Ticagrelor: A safe option as part of triple therapy?

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Abstract

Patients with atrial fibrillation who have concurrent coronary artery disease requiring percutaneous coronary intervention are subsequently prescribed dual antiplatelet therapy and anticoagulation resulting in triple therapy (TT). Ticagrelor, a reversibly binding P2Y12 antiplatelet agent, has shown superiority to clopidogrel in prevention of ischemic events and death, but is also associated with a small increase in the incidence of intracranial bleeding. This bleeding risk may be enhanced in the setting of TT. The objective of this report is to describe a case of a 70-year-old male prescribed TT with ticagrelor and to review the current literature on the safety of ticagrelor as a part of TT.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Around 30% of patients with AF have concurrent coronary artery disease (CAD), 15% of whom require percutaneous coronary intervention (PCI) during their lifetime.[1] Theoretically, such patients require the combination of oral anticoagulation (depending on CHA2DS2-VASC score) with dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, known collectively as triple therapy (TT).

Ticagrelor is a reversibly binding P2Y12 platelet inhibitor, which has been shown to have faster and greater platelet inhibition than clopidogrel.[2] Ticagrelor has shown superiority in prevention of ischemic events and death from any cause, as compared to clopidogrel. However, there is concern regarding an increase in the incidence of intracranial bleeding.[3] Here we discuss a case where initiation of ticagrelor, in addition to pre-existing chronic aspirin and apixaban use led to intracranial bleeding and significant neurological deficits.

Case Report

A 70-year-old man with medical history significant for coronary artery disease s/p CABG, hypertension, type 2 diabetes mellitus, AF, COPD, aortic stenosis s/p bioprosthetic aortic valve replacement, underwent cardiac catheterization and PCI with drug eluting stent placement to saphenous vein graft to circumflex artery. His CHA2DS2-VASC score was 3 and HAS-BLED score was 2. He was placed on ticagrelor 90 mg twice daily, in addition to his home medication aspirin 81 mg daily, and apixaban 5 mg twice daily and discharged home.

Three days later, he was found unresponsive on the floor and subsequently brought to the emergency room. He regained consciousness two hours later, and complained of a headache and left sided weakness. Blood pressure was 150/90, heart rate was irregularly irregular at 70 beats per minute. He was noted to have left facial, upper and lower extremity paralysis, and expressive aphasia. CT head revealed right-sided intraparietal hemorrhage with intraventricular extension. As apixaban reversal agent was unavailable, the patient was given anti-inhibitor coagulant complex, along with platelets to help control bleeding. However, after transfer to a tertiary care center, repeat CT head showed expansion of intracranial hemorrhage with midline shift, warranting emergent right parietal craniotomy and insertion of left ventricular catheter. After the bleeding was stabilized, aspirin and ticagrelor were restarted. Due to persistent major neurological deficits, including left sided paralysis and aphasia, he was discharged to a rehabilitation center.

Discussion

The management of acute coronary syndrome (ACS) in the presence of AF is a clinical challenge and an area of active investigation.[4,5] As mentioned above, in theory, such patients require DAPT in addition to OAC.[1,6-8] However, there is scant literature regarding different combinations of AC and DAPT drugs, and their clinical application in various scenarios.[6] Of greatest concern, is the increased potential for bleeding with TT. Studies have shown an immediately elevated risk of bleeding with TT and a 2-3 fold increase in bleeding complications as compared to OAC alone.[9-12]

Ticagrelor is the first reversibly binding P2Y12 inhibitor that reaches a higher level of platelet inhibition more rapidly than clopidogrel.[13] In the PLATO trial, the ticagrelor cohort was noted to have nearly twice the rate of hemorrhagic strokes and 11 intracranial bleeding related deaths, as compared to only 1 in the clopidogrel cohort.[14,15] While most patients studied on TT were on clopidogrel as the P2Y12 inhibitor,[16-18] recent meta-analyses of patients on TT or DT have shown a higher rate of bleeding with ticagrelor as compared to clopidogrel.[19] In a meta-analysis of 22,014 patients on OAC undergoing PCI, use of clopidogrel was associated with a lower rate of bleeding compared with ticagrelor.[20] In another systematic review analyzing 5659 patients on DT or TT, the use of ticagrelor was associated with higher rates of clinically significant hemorrhage as compared with clopidogrel.[19] Thus, the risk of major intracranial bleeding is likely enhanced when ticagrelor is used as a part of TT, as it was in our patient who suffered a massive intracranial bleed.

Our patient was given platelet transfusion as emergency management, as is often done in the absence of specific reversal agents. While platelet transfusions can readily reverse the antiplatelet effect of aspirin, it is found to be less effective for ticagrelor reversal due to longer half-lives of ticagrelor and its active metabolite.[21-24] During the first 24 hours, platelet transfusion is unlikely to substantially reverse P2Y12 antiplatelet effect.[22,25]

Patients with AF and ACS are at high risk for cardiovascular mortality and mobidity from both ischemic events such as

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stroke, MI or stent thrombosis, and bleeding events. Expert consensus recommendations from the European and North American cardiology societies address the management of these complex scenarios.[4,26-28] It is advised that initiation and duration of TT should be based on risks of thrombosis (CHA2DS2-VASC score) and bleeding (HAS-BLED score).[26] In patients with moderate stroke risk and low to moderate bleeding risk, the European Society of Cardiology recommends at least one month of TT followed by up to 12 months of OAC and P2Y12 inhibitor.[26]

Several recent trials in patients with AF who underwent PCI, have been investigating the use of a P2Y12 inhibitor and AC only, commonly termed *double therapy* (DT), and have found similar benefit with lower bleeding risk as compared to TT.[16-18] DT was found to be noninferior to TT with respect to risk of thromboembolic events in the RE-DUAL PCI trial, in which 12% of the patients studied were using ticagrelor as their P2Y12 inhibitor.[17] In subgroup analyses of patients on TT in the PIONEER AF-PCI trial, there was an increased rate of clinically significant bleeding events in patients prescribed ticagrelor (9/33 [28%]) as their P2Y12 inhibitor versus in those on clopidogrel (104/662 [17%]). However, in the DT cohort, the rate of clinically significant bleeding events was similar between patients on ticagrelor (5/36 [16%]) and clopidogrel (99/648 [16.3%]).[16] In addition, increased thromboembolic and ischemic cardiac events in patients on TT using ticagrelor has also been reported.[19] In the context of these results, ticagrelor as part of TT may cause more harm than benefit.

Conclusions

Although, ticagrelor may be a superior choice as part of DAPT alone, caution may be warranted when used as part of TT. Further in-depth investigation is needed to assess the safety of ticagrelor as a part of TT.

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