Effect of cangrelor on infarct size in ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: a randomized controlled trial (The PITRI trial)

Heerajnarain Bulluck PhD[1,2*], Jun Hua Chong PhD[3,4*], Jennifer Bryant PhD[3], Annitha Annathurai MBBS[5], Ping Chai MBBS[6], Mervyn Chan MBBS[4], Ashish Chawla MBBS[7], Chee Yang Chin MBChB[3], Yiu-Cho Chung PhD[8], Fei Gao PhD[9,10], Hee Hwa Ho MBBS[11], Andrew Fu Wah Ho PhD[12], John Hoe MBBS[13], Syed Saqib Imran MBBS[14], Chi-Hang Lee MBBS[6], Benji Lim MB BCh BAO[15], Soo Teik Lim MBBS[3], Swee Han Lim MBBS[5], Boon Wah Liew MBBS[15], Patrick Lim Zhan Yun MBBS[14], Marcus Eng Hock Ong MBBS[10,12], Valeria Paradies MD[3], Xuan Ming Pung MBBS[3], Julian Cheong Kiat Tay MBBS[3], Lynette Teo MBChB[16], Boon Ping Ting MD[5], Aaron Wong MBBS[3], Evelyn Wong MBBS[12], Timothy Watson MBBS[11], Mark Y Chan PhD[6,18], Yeo Khung Keong MBBS[3, 17], Jack WC Tan MBBS[3], Derek J Hausenloy PhD[4,9,18,19] on behalf of the PITRI investigators.

*These two authors should be considered joint first authors.

[1] Leeds Teaching Hospital NHS Trust, Leeds, UK
[2] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[3] Department of Cardiology, National Heart Centre Singapore, Singapore
[4] Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore
[5] Department of Emergency Medicine, Sengkang General Hospital, Singapore
[6] Department of Cardiology, National University Heart Centre Singapore, Singapore
[7] University of Colorado, School of Medicine, Denver CO, USA
[8] Siemens Healthcare, Singapore
[9] National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore
[10] Health Services and Systems Research, Duke-NUS Medical School, Singapore
[11] Department of Cardiology, Tan Tock Seng Hospital, Singapore
[12] Department of Emergency Medicine, Singapore General Hospital, Singapore
[13] Dept of Radiology, Mount Elizabeth Novena Hospital, Singapore
[14] Department of Cardiology, Khoo Teck Puat Hospital, Singapore.
[15] Department of Cardiology, Changi General Hospital, Singapore
[16] Department of Diagnostic Imaging, National University Hospital, Singapore
[17] Cardiovascular System Academic Clinical Program (CVS ACP), Duke-National University of Singapore Medical School, Singapore
[18] Yong Loo Lin School of Medicine, National University Singapore, Singapore
[19] The Hatter Cardiovascular Institute, University College London, London, UK

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Conflicts of interest

Dr Lynette Teo is on the Astra Zeneca International Advisory Board of Management of Adverse Events with the new antibody drug conjugate T-DXd in Asian patients with metastatic breast cancer, Roche Singapore Immunotherapy in Early stage NSCLC Patient Journey Advisory Board. Lynette Teo has received Philips speaker honorarium in kind and Siemens Healthineers speaker honorarium. Dr Yeo Khung Keong has received research funding from Amgen, Astra Zeneca, Abbott Vascular, Bayer, Boston Scientific, Shockwave Medical, Novartis (via institution); Consulting fees from Abbott Vascular, Medtronic, Novartis, Peijia Medical; Speaker fees from Shockwave Medical, Abbott Vascular, Boston Scientific, Medtronic, Alvimedica, Biotronik, Orbus Neich, Shockwave Medical, Amgen, Novartis, Astra Zeneca, Microport, Terumo, Omnicare. Dr Yeo is also co-founder and owns equity in Trisail

for which Orbus Neich is an investor. Dr Derek Hausenloy has received: consultant fees from Faraday Pharmaceuticals Inc. and Boehringer Ingelheim International GmbH; honoraria from Servier; and research funding from Astra Zeneca and Merck Sharp & Dohme Corp. Dr Chee Yang Chin has received speaker fees from Novartis and consultancy fees from Boston Scientific and Philips. All other authors declare that they have no relevant conflicts of interest.

Corresponding author:
Professor Derek J Hausenloy
Cardiovascular & Metabolic Diseases Program
Duke-NUS Medical School Singapore
8 College Road,
Singapore 169857
Tel +65 65166719
Email derek.hausenloy@duke-nus.edu.sg

Abstract

Background: The administration of intravenous cangrelor at reperfusion achieves faster onset of platelet P2Y12 inhibition than oral ticagrelor and has been shown to reduce myocardial infarct (MI) size in the pre-clinical setting. We hypothesized that the administration of cangrelor at reperfusion will reduce MI size and prevent microvascular obstruction (MVO) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

Methods: This was a Phase 2, multi-center, randomized, double-blind, placebo controlled clinical trial conducted between November 2017 to November 2021 in six cardiac centers in Singapore (NCT03102723). Patients were randomized to receive either cangrelor or placebo initiated prior to the PPCI procedure on top of oral ticagrelor. The key exclusion criteria included: presenting <6 hours of symptom onset, prior MI and stroke or transient ischemic attack; on concomitant oral anticoagulants; and a contraindication for cardiovascular magnetic resonance (CMR). The primary efficacy endpoint was acute MI size by CMR within the first week expressed as percentage of the left ventricle mass (%LVmass). MVO was identified as areas of dark core of hypoenhancement within areas of late gadolinium enhancement. The primary safety endpoint was Bleeding Academic Research Consortium (BARC)-defined major bleeding in the first 48 hours. Continuous variables were compared by Mann–Whitney *U* test [reported as median (1^{st} quartile– 3^{rd} quartile)] and categorical variables were compared by Fisher's exact test. A 2-sided $P<0.05$ was considered statistically significant.

Results: Of 209 recruited patients, 164 patients (78%) completed the acute CMR scan. There were no significant differences in acute MI size [placebo: 14.9 (7.3 – 22.6)%LVmass versus cangrelor: 16.3 (9.9 – 24.4)%LVmass, P=0.40] or the incidence [placebo: 48% versus cangrelor: 47%, P=0.99] and extent of MVO [placebo:1.63 (0.60 – 4.65)%LVmass versus cangrelor: 1.18 (0.53 – 3.37)%LVmass, P=0.46] between placebo and cangrelor despite a two-fold decrease in platelet reactivity with cangrelor. There were no BARC-defined major bleeding events in either group in the first 48 hours.

Conclusion: Cangrelor administered at time of PPCI did not reduce acute MI size or prevent MVO in STEMI patients given oral ticagrelor despite a significant reduction of platelet reactivity during the PCI procedure.

Keywords: ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, microvascular obstruction, cangrelor, ticagrelor, cardiovascular magnetic resonance, myocardial infarct size

Clinical Perspective

What is new?

- In this cohort of ST-segment elevation myocardial infarction (STEMI) patients pre-treated with oral ticagrelor and undergoing primary percutaneous coronary intervention (PPCI), intravenous cangrelor initiated at the beginning of the procedure did not reduce acute infarct size or prevent microvascular obstruction (MVO) despite achieving significantly greater platelet inhibition during the PCI procedure.

What are the clinical implications?

- In STEMI patients pre-treated with the oral ticagrelor at the time of PPCI, there is currently no added benefit for bridging with intravenous cangrelor during the PCI procedure in terms of reducing acute infarct size or preventing MVO.

Non-standard Abbreviations and Acronyms

AAR	Area-at-risk
BARC	Bleeding Academic Research Consortium
CMR	Cardiovascular magnetic resonance
CONSORT	Consolidated standards of reporting trials
HHF	Hospitalization for heart failure
IV	Intravenous
LAD	Left anterior descending
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricle ejection fraction
IMH	Intramyocardial hemorrhage
MACCE	Major adverse cardiac and cerebrovascular event
MI	Myocardial infarction
MVO	Microvascular obstruction
PITRI	Platelet Inhibition to Target Reperfusion Injury
PRU	Platelet reactivity unit
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
STR	ST-segment resolution
TIMI	Thrombolysis in myocardial infarction

Introduction

Prompt recanalization of the infarct-related artery by primary percutaneous coronary intervention (PPCI), and advancements in post-infarct treatments have reduced mortality in ST-segment elevation myocardial infarction (STEMI) patients – however, morbidity from heart failure remains significant.[1] This is partly due to 'myocardial reperfusion injury', whereby the re-establishment of coronary blood flow paradoxically induces cardiomyocyte death.[2] The irreversible contributors of myocardial reperfusion injury are microvascular obstruction (MVO) and cardiomyocyte death due to lethal myocardial injury. In STEMI, MVO occurs in up to one half of patients undergoing PPCI, and when it occurs it is associated with worse outcomes.[3-5] Taken together the presence of MVO and cardiomyocyte death (arising from lethal myocardial injury) cause up to 50% of the resultant MI size and mitigate the full beneficial effects of timely recanalization in terms of reduced MI size.[2] Even though a large number of pharmacological agents have shown cardioprotective effects in the pre-clinical setting, their application in STEMI clinical trials for patient benefit has been disappointing.[6]

Due to delayed absorption in PPCI-treated STEMI patients, currently oral P2Y12 inhibitors do not achieve optimal platelet inhibition during the PCI procedure. This may be expected to enhance the risk of developing MVO and contribute to an increase in acute MI size. Cangrelor is an intravenous P2Y12 inhibitor with fast onset of action and confers maximal platelet inhibition within a couple minutes of administration when compared to 4 to 6 hours for the oral P2Y12 inhibitors, ticagrelor and prasugrel. Therefore cangrelor is likely to offer maximal platelet inhibition at the time of PCI procedure in STEMI patients when compared to oral P2Y12 inhibitors.[7] The CHAMPION-PHOENIX trial demonstrated that the administration of cangrelor during elective or urgent PCI reduced ischemic events, including stent thrombosis when compared to oral clopidogrel, without increasing major bleeding at 48 hours.[8] Interestingly, cangrelor administered at reperfusion has been reported to also have cardioprotective effects in pre-clinical small and large animal studies as evidenced by reduced MI size through the recruitment of cytoprotective pathways including Akt and Erk1/2.[9-14] On this background, the intravenous administration of cangrelor as an adjunct to reperfusion may

have dual benefits in STEMI patients with effective platelet inhibition at the time of PPCI to minimize the risk of developing MVO and a cardioprotective effect at the level of the cardiomyocyte resulting in a reduction in MI size.

Therefore, we undertook the Platelet Inhibition to Target Reperfusion Injury (PITRI) trial,[15] to investigate whether administering cangrelor at the onset of reperfusion, on top of concurrent oral ticagrelor, could reduce acute MI size and prevent MVO in STEMI patients undergoing PPCI.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The PITRI trial (NCT03102723) was a Phase 2, multi-center, double-blind, placebo-controlled, randomized clinical trial conducted between November 2017 to November 2021 in six cardiac centers in Singapore (National Heart Centre Singapore, National University Heart Centre Singapore, Tan Tock Seng Hospital, Sengkang General Hospital, Khoo Teck Puat Hospital, and Changi General Hospital). We obtained approval from the SingHealth Centralized Institutional Review Board (2016/2576) and the trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The reporting of our trial complied with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized controlled trials[16] (CONSORT checklist available in the online supplemental material).

Suspected STEMI patients were screened on arrival to the hospital and written informed consent was obtained. Patients were orally loaded with ticagrelor (180mg) and aspirin (300mg). The inclusion criteria were: aged 21 to 79 years; STEMI defined by: at least 2mm ST-segment elevation in 2 or more anterior leads (V1–V4) or at least 1 mV ST-segment elevation in 2 or more limb leads (II, III and aVF, I, aVL) or ST-elevation in II, II, aVF less than 1 mm with ST-depression in aVL or posterior infarction with ST-depression of at least 1 mm in either V1, V2, or V3 and ST-elevation of at least 1 mm in either V7, V8 or V9; and

presentation within 6 hours onset of most severe chest pain to hospital admission. The main exclusion criteria were: history of previous MI, stroke, transient ischemia attack or prior coronary artery bypass graft surgery; known contraindications to cardiovascular magnetic resonance (CMR) such as severe allergy to gadolinium chelate contrast, severe claustrophobia, ferromagnetic implanted devices, renal insufficiency with an estimated glomerular filtration rate ≤40 mL/min/1.73 m^2; patients with prior therapy before admission within 7 days of P2Y12 inhibitor (ticagrelor, prasugrel, clopidogrel, cangrelor), glycoprotein IIBIIIA inhibitor, anticoagulant therapy or thrombolytic therapy; significant co-morbidities such as patients with cardiac arrest prior to randomization, cardiogenic shock, severe hepatic failure (international normalized ratio>2), bed-bound or wheelchair-bound, and in comatose or semi-conscious states; contraindications to heparinization or antiplatelet therapy; high bleeding risk (gastrointestinal bleeding, traumatic head injury); pregnancy; and on concomitant strong Cytochrome P4503A inducer or inhibitors (detailed list available in the online supplemental material).

Patients were randomized using a web-based platform by the Singapore Clinical Research Institute by unblinded staff and were stratified as per each recruiting center. Following randomization, patients were administered the allocated treatment before recanalization of the infarct-related artery and without delaying the onset of PPCI. Treatment allocation was blinded from the interventional cardiologist, patient and research study staff collecting clinical, CMR, and platelet aggregation data.

Patients randomly allocated to the cangrelor arm received intravenous (IV) cangrelor as a single IV bolus (30 μg/kg) followed by an IV infusion (4 μg/kg/min) for at least 120 minutes or until the PCI procedure had ended – whichever was longer. Those randomized to the placebo arm received IV normal saline as a single IV bolus followed by an infusion of at least 120 minutes or until the PCI procedure had ended – whichever was longer.

The PCI procedure was undertaken as per local practice and at the discretion of the PPCI operator. Glycoprotein IIb/IIIa inhibitor use was limited to bail-out for persistent high thrombus, distal embolization, or slow flow or no reflow as per current guidelines.[17]

Outcomes

Efficacy outcomes

The primary efficacy endpoint was acute MI size within the first week following PPCI, evaluated on the acute CMR scan (late gadolinium enhancement [LGE] mass as a percentage of LV mass).

The secondary efficacy endpoints included MVO (incidence and extent), myocardial salvage index on the acute CMR scan, indicators of successful myocardial reperfusion (ST-segment resolution [STR] at 1.5 hours on electrocardiography and thrombolysis in myocardial infarction [TIMI] flow grade on coronary angiography post-PCI), CMR-evaluated MI size at 6 months, adverse LV remodeling following infarction at 6 months and major adverse cardiac and cerebrovascular events (MACCE – all-cause death, stent thrombosis hospitalization for heart failure (HHF), stroke, repeat myocardial infarction, and ischemia-induced coronary revascularization).

Safety outcomes

The primary safety endpoint was Bleeding Academic Research Consortium (BARC)-defined[18] major bleeding at 48 hours (BARC 3 and 5). The secondary safety endpoint was BARC-defined minor bleeding at 48 hours (BARC 1 and 2).

Platelet function testing

Platelet function testing was evaluated by a point-of-care platelet aggregation test (VerifyNow System) as per manufacturer instruction to quantify platelet inhibition in a subset of STEMI patients as an exploratory analysis. Blood samples were taken at four time-points: (1) before the administration of cangrelor or placebo; (2) immediately post-PPCI; (3) following the cangrelor or placebo infusion; and (4) 120 minutes after the cangrelor or placebo infusion. Patients administered glycoprotein IIb/IIIa inhibitors were not included in the platelet

aggregation sub-study. High platelet reactivity was defined as ≥208 platelet reactivity unit (PRU) as per previous consensus recommendation.[19]

CMR scanning and analysis

CMR was performed using Siemens 1.5T scanners at 4 sites (National Heart Centre Singapore, Khoo Teck Puat Hospital, National University Hospital and Mount Elizabeth Hospital). Each patient underwent 2 CMR scans (acutely and at 6 months) and the CMR protocol has previously been published in the trial design paper.[15] There was a standardized CMR acquisition protocol in place prior to the start of the trial at the different sites and the CMR endpoints analysis plan was pre-defined prior to unblinding of any data. Patients underwent CMR scans acutely (aiming for days 3 post-PPCI and up to 7 days), and at 6 months post-PPCI.

CMR parameters were analyzed using dedicated software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). The scans were analyzed by two experienced observers (HB and JB), blinded to the treatment allocation. LV volumes were quantified using disk summation method, with papillary muscles included as part of the LV cavity.[20] The edema-based area-at-risk (AAR) was quantified from the T2-maps or T2-weighted images on the acute scan using the 2-SD semi-automated technique. MI size was quantified from the LGE images using the 5-SD semi-automated technique as previously described, expressed as the percentage of overall LV mass.[21] MVO was identified as areas of hypoenhancement on the LGE images within the areas of the hyperenhancement (not highlighted by the 5-SD semi-automated thresholding technique) and was manually included as part of the MI zone[22]. MVO was quantified as a percentage of overall LV mass and in a binary fashion as present or absent. Intramyocardial hemorrhage (IMH) was identified as the hypointense core within the infarct-related territory (using LGE images as reference when required) on the T2*-maps. A manual region of interest was drawn and a mean T2* value of <20ms on at least one of the basal, mid, or apical short axis T2*-maps was indicative of the presence of IMH.[23]

Sample size estimation

The sample size calculation has been previously described.[15] In brief, based on published prior studies[24] including patients with a pre-PCI TIMI flow 0 or 1 and presenting within 6 hours of symptoms onset, the weighted mean acute MI size was 22±12 %LVmass in the control arm. To aim for a reduction in MI size of 25%, we estimated a sample size of 95 STEMI in each treatment group or 190 in total (80% power, 2-sided test at 5% significance level). To allow for a 10 to 12% dropout, we aimed to recruit 210 STEMI patients.

Statistical analysis

Statistical analysis was performed using commercially available statistical software (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp). Continuous data were described as mean ± standard deviation (SD) or median (inter-quartile ranges [IQR]) as appropriate. Categorical data were described as frequencies and percentages. Independent groups (e.g., baseline and procedural characteristics, CMR parameters such as MI size, extent of MVO, platelet-induced aggregation between placebo and cangrelor groups) were compared with unpaired Student's *t* test for normally distributed data and with Mann–Whitney *U* test for non-normally distributed data. Fisher's exact test was undertaken to compare categorical variables (e.g., presence or absence of MVO and IMH). For paired acute and chronic LV volume comparisons, paired Student's *t* test was used for normally distributed data and Wilcoxon signed-rank test was used for non-normally distributed data. Furthermore, we undertook several pre-specific subgroup analyses: STEMI patients with TIMI flow $\leqslant$1 versus >1 prior to PPCI; STEMI of LAD versus non-LAD subtype; above and below the median age; and diabetes versus non-diabetes. We analyzed subgroups by undertaking an interaction test by fitting an interaction term of treatment and the relevant subgroups using the appropriate regression model. The time-to-event analysis for the cumulative incidence of MACCE per group was performed using univariable Cox proportional hazard and the hazard ratios (HRs) were computed with 95% CI. Kaplan-Meier curves were

used to assess survival for the follow-up period per group and were compared using log-rank test. Analysis was performed on an intention-to-treat basis. A 2-sided P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Between November 2017 and November 2021, 209 patients were recruited from 6 centers in Singapore as shown in **Figure 1**. Recruitment was temporarily halted and delayed during the Coronavirus disease (COVID-19) pandemic. The baseline characteristics and PPCI details are provided in **Table 1** and were well-balanced between the placebo and cangrelor arms (p values provided in the online supplemental Table 1). There was an unexpected borderline significant increase in the chest pain onset to balloon time in the group randomized to cangrelor when compared to placebo (P=0.052), although there was no difference in door to balloon times between the 2 treatment groups (**Table 1**). The average age of the patients was 56 years and 92% were male. The majority were Chinese (60%), followed by Indian (19%) and Malay (18%). In terms of conventional risk factors, 41% were current smokers, 48% had hypertension, 23% were diabetic and 44% had hyperlipidemia. The majority were in Killip class I and the median symptom onset to balloon time was 164 minutes. Half of the patients presented with anterior STEMI and 73% had a pre-PCI TIMI flow 0 or 1 and post-PCI TIMI flow of 3 was achieved in 85% of patients. Post-PPCI medications were as per current guideline-directed therapy with high proportion of patients discharged on dual anti-platelet therapy with aspirin and ticagrelor, a beta-blocker, an angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker and a statin as shown in **Table 1**.

Primary efficacy endpoint

Out of 209 patients enrolled into the trial, 164 completed the acute CMR scan at a median of 5 (3 – 7) days. The reasons for patients dropping out are listed in **Figure 1**. There was no significant difference in the acute MI size between the placebo and cangrelor arm [placebo:

median 14.9 (7.3 – 22.6)%LVmass versus cangrelor: median 16.3 (9.9 – 24.4)%LVmass, P=0.40], **Figures 2 and 3**, and **Table 2**.

Secondary efficacy endpoints

There was also no significant difference in the incidence of MVO [placebo: 48% versus cangrelor: 47%, P=0.99] and extent of MVO among those who had MVO [placebo: median 1.63 (0.60 – 4.65)%LVmass versus cangrelor: median 1.18 (0.53 – 3.37)%LVmass, P=0.46]. There was also no difference in acute left ventricle ejection fraction (LVEF), myocardial salvage index and IMH as listed in **Table 2**.

Six-month follow-up CMR scan was available in 127 patients (66 in the placebo arm and 61 in the cangrelor arm). There was no significant difference in chronic MI size [placebo: median 9.7 (4.7 – 14.9)%LVmass versus cangrelor: median 11.9 (4.7 – 14.9)%LVmass, P=0.23]. There was also no difference in chronic LVEF, the percentage of patients with residual iron or the percentage change in indexed LV diastolic and systolic volumes as shown in **Table 2**.

There was also no difference in the incidence of post-PCI TIMI flow (TIMI flow 3: 88% each in the placebo and cangrelor arms; TIMI flow 2: 13% in the placebo arm versus 11% in the cangrelor arm: P=0.57) and STR (complete STR: 35% in the placebo arm versus 41% in the cangrelor arm; partial STR: 33% in the placebo arm versus 37% in the cangrelor arm; P=0.30) between the 2 arms.

Pre-specified subgroup analyses

Pre-specified subgroup analyses were performed for STEMI patients with TIMI flow $\leqslant 1$ versus >1 prior to PPCI; STEMI of LAD versus non-LAD subtype; above and below the median age; and diabetes versus non-diabetes. There was no interaction between the treatment effect and these individual subgroups on acute MI size (P values 0.84, 0.26, 0.90 and 0.57 for interaction, respectively, **Figure 4)**.

Platelet function testing

Platelet function testing was available in a small subset of patients (Online supplemental **Table 4**). There was no difference in platelet-induced aggregation at baseline (prior to cangrelor/ placebo administration) between the 2 arms (placebo: 198 (100 – 244)PRU versus cangrelor: 197 (127 – 231)PRU; P=0.94). High platelet reactivity (≥208 PRU) was present in 48% of patients in the placebo arm and 39% of patients in the cangrelor arm (P=0.76) at baseline. However, platelet-induced aggregation was significantly lower at the end of the PCI procedure in the cangrelor arm (placebo: 225 (122– 280)PRU versus cangrelor: 96 (63 – 145)PRU; P<0.001). There was no significant difference in platelet-induced aggregation between the 2 groups immediately after the PCI procedure and 2 hours following the administration of cangrelor/ placebo (**Table 2**).

Primary and secondary safety endpoints

There was no BARC-defined major bleeding events in the first 48 hours in the 2 groups and there was no significant difference in BARC-defined minor bleeding between the 2 groups (6.5% in the placebo arm versus 8.8% in the cangrelor arm; P=0.82).

Major adverse cardiovascular and cerebrovascular events

After a median follow-up of 396 (370 – 738) days, there was no difference in MACCE rates between the 2 arms [10.3% in the placebo arm versus 9.8% in the cangrelor arm; HR 0.87 (0.34-2.06), log rank P=0.75, Supplemental Figure 1]. The individual components of the MACCE are provided in **Table 3**.

Discussion

In the PITRI trial, the addition of cangrelor at the onset of reperfusion to STEMI patients pre-treated with oral ticagrelor did not reduce acute MI size or prevent MVO when compared to placebo, despite achieving faster platelet inhibition during PCI by ~2-fold. Furthermore, there was no effect of cangrelor on chronic MI size and LV remodeling parameters at 6 months

compared to placebo. Of note there were no untoward effects with cangrelor administration in terms of increased bleeding risk when compared to placebo.

Despite the promising cardioprotective benefits of cangrelor in reducing MI size in preclinical studies in rabbits[25] and primates,[26] cangrelor failed to lower MI size in the clinical setting in our trial. Our findings are consistent with the trial by Ubaid et al,[27] who previously showed that cangrelor provided more potent P2Y12 platelet inhibition than ticagrelor alone at the time of balloon inflation in 100 patients undergoing PPCI in an open-labelled randomized controlled trial. However, there was no difference in MVO measured at the end of the PCI procedure and enzymatic infarct size at 24 hours. Although that trial was not powered for MI size by CMR, there was no difference in chronic MI size in a subset of patients with CMR data at 3 months (cangrelor arm: N=29; ticagrelor arm: N=25).[27]

It is well recognized that the bioavailability of the oral P2Y12 inhibitors is lower in STEMI patients and this has been attributed impaired intestinal absorption, systemic vasoconstriction, and hemodynamic disturbances. Furthermore, platelet inhibition is not maximal during the PCI procedure[28-30] with 4 hours or more required to achieve effective platelet inhibition in most patients with ticagrelor and prasugrel in a prior study.[7] Pharmacodynamic studies have already shown fast and effective platelet inhibition with cangrelor in STEMI pre-administered crushed ticagrelor[31] and prasugrel[32] and provided more effective platelet inhibition during PCI. Our trial builds on these previous studies to evaluate whether the more effective platelet inhibition provided by cangrelor during PCI translated to downstream reduction of acute MI size and prevention of MVO, and we showed that this was not the case. Of note, high residual platelet reactivity was present in 43% of our patients before administration of cangrelor or placebo. Pre-treatment with oral ticagrelor has previously been shown to limit MI size in rats[11,33,34]. The neutral findings in our trial could be in part explained by the effective platelet inhibition in a significant portion of patients with oral ticagrelor in our cohort of patients. Whether ethnicity played a role for the low percentage of patients with high residual platelet reactivity at baseline is a possibility[35]. In addition, we did find an unexpected borderline significant increase in the chest pain onset to balloon time in patients randomized

to cangrelor when compared to placebo, although there was no difference in door to balloon times between the 2 treatment groups - we cannot exclude the possibility that this increase in ischemic time dampened the cardioprotective effects of cangrelor.

The translation of novel cardioprotective therapies into the clinical setting for patient benefit has been extremely challenging. Over the last 30 to 40 years a vast number of therapies with proven efficacy for reducing acute MI size and preventing MVO in experimental animal studies (e.g., anti-oxidants, magnesium, calcium-channel blockers, anti-inflammatory agents, erythropoietin, atorvastatin, glucose-insulin-potassium therapy, adenosine), have produced disappointing results when investigated in the clinical setting as adjunctive therapy to reperfusion (reviewed in[6]). More recently, a number of attempts to reduce MI size in STEMI patients have also failed to meet their primary endpoint of cardioprotection - these have included studies investigating therapeutic hypothermia, targeting mitochondrial function, and modulation of nitric oxide signaling as adjuncts to myocardial reperfusion.[6] The reasons for this failure to translate cardioprotection into the clinical setting have been attributed to a number of factors including the presence of comorbidities, concomitant medications and pre-infarct angina. In the PITRI trial, although the age of the patients were relatively young, conventional risk factors were present in a significant proportion of patients (23% with diabetes mellitus, 48% with hypertension; 44% with dyslipidemia; 41% being current smokers). Furthermore, pre-infarct angina was present in 21% of patients and we included patients with all pre-PCI TIMI flows. Pre-specified subgroup analyses for: STEMI patients with TIMI flow $\leqslant$ 1 versus >1 prior to PPCI; STEMI of left anterior descending (LAD) versus non-LAD subtype; above and below the median age; and diabetes versus non-diabetes showed no interaction between the treatment effect and these individual subgroups on acute MI size.

Our study is not without limitations. The planned sample size was 190 patients, but we only recruited 164 patients (78%) with CMR data and only 127 (40%) patients attended the follow-up scan. The higher-than-expected dropout rate was due to a combination of performing acute STEMI research in an East Asian population and the disruption caused by

the COVID-19 pandemic. Of note, those who only had the acute CMR were 7 years younger and were less likely to have thrombus aspiration when compared to those who had both scans. But there was no difference other baseline, procedural and acute CMR parameters (Online supplemental table 3). The acute MI size was lower than the anticipated MI size and therefore reflects a lower-risk cohort. Among those in the platelet function test sub-study, only 43% of patients had high residual platelet reactivity at baseline, but we did not document the time of ticagrelor administration to baseline platelet function testing. However, ticagrelor was administered on arrival to hospital and the median door-to balloon-time was 50 minutes and therefore we would anticipate that the median time of ticagrelor administration to baseline platelet function testing would have been less than 50 minutes. Furthermore, the baseline platelet function test was from a sample of 44 patients and may not be representative of the whole cohort included in this trial.

Conclusion

In the PITRI trial, the addition of cangrelor at the onset of reperfusion by PPCI in this South-East Asian cohort of STEMI patients pre-treated with oral ticagrelor did not reduce acute MI size or prevent MVO despite a significant reduction in platelet reactivity during the PCI procedure.

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Supplemental Materials

Expanded Methods

Figures S1

Tables S1 - 4

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Table 1: Baseline patient characteristics and procedural details

	Total (N=209)	Placebo (N=107)	Cangrelor (N=102)
Age (years)	56±11	55 ±11	56 ±12
Male (%)	192 (92)	99 (93)	93 (91)
Ethnicity			
Chinese	125 (60)	60 (56)	65 (64)
Indian	39 (19)	23 (22)	16 (16)
Malay	38 (18)	21 (20)	17 (17)
Others	7 (3)	3 (3)	4 (4)
BMI (kg/m^2)	25.6±4.2	25.8±4.6	25.4±3.9
Smoking status (%)			
Current smoker	85 (41)	38 (36)	47 (46)
Ex-smoker	33 (16)	18 (17)	15 (15)
Never smoked	84 (40)	48 (45)	36 (35)
Hypertension	100 (48)	49 (46)	51 (50)
Diabetes Mellitus	48 (23)	25 (23)	23 (23)
Hyperlipidemia	92 (44)	47 (44)	45 (44)
Pre-infarct angina	44 (21)	23 (22)	21 (21)
Hemoglobin on admission	159±9	159±10	158±8
Creatinine on admission	87±24	87±24	87±23
HbA1C on admission	6.0 (5.5 – 6.9)	6.0 (5.5 – 6.9)	5.6 (6.0 – 7.1)
Killip class (%)			
I	144 (69)	74 (69)	70 (69)
II	4 (2)	1 (1)	3 (3)
III	2 (1)	0 (0)	2 (2)
IV	1 (1)	0 (0)	1 (1)
Not documented	51 (24)	26 (24)	25 (25)
Onset to balloon time (minutes)	164 (105 – 233) N=186	146 (100 – 216) N=96	191 (113 – 259) N=90
Door to balloon time (minutes)	50 (40 – 66) N=193	50 (39 – 66) N=98	51 (40 – 63) N=95
Infarct-related coronary artery (%)			
Left mainstem	3 (1)	2 (2)	1(1)

Left anterior descending	105 (50)	53 (50)	52 (51)
Circumflex	27 (13)	15 (14)	12 (12)
Right coronary artery	70 (34)	35 (33)	35 (34)
Pre-PCI TIMI flow			
0	134 (64)	72 (69)	62 (62)
1	19 (9)	6 (6)	13 (13)
2	26 (12)	14 (14)	12 (12)
3	25 (12)	12 (11)	13 (13)
Post-PCI TIMI flow			
0	1 (1)	0 (0)	1 (1)
1	0 (0)	0 (0)	0 (0)
2	24 (12)	13 (13)	11 (11)
3	178 (85)	91 (88)	87 (88)
Thrombus aspiration	89 (43)	47 (44)	42 (41)
Glycoprotein IIbIIIa inhibitor	32 (15)	18 (17)	14 (14)
ST-segment resolution			
Complete	79 (38)	37 (35)	42 (41)
Partial	73 (35)	35 (33)	38 (37)
None	34 (16)	22 (21)	12 (11)
Missing data	23 (11)	13 (12)	10 (10)
Medications			
Aspirin	195 (93)	98 (92)	97 (95)
Ticagrelor	183 (88)	95 (89)	88 (86)
Clopidogrel	30 (14)	15 (14)	15 (14)
Beta-blocker	177 (85)	93 (87)	84 (82)
ACEI/ ARB	165 (79)	84 (79)	81 (79)
Statin	199 (95)	103 (96)	96 (94)

BMI: body mass index; ACEI: angiotensin enzyme converting inhibitor; ARB: angiotensin receptor blocker.
Values are N (%), mean ±SD, or median (IQR)

Table 2: Effect of cangrelor on CMR outcomes

	Placebo	Cangrelor	P-value
Acute CMR scan	**N=86**	**N=78**	
Timing of CMR/ days	6 (3 – 7)	5 (3 – 8)	0.74
LVEF/ %	50 (42 – 56)	48 (43 – 53)	0.46
LVESVi/ ml.m^{-2}	36 (29 –42)	37 (31 –43)	0.51
LVEDVi/ ml.m^{-2}	69 (63 – 80)	72 (64 – 79)	0.79
LV mass/ g	89 (79 – 107)	90 (80 – 111)	0.57
MI size/ % of LV mass	14.9 (7.3 – 22.6)	16.3 (9.9 – 24.4)	0.40
Edema-based area at risk/ %LVmass	32 (25 – 40)	34 (24 – 41)	0.39
MSI	0.45 (0.32 – 0.69)	0.51 (0.33 – 0.62)	0.92
MVO/ %	39 (48)	36 (47)	0.99
MVO/ g	1.80 (0.53 – 4.60) N=39	1.02 (0.57 – 3.08) N=36	0.76
MVO/ %LVmass	1.63 (0.60 – 4.65) N=39	1.18 (0.53 – 3.37) N=36	0.46
IMH/ %	27 (34) N=79	23 (32) N=73	0.73
Left ventricular thrombus	5 (5.8)	4 (5.1)	0.99
Chronic CMR scan	**N=66**	**N=61**	
LVEF/ %	53 (45 – 57)	52 (47 – 57)	0.89
LVESVi/ ml.m^{-2}	34 (28 – 45)	33 (27 – 43)	0.48
LVEDVi/ ml.m^{-2}	73 (66 – 84)	69 (65 – 80)	0.12
LV mass/ g	84 (73 – 98)	85 (73 – 93)	0.56
MI size/ %LVmass	9.7 (4.7 – 14.9)	11.9 (4.7 – 14.9)	0.23
Residual iron/ %	17 (26) N=66	19 (31) N=61	0.56
Change in LV volumes	**N=64**	**N=61**	
Percentage change in LVESVi/ %	0 (-15 – 18)	-5 (-17 – 9)	0.15
Percentage change in LVEDVi/ %	4 (-4 – 14)	0 (-8 – 10)	0.11

LVEF: left ventricular ejection fraction; LVESVi: indexed left ventricular end systolic volume; LVEDVi: indexed left ventricular end diastolic volume; LV: left ventricular; MI: myocardial infarct; MSI: myocardial salvage index; MVO: microvascular obstruction; IMH: intramyocardial hemorrhage

Data presented as median (IQR) unless otherwise stated

Table 3: Effect of cangrelor on bleeding outcomes and MACCE

	Placebo N=107	**Cangrelor N=102**	
Bleeding*(BARC classification)/ %	7 (6.5)	9 (8.8)	P=0.82
Major	0 (0)	0 (0)	
Minor	7 (6.5)	9 (8.8)	
MACCE/ %	11 (10.3)	(9.8)	HR 0.87 (0.34-2.06)
Components of MACCE			P=0.75
Death	3 (2.8)	3 (2.9)	
Hospitalization for heart failure	4 (3.7)	0 (0)	
Myocardial infarction	4 (3.7)	3 (2.9)	
Stroke	0 (0)	4 (3.9)	

BARC: Bleeding Academic Research Consortium; MACCE: major adverse cardiovascular and cerebrovascular event

**Bleeding events are within the first 48 hours of admission*

Figure 1: CONSORT flow diagram of the PITRI trial

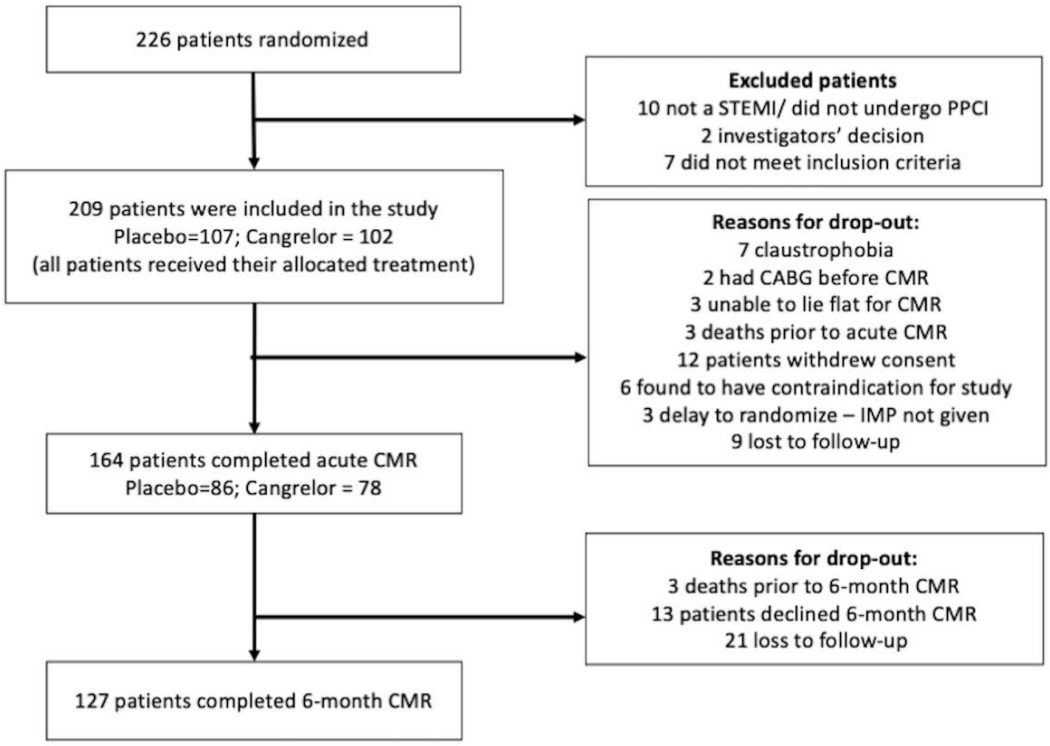


Figure 2: Representative T2 maps, T2* maps and LGE images of the acute CMR in 2 patients

(a) Patient A with subendocardial anterior MI (red arrow) and no MVO or IMH; (b) Patient B with a full thickness lateral MI (red arrow) with MVO and IMH (red arrows).

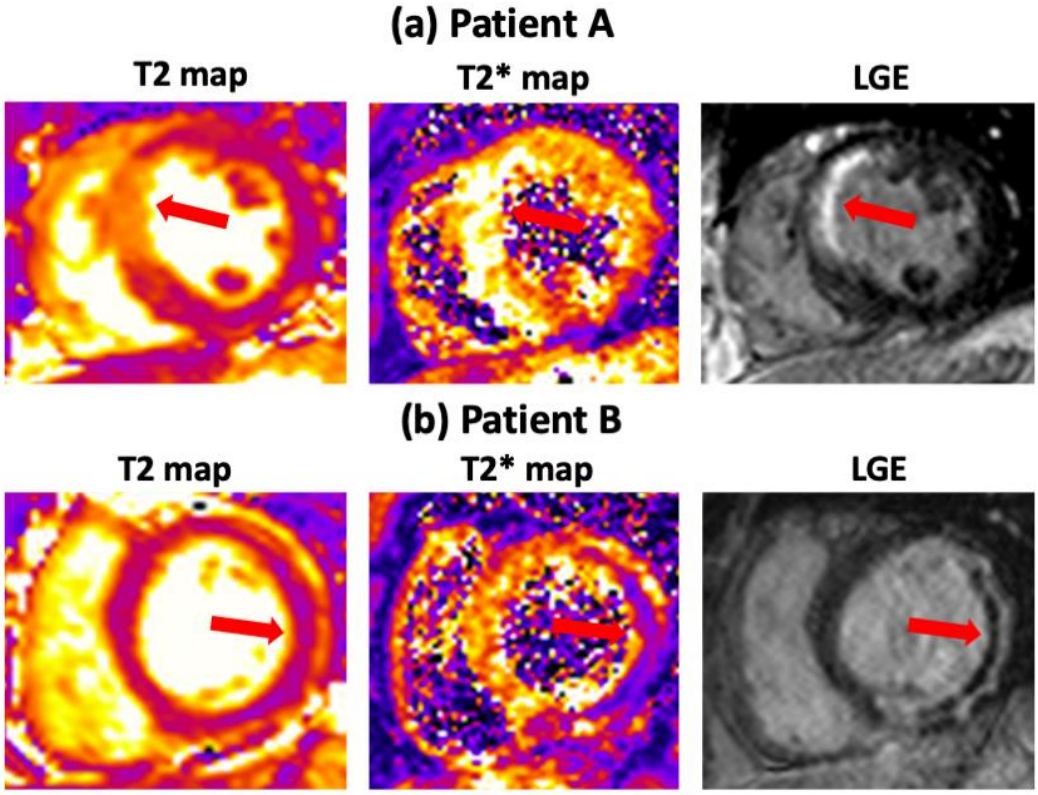


Figure 3: (a) Acute (primary efficacy endpoint) and (b) 6-month (secondary efficacy endpoint) MI size by CMR

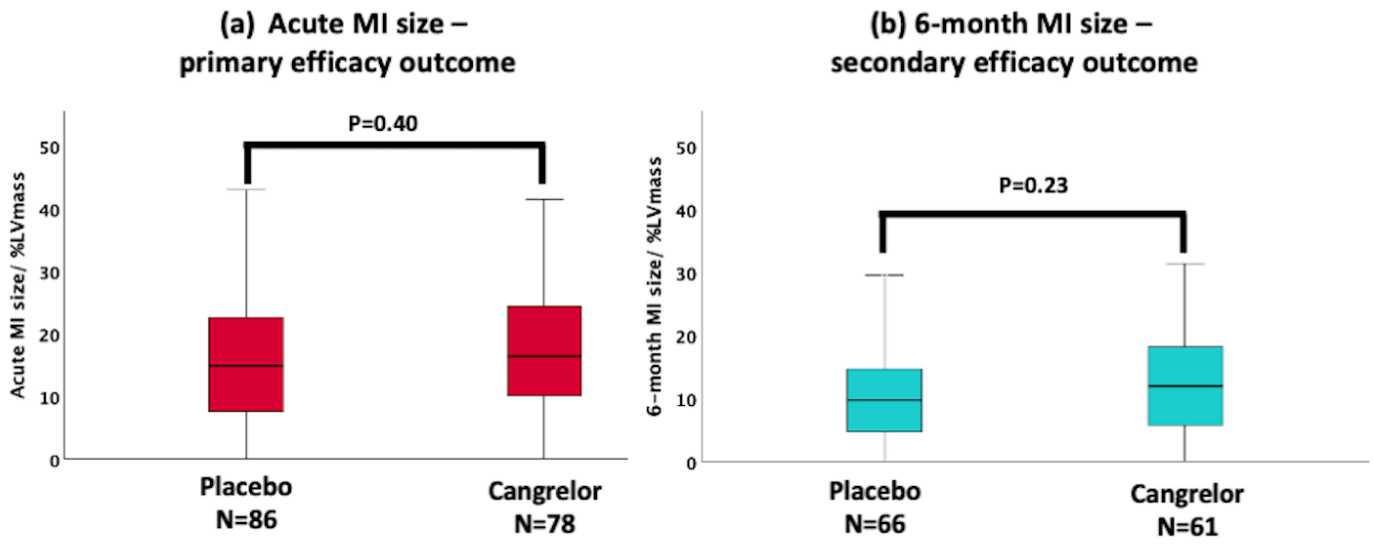
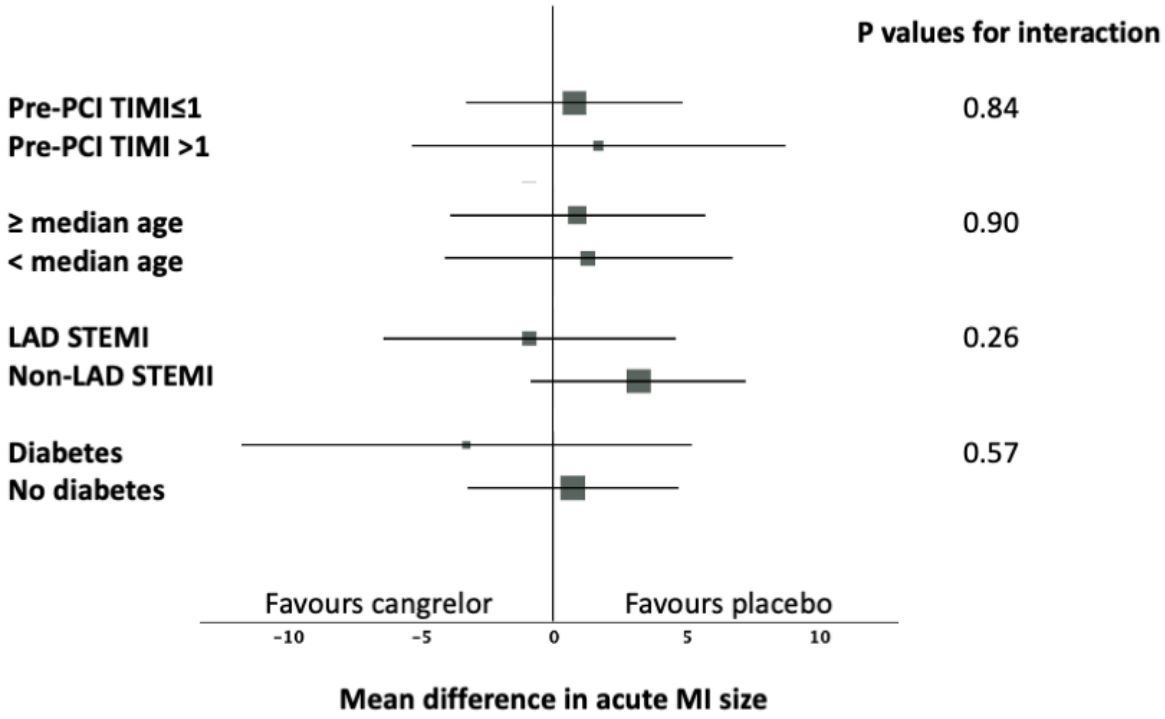


Figure 4: Forest plot for pre-specified subgroup analyses



APPENDIX

PITRI Investigators

Department of Cardiology, National Heart Centre Singapore, Singapore

Jack W. C. Tan, Derek J. Hausenloy, Chee-Tang Chi, Julian Tay, Pung Xuan Ming, Kamalesh Anbalakan, Keh Yann San, Kenneth Chew, Michelle Chan, Hong Rilong, Kui Swee Leng, Lim Soo Teik, Audry Lee, Felix Maverick Rubillar, James Cai, Jonathan Yap, Wong Ning Yan, Ho Kay Woon, Lim Fang Yi, Shen Xia Yen, Ruan Xucong, Yeo Khung Keong, Jun Hua Chong, Jennifer Bryant, Terrance Chua, Chee Yang Chin, Valeria Paradies, Aaron Wong, Leong Bahru, Tina Teo, Tan Ru San, Tang Hak Chiaw, Calvin Chin.

Clinical and Translational Research Office, National Heart Centre Singapore, Singapore

Florence Ang, Min-Tun Kyaw, S. Priyalatha, Jia-Mei Chua, Deborah Yip, Rosalind Lee, Katherina Oh, Ho Pei Yi, Leow Wanshan, Syamimi Atiqa Binte Rahmat, Gan Yar Chze.

National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore

Derek J Hausenloy, Fei Gao, Shi Yan Tan.

Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore:

Derek J. Hausenloy, Mervyn Chan.

Department of Emergency Medicine, Singapore General Hospital, Singapore

Lateef Fatimah, Andrew Ho, Wee Choon Peng Jeffrey, Swee Han Lim, Marcus Ong Eng Hock, Evelyn Wong, Kenneth Tan Boon Kiat, Anantharaman Venkataraman and DEM staff.

Department of Cardiology, National University Heart Centre Singapore, Singapore

Mark Y. Chan, Chi-Hang Lee, Chai Ping, Low Fatt Hoe Adrian, Chan Koo Hui, Loh Poay Huan, Wang Yi-Ting Laureen, Chen Zhengfeng Jason, Mayank Dalakoti, Perryn Ng, Sia Ching Hui, Shaun Chook, Alfred Yip, Ng Zhe Yan, Andie Hartanto Djohan, Marie Houdmont, Nicholas Chew, Siew Jiamin, Faclin Ng.

Department of Diagnostic Imaging, National University Hospital, Singapore

Lynette Teo, Ching Ching Ong, Junda Song, Choong Kuang Low, Nair Shalini and all MRI staff and radiographers.

Tan Tock Seng Hospital, Department of Cardiology, Singapore

Joseph Francis Prabath, Hee-Hwa Ho, Tasha Mahadi, Timothy Watson, Paul Ong, Koo Xin Ni, Tony Chai Jun Hui, Ho Yue Ting, Khoo Zhi Lin Deanna, Deborah Lee Jin Hyun, Li Ki Fung Cliff, Randal Low Jun Bang, Tan Joo Hor, Ng Ke Xuan Jessica, Chua Jia Min, Ong Wei Sheng Jonathan, Teoh Xuyan, Chiang Shu Qi Benita, Eran Sim Wen Jun, Ang An Shing, Quek Jia-ling Stephanie, Pang Rui Yi, Bin Ahmad Hatib Muhammad Alimi, Lee Jin Hyun, Lim Shiane, Tan Chong Keat, Ng Shonda and all cath lab staff.

Mount Elizabeth Hospital, Novena, Singapore

John Hoe and all CMR staff and radiographers.

Department of Cardiology, Sengkang General Hospital, Singapore

Jack Tan, Chin Chee Yang, Fam Jian Ming, Siti Raudha. Cath lab staff and all CRCs.

Department of Emergency Medicine, Sengkang General Hospital, Singapore

Annitha Annathurai, Boon Ping Ting.

Department of Cardiology, Khoo Teck Puat Hospital, Singapore.

Ashish Chawla, Syed Saqib Imran, Patrick Lim Zhan Yun, Alvin Tan, CMR staff and radiographers and all cath lab staff. CMR staff and radiographers and CMR reporting doctors.

Department of Cardiology, Changi General Hospital, Singapore

Benji Lim, Boon Wah Liew, Yong Thon Hon, all senior residents, and all cath lab sta