rankin Scale (mRS) scores were assessed at admission, discharge, and 90-day follow-ups. An mRS 0–2 was considered a favorable functional outcome. In the IG, the modified Thrombolysis in Cerebral Infarction (mTICI) scale was used to evaluate endovascular recanalization, in which an mTICI 2b-3 was considered successful recanalization. In the AG, occlusion effectiveness was evaluated using the Raymond-Roy classification (1—complete occlusion; 2—residual neck; 3—residual aneurysm). Device and vessel patency were assessed during imaging follow-up by digital subtracted angiography, magnetic resonance angiography, or computed tomographic angiography.

Statistical analysis

Demographics baseline and procedural characteristics were summarized and reported as mean ± standard deviation (SD) and median (interquartile range (IQR)) depending on data distribution. Categorical data was summarized using rates and percentages. The Mann-Whitney test was used for non-parametric continuous variables. Statistical tests were performed using SPSS (IBM, Armonk, New York, USA). Results were considered statistically significant when $p < 0.05$.

Results

Overall

A total of 66 patients were included. The mean age was 62.6 ± 15.9, and 41 (62.1%) were women. The majority of the included patients (89.4%) had a functionally independent life (mRS 0–2) at baseline. Medical comorbidity information was available for all but two. Hypertension (68.75%), dyslipidemia (40.6%), and diabetes (28.1%) were the most prevalent ones. Based on the initial presentation, 42 (63.6%) patients were allocated into the IG, while 24 (36.3%) into the AG.

Ischemic group

Among 42 included patients, 32 (76.2%) presented with LVO due to local thrombus and 10 (23.8%) with symptomatic flow-limitation due to atherosclerotic disease. Clinical presentation

Table 2 Cangrelor protocols by institution

	A	B	C	D
Cangrelor loading dose (μg/kg)	15	30	30	15
Cangrelor maintenance dose (μg/kg/min)	4	4	4	2
Cangrelor duration (median, hours)	1–1.5	2	12–48	12–36
Aspirin start (IO–dose or PO–dose)	PO–325	IO–250	PO–75	IO–325
Bridging therapy drug–dose (mg)	T–180	T–180	T–180	T–180
Overlapping bridging time (median, hours)	0	1	2	2
Discharge antiplatelet therapy	A + T	A + T	A + T	A + T

PO postoperative, *IO* intraoperative, *T* ticagrelor, *A* aspirin

and procedure features are detailed in Table 3. Successful recanalization was achieved in 95.2%; 23 patients had intracranial stenting, 17 carotid stenting, and 2 carotid angioplasties. Patients who presented with LVO due to acute thrombus had also undergone either MT (31/32, 96.9%) or aspiration (1/32, 3.1%). Postoperative platelet reactivity level was available for 22 patients, with a mean of 139.45 ± 49.97 PRU. There was no significant difference between creatinine levels before and after the procedure (1.08 ± 0.48 versus 1.03 ± 0.53, $p = 0.378$).

Periprocedural symptomatic events are detailed in Table 4. Overall, symptomatic complications occurred in 9.5% (4/42) of patients with ischemic disease, of which 25.0% (1/4; Case 1) were associated with retroperitoneal hematoma and 75.0% (3/4; Cases 2 to 4) with ICH. Neurological sequelae at discharge remained in 3 patients, with a drug-related morbidity of 7.1% (3/42). There was no drug-related mortality at discharge (0/42).

Two additional intraoperative events occurred but they were successfully managed before symptoms could occur. They were represented by 1 case of vessel dissection and 1 thromboembolic event during thrombus extraction (requiring vessel deconstruction using coiling). The latter patient also had in-stent thrombosis 2 weeks after the intervention while on DAPT, but no mRS shift from baseline was seen at any moment.

Favorable functional outcome at discharge was achieved in 47.6% (20/42), and the mortality rate was 2.4% (1/42). The patient who died had a tandem occlusion and underwent MT with carotid balloon angioplasty, but the stroke progressed with a sizeable acute infarction despite partial recanalization of the vessel. Among 21 patients with 90-day mRS follow up, 57.1% (12/21) had favorable outcome.

Aneurysm group

A total of 24 patients were included, with 16 being ruptured and 8 unruptured. Clinical presentation, aneurysms location, and procedural features are detailed in Table 5. The most common aneurysm site was the ICA (12/24, 50%). Flow-diverters were the device of choice (16/24, 66.7%). Postoperative platelet reactivity level was available for seven patients, with a mean of 54.43 ± 36.25 PRU. There was no significant difference between creatinine levels before and after the procedure (0.69 ± 0.18 versus 0.69 ± 0.16, $p = 0.727$).

Overall, symptomatic periprocedural events in patients with aneurysm occurred in 12.5% (3/24). They were represented by 1 thromboembolic event before cangrelor use (4.2%, Case 1) and 2 intracranial hemorrhages (8.3%, Case 2 and 3). One of these cases (Case 3) was adjudicated to be related to cangrelor, resulting in a drug-related morbidity and mortality at discharge of 4.2% (1/24), as detailed in Table 4.

In two cases (2/24, 8.3%) cangrelor was used as rescue agent. Both occurred in patients with unruptured aneurysms who had thrombus formation in the region of recently deployed devices (WEB and balloon-assisted coiling). Successful management and final discharge mRS of 0 was seen with the combination of cangrelor, aspirin, and heparin.

Favorable clinical outcome was seen in 56.2% (9/16) and 87.5% (7/8) of ruptured and unruptured aneurysm patients

Table 3 Ischemic patients— baseline, procedure and outcomes

Baseline characteristics ($n = 42$)	Value (%)
Gender, female	24 (57.1)
Age median, *y* (range)	68.5 (34–88)
Hypertension	31 (73.8)
Hyperlipidemia	21 (50)
Diabetes mellitus	16 (38.1)
Previous stroke	12 (28.6)
Smoking	17 (40.5)
Clinical presentation	
mRS score at baseline	
0–2	36 (85.7)
3–5	6 (14.3)
NIHSS, median (IQR)	15.5 (8.2–21)
ASPECTS, median (IQR)	9 (8–10)
IV-tPA	14 (33.3)
Baseline antiplatelet use	16 (38.1)
Baseline anticoagulation	3 (7.1)
Occlusion/stenosis location	
Internal carotid artery	18 (42.8)
Middle cerebral artery	32 (76.2)
Anterior cerebral artery	1 (2.4)
Posterior circulation	3 (7.1)
Tandem occlusion	12 (28.6)
Procedural features	
Mechanical thrombectomy or Aspiration	32 (76.2)
Carotid stenting	17 (40.5)
Intracranial stenting	23 (54.8)
Angioplasty	2 (4.7)
Number of passes[a]	
1	13 (40.6)
2	9 (28.1)
3 or more	10 (31.3)
Clinical outcomes	
Good outcome (mRS, 0–2)	
Discharge	20 (47.6)
90 days[b]	12 (57.1)
Mortality	
Discharge	1 (2.4)

Data are presented *n*/*N* (%) or median (IQR)

mRS modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early CT Score, *tPA* tissue plasminogen activator

[a] Available for all 32 patients who underwent thrombectomy

[b] Available for 21 patients

Table 4 Periprocedural events

Case	Complication	Cangrelor-related complication	Cangrelor-related sequelae at discharge	Discharge mRS	Commentaries
Ischemic group					
1	Retroperitoneal hematoma	Possible	No	1	Successfully managed with blood transfusion and continued cangrelor infusion.
2	sICH	Possible	Yes	4	Right ICA re-occlusion; underwent MT in combination with carotid stent placement. The patient had undergone MT and received tPA 3 days before. Cangrelor was started only during second intervention.
3	sICH	Possible	Yes	5	Right MCA occlusion; underwent MT in combination with intracranial stent placement. No IV-tPA.
4	sICH	Possible	Yes	4	Tandem left ICA occlusion; underwent MT in combination with carotid stent placement. No IV-tPA.
Rate		4 (9.5%)	3 (7.1%)		
Aneurysm group					
1	Thromboembolism	No	No	3	Unruptured basilar aneurysm managed with flow-diverter while on DAPT. Temporarily transitioned to cangrelor for EVD placement due to local thrombosis and hydrocephalus.
2	sICH	No	No	6	Ruptured MCA aneurysm managed with FD while on DAPT. Hemorrhage progressed, and the patient was transitioned to cangrelor in an attempt of better control.
3	sICH	Possible	Yes[b]	6	Ruptured basilar aneurysm managed with SAC under cangrelor infusion. Postoperative progression of sICH resulted in death.
Rate		1 (4.2%)	1 (4.2%)		

mRS more modified Rankin Score, *sICH* symptomatic intracranial hemorrhage, *EVD* external ventricular drainage, *FD* flow-diverter, *DAPT* dual-antiplatelet therapy, *SAC* stent-assisted coiling

[a] Possible cangrelor-related complication, but it was successfully managed and did not result in sequelae at discharge

[b] Mortality possibly related to cangrelor

upon discharge. Additionally, two patients with ruptured aneurysms and hemorrhagic complication were dead at discharge. At 90 days, 64.2% (8/14) of patients with ruptured aneurysms and 100% (8/8) with unruptured had a favorable clinical outcome. There was one case of delayed aneurysm rerupture, which resulted in death. The patient had undergone stent-assisted coiling for a ruptured vertebral aneurysm with an mRS of 1 at discharge. Detailed outcomes are presented in Table 6.

Discussion

The necessity of immediate endoluminal device deployment poses unique challenges to endovascular intervention in either stroke or aneurysm treatment. The optimal antiplatelet therapy regimen in such cases remains unclear [15, 16]. There is a growing body of literature supporting the use of cangrelor [10–14]. We report a retrospective multicenter experience of cangrelor use in neurovascular interventions, the single largest combined series in the literature. In our study, cangrelor is demonstrated as an effective antiplatelet agent for preventing thromboembolic events when immediate antiplatelet effect was needed.

Cangrelor and ischemic patients

Overall, the rate of ICH in stroke patients who undergo thrombectomy is approximately 4.4% [17]. When specific subpopulations are analyzed, such as elderly and large core patients, the rates of hemorrhagic complications increase to 5.6% and 13.0%, respectively [18, 19]. The risk of hemorrhagic complication is recognized to be multifactorial and should be carefully assessed on a case-by-case basis. Moreover, there has to be an equipoise with the necessity of antiplatelet use, given its proven benefits in patients with

Table 5 Aneurysm patients— baseline, procedure and outcomes

Baseline characteristics[a] ($n = 24$)	Value (%)
Gender, female	17 (70.8)
Age median, y [range]	57 [28–86]
Hypertension	13 (59)
Hyperlipidemia	5 (22.7)
Diabetes mellitus	2 (9.1)
Previous aneurysm treatment	1 (4.5)
Previous stroke	2 (9.1)
Smoking	5 (22.7)
Clinical presentation	
Ruptured aneurysms	16 (66.7)
Unruptured aneurysms	8 (33.3)
mRS score at baseline	
0–2	23 (95.8)
3–5	1 (4.2)
Hunt-Hess grade	
0	3 (12.5)
1–2	12 (50)
3–4	9 (37.5)
Modified Fisher scale	
0	8 (33.3)
1–2	7 (29.2)
3–4	9 (37.5)
Aneurysm location	
Internal carotid artery	12 (50)
Middle cerebral artery	4 (16.7)
Anterior cerebral artery	2 (8.3)
Posterior circulation	6 (25)
Procedural features	
Number of devices per patient, mean (SD)	1.25 (0.5)
Treatment modality	
Flow-diverter	16 (66.7)
Stent-assisted coiling	5 (20.8)
WEB device	1 (4.2)
Flow-diverter plus stenting	1 (4.2)
Balloon-assisted coiling	1 (4.2)

Data are presented *n*/*N* (%), or mean ± SD, or median (IQR)

mRS modified Rankin Scale

[a] Comorbidity data was available for 22 patients

Table 6 Aneurysm group—discharge and follow-up

	Ruptured	Unruptured	Combined
Number of patients	16	8	24
mRS score at discharge			
0–2	9 (56.2)	7 (87.5)	16 (66.7)
3–5	5 (31.2)	1 (12.5)	6 (25)
Mortality	2 (12.5)	0	2 (8.3)
mRS score 90-days			
0–2	9 (56.2)	8 (100)	17 (70.8)
3–5	4 (25)	0	4 (16.7)
Mortality	3 (18.7)	0	3 (12.5)

Data is presented as *n* (%)

mRS modified Rankin scale

stroke. However, alternative regimens using GPI failed to demonstrate benefit in preventing death or severe disability in patients with acute stroke who underwent endovascular intervention [20]. Besides, increased ICH risk was seen with GPI, association driven especially by abciximab [20]. Nonetheless, these alternative antiplatelet agents may have an indispensable role when endoluminal devices are required.

In two meta-analysis involving patients with tandem occlusions acutely managed, the risk of ICH was 7% to 8%, with an overall mortality rate of 13 to 15% [21, 22]. Optimization of antithrombotic medications showed to be necessary for patients with tandem occlusions. Without jeopardizing the risk of stent thrombosis, careful regimen tailoring has to be made assuming the increased risk of ICH in this population. In such circumstances, tirofiban presented as a safe alternative to DAPT without compromising stent patency [23]. Similarly, patients receiving rescue stenting are also at increased risk for postinterventional ICH and stent thrombosis [24]. These complications are not uncommon and particularly associated with a tendency to poor outcomes, endorsing that an adequate antithrombotic regimen is also required [24]. In our series, 7.1% (3/42) of the cases had ICH, which poses cangrelor as a safe surrogate in those situations in which immediate potent antiplatelet effect is desired.

Cangrelor and aneurysm patients

Considering all the complications related to endovascularly treated aneurysms, thromboembolic events are the most common. It may occur in 6–12% of the patients receiving a flow-diverter or stent-assisted coiling, and it is commonly associated with permanent neurological impairment [25, 26]. Adequate platelet inhibition at the time of the procedure seems to be associated with lower morbidity of TE [27, 28]. In our study, none of the patients with aneurysm had a TE while on cangrelor. Although one may argue that all patients with unruptured aneurysms undergoing neurointervention should be on DAPT regimen upfront, cangrelor was found to be useful when decision was made to proceed without DAPT and need for stent or flow-diverter was found during the procedure.

One case of ICH (4.2%) occurred during or after cangrelor, in a patient exposed to short time infusion. In patients with subarachnoid hemorrhage due to a ruptured aneurysm, the overall risk of hemorrhagic complications is around 7% when managed with either flow diverters or stent-assisted coiling

[26, 29]. When addressing new antiplatelet regimens, GPI inhibitors demonstrated their efficacy in preventing TE, with variable rates of associated bleeding. In an early series of tirofiban use in endovascular treated intracranial aneurysms combining different dosage protocols, Chalouhi et al. reported hemorrhagic complication in 6% of patients, with no TE events noted [30]. After drug protocol revision, they could mitigate the risk of hemorrhagic complication to 2.2%, although a slightly increase in the rate of TE events (2.2%) was perceived [30]. A low rate of bleeding complication (3%) has been similarly described by Samaniego and colleagues in their experience with tirofiban use in the treatment of intracranial aneurysms [31]. Regarding abciximab and eptifibatide use in aneurysm interventions, the rate of hemorrhagic complication ranged from 0 to 4%, with variable rates of TE [32].

Cangrelor and other considerations

The rapid onset of cangrelor allows prompt use in emergencies. Cangrelor pharmacokinetics is not influenced by age, sex, and renal function, but renal function worsening may be observed in patients with a baseline creatinine clearance of < 30 ml/min [6]. We did not observe any significant difference between creatinine levels prior to and after the intervention in the present study. In the setting of unexpected complications, cangrelor also concedes the ability of a rapid reversal of antiplatelet effect if surgery or other invasive procedure is required. According to the BRIDGE trial, cangrelor demonstrated its usability to maintain antiplatelet effects in patients scheduled for surgery, without increasing the risk for major bleeding or non-bleeding adverse events [33]. Evaluation of additional cardiology studies suggested that bridging to surgery using cangrelor has safety and efficacy rates similar to eptifibatide and tirofiban and that they are all preferred over abciximab use [34]. Cangrelor has the advantage over GPI because it is rapidly reversible with infusion discontinuation. Its effect duration is about 30–60 min, allowing normalization of platelet function 4 to 12 times faster than GPI [6].

It is not uncommon that patients with cerebral ischemic disease and intracranial aneurysms are incapable of receiving oral medication. Although nasogastric and orogastric tubes can be used in such circumstances, they may delay initial therapy and increase the risk of complications [35]. Cangrelor is a suitable option when the patient cannot to take oral medications, and emergent intervention is required. Moreover, the CANTIC study and the FABOLUS FASTER trial reasserted cangrelor ability to bridge the gap in platelet inhibition with oral P2Y12 inhibitors, which may have an erratic and delayed onset [36, 37]. Among the parental drugs, tirofiban demonstrated a higher platelet inhibition level, making it the first initially preferable antiplatelet to minimize the risk of acute ischemic complications [36]. However, the idea that such an effect may implicate an increased risk of bleeding precluded the advance of GPI use. Additionally, most of the currently available data comparing these agents came from cardiology studies. Therefore, it cannot be safely extrapolated to patients undergoing neurovascular interventions.

There is no consensus in the neurovascular field about cangrelor dosage, infusion duration, and bridging therapy. The protocols from each center were built based on the cardiology clinical trials [6]. Ticagrelor was the drug of choice after cangrelor was discontinued. The rationale for this combination is that no significant interaction between these drugs has been demonstrated; therefore, ticagrelor can be administered during or after cangrelor infusion [38]. Early administration of ticagrelor (> 1.25 h before stopping cangrelor infusion) appears to modestly attenuate the increase of platelet reactivity during the first hour after discontinuation of cangrelor and augment an apparent extent of platelet inhibition [38]. Conversely, clopidogrel may be unable to inhibit platelet aggregation and activation when it is administered concomitantly to cangrelor [39]. A potential limitation of cangrelor is cost, which is higher than other available P2Y12 inhibitors. The possibility of short infusion therapy and early safe transition to long-term oral antiplatelet therapy may mitigate the economic burden. The safety demonstrated by a modified dose of cangrelor in neurointervention described by Aguilar-Salinas et al. can also be used to mitigate the cost of medication [10]. Moreover, the real economic impact cannot be drawn until periprocedural complication and long-term patient outcomes are taken into consideration, with a possible tremendous upside of the short offset of cangrelor effect.

Limitations

The present study has several limitations related to its inherent retrospective nature, heterogeneity of the population, and possible selection bias that we aimed to reduce and clarify by presenting detailed and descriptive information. The lack of a control group and the absence of independent adjudicators limit the external validity of the study. Furthermore, some patients presented in this study may have been previously reported [10–12] A prospective clinical trial is essential for eliminating such biases and confirm the safety and efficacy of cangrelor in neurovascular interventions.

Conclusion

Cangrelor represents a viable alternative for neurointer ventionalists when the use of stents or flow diverters is needed in patients not on proper antiplatelet regimen. Cangrelor allows for a secure bridging to long-term DAPT and transition to surgery in cases of unexpected complications. Prospective

studies with larger samples comparing different agents are required to precisely clarify the best protocols, safety profile, and drug effectiveness.

Acknowledgements This study aligns with the STROBE statement for observational studies.

Author's contributions All the co-authors contributed equally to prepare and accomplish this manuscript. GC was responsible for writing the manuscript, with modification upon to the co-author's revisions and suggestions. RH supervised, coordinated, and critically reviewed the manuscript.

Funding A research grand was provided by Chiesi USA, Inc. to one of the centers (Grant Number: N/A). No other specific grant from funding agencies in the public, commercial, or not-for-profit sectors were received.

Compliance with ethical standards

Conflict of interest Dr. Sourour is a consultant for Medtronic, Balt, and Microvention. Dr. Clarençon reports conflict of interest with Medtronic, Guerbet, Balt Extrusion, Penumbra (payment for readings), Codman Neurovascular, and Microvention (core lab). Dr. Dabus is a consultant for Medtronic, Microvention, Cerenovus, and Penumbra. Dr. Linfante is a consultant for Medtronic, Stryker, and Prolong Pharmaceuticals and a stockholder for InNeuroCo and Three Rivers. Dr. Hanel reports conflict of interest with Medtronic, Stryker, Cerenovous, Microvention, Balt, Phenox, MiVI, and Codman and is a stockholder for Neurvana, Elum, Endostream, Three Rivers Medical Inc., Synchron, RisT, Cerebrotech, Deinde, BendIT, and InNeurCo. All the other authors have no disclosure to report.

We declare we do not have conflict of interest with the present study.

Consent for publication Not required.

Ethics approval This study was approved by each institution local ethics committee. As this was a retrospective analysis, additional written informed consent was waived.

References

1. Fiorella D (2010) Anti-thrombotic medications for the neurointerventionist: aspirin and clopidogrel. J Neurointerv Surg 2(1):44–49. https://doi.org/10.1136/jnis.2009.001859
2. Nishi H, Nakahara I, Matsumoto S, Hashimoto T, Ohta T, Sadamasa N, Ishibashi R, Gomi M, Saka M, Miyata H, Watanabe S, Okata T, Sonoda K, Kouge J, Ishii A, Nagata I, Kira J (2016) Platelet reactivity and hemorrhage risk in neurointerventional procedures under dual antiplatelet therapy. J Neurointerv Surg 8(9): 949–953. https://doi.org/10.1136/neurintsurg-2015-011844
3. Tapp L, Shantsila E, Lip GY (2010) Role of ticagrelor in clopidogrel nonresponders: resistance is futile? Circulation 121(10):1169–1171. https://doi.org/10.1161/CIR.0b013e3181d8d929
4. Delgado Almandoz JE, Kadkhodayan Y, Crandall BM, Scholz JM, Fease JL, Tubman DE (2014) Variability in initial response to standard clopidogrel therapy, delayed conversion to clopidogrel hyperresponse, and associated thromboembolic and hemorrhagic complications in patients undergoing endovascular treatment of unruptured cerebral aneurysms. J Neurointerv Surg 6(10):767–773. https://doi.org/10.1136/neurintsurg-2013-010976
5. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, Gurbel P, Jeong YH, Mehran R, Moliterno DJ, Neumann FJ, Pereira NL, Price MJ, Sabatine MS, So DYF, Stone GW, Storey RF, Tantry U, Trenk D, Valgimigli M, Waksman R, Angiolillo DJ (2019) Updated expert consensus statement on platelet function and genetic testing for guiding P2Y(12) receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 12(16):1521–1537. https://doi.org/10.1016/j.jcin.2019.03.034
6. Qamar A, Bhatt DL (2016) Current status of data on cangrelor. Pharmacol Ther 159:102–109. https://doi.org/10.1016/j.pharmthera.2016.01.004
7. Wang D, Yang XH, Zhang JD, Li RB, Jia M, Cui XR (2018) Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: a meta-analysis. BMC Cardiovasc Disord 18(1):217. https://doi.org/10.1186/s12872-018-0948-4
8. Grigoryan M, Haussen DC, Hassan AE, Lima A, Grossberg J, Rebello LC, Tekle W, Frankel M, Nogueira RG (2016) Endovascular treatment of acute ischemic stroke due to tandem occlusions: large multicenter series and systematic review. Cerebrovasc Dis 41(5–6):306–312. https://doi.org/10.1159/000444069
9. Angiolillo DJ, Bhatt DL, Steg PG, Stone GW, White HD, Gibson CM, Hamm CW, Price MJ, Prats J, Liu T, Mahaffey KW, Harrington RA (2015) Impact of cangrelor overdosing on bleeding complications in patients undergoing percutaneous coronary intervention: insights from the CHAMPION trials. J Thromb Thrombolysis 40(3):317–322. https://doi.org/10.1007/s11239-015-1233-3
10. Aguilar-Salinas P, Agnoletto GJ, Brasiliense LBC, Santos R, Granja MF, Gonsales D, Aghaebrahim A, Sauvageau E, Hanel RA (2019) Safety and efficacy of cangrelor in acute stenting for the treatment of cerebrovascular pathology: preliminary experience in a single-center pilot study. J Neurointerv Surg 11(4):347–351. https://doi.org/10.1136/neurintsurg-2018-014396
11. Abdennour L, Sourour N, Drir M, Premat K, Shotar E, Taylor G, Godier A, Mathout J, Lenck S, Bernard R, Carpentier A, Degos V, Clarençon F (2019) Preliminary experience with cangrelor for endovascular treatment of challenging intracranial aneurysms. Clin Neuroradiol 30:453–461. https://doi.org/10.1007/s00062-019-00811-2
12. Elhorany M, Lenck S, Degos V, Sourour NA, Frasca Polara G, Shotar E, Godier A, Drir M, Mahtout J, Premat K, Alamowitch S, Samson Y, Clarençon F (2020) Cangrelor and stenting in acute ischemic stroke: monocentric case series. Clin Neuroradiol. https://doi.org/10.1007/s00062-020-00907-0
13. Linfante I, Ravipati K, Starosciak AK, Reyes D, Dabus G (2020) Intravenous cangrelor and oral ticagrelor as an alternative to clopidogrel in acute intervention. J Neurointerv Surg. https://doi.org/10.1136/neurintsurg-2020-015841
14. Cervo A, Ferrari F, Barchetti G, Quilici L, Piano M, Boccardi E, Pero G (2020) Use of Cangrelor in cervical and intracranial stenting for the treatment of acute ischemic stroke: a "real life" single-center experience. AJNR Am J Neuroradiol. https://doi.org/10.3174/ajnr.A6785
15. Goyal M, Orlov K, Jensen ME, Taylor A, Majoie C, Jayaraman M, Liu J, Milot G, Brouwer P, Yoshimura S, Albuquerque F, Arthur A, Kallmes D, Sakai N, Fraser JF, Nogueira R, Yang P, Dorn F, Thibault L, Fiehler J, Chapot R, Ospel JM (2020) A DELPHI consensus statement on antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of mechanical thrombectomy. Neuroradiology. https://doi.org/10.1007/s00234-020-02556-z

16. Ospel JM, Brouwer P, Dorn F, Arthur A, Jensen ME, Nogueira R, Chapot R, Albuquerque F, Majoie C, Jayaraman M, Taylor A, Liu J, Fiehler J, Sakai N, Orlov K, Kallmes D, Fraser JF, Thibault L, Goyal M (2020) Antiplatelet management for stent-assisted coiling and flow diversion of ruptured intracranial aneurysms: a DELPHI consensus statement. AJNR Am J Neuroradiol 41(10):1856–1862. https://doi.org/10.3174/ajnr.A6814
17. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet (London, England) 387(10029):1723–1731. https://doi.org/10.1016/s0140-6736(16)00163-x
18. Sarraj A, Hassan AE, Savitz S, Sitton C, Grotta J, Chen P, Cai C, Cutter G, Imam B, Reddy S, Parsha K, Pujara D, Riascos R, Vora N, Abraham M, Kamal H, Haussen DC, Barreto AD, Lansberg M, Gupta R, Albers GW (2019) Outcomes of endovascular thrombectomy vs medical management alone in patients with large ischemic cores: a secondary analysis of the optimizing patient's selection for endovascular treatment in acute ischemic stroke (SELECT) study. JAMA Neurology 76(10):1147–1156. https://doi.org/10.1001/jamaneurol.2019.2109
19. Alawieh A, Chatterjee A, Feng W, Porto G, Vargas J, Kellogg R, Turk AS, Turner RD, Imran Chaudry M, Spiotta AM (2018) Thrombectomy for acute ischemic stroke in the elderly: a 'real world' experience. J Neurointerv Surg 10(12):1209–1217. https://doi.org/10.1136/neurintsurg-2018-013787
20. Ciccone A, Motto C, Abraha I, Cozzolino F, Santilli I (2014) Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. The Cochrane database of systematic reviews (3):Cd005208. https://doi.org/10.1002/14651858.CD005208.pub3
21. Sivan-Hoffmann R, Gory B, Armoiry X, Goyal M, Riva R, Labeyrie PE, Lukaszewicz AC, Lehot JJ, Derex L, Turjman F (2017) Stent-retriever thrombectomy for acute anterior ischemic stroke with tandem occlusion: a systematic review and meta-analysis. Eur Radiol 27(1):247–254. https://doi.org/10.1007/s00330-016-4338-y
22. Wilson MP, Murad MH, Krings T, Pereira VM, O'Kelly C, Rempel J, Hilditch CA, Brinjikji W (2018) Management of tandem occlusions in acute ischemic stroke - intracranial versus extracranial first and extracranial stenting versus angioplasty alone: a systematic review and meta-analysis. J Neurointerv Surg 10(8):721–728. https://doi.org/10.1136/neurintsurg-2017-013707
23. Neuberger U, Moteva K, Vollherbst DF, Schönenberger S, Reiff T, Ringleb PA, Bendszus M, Pfaff JAR, Möhlenbruch M (2020) Tandem occlusions in acute ischemic stroke—impact of antithrombotic medication and complementary heparin on clinical outcome and stent patency. J Neurointerv Surg 12:1088–1093. https://doi.org/10.1136/neurintsurg-2019-015596
24. Chang Y, Kim BM, Bang OY, Baek JH, Heo JH, Nam HS, Kim YD, Yoo J, Kim DJ, Jeon P, Baik SK, Suh SH, Lee KY, Kwak HS, Roh HG, Lee YJ, Kim SH, Ryu CW, Ihn YK, Kim B, Jeon HJ, Kim JW, Byun JS, Suh S, Park JJ, Lee WJ, Roh J, Shin BS, Kim JM (2018) Rescue stenting for failed mechanical Thrombectomy in acute ischemic stroke: a multicenter experience. Stroke 49(4):958–964. https://doi.org/10.1161/STROKEAHA.117.020072
25. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF (2013) Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke 44(2):442–447. https://doi.org/10.1161/STROKEAHA.112.678151
26. Zhang X, Zuo Q, Tang H, Xue G, Yang P, Zhao R, Li Q, Fang Y, Xu Y, Hong B, Huang Q, Liu J (2019) Stent assisted coiling versus non-stent assisted coiling for the management of ruptured intracranial aneurysms: a meta-analysis and systematic review. J Neurointerv Surg 11(5):489–496. https://doi.org/10.1136/neurintsurg-2018-014388
27. Adeeb N, Griessenauer CJ, Foreman PM, Moore JM, Shallwani H, Motiei-Langroudi R, Alturki A, Siddiqui AH, Levy EI, Harrigan MR, Ogilvy CS, Thomas AJ (2017) Use of platelet function testing before pipeline embolization device placement. Stroke 48(5):1322–1330. https://doi.org/10.1161/strokeaha.116.015308
28. Hanel RA, Kallmes DF, Lopes DK, Nelson PK, Siddiqui A, Jabbour P, Pereira VM, Szikora István I, Zaidat OO, Bettegowda C, Colby GP, Mokin M, Schirmer C, Hellinger FR, Given Ii C, Krings T, Taussky P, Toth G, Fraser JF, Chen M, Priest R, Kan P, Fiorella D, Frei D, Aagaard-Kienitz B, Diaz O, Malek AM, Cawley CM, Puri AS (2020) Prospective study on embolization of intracranial aneurysms with the pipeline device: the PREMIER study 1 year results. J Neurointerv Surg 12(1):62–66. https://doi.org/10.1136/neurintsurg-2019-015091
29. Cagnazzo F, di Carlo DT, Cappucci M, Lefevre PH, Costalat V, Perrini P (2018) Acutely ruptured intracranial aneurysms treated with flow-diverter stents: a systematic review and meta-analysis. AJNR Am J Neuroradiol 39(9):1669–1675. https://doi.org/10.3174/ajnr.A5730
30. Chalouhi N, Jabbour P, Kung D, Hasan D (2012) Safety and efficacy of tirofiban in stent-assisted coil embolization of intracranial aneurysms. Neurosurgery 71(3):710–714; discussion 714. https://doi.org/10.1227/NEU.0b013e31826213f9
31. Samaniego EA, Gibson E, Nakagawa D, Ortega-Gutierrez S, Zanaty M, Roa JA, Jabbour P, Hasan DM (2019) Safety of tirofiban and dual antiplatelet therapy in treating intracranial aneurysms. Stroke and vascular neurology 4(1):36–42. https://doi.org/10.1136/svn-2018-000192
32. Dornbos D 3rd, Katz JS, Youssef P, Powers CJ, Nimjee SM (2018) Glycoprotein IIb/IIIa inhibitors in prevention and rescue treatment of thromboembolic complications during endovascular embolization of intracranial aneurysms. Neurosurgery 82(3):268–277. https://doi.org/10.1093/neuros/nyx170
33. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ (2012) Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. Jama 307(3):265–274. https://doi.org/10.1001/jama.2011.2002
34. Van Tuyl JS, Newsome AS, Hollis IB (2019) Perioperative bridging with glycoprotein IIb/IIIa inhibitors versus cangrelor: balancing efficacy and safety. Ann Pharmacother 53(7):726–737. https://doi.org/10.1177/1060028018824640
35. Trapl M, Enderle P, Nowotny M, Teuschl Y, Matz K, Dachenhausen A, Brainin M (2007) Dysphagia bedside screening for acute-stroke patients: the Gugging swallowing screen. Stroke 38(11):2948–2952. https://doi.org/10.1161/strokeaha.107.483933
36. Gargiulo G, Esposito G, Cirillo P, Nagler M, Minuz P, Campo G, Gragnano F, Manavifar N, Piccolo R, Avvedimento M, Tebaldi M, Wahl A, Hunziker L, Billinger M, Heg D, Windecker S, Valgimigli M (2020) Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over PrasugreL: a MUlticenter Randomized Open-label Trial in PatientS with ST-elevation Myocardial InFarction Referred for PrimAry PercutaneouS InTERvention (FABOLUS FASTER) Trial: Design and Rationale : The FABOLUS FASTER Trial. J Cardiovasc Transl Res. https://doi.org/10.1007/s12265-020-09969-4
37. Franchi F, Rollini F, Rivas A, Wali M, Briceno M, Agarwal M, Shaikh Z, Nawaz A, Silva G, Been L, Smairat R, Kaufman M, Pineda AM, Suryadevara S, Soffer D, Zenni MM, Bass TA,

Angiolillo DJ (2019) Platelet inhibition with Cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation 139(14):1661–1670. https://doi.org/10.1161/circulationaha.118.038317

38. Schneider DJ, Agarwal Z, Seecheran N, Keating FK, Gogo P (2014) Pharmacodynamic effects during the transition between cangrelor and ticagrelor. JACC Cardiovasc Interv 7(4):435–442. https://doi.org/10.1016/j.jcin.2013.08.017

39. Steinhubl SR, Oh JJ, Oestreich JH, Ferraris S, Charnigo R, Akers WS (2008) Transitioning patients from cangrelor to clopidogrel: pharmacodynamic evidence of a competitive effect. Thromb Res 121(4):527–534. https://doi.org/10.1016/j.thromres.2007.05.020