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CORRESPONDENCE

Bridging antiplatelet therapy with cangrelor in patients with recent intracranial stenting undergoing invasive procedures: a prospective case series

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Editor-Dual antiplatelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ receptor antagonist is the standard of care to prevent thromboembolic events for patients undergoing intracranial artery stenting for aneurysm treatment.[1,2] The risk of stent thrombosis is particularly high during the first weeks, especially when antiplatelet therapy is prematurely discontinued. Therefore, DAPT is prescribed for 3-12 months followed by aspirin alone for several months.

Some patients require unplanned invasive procedures early after stent implantation. For moderate and high bleeding risk procedures, discontinuation of $P2Y_{12}$ antagonists is needed to restore platelet function,[3] but exposes patients to an increased risk of thromboembolic events. To reduce this risk, bridging with cangrelor might be proposed by analogy to patients at very high risk of coronary stent thrombosis for whom cardiologists recommend a bridging strategy based on i.v. antiplatelet agents including cangrelor.[4,5] Cangrelor is an i.v. $P2Y_{12}$ antagonist, characterised by potent, predictable, and reversible platelet inhibition, with a quick onset and offset of action. The BRIDGE trial demonstrated that cangrelor could be safely used in patients with coronary disease to maintain platelet inhibition, despite discontinuation of oral $P2Y_{12}$ antagonists before cardiac surgery.[6]

We report the first experience of bridging antiplatelet therapy with cangrelor in patients with recent intracranial stenting who were undergoing an invasive procedure requiring $P2Y_{12}$ antagonist discontinuation. We aimed to assess the efficacy of cangrelor infusion in maintaining platelet inhibition during discontinuation of the $P2Y_{12}$ antagonist according to a standardised cangrelor bridging protocol directly adapted from the BRIDGE trial.[6] This prospective, observational study was conducted from July 2017 to July 2018 in two centres in France, after institutional review board approval Fondation Rothschild, Paris, France (CE_20171208_2_AGR). All patients provided written informed consent.

Consecutive patients managed with the standardised cangrelor bridging protocol were included. This protocol was dedicated to patients receiving DAPT (aspirin associated with clopidogrel, prasugrel, or ticagrelor) for intracranial stenting with high thromboembolic risk and undergoing any unplanned invasive procedure requiring $P2Y_{12}$ antagonist discontinuation (i.e. moderate and high bleeding risk procedures).[7] High thromboembolic risk was defined as an intracranial stent implantation within 1 month, or within 3 months if other risk factors were associated.[8]

The protocol included platelet function testing at 12 predefined time points (Fig. 1), using, as in the BRIDGE trial, the validated point-of-care VerifyNow $P2Y_{12}$ Assay (Werfen, Le Pré-Saint-Gervais, France)[6,11,12] that measures platelet aggregation to assess platelet reactivity to $P2Y_{12}$ antagonists, quantified as $P2Y_{12}$ reaction units (PRU). Patients with PRU value below 240 were considered as responders to $P2Y_{12}$ antagonists, either cangrelor or oral $P2Y_{12}$ antagonist. Collected data included patient characteristics, stents and DAPT, antiplatelet agent management, and platelet function testing. Clinical thromboembolic or bleeding complications, cerebral CT scan results, and cangrelor-related side-effects (dyspnoea, thrombocytopenia) were recorded from protocol initiation to 7 days after surgery. Descriptive statistics used median (minimum-maximum) for quantitative variables and numbers (%) for qualitative ones.

The standardised protocol was applied seven times for five high bleeding risk procedures and two moderate bleeding risk

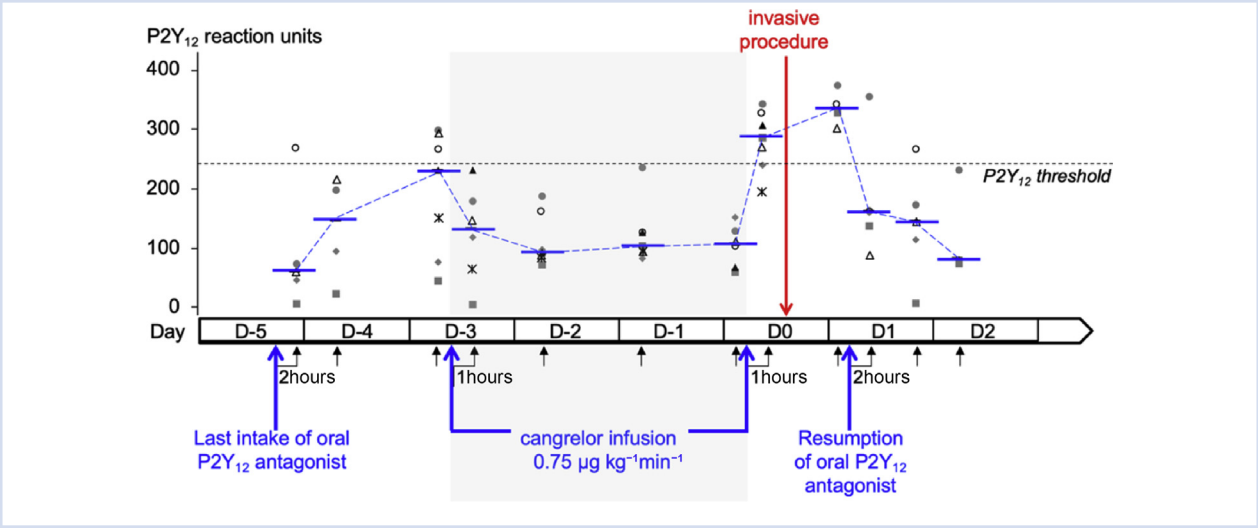

Fig 1. Time course of platelet reactivity measured with the VerifyNow $P2Y_{12}$ assay during the standardised cangrelor bridging protocol. According to the standardised protocol adapted from the BRIDGE trial,[6] last intake of oral $P2Y_{12}$ antagonists was 5 days before the procedure, and for aspirin if its discontinuation was also required (for prasugrel, last intake would have been 7 days before the procedure).[7] Cangrelor continuous i.v infusion was initiated in the ICU 3 days before the invasive procedure at 0.75 µg kg^{-1} min^{-1}, and continued up to 1 h before the procedure. Cangrelor was not administered after procedures. Brain CT was performed to exclude bleeding after neurosurgical procedures, then oral $P2Y_{12}$ antagonists were resumed 12–24 h after the procedure. The symbols represent individual results from the VerifyNow $P2Y_{12}$ assay expressed as $P2Y_{12}$ reaction units (PRU) for each of the seven episodes of bridging antiplatelet therapy with cangrelor. Long bars represent median data. The dashed line indicates 240 PRU, which is the platelet reactivity threshold for antithrombotic efficacy.[6,9,10] Small vertical arrows represent 12 predefined time points for platelet reactivity measurement, with specific timing indicated when needed. The pale grey box represents the period of cangrelor infusion. The red vertical arrow indicates the time of invasive procedure.

procedures (Table 1). Four procedures were performed within the first month after stent implantation, and three during the second month because of high thromboembolic risk factors (i.e. thrombotic events during stenting and giant-type basilar aneurysm).

Management of antiplatelet agents conformed to the protocol. Aspirin was discontinued before the five high bleeding risk procedures, and 66 VerifyNow $P2Y_{12}$ results were analysed (Fig. 1). After oral $P2Y_{12}$ antagonist discontinuation (one clopidogrel, six ticagrelor), platelet reactivity progressively increased from 63 (11–271) to 232 (47–299) PRU before cangrelor infusion. One hour after cangrelor initiation, platelet inhibition was achieved in all patients, with a median platelet reactivity of 134 (6–232) PRU, and remained stable during the 3 days of infusion, with all 26 tests showing platelet reactivity <240 PRU. One hour after cangrelor interruption, platelet function was restored in six of seven patients, with a median platelet reactivity of 287 (196–344) PRU. After the procedure, all tests showed reactivity ≥240 PRU. Resumption of oral $P2Y_{12}$ antagonists without loading dose was performed 14 (12–28) h after the procedure and induced progressive platelet inhibition with median platelet reactivity of 145 (9–267) PRU the day after the procedure.

No clinical thromboembolic or bleeding event related to antiplatelet agents occurred. All patients had a CT scan after the procedure, confirming the absence of thromboembolic or bleeding complications. No thrombocytopenia or dyspnoea was reported. One patient died a few hours after surgery, while no antiplatelet agent was restarted; the second CT scan revealed rupture of the giant aneurysm.

This first case-series of patients with recent intracranial stenting facing unplanned surgery illustrated that a standardised cangrelor bridging protocol adapted from the BRIDGE trial achieved and maintained platelet inhibition during oral $P2Y_{12}$ antagonist discontinuation, with a return to baseline platelet function within 1 h after cangrelor discontinuation.

Bridging with cangrelor aims to prevent stent thrombosis during $P2Y_{12}$ antagonist discontinuation. Recovery of platelet function observed in several patients just before cangrelor initiation suggests that a 36 h period from oral antagonist discontinuation to cangrelor infusion might be too long. Cangrelor infusion should be initiated earlier, we suggest 24 h, to maintain platelet inhibition and reduce thrombotic risk. Surgery with normal platelet function reduces procedure-associated bleeding risk. $P2Y_{12}$ antagonist discontinuation strictly limited to surgery and the initial following hours was associated with no bleeding in our study, in contrast to perioperative continuation of DAPT that can increase bleeding risk.[13] Bleeding prevention is essential, as patients treated with antiplatelet agents who experience perioperative bleeding are also at higher risk of major adverse cardiovascular events.[14–16] In a cohort study of 1134 consecutive patients with coronary stents undergoing non-cardiac surgery, 37% of patients with bleeding complications also had cardiovascular complications, and bleeding occurred first in 40% of patients.[14] Such results were also observed in patients without stents: in the PeriOperative ISchemic Evaluation-2 Trial that assessed aspirin *vs* placebo in patients undergoing non-cardiac surgery (<4% of patients had prior percutaneous coronary intervention), life-threatening or major bleeding was an

Table 1 Characteristics of seven cases of bridging with cangrelor.

Variable	Value
Patient characteristics	
Age (yr)	56 (50–62)
Female (*n*)	4
Weight (kg)	65 (50–100)
Medical history (*n*)	
Hypertension	6
Diabetes mellitus	2
Current smoker	5
Prior haemorrhagic or ischaemic stroke	0
Stent characteristics	
Type of stent (*n*)	
Flow diverter	4
Nitinol stent	3
Aneurysm location (*n*)	
Internal carotid artery	4
Anterior communicating artery	2
Basilar artery	1
Stenting for ruptured aneurysm	5
Invasive procedures (*n*)	
High bleeding risk procedures	
Ventriculo-peritoneal shunt placement	2
External ventricular drain change	1
External ventricular drain removal	2
Moderate bleeding risk procedures	
Gastrostomy	1
Mediastinal biopsy+lumbar puncture	1
Antiplatelet treatment before bridging (*n*)	
Aspirin+ticagrelor	6
Aspirin+clopidogrel	1

independent predictor of myocardial infarction, suggesting supply-demand mismatch of myocardial oxygen.[15] These data advocate for careful management of antiplatelet agents in the perioperative setting to prevent bleeding.

This study has several limitations: it was observational and included a small number of patients; a control group is lacking because ethical aspects prohibited the inclusion of a placebo control group in patients with high thrombotic risk; and platelet function testing is not available in many hospitals.

Bridging antiplatelet therapy with cangrelor exposes patients to thrombotic and bleeding risks and has cost implications related to the drug itself, platelet function testing, and hospitalisation duration. Thus, bridging should be restricted to patients with recent intracranial stenting undergoing invasive procedures requiring oral $P2Y_{12}$ antagonist discontinuation. In such situations, cangrelor may represent an effective strategy to maintain adequate platelet inhibition until the time of surgery, while avoiding complications of both intracranial stent thrombosis and surgical bleeding.

Authors' contributions

Study design: AG, CD, JMD, MMa.
Patient recruitment, data collection, and analysis: MMe, MdM, SD, LT.
Conceived figures, drafted manuscript, and wrote the manuscript: AG, MdM.
Discussed results, provided critical revisions of the manuscript, and approved final manuscript: all authors.

Declaration of interest

The authors declare that they have no conflicts of interest.

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