ABSTRACT

SUMMARY: In the field of interventional neuroradiology, antiplatelet agents are commonly used to prepare patients before the implantation of permanent endovascular materials. Among the available drugs, clopidogrel is the most frequently used one, but resistance phenomena are considered to be relatively common. Prasugrel and ticagrelor were recently added to the pharmacologic arsenal, but the safety of these agents in patients undergoing neuroradiological procedures is still a subject of discussion. The cumulative experience with both drugs is less extensive than that with clopidogrel, and the experience with patients in the neurology field is less extensive than in the cardiology domain. In the present article, we provide a narrative review of studies that investigated safety issues of oral P2Y12 inhibitors in interventional neuroradiology and discuss potential routes for future research.

ABBREVIATION: CYP = cytochrome P450

ANTIPLATELET AGENTS ARE COMMONLY USED TO PREPARE PATIENTS BEFORE THE IMPLANTATION OF PERMANENT ENDOVASCULAR MATERIALS. IN THE FIELD OF INTERVENTIONAL NEURORADIOLoGY, ORAL P2Y12 INHIBITORS ARE USED IN COMBINATION WITH ASPIRIN FOR DUAL-ANTIPLATELET THERAPY. CLOPIDOGREL IS THE MOST FREQUENTLY USED P2Y12 INHIBITOR FOR THIS KIND OF PREPARATION. AS A PRODRUG, IT IS TRANSFORMED INTO ITS ACTIVE FORM BY THE LIVER AND ACTS THROUGH AN IRREVERSIBLE BLOCKADE OF THE ADENOSINE DIPHOSPHATE RECEPTOR IN THE PLASMA MEMBRANE OF PLATELETS.1-7 THERE IS EVIDENCE OF A PROPHYLACTIC EFFECT IN SUBJECTS WITH A HISTORY OF TRANSIENT ISCHEMIC ATTACK AND ISCHEMIC STROKE.8,9 CLOPIDOGREL USE ALSO REDUCES THE OCCURRENCE OF THROMBOEMBOLIC ADVERSE EVENTS DURING ANGIOPLASTY AND STENT PLACEMENT.1,4,10-12 IN SOME INDIVIDUALS, HOWEVER, THE USE OF CLOPIDOGREL DOES NOT HAVE THE DESIRED EFFECT. NONRESPONSIVE PATIENTS ARE USUALLY CLASSIFIED AS DRUG-RESISTANT.2-5,10,13-17 BECAUSE INTERVENTIONAL NEURORADIOLOGY PROCEDURES NOT INFREQUENTLY INCLUDE THE IMPLANTATION OF DEFINITIVE ENDOVASCULAR PROSTHESES SUCH AS STENTS OR FLOW DIVERSERS, RESISTANCE MAY LEAD TO INTRASTENT THROMBOSIS WITH VESSEL OCCLUSION OR STENOSIS.5,11,16-21 THIS INCREASED RISK SEEMS TO NOT ONLY CONCERN THE PERIOPERATIVE PERIOD BUT EXTENDS POSTOPERATIVELY AS WELL.2,3,14

SINCE THE ADVICE OF THE FDA ON CLOPIDOGREL HYPORESPONSIVENESS IN 2010,22,23 ALTERNATIVE DRUGS HAVE BEEN STUDIED AT GREATER LENGTHS. IN THE CONTEXT OF BOTH PREOPERATIVE PREPARATION AND POSTOPERATIVE ANTIAGGREGATION, 2 OTHER ORAL AGENTS, PRASUGREL24-37 AND TICAGRELOR,38-46 HAVE BEEN INTENSIVELY DISCUSSED (ONLINE SUPPLEMENTARY DATA). PRASUGREL IS A THIRD-GENERATION THIENOPYRIDINE, A GROUP OF DRUGS THAT IRREVERSIBLY INHIBITS THE P2Y12 RECEPTOR AND, CONSEQUENTLY, ADENOSINE DIPHOSPHATE–DEPENDENT ACTIVATION AND PLATELET AGGREGATION.47 TICAGRELOR IS A CYCLOPENTYLTRIAZOLOPYRIMIDINE, WHICH IS DIRECTLY ACTIVE AFTER ADMINISTRATION, THEREBY DIFFERENTIATING IT FROM THIENOPYRIDINES.48 THE CUMULATIVE EXPERIENCE WITH THESE 2 ANTIPLATELET AGENTS IN INTERVENTIONAL NEURORADIOLOGY IS, HOWEVER, LESS EXTENSIVE THAN WITH CLOPIDOGREL. IN THE PRESENT ARTICLE, WE PROVIDE A NARRATIVE REVIEW OF STUDIES THAT INVESTIGATED SAFETY ISSUES WITH ORAL P2Y12 INHIBITORS (CLOPIDOGREL, PRASUGREL, AND TICAGRELOR) IN INTERVENTIONAL NEURORADIOLOGY AND DISCUSS POTENTIAL ROUTES FOR FUTURE RESEARCH.

CLOPIDOGREL RESISTANCE IN INTERVENTIONAL NEURORADIOLOGY

Resistance to clopidogrel increases the risk of endovascular procedures, a phenomenon that was first described in the cardiology literature.2-5,11,14,16,19,28,29,49-51 THE CRITERION STANDARD METHOD TO IDENTIFY RESISTANT PATIENTS IS LABORATORY LIGHT TRANSMISSION AGGREGOMETRY.5-7 TO DETECT POOR RESPONDERS PROMPTLY, POINT-OF-CARE TESTS HAVE BEEN DEVELOPED AND WIDELY USED BOTH FOR THEIR CONVENIENCE AND SPEED. SPECIFICALLY, THEY ASSAY THE ACTION OF THE DRUG AT
bedside and make possible adjustments to the care of high-risk patients. One of the most widely distributed is the VerifyNow P2Y12 assay (Accumetrics), a portable device that enables measurement in a blood sample without preparation or centrifugation.\textsuperscript{5,7} It presents the results initially in P2Y12 reactive units and allows the calculation of the percentage of inhibition.

The values (either the number of units or the percentage of inhibition) can be used to classify the patient as a responder or non-responder by applying a threshold defined by the operator. Many authors consider >40% to be an adequate inhibition rate.\textsuperscript{2,5,22,23} However, because an intermediate response is observed above 20%, others propose to consider only patients with <20% as resistant.\textsuperscript{14} The manufacturer presents 208 P2Y12 reactive units as the target under which specific evidence of a pharmacodynamic effect has been observed, being also associated with the reduction of thrombosis and increase of bleeding rates. Neurointerventional studies, however, have used different cutoffs in varied contexts, varying from 208 to 295.\textsuperscript{12,20,27,29,31,40,54} A value of <60 was reported to be associated with a higher risk of hemorrhagic complications.\textsuperscript{28,29} In a study of 279 patients under dual antiplatelet therapy, a value of 175 was observed to discriminate patients with hemorrhagic complications from those without.\textsuperscript{21} In another study in 47 patients, focused on the bleeding risk of the 7 patients defined as hyper-responders (\textgeq72% of platelet inhibition), 3 patients (42.8%) had a major bleeding complication.\textsuperscript{55}

An important clinical issue is the degree of platelet inhibition obtained after a single loading dose—ie, a higher dose of the drug that can be administered at the beginning of the treatment before dropping to a lower maintenance dose. By means of 40% as a threshold, up to 64% of patients exhibited a low response after 300 mg of clopidogrel.\textsuperscript{2,5,11,52,53} The absence of a precise definition of low response as well as the multiplicity of diagnostic methods have contributed to the variation in the figures reported, especially in the initial series. Some studies have suggested that the drug resistance is related to genetic polymorphisms, but individual factors, such as diabetes mellitus, age older than 65 years, hypercholesterolemia, weight, adherence to treatment, and concomitant drugs also play a role.\textsuperscript{2,3,5,6,15,56}

A typical example of genetic polymorphism is the alteration of the enzyme cytochrome (CYP)2C19, which is involved in the metabolism of clopidogrel. Altered alleles lead to high platelet reactivity despite clopidogrel administration, but great variability is noted within each genotype group.\textsuperscript{57} Genetic alterations involving the P2Y12 receptor also occur.\textsuperscript{1,5} Nevertheless, because resistant individuals have less exposure to the active metabolite, it is possible that the resistance is more associated with the concentration of the active metabolite than with insufficient sensitivity of the P2Y12 receptor.\textsuperscript{58} The effectiveness of clopidogrel depends on factors that influence both the metabolite concentration and final effect. The result is a variable response.\textsuperscript{57}

Specific genetic testing can identify patients with constitutional alterations in clopidogrel metabolism.\textsuperscript{14} In clinical practice, these tests are generally used after the patient shows a clinical or laboratory manifestation of resistance. A particular difficulty is the time these examinations usually demand (\textgeq5 days). It is also known that a subject can present with the normal allele and be resistant for other reasons. Conversely, a given patient who has the altered allele may have low platelet activity due to mechanisms not yet fully elucidated, limiting the predictive value of genetic testing.\textsuperscript{57} Considering the cost and impracticality of genetic testing and the great variability of the causal factors, it has been preferable in daily practice to perform tests that evaluate the final drug effect, ie, platelet aggregation.\textsuperscript{7}

Interest in the epigenetics of clopidogrel resistance has also increased in the past years. Most studies focus on microRNA and DNA methylation. MicroRNA molecules can bind to RNA and interfere with transcription. MiR-26, miR-28, and miR-96 are possible regulators of platelet activity through different mechanisms.\textsuperscript{59,60} Considerable discussion exists regarding miR-223 as a potential biomarker because higher miR-223 levels were associated with better platelet inhibition after clopidogrel administration.\textsuperscript{60,61} Hypomethylation of a number of promoters, such as abc1, abc3, and P2RY12 possibly decreases platelet reactivity, but the results have not been homogeneous.\textsuperscript{60,62} Decreased methylation of P2RY12 was associated with clopidogrel resistance in patients with coronary artery disease.\textsuperscript{60,63}

The FDA has recommended considering alternative dosing strategies for clopidogrel or using another antiplatelet drug in resistant patients.\textsuperscript{22,23} Although the increase in the loading dose from 300 to 600 mg decreases the percentage of low responses in general, doubling the dose in patients with the genetic mutation did not significantly alter final aggregation rates.\textsuperscript{3,5,22} Patients with increased baseline levels of platelet aggregation are also more susceptible to antiplatelet resistance; this issue is seen in those presenting with diabetes mellitus or recent thrombotic events.\textsuperscript{5,52,56} An illustration of this issue is that low-dose aspirin does not have the same antithrombotic effects if there is concomitant arthritis, surgical stress, or diabetes mellitus.\textsuperscript{65} In this specific situation, it is believed that the oxidative stress and elevated C-reactive protein can compensate for and overcome the inhibitory effect on cyclooxygenase 1.

Thromboembolic complications are multifactorial. Failure of therapy may also be a result of drug interactions. Among the main interactions, the use of proton pump inhibitors, particularly omeprazole, has been described as a factor that decreases the active metabolite of clopidogrel by altering the prodrug metabolism.\textsuperscript{7,14} Ketoconazole is a potent CYP3A inhibitor and has also been reported to reduce the plasma level of the active metabolite of clopidogrel by about 50% in addition to reducing the antiplatelet effect.\textsuperscript{66,67} The same was observed to a lesser degree with erythromycin and troleandomycin, which are CYP3A4 inhibitors.\textsuperscript{67} Aspirin resistance, though less frequent, also increases the risk of undesirable events in patients on dual-antiplatelet therapy.\textsuperscript{68} On the other hand, rifamycin is acknowledged to be a CYP3A4 inducer, capable of increasing the active metabolite formation and antiplatelet effect of clopidogrel.\textsuperscript{67,69} Similar observations have been made in smokers for reasons possibly related to the CYP1A1-inducing effect of polycyclic aromatic hydrocarbons.\textsuperscript{70-72}

An inverse relationship between body mass and response to clopidogrel has also been noted.\textsuperscript{2,6,11,15} In 2008, Lee et al\textsuperscript{2} reported an association between high body mass and a low response in a population of patients with cerebrovascular disease. In 2014, the results of 182 VerifyNow tests in a consecutive series of
interventional neuroradiology procedures were analyzed after a 300-mg loading dose.\textsuperscript{11} In subjects weighing >60 kg, significantly lower percentages of antiaaggregation and a higher prevalence of resistance were observed, regardless of the cutoff (20% or 40%). This phenomenon may have important implications regarding the way we prepare patients for neuroendovascular treatment. Although the exact mechanism is not yet understood, it is supposedly related to the volume of distribution and pharmacokinetics of the drug, as is the case with other antithrombotic agents (eg, heparin and platelet glycoprotein IIb/IIIa inhibitors).\textsuperscript{52} For clopidogrel, dose adjustment has not been regularly advocated in the past, and traditional preoperative preparation protocols have usually recommended a homogeneous single loading dose of 300 mg.\textsuperscript{2,52}

Some authors have observed an association between body mass index and resistance to clopidogrel.\textsuperscript{52,73} This association with the index, not just absolute values of body mass, favors implicating metabolic phenomena, not just a pharmacokinetic mechanism, in clopidogrel resistance. Wagner et al\textsuperscript{46} hypothesized that less exposure to the active metabolite may be a mechanism of low response in overweight patients. It has been suggested that overweight patients may have higher baseline platelet activity compared with normal-weight patients. This difference is maintained under clopidogrel, with overweight subjects presenting suboptimal responses more frequently.\textsuperscript{72}

It is important to distinguish truly resistant patients and those for whom clopidogrel inefficacy is due to pharmacokinetics. In individuals who are resistant due to pharmacodynamic factors, dose changes would have no significant effect. For the other patients, case-by-case dosage adjustment can be discussed. Consequently, the use of the term “resistance” to describe every therapeutic failure may not be appropriate because it would denote a necessarily persistent situation. In patients undergoing coronary stent angioplasty, increasing the standard dose was reported to improve platelet inhibition without increasing the risk of bleeding.\textsuperscript{52} Nevertheless, these data should be interpreted with caution because patients with cerebrovascular disease belong to a very different population, and hemorrhagic accidents are more frequent in neuroendovascular procedures than in interventional cardiology. Interest in tailoring doses was, however, first and more frequently addressed in cardiology than in neuroradiology.\textsuperscript{54,74-77} A loading dose of 600 mg was reported to reduce the proportion of low responders, though not all patients would benefit from such an increased dose.\textsuperscript{12,64}

**Novel Oral P2Y12 Inhibitors: Prasugrel and Ticagrelor**

**Prasugrel.** In 1993, Japanese researchers claimed the patent for a series of hydrothiopyridine derivatives with antithrombotic activity.\textsuperscript{78,79} Among these, prasugrel was shown to have a greater antithrombotic effect than clopidogrel. Studies in rodents showed that it had additional properties, such as a longer and more intense effect.\textsuperscript{78} In 2009, the FDA approved prasugrel for use in patients with acute coronary syndrome undergoing percutaneous coronary intervention.\textsuperscript{80}

Prasugrel is also a prodrug and must be metabolized to be active. After being absorbed, it is rapidly ester-hydrolyzed to an inactive thiolactone, which, in turn, is oxidized in the liver by CYP, leading to the formation of the active metabolite R-138727.\textsuperscript{47,78} Despite being extensive, the metabolism of prasugrel is rapid. The presence of the active metabolite in the plasma approximately 15 minutes after its administration is a consequence of this phenomenon.\textsuperscript{81} Its half-life is around 7.4 hours, the maximum plasma concentration occurs around 30 minutes, and the antplatelet action lasts for about 96 hours.\textsuperscript{66,78,81} It is possible to obtain clinically meaningful levels of the active metabolite with daily maintenance doses of 5 or 10 mg, much lower than those used for clopidogrel (75 mg per day).\textsuperscript{78} The activation, which occurs in 1 hepatic step, is different from that of clopidogrel, which requires a second oxidation stage.

Prasugrel is mainly converted by CYP3A4. Because it is converted by a number of isoenzymes of the CYP complex, some studies have observed that when a single isoenzyme involved in the formation of R-138727 is compromised, the others may fulfill the need instead, ensuring the formation of the active metabolite.\textsuperscript{78} In this case, it is possible that prasugrel is less subject to hypersensitivity phenomena than clopidogrel.\textsuperscript{67} The use of prasugrel is contraindicated in patients with severe hepatic impairment due to their metabolism by CYP, and the dose adjustment may be used in the case of mild liver disease, though there is no clear evidence on the subject.

Proton pump inhibitors, such as omeprazole and pantoprazole, are known to reduce the effect of clopidogrel due to interference with CYP2C19.\textsuperscript{85} Interaction of these drugs with prasugrel was not observed.\textsuperscript{78} It is believed that prasugrel does not require dosage adjustment when administered concomitantly with drugs that are metabolized by the CYP.\textsuperscript{77} The use of the antiretroviral ritonavir has, however, been reported to inhibit the formation of the active metabolite.\textsuperscript{67} Additionally, concomitant administration of ketoconazole (a potent CYP3A5 inhibitor) decreased the maximum active metabolite concentration of prasugrel by 46%, despite its antplatelet effect being preserved.\textsuperscript{66,67}

Patients with diabetes mellitus have been reported to respond favorably to prasugrel as part of dual-antiplatelet therapy.\textsuperscript{78,82} The greater efficacy of prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) over clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) in reducing the combined rate of death from cardiovascular disease, nonfatal acute myocardial infarction, and stroke after percutaneous coronary intervention in patients with acute coronary syndrome was observed in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) study.\textsuperscript{83,84} but prasugrel led to an increase in the rate of bleeding. In the secondary prevention of recurrent stroke, a lower dose (3.75 mg) was assessed in a clinical trial with 3747 Japanese patients, the comparison of PRAsugrel and clopidogrel in Japanese patients with ischemic STROkE (the PRASTRO-I trial).\textsuperscript{85} The study failed to demonstrate that this lower dose of prasugrel was noninferior to 75 mg of clopidogrel because the relative-risk confidence interval exceeded predefined margins. In the trial, the proportion of patients who experienced bleeding was similar. This was also the case in the subsequent study (PRASTRO-II), which compared 2.5 and 2.75 mg of prasugrel with 50 mg of clopidogrel.\textsuperscript{86}

Prasugrel is similar in its structure and mechanism of action to clopidogrel, but its greater potency and the faster onset may be advantageous when a fast preoperative preparation or rescue
antiaggregation is needed.\textsuperscript{47} Conversely, these characteristics increase the severity of bleeding if it occurs. In addition, considerable discussion exists on whether they increase the risk of intracranial hemorrhage per se.

A comparative study with 76 patients in neurology procedures ($n = 86$) found a higher risk of bleeding with dual-antiplatelet therapy when using a full dose of prasugrel (60-mg loading dose and 10-mg/day maintenance) than when using clopidogrel.\textsuperscript{24} Hemorrhagic complications were observed in a total of 3.6\% patients treated with clopidogrel and aspirin and 19.4\% of those treated with prasugrel and aspirin. This observation suggests that the antiplatelet regimen could be related to an increase in the rate of bleeding. Various degrees of vascular injury may occur during endovascular procedures, ranging from clinically insignificant arterial wall damage to clear perforations with active extravasation. The platelet inhibition obtained with prasugrel and aspirin may facilitate occult bleeding progressing to a major, clinically significant hemorrhagic event.\textsuperscript{24} For many authors, clopidogrel remains the drug of choice. In cases of resistance, other antiplatelet agents may be necessary. Patients under prasugrel in interventional neuroradiology series were mostly those who presented with resistance to clopidogrel.\textsuperscript{24,78} Moreover, sample sizes in interventional neuroradiology have been relatively smaller.

With a 60-mg loading dose of prasugrel, approximately 50\% platelet inhibition is observed at 30 minutes and approaches the maximum effect before 2 hours.\textsuperscript{78} A daily dose of 10 mg also results in a greater platelet inhibition than that achieved with the usual 75 mg of clopidogrel.\textsuperscript{47,78} Patients taking clopidogrel who switch to prasugrel do not lose the antiplatelet effects in the transition. Because prasugrel is an irreversible inhibitor, it takes 7–10 days for the patient to experience normal platelet function.\textsuperscript{13,47} The high risk of hemorrhage and the increasing use of prasugrel in an at-risk population made it necessary for the FDA to issue a warning.\textsuperscript{47} It was recommended to prefer a reduced maintenance dose (5 mg/day) in patients weighing <60 kg and to reserve this drug for patients younger than 75 years of age in the presence of a risk factor for thrombosis.

In 2013, a chart review of 16 cases of patients allergic or hyporesponsive to clopidogrel who received prasugrel and underwent neurointerventional procedures reported favorable results with no cerebral ischemia or evident intracranial hemorrhage.\textsuperscript{36} In a French study with 2 parallel groups of 100 patients, the use of prasugrel in patients undergoing endovascular treatment of non-ruptured cerebral aneurysms was not related to hemorrhagic events.\textsuperscript{37} Prasugrel also potentially reduced, in comparison with clopidogrel, the clinical consequences of thromboembolic complications. In a retrospective study on 297 cases, a notable reduction in the frequency of procedure-related thromboembolism in subjects with unruptured cerebral aneurysms was observed.\textsuperscript{27} The VerifyNow system showed lower values of P2Y12 reactive units and higher inhibition percentages in the prasugrel group, but the rate of hemorrhagic complications did not increase.

In a recent study, Higashiguchi et al.\textsuperscript{31} in 2021, proposed a tailored therapy in which prasugrel replaced clopidogrel when the result of the VerifyNow assay was inferior to 240 P2Y12 reactive units. They observed a reduction in the frequency of thromboembolic complications after treatment of unruptured aneurysms (16\% versus 6\%, $P < .048, n = 217$) after a 1-month follow-up without an increase in the rate of hemorrhagic complications. It is, therefore, clear that specific prospective studies on patients in neurovascular procedures and larger samples are now necessary.\textsuperscript{36}

**Ticagrelor.** Ticagrelor is rapidly absorbed, has a half-life of 7–12 hours, and reaches its maximum concentration approximately 2–3 hours after administration.\textsuperscript{48} A classic loading dose is 180 mg, and the maintenance dose is 90 mg.\textsuperscript{60} The drug has a reversible effect on P2Y12 receptors, making it a temporary allosteric antagonist. Thus, its effect can be assessed by VerifyNow.\textsuperscript{89} Because ticagrelor does not require hepatic activation, it may be advantageous in patients with a genetic mutation in the enzyme CYP2C19 or when the situation calls for urgent antiaggregation.\textsuperscript{86} The prevalence of hyporesponsiveness appears to be extremely low.\textsuperscript{39}

Ticagrelor is known to be a substrate and a weak inhibitor of CYP3A. It is extensively metabolized by CYP3A4 and, to a lesser, extent by CYP3A5.\textsuperscript{50} As a consequence, strong CYP3A4 inhibitors, such as ketoconazole, increase ticagrelor exposure, and combined use is not recommended.\textsuperscript{48,91} Moderate inhibitors, however, such as diltiazem are not contraindicated. Additionally, potent inducers of CYP3A4 may reduce the efficacy of the drug. For example, rifampicin may decrease its maximum concentration. Coadministration of ticagrelor with CYP3A4 substrates with a narrow therapeutic index is also not recommended because it can increase the exposure of these drugs. Statins are metabolized by CYP3A4. Within an inter-study action study in healthy volunteers, an increase in the maximal concentration of simvastatin was observed when coadministered with ticagrelor.\textsuperscript{62} Coadministration of ticagrelor with doses of simvastatin or lovastatin of >40 mg/day could result in adverse effects caused by the statins, such as gastrointestinal disorders and headache.\textsuperscript{91}

Ticagrelor leads to platelet inhibition faster and more intensively than clopidogrel.\textsuperscript{93} Its effects also fade more quickly. Ticagrelor coadministered with aspirin has been shown to lead to adequate P2Y12 inhibition in patients resistant to clopidogrel.\textsuperscript{25} A randomized, double-blind trial comparing ticagrelor with clopidogrel in patients with coronary artery disease found that ticagrelor was associated with higher rates of inhibition, including in low responders to clopidogrel.\textsuperscript{90} A multicentric trial of 18,624 patients with acute coronary syndrome showed that ticagrelor was characterized as a fast and potent antiplatelet agent, with an overall favorable safety profile in patients in cardiology studies.\textsuperscript{48,94,95} Compared with classic treatment regimens, the drug appears to be more effective in preventing ischemic coronary events but comes with an increase in the rate of non-procedure-related bleeding.\textsuperscript{48,95}

In an interventional neuroradiology series in 2014, eighteen subjects who did not respond to clopidogrel were treated with ticagrelor.\textsuperscript{39} The result was favorable, in the sense that ticagrelor could effectively replace clopidogrel, but 1 event is worth noting: A patient nonresponsive to clopidogrel was forced to switch from ticagrelor to clopidogrel after a flow-diverter placement due to a shortage of the drug. This patient developed partial thrombosis after his treatment was changed. This incident further suggests the efficacy of ticagrelor but calls attention to the potentially serious consequences of stopping treatment with the drug. In this context, ticagrelor may be considered an alternative antiplatelet agent, but its indication should be evaluated on a case-by-case
basis. Chronic use of ticagrelor is associated with greater drawbacks than clopidogrel.

Elderly patients have a higher drug exposure compared with younger ones, and women have greater exposure than men. Most interesting, elderly patients also have a lower platelet aggregation index, suggesting that platelets are less sensitive in this subgroup. Despite these differences, no age- or sex-related dose adjustment has been recommended. Renal insufficiency does not seem to influence dosing needs to a significant degree. However, exposure is increased in patients with mild hepatic impairment. Because changes in pharmacodynamics or tolerability are not significant, dose adjustment in these groups does not seem necessary, but caution must be used because there are still no available data on patients with moderate or severe hepatic impairment.46

Bleeding is the main safety concern. An increased risk of minor bleeding with ticagrelor compared with clopidogrel was reported, though there were few major bleeding events. Although the percentages were small, an increase in fatal intracranial bleeding with ticagrelor compared with clopidogrel (0.1% versus 0.01%) was noted in the PLATelet inhibition and patient Outcomes (PLATO) trial in patients with a cardiovascular study.46 Bleeding times also increase in patients on ticagrelor compared with those on clopidogrel.46,47 Dyspnea is another frequent adverse event, but the need to discontinue therapy because of it does not seem to be very common.46,49

Narata et al,46 in 2019, analyzed a consecutive series of 154 patients with unruptured aneurysms undergoing stent placement or flow-diverter implantation procedures under aspirin and ticagrelor. The authors observed more neurologic complications than in previous neurointerventional reports that used aspirin with ticagrelor or clopidogrel, but all observed deaths (n = 4) were related to intracranial hemorrhaging. They reported that the number of neurologic complications was lower when a lower dose of heparin was used and indicated that more neurovascular studies comparing clopidogrel with ticagrelor under different heparin regimens are necessary.46 In the same year, Soize et al45 reported a study of 80 patients undergoing aneurysm treatment with a flow diverter/disrupter in which dual-antiplatelet therapy with aspirin and clopidogrel was compared with aspirin and ticagrelor. After 1 month, no significant difference was observed between groups regarding thromboembolic complications or hemorrhage. After 3 months, no delayed infarction or hemorrhage was observed.

In a 2020 study of 72 patients comparing rates of thromboembolism after stent-assisted coiling for unruptured aneurysms, post-procedural infarction was observed on diffusion-weighted imaging more frequently in the ticagrelor group than in the aspirin-plus-clopidogrel group. After multivariable logistic regression analysis, however, the authors concluded that postprocedural infarction was more associated with aneurysm type than antiplatelet medication per se in their series.

In the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial, which compared ticagrelor with aspirin in 13,199 patients with acute stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days, and no increase in intracranial bleeding was observed. Nevertheless, increased rates of minor bleeding and dyspnea were noted. The rates of discontinuation of treatment due to dyspnea or any bleeding were 6.2% and 1.3%, respectively, in the ticagrelor group and 1.4% and 0.3%, respectively, in the aspirin group. More recently, the Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES) trial compared ticagrelor and aspirin to aspirin alone for the same conditions in a total of 11,016 patients. The risk of a stroke or death within 30 days was lower with dual therapy, but there was no difference in the incidence of disability. Severe bleeding was more frequent with ticagrelor (n = 28, 0.5% of severe bleeding, 0.4% intracranial bleeding). These rates of bleeding in the intracranial space were within the range observed with patients taking clopidogrel and aspirin in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial (0.3% with moderate and severe hemorrhage, 0.3% with hemorrhagic stroke) and the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (0.9% with major hemorrhage, 0.2% with intracranial bleeding).3,49

An important topic of discussion is the reversibility of the effect of ticagrelor. It was reported that although the antiaggregation induced by aspirin could be efficiently reversed by platelet transfusion, the same cannot be accomplished with ticagrelor. Even in high doses, platelets do not seem to be a potent antidote. Because the drug reversibly binds the P2Y12 receptor, the suggested mechanism is that circulating ticagrelor and its active metabolite inhibit the fresh platelets administered. In an in vitro and ex vivo study, gel-filtered platelets from patients who had received ticagrelor were shown to suppress donor platelet function after mixing, suggesting the transfer of ticagrelor to the donor platelets without recovery of the responsiveness of the patient’s platelets. Antibody-based strategies are emerging as a potential pathway for achieving rapid drug reversal.

CONCLUSIONS

In the domain of interventional neuroradiology, antiplatelet treatment is intended to reduce the risk of perioperative thromboembolic phenomena. For preoperative preparation, clopidogrel is used very frequently and point-of-care aggregometry tests have been developed. Nevertheless, in a considerable number of patients, significant resistance to the drug is observed in association with a risk for cerebral ischemia after implantation of intracranial endovascular material. Prasugrel and ticagrelor are proving to be promising drugs, given their effective use in patients with resistance to clopidogrel. There remains, however, a need for larger studies on patients in neurointerventional procedures, in particular regarding treatment tailoring. The same is true of reversal strategies, particularly for ticagrelor.

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