Real-world use of ticagrelor versus clopidogrel in percutaneous coronary intervention-treated ST-elevation myocardial infarction patients: A single-center registry study

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Objectives: **The primary aim was to investigate the efficacy and safety of dual antiplatelet therapy (DAPT) using ticagrelor (T-DAPT) versus clopidogrel (C-DAPT) in a real-world ST-elevation myocardial infarction (STEMI) population.**

Methods: **We retrospectively analyzed 655 consecutive patients having primary percutaneous coronary intervention (PCI) for STEMI at Liverpool Hospital, Sydney, Australia (from January 2013 to April 2016). Medical and procedural therapies were at clinician discretion. Patient data were retrieved from hospital records and primary clinicians.**

Results: **T-DAPT (65%) was used more frequently, and in patients with lower mean CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) score, than C-DAPT (24.6 vs. 32.2; $p < 0.0001$, respectively). All-cause mortality was 9.0% at 2.7 years follow-up, with fewer deaths for T-DAPT (4.5% vs. 17.2%; $p < 0.0001$). T-DAPT incurred less BARC (Bleeding Academic Research Consortium) 3–5 major bleeding (5.0% vs. 12.4%; $p < 0.0001$). Multivariate regression showed that C-DAPT, GRACE (Global Registry of Acute Cardiac Events) score, and renal insufficiency were independently associated with mortality. Intra-aortic balloon pump (IABP) and GRACE score independently predicted BARC 3–5 bleeding. Early DAPT discontinuation (1.7%) and ticagrelor intolerance (7.6%) was rare. Switching DAPT regimen was infrequent (21.7%) and mostly attributed to clinician preference (73.2%). Independent determinants of C-DAPT selection were older age, diabetes, prior PCI, IABP, and higher CRUSADE score.**

Conclusion: **Ticagrelor was preferred in low bleeding risk patients, which may have contributed to less BARC 3–5 bleeding and lower mortality for T-DAPT. Thus, bleeding mitigation is a clinical priority when selecting DAPT for PCI-treated STEMI patients. Continuation of initial DAPT regimen was typical, but early switching from clopidogrel to ticagrelor shows willingness to optimize DAPT. Patients with very low CRUSADE scores (<21.5) may be appropriate for switching to a potent P2Y12 inhibitor.**

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1. Introduction

Clopidogrel has been the traditional P2Y12 inhibitor of choice, but variability in platelet inhibition and delayed onset of action can result in limited efficacy [1]. Ticagrelor is a newer P2Y12 inhibitor featuring greater potency and more consistent antiplatelet action [2,3]. These attributes were tested in the Platelet Inhibition and Patient Outcomes (PLATO) RCT in patients with acute coronary syndrome (ACS) managed medically, or revascularized using percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Patients treated with ticagrelor benefited with improved cardiovascular outcomes, but this was counterbalanced by increased rates of PLATO-defined major (non-CABG related) bleeding [2]. The adverse impact of major bleeding on clinical outcomes underscores the challenge confronting clinicians when selecting a dual antiplatelet therapy (DAPT) regimen for high-risk patients. Based on findings from RCT and registry studies, international guidelines have recommended ticagrelor based DAPT for treatment of patients with ST-elevation MI (STEMI). This has excluded patients receiving thrombolysis and oral anticoagulant therapy [4], although recent trial data suggest ticagrelor may be safe in these settings [5]. Clinical outcome data from some trials have been contradictory regarding efficacy and rates of bleeding for ticagrelor versus clopidogrel in high-risk patient subsets [6]. Patients in RCTs can be highly selected because of rigorous exclusion criteria, and adverse events may be underrepresented. Patients with STEMI represent 25–40% of ACS presentations, with in-hospital mortality ranging from 5% to 15% depending on geographic and patient characteristics [7]. Further insights into bleeding outcomes are needed to help guide DAPT selection in contemporary practice. Moreover, there is a lack of data related to discontinuation and switching between P2Y12 inhibitors in real-world populations. We conducted a single-center registry study of clinical outcomes, including major bleeding, in STEMI patients treated with primary PCI and administered ticagrelor or clopidogrel. The primary aim was to report clinical and PCI factors influencing real-world use of ticagrelor versus clopidogrel in a STEMI population. In addition, we investigated rates of discontinuation and switching between ticagrelor and clopidogrel, relative to patient bleeding risk.

Abbreviations

BARC	Bleeding Academic Research Consortium
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines
DAPT	dual antiplatelet therapy
PCI	percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
C-DAPT	clopidogrel-dual antiplatelet therapy
T-DAPT	ticagrelor-dual antiplatelet therapy
IABP	intra-aortic balloon pump
CABG	coronary artery bypass grafting
ACS	acute coronary syndrome
TIMI	Thrombolysis In Myocardial Infarction
GRACE	Global Registry of Acute Cardiac Events
Re-MI	re-myocardial infarction
ROC	receiver operating characteristic
AUC	area under curve
Hb	hemaglobin
DES	drug-eluting stent

2. Materials and methods

We performed a single-center, retrospective, observational study of consecutive adult patients (>18 years old) having primary PCI for STEMI at Liverpool Hospital, Sydney, Australia (from January 2013 to April 2016; $n = 655$). Excluded from the study cohort were patients not receiving primary PCI, those treated medically, having thrombolysis, a contraindication or known intolerance to ticagrelor or clopidogrel, and those administered prasugrel. The study cohort was divided according to DAPT regimen comprising aspirin in combination with ticagrelor or clopidogrel. Patient demographic, clinical, procedural, and outcomes

data were primarily retrieved from hospital electronic records, and by telephone follow-up from primary care physicians and treating cardiologists.

All patients were treated at Liverpool Hospital, which is a tertiary referral, high-volume PCI center providing a round-the-clock primary PCI for STEMI. State-of-the-art field transmission of the ECG was available to the interventional cardiologist who instituted medical and PCI strategies. All patients received medical pretreatment by first responders according to standard practice guidelines, including administration of aspirin (300 mg oral loading dose and 100–150 mg daily maintenance) and supplemental oxygen as required. Administration of P2Y12 inhibitor occurred on first hospital presentation, typically in consultation with the cardiology team. Patients in the study cohort received either ticagrelor (T-DAPT: 180 mg oral loading dose and 90 mg twice daily maintenance), or clopidogrel (C-DAPT: 600 mg oral loading dose and 75 mg daily maintenance). Selection and duration of DAPT regimen was at the discretion of the treating cardiologist, and this included the prerogative to discontinue or switch between ticagrelor and clopidogrel. An experienced interventional cardiologist performed primary PCI according to established principles and using standard techniques [8]. The recommendation was for all study patients to receive DAPT for at least 1 year, according to the current European and American guidelines [9,10].

Bleeding risk for the study cohort was calculated using the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) bleeding risk score [11], using the sum of weighted scores from clinical and laboratory values on admission (www.crusadebleedingscore.org). The patients were stratified into risk quintiles based on the CRUSADE score: $\leq$20 (very low), 21–30 (low), 31–40 (moderate), 41–50 (high), and > 50 (very high). The TIMI (thrombolysis in myocardial infarction; www.timi.org) [12] and GRACE (Global Registry of Acute Cardiac Events; www.gracescore.org) [13] risk scores were calculated using the standard variables. Any bleeding was defined as a bleeding complication recorded by the treating cardiologist. Major bleeding was defined as significant, actionable bleeding according to the BARC 3–5 (Bleeding Academic Research Consortium, grade 3–5) standardized bleeding definition [9].

The primary end point was any BARC 3–5 bleeding event, subcategorized as occurring in-hospital, after discharge, or procedure-related. The secondary end point was any major adverse cardiac event (MACE), comprising: all cause death, remyocardial infarction (re-MI), stroke, and BARC 3–5 bleeding, at long-term follow-up. MI and stroke were defined according to universal definitions reported in the literature [14]. The study was conducted in accordance with the principles of the Helsinki Declaration and received Institutional Ethics Review Board approval for quality assurance purposes (QA2008/034).

Baseline patient and procedural characteristics are presented as mean ± standard deviation, median (interquartile range), or frequency (%). The normal distribution of continuous variables in the study was determined by Shapiro–Wilks and Kolmogorov–Smirnov tests. Normally distributed continuous variables were compared using Student *t* test and those with skewed distributions using the Mann–Whitney *U*-test. Patient groups were compared using Student *t* test for continuous variables and the chi-square or Fisher's exact test for categorical variables. The cumulative survival curves were constructed using the Kaplan–Meier method and groups were compared using log rank test. A multivariate binary logistic regression model was constructed to evaluate predictors of DAPT regime selection. A Cox regression analysis was used to identify demographic and clinical factors predicting death and BARC 3–5 bleeding. Variables that were significant at the bivariate level ($p < 0.05$) and having clinical relevance were included in the multivariable model. Receiver operating characteristic (ROC) curves were analyzed to derive a threshold CRUSADE score predictive of BARC 3–5 bleeding for both DAPT groups, and area under the curve (AUC), sensitivity, and specificity were calculated. With the exception of the Kolmogorov–Smirnov test, all statistical tests were two-tailed and a p value <0.05 was deemed significant. Statistics were calculated using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 655 STEMI patients having primary PCI (using stenting or balloon angioplasty) were analyzed. Demographic and baseline clinical data are reported in Table 1. The median age was 61.1 years and 80% of the participants were male. Overall, T-DAPT ($n = 423$; 65%) was used more frequently than C-DAPT ($n = 232$; 35%). Compared to T-DAPT patients, those receiving C-DAPT were older (64.5 years vs. 59.5 years;

Table 1. Demographic and baseline clinical presentation data based on-treatment DAPT.

	All *n* = 655	Clopidogrel *n* = 232 (35)	Ticagrelor *n* = 423 (65)	*p* Value
Age (yr)	61.1 (52.3–70.2)	64.5 (56.0–75.5)	59.5 (51.3–68.3)	<0.0001
Male	521 (79.5)	177 (76.3)	344 (81.3)	0.13
BMI (kg/m^2)	28.1 (24.8–31.5)	27.8 (24.8–31.1)	28.3 (24.7–32.1)	0.28
Body weight <60 kg	32 (4.9)	14 (6.0)	18 (4.3)	0.31
Hypertension	392 (59.8)	161 (69.4)	231 (54.9)	<0.0001
Dyslipidemia	382 (58.3)	137 (59.6)	245 (58.9)	0.87
Smoker	289 (44.1)	82 (35.7)	207 (49.1)	0.001
Diabetes mellitus	182 (27.8)	86 (37.1)	96 (22.8)	<0.0001
Family history of CAD	141 (21.5)	42 (18.5)	99 (24.0)	0.11
History of angina	158 (24.1)	79 (34.5)	79 (18.7)	<0.0001
Prior MI	135 (20.6)	71 (30.7)	64 (15.2)	<0.0001
Prior PCI	110 (16.8)	61 (26.5)	49 (11.6)	<0.0001
Prior CABG	26 (4.0)	13 (5.7)	13 (3.1)	0.11
Prior PVD/stroke	42 (6.4)	18 (7.8)	24 (5.7)	0.29
Known AF	17 (2.6)	10 (4.8)	7 (1.9)	0.01
Closure device	153 (23.4)	58 (25.0)	95 (22.7)	0.5
Intra-aortic balloon pump	67 (10.2)	40 (17.2)	27 (6.4)	<0.0001
Systolic blood pressure (mmHg)	121 (107–139)	122 (109–140)	120 (105–137)	0.04
Heart rate (beats/min)	78.0 (64.8–91.3)	78.0 (65.3–94.8)	78.0 (64.0–90.0)	0.17
Cardiogenic shock	80 (12.2)	43 (18.5)	37 (8.8)	<0.0001
Prior antiplatelet at admission	137 (20.9)	74 (32.0)	63 (14.9)	<0.0001
Cardiac arrest at admission	63 (9.6)	28 (12.2)	35 (8.3)	0.12
Killip class ≥3 (%)	60 (9.2)	35 (15.2)	25 (5.9)	<0.0001
Creatinine clearance (μmol/L)	85 (64.9–108)	78 (50.0–99.7)	88 (71.0–112)	<0.0001
Peak troponin (μg/L)	3.42 (1.34–6.96)	3.16 (1.20–6.54)	3.61 (1.42–7.16)	0.7
Baseline hemoglobin (g/dL)	147 (135–156)	144 (128–155)	148 (137–157)	<0.0001
Baseline HCT (%)	0.43 (0.39–0.46)	0.42 (0.38–0.46)	0.43 (0.40–0.46)	0.008
Nadir hemoglobin (g/dL)	132 (114–143)	129 (102–140)	135 (120–144)	0.0001
Nadir HCT (%)	0.39 (0.34–0.42)	0.38 (0.31–0.40)	0.40 (0.35–0.42)	0.42
Hemoglobin drop (g/dL)	13.0 (6.0–22)	14.0 (7.3–27)	12.0 (5.0–20)	<0.0001
Platelet (g/l)	240 (200–280)	232 (196–274)	240 (200–280)	0.63
GRACE score	156 ± 40	169 ± 46	149 ± 34	<0.0001
TIMI risk score	3.2 ± 2.4	3.2 ± 2.3	3.2 ± 2.5	0.99
CRUSADE total	27.3 ± 14.5	32.2 ± 16.1	24.6 ± 12.8	<0.0001
≤20 (very low)	231 (35.3)	64 (27.6)	167 (39.5)	
21–30 (low)	188 (28.7)	56 (24.1)	132 (31.2)	
31–40 (moderate)	121 (18.5)	40 (17.2)	81 (19.1)	
41–50 (high)	64 (9.8)	36 (15.5)	28 (6.6)	
>50 (very high)	51 (7.8)	36 (15.5)	15 (3.5)	
Discharge medication				
ACE inhibitor	494 (80.9)	162 (80.2)	332 (81.2)	0.77
Beta blocker	565 (92.5)	181 (89.6)	384 (93.9)	0.06
Statin	581 (95.2)	189 (94.0)	392 (95.8)	0.32
Spironolactone	57 (9.4)	24 (12.0)	33 (8.1)	0.13

Values are means ± standard deviation, median (25th, 75th percentile), or *n* (%).
ACE = angiotensin converting enzyme; AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines; DAPT = dual antiplatelet therapy; GRACE = Global Registry of Acute Cardiac Events; HCT = hematocrit; IABP = intra-aortic balloon pump; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIMI = thrombolysis in myocardial infarction.

$p < 0.0001$), and more likely to have diabetes mellitus (DM; 37.1% vs. 22.8%; $p < 0.0001$), hypertension (69.4% vs. 54.9%; $p < 0.0001$), history of angina (34.5 vs. 18.7; $p < 0.0001$), prior PCI (26.5 vs. 11.6; $p < 0.001$), and atrial fibrillation (AF; 4.8% vs. 1.9%; $p = 0.01$). C-DAPT patients were more likely to have cardiogenic shock (18.5% vs. 8.8%; $p < 0.0001$) and insertion of intra-aortic balloon pump (IABP; 17.2% vs. 6.4%; $p < 0.0001$). Notably, C-DAPT had comparatively lower median baseline hemoglobin (Hb; 144 vs. 148 g/dL; $p < 0.0001$) and a more profound median Hb drop (14 g/dL vs. 12 g/dL; $p < 0.0001$), resulting in a lower median Hb nadir (129 g/dL vs. 135 g/dL; $p < 0.0001$).

Overall bleeding risk for the study cohort was low, with a mean CRUSADE score of 27.3 ± 14.5. T-DAPT patients had a lower mean CRUSADE score than C-DAPT patients (24.6 vs. 32.2;

$p < 0.0001$). In the CRUSADE very low and low bleeding risk quintiles, T-DAPT was preferred over C-DAPT (39.5% vs. 27.6% and 31.2% vs. 24.1%, respectively). Conversely, in the high and very high bleeding risk quintiles C-DAPT was preferred over T-DAPT (15.5% vs. 6.6% and 15.5% vs. 3.5%, respectively). Procedural and PCI data are reported in Supplementary Table S1. Transradial access was more frequent in T-DAPT patients (30.3% vs. 19.8%; $p = 0.004$), whereas mean procedural time was longer for the C-DAPT patients. Use of drug-eluting stents (DES) was higher in T-DAPT patients (42.5% vs. 35.7%; $p = 0.007$); otherwise, stent number, total stent length, and rates of multivessel PCI were not different between groups. PCI procedural success was similarly high for both groups.

Bleeding and clinical outcomes data are reported in Table 2. The median follow-up duration was 2.7 (1.9–3.8) years. The rate of BARC 3–5 bleeding was higher for C-DAPT compared to T-DAPT (12.4% vs. 5.0%; $p < 0.0001$). For both groups, most bleeding events (76–86%) occurred during the index hospitalization and were procedure related (31–43%). Table 2 and Supplementary Fig. S2 show BARC 3–5 bleeding events for C-DAPT versus T-DAPT subgroups, and stratified by CRUSADE quintile scores, respectively. For T-DAPT patients, a higher CRUSADE score corresponded with higher frequency of BARC 3–5 events, although absolute numbers in each quintile were small. A similar trend was observed for C-DAPT patients. All-cause mortality was 9.0%, with proportionately more deaths in C-DAPT versus T-DAPT patients (17.2% vs. 4.5%; $p < 0.0001$; Supplementary Fig. S1A). Total BARC 3–5 bleeding was 7.6%, with higher rate in C-DAPT versus T-DAPT patients (12.4% vs. 5%; $p < 0.0001$; Supplementary Fig. S1B). Similarly, the rate of MACE (combined death, re-MI, stroke, and BARC 3–5 bleeding) was higher for the C-DAPT (18% vs. 10.9%; $p = 0.003$). Independent predictors of all-cause mortality (Supplementary Table S2), analyzed by multivariate Cox regression, were: GRACE score [hazard ratio (HR) = 1.02; 95% CI, 1.02–1.03; $p < 0.0001$], creatinine clearance (CrCl; HR = 0.98; 95% CI, 0.97–0.99; $p = 0.001$), and T-DAPT (HR = 0.48; 95% CI, 0.27–0.86; $p = 0.001$). Multivariate regression analysis showed that independent predictors of BARC 3–5 bleeding, were: IABP (HR = 3.47; 95% CI, 1.51–7.98; $p = 0.003$) and GRACE score (HR = 1.01; 95% CI, 0.29–1.03; $p = 0.04$; Supplementary Table S2).

In total, 153 (23.3%) patients had a change in DAPT regimen during the index hospitalization (Table 3). Discontinuation of P2Y12 inhibitor (ticagrelor or clopidogrel) occurred rarely (1.7%), with no difference between subgroups. Continuation through to hospital discharge of the initially selected P2Y12 inhibitor was more likely for ticagrelor than clopidogrel (82.5% vs. 65.9%). Patients continuing C-DAPT had higher CRUSADE and GRACE scores compared with patients continuing T-DAPT. Switching of P2Y12 inhibitor during the index hospitalization occurred in 142 (21.7%) patients, with no subgroup difference in CRUSADE or GRACE scores. Switching from C-DAPT to T-DAPT (32.8%) was more common than switching T-DAPT to C-DAPT (15.6%). Clinician discretion accounted for 97.4% of C-DAPT to T-DAPT switching, and 45.5% of T-DAPT to C-DAPT switching. BARC 3–5 bleeding and commencement of oral anticoagulation resulted in T-DAPT to C-DAPT switching in eight (12.1%) and 17 (25.8%) patients, respectively. Multivariate logistic regression modeling (Supplementary Table S2) showed that age [odds ratio (OR) = 0.98, $p = 0.04$], diabetes (OR = 0.65, $p = 0.03$), prior PCI (OR = 0.39, $p < 0.0001$), IABP (OR = 0.47, $p = 0.008$), and CRUSADE risk score (OR = 0.98, p = 0.005) were independent determinants for C-DAPT selection. Analysis of ROC curves

Table 2. Procedural and hospital outcomes based on-treatment DAPT at follow-up 2.7 (1.9–3.8) years.

	All *n* = 655	Clopidogrel *n* = 232 (35)	Ticagrelor *n* = 423 (65)	*p* Value
Any bleeding	95 (14.5)	38 (16.4)	57 (13.5)	0.32
BARC 3–5	50 (7.6)	29 (12.4)	21 (5)	<0.0001
In-hospital bleeding	41 (82)	25 (86.2)	16 (76.2)	
Post-discharge bleeding	9 (18)	5 (10)	4 (8)	
Procedure related bleeding	18 (36)	9 (31)	9 (42.9)	
Recurrent MI	33 (5.0)	11 (4.8)	22 (5.2)	0.8
Stroke	10 (1.5)	4 (1.7)	6 (1.4)	0.76
Death	59 (9.0)	40 (17.2)	19 (4.5)	<0.0001
MACE	88 (13.4)	42 (18)	46 (10.9)	0.01

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; MACE = composite of all cause death; MI = myocardial infarction; re-MI = stroke and BARC 3–5 bleeding.

Table 3. Switching data based on initially selected DAPT.

	All *n* = 655	Clopidogrel *n* = 232 (35)	Ticagrelor *n* = 423 (65)	*p* Value
P2Y12 inhibitor use				<0.0001
Discontinuation of P2Y12 Inh	11 (1.7)	3 (1.3)	8 (1.9)	
Continued initial P2Y12 Inh	502 (76.6)	153 (65.9)	349 (82.5)	
CRUSADE score	27.26 ± 14.56	34.52 ± 15.84	24.07 ± 12.79	<0.0001
GRACE score	155 ± 39	173 ± 43	148 ± 35	<0.0001
BARC 3–5 events	29 (5.8)	17 (11.1)	12 (3.4)	0.001
Switching of P2Y12 Inh	142 (21.7)	76 (32.8)	66 (15.6)	<0.0001
Anticoagulation (triple therapy)	17 (12)	0 (0)	17 (25.8)	
Adverse event	7 (4.9)	2 (2.6)	5 (7.6)	
Urgent CABG	6 (4.2)	0 (0)	6 (9.1)	
Clinician preference	104 (73.2)	74 (97.4)	30 (45.5)	
CRUSADE score	27.18 ± 14.5	27.13 ± 15.87	27.23 ± 12.91	0.97
GRACE score	157 ± 40	157 ± 48	157 ± 30	0.97
BARC 3–5 events	19 (13.4)	8 (10.5)	11 (16.7)	0.28

CABG = coronary artery bypass grafting; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines; DAPT = dual antiplatelet therapy; GRACE = Global Registry of Acute Cardiac Events.

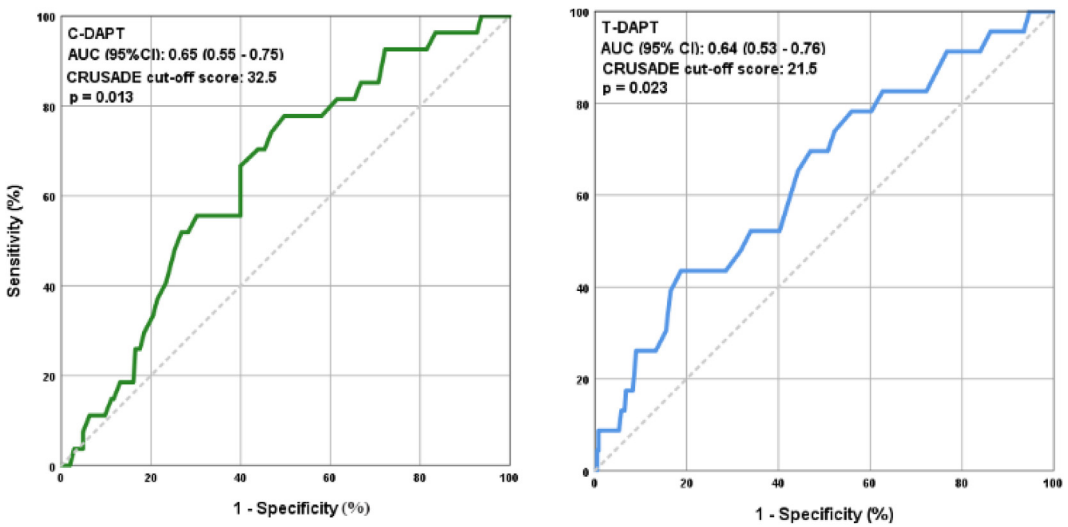

Figure 1. Receiver operating characteristic (ROC) analysis showing CRUSADE scores thresholds predicting BARC 3–5 bleeding. AUC = area under the curve; BARC = Bleeding Academic Research Consortium; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines; DAPT = dual antiplatelet therapy.

(Fig. 1) indicated optimal CRUSADE score thresholds predictive of BARC 3–5 bleeding for T-DAPT (21.5) and C-DAPT (32.5).

4. Discussion

This retrospective study of STEMI patients having primary PCI has yielded several key findings relating to DAPT treatment using ticagrelor versus clopidogrel. Notably, T-DAPT was preferentially administered to patients at lower risk of bleeding and adverse cardiac events, evidenced by lower CRUSADE and GRACE risk scores, respectively. Thus, bleeding mitigation appeared to be a priority when selecting the DAPT regimen. Patients given T-DAPT recorded fewer BARC 3–5 bleeding events and had a lower rate of all-cause death at 2.7 (1.9–3.8) years follow-up. GRACE score, renal insufficiency, and C-DAPT were independent predictors of mortality, whereas GRACE score and IABP insertion were predictive of BARC 3–5 bleeding. For most patients, the P2Y12 inhibitor initially selected was continued through to hospital discharge. Switching from C-DAPT to T-DAPT (32.8%) was less than expected and suggests there may be undertreatment of ischemia risk in some STEMI patients who persisted on C-DAPT in spite of low CRUSADE risk scores.

The PLATO trial showed superior efficacy in ACS patients for ticagrelor compared to clopidogrel, regardless of whether PCI or medical therapy was planned. However, the rate of PLATO-defined major (non-CABG related) bleeding was higher for ticagrelor (4.5% vs. 3.8%, $p = 0.03$) [2,15]. The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction (PEGASUS-TIMI) 54 trial showed favorable clinical outcomes for longer-term use of ticagrelor, but there was more major (nonfatal) bleeding compared to placebo (2.6% vs. 1.06%, $p < 0.001$) [16]. The PHILO trial investigated an Asian cohort and the incidence of major (life-threatening or actionable) bleeding was higher for ticagrelor compared with clopidogrel (10.3% vs. 6.8%) [17]. Registry data are crucial to guide DAPT optimization in real-world populations. The SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry is the largest observational study of ticagrelor in ACS patients, and findings generally support the PLATO data. However, in SWEDEHEART, ticagrelor patients had more procedure related bleeding (OR = 1.57; 95% CI, 1.30–1.90) [18]. The Korea Acute Myocardial Infarction Registry (KAMIR) - National Institutes of Health (NIH) registry of Korean ACS patients having PCI showed no difference in efficacy between ticagrelor and clopidogrel (3.7% vs. 4.2%, $p = 0.637$), but ticagrelor was associated with higher rates of in-hospital bleeding (2.6% vs. 1.2%, $p = 0.008$) [6].

The adverse impact of bleeding could potentially negate the benefits of DAPT [19,20]. Indeed, PLATO subgroup analysis showed that significant bleeding, regardless of the definition used, was associated with a marked increase in short-term mortality [21]. Variation in bleeding definitions across RCT and registry studies may affect reporting of outcomes [2,22]. Furthermore, trial heterogeneity in ACS subtype and treatment strategy may have impacted bleeding rates [2]. Trials from Korea and Japan report a lower incidence of ischemia-related adverse outcomes compared with Western registry data, suggesting that ethnic anthropometric polymorphisms may impact bleeding through altered responsiveness to P2Y12 inhibition [23–25].

A recent meta-analysis of nine DAPT trials indicated that patients taking ticagrelor had lower rates of adverse events (OR = 0.88; 95% CI, 0.81–0.95) [26]. This is consistent with our finding that T-DAPT patients had less MACE (10.9% vs. 18%, $p = 0.003$) and reduced all-cause mortality (HR = 0.48; $p = 0.001$). The overall rate of BARC 3–5 major bleeding for our study cohort was low (7.6%), and T-DAPT patients had fewer major bleeds (5% vs. 12.4%, $p < 0.0001$). Primary PCI for treatment of STEMI is performed in an emergency setting, and this may increase periprocedural bleeding complications. Our in-hospital (mostly periprocedural) bleeding rate was low despite 30% use of a GpIIbIIIa antagonist, and this may be partly explained by increasing transradial access (27%). Use of transfemoral arterial access to accommodate larger catheters may predispose to bleeding [27]. C-DAPT patients underwent PCI of longer duration, implying greater procedural complexity, and were more likely to have transfemoral IABP insertion, which was most strongly associated with BARC 3–5 bleeding (HR = 3.47; $p = 0.003$). T-DAPT patients had more transradial access, which has been associated with less bleeding, and lower all-cause mortality [28,29]. Finding the right balance between thrombotic prophylaxis and minimizing bleeding remains challenging, and this may account for use of less potent antiplatelet therapy in higher-risk patients.

Following PLATO and guideline recommendations [30,31], our facility implemented a policy in late 2012 favoring ticagrelor for treatment of ACS patients. Our use of T-DAPT (65%) was higher than that reported in SWEDEHEART (44%) [32] but less than that in Change of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome (CHANGE-DAPT) (85%) [33]. The timeline of T-DAPT uptake at our facility was comparable with that in SWEDEHEART, and predates the CHANGE-DAPT registry by about 2 years. We speculate that the later uptake of ticagrelor in CHANGE-DAPT may have enhanced the frequency of use because of diminished concerns regarding bleeding. The CRUSADE bleeding risk score was first validated in non-ST-elevation MI (NSTEMI) patients [34], and later in DAPT-treated STEMI patients, to predict bleeding outcomes to 1 year [35,36]. In the current study, patients receiving T-DAPT had a lower CRUSADE risk score compared to those receiving C-DAPT (24.6 vs. 32.2), which concurs well with CRUSADE scores reported previously for STEMI patients (range, 23–27) [37]. Of note, C-DAPT was more prevalent in the high and very high risk quintiles, and in patients with adverse demographic and clinical characteristics: older age, DM, AF, and known cardiovascular disease.

Indeed, DAPT selection was independently associated with older age, prior PCI, DM, and CRUSADE risk score (Supplementary Table 2). The initial administration of clopidogrel to patients deemed at higher risk of bleeding suggests that bleeding mitigation is a priority for clinicians. Notably, C-DAPT patients also had higher GRACE risk scores, which is consistent with previous reports [38]. There was no difference in CRUSADE and GRACE scores (27 and 157, respectively) for switching subgroups, which indicates that some patients at moderate risk of bleeding and recurrent cardiac events had DAPT switching. We interpret these data to suggest that persisting with clopidogrel, in lieu of ticagrelor, may have resulted in undertreatment of ischemia risk for some C-DAPT patients.

Discontinuation and switching of DAPT regimen is a feature of real-world practice, yet it is rarely studied. Convalescing STEMI patients are vulnerable to MACE; therefore, we analyzed changes of P2Y12 inhibitor occurring during the index hospitalization. Reported discontinuation rates for ticagrelor vary considerably, from 0.9% in the PLATO trial to 14.3% in a retrospective cohort study [2,16,39]. In our study, discontinuation of P2Y12 inhibitor occurred rarely (1.7%) in accordance with guideline recommendations [4]. Typically, the initial DAPT regimen was continued through to hospital discharge. This may be desirable in patients who continued on T-DAPT (82.5%), but indicates potential undertreatment in some patients who persisted on C-DAPT (65%). Clinician discretion was the dominant reason for switching C-DAPT to T-DAPT, which reflects our strategy of DAPT optimisation using ticagrelor. There is some evidence that clinicians are willing to switch high bleeding risk patients to ticagrelor [38]. We recorded only five cases of ticagrelor-related dyspnea or bradycardia necessitating switching, which should encourage compliance. Therefore, it may be reasonable to target factors influencing clinician prescribing when formulating strategies to optimize DAPT.

At our center the availability of ticagrelor to first responders is limited, and clopidogrel may be preferred in acute STEMI [33] because of unknown patient bleeding risk. Although upstream administration of ticagrelor has been shown to not enhance efficacy [40], facilitating early availability may increase the initial allocation of T-DAPT in appropriate patients. In the CHANGE-DAPT trial, patients switching to ticagrelor showed no benefit in ischemic end points but incurred more major bleeds [33]. This is similar to the Timing of Platelet Inhibition After Acute Coronary Syndrome (TOPIC) trial, where patients taking a potent P2Y12 inhibitor (ticagrelor or prasugrel) had higher rates of major bleeding compared to those switched to clopidogrel (14.9% vs. 4%; $p < 0.01$) [41]. These bleeding rates are comparable to those for switching subgroups in our study (10.5–16.7%), which was not powered to measure longer-term ischemic outcomes. We analyzed ROC curves (Fig. 1) to derive optimal CRUSADE score thresholds for BARC 3–5 bleeding for C-DAPT (32.5) and T-DAPT (21.5). Further studies are necessary, but better delineation of CRUSADE score thresholds for bleeding may help identify C-DAPT patients suitable for switching to T-DAPT.

This observational study yields insights into contemporary use of ticagrelor and clopidogrel in real-world high risk patients, but is prone to several limitations. Inherent to the study design, patients were not randomized and this would have introduced selection bias. Therefore, it is not possible to determine clinical superiority for a DAPT regimen without a randomized comparison of treatment groups. Study power is limited by sample size, although this is among the largest registry cohort analyses of ticagrelor versus clopidogrel in Australasia. Data relating to post-discharge changes to DAPT regimen are not available because of the retrospective nature of data acquisition. Nevertheless, each patient was recommended to continue DAPT for a minimum of 12 months after STEMI, in keeping with the current guidelines. The use of transradial access was lower than current standards, but this access route was less prevalent during the early phase of the study. Bleeding severity was determined retrospectively and is likely subject to adjudication error. However, the BARC criteria have been designed to obviate multiple bleeding definitions, and are now favored in contemporary studies [9,42]. Underreporting of data may occur in observational analysis and this may have led to a type II error, as in other registry studies.

5. Conclusion

This retrospective, single-center registry analysis suggests that bleeding mitigation is a priority for clinicians selecting DAPT for STEMI patients having PCI. Patients deemed at lower risk of bleeding received the more potent P2Y12 inhibitor ticagrelor, whereas those at higher risk of bleeding and having more complex PCI received clopidogrel. This may have influenced clinical outcomes as T-DAPT patients recorded fewer BARC 3–5

major bleeding events and less all-cause mortality. Continuation of the initially selected P2Y12 inhibitor was most common, although switching of clopidogrel to ticagrelor indicates clinician willingness to optimize DAPT. For T-DAPT and C-DAPT patients, CRUSADE scores corresponding to low risk (<21.5) and moderate risk (<32.5), respectively, were associated with low BARC 3–5 bleeding events. Further studies are warranted to determine how best to optimize DAPT based on individual appraisal of bleeding and ischemia risk.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsha.2019.05.005.

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