Angiotensin Receptor Blockers Worsen Renal Function and Dyspnea on Ticagrelor: A Potential Ticagrelor-Angiotensin Receptor Blocker Interaction?

Address for correspondence:
James J. DINicolantonio, PharmD
500 South Meadow Street
Ithaca, NY 14850
jjdinicol@gmail.com

James J. DiNicolantonio, PharmD and Victor L. Serebruany, MD, PhD
Wegmans Pharmacy (DiNicolantonio), Ithaca, New York; HeartDrug Research Laboratories (Serebruany), Osler Medical Center, Johns Hopkins University, Baltimore, Maryland

ABSTRACT

Ticagrelor is a new antiplatelet agent that was pitted against clopidogrel in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Because ticagrelor is the first oral, reversible, twice-daily agent, sufficient information on drug interactions is not available. Our objective was to ascertain the safety of ticagrelor with other common medications. The US Food and Drug Administration Complete Response Review indicates that renal adverse events (AEs) and renal function AEs were higher in ticagrelor-treated patients who were concomitantly treated with angiotensin receptor blockers (ARBs) >50% of study days compared to ticagrelor-treated patients who did not receive ARBs >50% of study days. Clopidogrel-treated patients showed a trend for an increase in adverse renal events with ARB use. However, this was not as pronounced as that observed with ticagrelor. Dyspnea was also significantly increased in patients on concomitant ticagrelor-ARB compared to ticagrelor without concomitant ARB and clopidogrel (21.4% vs 14.6% vs 9.9%, respectively) as well as angioedema (0.15% vs 0.09%). Furthermore, in patients with a baseline estimated glomerular filtration rate (eGFR) <30 mL/min, the risk of major bleeding, death, and renal failure was increased in patients on ticagrelor compared to patients on clopidogrel. In patients on ticagrelor, ARBs significantly increased the frequency of renal related AEs, renal function AEs, and dyspnea. Moreover, in patients with a baseline eGFR <30 mL/min, the risk of major bleeding, death, and renal failure was increased in patients on ticagrelor compared to patients on clopidogrel.

The PLATO trial was a phase 3, randomized, double-blind, parallel-group, multinational, clinical study, comparing the efficacy of ticagrelor (formerly known as AZD6140 and currently marketed as Brilinta) vs standard care treatment with clopidogrel. Patients (n = 18624) with moderate to high-risk acute coronary syndromes undergoing coronary intervention were randomized to ticagrelor 180 mg loading dose followed by 90 mg twice daily thereafter, or clopidogrel 300 to 600 mg loading dose followed by 75 mg once daily for 6 to 12 months. The primary end point was the time of the first event of death from vascular causes, myocardial infarction, or stroke, which occurred in 11.7% of patients treated with clopidogrel vs 9.8% of patients randomized to ticagrelor, representing a highly significant benefit (hazard ratio: 0.84, confidence interval [CI]: 0.77–0.92; $P < 0.001$) for ticagrelor.[1] Importantly, the benefit of ticagrelor was driven equally by the reduction of vascular death ($P < 0.001$) and myocardial infarction ($P < 0.005$), with 89 events favoring ticagrelor, but not stroke ($P = 0.22$), with 19 fewer events in the clopidogrel arm.[1]

However, this overoptimistic interpretation of the trial results was somewhat clouded by the US Food and Drug Administration (FDA) Secondary Review, which revealed several shortcomings with the PLATO design and data interpretation including incomplete follow-up, short trial duration, and reverse outcomes in the North American cohort.[2] In addition, the FDA posted the Review of Complete Response, revealing important information on potential drug interactions in PLATO.[3] The FDA documents indicate that renal-related adverse events (AEs) and renal function AEs were higher in ticagrelor-treated patients who were on angiotensin receptor blockers (ARBs) over half of study days compared to ticagrelor-treated patients who did not receive ARBs over half of study days (Table 1).[3] Compared to clopidogrel, ticagrelor patients receiving ARBs had a significantly higher increase in creatinine increase >50% (11.2% vs 7.1%), renal-related AEs (6.5% vs 4.3%), and renal function AEs (4.5% vs 2.8%).[3] The original PLATO publication had indicated that "the levels of creatinine increased slightly more during the treatment period with ticagrelor than with clopidogrel,"[1] with no mention of an increase in renal AEs.[3] Thus, in patients on ticagrelor with concomitant ARB use, the slight increase in creatinine is an obvious underestimation of the risk for the renal AEs. It appears that the increase in creatinine in patients on

Dr. Serebruany is listed as an inventor for the US patent application: TREATING CARDIAC ARRHYTHMIAS, HEART FAILURE, PERIPHERAL ARTERY DISEASE AND STROKE WITH CYCLOPENTYL-TRIAZOLO-PYRIMIDINE OR DERIVATIVE THEREOF (USN 61/253,829) assigned to HeartDrug™ Research, and received funding for research studies with clopidogrel, and consultant fees from both clopidogrel and ticagrelor manufacturers.

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Table 1. Increased Adverse Events With the Concomitant Use of Ticagrelor–ARB in the PLATO Trial

Adverse Event	Ticagrelor + ARB (n = 511)	Clopidogrel + ARB (n = 508)
Creatinine increase >50%	57 (11.2%)	36 (7.1%)
ACE-I	228 (8.4%)	187 (6.8%)
Renal-related AE	73 (6.5%)	48 (4.3%)
ACE-I	249 (4.1%)	206 (3.4%)
Renal-function AE	51 (4.5%)	31 (2.8%)
ACE-I	119 (2.0%)	82 (1.4%)
Dyspnea	176 (21.4%)[a]	80 (9.9%)[a]
Entire population	1345/9235 (14.6%)	803/9186 (8.7%)
Angioedema	14 (0.15%)[b]	8 (0.09%)[b]

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker: PLATO, Platelet Inhibition and Patient Outcomes. [a]N = 823 for ticagrelor and 807 for clopidogrel. [b]Based on entire population.

Table 2. Increased Risk of Death, Major Bleeding, and Renal Failure in Patients With a Baseline Glomerular Filtration Rate <30 mL/min on Ticagrelor Compared to Clopidogrel

Clinical Outcome	Ticagrelor (n = 117)	Clopidogrel (n = 144)
Death	31 (26.5%), NNH = 35 (95% CI: −7 to 13)	34 (23.4%)
Major bleeding	23 (19%), NNH = 12 (95% CI: −6 to 514)	16 (11.3%)
Renal failure	12 (13.6%), NNH = 15 (95% CI: 7 to 156)	5 (5.4%)

Abbreviations: CI, confidence interval; NNH, number needed to harm.

concomitant ticagrelor-ARB therapy is clinically relevant. In fairness, clopidogrel-treated patients also showed a trend for an increase in adverse renal events with ARB use. However, this AE was not as pronounced as that seen with ticagrelor.[3] Importantly, in contrast to ARBs, angiotensin-converting enzyme inhibitor use was not associated with an increase in the frequency of renal AEs.[3]

Due to the renal safety concern of ticagrelor-ARB therapy, differences in effectiveness of ticagrelor by baseline estimated glomerular filtration rate (eGFR) were also calculated in the FDA materials.[3] Shockingly, the frequency of death was significantly increased with ticagrelor compared to clopidogrel in patients with an eGFR <15 mL/min and eGFR <30 ml/min (table 2).[2] In patients with an eGFR <15 mL/min, 4 out of 4 patients died in the ticagrelor treatment group, whereas none of the 11 patients on clopidogrel died. In patients with an eGFR <30 mL/min, 31 out of 117 (26.5%) patients died in the ticagrelor treatment group, compared with 34 out of 145 (23.4%) clopidogrel-treated patients.[3] In patients with a baseline eGFR <30 mL/min, for every 15 patients treated with ticagrelor compared to clopidgorel, 1 extra patient would go into renal failure (number needed to harm [NNH] = 15) (Table 2).[3] Moreover, in patients on ticagrelor with a baseline eGFR <30 mL/min, there were numerically more patients with major bleeding events (23 [19%] vs 16 [11.3%], NNH = 12) and renal failure (12 [13.6%] vs 5 [5.4%], NNH = 35) compared to the clopidogrel-treated group (Table 2).[3]

Considering that ARBs significantly worsen renal function on ticagrelor, a greater amount of patients could precipitate into a eGFR <30 mL/min, a potentially dangerous situation considering that major bleeding complications, renal failure, and death are increased in patients on ticagrelor compared to patients on clopidogrel.[3] Moreover, the FDA transcript states that patients having poor baseline renal function generally rely on hemodynamic changes within the kidney to maintain their GFR. It is possible that ticagrelor is more likely than clopidogrel to lead to the decompensation of renal function in patients who are completely reliant on hemodynamic factors to maintain their GFR.[3] Thus, in patients after acute coronary syndromes who have poor baseline renal function, it may be wise to avoid ticagrelor, especially with the concomitant use of an ARB, as there is a higher risk for renal AEs such as renal failure, major bleeding, and even death.[3]

Last but not least, dyspnea occurred more frequently in PLATO patients treated with ticagrelor compared to patients treated with clopidogrel (14.6% vs 8.7%, respectively).[1] The FDA documents clearly acknowledges that being on an ARB was an added risk for developing dyspnea on ticagrelor (176/823, 21.4%), recommending further that if patients develop dyspnea, consideration should be given to discontinuation of ARBs if possible.[3] Thus, ARBs seem to significantly increase the risk of developing dyspnea on ticagrelor. Moreover, the risk of angioedema was increased by 74% with ticagrelor compared to clopidogrel (14 [0.15%] vs 8 [0.09%]; relative risk: 1.74, 95% CI: 0.73–4.15),[3] representing another important reason to avoid ARBs in patients on ticagrelor.

In summary, the FDA documents suggest a potential interaction with the concomitant use of ARBs and ticagrelor, with negative effects on renal function (increased risk of renal AEs) and an increased risk of dyspnea.[2] Routine monitoring of serum creatinine and GFR, especially in ticagrelor patients with lowered baseline renal function, may be indicated. Patients on ticagrelor with a baseline GFR <30 mL/min were shown to have an increased risk of major bleeding, renal failure, and death compared to patients on clopidogrel.[3] Postmarketing data should be collected to further elucidate the negative renal effects ARBs may have with concomitant ticagrelor use, especially in patients with a low baseline GFR. Until the safety of ticagrelor can be further confirmed, use in patients with a baseline GFR <30 mL/min, as well as concomitant use of ARBs, should perhaps be avoided.

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