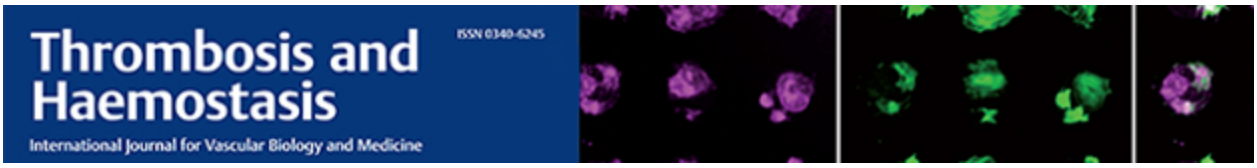

Cangrelor vs. Ticagrelor in Patients Treated with Primary Percutaneous Coronary Intervention: Impact on Platelets, Microcirculation & Infarct Size

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Cangrelor vs. Ticagrelor in Patients Treated with Primary Percutaneous Coronary Intervention: Impact on Platelet Activity, Myocardial Microvascular Function and Infarct Size: A randomized controlled trial

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Conflict of Interest

James Cotton has received consultancy fees and travel support from Astra Zeneca. Salahaddin Ubaid, Thomas Ford, Mark Thomas, Colin Berry, Nazish Khan, Heather Murray, Benjamin Wrigley, Joe Martins, Angel Armesilla, Jon Townend, Sandeep Hothi, Shahzad Munir, Elisa MacAlindon and Saib Khogali have no personal financial disclosures. The University of Glasgow holds research and consultancy agreements with Abbott Vascular, AstraZeneca, Coroventis and Opsens.

Abstract

Background

Oral P2Y12 inhibitors take more than 2 hours to achieve full effect in healthy subjects and this action is further delayed in patients with acute myocardial infarction. Intravenous (IV) P2Y12 inhibition might lead to more timely and potent anti-platelet effect in the context of emergency primary angioplasty, improving myocardial recovery.

Objectives

To compare the efficacy of IV cangrelor vs. ticagrelor in a STEMI population treated with primary percutaneous coronary intervention (PPCI).

Patients/Methods

In an open-label, prospective, randomized controlled trial, 100 subjects with STEMI were assigned 1:1 to IV cangrelor or oral ticagrelor. The co-primary endpoints were platelet P2Y12 inhibition at infarct vessel balloon inflation time, 4 hours and 24 hours. Secondary endpoints included indices of coronary microcirculatory function: Index of microvascular resistance (IMR), initial infarct size (troponin at 24 hours) and final infarct size at 12 weeks (cardiac magnetic resonance-CMR). Corrected TIMI frame count (cTFC), TIMI Flow grade (TFG), myocardial perfusion grade (MPG) and ST-segment resolution (STR). (ClinicalTrials.gov NCT02733341).

Results

P2Y12 inhibition at first balloon inflation time was significantly greater in cangrelor treated patients (cangrelor PRU 145.2 ± 50.6 vs. ticagrelor 248.3 ± 55.1). There was no difference in mean PRU at 4 hours and 24-36 hours post dosing. IMR, final infarct size, angiographic and electrocardiographic measures of reperfusion were all similar between groups.

Conclusion

Cangrelor produces more potent P2Y12 inhibition at the time of first coronary balloon inflation time compared with ticagrelor. Despite this enhanced P2Y12 inhibition, coronary microvascular function and final infarct size did not differ between groups.

Key Words

Antiplatelet, infarct size, microcirculation, myocardial infarction, percutaneous coronary intervention.

Abbreviations

Myocardial infarction	(MI)
ST-segment elevation myocardial infarction	(STEMI)
Primary percutaneous coronary intervention	(PPCI)
Index of microvascular resistance	(IMR)
Coronary flow reserve	(CFR)
ST-segment resolution	(STR)
Corrected TIMI frame count	(cTFC)
TIMI flow grade	(TFG)
Myocardial perfusion grade	(MPG)
Cardiac magnetic resonance	(CMR)
Intravenous	(IV)

What is known on this topic

- Antiplatelet therapy with potent oral P2Y12 receptor antagonists improves outcomes in STEMI with both ticagrelor and prasugrel showing superior efficacy to clopidogrel.
- One important limitation of all orally administered P2Y12 inhibitors is delayed antiplatelet effect, which can take several hours to achieve in the setting of STEMI. Therefore PPCI is likely to be performed in the context of sub-optimal P2Y12 inhibition.
- Cangrelor being a direct reversible P2Y12 inhibitor with rapid onset and offset of action overcomes many of the limitations associated with oral P2Y12 inhibitors, making its use in the setting of acute STEMI undergoing primary PCI where prompt antiplatelet inhibition is required, appealing.

What this paper adds

- This study confirms that cangrelor produces early, potent P2Y12 inhibition in patients treated with PPCI.
- It supports the periprocedural administration of cangrelor in the setting of primary PCI as a potential bridging IV antiplatelet therapy until the full antiplatelet effect is achieved with oral P2Y12 receptor inhibitors. This approach would help overcome the main issue encountered with oral P2Y12 inhibitors in the setting of primary PCI, which is their delayed onset of action.
- In our cohort, acceptable levels of P2Y12 inhibition were achieved with oral ticagrelor by 4 hours following loading, and in cangrelor treated patients, the post PPCI transition to ticagrelor did not appear to lead to a significant rebound in platelet activity.

Introduction

Coronary artery disease is the primary cause of premature mortality in the developed world and STEMI is its most lethal acute manifestation. [1] Antiplatelet therapy with potent oral $P2Y_{12}$ receptor antagonists improves outcomes in STEMI with both ticagrelor and prasugrel showing superior efficacy to clopidogrel. [2] One important limitation of all orally administered $P2Y_{12}$ inhibitors is delayed antiplatelet effect, which can take several hours to achieve in the setting of STEMI. [3]

Cangrelor, an IV adenosine triphosphate analogue, has an onset of action of 1-3 minutes and does not require metabolic transformation to become fully active. It induces marked platelet inhibition very rapidly and has a plasma half-life of just 3-6 minutes. Three large randomized trials have compared its use to oral clopidogrel. [2] The CHAMPION PHOENIX showed cangrelor reduced the combined endpoint of death, MI, ischemia driven revascularization or stent thrombosis at 48 hours when compared to clopidogrel. The notion that earlier more potent $P2Y_{12}$ inhibition will benefit patients undergoing PPCI is biologically plausible and is supported by the current ACC/AHA/ESC guidelines for ACS, which give a class 1 recommendation for early treatment with a $P2Y_{12}$ inhibitor. [2]

A recent randomized pharmacodynamic study has assessed the antiplatelet effect of cangrelor vs. ticagrelor plus cangrelor at the time of PPCI in 30 patients, showing enhanced early $P2Y_{12}$ inhibition in patients treated with both ticagrelor and cangrelor. Intriguingly, in this study, a proportion of the patients receiving both agents exhibited an increase in platelet reactivity after stopping the cangrelor infusion. [4]

In the recently published CANTIC study, 50 patients undergoing PPCI received crushed ticagrelor and were then randomized to be treated with simultaneous cangrelor or matching placebo. Cangrelor reduced the PRU throughout the infusion, compared to placebo and consequently therefore high on-treatment platelet reactivity (HPR) rates were reduced in the cangrelor arm. After stopping the infusion, no rebound increase in platelet activity occurred, suggesting no drug-drug interaction. [5] The clinical importance of optimal $P2Y_{12}$ inhibition at the time of PPCI remains

incompletely explored, and in addition, safe transition from IV therapy to an oral P2Y12 inhibitor is an important issue. [6]

Even with timely PPCI, up to half of patients have limited microvascular perfusion despite restoration of normal epicardial flow.[7] These patients have larger infarcts [8] and are at higher risk of adverse events [9]. Recent studies highlight the role of platelets in contributing to microvascular dysfunction in the context of acute STEMI through various mechanisms including ischemia, reperfusion injury and distal embolization. [10].

We set out to determine the differential effect of cangrelor vs. ticagrelor on P2Y12 inhibition at the time of first balloon inflation in the culprit coronary artery, and following PCI in a cohort of patients undergoing PPCI for STEMI. Additionally, we studied the impact of these two treatment strategies on a variety of measures of microvascular function and infarct size following PPCI.

Study Endpoints

The co-primary endpoints for this trial were the between-group difference in P2Y12 inhibition at the time of first intracoronary balloon inflation, 4 hours and 24 hours following initial dosing. Secondary surrogate outcome measures were the assessment of microcirculatory and epicardial reperfusion in addition to myocardial infarct size.

Methods

Study Population and STEMI Management

This is an open label, prospective, randomized controlled trial enrolling patients with acute STEMI undergoing PPCI. Acute STEMI was defined as chest pain lasting for >30 minutes associated with ST-segment elevation >2 mm in 2 contiguous chest leads or 1mm in 2 contiguous limb leads. Following informed consent, subjects were randomized 1:1 to routine care (aspirin and ticagrelor) or aspirin and IV cangrelor immediately prior to PPCI. Patients were eligible if they had an indication for PPCI, were able to give informed consent, were P2Y12 receptor inhibitor naïve and had no

contra-indication to ticagrelor or cangrelor. Exclusion criteria included significant active bleeding, current oral anticoagulation therapy, established cardiogenic shock, previous myocardial infarction (MI), and contraindications to CMR imaging. Patients treated with GP IIb/IIIa receptor antagonist therapy during PPCI were withdrawn from the analysis. All patients provided written consent and continued in the study for 3 months. The study was approved by the UK National Research Ethics Service (reference 16/EM/0094).

Drug Therapy

A total of 100 subjects were enrolled, 50 in the cangrelor arm and 50 in the ticagrelor arm. All patients received aspirin 300mg loading at the time of first medical contact, prior to randomisation. Patients allocated to ticagrelor received a loading dose of 180 mg of the drug orally immediately following randomization and prior to admission to the catheter suite followed by a dose of 90mg twice daily for 12 months. Patients in the cangrelor arm were treated with a bolus of 30mcg/kg then 4mcg/kg/min IV infusion immediately following randomization and then transferred to the cardiac catheter suite to undergo PPCI. Cangrelor infusion was continued for 2 hours or for duration of the procedure; whichever was longer. Ticagrelor 180 mg was given 30 minutes prior to stopping the infusion, as per manufacturers instructions, followed by a dose of 90mg twice daily for 12 months. Use of morphine was recorded prospectively.

Primary Endpoint Measures

Platelet Function Testing

$P2Y_{12}$ inhibition was measured using VerifyNow ™ (ACCRIVA diagnostics, San Diego, California, USA) rapid platelet function analyzer at the time of infarct vessel balloon inflation, 4 hours following study drug loading and at 24-36 hours.

Results are expressed as $P2Y_{12}$ reaction units (PRU), indicating the degree of ADP-mediated aggregation specific to the $P2Y_{12}$ receptor. PRU values of $\geq$208 are indicative of a suboptimal response and are associated with poor clinical outcomes including death, MI and stroke at one year. [11]

Surrogate Endpoint Measures

Index of Micro-vascular Resistance and Coronary Flow Reserve

IMR and Coronary Flow Reserve (CFR) were measured in the culprit coronary at the end of the PPCI procedure. IMR, a combined pressure-/temperature-tipped guidewire based quantitative assessment of coronary microvasculature function, is defined as the distal coronary pressure multiplied by the mean transit time of a 3-mL bolus of saline at room temperature measured simultaneously during maximal coronary hyperemia (Certus, ST Jude medical, St Paul Minnesota). [12] Maximal coronary hyperemia was induced with IV adenosine at a dose of 140 micrograms/kg/min. The dose was increased at operator's discretion if there was a sub-optimal symptomatic or hemodynamic response at the standard dose.

We set out to assess the absolute IMR values in each group and the proportion of subjects in each group with an IMR > 40. CFR is calculated as the ratio of maximal blood flow during maximal coronary hyperemia to resting flow. It is influenced by both epicardial arterial and microvascular function. A CFR < 2.0 is considered abnormal and is associated with cardiovascular disease states. We report the mean CFR in each group. [13]

All physiological metrics were independently assessed by two experienced cardiologists at the University of Glasgow Physiology Core Laboratory (TF & CB) blinded to treatment group assignment.

Angiographic Analysis

Thrombolysis in Myocardial Infarction (TIMI) Flow Grade (TFG), Corrected TIMI Frame Count (cTFC) and TIMI Myocardial Perfusion Grade (MPG) were measured using standard techniques and a frame counter. [14]

ST-segment Resolution

A 12 lead EKG was recorded before coronary reperfusion and 90-120 minutes following PPCI to assess ST-segment resolution (STR). This variable was expressed as complete (>70%), incomplete (>30% to < 70%) or none (<30%).[15]

Initial Infarct Size Estimation by Peak Troponin Level

High sensitivity cardiac troponin T (cTnT) was measured at 24-36 hours following PPCI (Roche, Rotkreuz, Switzerland).

Final Infarct Size Assessment by CMR Imaging

Patients were studied at 3 months post presentation using a 1.5 Tesla scanner (Philips Ingenia) with a standard 12-channel matrix coil configuration.[16]

All measurements were performed by 2 observers (EM and SH, level 3 SCMR) blinded to clinical and angiographic data. Where a discrepancy of >10% was evident between reports, the final figure was reached by consensus. Image analysis for LV volumes, LV function and LV mass were performed using semi-automated software (CMR42 Circle Cardiovascular Imaging, Canada). Infarct size was expressed as a percentage of LV mass.

Safety Endpoints

Bleeding events were prospectively assessed using the Bleeding Academic Research Consortium (BARC) criteria during the index admission. [17]

Statistics and Data Analysis

Categorical variables are reported as number and percentage (n (%)). Continuous variables are summarized by mean and standard deviation (SD) if normally distributed and median and interquartile range (IQR) if non-normally distributed. Continuous outcome measures were compared between groups with two sample t-tests or Wilcoxon rank sum tests. Categorical outcome measures were compared using Chi-squared tests or Fisher Exact tests. All p-values are two-sided and statistical significant was considered as $p \leq 0.05$. Data were analyzed by the Robertson Centre for Biostatistics, University of Glasgow using SAS for windows v9.3 (SAS Institute Inc., Cary, North Carolina). Graphs were produced using Prism software (GraphPad Prism version 5.0, La Jolla Ca.). A sample size calculation was performed using preliminary data on a prior study of 15 patients with a mean (SD) for $P2Y_{12}$

Reaction Units (PRU) of 257 (61.1). A sample size of 50 in each group would have 80% power to detect an effect size of 0.566 using a two-group t-test with a 5% two-sided significance level. This is equivalent to a difference of 34.6 units of PRU between the cangrelor and ticagrelor groups. Post-hoc analysis shows that 50 patients per group provides 95% power to demonstrate a 30% reduction in PRU at first coronary balloon inflation time in the cangrelor group compared to the ticagrelor group.

RESULTS

Study Population

Patient, treatment and procedure characteristics are described in table 1 and table 2. Two hundred twenty six patients presenting with STEMI were screened, 117 randomized. Of the 109 excluded patients, 42 had previously received a $P2Y_{12}$ inhibitor and 37 had suffered previous MI. Other exclusions included cardiogenic shock (n=13), oral anticoagulant therapy (n=8), lacking capacity for consent (n=4), history of bleeding (n=3) and renal failure requiring dialysis (n=2), (Figure 1). Seventeen subjects were withdrawn from the study after randomization due to either the use of GPIIb/IIIa inhibitors (cangrelor n=6, ticagrelor n=5, total n=11; 9.4%), extreme clinical instability (n=2) or the presence of an alternative diagnosis (myocarditis n=2; Takotsubo cardiomyopathy n=2). Of the 117 randomized patients, 1 died after withdrawal from the study. After these exclusions/withdrawals, 100 randomized patients were included for analysis (cangrelor n=50, ticagrelor n=50). All patients received $P2Y_{12}$ inhibitors as per protocol. Of the 100 patients, 90 were assessed for microvascular function using IMR (ticagrelor n=45 cangrelor n=45) with hemodynamic instability precluding measurement in 10 subjects. Angiographic analysis was performed on all subjects and CMR at three months was performed in 75 (cangrelor n=37, ticagrelor n=38). Reasons for not undertaking CMR included renal failure (n=2), lengthy intensive care unit stay (n=1), procedure intolerance/ claustrophobia (n=2) and 20 patients declined. Morphine for pain relief was administered to 37 out of 50 (74%) cangrelor-treated patients, at an average dose of 9.7mg, and to 40 out of 50 (80%) ticagrelor-treated patients, at an average dose of 8.5mg. The mean time from morphine administration to study drug loading was 60 minutes in the cangrelor arm and 55 minutes in ticagrelor arm.

All 100 patients survived to discharge. One patient underwent in-patient coronary artery bypass operation necessitating a prolonged intensive care unit stay. Two patients became hemodynamically unstable during PPCI and needed the insertion of intra-aortic balloon pump.

Primary Endpoints

Platelet Inhibition

At the time of initial coronary balloon inflation, cangrelor produced significantly greater $P2Y_{12}$ inhibition, (cangrelor 145.2 ± 50.6 vs. ticagrelor 248.3 ± 55.1; p<0.001, Mean, SD). This difference was no longer apparent at 4 hours (cangrelor 158.1±92.1 vs. ticagrelor 131.2±92.9; p= 0.15) and 24-36 hours after study drug administration (cangrelor 61.0±50.0 vs. ticagrelor 60.1±56.3 p= 0.93). (Figure 2) Whilst there was a slight numerical increasing PRU in patients within the cangrelor group after transitioning to ticagrelor (cangrelor 145.2 ± 50.6 to 158.1±92.1) this was not statistically significant, indicating that this transitioning period is safe in the context of STEMI. With the randomization and treatment allocation in the emergency setting, both drugs were given as soon as practicable after randomisation, before PPCI. The preparation time of IV cangrelor was longer than that for administering ticagrelor; this translated into a longer ticagrelor initiation-balloon inflation time than cangrelor initiation-balloon inflation time (23.0±12.8 minutes for cangrelor vs. 36.3±16.9 for ticagrelor; P<0.0001). At balloon inflation, 45 out of 50 (90%) cangrelor treated patients achieved an optimal PRU (<208 units). Only 11 out of 50 (22%) ticagrelor treated subjects were in range (P<0.0001). (Table 3) At 4 hours post initial drug dosing, 15 out of 50 ticagrelor-treated patients (30%) and 20 out of 50 cangrelor-treated patients (40%) had PRU values above 208, indicating high-on treatment platelet reactivity (HPR). In the cangrelor treated group this measure was taken 2.5 hours following transitional ticagrelor loading and 2 hours after the cangrelor infusion had ended. The administration of morphine did not influence the degree of $P2Y_{12}$ inhibition at the time of coronary balloon inflation in either of the treatment groups (p=0.48).

Surrogate Endpoints

Index of Microvascular Resistance and Coronary Flow Reserve

The mean time from administration of study drugs to IMR measurement was 88 minutes. Following PPCI, IMR was similar in each group, (Figure 3A), (cangrelor 30 (22,58), ticagrelor 28 (21,40), median (IQR); p=0.52). Similarly, the proportion of patients with IMR greater than 40 (cangrelor 18 (40%) vs. ticagrelor 11(24%), p=0.11) was not different. CFR results were also similar between groups (Figure 3B) (cangrelor median (18) 1.3 (19), ticagrelor 1.4 (20) p=0.30).

Angiographic Analysis

There was no significant difference in the occurrence of post-PCI MPG 3 (cangrelor n=31 vs. ticagrelor n=32; p=0.54) and TFG 3 (cangrelor n=38 vs. ticagrelor n=42; p=0.27) between treatment groups. Likewise, there was no difference in the mean cTFC (21.7±14.2 for cangrelor vs. 21.4±10.2 for ticagrelor; p=0.93). Suboptimal TIMI flow grades (1 and 2) were present at the end of the PPCI procedure in 12 cangrelor-treated patients and 7 ticagrelor-treated patients.

EKG Analysis

At 90-120 minutes following PPCI, no difference was seen in STR between the cangrelor and ticagrelor groups (complete=32%, partial=11%, none=7% for cangrelor vs. complete=36%, partial=7%, none=7% for ticagrelor; p= 0.57).

Myocardial Infarct Size

CMR was performed at a median of 13 weeks after PPCI in both of the groups (Figure 3C;Table 4). Infarct scar was revealed on late gadolinium enhancement in 68 out of 75 (90.6%) patients who had CMR performed (cangrelor 31, ticagrelor 37 patients). There was no difference in infarct size as a percentage of LV mass between groups (cangrelor 13.7 (7.7,17.5), ticagrelor 10.9 (6.6,17.5), Median, (IQR); p=0.61). Similarly, left ventricular ejection fraction was not different (cangrelor 56.50 (47.50,59.25), ticagrelor 55 (44.50,61.50) median, (IQR); p=0.96). Peak troponin levels at 24-36 hours post drug administration did not differ significantly between the treatment groups (Table 4).

Safety Endpoints

Two out of 50 cangrelor-treated patients and 3 out of 50 ticagrelor-treated patients developed hematoma at the radial access site around 20-50 minutes following PPCI (Type 2 BARC). This was managed conservatively and required no surgical intervention in either of the treatment arms. One patient in the ticagrelor arm developed limiting shortness of breath 2 days after initiation necessitating replacement with clopidogrel, which resulted in complete resolution of symptoms.

DISCUSSION

This randomized-controlled and assessor blinded study assesses the effect of a strategy of IV cangrelor transitioning to ticagrelor, compared to ticagrelor standard therapy on $P2Y_{12}$ inhibition; coronary microcirculation and infarct size in a STEMI population treated with PPCI. The main findings are as follows:

Firstly, IV cangrelor, compared to oral ticagrelor produced a markedly greater $P2Y_{12}$ inhibition at the time of infarct-related artery balloon inflation during PPCI.

Secondly, IV cangrelor was not shown to be superior to oral ticagrelor in improving coronary microcirculatory reperfusion as assessed by IMR and CFR and no difference was seen in terms of the angiographic markers of coronary reperfusion and STR. Similarly no significant difference was seen between groups in the initial infarct size assessed by peak troponin and the final infarct size assessed by CMR at 3 months.

These results support our hypothesis that IV cangrelor when compared with oral ticagrelor will yield greater $P2Y_{12}$ inhibition at the time of coronary balloon inflation by PPCI. This greater early $P2Y_{12}$ inhibition did not appear to lead to improved microcirculatory function/perfusion, or result in a reduced myocardial infarct size.

If the degree of peri-interventional $P2Y_{12}$ inhibition in STEMI treatment is of significant importance, strategies to both provide strong inhibition and also limit the possible negative effect of transitioning to an oral agent might be valuable. Two recently published studies have investigated the pharmacodynamic effect of cangrelor compared to different ticagrelor loading regimens during PPCI.

In the first, 30 patients received ticagrelor loading prior to angiography and then were randomised in the catheter lab to either cangrelor or no additional antiplatelet treatment. [4] It showed markedly more potent $P2Y_{12}$ inhibition (PRU) 15 minutes following loading in subjects treated with cangrelor. There was a suggestion, in this trial, of an increase in platelet reactivity following cessation of the cangrelor infusion with 4 out of 15 patients exhibiting an increase in PRU at 2-4 hours. The loading regimen used was in contrast to our current study, where cangrelor was administered as monotherapy before angiography and during PPCI in the cangrelor arm, and the transition to ticagrelor occurred following PPCI, with the oral agent being given 30 minutes prior to cangrelor cessation.

In the CANTIC trial whereby 50 subjects received ticagrelor loading as crushed tablets at the time of randomisation to cangrelor or placebo, once again more potent $P2Y_{12}$ inhibition was demonstrated in the cangrelor treated patients, particularly at the primary endpoint time of 30 minutes. [5] Interestingly, in this study with assessment of $P2Y_{12}$ inhibition at 8 time points, no increase in PRU was seen after the cangrelor infusion was stopped, suggesting no rebound in platelet activity and no drug-drug interaction. These finding are in line with our study of 100 STEMI patients in which no significant increase in $P2Y_{12}$ inhibition was evident in the cangrelor treated subjects, when measured at 4 hours after randomisation, following the transition from cangrelor to ticagrelor. This issue of transition from cangrelor to an oral agent was elegantly studied in more stable patients undergoing PCI in the ExcelsiorLOAD2 trial. Despite the previously demonstrated drug-drug interaction shown between the thienopyridine clopidogrel and cangrelor, prasugrel (and also ticagrelor), when given at the onset of the cangrelor infusion yielded very good levels of $P2Y_{12}$ inhibition soon after cangrelor cessation seemingly preventing a clinically relevant gap in platelet inhibition cangrelor. [18]

The paradigm of potent antiplatelet agents to improve STEMI PPCI outcomes and reduce myocardial infarct size

STEMI is associated with a high degree of intrinsic platelet activation, the level of which is associated with the magnitude of both subsequent antiplatelet therapy effect and clinical outcomes. [19] Furthermore, PPCI is the coronary interventional procedure associated with the highest frequency of severe thrombotic complications and therefore rapid and consistent platelet inhibition is a key objective in STEMI management [20]. Prasugrel and ticagrelor are potent and rapidly acting $P2Y_{12}$ inhibitors that reduce adverse ischemic events in STEMI patients when compared to clopidogrel. [3] The therapeutic effect of prasugrel and ticagrelor is markedly delayed in the context of STEMI, [3] and so PPCI is likely to be performed in the context of sub-optimal $P2Y_{12}$ inhibition. We showed that over three quarters of study participants randomized to oral ticagrelor have a suboptimal level of $P2Y_{12}$ inhibition at the time of first coronary balloon inflation.

Does potent antiplatelet activity at the time of reperfusion with PPCI matter?

There is theoretical concern about inadequate antiplatelet effect during PPCI. In the STEMI sub analyses of both the TRITON-TIMI 38 (prasugrel) and PLATO (ticagrelor) trials, the incidence of early stent thrombosis (in the first 24 hours) was similar between groups, possibly implicating delayed onset of action for these orally acting $P2Y_{12}$ agents. Suboptimal early $P2Y_{12}$ inhibition may also be implicated in the PLATO STEMI subset finding that ticagrelor did not improve post PPCI STR and also that no increase in the incidence of post procedural TIMI 3 flow was seen with this agent. [21, 22] Attempts to circumvent this limitation of the oral route include upstream administration, [23] dose modification [24] and changes in formulation such as crushing tablets before administration. [25]

Cangrelor, the rapidly acting potent intravenous $P2Y_{12}$ inhibitor might mitigate against the perceived failings of oral $P2Y_{12}$ inhibition in the context of STEMI. It has been studied in three major clinical trials, each using clopidogrel as the comparator. CHAMPION PCI and CHAMPION PLATFORM both failed to meet their primary objective, whereas in the later CHAMPION PHOENIX trial, randomizing 10,942 subjects with stable angina and ACS, cangrelor reduced the primary endpoint (a

composite of Death, MI, ischemia driven revascularization and stent thrombosis). In a pooled analysis of patient level data cangrelor was superior to clopidogrel in reducing the primary endpoint of all cause death, MI, ischemia driven revascularization at 48 hours (OR 0.81, 95% CI 0.71-0.91, P=0.0007). Results in the 2891 subjects treated for STEMI were consistent with this, but did not reach significance (OR 0.84, 95%CI 0.55-1.27 P=0.41). Of interest clopidogrel was given before PPCI in only 55.7% of subjects in this analysis. [26] The rate of intra-procedural stent thrombosis in clopidogrel treated patients was markedly higher than in the cangrelor treated patients. [26] Many have questioned whether the early antiplatelet advantage seen with cangrelor vs. clopidogrel would be seen if a more rapidly acting and potent oral agent was used as the comparator and the results of our study inform this debate and adds to our knowledge regarding the utility of early $P2Y_{12}$ inhibition in the setting of PPCI.

Theoretically sound strategies that have failed to translate into improved myocardial tissue perfusion post PPCI include glycoprotein (GP) IIb/IIIa inhibitors and aspiration thrombectomy.[27] Ischemia reperfusion injury or other factors may be more important causes of impaired myocardial tissue perfusion post PPCI rather than distal microvascular thrombosis.

Many other on-going lines of research aim to improve patient outcomes following PPCI. Changes in clinical pathways, mechanical reperfusion techniques and pharmacotherapy are all being investigated. The current study adds to our knowledge regarding the utility of early $P2Y_{12}$ inhibition in the setting of PPCI.

The principal finding of our study - that cangrelor leads to more potent $P2Y_{12}$ inhibition at the time of coronary balloon inflation during PPCI than oral ticagrelor- lends support to its use for STEMI patients undergoing PPCI if an oral agent cannot be administered. Such circumstances are relatively common; examples include intubated patients having suffered out of hospital cardiac arrest, those with severe nausea and patients in whom the diagnosis is uncertain prior to angiography who might need early surgical intervention.

However, despite the impressive pharmacodynamic results achieved with cangrelor in our, and recent studies, the clinical significance for cangrelor vs. ticagrelor remains unclear. We were unable to demonstrate a significant difference in the tested

surrogate measures of STEMI outcome or in terms of final infarct size. The clinical importance of potent P2Y12 inhibition in the early course of STEMI treatment with PPCI remains to be determined and requires further investigation in larger scale clinical trials.

Limitations

This trial was an open label randomized trial and therefore subject to risk of operator bias. To minimise this risk, all surrogate endpoints were analyzed by researchers blinded to treatment allocation.

Another principle limitation is the study size. The current study has randomized larger numbers than recently published trials of cangrelor vs. ticagrelor, but was not fully powered for the secondary surrogate endpoints assessing PPCI success. These secondary outcome findings should be regarded as hypothesis generating therefore.

Taking the primary endpoint of P2Y12 inhibition at first balloon inflation time, it should be noted that no baseline Verify-Now measures were taken before study drug administration, and so in the ticagrelor arm, where the sample was taken at an average of 36 minutes post drug loading, the limited effect seen might, in part, be related to baseline non-drug P2Y12 activity.

Conclusions

Cangrelor greatly increases P2Y12 inhibition at the time of coronary balloon inflation compared with ticagrelor in patients with STEMI undergoing PPCI. Our data suggest that cangrelor can be considered for patients undergoing PPCI not pre-treated with oral P2Y12 receptor inhibitors. This approach would allow bridging of the gap that results from the delayed onset of action of oral P2Y12 receptor inhibitors.

This pharmacodynamic advantage did not translate into a measurable clinically relevant effect in the secondary endpoints, however these need to be interpreted with caution and should be seen as hypothesis generating only and can form the basis for future studies.

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Thrombosis and Haemostasis Figure One

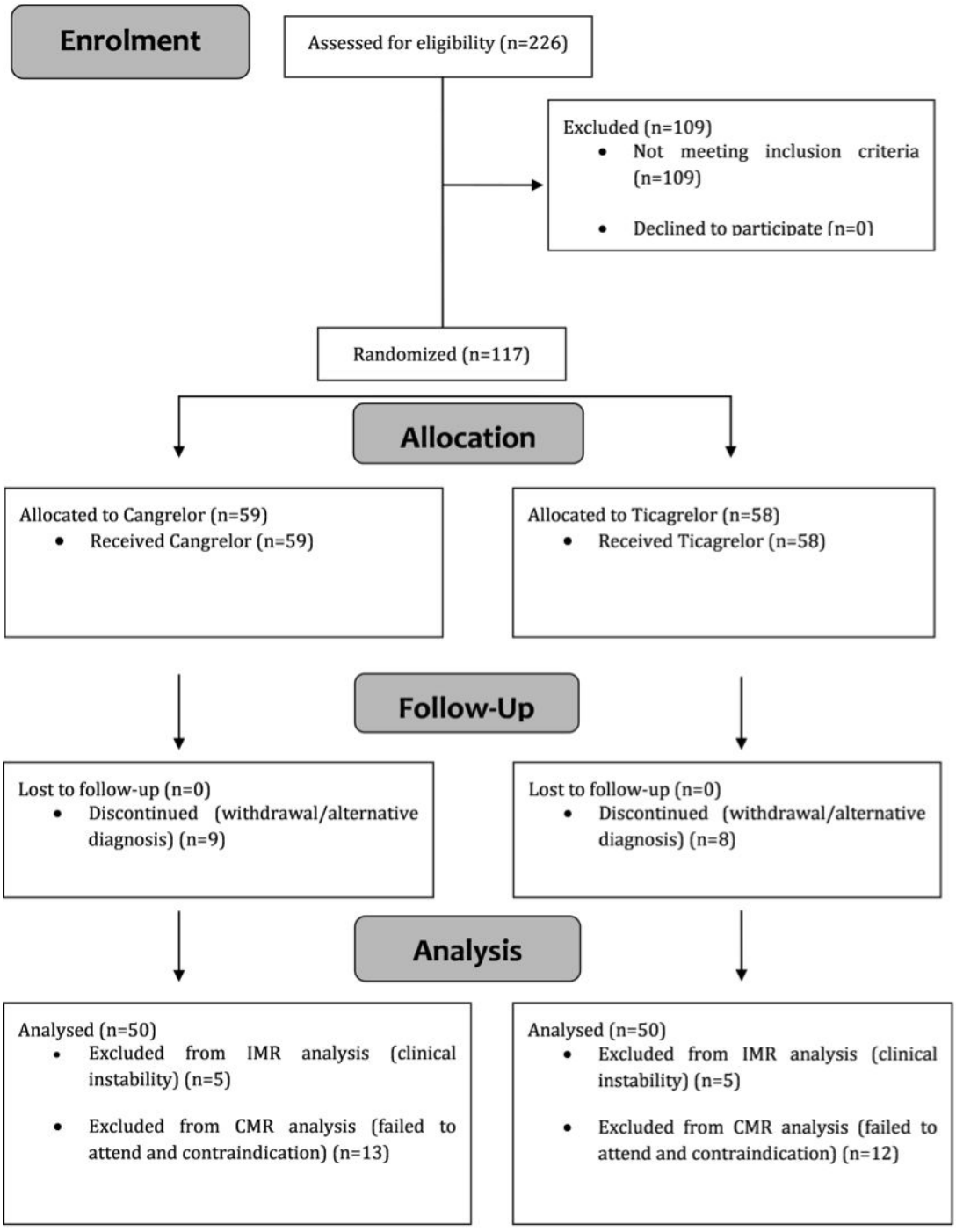

Figure 1. Study Flow Diagram

Thrombosis and Haemostasis Figure Two

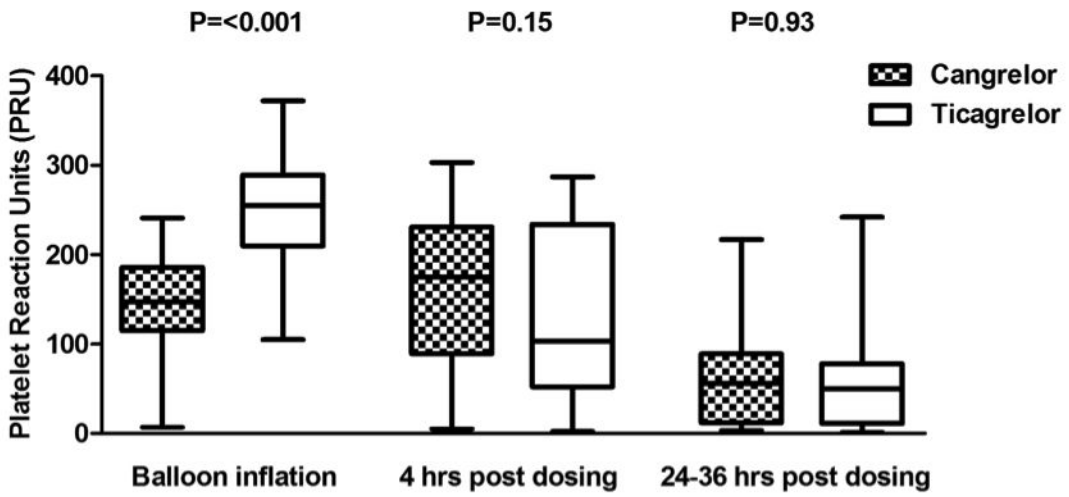

Figure 2. Box and whiskers plots showing comparison of the degree of P2Y12 inhibition measured by platelet reaction units at balloon inflation (vessel opening) time, 4 hours and 24-36 hours post antiplatelet drugs administration. Group data shown (median, IQR range). IQR = interquartile range, PRU= Platelet Reaction Units.

Thrombosis and Haemostasis Figure Three

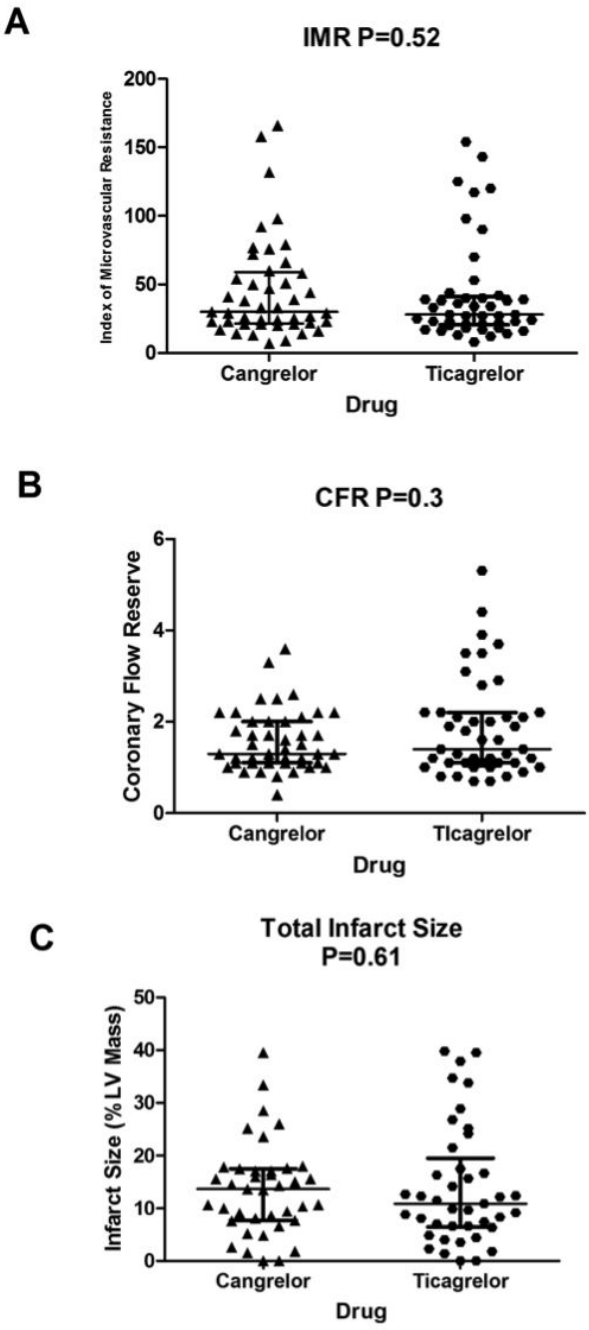

Figure 3. Graphs comparing the effect of cangrelor and ticagrelor on IMR (A) and CFR (B) immediately post index PPCI procedure, and total infarct size (C) by CMR imaging at three months follow up. Group (median and interquartile range) and individual data shown (▲ indicates cangrelor while ● indicates ticagrelor). CFR = coronary reserve flow, CMR = cardiac magnetic resonance, IMR = index of microvascular resistance, PPCI = primary percutaneous coronary intervention

Table 1 Patient characteristics

Characteristic	All (n = 100)	Cangrelor (n = 50)	Ticagrelor (n = 50)
Demographics			
Age, years	62.3 ±13.4	61.2 ±13.9	63.4 ± 12.9
Males	72 (72)	39 (78)	33 (66)
BMI, kg/m^2	28.3 ± 6.0	28.5 ± 6.3	28.1 ± 5.7
Smoking status			
Current smoker	50 (50)	26 (52)	24 (48)
Former smoker	16 (16)	7 (14)	9 (18)
Medical history			
CVD Family history	31 (31)	18 (36)	13 (26)
Diabetes	19 (19)	10 (20)	9 (18)
Hypertension	44 (44)	20 (40)	24 (48)
Hyperlipidemia	20 (20)	13 (26)	7 (14)
Previous MI	0	0	0
Previous CABG	0	0	0
Previous TIA/CVA	0	0	0
Previous PCI	4 (4)	1 (2)	3 (6)
Pre-infarct angina	4 (4)	3 (6)	1 (2)
Admission blood tests			
Hemoglobin, g/L	138.2 ± 18.0	138.1 ± 16.6	138.4± 19.4

Neutrophils, 10^9 g/L	9.4 ± 3.6	9.6 ± 3.7	9.2 ± 3.5
Platelet count, 10^9 g/L	250.6 ± 65.9	245.8 ± 66.0	255.5 ± 66.1
WCC, 10^9 g/L	12.2 ± 4.1	12.4 ± 4.4	12.0 ± 3.8
Angiographic variables			
MI Localisation			
Anterior	31 (31)	13 (26)	18 (36)
Inferior	61 (61)	32 (64)	29 (58)
Infero-lateral	1 (1)	0	1 (2)
Lateral	5 (5)	4 (8)	1 (2)
Posterior	2 (2)	1 (2)	1 (2)
Culprit Vessel			
LMS	1 (1)	0	1 (2)
LAD	31 (31)	15 (30)	16 (32)
LCX	14 (14)	8 (16)	6 (12)
INT	1 (1)	0	1 (2)
RCA	53 (53)	27 (54)	26 (52)
Number of vessels diseased			
0	1 (1)	0	1 (2)
1	28 (28)	11 (22)	17 (34)
2	30 (30)	16 (32)	14 (28)

3	41 (41)	23 (46)	18 (36)
Number of vessels treated			
0	2 (2)	1 (2)	1 (2)
1	89 (89)	42 (84)	47 (94)
2	9 (9)	7 (14)	2 (4)

Values are mean ± SD, n (%) or median (IQR) as appropriate. IQR = interquartile range; SD = standard deviation; BMI = body mass index; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; CVD = cardiovascular disease; INT = Intermediate artery; LAD = left anterior descending artery; LCX = left circumflex artery; LMS = Left main stem; MI = Myocardial Infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIA = transient ischemic attack; WCC = white cell count.

Table 2 Treatment and procedure characteristics

Characteristic	All (n = 100)	Cangrelor (n = 50)	Ticagrelor (n = 50)	p value
Call to balloon time, minutes	121 [102, 140]	116 [100, 136]	126 [106, 150]	0.16
Door to balloon time, minutes	57 [45, 71]	53 [45, 71]	59 [44, 70]	0.83
Treatment duration, minutes	28 [20, 37]	24 [12, 30]	33 [23, 48]	<0.001
Ischemia duration, minutes	192 [143, 289]	164 [133, 233]	195 [148, 345]	0.26
Morphine given	77 (77)	37 (74)	40 (80)	0.48
Total heparin, units	8000 [6500, 10000]	8500 [5000, 10000]	8000 [7000, 10000]	0.83
Total length of stent, mm	42.1 ± 22.1	43.2 ± 22.9	40.8 ± 21.4	0.59
Thrombectomy	14 (14)	7 (14)	7 (14)	1.00

Values are mean ± SD, n (%) or median [IQR] as appropriate. P-values are from Two-sample t test, Wilcoxon sum rank test or Chi-squared test as appropriate. IQR = interquartile range.

Table 3 Comparison of P2Y12 reaction units (PRU) at coronary reperfusion (balloon inflation) time, by treatment group.

Characteristic	Category	Cangrelor (n = 50)	Ticagrelor (n = 50)	p value
PRU units at balloon inflation	<=208	45 (90%)	11 (22%)	<0.0001
	>208	5 (10%)	39 (78%)	

P-values from chi-squared test. PRU= platelet reaction units.

Table 4 Infarct size by CMR and peak troponin levels

Characteristic	All (n = 64)	Cangrelor (n = 29)	Ticagrelor (n = 25)	p value
Infarct size (CMR, %)	11.8 [6.8,17.5]	13.7 [7.7, 17.5]	10.9 [6.6, 17.5]	0.61
Infarct size (Peak Troponin, ng/L)	29556 [13879, 58988]	37169 [14230, 56740]	23896 [13663, 66565]	0.84

Values are median [IQR]. P-values are from Wilcoxon sum rank test. CMR = cardiac magnetic resonance; IQR = interquartile range