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Commentary to: Ticagrelor Use in Indian Patients Undergoing Neuroendovascular Procedures: A Single-Center Experience

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The use of antiplatelet drugs is a strategy that is adopted regularly during peri-neurointervention treatments.[1] As suggested by the authors,[2] the objective of anti-platelet therapy is a target to prevent thromboembolic complication during neurointerventional procedure with stents and flow diverters. Despite use of anti-platelets and anti-coagulant like a heparin, patients may present unexpected the thromboembolic event due to the variable response throughout pre-medication.[3]

In this single-center experience, the authors used pre-intervention light transmission aggregometry to find out cases of clopidogrel resistance. Lemesle et al.[4] reported difficulties in the correlation between different techniques (light transmission aggregometry [LTA], Verify Now [VN] P2Y, and vasodilator-stimulated phosphoprotein [VASP]) to identify "true poor responders" to clopidogrel. Among the available tests for clopidogrel resistance, 3 methods are widely used and accepted: light transmission aggregometry with ADP, Verify Now, and VASP. However, none of these tests are recommended as the gold standard for the same. Lemesle et al.[4] demonstrated the same assessing response from clopidogrel use in 100 cases for platelet reactivity with 600 mg clopidogrel loading dose using 3 tests between 18 and 24 hours. When clopidogrel response was tested using a continuous variable, there was a good correlation among each test. However, when clopidogrel response was analyzed by a pre-specified cut-off point to define patients as "poor or good responders", only 47% of patients were defined as "good" or "poor responders" by the 3 tests. Altogether, 33% of the patients were defined as "poor responders" by only 1 test, 20% by 2 tests and only 16% by 3 tests. Thus, while light aggregometry did help the authors in this series, it was perhaps because of the small sample size of Ticagrelor treated cases (n=32) and an even smaller number of intracranial aneurysm cases (n=20) that this finding never emerged. This is because while all 3 tests specifically test for the ADP pathway, there are several ways in which the ADP pathway is activated: P2Y1, P2Y12, and P2X1. Clopidogrel is only specific for P2Y12 and thus will not affect the other 2 receptors, which may be still activated, and thus show false positive values, es-

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pecially in VN and LTA tests. It is only the VASP assay that analyzes directly and specifically the P2Y12 and hence is specific for clopidogrel. It thus follows that many of the cases may have been given Ticagrelor instead of the trusted clopidogrel. In another study by Limaye et al.[5], they used continuous tirofiban as a mono-antiplatelet therapy for ruptured aneurysms, which were treated with flow diverters and reported a hemorrhage rate of 28.5%.[1] The study included 19 subjects with 25 procedures. Only 7 patients had procedures after the tirofiban was started, leading to a hemorrhage rate of 28.5%. The remaining procedures were performed 12 hours prior to the tirofiban injection, and had no hemorrhagic complications, suggesting that tirofiban is safe to resume after 12 hours of a ventriculostomy. However, in the paper, they reported an platetelet aggregate rate of 8.3% (2/25), since the useof tirofiban after a ventriculostomy may lead to a delayed hemorrhage, and, thus, they included those procedures in the calculation. Another reason for including the procedures where tirofiban was resumed after 12 hours was to compare the hemorrhage rate among subjects who had received dual antiplatelet therapy, instead of tirofiban, since the rate was calculated in the dual antiplatelet arm using this method. Thus even tirofiban is "not a zero-risk drug," and it follows that thrombocytopenia requires further investigation. This study had a higher rate of thrombocytopenia compared to the literature; but again the numbers are too small to confirm this finding. LTA has proven to be a reasonable "gold standard" for measuring high on- treatment platelet reactivity; as it is the oldest and most established technology, but the letter is not specific for clopidogrel response. There is very high variability in LTA practices worldwide, and, as a consequence, methodological standardization is necessary.[6]

The authors have mentioned that in cases where Ticagrelor was used they monitored the creatinine. Recently there has been a spate of cases[7,8] where ticagrelor has caused rhabdomyolysis when used in conjunction with statins. Thus, it is pertinent that we are aware of this devastating complication while using this particular drug.[7] As the present study[2] only had 9 cases of arterial stenosis, it is safe to assume that all of these cases might be receiving statins, and thus they were at high risk of rhabdomyolysis as has been previously reported. The authors mention that unlike clopidogrel, ticagrelor and its metabolites are primarily metabolized via the CYP3A4 enzyme and, hence, do not require hepatic activation. Herein, lies the conundrum. Ticagrelor is metabolized through the enzymes cytochrome P450 (CYP) 3A4/3A5 and is also a weak inhibitor of CYP3A.[7] Thus, ticagrelor may increase the potency of statins, which require CYP3A4 for their metabolism. Therefore, concomitant use of ticagrelor with simvastatin or lovastatin greater than 40 mg dose is not recommended. Thus, for the authors and any such cases, an alternative of Fluvastatin, which is metabolized by P450 CYP2C9, is suggested. While it is routinely safe to use the 2 drugs together, caution may be advisable, especially in elderly cases,[8] as most of the ages reported were above 60 years, and the author population reported the age range was wide (20–75 years). Also, it might be advisable to monitor cases with creatinine kinase and myoglobin values rather than creatinine alone, as they might be more specific.

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