Infarct Size Following Treatment With Second- Versus Third-Generation P2Y$_{12}$ Antagonists in Patients With Multivessel Coronary Disease at ST-Segment Elevation Myocardial Infarction in the CvLPRIT Study

Jamal N. Khan, MBChB, BMedSci; John P. Greenwood, MBChB, PhD; Sheraz A. Nazir, MBBChir, BSc; Florence Y. Lai, MPhil; Miles Dalby, MBBS, MD; Nick Curzen, BM, PhD; Simon Hetherington, MBChB, MD; Damian J. Kelly, MBChB, MD; Daniel Blackman, MD; Charles Peebles, MBBS; Joyce Wong, MBBS, MD; Marcus Flather, MBBS; Howard Swanton, MBBChir, MD; Anthony H. Gershlick, MBBS; Gerry P. McCann, MBChB, MD

**Background**—Third-generation P2Y$_{12}$ antagonists (prasugrel and ticagrelor) are recommended in guidelines on ST-segment elevation myocardial infarction. Mechanisms translating their more potent antiplatelet activity into improved clinical outcomes versus the second-generation P2Y$_{12}$ antagonist clopidogrel are unclear. The aim of this post hoc analysis of the Complete Versus Lesion-Only PRimary PCI Trial-CMR (CvLPRIT-CMR) substudy was to assess whether prasugrel and ticagrelor were associated with reduced infarct size compared with clopidogrel in patients undergoing primary percutaneous coronary intervention.

**Methods and Results**—CvLPRIT-CMR was a multicenter, prospective, randomized, open-label, blinded end point trial in 203 ST-segment elevation myocardial infarction patients with multivessel disease undergoing primary percutaneous coronary intervention with either infarct-related artery-only or complete revascularization. P2Y$_{12}$ inhibitors were administered according to local guidelines. The primary end point of infarct size on cardiovascular magnetic resonance was not significantly different between the randomized groups. P2Y$_{12}$ antagonist administration was not randomized. Patients receiving clopidogrel (n=70) compared with those treated with either prasugrel or ticagrelor (n=133) were older (67.8±12 versus 61.5±10 years, $P<$0.001), more frequently had hypertension (49% versus 29%, $P=0.007$), and tended to have longer symptom-to-revascularization time (234 versus 177 minutes, $P=0.05$). Infarct size (median 16.1% [quartiles 1–3, 10.5–27.7%] versus 12.1% [quartiles 1–3, 4.8–20.7%] of left ventricular mass, $P=0.013$) and microvascular obstruction incidence (65.7% versus 48.9%, $P=0.022$) were significantly greater in patients receiving clopidogrel. Infarct size remained significantly different after adjustment for important covariates using both generalized linear models ($P=0.048$) and propensity score matching ($P=0.025$).

**Conclusions**—In this analysis of CvLPRIT-CMR, third-generation P2Y$_{12}$ antagonists were associated with smaller infarct size and lower microvascular obstruction incidence versus the second-generation P2Y$_{12}$ antagonist clopidogrel for ST-segment elevation myocardial infarction.

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**Key Words:** antiplatelet therapy • cardiovascular magnetic resonance • infarct size • myocardial infarction • primary percutaneous coronary intervention
Dual antiplatelet therapy is a key component of management of ST-segment elevation myocardial infarction (STEMI). Administration of a P2Y12 adenosine diphosphate receptor antagonist in addition to aspirin is advocated by the major international guidelines on STEMI management.1,2 Third-generation P2Y12 antagonists prasugrel and ticagrelor are recommended based on improved clinical outcomes and more potent platelet inhibition compared with the second-generation prodrug clopidogrel. The large TRITON TIMI-38 (n=13 608)3 and PLATO (n=18 624)4 studies demonstrated reduced medium-term combined major adverse cardiac events (MACE) with prasugrel and ticagrelor, respectively, compared with clopidogrel in acute coronary syndromes including STEMI.3–5

Mechanisms translating the more potent antiplatelet activity of prasugrel and ticagrelor into improved clinical outcomes are unclear. Cardiovascular magnetic resonance (CMR) accurately characterizes myocardial injury and function following STEMI. Late gadolinium enhancement (LGE) imaging–derived infarct size6 is a powerful medium-term prognostic marker following primary percutaneous coronary intervention (PPCI). A retrospective analysis of the INFUSE-AMI trial demonstrated a trend toward reduced 30-day CMR infarct size and reduced 12-month mortality with prasugrel compared with clopidogrel in anterior STEMI treated with PPCI.7 No other CMR data compare the effect of the third-generation P2Y12 antagonists and clopidogrel after PPCI.

The primary aim of this post hoc analysis of Complete Versus Lesion-Only PRImary PCI Trial-CMR (CvLPRIT-CMR) substudy was to assess whether the third-generation P2Y12 antagonists prasugrel and ticagrelor were associated with reduced infarct size compared with the second-generation P2Y12 antagonist clopidogrel.

**Methods**

**Study Design**

The study design and main results were published previously.8,9 CvLPRIT-CMR was a prespecified substudy of a multicenter, prospective, randomized, controlled, open-label, clinical trial8 with blinded CMR end point analysis conducted at 7 UK centers between May 2011 and May 2014. Infarct size in patients treated with complete revascularization and in those treated with an infarct-related artery–only strategy was not significantly different.10 Inclusion and exclusion criteria were the same as for the main trial with absolute contraindications to CMR imaging as an additional exclusion. The study was approved by the Trent Research Ethics Committee (reference 11/H0405/4) and conducted according to the Declaration of Helsinki. Patients provided written informed consent.

**Patient Recruitment and Treatment**

STEMI patients presenting within 12 hours of symptom onset were administered contemporary oral antiplatelet agents according to local guidelines. All patients received aspirin 300 mg plus 1 P2Y12 antagonist: (1) clopidogrel (Plavix; Sanofi), 600-mg loading dose followed by 75-mg maintenance; (2) prasugrel (Effient; Daiichi-Sankyo), 60-mg loading dose and 10 mg daily; or (3) ticagrelor (Brilique; AstraZeneca), 180-mg loading dose and then 90 mg twice daily. Administration of the loading dose was permitted by paramedic staff before hospital arrival or in hospital on arrival at the cardiac catheterization room.

**Angiographic Analysis**

Pre- and post-PPCI epicardial coronary flow was assessed using Thrombolysis In Myocardial Infarction (TIMI) scoring,11 Collateral flow to the infarct-related artery (IRA) before PPCI was graded using the Rentrop system.12 Quantitative coronary angiography was undertaken using QAngioXA v1.0 software (Medis).

**CMR Imaging**

CMR was performed before discharge, and the methods were described in detail previously.10 Briefly, after localizers and long-axis cine imaging, contiguous short-axis stacks covering the entire left ventricle were acquired with (1) T2-weighted short T inversion recovery to determine the ischemic area at risk (edema), (2) steady-state free-precession cine imaging for left ventricle volumetric analysis, and (3) LGE imaging to determine infarct size and microvascular obstruction (MVO) after administration of gadolinium contrast (0.2 mmol/kg Magnevist; Bayer).

**CMR Analysis**

CMR analysis was performed, as described previously, at the University of Leicester core laboratory, blinded to all clinical data including treatment allocation. If infarction was seen in >1 coronary territory on acute CMR, this was recorded as being in the IRA territory (associated edema and/or MVO) or the non-IRA territory, with the consensus of 3 observers (J.N.K., G.P.M., J.P.G.). Non-IRA infarcts were also classified as likely to be acute or chronic (presence of wall thinning and no edema or MVO). Infarct size was recorded for both IRA and non-IRA LGE, and total infarct size was the sum of all LGE.

**Clinical Outcomes and Follow-up**

MACE was a composite of all-cause mortality, recurrent MI, heart failure, and ischemia-driven revascularization. Secondary end points included individual components of the primary end point. Safety end points comprised stroke, major

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bleeding, vascular access site injury, and contrast-induced nephropathy. Data were collected by an independent clinical trials unit (Royal Brompton Hospital), and events were adjudicated by blinded clinicians.

**Statistical Analysis**

The primary CMR outcome was infarct size (expressed as percentage of left ventricular mass) on CMR, analyzed on a log-transformed scale due to right skew. This was adjusted for known baseline predictors of infarct size (anterior myocardial infarction, diabetes mellitus, TIMI flow before PPCI, time to revascularization) and important baseline variables that significantly differed between the 2 groups (age, hypertension prevalence, timing of P2Y12 antagonist loading), using generalized linear models. Propensity score–based stratification (quartiles) was also performed to adjust for the imbalance of baseline covariates between the 2 groups.13 Starting with the noted baseline covariates, the propensity score model was built based on a backward selection process and the assessment of balance between the 2 groups. Normally distributed variables were expressed as mean±SD and compared using Student t tests. Nonnormally distributed data were expressed as median (quartiles 1–3) and analyzed using Mann–Whitney testing. Categorical variables were compared using chi-square testing. Clinical outcomes were assessed using time-to–first event survival analysis (log-rank test with right censoring), and Cox proportional hazards models were fitted to estimate hazard ratios and 95% CIs for treatment comparisons.

**Results**

**Baseline Characteristics**

Patients receiving clopidogrel were slightly older (67.8±12.3 years versus 61.5±9.6 years, \( P < 0.001 \)) and had a higher prevalence of hypertension compared with those receiving prasugrel or ticagrelor. Other baseline characteristics and comorbidities were closely matched in patients receiving clopidogrel and the third-generation P2Y12 antagonist agents and were similar to those in the overall CvLPRIT study cohort (Table 1).

Baseline characteristics for patients receiving the 3 individual P2Y12 antagonists are shown in Table S1. Patients receiving clopidogrel were older than those receiving prasugrel because age >75 years is a contraindication to prasugrel therapy.

**Angiographic and PCI Details**

Details of angiography and PCI are shown in Table 2. There was a trend toward longer median time from symptom onset to revascularization in patients receiving clopidogrel (\( P = 0.05 \)). Prehospital P2Y12 antagonist administration was more

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**Table 1. Baseline Characteristics of the Main CvLPRIT Study Population and Patients Receiving Clopidogrel and the Third-Generation P2Y12 Antagonist Antiplatelet Agents (Prasugrel, Ticagrelor)**

| Variable                          | Main CvLPRIT (n=296) | Newer P2Y12, Antagonists (n=133) | Clopidogrel (n=70) | \( P \) Value |
|-----------------------------------|----------------------|----------------------------------|-------------------|--------------|
| Age, y                            | 64.9±11.6            | 61.5±9.6                         | 67.8±12.3         | <0.001       |
| Male sex                          | 240/296 (81.1)       | 114/133 (85.7)                   | 56/70 (80.0)      | 0.29         |
| Body mass index, kg/m²             | 27.3 (24.4–30.2)     | 27.5 (24.8–29.9)                 | 27.6 (24.3–30.5)  | 0.61         |
| Systolic blood pressure, mm Hg    | 137.6±27.1           | 133.5 (116–156)                  | 137 (120–153)     | 0.86         |
| Anterior infarct                  | 106 (35.6)           | 46 (34.6)                        | 26 (37.1)         | 0.72         |
| Estimated glomerular filtration rate, mL/min/1.73 | 95.74±34.7          | 100.0±29.0                       | 87.7±37.3         | 0.013        |
| Hypertension                      | 105/287 (36.6)       | 39/133 (29.3)                    | 34/70 (48.6)      | 0.007        |
| Hypercholesterolemia              | 75/287 (26.1)        | 36/133 (27.1)                    | 20/70 (28.6)      | 0.82         |
| Diabetes mellitus                 | 39/287 (13.6)        | 19/133 (14.3)                    | 9/70 (12.9)       | 0.78         |
| Current smoker                    | 87/285 (30.5)        | 46/133 (34.6)                    | 18/70 (25.7)      | 0.20         |
| Previous myocardial infarction    | 12/287 (4.2)         | 4/133 (3.0)                      | 4/70 (5.7)        | 0.35         |
| Previous percutaneous coronary intervention | 9/287 (3.1) | 4/133 (3.0)                      | 3/70 (4.3)        | 0.64         |
| Antianginal medication, beta blockers or nitrates | 54/287 (18.8) | 18/133 (13.6)                    | 15/70 (21.4)      | 0.16         |
| Killip class II to III            | 24/286 (8.4)         | 11/133 (8.3)                     | 5/70 (7.1)        | 0.78         |

Data expressed as mean±SD, median (quartiles 1–3), or frequency (percentage) of patients, as appropriate. \( P \) values compare the treatment groups (clopidogrel vs third-generation P2Y12 antiplatelet agents).

CvLPRIT indicates Complete Versus Lesion-Only PRimary PCI Trial.
Table 2. Periprocedural Details in Patients Receiving Clopidogrel and the Third-Generation P2Y<sub>12</sub> Antiplatelet Agents (Prasugrel, Ticagrelor)

| Variable                                                                 | Newer P2Y<sub>12</sub> Antagonists (n=133) | Clopidogrel (n=70) | P Value |
|--------------------------------------------------------------------------|---------------------------------------------|--------------------|---------|
| Radial access                                                            | 106/132 (80.3)                              | 57/70 (81.4)       | 0.85    |
| Time from symptoms to PCI (time to revascularization), min               | 177 (125–240)                               | 234 (144–320)      | 0.051   |
| Glycoprotein IIb/IIIa inhibitors                                         | 45/131 (34.4)                               | 25/70 (35.7)       | 0.85    |
| Bivalirudin                                                              | 59/122 (48.4)                               | 36/64 (56.2)       | 0.31    |
| Visible thrombus                                                         | 79/133 (59.8)                               | 52/70 (74.3)       | 0.041   |
| Thrombectomy catheter                                                   | 89/132 (67.4)                               | 57/70 (81.4)       | 0.034   |
| Contrast dose, mL                                                        | 220 (180–300)                               | 250 (180–367.5)    | 0.13    |
| Screening time, min                                                      | 12 (8–19)                                   | 13 (8.25–18.75)    | 0.37    |
| Procedure length, min                                                    | 46 (31–70)                                  | 56.5 (40–74.3)     | 0.041   |
| Quantitative coronary angiography, vessels with ≥75% stenosis            | 1.48±0.6                                    | 1.53±0.6           | 0.60    |
| Quantitative coronary angiography, lesions ≥75% stenosis                 | 1.59±0.7                                    | 1.66±0.7           | 0.51    |
| Quantitative coronary angiography, stenosis in non-infarct-related artery lesions | 72.0±12.3                                   | 70.8±10.6          | 0.49    |
| SYNTAX score (total)                                                     | 17.5 (13–22.5)                              | 18 (14–23.5)       | 0.99    |
| Left anterior descending infarct-related artery                          | 48/133 (36.1)                               | 24/70 (34.3)       | 0.80    |
| Left circumflex infarct-related artery                                   | 26/133 (19.5)                               | 12/70 (17.1)       | 0.68    |
| Right coronary infarct-related artery                                    | 59/133 (44.4)                               | 33/70 (47.1)       | 0.71    |
| Rentrop grade                                                            | 0 (0–1)                                     | 0 (0–1)            | 0.51    |
| Rentrop grade 2–3 before PCI                                            | 6/133 (4.5)                                 | 7/70 (10.0)        | 0.13    |
| Thrombolysis In Myocardial Infarction grade before PCI                   | 0 (0–1), 0.58±1.0                           | 0 (0–0), 0.36±0.8  | 0.95    |
| Thrombolysis In Myocardial Infarction grade after PCI                    | 3 (3–3), 2.77±0.5                           | 3 (3–3), 2.92±0.4  | 0.39    |
| Infarct-related artery, no reflow                                        | 6/133 (4.5)                                 | 4/70 (5.7)         | 0.71    |
| Total number of stents                                                   | 2 (1–3), 2.2±1.3                             | 2 (1–3), 2.1±1.3   | 0.54    |
| Drug-eluting stent use                                                   | 127/133 (95.5)                              | 66/70 (94.3)       | 0.71    |
| Multivessel PCI (complete revascularization)                             | 64/133 (48.1)                               | 34/70 (48.6)       | 0.95    |
| Peak CK, IU/L                                                            | 992 (550–1631)                              | 1214 (649–1960)    | 0.35    |
| Aspirin                                                                  | 132/133 (99.2)                              | 70/70 (100)        | 0.47    |
| Timing of aspirin administration                                         |                                            |                    |         |
| Prehospital                                                              | 113/124 (91.1)                              | 56/67 (83.6)       | 0.12    |
| In-hospital before angiogram                                             | 11/124 (8.9)                                | 11/67 (16.4)       |         |
| P2Y<sub>12</sub> antagonist administration                               |                                            |                    |         |
| Prehospital                                                              | 11/132 (8.3)                                | 17/64 (26.6)       | 0.001   |
| In-hospital before angiogram                                             | 121/132 (91.7)                              | 47/64 (73.4)       |         |
| Discharge medication                                                     |                                            |                    |         |
| Beta blocker                                                             | 125/133 (94.0)                              | 65/70 (92.9)       | 0.76    |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker  | 126/133 (94.7)                              | 70/70 (100)        | 0.06    |
| Lipid-lowering therapy                                                   | 132/133 (99.3)                              | 70/70 (100)        | 0.47    |
| Loop diuretic                                                            | 14/133 (10.5)                               | 8/70 (11.3)        | 0.86    |
| Aldosterone inhibitor                                                    | 7/133 (5.3)                                 | 3/70 (4.3)         | 0.76    |

Data expressed as mean±SD, median (quartiles 1–3), or frequency (percentage) of patients, as appropriate. P values compare the treatment groups (clopidogrel vs third-generation P2Y<sub>12</sub> antiplatelet agents). CK indicates creatine kinase; PCI, percutaneous coronary intervention; SYNTAX, SYnergy between PCI with TAXus and cardiac surgery.
common in patients receiving clopidogrel compared with those receiving prasugrel or ticagrelor ($P=0.001$). There was a higher prevalence of visible thrombus ($P=0.041$) and thrombectomy catheter use ($P=0.034$) in patients receiving clopidogrel. Complexity of coronary artery disease, prevalence of well-collateralized IRA territory, use of glycoprotein IIb/IIIa inhibitors and bivalirudin, and performance of multivessel PCI were similar in patients receiving clopidogrel and prasugrel or ticagrelor.

Approximately a quarter of patients receiving clopidogrel and ticagrelor were administered loading doses before arriving at the hospital; however, only 7% of prasugrel patients were loaded before arrival (Table S1).

### CMR Outcomes

CMR results are displayed in Table 3. CMR was undertaken at a median of 2.9 days after PPCI in both groups. Left ventricular volumes were similar in the 2 groups, and ejection fraction was not significantly different. Overall, 94% of patients in each group demonstrated infarct on LGE. There was a similar prevalence of multiple infarcts in patients receiving clopidogrel and prasugrel or ticagrelor. The primary end point of median total infarct size was significantly larger in patients receiving clopidogrel (16.1% [quartiles 1–3, 10.5–27.7%] versus 12.1% [quartiles 1–3, 4.8–20.7%]) of left ventricular mass, $P=0.013$. After adjustment for key covariates, infarct size remained larger in patients receiving clopidogrel.

#### Table 3. Acute Cardiovascular Magnetic Resonance Data in Patients Receiving Clopidogrel and the Third-Generation P2Y$_{12}$ Antiplatelet Agents (Prasugrel, Ticagrelor)

| Variable | Newer P2Y$_{12}$ (Antagonists (n=133)) | Clopidogrel (n=70) | $P$ Value |
|----------|----------------------------------------|-------------------|-----------|
| Acute cardiovascular magnetic resonance | | | |
| Total infarct size, % LVM | 12.1 (4.8–20.7) | 16.1 (10.5–27.7) | 0.013 |
| Time to acute cardiovascular magnetic resonance, day | 2.9 (1.9–4.1) | 2.9 (2.0–3.8) | 0.33 |
| Infarct present on late gadolinium enhancement | 124/133 (93.6) | 66/70 (94.3) | 0.77 |
| Patients with >1 infarct | 22/133 (16.5) | 11/70 (15.7) | 0.88 |
| Patients with >1 acute infarct | 14/133 (10.5) | 8/70 (11.4) | 0.84 |
| Infarct-related artery infarct size (main infarct), % LVM | 10.0 (4.4–18.9) | 15.6 (9.8–26.3) | 0.002 |
| Non–infarct-related artery infarct size (total), % LVM | 0.00 (0.00–0.00) | 0.00 (0.00–0.00) | 0.47 |
| Total infarct size (% LVM) of acute infarcts | 10.6 (4.4–19.0) | 16.0 (10.4–27.6) | 0.013 |
| Area at risk, % LVM$^\dagger$ | 32.8±12.9 | 36.8±11.4 | 0.07 |
| Myocardial salvage index, % | 63.3 (42.9–82.6) | 46.2 (24.7–70.2) | 0.06 |
| Microvascular obstruction present | 65/133 (48.9) | 46/70 (65.7) | 0.022 |
| Microvascular obstruction, % LVM* | 0.0 (0–1.1) | 0.25 (0–2.3) | 0.06 |
| Left ventricular mass index, g/m$^2$ | 51.7 (45.6–60.6) | 52.6 (45.9–60.0) | 0.99 |
| Left ventricular end-diastolic volume index, mL/m$^2$ | 89.5 (80.6–102.0) | 91.1 (80.5–101.2) | 0.62 |
| Left ventricular end-systolic volume index, mL/m$^2$ | 46.4 (37.9–60.6) | 48.9 (41.6–59.3) | 0.64 |
| Left ventricular ejection fraction, % | 46.0±10.5 | 44.4±7.8 | 0.20 |

Data expressed as mean±SD, median (quartiles 1–3), or frequency (percentage) of patients, as appropriate. LVM indicates left ventricular mass.

* $P$ value adjusted for known baseline predictors of infarct size (anterior myocardial infarction, time to revascularization, diabetes, Thrombolysis In Myocardial Infarction flow before primary percutaneous coronary intervention) and important baseline variables significantly differing between the groups (age, hypertension prevalence, timing of P2Y$_{12}$ antagonist loading) using regression analysis.

† $P$ value based on propensity score analysis with the propensity scores estimating from age, presence of hypertension, time to revascularization, and timing of P2Y$_{12}$ antagonist loading. Analyzable edema imaging available in ~75% of patients in both groups.
clopidogrel, using both generalized linear models ($P=0.048$) and propensity score analysis ($P=0.025$). When chronic infarcts were excluded, median total acute infarct size ($P=0.034$) and median extent of the main IRA-related infarct ($P=0.033$) were significantly greater in the clopidogrel group (Figure).

The prevalence of microvascular obstruction was higher in patients receiving clopidogrel (65.7% versus 48.9%, $P=0.022$). In 52 patients (26%), area at risk could not be reliably quantified because no artifact but no edema was discernable ($n=33$), imaging was not performed because of arrhythmia or suboptimal breath holding ($n=14$), or severe artifact was present ($n=5$). There was a trend toward lower myocardial salvage index in the clopidogrel group ($P=0.12$).

CMR outcomes on an individual P2Y$_{12}$ antagonist basis are shown in Table S2. Total infarct size, IRA-related infarct size, and total acute infarct size were similar in patients receiving prasugrel and ticagrelor but were significantly smaller with both of these agents compared with clopidogrel.

**Clinical Outcomes**

Discharge medication was similar between the groups (Table 2). Median follow-up was 368 days (clopidogrel group 355 days, prasugrel/ticagrelor group 372 days; $P=0.05$) (Table 4). Length of inpatient stay was longer (4.4±3.6 versus 3.3±2.0, $P=0.017$) in patients receiving clopidogrel. There was a nonsignificant trend toward reduced overall 12-month MACE (17.1% versus 10.5%, $P=0.18$) driven mainly by a reduced incidence of heart failure ($P=0.04$). There was no difference in the incidence of safety end points between the groups. On an individual P2Y$_{12}$ antagonist basis, there was a trend toward reduced 12-month MACE with both prasugrel and ticagrelor compared with clopidogrel (Tables S3–S5).

**Infarct Size and MVO**

The greater total and IRA-related infarct size and incidence of MVO in patients receiving clopidogrel may be influenced by baseline differences, in particular, the trend toward longer time to revascularization, which is a determinant of CMR infarct size$^{14,15}$ and prognosis in STEMI.$^{16}$ Importantly, the differences in infarct size and MVO incidence persisted after correction for baseline differences in patient characteristics and their known predictors. It is unlikely that patients receiving clopidogrel had larger infarcts because the proportion having anterior STEMI and Killip class were similar in the groups, and there was greater prehospital clopidogrel administration.$^{17}$ Although the prevalence of visible thrombus was higher in the clopidogrel group, TIMI flow grade before PPCI and technical success at PPCI were similar, and the former

**Discussion**

This post hoc analysis of the CvLPRIT-CMR substudy participants is, to our knowledge, the first imaging-based study assessing myocardial and microvascular injury associated with the second-generation P2Y$_{12}$ antagonist clopidogrel and the third-generation P2Y$_{12}$ antagonists prasugrel and ticagrelor in STEMI. P2Y$_{12}$ antagonism with prasugrel and ticagrelor was associated with reduced total and IRA-associated infarct size and reduced microvascular obstruction incidence on CMR LGE imaging after PPCI. This post hoc analysis was nonrandomized; therefore, there were baseline differences, with higher age, prevalence of hypertension, and prehospital administration of P2Y$_{12}$ antagonists, and a trend toward increased symptom time to reperfusion in patients receiving clopidogrel. Despite adjusting for these variables and known baseline predictors of infarct size, the results may still suffer from biases and thus should be considered as hypothesis generating but warranting investigation in larger randomized studies.

**Figure.** Median acute IS in patients receiving clopidogrel and the newer (third-generation P2Y$_{12}$ antagonist) antiplatelet agents prasugrel (P) and ticagrelor (T). IRA indicates infarct-related artery; IS, infarct size; LV, left ventricular.
was adjusted to correct for higher thrombus burden. In addition, all patients receiving clopidogrel had the larger 600-mg loading dose, which, in a previous retrospective study in 198 patients, was associated with reduced CMR-derived infarct size and MVO and increased myocardial salvage after PPCI. The higher infarct size and MVO incidence occurred despite a weak trend toward greater degree of IRA collateralization, which can attenuate infarct size and MVO, in the patients receiving clopidogrel.

Our results are consistent with the only imaging-based study comparing second- and third-generation P2Y12 antagonists. Brener et al demonstrated a strong trend toward reduced total infarct size measured on CMR at 30 days with prasugrel compared with clopidogrel in acute anterior STEMI treated with PPCI (16.4% versus 17.6% left ventricular mass, \( P = 0.06 \)). Our results are also supported by the findings of Nanhwan et al, who demonstrated that ticagrelor but not clopidogrel reduced infarct size in rats measured histologically.

The lower myocardial and microvascular injury observed in patients receiving prasugrel and ticagrelor in our study may be affected by the faster (peak effect after loading dose at 2 hours for ticagrelor, 4 hours for prasugrel, and 6 hours after clopidogrel) and more potent antiplatelet activity of these drugs compared with the prodrug clopidogrel. Indeed, clopidogrel typically achieves a maximum of only 50% platelet inhibition in combination with aspirin in acute coronary syndromes compared with \( \approx 94\% \) with ticagrelor and aspirin. This remains the case even when the larger 600-mg clopidogrel loading dose is administered. In addition, the prodrug forms only 15% of the clopidogrel metabolite, with 85% deesterised into an inactive carboxylic acid. Prasugrel has also been shown to be associated with lower drug resistance than clopidogrel. Brandt et al demonstrated that 42% of clopidogrel-treated patients were associated with \( < 20\% \) platelet noninhibition at 4 hours after administration compared with 0% of prasugrel-treated patients. This may be related to the fact that prasugrel and ticagrelor metabolism have been shown not to be affected by cytochrome P450 polymorphisms. It is interesting to speculate that prasugrel and ticagrelor, which have anti-inflammatory and antiapoptotic activity, may protect against reperfusion injury, which is known to contribute to CMR-derived infarct size, MVO, and intramyocardial hemorrhage.

### Clinical Outcomes

This study was not powered to detect differences in clinical outcomes; however, we saw reduced incidence of heart failure (\( P = 0.04 \)), with a weak nonsignificant trend toward reduced combined 12-month MACE (17.1% versus 10.5%, \( P = 0.18 \)) with the newer agents versus clopidogrel. These findings are consistent with previous studies demonstrating improved medium-term clinical outcomes with ticagrelor and prasugrel in STEMI, in particular, the work of Brener et al.

### Table 4. Clinical Outcomes in Patients Receiving Clopidogrel and the Third-Generation P2Y12 Antiplatelet Agents (Prasugrel, Ticagrelor)

| Variable                        | Newer P2Y12 Antagonists (n=133) | Clopidogrel (n=70) | Hazard Ratio (95% CI) | P Value |
|---------------------------------|---------------------------------|-------------------|-----------------------|---------|
| 12-month follow-up              |                                 |                   |                       |         |
| Major adverse cardiac events    | 14/133 (10.5)                   | 12/70 (17.1)      | 0.59 (0.27–1.3)       | 0.18    |
| All-cause mortality             | 1/133 (0.8)                     | 1/70 (1.4)        | 0.52 (0.03–8.5)       | 0.64    |
| Recurrent myocardial infarction | 3/133 (2.3)                     | 0/70 (0.0)        | —                     | 0.21    |
| Type 1                          | 2/133 (1.6)                     | 0/70 (0.0)        | —                     | 0.43    |
| Type 4b                         | 1/133 (0.8)                     | 0/70 (0.0)        | —                     | 0.66    |
| Heart failure                   | 2/133 (1.5)                     | 5/70 (7.1)        | 0.20 (0.04–1.0)       | 0.04    |
| Revascularization               | 8/133 (6.0)                     | 6/70 (8.6)        | 0.66 (0.23–1.9)       | 0.45    |
| Safety end points               |                                 |                   |                       |         |
| Contrast nephropathy            | 1/133 (0.8)                     | 0/70 (0.0)        | —                     | 0.47    |
| Vascular access injury          | 0/133 (0.0)                     | 0/70 (0.0)        | —                     | 1.00    |
| Cerebrovascular accident/transient ischemic attack | 1/133 (0.8) | 1/70 (1.4) | 0.52 (0.03–8.5) | 0.64 |
| Major bleed                     | 2/133 (1.6)                     | 2/70 (2.9)        | 0.52 (0.07–3.8)       | 0.51    |

Data expressed as frequency (percentage) of patients.
demonstrating reduced infarct size, mortality, and heart failure at 12-month follow-up with prasugrel compared with clopidogrel. The reduction in heart failure incidence in our study could be caused by the lower infarct size.

Limitations
In this post hoc analysis, patients were not randomized to a particular P2Y12 antagonist. The differences in baseline characteristics, in particular, symptom time to reperfusion, may influence the observed differences in infarct size and MVO incidence between the patients; however, our findings persisted after correction for baseline differences and important covariates. The study was not powered to detect differences in clinical outcomes. Patients who died early or who were unstable after PPCI were unlikely to have participated in the CMR study, which may have underestimated hard end points. We combined patients receiving prasugrel and ticagrelor into a single group in the main analysis of this study because of the relatively small number of patients receiving ticagrelor (31 of 203 [15%]) and because patients receiving these P2Y12 antagonists agents were very similar at baseline and had similar infarct sizes.

Conclusions
In this post hoc analysis of the CvLPRIT study, patients with multivessel coronary disease undergoing PPCI and receiving prasugrel or ticagrelor had smaller total infarct size and reduced incidence of MVO on CMR imaging compared with those receiving clopidogrel. These findings persisted after correction for baseline differences in patient characteristics and important covariates. These findings may help explain the improved clinical outcomes with the use of third-generation antiplatelet agents compared with clopidogrel.

Author Contributions
Khan and McCann conceived the idea for this substudy. Khan, McCann, Nazir, Greenwood, Wong and Peebles supervised cardiovascular magnetic resonance study visits. Khan performed cardiovascular magnetic resonance and quantitative coronary angiography analyses (supervised by McCann and Gershlick). Khan and Lai performed statistical analyses. Khan wrote the paper that was revised by McCann. All authors critically reviewed the manuscript for intellectual content.

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SUPPLEMENTAL MATERIAL
Table S1: Baseline characteristics by dual antiplatelet agent received

(Clopidogrel, Prasugrel, Ticagrelor)

| Variable                        | Clopidogrel (n=70) | Prasugrel (n=102) | Ticagrelor (n=31) | p       |
|---------------------------------|-------------------|-------------------|-------------------|---------|
| **Baseline characteristics**    |                   |                   |                   |         |
| Age (y)                         | 67.8±12.2         | 60.8±9.1          | 63.0±11.4         | <0.001  |
| Male sex (n, %)                 | 57/70 (81.4)      | 86/101 (84.7)     | 29/32 (87.9)      | 0.55    |
| Anterior infarct (%)            | 26/70 (36.6)      | 36/101 (35.6)     | 11/32 (34.3)      | 0.95    |
| Hypertension (%)                | 34/70 (48.6)      | 27/101 (26.5)     | 12/32 (38.7)      | 0.012   |
| SYNTAX score (total)            | 18 (14-23.5)      | 18 (13.3-23.5)    | 16 (10-20.3)      | 0.16    |
| Sym-PCI time (TTR, min)         | 227.5 (144-318)   | 169 (125-238)     | 177 (117-259)     | 0.16    |
| TIMI grade pre PCI              | 0 (0-0)           | 0 (0-1)           | 0 (0-2)           | 0.07    |
|                                | 0.36±0.8          | 0.49±0.9          | 0.87±1.3          |         |
| TIMI grade post PCI             | 3 (3-3)           | 3 (3-3)           | 3 (3-3)           | 0.93    |
|                                | 2.9±0.4           | 2.9±0.4           | 2.9±0.3           |         |
| Timing of DAPT administration   |                   |                   |                   | <0.001  |
| • Pre-hospital (n, %)           | 17 (26.6)         | 2 (7.1)           | 9 (29.0)          |         |
| • In-hospital pre-angiogram (n, %) | 47 (73.4)         | 99 (98.0)         | 22 (71.0)         |         |

PCI= percutaneous coronary intervention, TTR= time to revascularisation (symptom time), TIMI= thrombolysis in myocardial infarction; DAPT= dual antiplatelet therapy, SYNTAX= Synergy Between PCI With Taxus and Cardiac Surgery
Table S2: Acute CMR data by dual antiplatelet agent received (Clopidogrel, Prasugrel, Ticagrelor)

| Variable                                      | Clopidogrel (n=70) | Prasugrel (n=102) | Ticagrelor (n=31) | p       |
|-----------------------------------------------|--------------------|-------------------|-------------------|---------|
| **Acute CMR**                                |                    |                   |                   |         |
| Total Infarct Size (% LVM)                   | 16.1 (10.5-27.7)   | 12.2 (4.8-21.5)   | 9.8 (3.5-16.5)    | 0.002   |
| CYP p=0.040                                  |                    |                   |                   |         |
| CYP T p=0.002                                |                    |                   |                   |         |
| PV T p=0.26                                  |                    |                   |                   |         |
| Time to acute CMR (d)                        | 2.8 (2.0-3.7)      | 2.9 (1.9-4.1)     | 2.9 (1.9-4.1)     | 0.84    |
| Infarct present on LGE (n, %)                | 66/70 (94.3)       | 94/102 (92.2)     | 30/31 (96.8)      | 0.63    |
| Patients with >1 infarct                     | 11/70 (15.7)       | 19/102 (18.6)     | 3/31 (9.7)        | 0.49    |
| Patients with >1 acute infarct               | 8/70 (11.4)        | 13/102 (12.7)     | 1/31 (3.4)        | 0.32    |
| IRA IS (main infarct, % LVM)                 | 15.6 (9.8-26.3)    | 10.8 (4.8-19.2)   | 8.9 (2.7-16.5)    | 0.001   |
| CYP p=0.020                                  |                    |                   |                   |         |
| CYP T p=0.001                                |                    |                   |                   |         |
| PV T p=0.28                                  |                    |                   |                   |         |
| NIRA IS (total, % LVM)                       | 0.0 (0-0)          | 0.0 (0-0)         | 0.0 (0-0)         | 0.55    |
| Total IS (% LVM) of acute infarcts           | 16.0 (10.4-27.6)   | 11.3 (4.8-19.9)   | 9.8 (2.7-16.5)    | 0.036   |
| CYP p=0.021                                  |                    |                   |                   |         |
| CYP T p=0.001                                |                    |                   |                   |         |
| PV T p=0.26                                  |                    |                   |                   |         |
### Table

| Metric                  | Group 1 | Group 2 | Group 3 | p-value |
|-------------------------|---------|---------|---------|---------|
| AAR (% LVM)             | 36.8±11.4 | 32.6±13.2 | 33.4±12.1 | 0.17    |
| Acute MSI (%)           |         |         | 64.9 (56.9-93.0) | 0.002 (0.004)* |
| CvP p=0.12              |         |         |         |         |
| CvT p=0.003             |         |         |         |         |
| PvT p=0.19              |         |         |         |         |
| MVO present (n %)       | 46/70 (65.7%) | 49/102 (44.1%) | 16/31 (51.6%) | 0.07    |
| MVO (% LVM)             | 0.25 (0-2.3) | 0 (0-1.3) | 0.05 (0-0.9) | 0.17 (0.63)* |
| LVEDVI (ml/m2)          | 91.1 (80.5-101.2) | 93.2 (83.3-104) | 83.3 (76.3-98.4) | 0.05    |
| LVESVI (ml/m2)          | 48.9 (41.6-59.3) | 48.0 (39.0-62.1) | 45.2 (35.3-53.3) | 0.23    |
| LVEF (%)                | 44.2±7.8 | 46.0±10.9 | 46.1±9.4 | 0.53    |
| Wall motion score       | 23 (21-26) | 22 (19-27) | 22 (19.3-26) | 0.60    |

* p-value corrected for covariates

**IRA= Infarct related artery; LVMI= left ventricular mass index; LVEDVI= left ventricular end-diastolic volume index; LVESVI= left ventricular end-systolic volume index; LVEF= left ventricular ejection fraction; LGE= late gadolinium enhancement; NIRA= non-infarct related artery; IS=infarct size; AAR= area at risk; MVO= microvascular obstruction; MSI= myocardial salvage index**
Table S3: Clinical outcomes in patients receiving Clopidogrel and Prasugrel

| Variable                      | Clopidogrel (n=70) | Prasugrel (n=102) | HR (95% CI) | p     |
|-------------------------------|-------------------|-------------------|-------------|-------|
| **12 month follow-up**        |                   |                   |             |       |
| MACE (n, %)                   | 12/70 (17.1)      | 10/102 (9.8)      | 0.53 (0.21, 1.3) | 0.17  |
| All-cause mortality (n, %)    | 1/70 (1.4)        | 1/102 (1.0)       | 0.68 (0.04, 11.1) | 0.79  |
| Recurrent MI (n, %)           |                   |                   |             |       |
| • Type I                      | 0/70 (0.0)        | 3/102 (2.9)       | **          | 0.15  |
| • Type 4b (ST)                | 0/70 (0.0)        | 2/102 (2.0)       | **          | 0.24  |
|                              | 0/70 (0.0)        | 1/102 (1.0)       | **          | 0.41  |
| Heart failure (n, %)          | 5/70 (7.1)        | 2/102 (2.0)       | 0.26 (0.05, 1.4) | 0.11  |
| Revascularisation (n, %)      | 6/70 (8.6)        | 4/102 (3.9)       | 0.44 (0.12, 1.6) | 0.20  |
| **Safety Endpoints**          |                   |                   |             |       |
| Contrast nephropathy (n, %)   | 0/70 (0.0)        | 1/102 (1.0)       | **          | 0.41  |
| Vascular access injury (n, %) | 0/70 (0.0)        | 0/102 (0.0)       | **          | 1.00  |
| CVA/TIA (n, %)                | 0/70 (0.0)        | 0/102 (0.0)       | **          | 1.00  |
| Major bleed (n, %)            | 1/70 (1.4)        | 1/102 (1.0)       | 0.68 (0.04, 11.1) | 0.79  |

MACE= major adverse cardiovascular event, ST= stent thrombosis, CV= cardiovascular, CVA= cerebrovascular accident
Table S4: Clinical outcomes in patients receiving Clopidogrel and Ticagrelor

| Variable                        | Clopidogrel (n=70) | Ticagrelor (n=31) | HR (95% CI)    | p   |
|--------------------------------|--------------------|-------------------|----------------|-----|
| **12 month follow-up**         |                    |                   |                |     |
| MACE (n, %)                    | 12/70 (17.1)       | 4/31 (12.9)       | 0.72 (0.21, 2.4) | 0.54|
| All-cause mortality (n, %)     |                    |                   |                |     |
| • CV mortality                 | 1/70 (1.4)         | 0/31 (0.0)        | **             | 0.50|
| • Non-CV mortality             | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| Recurrent MI (n, %)            | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| • Type I                       | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| • Type 4b (ST)                 | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| Heart failure (n, %)           | 5/70 (7.1)         | 0/31 (0.0)        | **             | 0.12|
| Revascularisation (n, %)       | 6/70 (8.6)         | 4/31 (12.9)       | 1.58 (0.41, 6.1) | 0.56|
| **Safety Endpoints**           |                    |                   |                |     |
| Contrast nephropathy (n, %)    | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| Vascular access injury (n, %)  | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| CVA/TIA (n, %)                 | 0/70 (0.0)         | 0/31 (0.0)        | **             | 1.00|
| Major bleed (n, %)             | 1/70 (1.4)         | 0/31 (0.0)        | **             | 0.50|

MACE= major adverse cardiovascular event, ST= stent thrombosis, CV= cardiovascular, CVA= cerebrovascular accident
Table S5: Clinical outcomes in patients receiving Prasugrel and Ticagrelor

| Variable                  | Prasugrel (n=102) | Ticagrelor (n=31) | HR (95% CI) | p    |
|---------------------------|-------------------|-------------------|-------------|------|
| **12 month follow-up**    |                   |                   |             |      |
| MACE (n, %)               | 10/102 (9.8)      | 4/31 (12.9)       | 1.36 (0.40, 4.7) | 0.65 |
| All-cause mortality (n, %)|                   |                   |             |      |
|   • CV mortality          | 1/102 (1.0)       | 0/31 (0.0)        | **          | 0.58 |
|   • Non-CV mortality      | 0/70 (0.0)        | 0/31 (0.0)        | **          | 1.00 |
| Recurrent MI (n, %)       |                   |                   |             |      |
|   • Type I                | 2/102 (2.0)       | 0/31 (0.0)        | **          | 0.43 |
|   • Type 4b (ST)          | 1/102 (1.0)       | 0/31 (0.0)        | **          | 0.58 |
| Heart failure (n, %)      | 2/102 (2.0)       | 0/31 (0.0)        | **          | 0.43 |
| Revascularisation (n, %)  | 4/102 (3.9)       | 4/31 (12.9)       | 3.63 (0.85, 15.5) | 0.07 |
| **Safety Endpoints**      |                   |                   |             |      |
| Contrast nephropathy (n, %)| 1/102 (1.0)      | 0/31 (0.0)        | **          | 0.58 |
| Vascular access injury (n, %)| 0/102 (0.0)    | 0/31 (0.0)        | **          | 1.00 |
| CVA/TIA (n, %)            | 0/102 (0.0)       | 0/31 (0.0)        | **          | 1.00 |
| Major bleed (n, %)        | 1/102 (1.0)       | 0/31 (0.0)        | **          | 0.58 |

MACE= major adverse cardiovascular event, ST= stent thrombosis, CV= cardiovascular, CVA= cerebrovascular accident
Infarct Size Following Treatment With Second– Versus Third-Generation P2Y₁₂ Antagonists in Patients With Multivessel Coronary Disease at ST–Segment Elevation Myocardial Infarction in the CvLPRIT Study

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