Ticagrelor in Triple Antithrombotic Therapy: Predictors of Ischemic and Bleeding Complications

Address for correspondence:
Derek Y. F. So, MD FRCPC,
Division of Cardiology,
University of Ottawa Heart Institute,
Room H3408,
40 Ruskin Street,
Ottawa, ON K1Y 4W7 Canada,
dso@ottawaheart.ca

Angel Fu, BMSc; Kuljit Singh, MBBS, FRACP, PHD; Joseph Abunassar, MD, FRCPC; Nikita Malhotra, BHSc; Michel Le May, MD, FRCPC; Marino Labinaz, MD, FRCPC; Christopher Glover, MD, FRCPC; Jean-Francois Marquis, MD, FRCPC; Michael Froeschl, MD, FRCPC; Alexander Dick, MD, FRCPC; Benjamin Hibbert, MD, PHD, FRCPC; Aun-Yeong Chong, MRCP(uk), MBBS; Derek Y. F. So, MD, FRCPC; on behalf of the CAPITAL Investigators
Department of Medicine (Cardiology), University of Ottawa Heart Institute, Ottawa, Canada

ABSTRACT

Background: Patients on dual antiplatelet therapy following percutaneous coronary intervention often have indications for concurrent oral anticoagulation or triple antithrombotic therapy (TT). Although TT may decrease ischemic complications, it may confer increased bleeding risk.

Hypothesis: We hypothesize that the use of ticagrelor in TT is associated with higher risk of complications; accordingly, we sought to determine predictors of complications in patients on TT.

Methods: Patients discharged on TT after percutaneous coronary intervention were followed prospectively for 12 months. The primary endpoint was a composite of ischemic (death, myocardial infarction, stroke) and major bleeding complications or net adverse clinical event (NACE). A major secondary endpoint was BARC (Bleeding Academic Research Consortium) types 2, 3, or 5 bleeding. Outcomes were compared between ticagrelor- and clopidogrel-treated patients. Multivariable analyses were performed to elucidate predictors of complications.

Results: Twenty-seven of 152 patients discharged on TT were on ticagrelor. NACE occurred in 52% of patients and BARC 2, 3, or 5 bleeding occurred in 18%. There was no difference in the primary or secondary outcome between ticagrelor vs clopidogrel subgroup. On logistic regressions, use of TT in patients with acute coronary syndrome ($P = 0.002$) and bridging in with ticagrelor ($P = 0.02$) were associated with increased NACE. Low estimated glomerular filtration rate was an independent predictor of bleeding ($P = 0.03$).

Conclusions: The risk of bleeding and ischemic complications among patients on TT is similar between those on ticagrelor and clopidogrel. However, caution with use of bridging anticoagulation should be taken when using ticagrelor.

Introduction

In patients undergoing percutaneous coronary intervention (PCI) with stent deployment, dual antiplatelet therapy (DAPT) is thought to be necessary to prevent ischemic complications.[1–3] Aspirin and clopidogrel has been the standard DAPT for more than a decade; however, the availability of more potent P2Y12 inhibitors, coupled with their proven efficacy in reducing ischemic outcomes in patients with acute coronary syndromes (ACS), has resulted in an increase adoption of prasugrel and ticagrelor.[4–6]

Up to 10% of patients undergoing PCI have a clinical indication for concurrent anticoagulation therapy.[7] Indications include atrial fibrillation (AF),[8] development of mural thrombus post–myocardial infarction (MI), or previous venous thromboembolism.[9] The standard approach for these patients, endorsed by current guidelines, is the use of triple therapy (TT) using an anticoagulant with DAPT.[7,10] Previous studies have shown the risk of bleeding with TT using clopidogrel is nearly 4× than that with the use of DAPT or oral anticoagulant alone.[11] In the only study of TT with prasugrel, there was a significant increase in bleeding complications compared with those on clopidogrel.[12]

Ticagrelor has been increasingly used as the P2Y12 inhibitor of choice in ACS based on its superiority over clopidogrel in this cohort.[4] No study to date has evaluated the impact of ticagrelor in TT on bleeding and ischemic complications. Accordingly, we evaluated a contemporary cohort of consecutive patients on TT following PCI to determine incidence of ischemic and bleeding complications. In particular, we attempted to determine whether ticagrelor-treated patients have increased bleeding risks and whether its presence may preclude ischemic risks compared with clopidogrel-treated patients. Furthermore, we attempted to elucidate particular factors that may predispose patients to complications when receiving TT.

Angel Fu and Kuljit Singh are equally contributing authors.
The study was supported by a peer-review grant from the Canadian Institutes of Health Research (CIHR-FRN 115129).
Additional Supporting Information may be found in the online version of this article.

Received: June 11, 2015
Accepted with revision: September 23, 2015

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22486

Methods

The study was reviewed and approved by the local human research ethics board. We identified consecutive patients who were discharged on TT after PCI between January 1, 2012, and June 30, 2013, from the Cardiovascular Percutaneous Intervention Trial (CAPITAL) PCI Registry.[13,14] This was a retrospective analysis with prospective postdischarge follow-up of patients. Patients were included if discharged on TT consisting of aspirin, a vitamin K antagonist, and a P2Y12 inhibitor after PCI. Patients who underwent coronary artery bypass grafting post-PCI were excluded from the analysis. Patients discharged on a novel oral anticoagulant (NOAC) were also excluded. Decision for treatment with TT was at the discretion of the treating physician. Patient follow-up was conducted up to 1 year postdischarge.

All medical records were reviewed, and patients were interviewed by telephone at 1 year. Patients treated with ticagrelor were compared with those on clopidogrel. Occurrence of death, MI, target-vessel revascularization, stent thrombosis, bleeding by Thrombolysis In Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium (BARC) definitions,[15] and stroke were collected at various time periods including 30 days, 6 months, and 12 months.

The primary endpoint was defined as net adverse clinical event(s) (NACE) as defined by a composite of major adverse cardiac and cerebrovascular events (MACCE) and non–coronary artery bypass related major bleeding.[16] MACCE was defined as cardiovascular death, MI, or cerebrovascular accident. The major secondary endpoint was significant bleeding as defined as BARC types 2, 3, or 5 bleeding. Bleeding was also concurrently defined using TIMI and BARC definitions.[15,17]

Statistical Analysis

Continuous variables were compared using a Student *t* test for normally distributed variables and Wilcoxon test for skewed data. All data were presented as mean ± SD unless otherwise specified. Categorical variables were compared with the χ^2 or Fisher exact test and presented as percentages and frequencies.

To find the predictors of NACE and significant bleeding events, we used logistic regression analyses. Variables with a 2-sided *P* value <0.2 on univariate correlation were included in the multivariable model. Results of logistic regression are presented as odds ratio (OR) with 95% confidence interval (CI). SPSS version 17 (SPSS Inc., Chicago, IL) and Graph Pad Prism version 6 were the statistical software packages used.

Results

Between January 2012 and June 2013, a total of 152 patients were discharged on TT following PCI. Clopidogrel was prescribed in 125 patients and ticagrelor in 27. The patients who received ticagrelor were younger and had better renal function and lower frequency of heart failure. Ticagrelor was predominantly prescribed for patients presenting with an ST-segment elevation MI. More patients on ticagrelor received bridging with unfractionated heparin for initiation of warfarin therapy. (For baseline clinical characteristics of the study population, interventional procedural characteristics of the 2 groups, and indications for anticoagulation, see Supporting Information, tables 1, 2, and 3, respectively, in the online version of this article.)

Table 1. Primary and Secondary Endpoints in the 2 Groups

Adverse Events	Ticagrelor, n = 27 (%)	Clopidogrel, n = 125 (%)	*P* Value
NACE	14 (52)	65 (52)	0.98
BARC 2, 3, and 5	5 (18.5)	22 (17.8)	1.0
MACCE	2 (7.4)	17 (13.6)	0.53
TIMI bleeding	12 (40.7)	58 (46.4)	0.67
Major	3 (11.1)	10 (8.0)	0.70
Minor	0 (0)	4 (3.2)	1.0
Minimal	9 (33.3)	39 (31.2)	0.82
Requiring medical attention	2 (7.4)	8 (6.4)	1.0
BARC			
Type 1	9 (33.3)	39 (31.2)	0.82
Type 2	2 (7.4)	7 (5.6)	0.66
Type 3a	0 (0)	5 (4.0)	0.59
Type 3b	2 (7.4)	8 (6.4)	1.0
Type 3c	1 (3.7)	1 (0.8)	0.32
Type 5b	0 (0)	1 (0.8)	1.0
Death	0 (0)	11 (8.8)	0.21
ST	2 (7.4)	1 (0.8)	0.08
MI	2 (7.4)	4 (3.2)	0.29
Ischemic stroke	0 (0)	6 (4.8)	0.59

Abbreviations: BARC, Bleeding Academic Research Consortium; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NACE, net adverse clinical event; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction.

The primary endpoint of NACE was observed in 52% of patients, 14/27 (52%) among patients on ticagrelor and 65/125 (52%) in clopidogrel patients (*P* = 0.98). The secondary endpoint of BARC types 2, 3, or 5 bleeding at 12 months occurred in 27 patients, 5 (20%) on ticagrelor and 27 (20%) on clopidogrel (*P* = 0.96; Table 1).There was no significant difference in MACCE, TIMI, or BARC bleeding between the 2 groups at 1-month, 6-month, and 12-month intervals. (For endpoints divided by time periods of 30 days, 6 months, and 1 year, see Supporting Information, tables 4 and 5, in the online version of this article.)

Predictors of Net Adverse Clinical Event and Bleeding Academic Research Consortium Bleeding Events in Overall Cohort

On univariate analyses, patients receiving bridging anticoagulation therapy before PCI (*P* = 0.015), those with high body mass index (*P* = 0.008), and those with ACS at presentation (*P* = 0.009) were associated with increased NACE.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22486

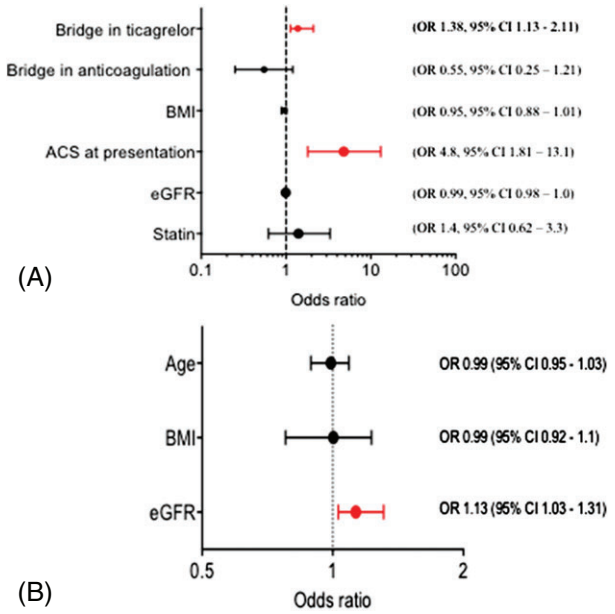

Figure 1. Stepwise multiple logistic regression analysis for (A) NACE and (B) BARC type 2, 3, and 5 bleeding. Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; NACE, net adverse clinical event; OR, odds ratio.

Conversely, use of a statin ($P = 0.017$) was associated with lower NACE. On multivariable analysis, ACS at presentation (OR: 4.8, 95% CI: 1.81-13.1, $P = 0.002$) and use of anticoagulation with ticagrelor (OR: 1.13, 95% CI: 1.38-2.11, $P = 0.02$) was associated with increased NACE in patients started on TT (Figure 1A).

There was no significant univariate correlate for BARC types 2, 3, or 5 bleeding events. On multivariable analysis, lower glomerular filtration rate was the only variable associated with higher risk of BARC types 2, 3, or 5 bleeding events (OR: 1.13, 95% CI: 1.02-1.31, $P = 0.03$) in patients on TT (Figure 1B).

Discussion

In the present study, we assessed NACE and bleeding complications in a contemporary cohort of patients on triple antithrombotic therapy in the first 12 months following PCI. Significantly, NACE occurred in nearly half of the patients, and BARC type 2, 3, or 5 bleeding occurred in nearly one-fifth of the cohort. On the other hand, there was no difference in the composite endpoint between ticagrelor and clopidogrel groups at any time period or at 12 months. Moreover, there was no difference in the 2 groups with regard to bleeding events. Renal insufficiency was the only independent predictor of significant bleeding.

The use of TT has been endorsed by guidelines on the basis of observational studies.[9,18] The rationale of TT is to confer ischemic protection in patients after coronary stenting while concurrently treating an alternate indication for the need of an anticoagulant.[19] In the literature, it is estimated that up to 10% of patients after PCI need to be on an anticoagulant.[20] Common reasons for requiring an anticoagulant include AF,[21] a history of a venous thromboembolic event, mechanical valves, and the risk or presence of thrombus after large MIs. Multiple studies have evaluated the risk of bleeding among patients on TT, and consistently it has been shown that those on TT have up to 3× the risk for bleeding compared with those on DAPT.[22,23] No study to date has evaluated the role of ticagrelor in TT, as this was an exclusion in the Platelet Inhibition and Patient Outcomes (PLATO) study.

Ticagrelor is different from both clopidogrel and prasugrel in its reversible binding, direct antagonism of P2Y12 receptor, and more rapid onset and offset of platelet inhibition when compared with clopidogrel.[24–26] In the PLATO study, there was no significant difference in overall major bleeding between those on clopidogrel compared with those on ticagrelor.[4] Accordingly, one may infer that the lack of difference would be conserved in TT, although until the current report, data were lacking. In our real-world cohort, there were similar rates of combined ischemic and bleeding complications among patients using clopidogrel or ticagrelor. The lack of difference between the NACE and significant bleeding between the 2 groups could be attributed to ticagrelor pharmacodynamics. A possible reason accounting for this may be its potency to prevent ischemic outcomes, coupled with fast offset, if bleeding does occur.[24]

The observed high bleeding event rate we observed mirrors findings from other studies. However, most of the previous studies have evaluated these complications during the index hospital stay or at 30 days after discharge.[27,28] The current report now expands these findings out to 12 months, again highlighting the increased risk of TT. Of importance, no study included patients on ticagrelor in the TT because of presumed potential bleeding complications. The lack of increase in bleeding may be the differences in the types of patients receiving ticagrelor compared with clopidogrel. The majority of the patients on ticagrelor were started on TT post-STEMI predominantly because of a ventricular thrombus. This group of patients was relatively young and had less comorbidity as compared with patients on clopidogrel.

A key objective of our study was to determine groups at risk for complications when receiving TT, and in particular to see if ticagrelor was a predisposing factor. To evaluate this, we performed multivariable analyses to find the predictors of NACE and BARC 2, 3, and 5 bleeding. In our cohort, ticagrelor was not a predictor of NACE or significant bleeding. However, of clinical importance, patients who started TT following ACS-related coronary intervention had higher NACE on multivariable regression.

The only factor predicting significant bleeding was renal insufficiency. Although the effect of renal dysfunction on increased risk of bleeding has been reported before in the literature,[29,30] this is the first time renal dysfunction has been demonstrated to be an independent predictor of bleeding in TT. Patients with renal insufficiency have a higher tendency to bleed, in part because of effects contributing to dysfunctional platelets and hemostasis.[29] Accordingly, this group of patients requires close monitoring if TT is initiated.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22486

Study Limitations

Our study does have some limitations. The study was not randomized and was relatively small in size. Furthermore, the univariate and multivariable analysis in the setting of small numbers can miss important associations. However, these were consecutive patients from a large-volume center. Our ticagrelor group was small; however, as the use of ticagrelor in the context of TT is novel and deemed "off-indication," the presence of these patients is relatively rare. Of note, our study represents the first comprehensive analysis of ticagrelor in this clinical context. The use of ticagrelor was mainly in younger patients. However, ticagrelor did not show any correlation with NACE or BARC 2, 3, and 5 bleeding. Lastly, our study did not include patients treated with NOAC. Although there may be increased use of NOAC for AF, its use in TT is controversial. Upcoming randomized studies may further elucidate clinical outcomes in NOAC-treated patients requiring TT. Until the results of these trials become available, concurrent use of these agents with ticagrelor on a routine basis would be unlikely.

Conclusion

Nearly half of the patients on TT suffer NACE, and one-fifth will have major bleeding event. The use of ticagrelor in TT is neither associated with higher bleeding events or increased NACE when compared with clopidogrel. Furthermore, association of renal dysfunction with bleeding indicates cautious use of TT in patients with low eGFR.

References

1. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation.* 2007;116:745–754.
2. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126–2130.
3. Reed GW, Cannon CP. Triple oral antithrombotic therapy in atrial fibrillation and coronary artery stenting. *Clin Cardiol.* 2013;36:585–594.
4. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–1057.
5. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001–2015.
6. Mehta SR, Yusuf S; CURE Study Investigators. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial programme: rationale, design and baseline characteristics, including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J.* 2000;21:2033–2041.
7. Paikin JS, Wright DS, Crowther MA, et al. Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. *Circulation.* 2010;121:2067–2070.
8. Rubboli A, Schlitt A, Kiviniemi T, et al; AFCAS Study Group. One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry. *Clin Cardiol.* 2014;37:357–364.
9. Faxon DP, Eikelboom JW, Berger PB, et al. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. *Thromb Haemost.* 2011;106:572–584.
10. Gao XF, Chen Y, Fan ZG, et al. Antithrombotic regimens for patients taking oral anticoagulation after coronary intervention: a meta-analysis of 16 clinical trials and 9185 patients. *Clin Cardiol.* 2015;38:499–509.
11. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet.* 2009;374:1967–1974.
12. Sarafoff N, Martischnig A, Wealer J, et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol.* 2013;61:2060–2066.
13. Hibbert B, Maze R, Pourdjabbar A, et al. A comparative pharmacodynamic study of ticagrelor versus clopidogrel and ticagrelor in patients undergoing primary percutaneous coronary intervention: the CAPITAL RELOAD study. *PloS One.* 2014;9:e92078.
14. Maze R, Le May MR, Froeschl M, et al; Cardiovascular Percutaneous Intervention Trial (CAPITAL) Investigators. Endovascular cooling catheter–related thrombosis in patients undergoing therapeutic hypothermia for out-of-hospital cardiac arrest. *Resuscitation.* 2014;85:1354–1358.
15. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736–2747.
16. Sanborn TA, Tomey MI, Mehran R, et al. Femoral vascular closure device use, bivalirudin anticoagulation, and bleeding after primary angioplasty for STEMI: results from the HORIZONS-AMI trial. *Catheter Cardiovasc Interv.* 2015;85:371–379.
17. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI), phase II trial. *Ann Intern Med.* 1991;115:256–265.
18. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) [published correction appears in *Europace.* 2011;13:1058]. *Europace.* 2010;12:1360–1420.
19. Zhao HJ, Zheng ZT, Wang ZH, et al. "Triple therapy" rather than "triple threat": a meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. *Chest.* 2011;139:260–270.
20. Smith JG, Wieloch M, Koul S, et al. Triple antithrombotic therapy following an acute coronary syndrome: prevalence, outcomes and prognostic utility of the HAS-BLED score. *EuroIntervention.* 2012;8:672–678.
21. Vardi M, Debidda M, Bhatt DL, et al. Evolving antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: results from a survey among US cardiologists. *Clin Cardiol.* 2014;37:103–107.
22. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med.* 2010;170:1433–1441.
23. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J.* 2007;28:726–732.
24. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation.* 2009;120:2577–2585.
25. L'Allier PL, Ducrocq G, Pranno N, et al; PREPAIR Study Investigators. Clopidogrel 600-mg double loading dose achieves stronger platelet inhibition than conventional regimens: results from the PREPAIR randomized study. *J Am Coll Cardiol.* 2008;51:1066–1072.
26. Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis:

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22486

a double-blind comparison to clopidogrel with aspirin. *Eur Heart J.* 2006;27:1038–1047.
27. Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol.* 2006;18:162–164.
28. Lip GY, Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: the need for consensus and a management guideline. *Chest.* 2006;130:1823–1827.
29. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. *Semin Thromb Hemost.* 2010;36:34–40.
30. Pilgrim T, Rothenbühler M, Kalesan B, et al. Additive effect of anemia and renal impairment on long-term outcome after percutaneous coronary intervention. *PloS One.* 2014;9:e114846.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22486