

PLATO Trial

by Tina Liu, PharmD and Craig Stern, PharmD, MBA, FASHP, FCPbA.
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Introduction

The Platelet Inhibition and Patient Outcomes (PLATO) trial was conducted to determine if ticagrelor is superior compared with clopidogrel for the prevention of vascular events and death in patients with acute coronary syndrome (ACS). Patients were included if they were hospitalized and met specific pre-defined criteria for ST-elevated or non-ST elevated ACS then randomized to receive either ticagrelor (loading dose 180mg once then 90mg twice daily) or clopidogrel (loading dose 300mg once then 75mg daily).

The maintenance doses were comparable according to early dose confirmation studies of ticagrelor. However, it is not clear if the loading doses were compared in these studies. Patients were excluded if they had contraindications to clopidogrel, increased risk of bleeding or bradycardia and were taking concomitant strong CYP450 3A inhibitors or inducers. The primary outcome of the trial

was the time to first occurrence of composite death from cardiovascular causes, myocardial infarction (MI), or stroke. Occurrences of bleeding was also measured and compared.

Results:

A total of 18,624 patients were randomized to ticagrelor (n=9333) or clopidogrel (n=9291). The primary endpoint occurred significantly

less often in the ticagrelor arm compared with the clopidogrel arm at 12 months (9.8 vs. 11.7%, respectively; HR=0.84, 95%CI 0.77 to 0.92, $p<0.001$). The rates of major bleeding between ticagrelor and clopidogrel did not differ significantly (11.6 vs. 11.2%, respectively; HR= 1.04, 95%CI 0.95 to 1.13%, $p=0.43$ from Supplementary Appendix). Dyspnea and asymptomatic ventricular pauses during the first week of treatment as well as discontinuation due to adverse effects were more common in the ticagrelor arm. The authors of the study concluded that in patients with ACS, ticagrelor significantly decreased the rates of vascular death, MI or stroke without the risk of increased overall major bleeding events compared with clopidogrel.

Reviewer's Analysis:

There were several important limitations to the PLATO trial that threatens the validity of the study including:

- No details regarding blinding were provided. It was only by personal communication with lead author

Element	Criteria	Comments
Study Design Assessment	Is the design appropriate to the research question? Is the research question useful?	-Yes. PLATO was a multicenter, randomized, double-dummy, double-blind trial, which represents the gold standard trial design to address questions of therapy. Standard clinical outcomes were studied.
Internal Validity Assessment	Can bias, confounding or chance explain the study results?	-The research question, population, outcome measures, analysis methods, population size and level of significance were appropriate. However, there are some threats to the validity in the study methods which are described below.
Selection Bias	<input type="checkbox"/> Groups are appropriate for study <input type="checkbox"/> Methods for generating the group assignment sequence are truly random <input type="checkbox"/> Concealment of allocation strategies are employed	-Threat: No details of concealment of allocation were provided. -Eligible subjects were randomized to the study arms in a 1:1 ratio from a schedule blocked by site but it is not clear if this list was computer generated to provide true randomization. However, baseline characteristics were similar in the two groups, suggesting that randomization was successful.
Performance Bias	<input type="checkbox"/> Double-blinding employed <input type="checkbox"/> Reasonable intervention and comparator used <input type="checkbox"/> No bias or difference, except for what is under study, between groups during course of study	- Threat: The authors stated that the study was double-dummy, double blinded and placebo-controlled. However, no details were given to ensure that all investigators, clinicians, outcome assessors and data collectors were blinded, thereby potential bias can exist. -Threat: Patients in the two arms may have received different LDs. Patients in the clopidogrel arm who received open-labeled clopidogrel LD did not receive LD doses of clopidogrel again. However, patients in the ticagrelor arm who received open-labeled clopidogrel may have also received LD of ticagrelor. This difference can potentially affect the acute efficacy and safety outcomes in the initial phase of the trial. -Threat: Patients were allowed to leave the study at their 6 or 9 month visit if the targeted number of primary endpoints were reached. A uniform duration of follow-up to the planned 12 months can ensure that all endpoints that occurred up to 12 months were captured. -Threat: Some of the patients in the ticagrelor arm received clopidogrel within 24 hours after randomization and this represents contamination. A sensitivity analysis would have been helpful to see if this could have influenced the results. -The authors did not mention specific co-interventions but the baseline characteristics, medications used at admission and discharge, adherence and exposure rates to the study drug, as well as rates of PCI with either DES or BMS and CABG rates were similar between the two groups throughout the study.
Attrition Bias	<input type="checkbox"/> Zero or minimal missing data points or loss from randomization unless good Intention-to-Treat (ITT) Analysis	-Threat: Only 5 patients' vital status (5/18552= 0.03%) were unavailable but the discontinuation rate for both study arms was >20%. Kaplan-Meier estimates were used but the study did not clearly define who was censored.
Assessment Bias	<input type="checkbox"/> Assessors are blinded <input type="checkbox"/> Low likelihood of findings due to chance, false positive and false negative outcomes <input type="checkbox"/> Non-significant findings are reported, but the confidence intervals include clinically meaningful differences <input type="checkbox"/> ITT performed <input type="checkbox"/> Use of modeling only with use of reasonable assumptions	-Threat: It is not specified whether the assessors were blinded, therefore potential bias may exist. -Threat: ITT analysis was performed but the authors did not give details of data imputation methods. - The confidence interval for the primary endpoint was narrow, which provides greater precision of the likely possible difference in size of results.

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Dr. Lars Wallentin, clarification was made that patients, outcome assessors, investigators, data collector and clinicians of the trial were all blinded. This information should have been included for better clarity.

- No details regarding randomization sequence or concealment of allocation were provided.

- Contamination between the groups occurred after randomization.
- Possibility of differences in loading doses may affect acute efficacy and safety outcomes.
- There was greater than 20% discontinuation in both groups.
- Unequal duration of follow-up may lead to potential events not captured.
- No details regarding how missing data was

- imputed for ITT analysis were provided
 - No details of censoring in Kaplan-Meier analysis were provided.
- Data from this study may be used in clinical decision-making; however, more studies are necessary to confirm these results as several threats to the validity of the study were identified.
- Ticagrelor may offer some advantages

Element	Criteria	Comments
Usefulness Assessment	<input type="checkbox"/> Clinically significant area + sufficient benefit size = meaningful clinical benefit	<p>-The primary outcome was a clinical endpoint, which provides more meaning compared with surrogate outcomes.</p> <p>-Based on the data provided, the NNT= 53 (ticagrelor prevents 1 adverse primary outcomes for every 53 patients treated) and the NNH for major bleeding based on the study criteria is 142 (for every 142 patients treated with ticagrelor, 1 patient will have a major bleed). If 1,000 patients were treated, 19 patients would receive benefit while 7 patients would be harmed. Ticagrelor reduced the primary outcome but increased risk of bleeding compared to clopidogrel. However, since the NNT is small (good) and the NNH is larger in comparison (good), the net benefit appears to favor ticagrelor.</p> <p>-Major bleeding between the two groups did not show statistical significance. However, further studies may be required to confirm this result since the confidence interval shows there can be up to 13% more major bleeding with ticagrelor, which can be clinically significant.</p>
External Validity	How likely are research results to be realized in the real world?	The trial was conducted in a controlled setting, which may provide different results from what could be achieved in the real world setting if a slightly different population uses ticagrelor such as in patients who require anticoagulation (not included in study).
Patient Perspective	<input type="checkbox"/> Advantages and disadvantages of ticagrelor in the patient perspective	<p><u>Advantage:</u></p> <p>-Greater efficacy for the primary outcome.</p> <p><u>Disadvantages:</u></p> <p>-More expensive.</p> <p>-Possibility of more non-CABG and intracranial bleeding.</p> <p>-Possibility of more dyspnea.</p> <p>-Twice daily dosing compared with once daily.</p>
Provider Perspective	<input type="checkbox"/> Advantages and disadvantages of ticagrelor in the provider perspective	<p><u>Advantages:</u></p> <p>-Useful if a patient's coronary anatomy is unknown or CABG/ other operations is required since ticagrelor has a shorter half life and have less risk of bleeding during procedures compared with clopidogrel.</p> <p>-Clopidogrel may show resistance in some patients and possible drug-interaction with PPI.</p> <p><u>Disadvantages:</u></p> <p>-Possibility of more dyspnea and asymptomatic ventricular pauses, may not be good in patients with breathing problems or bradycardia/heart blocks without functioning pacemaker.</p> <p>-No data beyond one year (median duration of exposure to study drug was only 277 days).</p>

BMS=bare-metal stent; CABG=coronary artery bypass graft; DES=drug-eluting stent; LD=loading dose; MD=maintenance dose; NNH=number needed to harm; NNT=number needed to treat; PCI=percutaneous coronary intervention; PPI=proton-pump inhibitor

in certain groups of patients. Ticagrelor is likely safer in the setting of CABG or other operations since it has a shorter half-life and is associated with less CABG-bleeding compared with clopidogrel (although at a cost of twice-daily dosing for the patients). In addition, ticagrelor is not a thienopyridine and is an alternative to clopidogrel when clopidogrel resistance occurs or is suspected.

Overall Grade: B-U (possibly valid and useful evidence. However, because of the threats to validity, some uncertainty remains for the accuracy of the results, but threats to validity are not sufficient to result in a grade of U, i.e., uncertain validity and/or usefulness).

About the Authors:

Tina Liu graduated from Loma Linda University School of Pharmacy in 2007. She completed a PGY1 Hospital Practice Residency at St Joseph's Medical Center in 2008 and a PGY2 Cardiology Residency at Western University of Health Sciences/VA Greater Los Angeles Health Care Systems in 2009. She is currently working at Riverside County Regional Medical Center as an Emergency Department Pharmacist.

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Delfini Group LLC

Dr. Michael E. Stuart and Sheri A. Strite of Delfini Group are experts at systematic literature

reviews. The chart template is adapted from "Delfini Group, LLC. Short Critical Appraisal Checklist: U

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