

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

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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 morbidity from both ischemic events such as

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.

References

- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-962.
- Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y₁₂ receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50(19):1852-6.
- Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. *Eur Heart J*. 2014;35(31):2083-93.
- Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, et al. Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention. *Circulation*. 2018;138(5):527-36.
- Lopes RD, Vora AN, Liaw D, Granger CB, Darius H, Goodman SG, et al. An open-Label, 2 x 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: Rationale and design of the AUGUSTUS trial. *American heart journal*. 2018;200:17-23.
- Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. *Eur Heart J*. 2017;38(27):2137-49.
- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.
- Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082-115.
- Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation*. 2012;126(10):1185-93.
- Hansson EC, Shams Hakimi C, Astrom-Olsson K, Hesse C, Wallen H, Dellborg M, et al. Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. *Br J Anaesth*. 2014;112(3):570-5.
- Faxon DP, Eikelboom JW, Berger PB, Holmes DR, Bhatt DL, Moliterno DJ, et al. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. *Thromb Haemost*. 2011;106(4):572-84.
- Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127(5):634-40.
- Xin YG, Zhang HS, Li YZ, Guan QG, Guo L, Gao Y, et al. Efficacy and safety of ticagrelor versus clopidogrel with different dosage in high-risk patients with acute coronary syndrome. *International journal of cardiology*. 2017;228:275-9.
- Anderson SD, Shah NK, Yim J, Epstein BJ. Efficacy and safety of ticagrelor: a reversible P2Y₁₂ receptor antagonist. *Ann Pharmacother*. 2010;44(3):524-37.
- Nawarskas JJ, Snowden SS. Critical appraisal of ticagrelor in the management of acute coronary syndrome. *Ther Clin Risk Manag*. 2011;7:473-88.
- Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *The New England journal of medicine*. 2016;375(25):2423-34.
- Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *The New England journal of medicine*. 2017;377(16):1513-24.
- Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107-15.
- Andreou I, Briasoulis A, Pappas C, Ikonomidis I, Alexopoulos D.

- Ticagrelor Versus Clopidogrel as Part of Dual or Triple Antithrombotic Therapy: a Systematic Review and Meta-Analysis. *Cardiovasc Drugs Ther.* 2018;32(3):287-94.
20. Lupercio F, Giancaterino S, Villablanca PA, Han F, Hoffmayer K, Ho G, et al. P2Y12 inhibitors with oral anticoagulation for percutaneous coronary intervention with atrial fibrillation: a systematic review and meta-analysis. *Heart.* 2020;106(8):575-83.
 21. Li C, Hirsh J, Xie C, Johnston MA, Eikelboom JW. Reversal of the anti-platelet effects of aspirin and clopidogrel. *J Thromb Haemost.* 2012;10(4):521-8.
 22. Kruger P, Chan N, Eikelboom JW. Platelet Transfusion for Ticagrelor Reversal. *Circ Cardiovasc Interv.* 2017;10(8).
 23. Teng R, Carlson GF, Nylander S, Andersson TL. Effects of autologous platelet transfusion on platelet inhibition in ticagrelor-treated and clopidogrel-treated subjects. *J Thromb Haemost.* 2016;14(12):2342-52.
 24. Martin AC, Berndt C, Calmette L, Philip I, Decouture B, Gaussem P, et al. The effectiveness of platelet supplementation for the reversal of ticagrelor-induced inhibition of platelet aggregation: An in-vitro study. *Eur J Anaesthesiol.* 2016;33(5):361-7.
 25. Cohn SM, Jimenez JC, Khoury L, Perez JM, Panzo M. Inability to Reverse Aspirin and Clopidogrel-induced Platelet Dysfunction with Platelet Infusion. *Cureus.* 2019;11(1):e3889.
 26. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J.* 2014;35(45):3155-79.
 27. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, et al. Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A North American Perspective-2016 Update. *Circ Cardiovasc Interv.* 2016;9(11).
 28. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* 2013;34(35):2746-51.