# The Effect of Intravenous Cangrelor and Oral Ticagrelor on Platelets, the Microcirculation and Myocardial Damage in Patients admitted with STEMI Treated by Primary Percutaneous Coronary Intervention

# A randomized controlled pilot trial

Version 3 14/03/2016

SPONSOR: The Royal Wolverhampton NHS Trust
FUNDERS: Tripartite Charitable Research Funds

NHS REC reference: 16/EM/0094

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## GLOSSARY OF ABBREVIATIONS AND TECHNICAL TERMS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| ADP | Adenosine diphosphate |
| AE | Adverse event |
| CABG | Coronary artery bypass graft |
| CMR | Cardiovascular magnetic resonance |
| ECG | Electrocardiogram |
| IMR | Index of microvascular resistance |
| HTPR | High on-treatment platelet reactivity |
| MVO | Microvascular obstruction |
| PW | Pressure Wire |
| PPCI | Primary percutaneous coronary intervention |
| SAE | Serious adverse event |
| STEMI | ST-segment elevation myocardial infarction |
| TIMI | Thrombolysis in myocardial infarction |
| UA | Unstable angina |
| VASP | Vasodilator stimulated phosphoprotein phosphorylation |

## KEYWORDS

Pharmacodynamic
Antiplatelet
Myocardial Infarction
Cangrelor
Ticagrelor
STEMI
IMR
CMR

# 1. LAY SUMMARY

Major heart attacks are caused by a number of factors, the two major of which are furring up of a coronary artery with atheroma and then sudden clot formation on this area leading to a blockage and interruption of blood flow. The clots that lead to heart attacks are largely made of clotting blood cells (platelets) that in health repair blood vessels and inhibit spontaneous bleeding. One of the main treatment strategies for heart attacks is to make these cells less "sticky". Aspirin is a main stay of anti-platelet treatment in the UK and in addition one of three other oral antiplatelet agents acting on the same platelet activation pathway ($P2Y_{12}$ receptor) is licensed for use. When a patient is admitted with a major heart attack, they are treated with emergency primary percutaneous coronary intervention (PPCI) a technique where a wire and balloon are used to reopen the coronary artery and then usually a stent (a slotted metal tube) is placed to keep the artery open. Aspirin and one of the $P2Y_{12}$ inhibitor agents are given to prevent further clots and all have been shown to reduce negative events following heart attacks and angioplasty with stent insertion. There are increasing data, including from our own institution, showing that in the setting of heart attacks, the oral P2Y12 inhibitors are poorly absorbed and have little effect at the time of most need, i.e. soon after dosing while the primary PCI is being performed.
All three current $P2Y_{12}$ inhibitor agents are taken in tablet form immediately before the emergency PPCI procedure. It appears that in healthy stable patients these agents take at least 30 min to 2 hours to have an adequate effect. In heart attack patients the angioplasty procedure is usually performed well within this timescale. Furthermore, patients who are having a heart attack do not have normal drug absorption with blood being diverted away from the stomach and gut activity being suppressed by other drugs such as morphine.

In this current study, patients with major heart attacks will be given our standard oral agent, Ticagrelor, or the newer intravenous agent Cangrelor prior to PPCI. Blood samples will be taken to assess the effect of the anti-platelet agents when the balloon opens the artery and 4 hours after taking the drugs. A final sample will be taken at 24-36 hours to assess effect of the anti-platelet agents and also to assess myocardial damage.

We will assess the two drug therapies by looking at

i) The effect of the drugs on blood platelet "stickiness"
ii) The effect on patency of the treated artery (TIMI Flow Grade)
iii) The effect on the ECG markers of success
iv) The effect on the extent of heart muscle damage using Cardiac MRI scanning
v) The effect on the flow in the capillary blood vessels in the heart muscle (Index of Microcirculatory Resistance, IMR) using an intracoronary pressure wire.

In total the patients in the study will require up to 3 extra blood tests, each using around 10-15 ml of blood (approximately 3 teaspoons of blood). This will not cause any ill effects but may involve up to 2 extra needle pricks (as the first sample will be taken from the radial or femoral sheaths and does not involve a needle prick). The angioplasty procedure itself will be prolonged slightly (after the "life-saving" part of the procedure when flow in the artery has been restored) by the introduction of a further coronary wire (pressure wire) to measure coronary pressure flow and the index of microcirculatory resistance (IMR).
Three months after the index admission, patients will undergo a Cardiac Magnetic Resonance Scan to assess the amount of heart muscle damaged.

# 2. INTRODUCTION

## 2.1 BACKGROUND

The success of modern treatment for ST-segment elevation myocardial infarction (STEMI) is dependent, in part, on the adequate suppression of platelet activity. Primary percutaneous coronary intervention (PPCI) for STEMI management has led to marked reductions in morbidity and mortality (1, 2). Aspirin is the mainstay anti-platelet agent. It is rapidly absorbed in the upper gastrointestinal (GI) tract and results in a measurable inhibition of platelet function within 60 minutes (3, 4). The advent of the platelet $P2Y_{12}$ inhibitors has led to further improvement in outcomes in patients with acute coronary syndromes (ACS) undergoing PCI with reduced ischaemic complications (5) albeit at an increase in rate of bleeding complications. These agents have a synergistic effect on platelet function with the addition of Clopidogrel to Aspirin leading to approximately 20% reduction in negative cardiovascular events (6).

Activation of platelets leads to a conformational change in the surface glycoprotein IIb/IIIa receptor that allows cross bridging with fibrinogen and rapid aggregation (platelet thrombus formation) (7, 8)
During PPCI, thrombus formation and dispersion can have a major impact on outcome. Intravenous platelet IIb/IIIa receptor antagonists such as Abciximab were initially shown to have a positive impact on primary angioplasty outcomes leading to a class IIa indication within the European Society of Cardiology (ESC) guidelines for use in the treatment of STEMI with angioplasty (9).

As oral antiplatelet inhibition has improved (specifically with the addition of Clopidogrel, Prasugrel or Ticagrelor) there has been a concomitant reduction in the use of intravenous IIb/IIIa agents during PCI for patients with ACS. This has been partly informed by later studies suggesting that the additive value of these agents to dual anti-platelet therapy is questionable (10).
In addition, the extra bleeding complications are seen by some to be excessive (11).

Current NICE recommendations for the treatment of STEMI include Aspirin plus one of the P2Y12 agents Clopidogrel, Prasugrel or Ticagrelor.
Ticagrelor, a reversible p2Y12 agent (cyclopentyltriazolopyrimidine CPTP) has been shown to be superior to Clopidogrel in ACS patients in the PLATO trial (12).
In this multicenter, randomized, double-blind trial, 18,624 patients were recruited. 7544 patients with STEMI were allocated to either Ticagrelor 180mg loading dose followed by 90 mg twice daily or Clopidogrel 300mg loading dose followed by 75 mg daily for 6 to 12 months. At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving Ticagrelor as compared with 11.7% of those receiving Clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the Ticagrelor group vs. 6.9% in the Clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of death from any cause was also reduced with Ticagrelor (4.5%, vs. 5.9% with Clopidogrel; P<0.001) (12)

We currently use Ticagrelor in patients admitted with STEMI prior to PPCI. Recently published data suggests however that even with this rapidly effective oral agent, it is not fully functional at the time of PPCI given the short timelines involved (13, 14)

Ticagrelor differs from the thienopyridine class of antiplatelet agents (Clopidogrel, Prasugrel, and Ticlopidine) as it does not exist as a prodrug and thus does not require biotransformation by hepatic enzymes before becoming active. Also Ticagrelor binds reversibly to $P2Y_{12}$ receptors leading to a faster onset and offset than Clopidogrel (15).
Moreover, in the RESPOND study, Ticagrelor therapy was associated with uniform and superior platelet inhibition in both previously identified Clopidogrel responders and non-responders, and that inhibition, in turn, was associated with an extremely low prevalence of high on-treatment platelet reactivity (16).

Ticagrelor has recently received recommendation in the ESC guideline as a front-line treatment option for STEMI and NSTEMI (17, 18)

Ideally a full antiplatelet effect would be evident at the start of the PPCI, whereas in practice dosing of Clopidogrel, Prasugrel or Ticagrelor typically occurs on admission to hospital (possible only 10-20 minutes prior to PPCI).
Cangrelor is an adenosine diphosphate analogue that reversibly binds to and inhibits the P2Y12 ADP receptor. It has a half-life of 3 to 6 minutes and, when given as a bolus plus infusion, quickly and consistently inhibits platelets to a high degree, with normalisation of platelet function within 60 minutes after discontinuation (19).

Cangrelor [Kengrexal (EU), Kengreal (USA)] has been licensed for use in Europe, USA and the UK since March 2015, June 2015 and July 2015 respectively. Co-administered with Aspirin, is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

The use of Cangrelor in patients undergoing PCI has been studied in three phase 3 trials, the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI study, the CHAMPION PLATFORM study and the CHAMPION PHOENIX study (19)(20)(21). In the CHAMPION PCI and the CHAMPION PLATFORM studies, Cangrelor, compared to oral Clopidogrel was not associated with a significant reduction in the primary efficacy end point (All cause death, MI or ischaemia driven revascularization at 48 hours) but was associated with reductions in secondary end points, including the rate of stent thrombosis, with no excess in severe bleeding. In the CHAMPION PLATFORM study there was also a reduction of the pre-specified secondary endpoint of death in the Cangrelor arm. The CHAMPION PHOENIX trial enrolled 11,145 patients undergoing PCI for SA, NSTEMI/UA or STEMI. Patients were randomized to either IV Cangrelor followed by Clopidogrel or oral Clopidogrel (300 or 600 mg) before during or immediately after PCI. In this study patients treated with the intravenous agent were significantly less likely to experience one of the primary endpoints (all cause death, MI or ischaemia driven revascularization at 48 hours), with no significant increase in bleeding. The study included 1992 patients with STEMI, who appeared to have a similar benefit to the SA and NSTEMI patients. Currently there are no data comparing the relative efficacy of Cangrelor with the more potent and rapidly acting Ticagrelor in patients undergoing PPCI for acute STEMI of less than 12 hours duration.

## 2.2 RATIONALE FOR CURRENT STUDY

Gastrointestinal absorption during a STEMI is not equivalent to that of a resting patient (22). Hypotension and/or diversion of splanchnic blood flow are likely to slow drug absorption and the intrinsic increase in platelet activity seen during STEMI (23) (24) may also inhibit the antiplatelet effect of drugs. A previous pharmacokinetic study has shown reduced drug absorption during STEMI (25). Administration of Morphine to ease STEMI pain appears to attenuate the antiplatelet effects of newer P2Y12 inhibitors in the hours after primary PCI (26).

In the current study we aim to demonstrate whether intravenous Cangrelor has a better antiplatelet effect than Ticagrelor during the primary angioplasty (STEMI patients), and investigate the pharmacodynamics properties of these agents in the setting of STEMI by assessing the impact of these agents on a variety of STEMI related outcome variables.

A number of methods have been developed to assess the effect of $P2Y_{12}$ receptor inhibition. Their effect is probably best measured using techniques that specifically measure $P2Y_{12}$ ADP receptor activation, such as vasodilator stimulated phosphoprotein phosphorylation (VASP) utilising flow cytometry, and the VerifyNow $P2Y_{12}$ near patient system (Accumetrics, San Diego, CA).

We will utilise both of these methods in this study.

# 3. STUDY OBJECTIVES

1) To determine the degree and time-course of platelet inhibition in patients admitted with STEMI treated with IV Cangrelor vs oral Ticagrelor.
2) To assess the impact of Cangrelor vs Ticagrelor on the index of myocardial microcirculatory resistance using IMR.
3) To investigate the impact of Cangrelor vs Ticagrelor on markers of PPCI success (TIMI flow grade assessment to evaluate coronary blood flow after PPCI).
4) To assess ST segment resolution post PPCI.
5) To investigate the impact of Cangrelor vs Ticagrelor on initial myocardial infarct size based on Peak Troponin.
6) To investigate the impact of Cangrelor vs Ticagrelor on final myocardial infarct size by CMR at three months post PPCI.

# 4. STUDY DESIGN

This is an open label randomised controlled pilot trial. We will enrol 100 patients (50 in each arm). We anticipate the conclusion of subject recruitment in 12 months from the study start date, with a further 6 months for data analysis and manuscript preparation. Patients in the intravenous Cangrelor arm will receive Cangrelor as an initial bolus dose given as per body weight followed by an intravenous infusion for no longer than three hours (The total dose of IV Kengrexal to be administered based on average body weight of 80 Kg is 510 micrograms/kg given over two hours), they will then switch to oral Ticagrelor given at maintenance dose of 90mg twice daily for 12 months. Patients in the oral Ticagrelor arm will receive Ticagrelor at a loading dose of 180mg followed by maintenance dose of 90mg twice daily for 12 months. All the 100 participants will undergo a CMR scan three months post PPCI.

## 4.1 STUDY OUTCOME MEASURES

a) Degree of platelet inhibition measured with VerifyNow $^{TM}$ rapid platelet function analyser and also VASP flow cytometry at infarct vessel open time (also known as balloon time), 4 and 24-36 hours post dosing.
b) Index of Microvascular Resistance (IMR) measurement using pressure wire studies immediately following the PPCI procedure.
c) Measurement of thrombolysis in myocardial infarction (TIMI) flow grade using TIMI Frame Count.
d) ST Segment Resolution by ECG at 90-120 minutes post PPCI.
e) Infarct size by Peak Troponin at 24-36 hours post PPCI.
f) Final infarct size by CMR at three months in both patient groups (total of 100 subjects).

This study is not powered for clinical outcomes; however clinical and safety data will be recorded.

## 4.2 IN PATIENT SAFETY ENDPOINTS

- BARC definition for bleeding (see appendix 1)
- Target Vessel Failure
- Vital Status at Discharge

# 5 PARTICIPANT ENTRY

## 5.1 CONSENT

Consent will be a two-stage process for patients undergoing PPCI for STEMI. Verbal assent will be brief prior to the PPCI and first blood sample, so as not to lead to a reduction in the quality of patient care (MI outcomes are related to the door to balloon time with PPCI). A

shortened patient information sheet will be read to the patient and if verbal assent is gained it will be recorded in the clinical notes and the site file. This is in line with NRES guidelines that suggest that patients admitted with STEMI are considered as unconscious patients initially.

Following emergency PCI and IMR measurement, when the patient is pain free and has been able to rest, a full patient information sheet will be proffered and written consent sought. If the patient does not want to be part of the trial, he or she will be withdrawn from the study and future tests will not be performed. Treatment will continue in accordance with clinical guidelines. The patients' participation in the trial will last for 3 months. At the end of three months a Cardiac MRI scan will be performed unless there are specific contraindications. Vital status will be determined on discharge and at three months when patients turn up to have their cardiac MRI scan. If a patient fails to attend Cardiac MRI scan appointment in three months' time, a telephone call will be made to the relevant GP to determine the vital status of the patients.

## 5.2 ELIGIBILITY CRITERIA

All research subjects will be identified from STEMI patients admitted for PPCI at the Heart and Lung Centre in Wolverhampton.

## 5.3 RANDOMISATION

Potential patients will be reviewed by a member of the research team before randomisation to confirm eligibility. Once the eligibility of the patient is confirmed by the trial coordinators and the verbal assent is gained, randomisation will be carried out prior to patient's transfer to the cardiac catheter suite. Randomisation will be performed via a secure online web-based service. There will be a single password which will give access for randomisation for the trial on fully encrypted password-protected computers at the heart and lung centre, New Cross Hospital. The system is accessed via a secure connection (SSL) over the internet. This connection encrypts data between the user's internet browser and the server. Online randomisation is achieved by the trial coordinator entering a patient identifier (text field – will be unique), own email address and the randomisation system password. Randomisation is by random permuted blocks to oral Ticagrelor or IV Cangrelor in 1:1 ratio.
An email notification is generated displaying the chosen treatment group or code and sent to the email address given by the user randomising and the administrator email address. The administrator email address is the one provided when the system is set up (usually a trial coordinator or central trial email address).There is only one password and only members of the research team can perform a randomisation.

### 5.4 INCLUSION CRITERIA

1) Patients presenting with STEMI eligible for PPCI
2) Able to give verbal assent pre procedure and written consent following the procedure.
3) Age ≥18 years
4) No contraindication to Cangrelor or Ticagrelor

5) Thienopyridine naïve

Women of childbearing potential would be advised to use appropriate contraceptive measures to avoid pregnancy during treatment with the IMPS following the acute event.

If a patient gives verbal assent but is unable to provide a written consent at a later stage due to continued incapacitation, presumed consent will be continued. The reasons why a patient becomes incapacitated and becomes unable to provide a written consent will be recorded during data collection. As soon as the patient is able to provide written consent, written consent will be sort for continued participation or withdrawal as the patient wishes.

### 5.5 EXCLUSION CRITERIA

1) Be unable to provide verbal assent and written consent
2) Allergic to Aspirin or any of the $P2Y_{12}$ antagonists in the trial
3) Have pre-existing cardiogenic shock
4) Previous myocardial infarction
5) Have a concurrent septic or inflammatory disease e.g. rheumatoid arthritis, lupus, and pneumonia.
6) Already taking a $P2Y_{12}$ inhibitor
7) Known bleeding diathesis
8) Significant active bleeding
9) History of intracranial hemorrhage
10) Patients who are being treated with formal anticoagulation (Vitamin K antagonist, Factor II or Xa inhibitors) or have an indication for anticoagulation during the first four hours of the study period. Example is patients known to have atrial fibrillation, pulmonary embolism or deep vein thrombosis.
11) Known severe renal dysfunction requiring renal replacement therapy.

## 5.6 WITHDRAWAL CRITERIA

Patients are able to withdraw from the trial if they wish without the need to provide reasons and without their care being affected or compromised. Patients who decide to withdraw their consent to participate in the study will have all samples collected up to the time of withdrawal disposed of in appropriate manner. All information collected on the patient for the purpose of the study will be erased. The withdrawal shall be recorded in the study patient identification log. The treatment of the patient will continue in accordance with clinical guidelines should the participant choose to withdraw or not. If a patient dies after obtaining verbal assent but before gaining a written consent, they will still be included in the study and data collected up to the time of death will still be used. Patients who will need administration of glycoprotein IIb/IIIa inhibitors during or post PPCI procedure and patients who fail to have Cangrelor or

Ticagrelor for unexpected circumstances will be withdrawn from the study and their data will not be collected.

**Safety stopping criteria:**

A participant would be withdrawn from the trial if the Clinician feels that continued participation would be unsafe for the participant.
This could include, but not restricted to:

- An anaphylactic shock
- An SAE occurring

# 6. ASSESSMENT AND FOLLOW-UP

**6.1 Subjects:** A total of 100 subjects will be included in the study. Patient's demographic data will be collected.

**6.2 Sampling and Dosing**

**6.2.1** Study subjects will have a $P2Y_{12}$ inhibitor administered (Ticagrelor or Cangrelor) after recorded verbal assent following randomisation. The time of loading dose will be recorded and the patient transferred to the cardiac catheterization suite. After the insertion of the radial or femoral sheath, 10 ml of whole blood will be drawn from this sheath at the first intracoronary balloon inflation time. A further 10 ml will be taken 4 hours post dosing (or as close as is practicable). Further sampling (15 ml) on the ward will take place 24-36 hours post dosing from an anticubital vein using a 21-gauge needle (see study summary tables). Samples taken will be analysed to assess $P2Y_{12}$ activity using VerifyNow ™ (Accumetrics, San Diego, California, USA) and VASP Flow Cytometry tests. Peak Troponin levels will be assessed as well using the same blood samples.

6.2.2 Dosing: Patients will be divided into two arms; Oral Ticagrelor (50 patients) and Intravenous Cangrelor (50 patients) arms.

**Ticagrelor arm**: Patients will receive Ticagrelor 180mg loading dose on the cardiology ward prior to transfer to the catheter lab. Thereafter, a maintenance dose of 90mg twice daily will be given and continued for 12 months duration.

**Cangrelor arm:** Patients will receive Cangrelor administered at a rate of 30 micrograms/kg intravenous bolus followed immediately by 4 micrograms/kg/min intravenous infusion. The bolus and infusion will be initiated in the cardiac catheter lab prior to the PCI procedure and continued for at least two hours or for the duration of the procedure (to increase up to three hours), whichever is longer. 30 minutes prior to stopping Cangrelor infusion, Ticagrelor 180 mg will be given followed by 90mg twice daily maintenance dose continued for duration of 12 months. Cangrelor will be obtained directly from The Medicines Company, retained at the

pharmacy department at New Cross Hospital and issued by the pharmacy department for our clinical trial purposes only. Ticagrelor will be received by the pharmacy department and designated for our clinical trial purposes only.

Cangrelor vials and Ticagrelor tablets will be stored at controlled room temperatures (20°C to 25°C) in special cupboards on the cardiology ward. Only members of the research team will have access to the drug. Each vial contains Cangelor tetrasodium corresponding to 50 mg Cangrelor. After reconstitution 1 mL of concentrate contains 10 mg Cangrelor. After dilution 1 mL of solution contains 200 micrograms Cangrelor. Weight conversion charts in the catheter lab will be used to calculate the required dose of Cangrelor to be administered.

## 6.3 PHARMACODYNAMIC ANALYSIS

### 6.3.1 VerifyNow for $P2Y_{12}$ Activity Analysis

VerifyNow ™ (Accumetrics, San Diego, California, USA) is a near patient test comprising a turbidimetric based optical detection system that measures platelet aggregation as an increase in light transmittance.

We are already using this system for clinical research in our department and it has regulatory approval for the assessment of $P2Y_{12}$ activity. VerifyNow has also been used in the assessment of Ticagrelor activity in a number of studies (16, 27, 28). 2 ml of whole blood is transferred into a Greiner Bio-One Vacuette containing 3.2% sodium citrate (Accumetrics, San Diego, California, USA) and inverted carefully, after which the tube is left at room temperature for a minimum of 15 and 30 minutes for $P2Y_{12}$ activity assay. The tube is then loaded into a specific assay device and analysed (within 4 hours from blood sampling) as per the manufacturers' instructions (Accumetrics). The system is calibrated daily electronically and full quality control is performed with each batch of assay devices. This system uses a similar principle to formal platelet aggregometry.

Results are shown as $P2Y_{12}$ reaction units (PRU) for $P2Y_{12}$ assay

### 6.3.2 VASP Flow Cytometry

VASP, an intracellular actin regulatory protein, is a substrate of both cyclic adenosine monophosphate (cAMP)- and cyclic guanosine monophosphate (cGMP)-dependent protein kinases (29) .

Dephosphorylation of VASP follows $P2Y_{12}$ stimulation. Conversely, inhibition of the $P2Y_{12}$ receptor by Clopidogrel and stimulation of prostaglandin $E_1$-activated adenylyl cyclase induce phosphorylation of VASP by cAMP-dependent protein kinases. Thus levels of VASP phosphorylation/dephosphorylation reflect $P2Y_{12}$ inhibition/activation. Despite using a commercially available assay (Biocytex, Asnieres, France), VASP flow cytometry is primarily a research-based assessment owing to the complexity of the procedure and the requirement for significant technical expertise. It is seen by some as a gold standard test for $P2Y_{12}$ inhibition. Whole blood transferred to tubes containing 3.2% sodium citrate is

incubated with PGE1 or PGE1 and ADP for 10 minutes then fixed with paraformaldehyde, then platelets are permeabilized with non – ionic detergent. The cells are than labelled with a monoclonal antibody against 239-phosphorylated VASP and then a secondary fluoroscein isothicyanate-conjurgated polyclonal antibody. Analysis will be performed on a Becton Dickinson (Plymouth, UK) FACS Calibur flow cytometer, and 10,000 platelets will be gated per assessment as per the manufacturer's instructions. Results are expressed as percentage platelet reactivity index (% PRI). Samples will be taken to clinical chemistry department at New Cross Hospital and stored in freezers at minus 80 degrees. Samples will then be transferred in sealed protective containers to Wolverhampton University where flow cytometric analysis is performed under the supervision of Dr James Vickers.

VASP Flow cytometric analysis measures activity at the $P2Y_{12}$ receptor very effectively and thereby indirectly the activity of $P2Y_{12}$ inhibitor and has been shown to be of value in a number of clinical trials including one carried out by our own research group (30) (31).

## 6.4 TIMI Flow Grade

In acute ST elevation myocardial infarction early reperfusion of the occluded coronary artery, limits the size of infarction, reduces the degree of left ventricular dysfunction, and improves survival (32). Assessment of the degree of reperfusion was achieved using the Thrombolysis in Myocardial Infarction (TIMI) flow grading system developed in the TIMI 1 trial (Grade 0—No perfusion; Grade 1—Penetration without perfusion; Grade 2—Partial perfusion; Grade 3—Complete perfusion) (33). A larger improved survival was observed in patients who achieved TIMI grade 3 flow (34, 35). There is a nearly linear correlation between higher rates of early TIMI grade 3 flow and improved survival (35).

In our study, we will assess the index of blood flow through the culprit coronary artery using TIMI Frame Count (TFC). The TFC is a simple, reproducible, objective, and quantitative index of coronary flow that allows standardization of TIMI flow grades and facilitates comparisons of angiographic end points between trials (36).

The number of cine-frames required for contrast to first reach standardized distal coronary landmarks in the infarct-related artery (the TIMI frame count) will be measured with a frame counter on the GE cine-viewer. The first frame to be used for TIMI frame counting will be the first frame in which dye fully enters the artery. The last frame is defined as the frame when dye first enters the distal landmark branch.

## 6.5 Enzyme Estimation of Myocardial Infarct Size

After an acute myocardial infarction, infarct size quantification is clinically important because it correlates with mortality and morbidity (37).

The gold standard for infarct size quantification is cardiac magnetic resonance imaging (CMR). We will use CMR in all subjects in this trial. In addition, biochemical markers remain a realistic and simple method for infarct size estimation. Troponin is a protein complex consisting of three subunits (I, C and T) that modulate the calcium-mediated interaction between actin and myosin in skeletal and cardiac muscle tissue (38).

Circulating levels of highly sensitive troponin not only correlate with infarct size and ejection fraction but also predict clinical outcomes after a ST-segment elevation myocardial infarction (STEMI) (39).
The first articles detailing the relationship between cTnT and infarct size were published in 1993 (40). (41).
All studies have found a consistent and positive correlation between cardiac troponin and infarct size determined by both CMR and SPECT. Therefore, cardiac troponin T (cTnT) can be used as a surrogate measure for this purpose. The 24 hours value of troponin after the onset of symptoms had the nearest associations with all outcomes (42).
In our study, cardiac troponin will be employed as a surrogate endpoint for infarct size.

A blood sample will be taken 24-36 hours post PPCI to determine peak high sensitivity troponin I levels. This blood test is performed routinely in our centre in patients presenting with STEMI and analysis is performed in clinical chemistry department at New Cross Hospital.

### 6.6 Index of Microvascular Resistance (IMR) Estimation

At the end of the clinical procedure a coronary pressure-/ temperature-sensitive guidewire (Radi Medical Systems, Uppsala, Sweden) will be utilised. The guidewire will be calibrated outside the body then equalized within the guide catheter, with the pressure sensor positioned at the ostium of the guide catheter. The guidewire microsensor will be advanced into the distal third of the culprit artery. The apparent IMR is calculated by multiplying the distal coronary pressure by the mean transit time of a 3 ml bolus of saline at room temperature during coronary hyperaemia induced by intravenous adenosine (43)

Adenosine 140 mcg/kg/min will be used to induce maximal hyperaemia via a large peripheral vein. The mean aortic and distal coronary pressures will be recorded during maximal hyperaemia.

IMR is calculated as the distal coronary pressure multiplied by the mean transit time of the 3-ml saline bolus at maximal hyperaemia, measured simultaneously (automated on the St Jude Medical RadiAnalyzer $^{TM}$ Xpress). This assessment is expected to add no more than thirty seconds to screening time during a coronary angioplasty procedure. Having to screen for duration of thirty seconds long will increase radiation exposure by approximately 3%

### 6.7 ST Segment Resolution post-acute Myocardial Infarction

Percutaneous coronary intervention is the preferred treatment strategy in patients with acute ST-Elevation myocardial infarction (STEMI). It promotes an early and sustained restoration of epicardial blood flow in the target vessel (17). (45).

Successful reperfusion of the epicardial vessel is essential, but it is the microvascular flow that most strongly correlates with outcome. ST-segment changes reflect myocardial rather than epicardial flow and hence provide prognostic information beyond that provided by coronary angiogram alone (46-49).

The resolution of the ST-segment after the institution of reperfusion therapy is an important

predictor of patency of the artery related to the event and of effective microcirculatory perfusion (50).

Various studies have shown a remarkably consistent relationship between the degree of ST resolution and subsequent mortality (51). ECG is useful, simple, noninvasive, broadly accessible, easily repeatable/applied, and affordable tool (52).

The persistence of ST-segment elevation on the ECG, despite the restoration of a normal epicardial flow, reflects a poor prognosis and correlates with larger infarct size and higher combined rate of severe cardiovascular adverse events (53). In our study, an ECG will be recorded 90-120 minutes post PPCI to assess the degree of ST segment resolution.

### 6.8 CMR Assessment of Myocardial Infarct Size

CMR has become the gold standard for surrogate endpoints in clinical trials. CMR of myocardial infarction has been correlated with histology (54). It can accurately measure infarct size (55), LV volumes (56), myocardial salvage (57), microvascular obstruction (MVO) (58) and myocardial oedema (area at risk). Myocardial infarct size, myocardial salvage and MVO have all been shown to be associated with worse outcomes.

CMR assessment of final infarct size will be performed at three months post STEMI. Infarct size will be quantified by planimetering the region of hyperintensity in the myocardium 10 minutes following gadolinium contrast administration. We will notify patients and their responsible general practitioners about the CMR examination result in writing.

## 7. STATISTICS AND DATA ANALYSIS

All statistical analysis will be performed in collaboration with Professor Nevill, Professor of biomedical statistics at University of Wolverhampton on fully encrypted password-protected computers at New Cross Hospital.
Continuous variables will be compared using parametric and non-parametric tests as appropriate. Dichotomous variables will be compared by Fishers exact test. Logistic regression analysis will be used to predict the significant independent predictors of poor outcome post angiography.

7.1 Sample Size Calculation
A previous open label, multicentre study assessed the pharmacodynamics of Cangrelor in a number of patients with acute coronary syndrome (39 patients) (66). Our study is an open label single centre pilot trial planning to enrol 100 patients. Our study will provide the basis for power calculation for future similar studies. This study is a pilot study and not designed to test or determines clinical outcomes such as mortality, but rather we will be looking at the clinical efficacy of Cangrelor versus Ticagrelor in the context of platelet inhibition and effect on myocardial necrosis. Therefore, no formal sample size calculation has been conducted.

## 8. END OF STUDY

End of the study will be marked by the last patient's last visit samples when they have been analysed. The data will then be scrutinised, and finally an article summarising the study written and submitted to a peer-reviewed journal for consideration of publication. Positive trial results might lead to implementation of the use of intravenous Cangrelor in clinical practice.

**Study termination**

The safety monitoring committee/Steering Committee will meet on a regular basis. The trial will be terminated early if there is evidence of unexpected excess bleeding with cangrelor or severe or unexpected complications from the IMR procedure.

# 9. ADVERSE EVENTS

## 9.1 DEFINITIONS

**9.1.1 Adverse Event (AE):** any untoward medical occurrence in a patient or clinical study subject. Adverse events will stop being recorded after 36 hours from the index admission.

**9.1.2 Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Common expected post-procedural adverse events listed below are the conditions not going to be classed as SAEs:

- Acute renal failure requiring haemodialysis, peritoneal dialysis or haemofiltration
- Ventricular arrhythmia requiring direct-current (DC) cardioversion
- Atrial arrhythmia requiring intervention
- Significant heart block requiring temporary or permanent pacing
- Cardiac tamponade requiring urgent surgical intervention
- Cardiogenic shock requiring intra-aortic balloon pump or other assist device
- Emergency coronary artery bypass graft operation

- Arterial complications
- Blood or platelet transfusion

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

## 9.2 REPORTING PROCEDURES

All serious adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning serious adverse events reporting will be directed to the Chief Investigator in the first instance.w3433;

### 9.2.1 Non serious AEs

All such events, whether expected or not, will be recorded.

### 9.2.2 Serious AEs

An SAE form will be completed and faxed to the Chief Investigator within 24 hours. However hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form and faxed to the R&D Directorate at New Cross Hospital within 24 hours of learning of its occurrence.
All serious adverse events will be reported to the appropriate regulatory and ethical authorities.

**Contact details for reporting SAEs**
**Fax: 01902 695646, attention Prof James Cotton**
**Please send SAE forms to: Prof James Cotton Tel: 01902 694200 (Mon to Fri 09.00 – 17.00)**

## 10 ETHICAL CONSIDERATIONS

10.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the trial and other trial related essential documents (e.g. patient information sheet, consent form…) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

10.2 Potential Risks and Benefits of Participation

**Potential Benefits to Participants:** CMR clinical report will be generated and available to clinical care team with assessment of LV function and infarct characteristics that may guide future management.

**Potential Harms to Participants:** The magnetic fields and radio waves used in cardiac MRI have no side effects. This method of taking pictures of organs and tissues doesn't carry a risk of causing cancer

or birth defects. There is a small risk of side effects due to contrast administration during CMR. Gadolinium contrast medium is generally very safe. Side effects or reactions are uncommon but may occur. The most common adverse reactions are brief headache, nausea (feeling sick) and dizziness for a brief time following the injection. This occurs in 1% to 5% of contrast injections. Infrequently, a feeling of coldness may occur at the injection site. There is a negligible incremental risk of IMR measurement above those for PPCI. IMR measurement is expected to add no more than thirty seconds to screening time during a coronary angioplasty procedure. Having to screen for duration of thirty seconds long will increase radiation exposure by approximately 5% of the total PPCI radiation dose. Blood Sampling from arm: may cause bruising and discomfort.

**Benefits to Society:** this study will allow better understanding of antiplatelet function in patients with STEMI with potential benefits to future patients.

## 11. REGULATORY ISSUES

### 11.1 CONFIDENTIALITY

Blood samples will be anonymised with members of the research team at New Cross Hospital having access to the patient's details. All data collected on the patient will be stored in an anonymised fashion on fully encrypted password-protected computers at New Cross Hospital. The study will be archived for 5 years after the study has ended and then destroyed in line with the Research and Development Department policy.

### 11.2 SAFETY AND DATA MONITORING

Due to the nature of the study, data monitoring committee will not be required.

### 11.3 INDEMNITY

Standard NHS Indemnity is in place for this study.

### 11.4 SPONSOR

The Royal Wolverhampton NHS Trust will act as Sponsor for this Study.

### 11.5 FUNDING

Part funding is being successful. Further funding is being applied for.

### 11.6 AUDITS AND INSPECTIONS

The study will be audited and monitored by the sponsor's monitoring team.

### 11.7 TRAINING

The required training to undertake this project will be provided to members of the research team and the cardiac catheter lab nurses. An example is the administration of intravenous Cangrelor.

## 12. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated by Dr Salahaddin Ubaid

**Trial Management Committee:** J Cotton, S Ubaid, A Smallwood and E McAlindon. Study management committee will meet up on a 1-2 monthly basis.

## 13. PUBLICATION POLICY

We intend to submit an article detailing the results of the study to a peer review journal for consideration of publication.

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# 15 APPENDICES:

15.1 Appendix 1 – The Bleeding Academic Research Consortium (BARC) proposes 5 bleeding types (67)

- Type 0: no bleeding
- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- Type 2: any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- Type 3
    - Type 3a
        - Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)
        - Any transfusion with overt bleeding
    - Type 3b
        - Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)
        - Cardiac tamponade
        - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
        - Bleeding requiring intravenous vasoactive agents

- Type 3c
    - Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)
    - Subcategories confirmed by autopsy or imaging or lumbar puncture
    - Intraocular bleed compromising vision
- Type 4: CABG-related bleeding
    - Perioperative intracranial bleeding within 48 h
    - Reoperation after closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
    - Chest tube output ≥2L within a 24-h period
- Type 5: fatal bleeding
    - Type 5a
        - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
    - Type 5b
- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Appendix 2: Study Summary Tables

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| **Timepoint reference** | **Prior to PPCI** | **First IC balloon inflation** | **End of PPCI (following the life-saving part)** | **90-120 minutes post PPCI** | **4 hours post dosing** | **24-36 hours post dosing**<br><br>**(15 ml blood for VASP/VerifyNow and peak Troponin)** | **Discharge** | **Three months post PPCI** |
| Eligibility | X | | | | | | | |
| Medical History | X | | | | | | | |
| Verbal Assent | X | | | | | | | |
| Randomisation | X | | | | | | | |
| Dispensation of treatment | X | | | | | | | |
| Initiation of either oral Ticagrelor or IV Cangrelor therapy | X | | | | | | | |
| Written Informed consent | | | X | | | | | |
| Demographic data collection | X | | | | | | | |
| 10ml blood collection for VASP/ VerifyNow | | X | | | X | X | | |
| IMR | | | X | | | | | |
| ECG | | | | X | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10ml blood collection for Peak Troponin Level (routine) | | | | | | X | | |
| TIMI Flow Grade | | | X | | | | | |
| Vital Status assessment | | | | | | | X | X |
| BARC definition for bleeding | | | X | | | | | |
| Target Vessel Failure | | | X | | | | | |
| CMR | | | | | | | | X |
| Concomitant Medications | X | X | X | X | X | X | X | X |
| Adverse Events review | X | X | X | X | X | X to stop at 36 hours | | |

| Study Steps | Time |
|---|---|
| 1-Quick initial assessment of patients suitable for enrollment in the trial | Upon arrival at the Heart and Lung centre, New Cross Hospital |
| 2-Verbal assent | After the initial assessment |
| 3-Randomisation to either one of the two trial treatment groups | After obtaining verbal assent |
| 4-Initiation of either oral Ticagrelor or IV Cangrelor therapy | Based on randomisation result |
| 5-Primary PCI procedure | Once the second antiplatelet therapy is initiated (Ticagrelor or Cangrelor) |
| 6-Blood sampling for P2Y12 inhibition estimation (using VASP phosphorylation and VerifyNow tests) | A- At the time of first intracoronary balloon inflation (10 ml of blood from the femoral or radial sheath)<br>B- 4 hours post dosing (10 ml of blood from an anticubital vein)<br>C- 24-36 hours post dosing (15 ml in total. 10 ml for VASP/VerifyNow and 5 ml for peak Troponin level. One needle prick) |
| 7-IMR measurement | Immediately following PPCI (same procedure setting) |
| 8-Patient information sheet will be provided and written consent sought | After successful completion of PPCI |
| 9-ECG recording to assess the degree of ST-segment resolution. | 90-120 minutes post PPCI |

| | |
|---|---|
| 10-Peak Troponin level assessment | 24-36 hours post PPCI. |
| 11-TIMI flow grade assessment | Post PPCI |
| 12-Vital Status assessment | On discharge and at three months post PPCI |
| 13-CMR estimation of final myocardial infarct size | At three months post PPCI |

## STUDY COSTS

| | | |
|---|---|---|
| **CMR** | **100 scans @ reduced research rate £100** | **= £10,000** |
| **IMR estimation** | **100 pressure wires @ £300 Unit** | **= £30,000** |
| **Blood Tests** | **300 Verify now @ £38.78 per sample** | **= £11,634** |
| | **100 Troponin @ £9** | **= £900** |
| | **300 VASP @ £16 per sample** | **= £4,800** |
| **Drug Costs** | **50 doses Cangrelor** | **= £7500** |
| **Sponsor Monitoring Costs** | | **= £2,000** |
| **Travel/Presentation costs** | | **= £2,000** |
| **Total Cost** | | **= £68,834** |