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| **IMproving coronary graft Patency with postoperative Aspirin and Clopidogrel versus Aspirin and Ticagrelor: IMPACT study.** |
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| title page |
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# Introduction

## Background

Coronary artery bypass grafting (CABG) reduces symptoms and improves survival in patients with severe coronary artery disease. However, benefits are compromised by graft disease 1. In some series up to 15 – 20% of grafts occlude within a year 2 and graft failure is independently predictive of the subsequent risk of death, MI and need for repeat revascularization 3. Various mechanisms implicated in graft disease include thrombosis, intimal hyperplasia, and atherosclerosis 4. Anti-platelet therapy after CABG can reduce the formation of thrombus and improve graft patency 5. Despite the routine use of aspirin, incomplete inhibition of thromboxane production occurs in over 50% of patients undergoing CABG, due to aspirin resistance 6. Patients who develop aspirin resistance are at increased risk of cardiovascular events and may have an increased risk of developing graft failure 7,8. The additional protective value of clopidogrel in routine CABG patients is uncertain 9. A recently published randomised single-centre study revealed a significant benefit of Aspirin and Clopidogrel combination therapy on venous bypass-graft patency rate after three months, compared with Aspirin alone 10. Clopidogrel resistance is increasingly recognised and is associated with adverse outcomes 11. In a recent, large randomised trial, the novel anti-platelet agent, Ticagrelor was superior to Clopidogrel in the prevention of cardiovascular events including myocardial infarction, cardiovascular deaths and stent thrombosis in patients with acute coronary syndromes 12. In this study a subset of patients who progressed to have CABG after randomisation continued to show a 50% relative risk reduction in total and cardiovascular mortality in favour of Ticagrelor versus Clopidogrel 13. To the best of our knowledge, there is no trial to date, that has prospectively evaluated the synergistic effects of aspirin plus Ticagrelor compared with aspirin and Clopidogrel on coronary artery graft patency after CABG. Graft patency may in part explain the differences noted in PLATO CABG.

## Research hypothesis

The hypothesis is that graft patency is superior with aspirin and ticagrelor to aspirin and clopidogrel in patients undergoing surgical revascularisation following an acute coronary syndrome presentation.

## Rationale for conducting this study

In PLATO CABG patients randomized to Ticagrelor continued to have a benefit, with a 50% relative risk reduction in total and cardiovascular mortality at 12 months 13. The mechanisms for this are unclear and may be related to graft patency. There is no trial to date, that has prospectively evaluated the synergistic effects of Aspirin plus Ticagrelor on coronary artery graft patency after CABG. The primary objective is therefore to determine the effect of dual anti-platelet therapy on the incidence of graft occlusion at 12 months after bypass surgery, as assessed by multi slice computed tomography angiography or by angiography in those who require angiographic study during the first 12 months.

## Benefit/risk and ethical assessment

CABG reduces symptoms and improves long-term survival in patients with severe coronary artery disease. However, long-term survival benefits of CABG are compromised by venous graft disease. In some series up to 15 – 20% of venous grafts occlude within a year and graft failure is independently predictive of the subsequent risk of death, MI, and need for repeat revascularization. Various mechanisms implicated in graft disease include thrombosis, intimal hyperplasia, and atherosclerosis. Anti-platelet therapy after CABG can lessen the formation of thrombus and improve graft patency. The reduction in clinical events noted with Ticagrelor in PLATO-CABG may be influenced by superior graft patency to Clopidogrel. If this is confirmed it has the potential to impact significantly on patient management post – CABG.

The risks to patients of participating in this trial we believe are minimal. Bleeding is a recognised side effect of both agents.

Bleeding was not increased in PLATO-CABG in patients randomized to Ticagrelor. Ticagrelor and Clopidogrel will commence post – operatively. Post-operatively dual anti-platelet treatment will be commenced within 72 hours of the procedure, once the cardiac surgeon / ICU Team assessment indicates bleeding is not a concern.

The only additional investigation patients will undergo, not considered routine practice post CABG is CT angiography. We believe the risk to patients with this investigation is minimal. Specifically current diagnostic protocols allow this to be performed with minimal radiation exposure and thus risk to patients.

Informed consent will be obtained from all participants pre CABG. This process will involve discussion of risks and benefits of treatment and CT angiography.

# Study Objectives

## Primary objective

The primary objective is to determine the effect of dual anti-platelet therapy on the incidence of graft occlusion at 12 months after coronary artery bypass surgery undertaken following an acute coronary syndrome presentation, as assessed by multi slice computed tomography angiography or by coronary angiography if required in the 12 months after surgery. The hypothesis is that graft patency with post-operative use of aspirin and Ticagrelor is superior to aspirin and Clopidogrel.

## Secondary objectives

According to previous studies, the combination of aspirin and Clopidogrel has a graft occlusion rate of about 10% at 1 year after CABG. We estimate that a 5% difference between 2 arms can be reliably detected with a power of 80%, if we have 435 coronary grafts in each arm (2 sided T test with a p-value <0.05). In addition, expecting a 10% drop out rates, we estimate 175 patients in each arm (average of three grafts per patient)

**2.2.1 The need for revascularization** (repeat operation or angioplasty reported by patient or cardiologist) through 12 months after CABG.

**2.2.2 Presentation with symptomatic graft failure –** The angiographic evidence of graft failure is defined as: clinical presentation with ischaemic chest pain associated with occlusion of coronary artery bypass graft (TIMI 0 or 1) flow at angiography

**2.2.3 Assessment of platelet function with VERIFY-NOW assay at Day 3 post CABG and Pre CT Coronary angiography, 6 hours after the last dose of trial drug.** This will be assessed in an optional sub-study.

## Safety objective

Bleeding is the primary safety endpoint. Bleeding complications will be assessed using the TIMI Bleeding Criteria (15-18)

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|  | **2.3.1 Non-CABG Related Bleeding:**1. Major* Any [intracranial bleeding](http://www.wikidoc.org/index.php/Intracranial_hemorrhage) (excluding microhaemorrhages <10 mm evident only on gradient-echo MRI)
* Clinically overt signs of [hemorrhage](http://www.wikidoc.org/index.php/Hemorrhage) associated with a drop in hemoglobin of ≥50 g/L or a ≥15% absolute decrease in [haematocrit](http://www.wikidoc.org/index.php/Hematocrit)
* Fatal bleeding (bleeding that directly results in death within 7 days)

2. Minor* Clinically overt (including imaging), resulting in hemoglobin drop of 30 to <50 g/L or ≥10% decrease in [haematocrit](http://www.wikidoc.org/index.php/Hematocrit)
* No observed blood loss: ≥40 g/L decrease in the haemoglobin concentration or ≥12% decrease in [haematocrit](http://www.wikidoc.org/index.php/Hematocrit)
* Any overt sign of [hemorrhage](http://www.wikidoc.org/index.php/Hemorrhage) that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
* Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat [bleeding](http://www.wikidoc.org/index.php/Bleeding), including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
* Leading to or prolonging hospitalization
* Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

3. Minimal* Any overt bleeding event that does not meet the criteria above
* Any clinically overt sign of [haemorrhage](http://www.wikidoc.org/index.php/Haemorrhage) (including imaging) associated with a <30 g/L decrease in haemoglobin concentration or <9% decrease in [haematocrit](http://www.wikidoc.org/index.php/Hematocrit)

**2.3.2 Bleeding in the Setting of CABG:*** Fatal bleeding (bleeding that directly results in death)
* Perioperative [intracranial bleeding](http://www.wikidoc.org/index.php/Intracranial_hemorrhage)
* Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
* Transfusion of ≥5 U PRBCs or whole blood within a 48-h period. Cell saver transfusion will not be counted in calculations of blood products.
* Chest tube output >2 L within a 24-h period
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# Study plan and procedures

This is a randomised, open label, multi-centre New Zealand, Investigator initiated trial. The study will be conducted at Waikato Hospital and Wellington Hospital.

All patients who are undergoing isolated CABG following an ACS presentation and do not meet pre-operative exclusion criteria will be eligible for enrolment and will be approached to consider participation.

* After CABG patients who do not meet post- operative exclusion criteria will be randomised to receive enteric coated Aspirin 100 mg PO daily and either Ticagrelor 90 mg PO BD or Clopidogrel 75 mg PO daily for 12 months post CABG. Randomisation and commencement of dual anti-platelet treatment will be within 72 hours of the procedure. The study drug initial dose after surgery is going to be the maintenance dose, 75 mg daily for Clopidogrel and 90 mg twice daily for Ticagrelor.

Both Aspirin and study drug Clopidogrel and Ticagrelor will be administered orally as integral tablets.

Patients will be followed up in routine cardiology/ post-surgery clinic post CABG and with a telephone consultation at 3, 6 and 9 months post CABG to assess compliance with treatment and assess for adverse events.

CT coronary angiogramAt 12 months (+/- 30 days) post CABG, graft patency will be assessed by a CT coronary angiogram. This will be performed as per local protocols for CT angiography. CT analysis will be performed for all patients randomised by a cardiologist blinded to treatment allocation.

64 slice MDCT is the minimum scanner requirement. Administration  of pre-scan beta blockers will be in accordance to individual units and their practice. Scanning protocol (flash/sequential/) can vary depending on heart rate.  Field of interest of the scan should include the origin of LIMA.  Area of interest for CTCA is graft patency. It is not a requirement to reconstruct the native coronary artery unless clinically indicated .Non cardiac anatomy will be reported by radiologist.

* Subjects who have a coronary angiogram for any reason that shows the patency or otherwise of the coronary grafts (or the patency of all the grafts can be inferred from the study) and that study shows **at least one blocked graft**, then this should be considered to be an endpoint and the graft patency should be counted as part of the primary endpoint.
* Subjects who have a coronary angiogram for any reason that shows the patency or otherwise of the coronary grafts (or the patency of all the grafts can be inferred from the study) and that study shows **all grafts are open** shall:
	+ If the coronary angiogram is performed in the first 9 months from randomisation, then the CTCA will be performed at 12 months and the results included in the primary end point calculations.
	+ If the coronary angiogram is performed between 9 months and 12 months of randomisation, then CTCA will not be performed at 12 months and the subject will be considered as having patient grafts and this result included in the primary endpoint.
* Subjects who have a coronary angiogram for any reason that does not show the patency or otherwise of the coronary grafts (or the patency of all the grafts cannot be inferred from the study) shall have the CTCA at 12 months and the results included in the primary endpoint.

**VerifyNow Optional Sub-study**

At participating sites Platelet Function testing (VerifyNow) will be assessed at day 3 and pre CT angiography at 12 months, around 6 hours after the last dose.

## Overall study design and flow chart

# Subject Selection Criteria

All patients who are undergoing isolated CABG following an ACS and who do not have any pre-operative exclusion criteria will be eligible and will be approached to consider participation and informed written consent.

Patients included in this study will be managed surgically, the planned procedure is isolated CABG (bypass grafting only). CABG will be performed during index ACS admission.

## Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Provision of informed consent
2. Patients undergoing isolated CABG post ACS presentation

## Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

Pre-operative:

* Patients with low platelets before operation (<100 x109 g/L)
* Previous CABG or other cardiac surgery
* Need for concomitant valve surgery or aneurysm resection
* Active pathological bleeding such as gastro-duodenal ulcer, post-operative gastrointestinal bleeding or intra-cranial bleeding
* Previously documented intolerance to either Clopidogrel or Ticagrelor.
* Patients with relative contraindications for CTCA assessment of grafts. (Patients who are intolerant to Beta-Blockers ,Patients who are in Chronic Atrial Fibrillation ,Patients who have anaphylaxis to contrast, serum Creatinine >140 or eGFR <45ml/min)
* Patients with contraindications to Aspirin and the study drugs Clopidogrel or Ticagrelor
* Moderate to severe hepatic dysfunction
* Co-administration with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir).

Post-operative:

* Need for post-operative warfarin or dabigitran
* Profuse post-operative bleeding (chest tube drainage >200 ml/hour for 2 hours or more)
* Need for secondary thoracotomy to stop bleeding for cardiac tamponade.
* Poor cardiac output postoperatively - requirement for high levels of heamodynamic support (more than 2 inotropes for more than 24 h and/or intra-aortic balloon pump)

# Study conduct

1. ***Procedure for Enrolment and Randomization***

Potential participants will be identified pre-operatively and consent obtained.

To minimize “failed randomisations” patients will not be randomised until approval given by the treating surgeon or ICU consultant post operatively. Randomisation will be by use of pre-printed randomisation envelopes that will be provided to each site. Patients at each site will be randomised in sequential order by numbers recorded on the outside of the envelopes.

1. ***Blinded CT reporting***

Cardiologists reporting CT will be blinded to treatment allocation. Un-blinding of the Cardiologist reporting the CT is not foreseen as necessary.

1. ***Study Treatments***

Patients will be randomized to Ticagrelor and Aspirin or Clopidogrel and Aspirin for 12 months. Both Clopidogrel and Ticagrelor are commercially available and are indicated post ACS and post CABG presentation. Clopidogrel or Ticagrelor will be obtained by prescription from local pharmacy.

1. ***Doses and treatment regimens***

Ticagrelor 90mg BD or Clopidogrel 75 mg/day x 12 months and Aspirin enteric coated tablet 100 mg/day x12 months will be given to all patients in the trial.

1. ***Treatment compliance***

Patients will be followed up in routine cardiology or post- surgical clinic post CABG and by a telephone consultation at 3, 6, 9 and 12 months post CABG to assess compliance with treatment and assess for occurrence of endpoints and adverse events.

1. ***Procedures for discontinuation of a subject from investigational product***

It is possible patients will develop recognized side effects with either Ticagrelor or Clopidogrel which will require discontinuation of these agents. This will however be discouraged unless significant ongoing side effects are encountered. Discontinuation will not be made until reviewed by the local PI or delegate.

1. ***Withdrawal from study***

Patients will be able to withdraw from the study at any stage.

Review will occur with the PI to discuss the patient’s concerns prior to consideration of withdrawal. Analysis will be on an intention to treat basis and follow up participation in CT imaging at 12 months will still be encouraged in patients with treatment withdrawal

# Collection of study variables

## Recording of data

Data will be recorded electronically on data forms that will be sent as email attachments to the Study Coordinating Centre, Cardiology Clinical Trials Unit, Waikato Hospital.

## Safety and Adverse Event Reporting

Both the drugs Clopidogrel, Ticagrelor and the CT Coronary Angiography procedure to be used in this trial have been extensively evaluated and have established safety profiles with known risks and benefits and are routinely used in clinical practice.

Therefore only AEs and SAEs that are considered related to Ticagrelor or Clopidogrel will be recorded.

## Events that are trial endpoints

Selected trial endpoints (e.g. bleeding) will be monitored at regular intervals during the course of the trial for the purpose of protecting participants’ safety.

## Efficacy

The primary end point of the trial is Graft patency as assessed by CT Coronary angiography or by prior coronary angiography.

CT will be performed 12 months post CABG. Studies will be reviewed by investigators blinded to treatment allocation.

## Safety

Both Ticagrelor and Clopidogrel are indicated and registered for use post ACS presentation.

This includes patients undergoing CABG. Bleeding is the primary safety endpoint. Bleeding complications will be assessed using the TIMI Bleeding Criteria. To minimize the likelihood of post CABG related bleeding study drugs will not be commenced post operatively until concerns about haemostasis have resolved.

No new treatments or indications are assessed in IMPACT. Side-effects with both Ticagrelor and Clopidogrel are uncommon, are well known in day to day practice and will be reported in the CRF. Side effects to Clopidogrel include rash (0.5 % of patients) and diarrhoea (0.4% of patients). Side effects of Ticagrelor include dyspnoea- a sensation of breathlessness (2.2 % of patients).

Bleeding endpoints will be classified as minor or major as per TIMI definition.

Patients will also undergo CT angiography at 12 months post CABG which is not routine practice

Contrast reactions are uncommon but can occur. However as not related to study medication they will be recorded as a CT related adverse event or serious adverse event not treatment related adverse event.

## Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

For treatment of overdose see the local prescribing information

# Ethical and regulatory requirements

## Ethical conduct of the study

The study will be conducted in accordance with ICH-GCP and applicable Ethics Committee guidelines.

## Ethical and regulatory review

Approvals will be obtained from appropriate national/local bodies.

## Informed consent

Informed consent will be obtained prior enrolment in the study using the EC approved patient Information sheet and consent form.

# Statistical Methods and sample size determination

According to previous studies, the combination of aspirin and Clopidogrel has a graft occlusion rate of about 10% at 1 year after CABG. We estimate that a 5% difference between 2 arms can be reliably detected with a power of 80%, if we have 435 coronary grafts in each arm (2 sided T test with a p-value <0.05). In addition, expecting a 10% drop out rates, we estimate 175 patients in each arm (average of three grafts per patient).

The analysis will be based on an estimate of the proportion of failed grafts within each patient and compare these patient graft failure proportions between treatments using a non-parametric test like Wilcoxon.

Analysis will be performed on an intention to treat AND treatment received at time CT

The effect on power compared to a potentially biased Chi-square test is very limited. Based on simulations, would the power to detect a reduction from 10% graft failure to 5% with 165 patients per arm and 3 grafts / patient in mean, be over 80% with large probability and such a study would deliver a significant result at a 5% level with an observed absolute reduction of 2.5 percentage points.

One note is that for a study this large is probably a parametric approach like a t-test or z-test acceptable approximations, but picky statistical peer reviewers might frown upon such an approach.

Continuous variables will be expressed as mean (SD) or median (interquartile range [IQR]), and categorical variables reported as number (percentage). The significance of any difference between treatment groups in the proportion of patients with ≥1 occluded graft or with a secondary outcome will be assessed using Fisher exact test, and continuous variables (chest tube output, transfusion) assessed using 2-sample t tests. The significance of any differences between randomized treatment groups in the total numbers of occluded bypass grafts will be assessed by logistic regression using the generalized estimating equations method for non-independent outcomes. A 2-sided P value < .05 will be considered statistically significant.

# Schedule of Events

