

# Thrombosis and hemostasis in coronary artery bypass grafting surgery

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# **Thrombosis and Hemostasis in Coronary Artery Bypass Grafting Surgery**

Laura Marijke Willemsen

**Thrombosis and Hemostasis in Coronary Artery Bypass Grafting Surgery**

Academic Thesis, Maastricht University, Maastricht, The Netherlands

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# Chapter 1

## General Introduction and Thesis Outline

## Introduction

### *Coronary artery disease and coronary artery bypass grafting surgery*

According to the World Health Organization, cardiovascular disease is the leading cause of death worldwide. An estimated 17.9 million people died from cardiovascular diseases in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke (1).

Surgical treatment of coronary artery disease (CAD) by coronary artery bypass grafting surgery (CABG) is the most commonly performed cardiac surgery procedure (2), performed at a rate of 44 per 100 000 individuals in the Western world (3). CABG is still the favored method of revascularization above percutaneous coronary intervention (PCI) in patients with diabetes, reduced left ventricular ejection fraction and extensive multivessel coronary artery disease (CAD) (4) and improves survival as well as quality of life (5,6).

Although he may not be the first to have performed a coronary artery bypass grafting procedure, Rene Favaloro was the first surgeon who used a saphenous vein graft for myocardial revascularization. Nowadays, he is generally credited as being the physician who understood the potential of CABG and introduced it to the rest of the medical world in 1967.

Many improvements to CABG surgery have been made since the time of Favaloro. This includes improvements in myocardial preservation (cardioplegia solutions, anesthesia), the use of arterial conduits (left internal thoracic artery (LITA) to left anterior descending artery (LAD) grafting becoming mainstream, multiple arterial grafting) and off-pump surgery (7). Notwithstanding the achieved improvements, the process of optimizing CABG surgery is ever ongoing and many challenges remain.

### *Thrombosis and hemostasis during CABG*

Maintaining the optimal perioperative equilibrium between thrombosis and hemostasis during and directly after CABG is one of those challenges. Naturally, the balance between bleeding complications and thrombotic complications is always a delicate one, as decreasing the thrombotic risk inevitably comes with an increased bleeding risk, and vice versa. Thrombosis and hemostasis during CABG surgery are affected by multiple perioperative factors of varying etiology.

Patient-related factors (such as gender, body mass index, kidney function and baseline hemoglobin) can influence thrombosis and hemostasis. In addition to that, certain drugs that are necessarily administered during surgery, as well as the medication that is used to treat patients with coronary artery disease makes patients prone to bleeding complications by debilitating the coagulation cascade, mostly by inhibiting platelet function. Furthermore, surgery-related factors, such as hypothermia and acidosis during and after surgery can impair coagulation. Use of a cardiopulmonary bypass can greatly

and complexly influence the hemostatic equilibrium of patients undergoing CABG (8). Tissue factor release during surgery and contact of blood with the foreign surface of the cardiopulmonary bypass is thrombogenic, causing activation of the coagulation cascade, leading to platelet activation and consumption of coagulation factors. This prothrombotic state needs to be countered by strong anticoagulation (with heparin and bivalirudin) throughout cardiopulmonary bypass use, heparin in turn needs to be antagonized with protamine after weaning from the cardiopulmonary bypass. However, this ensues a decreased number of thrombocytes, disturbed thrombocyte function (probably by decreasing the amount of GP1b/IX binding site for Van Willebrand factor (9)) and also depleted coagulation factors (10,11), resulting in an impaired coagulation function, further exacerbated by the priming solution for cardiopulmonary bypass causing dilution of coagulation factors and red blood cells. Subsequent cell salvaging returns only red blood cells, while coagulation factors, platelets and plasma are filtered out (8). After surgery, thrombus formation is stimulated by tissue injury, and is further encouraged by the inflammatory response after CABG (8,12–14).

Several promising (point-of-care) tests to measure hemostasis have been developed and the use of platelet function tests to determine the optimal timing of cardiac surgery is proposed by guidelines (15,16). Point-of-care coagulation tests permit instant monitoring of hemostasis during surgery. Despite this, determining the adequate balance between thrombosis and hemostasis in an individual patient remains challenging and reliably distinguishing patients at risk for perioperative bleeding or thrombotic events is not yet possible. Eventually, definitely preventing these events by measuring hemostasis, is an aspiration for the future.

### *Graft patency*

A specific challenge with regard to thrombosis in CABG surgery is graft patency. It is assumed that the underlying process of SVG occlusion evolves in three phases and is a complex, multifactorial process. However, it is likely that platelet activation and subsequent thrombosis plays a pivotal role (17–19). The first phase of early SVG occlusion is in most cases attributable to conduit-related and technical factors that induce platelet activation. Surgical damage or ischemia amongst others can lead to endothelial cell activation that initiates the thrombotic cascade (19). The thereby activated platelets not only induce thrombosis, but also initiate inflammation (20). Growth factors and cytokines cause smooth muscle cell proliferation as well as early leukocyte response is induced by the secretion of cytokines and growth factors. Smooth muscle cells proliferate and then migrate from the media to the intima. The smooth muscle cells synthesize and deposit extracellular matrix in the intima, leading to further fibrosis. The progressive thickening of the intimal wall is intimal hyperplasia. Atherosclerosis is the last phase of SVG occlusion though atherosclerotic plaques can be seen as early as one year after CABG in the SVG and can progress rapidly. The damage of the endothelium as well as thrombosis and intimal hyperplasia precede atherosclerosis, causing lipids to start accumulate in the intima, thereby marking the beginning of atherosclerosis (17–19).

An estimated 15% of all SVGs occlude in the first postoperative year after CABG, despite the use of aspirin (21–23). SVG occlusion is correlated with angina pectoris, myocardial infarction (MI), and long-term mortality (24–26), whereas reinterventions for SVG occlusions are related with an increased risk for major adverse cardiac events (27–29). As bypassing a stenosis in the LAD with the LITA has superior patency rates and reduces adverse events, this procedure has become the standard of care. It has been suggested patency rates and outcomes would be better with a second arterial conduit (30–35) but this remains a topic for fervent discussion. Nevertheless, the SVG remains the most frequently used graft for a second conduit (3).

Graft patency after CABG is associated with many variables (apart from the already mentioned conduit choice). Technical factors include a distal anastomosis side with a good runoff (36), choosing the appropriate length of the graft (37), sequential grafting (38–40), choice of SVG preservation solution (buffered vs. saline or blood-based solution) and harvesting technique (open vs. no-touch vs. endoscopic (19,41). Off-pump surgery is associated with decreased graft patency, but consensus nowadays is that both off-pump and on-pump surgery perform well in most patients (42).

Postoperative factors associated with graft patency have predominantly to do with lifestyle (4,43–45). These factors include smoking cessation, blood pressure monitoring, lipid management, physical activity and weight control management. Furthermore, preserving SVG patency is supported by two important pharmaceutical pillars: lipid-lowering medication and antithrombotic medication.

#### *Improving graft patency with antiplatelet therapy*

As mentioned, it is fairly certain that platelet activation influences graft occlusion, therefore it follows that the other pharmaceutical pillar for preserving graft patency is antithrombotic medication.

Initially, the perceived risks of CABG surgery focused on excessive bleeding (46,47) in contrast to possible thrombotic risks caused by platelet activation. Aspirin had been around for a long time, but only until the first trials in the 1970`s demonstrated that aspirin could be safely administered in the postoperative period, this became common practice. These trials did not show any benefit of aspirin on graft patency, probably due to late commencement of aspirin and small sample size (48,49). Nonetheless, soon the first studies suggesting aspirin had a beneficial effect on graft patency were published (50–52), a finding that was confirmed in later studies (53,54). In addition to that, it became clear that aspirin use after CABG reduced mortality and was associated with improved clinical outcomes due to reduction of ischemic complications (55,56). Studies assessing the long-term effect of aspirin after CABG showed improved survival with aspirin (57,58).

Therefore, all relevant guidelines (59–62) soon started recommending the use of aspirin after CABG indefinitely and still do (61,63–65).

However, it appears that some patients are transiently unable to metabolize aspirin adequately after CABG, resulting in higher platelet reactivity. The exact incidence of this so-called aspirin resistance is not established, as incidences from 10 to 90% of patients have been reported in the literature (66–69), depending on the method used and time of measurement of aspirin resistance. The underlying mechanisms of aspirin resistance are still unclear, but possible factors contributing to its occurrence after CABG are increased platelet turnover, enhanced platelet reactivity and systemic inflammation (70). Consequently, the idea was raised that stronger platelet inhibition might provide better SVG patency. Some studies investigated whether an increase in dosage of aspirin could improve graft patency rates or clinical outcomes. This has never been proven convincingly (71,72).

Some trials investigated whether SVG patency could be improved by targeting the clotting factors, rather than platelet function. Trials investigating improvement in SVG patency with oral anticoagulant therapy as compared with no antithrombotic therapy are old and have small patient populations, but were unable to establish a convincing beneficial effect of anticoagulation on patency rates (48,73–75). Moreover, it is assumed oral anticoagulation (OAC) provides no superior patency rates when compared with aspirin (76–79) and probably causes more bleeding complications.

As it is known that the combination of OAC and aspirin significantly increases the risk of bleeding (80), guidelines suggest against routinely administering OAC in patients undergoing CABG without indication for OAC (60). For patients that have a definite indication for CABG and whose indication for CABG is Acute Coronary Syndrome (ACS), guidelines recommend resuming OAC as soon as deemed safe, preferably in combination with single antiplatelet therapy (81). Guidelines do not declare so distinctly whether or not antiplatelet medication should be added to OAC in patients with a definite indication for OAC undergoing CABG for chronic coronary syndrome, and generally this is regarded as ‘physician’s choice’ (4,60,65).

Recently, concerning graft patency, this concept of Dual Pathway Inhibition (referring to impairing the coagulation cascade from two separate ways, targeting both platelets as well as clotting factors) has become relevant again with the introduction the direct oral anticoagulants (DOACs). Even so, until present we have only limited evidence relating to DOACs after CABG. The placebo-controlled COMPASS trial investigated the combination of rivaroxaban plus aspirin, monotherapy rivaroxaban or monotherapy aspirin in patients with stable CAD or peripheral arterial disease on MACCE (cardiovascular death, MI, or stroke) (82). The COMPASS-CABG was a pre-planned sub study of the main placebo-controlled COMPASS study, randomizing 1448 patients 4–14 days after CABG, of which the primary endpoint was graft patency. The authors of the study concluded that neither the



combination of rivaroxaban plus aspirin, nor monotherapy with rivaroxaban showed benefit above aspirin monotherapy regarding graft patency, thus being in line with presented studies about VKA regarding SVG patency (83).

Another method to improve platelet inhibition is to add additional antiplatelet agents to intensify platelet inhibition. The addition of dipyridamole to aspirin showed no additional benefit on SVG patency (51,53,84). The CABADAS trial (76) assessed 1-year SVG patency in 948 patients assigned to receive aspirin, aspirin plus dipyridamole, or acenocoumarol/phenprocoumon. This study also provided no convincing evidence that the addition of dipyridamole to aspirin might improve SVG patency, but increased clinical outcome events (myocardial infarction, thrombosis, major bleeding and death), after which guidelines recommended against addition of dipyridamole(59).

The antiplatelet drug clopidogrel works by inhibiting the P2Y<sub>12</sub>-receptor on platelets. Addition of clopidogrel to aspirin proved to reduce atherothrombotic events in patients with acute coronary syndrome and patients with PCI and stent implantation (85,86). Results in improving SVG patency and clinical events after CABG were not so convincing. Several studies concluded addition of clopidogrel to aspirin did not provide better SVG patency (87–89), whereas other studies suggested improvement (90). As it is known that 30% of patients have an inadequate inhibitory response to clopidogrel, determined by their genetic profile, this might be the explanation for the contradicting results between studies investigating graft patency.

The stronger P2Y<sub>12</sub>-inhibitor ticagrelor hardly has any interindividual variability in response profile. Since its introduction, ticagrelor was incorporated in the international guidelines regarding treatment of ACS and replaced clopidogrel as P2Y<sub>12</sub>-inhibitor of choice. It was hypothesized to be a more suitable antiplatelet agent to prevent SVG occlusions than clopidogrel. Three studies investigated the effect of addition of ticagrelor to aspirin on SVG patency after CABG. A small prematurely terminated study showed numerically lower SVG occlusion rates with aspirin and ticagrelor than compared with aspirin alone, but was underpowered to draw conclusions therefrom (91). The DACAB trial randomized 500 participants to aspirin monotherapy, ticagrelor monotherapy and dual antiplatelet therapy with aspirin and ticagrelor (92). They found a significant difference in SVG patency rates with dual antiplatelet therapy, as opposed to monotherapy with aspirin. The difference between monotherapy with aspirin or ticagrelor was not significant.

In conclusion, the effect of dual antiplatelet therapy on SVG patency after CABG is still debated. Therefore, we conducted a randomized, double-blind, placebo-controlled multicenter trial to investigate the effect of the addition of ticagrelor to standard therapy with aspirin on SVG occlusion rates. We hypothesized that the dual antiplatelet therapy and stronger platelet inhibition would reduce the rate of SVG occlusions. In this thesis, we present the POPular CABG trial (93).

## Aim and outline of the thesis

This thesis aims to improve our knowledge of optimally regulating thrombosis and hemostasis in patients undergoing CABG surgery. Thereby we hope to contribute new insights concerning prevention of complications and treatment of patients undergoing CABG surgery, both short-term and long-term.

The first part of this thesis focuses on the prevention of bleeding complications during or shortly after CABG surgery. **Chapter 2** investigates the potential of determining a patient's preoperative aspirin-responsiveness in predicting blood loss after surgery. **Chapter 3** evaluates the additional value of point-of-care monitoring of platelet function at four different time points during high-risk cardiac surgery in order to identify patients at risk for bleeding complications. **Chapter 4** continues with analyzing the association of perioperative fibrinogen concentration and point-of-care viscoelastic tests and postoperative blood loss in patients undergoing high-risk cardiac surgery.

The second part of this thesis discusses optimization of saphenous vein graft patency and prevention of graft occlusion, a feared and frequent development after CABG surgery. **Chapter 5** contains a review of available knowledge concerning saphenous vein graft patency. The next three chapters all concern the POPular CABG trial: a randomized, placebo-controlled trial investigating the effect of the addition of ticagrelor to standard aspirin therapy on saphenous vein graft patency after CABG surgery. **Chapter 6** describes the rationale and design of the trial, **Chapter 7** contains the primary results of the trial, and **Chapter 8** elaborates the mistake we made in the analysis of the trial and addresses insights we acquired concerning trial conduct and trial logistics. In **Chapter 9**, we assess the perioperative management of antiplatelet treatment in patients undergoing CABG surgery in Dutch cardiothoracic centers.

In the last part of this thesis, some long-term consequences of thrombosis and hemostasis management are examined. **Chapter 10** compares outcomes of elderly patients undergoing CABG surgery vs. percutaneous coronary intervention. **Chapter 11** discusses platelet inhibition and bleeding risks in patients that undergo non-cardiac surgery.

Finally, the conclusions and implications of this thesis are summarized and reviewed in the **Discussion**.

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# **Part I**

## **Preventing Bleeding Complications During Surgery**



# Chapter 2

## **Blood loss after coronary artery bypass by aspirin responsiveness assessed with preoperative VerifyNow aspirin testing.**

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## Abstract

### Background

Aspirin is important for preventing thrombotic events but also increases bleeding complications. Minimizing bleeding while preventing thrombotic events remains challenging in patients undergoing coronary artery bypass grafting (CABG). Establishing the patient's preoperative aspirin response could distinguish patients at risk for perioperative blood loss.

### Objective

Aim was to compare 12-hour blood loss after CABG between aspirin-sensitive and aspirin-resistant patients.

### Patients/methods

The primary analysis of this substudy of the POPular CABG trial (NCT02352402) included patients that used aspirin monotherapy preoperatively. A preoperative platelet function test by the VerifyNow aspirin assay was performed before CABG and patients were classified as aspirin-sensitive or aspirin-resistant based on an Aspirin Reaction Units (ARU) cutoff value of 550. Primary endpoint was 12-hour blood loss after CABG. Secondary endpoint was, amongst others, clinical bleeding events after CABG.

### Results

A total of 128 patients were included in the primary analysis. Thereof, 116 patients were aspirin-sensitive and 12 were aspirin-resistant. Mean blood loss 12 hours after CABG was  $555 \pm 278$  ml in aspirin-sensitive patients and  $406 \pm 110$  ml in aspirin-resistant patients ( $p=0.041$ ). All bleeding events ( $n=15$ ; 11.7%) occurred in aspirin-sensitive patients.

### Conclusions

In patients who are on aspirin preoperatively, aspirin-sensitivity was associated with 12-hour blood loss after CABG, suggesting preoperative VerifyNow aspirin testing could identify patients undergoing CABG at high risk for perioperative bleeding.

## Introduction

Relevant guidelines, including the 2018 ESC/ACTS Guidelines on myocardial revascularization, recommend initiating or continuing aspirin throughout the perioperative period in both stable and unstable patients undergoing coronary artery bypass grafting (CABG) [1–3], as early postoperative use of aspirin is associated with a reduction in death and ischemic complications involving heart, brain, kidneys and the gastrointestinal tract [4]. Nonetheless, the advantages of perioperative aspirin-use are accompanied with a higher risk of perioperative and postoperative bleeding complications [5–8].

Not all patients display the same level of inhibitory response to aspirin. A proportion of patients, ranging from 10-90% (depending on the platelet function test used and timing of platelet function testing [9]) demonstrate insufficiently suppressed platelets after CABG despite optimal perioperative aspirin administration. This phenomenon is known as 'aspirin-resistance' [9,10]. Although it is hypothesized that aspirin-resistant patients are at increased risk of thrombotic events [11], they might also have a lower bleeding risk, whereas aspirin-sensitive patients might have lower risk of thrombotic events but increased bleeding risks. Quickly and correctly identifying the preoperative, baseline response to aspirin could be an important factor in distinguishing patients at risk for perioperative blood loss in cardiovascular surgical procedures. Therefore, the aim of this study was to determine if aspirin-responsiveness, determined by preoperative VerifyNow aspirin assay testing (Accumetrics, San Diego, California, USA), is associated with blood loss within 12 hours after CABG.

## Methods

### Study design

This was a post-hoc substudy from the POPular CABG trial (Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Bypass Grafting; NCT02352402). The study was designed in compliance with the Declaration of Helsinki and was approved by the relevant ethics committees and review boards. The POPular CABG was a randomized, double-blind, placebo-controlled trial, that investigated the effect of ticagrelor in addition to standard aspirin on saphenous vein graft (SVG) patency 1 year after CABG. The rationale and design of the trial have been published, as well as the results of the primary endpoint [12,13].

*Population*

Patients who underwent planned CABG with one or more SVGs were eligible for participation. Major exclusion criteria were, among others, use of oral anticoagulation after CABG or a definite indication for use of a P2Y<sub>12</sub>-inhibitor or antithrombotic agent other than aspirin after CABG. All patients provided written informed consent for the POPular CABG trial and patients who wanted to participate in this substudy also provided oral informed consent for the blood sampling. In the main study, patients were randomized in the two study groups after a second screening after CABG to ensure that patients did receive a SVG during surgery as planned. Patients that were not included in the POPular CABG trial because they did not meet the criteria of this second screening, but did consent to the trial and underwent blood sampling preoperatively, were included in this substudy. For this substudy, all patients that used a P2Y<sub>12</sub>-inhibitor within 48 hours before CABG were excluded, as P2Y<sub>12</sub>-inhibition before cardiac surgery is a well-known risk factor for blood loss.

*Platelet function testing by the VerifyNow assay*

Blood was sampled using venipuncture with 21-gauge needles before CABG. After a 5 ml discard tube, 1 Greiner Bio-One partial fill Vacuette vacuum collection tube of whole blood (2 ml), anticoagulated with 3,2% sodium citrate, was withdrawn from each subject. The tubes were gently rotated at least 5 times to ensure complete mixing of the citrate with blood. The assay was performed according to manufacturer's instructions. All platelet function analyses were performed between 30 minutes and 4 hours after blood sampling. Results of the preoperative VerifyNow assay remained unknown to all operation personnel. Based on the results of the preoperative VerifyNow assay, patients were classified as aspirin-sensitive (Aspirin Reaction Units (ARU) value < 550) or aspirin-resistant (ARU value ≥ 550). This cut-off value for aspirin-responsiveness is set by the manufacturer [14] and has been accepted in the medical literature [15–17].

*Blood loss*

The primary endpoint of this study was blood loss 12 hours after CABG, defined as 12-hour chest tube production. We also evaluated total drain production 12 hours after CABG (chest tube + leg drainage), as well as chest tube and total drain production at 1 hour and 6 hours after CABG, and clinical bleeding events 12 hours after CABG. All bleeding events, except for chest tube output, were defined according to the universal definition of perioperative bleeding in cardiovascular surgical procedures [18] (Supporting Information Table 1). As packed red blood cell transfusions were often supplied during surgery to correct for a low baseline hemoglobin or induced hemodilution as a consequence of cardiopulmonary bypass (CPB) and not always for bleeding, it was decided to exclude class 1 bleeding events.

*Statistical analysis*

Continuous data are presented as mean ± standard deviation (SD) for normally distributed data, and median and interquartile range for non-normally distributed data. Categorical data are presented as numbers and percentages. To compare independent continuous variables between groups for normally and non-normally distributed variables, the Student's t-test and the Mann-Whitney U-test were used. For categorical data the chi-squared test or the Fisher's exact test was used.

Statistical significance was assumed when the p-value was <0.05. All statistical analyses were performed using SPSS statistical software for windows (SPSS version 24, IBM corporation, New York, USA).

**Results***Trial population*

Table 1 shows baseline and procedural characteristics of patients and procedures, respectively. Of 128 patients included, 12 patients displayed a preoperative ARU-value of ≥ 550 ARU and were classified as aspirin-resistant. In the total population, the mean age was 69 years and 87% were male. Indication for CABG was acute coronary syndrome (ACS) in 24% of cases, and CABG was performed with cardiopulmonary bypass (CPB) in 99% of cases. No significant differences in the baseline characteristics of aspirin-resistant and aspirin-sensitive patients were identified. Preoperative and direct postoperative hemoglobin, hematocrit and platelet count were comparable in both groups (Table 1). All patients used aspirin preoperatively. None of the patients used preoperative anticoagulation therapy. Five patients used a P2Y<sub>12</sub>-inhibitor > 48 hours before CABG. Four patients used ticagrelor, this was discontinued 5 days preoperatively in one patient, and three days preoperatively in three patients. One patient used clopidogrel; this was halted five days preoperatively. All five patients were aspirin-sensitive. and none of the patients used antithrombotic therapy other than aspirin or anticoagulation therapy within 12 hours after CABG (as this was an exclusion criterion for the trial).



**Table 1.** Baseline and procedural characteristics.

|                                                                       | Total<br>Population<br>(N=128) | aspirin-<br>sensitive<br>patients<br>(N=116) | aspirin-<br>resistant<br>patients<br>(N=12) | P-value |
|-----------------------------------------------------------------------|--------------------------------|----------------------------------------------|---------------------------------------------|---------|
| <b>Demographic characteristics</b>                                    |                                |                                              |                                             |         |
| Age (years) – mean ± SD                                               | 69±8                           | 69±8                                         | 67±9                                        | 0.494   |
| Male gender - N (%)                                                   | 111 (86.7)                     | 100 (86.2)                                   | 11 (91.7)                                   | 1.000   |
| Body Mass Index (kg/m <sup>2</sup> ) –<br>mean ± SD                   | 27.2±3.9                       | 27.2±3.9                                     | 26.6±4.2                                    | 0.610   |
| eGFR <60 (ml/min/1.37m <sup>2</sup> )<br>– N (%)                      | 24 (18.8)                      | 22 (19.0)                                    | 2 (16.7)                                    | 1.000   |
| Current smoker*– N (%)                                                | 19 (14.8)                      | 15 (13.0)                                    | 4 (33.3)                                    | 0.081   |
| Indication for CABG                                                   |                                |                                              |                                             |         |
| Acute Coronary Syndrome<br>(ACS) – N (%)                              | 31 (24.2)                      | 30 (28.3)                                    | 1 (9.1)                                     | 0.284   |
| Chronic Coronary<br>Syndrome (CCS) – N (%)                            | 86 (67.2)                      | 76 (71.7)                                    | 10 (90.9)                                   |         |
| <b>Medical History</b>                                                |                                |                                              |                                             |         |
| Diabetes Mellitus – N (%)                                             | 28 (21.9)                      | 25 (21.6)                                    | 3 (25.0)                                    | 0.724   |
| Hypertension - N (%)                                                  | 79 (61.7)                      | 74 (63.8)                                    | 5 (41.7)                                    | 0.210   |
| Hypercholesterolemia † – N<br>(%)                                     | 56 (43.8)                      | 48 (41.4)                                    | 8 (66.7)                                    | 0.093   |
| Prior PCI - N (%)                                                     | 28 (21.9)                      | 26 (22.4)                                    | 2 (16.7)                                    | 1.000   |
| Prior CABG – N (%)                                                    | 2 (1.6)                        | 2 (1.7)                                      | 0 (0)                                       | n.a.    |
| <b>Preoperative laboratory results</b>                                |                                |                                              |                                             |         |
| Hemoglobin (mmol/L) –<br>mean ± SD                                    | 9.0±0.8                        | 9.0±0.8                                      | 9.0±0.9                                     | 0.987   |
| Hematocrit (l/l) – mean ± SD                                          | 0.42±0.04                      | 0.42±0.04                                    | 0.42±0.04                                   | 0.712   |
| Platelet count (x10 <sup>3</sup> per<br>mm <sup>3</sup> ) – mean ± SD | 241±59                         | 242±59                                       | 231±64                                      | 0.705   |
| <b>Medication</b>                                                     |                                |                                              |                                             |         |
| Start of aspirin <5 days<br>preoperatively – N (%)                    | 11 (8.6)                       | 10 (8.6)                                     | 1 (8.3)                                     | 1.000   |
| Use of P2Y12-inhibitor > 48<br>hours before CABG                      | 5 (3.9)                        | 5 (4.3)                                      | 0 (0)                                       | 1.000   |

**Table 1.** Baseline and procedural characteristics. (continued)

|                                                                       | Total<br>Population<br>(N=128) | aspirin-<br>sensitive<br>patients<br>(N=116) | aspirin-<br>resistant<br>patients<br>(N=12) | P-value |
|-----------------------------------------------------------------------|--------------------------------|----------------------------------------------|---------------------------------------------|---------|
| <b>Intraoperative characteristics</b>                                 |                                |                                              |                                             |         |
| On-pump CABG - N (%)                                                  | 127 (99.2)                     | 115 (99.1)                                   | 12 (100.0)                                  | 1.000   |
| Time on cardiopulmonary<br>bypass (hh:mm) – mean<br>± SD              | 01:28 ± 00:25                  | 01:27±00:23                                  | 01:35±00:37                                 | 0.609   |
| Administering of<br>tranexamic acid - N (%)                           | 183 (64.8)                     | 75 (64.7)                                    | 8 (66.8)                                    | 1.000   |
| Intraoperative RBC<br>transfusion ‡ - N (%)                           | 7 (5.5)                        | 7 (6.0)                                      | 0 (0)                                       | n.a.    |
| Cellsaver transfusion (ml)<br>–mean ± SD                              | 322 (269)                      | 321 (270)                                    | 333 (268)                                   | 0.887   |
| <b>Direct postoperative laboratory results****</b>                    |                                |                                              |                                             |         |
| Haemoglobin (mmol/L) –<br>mean ± SD                                   | 6.6±0.9                        | 6.6±0.8                                      | 7.0±1.0                                     | 0.101   |
| Haematocrit (l/l) – mean<br>± SD                                      | 0.32±0.07                      | 0.31±0.07                                    | 0.33±0.05                                   | 0.112   |
| Platelet count (x10 <sup>3</sup> per<br>mm <sup>3</sup> ) – mean ± SD | 153±40                         | 153±39                                       | 156±51                                      | 0.816   |

Plus–minus values are means ±SD. Abbreviations: eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; n.a., not available, RBC, red blood cell.

\*Defined as current smoker or quit smoking < three months † Defined as diagnosis in medical history or LDL ≥ 2.5, mmol/l, HDL < 1.1mmol/l, total cholesterol > 6,5 mmol/l and/or triglycerides ≥ 2,2mmol/l ‡ Defined as administered intraoperatively or <1 hour after operation. § Defined as first lab results after CABG, in 90% of cases within 1 hour after CABG.

#### Primary outcome

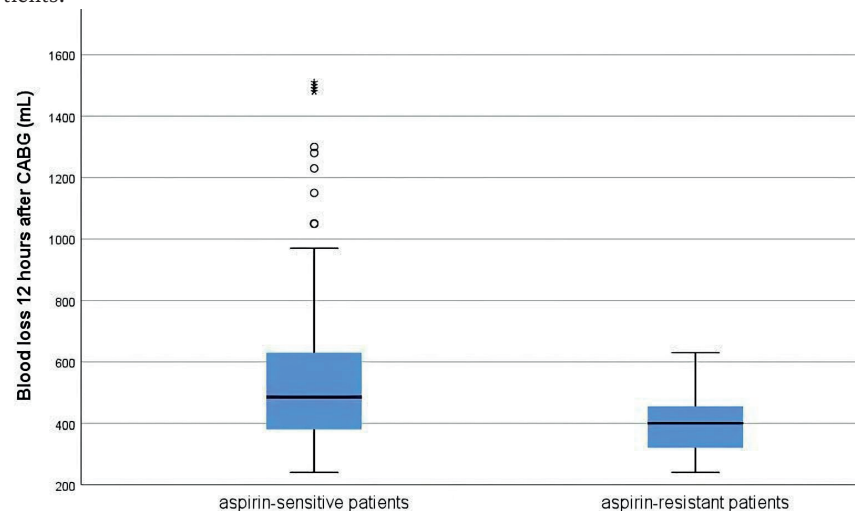
Mean blood loss 12 hours after CABG was 555±278 ml in the aspirin-sensitive group and 406±110 in the aspirin-resistant group (p=0.041, Table 2, Fig. 1). Individual ARU values and 12-hour blood loss are plotted in Figure 2.

**Table 2.** Primary and secondary outcomes regarding chest tube and total drain production over time.

|                                                              | Total Population (N=128) | aspirin-sensitive patients (N=116) | aspirin-resistant patients (N=12) | P-value |
|--------------------------------------------------------------|--------------------------|------------------------------------|-----------------------------------|---------|
| Chest tube production at 1 hour after CABG (mL) – mean ± SD  | 103±76                   | 105±78                             | 78±40                             | 0.355   |
| Total drain production 1 hour after CABG (mL) – mean ± SD    | 159±121                  | 163±124                            | 122±81                            | 0.400   |
| Chest tube production at 6 hours after CABG (mL) – mean ± SD | 375±220                  | 386±226                            | 265±88                            | 0.048   |
| Total drain production 6 hours after CABG (mL) – mean ± SD   | 438±239                  | 451±245                            | 316±114                           | 0.060   |
| Chest tube production 12 hours after CABG (mL) – mean ± SD   | 541±271                  | 555±278                            | 406±110                           | 0.041   |
| Total drain production 12 hours after CABG (mL) – mean ± SD  | 615±294                  | 631±302                            | 458±128                           | 0.035   |

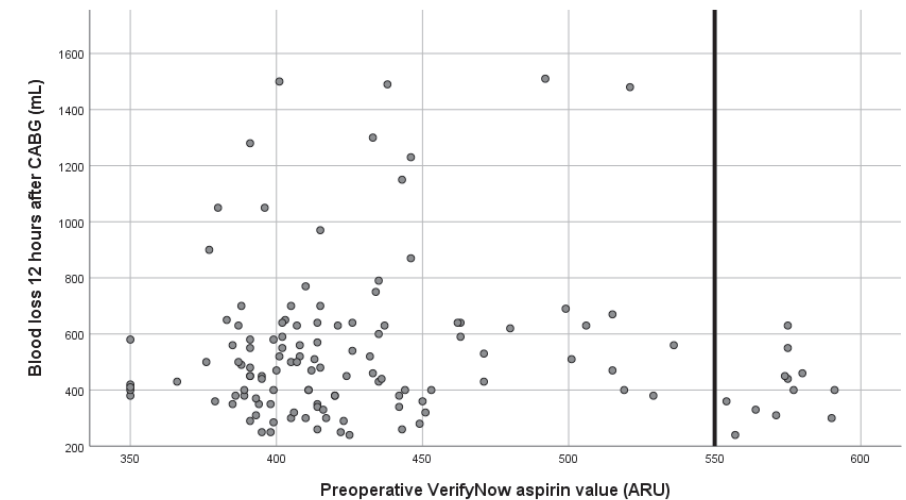
Plus-minus values are means ±SD. Abbreviations: CABG denotes coronary artery bypass grafting.

**Figure 1.** Boxplot of 12-hour blood loss after CABG by aspirin resistant or aspirin-sensitive patients.



The horizontal black line is the median value; boxes extend from the 25<sup>th</sup> to the 75<sup>th</sup> percentile of each groups' distribution of values; whiskers represent 1.5 times the interquartile range; dots denote outliers (observations outside the range of 1.5 times the interquartile range) and asterisks denote extremes (observations more than 3 times the interquartile range). Abbreviations: CABG denotes coronary artery bypass grafting.

**Figure 2.** Scatterplot of 12-hour blood loss (mL) after CABG by individual ARU values.



The vertical line at 550 ARU is the cut-off value for aspirin-resistance. Abbreviations: CABG denotes coronary artery bypass grafting, ARU denotes Aspirin Reaction Units.

*Secondary outcomes*

Total drain production at 12 hours was 631±302 ml in the aspirin-sensitive group and 458±128 in the aspirin-resistant group (p=0.035). Results of chest tube and total drain production at 1 hour were comparable between aspirin-resistant and aspirin-sensitive groups. At 6 hours, both results of chest tube and total drain production differed between aspirin-sensitive and aspirin-resistant groups. All secondary outcomes rendered higher blood loss in the aspirin-sensitive group (Table 2). In total, 15 patients (11.7%) experienced bleeding events during or up to 12 hours after CABG, 12 events were categorized as class 2 events and 3 events as class 3. All patients experiencing bleeding events were classified as aspirin-sensitive.

**Discussion**

This substudy of the POPular CABG randomized controlled trial investigated whether preoperative platelet function testing of aspirin-responsiveness with the VerifyNow aspirin assay was associated with blood loss after CABG. We found a significant association between VerifyNow aspirin-responsiveness and blood loss in patients that used aspirin preoperatively. In addition, all bleeding complications occurred in the aspirin-sensitive group.

Some studies have investigated the relationship between aspirin-responsiveness as measured with the VerifyNow aspirin assay and postoperative blood loss in cardiovascular surgical procedures. Takiuchi et al [19] enrolled 114 Japanese patients undergoing cardiac surgery of which 30 underwent off-pump CABG, of which 11 used only aspirin preoperatively (11 used aspirin + clopidogrel, 1 used aspirin + cilostazol, 1 used warfarin, 1 used aspirin + warfarin and 4 used no antithrombotic medication). In these patients undergoing CABG, they established a weak inverse correlation ( $rS=-0.176$ ), between preoperative ARU values and 24-hour blood loss, but this was not significant, probably because of the small sample size. Welsh et al. [20] retrospectively enrolled 88 patients that underwent cardiac surgery (12.5% CABG) and had VerifyNow aspirin testing. Of 88 patients in this study, 11 (12.5%) had significant bleeding during or after surgery. Five of these patients were aspirin-sensitive ( $p=0.32$ ). VerifyNow ARU values for patients with significant bleeding did not significantly differ from patients without significant bleeding ( $546.5\pm 61.2$  vs.  $519.1\pm 77.2$ ). The study of Kim et al. [21] prospectively included 220 aspirin-taking patients undergoing elective off-pump CABG. Patients who used other antiplatelet or anticoagulant medication were excluded from the study. The patients were divided in aspirin-responders and aspirin-non responders according to the VerifyNow aspirin assay. They identified 181 aspirin responders (82.3%) and 39 aspirin non-responders (17.7%). Blood loss 12 hours after surgery, defined as the volume of the mediastinal and pleural chest tube drainage, did not differ between both groups ( $858\pm 530$  ml in the aspirin responder group,  $883\pm 474$  ml in the aspirin non-responder group,  $p=0.52$ ), nor did transfused packed red blood cells and the rate of re-exploration for bleeding.

These results are not in line with the results of our study, as we can establish a significant difference when analyzing aspirin responders versus non-responders. We can only speculate on the reasons why these studies do not demonstrate a relation between aspirin-responsiveness and blood loss after cardiovascular surgical procedures.

First, the study of Takiuchi et al. is conducted in Japanese patients, and the study of Kim et al. is conducted in Korean patients, while our study population exists of European patients. These populations are not necessarily comparable. Vascular disease seems to manifest differently in Asians (higher stroke incidences but lower incidences of acute myocardial infarction)[22]. Genetic differences may cause a dissimilar bleeding risk (and risk factors for bleeding), as well as changes in the aspirin metabolism [23], as is the case with clopidogrel resistance [24].

Second, opposed to our study (>99% on-pump surgery), the study population of Takiuchi et al. and Kim et al. consists of patients undergoing off-pump CABG (the study of Welsh et al. does not comment on the type of CABG). Although the effect of off-pump surgery on blood loss remains a topic for discussion [25,26], the difference in thrombocyte (dys-

function and (transient) aspirin-resistance between on-pump and off-pump CABG might explain some of the discrepancies between the outcomes of our studies.

Last, the study of Kim et al. is the only study that selected a similar study population with regard to preoperative antithrombotic and anticoagulation drugs (Welsh et al. do not mention preoperative medication use, and as mentioned the population of Takiuchi et al differs in medication use). These other drugs might have influenced blood loss. Given our results, it could be proposed that preoperative testing of aspirin-responsiveness might have value in predicting blood loss in patients undergoing cardiovascular surgical procedures who use aspirin preoperatively. Whether this difference in blood loss between aspirin-sensitive and aspirin-resistant patients is clinically meaningful, can aid in determining the timing of surgery [27], and whether classification according to aspirin-responsiveness with the preoperative VerifyNow aspirin assay can help identifying patients undergoing CABG at risk for high blood loss, and eventually could prevent bleeding events needs to be further investigated.

The following limitations should be considered. First, this is a relatively small study, with a small proportion of patients that were aspirin-resistant. Secondly, no correction for aforementioned other possible factors influencing blood loss was made. Therefore, it cannot be excluded that these factors influenced the results. Thirdly, although results of the preoperative VerifyNow aspirin assay were unknown to all except the study team, blood transfusion management was left to discretion of treating physicians which could have influenced postoperative blood loss.

## Conclusion

In conclusion, in patients that used aspirin preoperatively, aspirin-responsiveness as classified by preoperative platelet function testing by the VerifyNow aspirin assay was associated with 12-hour blood loss after CABG. Further investigation is needed to determine if and in which population preoperative VerifyNow aspirin testing can identify patients undergoing CABG at high risk for perioperative bleeding and whether this can prevent clinically relevant bleeding events.

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**Supporting Information Table 1:** Bleeding categories according to the Universal Definition of Perioperative Bleeding in adult cardiac surgery [1].

| Bleeding definition            | Sternal closure delayed | Postoperative chest tube blood loss within 12 hours (mL) | PRBC (units) | FFP (units) | PLT (units) | Cryoprecipitate | PCCs | RFVIIa | Reexploration/tamponade |
|--------------------------------|-------------------------|----------------------------------------------------------|--------------|-------------|-------------|-----------------|------|--------|-------------------------|
| <b>Class 0 (insignificant)</b> | No                      | <600                                                     | 0*           | 0           | 0           | No              | No   | No     | No                      |
| <b>Class 1 (mild)</b>          | No                      | 601-800                                                  | 1            | 0           | 0           | No              | No   | No     | No                      |
| <b>Class 2 (moderate)</b>      | No                      | 801-1000                                                 | 2-4          | 2-4         | Yes         | Yes             | Yes  | No     | No                      |
| <b>Class 3 (severe)</b>        | Yes                     | 1001-2000                                                | 5-10         | 5-10        | N/A         | N/A             | N/A  | No     | Yes                     |
| <b>Class 4 (massive)</b>       | N/A                     | >2000                                                    | >10          | >10         | N/A         | N/A             | N/A  | Yes    | N/A                     |

If different categories indicate mixed definitions of bleeding, the worst definition applies. PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet concentrates; PCCs, prothrombin complex concentrates; rFVIIa, recombinant activated factor VII; N/A, not applicable. \*Correction of preoperative anemia or hemodilution only; the number of PRBCs used should only be considered in the UDPB when accompanied by other signs of perioperative bleeding.



# Chapter 3

## Perioperative point of care platelet function testing and postoperative blood loss in high-risk cardiac surgery patients

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## Abstract

Postoperative coagulopathic bleeding is common in cardiac surgery and associated with increased morbidity and mortality. Platelet function is affected by multiple factors, including patient and procedural characteristics. Point-of-care (POC) multiple electrode aggregometry (MEA) can rapidly detect and quantify platelet dysfunction and could contribute to optimal patient blood management.

In patients undergoing CABG and heart valve surgery platelet function was assessed using POC MEA at four different perioperative timepoints in response to stimulation with four specific receptor agonists (ADP, AA, COL, TRAP). Postoperative bleeding was recorded during 24 hours after surgery. Regression analyses were performed to establish associations between perioperative platelet function and postoperative blood loss.

Ninety-nine patients were included in the study. Fifty-nine patients (60%) were on antiplatelet therapy (APT) at time of surgery. ADP and AA induced platelet aggregation declined during CPB and after decannulation from CPB, with a maximum decrease of 55% for ADP (35 vs 77 AU at baseline;  $P < 0.001$ ) and 78% for ASPI (14 vs 64 AU at baseline;  $P < 0.001$ ). A linear relationship was present between ADP induced platelet aggregometry at baseline and postoperative blood loss ( $r = -0.249$ ;  $P = 0.015$ ). In aspirin users, the maximum decline in platelet function between baseline and CPB decannulation was related to postoperative blood loss ( $r = 0.308$ ;  $P = 0.037$ ). In multivariate analysis, a reduced ADP platelet function prior to surgery remained associated with postoperative blood loss ( $r = -0.239$ ;  $P = 0.012$ ).

Reduced ADP-induced platelet aggregation at baseline is associated with increased postoperative blood loss in high-risk cardiac surgery patients.

## Introduction

Hemostatic impairment is common following cardiac surgery with cardiopulmonary bypass (CPB) and peri-operative coagulopathic bleeding is a clinically important complication that is associated with increased morbidity and mortality [1,2]. Despite the significant use of blood transfusion products in patients undergoing high-risk cardiac surgery, it is not clear which coagulation parameters are affected most during surgery and what triggers for hemostatic therapy are appropriate. In order to reduce bleeding real time monitoring of perioperative changes in hemostasis are essential. For this reason, point of care coagulation tests might be useful to optimize patient blood management [3,4].

In cardiac surgery, platelet function is affected by multiple factors, including patient and procedural characteristics. Antiplatelet therapy (APT) is well established in the long term treatment of coronary disease and routinely continued during cardiac surgery to reduce the risk of perioperative myocardial infarction [5]. However, a recent meta-analysis showed that APT use during surgery contributes to blood loss [6], especially in patients with dual APT [7]. During surgery, the exposition of blood to CPB leads to hemodilution and activation of coagulation with a subsequent reduction in platelet count (PC) and function [8,9]. Additionally, shed blood from the operative field is washed by the cell salvage system and red blood cells are returned to the patient, deprived of platelets and other coagulation factors. After the surgical procedure, continuous blood loss and hypothermia may further decrease platelet function.

Monitoring of perioperative platelet function is traditionally done by standard laboratory tests that involve a long turnaround time, limiting its use in cardiac surgery. Visco-elastic point-of-care (POC) monitoring with thromboelastography (TEG) or thromboelastometry (ROTEM) is increasingly used in cardiac surgery patients and has been associated with a reduction in the number of patients with allogeneic blood transfusion and bleeding complications [10-11]. However, diagnosing platelet dysfunction with these tests is limited because current routine visco-elastic tests are blind to the effect of APT. Point-of-care platelet function testing with whole blood multiple electrode aggregometry (MEA) can rapidly detect and quantify changes in platelet function and could contribute to optimal patient blood management.

The present study was initiated to gain further insight into the possible association between perioperative POC platelet function testing and postoperative blood loss in patients undergoing high-risk cardiac surgery.

## Methods

### *Study design and population*

Prospective observational single center cohort study of adult patients undergoing complex cardiac surgery between april 1st 2015 and may 1st 2016. Inclusion was restricted to patients  $\geq 18$  years scheduled for coronary artery bypass grafting (CABG) in combination with open heart valve surgery or isolated open heart double or triple valve surgery. Study exclusion criteria were hereditary bleeding disorders, cardiac reoperation, GIIb-IIIa inhibitor use and pregnancy. The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethical committee (Medical research Ethics Committee United, Ref: NL51434.100.14). All patients provided written informed consent.

### *Data collection*

Data regarding medical history and preoperative drug therapy were registered at the outpatient anesthesia clinic during routine preoperative screening. Standard laboratory hematology and coagulation parameters were retrieved from the hospital electronic patient records. Information regarding surgery and cardiopulmonary bypass (CPB), perioperative blood product transfusion and postoperative blood loss were collected from computerized perioperative medical records (Metavision Suite 5.46.44, iMDsoft®, Düsseldorf, Germany).

### *Outcome measures*

The primary outcome measure was postoperative chest tube output during 24 hours after ICU arrival, further denominated as postoperative blood loss. Secondary outcomes included units of erythrocyte concentrate (EC), plasma or platelet transfusion, reoperation for bleeding until 24 hours after surgery and hospital mortality.

### *Study procedures*

#### *Blood sampling*

Blood samples were collected using the radial arterial line at all four time points: (i) baseline, after induction of anesthesia, (ii) during CPB, after initiation of rewarming from hypothermia, (iii) after CPB decannulation and administration of protamine and (iv) arrival at the ICU.

Whole blood was sampled in K2EDTA and 3.2% sodium citrate tubes (BD Vacutainer) for standard blood tests including hemoglobin, hematocrit, PC, fibrinogen (Clauss), protrombin time (PT) and INR (international normalized PT ratio). Standard blood tests were performed at the hospital laboratory.

#### *Multiple electrode impedance aggregometry*

For platelet function analysis at all time points (i-iv) 3 ml blood was added with a syringe to non-vacuumized hirudin-containing blood sampling tubes (25  $\mu\text{g}/\text{ml}$ ). Hirudin tubes were sealed and kept in upright position at room temperature. Platelet function was assessed by MEA using the Multiplate® analyser (Roche Diagnostics, Rotkreuz, Switzerland) according to the manufacturer's instructions as previously described [12]. Platelet function was determined in response to stimulation with 4 specific receptor agonist reagents to test different pathways of aggregation; 1. arachidonic acid (AA), with a final concentration of 0.5 mmol/L (ASPI-test; assay to evaluate the thromboxane pathway), 2. adenosine diphosphate with a final concentration of 6.5  $\mu\text{mol}/\text{L}$  (ADP-test; assay to evaluate ADP-receptor function and thienopyridine efficiency), 3. collagen with a final concentration of 3.2  $\mu\text{g}/\text{ml}$  (COL-test, assay for quantitative collagen induced platelet aggregation) and 4. thrombin receptor activating peptide-6 with a final concentration of 32  $\mu\text{mol}/\text{L}$  (TRAP-test, assay for quantitative platelet function triggered by TRAP-6 via receptor PAR-1). The recorded aggregation was expressed as arbitrary aggregation units (AU) plotted against time (1U= 10 AU\*min). Platelet function point of care testing was performed by a research professional at the operation complex and all platelet function tests were conducted within 15 minutes after sampling.

### *Clinical management*

#### *Anesthesia management and cardiopulmonary bypass*

Antiplatelet therapy was routinely continued in patients using aspirin or P2Y12 receptor inhibitor (P2Y12i). In case of dual APT, P2Y12i use was discontinued 5 days prior to surgery if possible. Patients with P2Y12i continued or stopped < 5 days before surgery were included in the P2Y12i treatment group. Routine anesthetic care included induction of general anesthesia with midazolam, propofol, fentanyl and pancuronium and maintenance of anesthesia with propofol and fentanyl or remifentanyl. Vasoactive medications (e.g. norepinephrine, dopamine, milrinone and/or nitroglycerine) were used by discretion of the attending anaesthetist. All patients received antimicrobial prophylaxis (cefazolin) at induction of anesthesia followed by additional cefazolin every four hours for the duration of surgery. This antibiotic prophylaxis is extended postoperatively until a total of 5 doses in 24 hours in all patients with valve surgery. For cardiopulmonary bypass (CPB), non-pulsatile perfusion was used with a flow of 2.0 to 2.4 L/min/m<sup>2</sup>. All patients were anticoagulated with 300 IU/kg intravenous unfractionated heparin before CPB to achieve an adequate kaolin activated clotting time (ACT target >400 s). Additional heparin was given when needed to keep ACT above target during CPB. After aortic cross-clamping, cardiac arrest was initiated using a cold crystalloid St. Thomas cardioplegia solution (Pharmacy 'Haagse Ziekenhuizen', The Hague, The Netherlands). During CPB patients were cooled to a rectal temperature of 32°C to 34°C. Patients were weaned from CPB after rectal temperature reached 35.5°C. In general, intraoperative management targeted a hematocrit of 22%, SvO<sub>2</sub> of 65% and a MAP



of 50 mmHg during CPB. According to institutional customary process, heparin was reversed with protamine sulfate, 0.75 mg for every 100 U of previously administered heparin after CPB decannulation and a bolus of 1 gram of intravenous tranexamic acid was administered to all patients.

After surgery patients were transferred to the ICU and weaned from mechanical ventilation after exhibiting complete recovery from anesthesia, hemodynamic stability with no evidence of significant bleeding, core temperature  $> 36^{\circ}\text{C}$  and normal blood gas values. Patients were discharged from the ICU the following morning after surgery when meeting institutional discharge criteria.

#### *Bleeding and transfusions*

Blood loss was defined as 24 hour postoperative chest tube output and classified according to the universal definition of perioperative bleeding (UDPB)[13].

Blood product transfusion was performed according to a local transfusion protocol. The trigger for intraoperative EC transfusion of 1 or more units was a threshold hematocrit value below 0.20 during CPB or 0.25 after separation from CPB. After surgery, PRBC transfusion was dependent of clinical and haemodynamic status, with a hemoglobin value below 4.4 mmol/L as absolute trigger.

Plasma was transfused depending on the amount of blood loss, total number of transfused cell saver units, clinical signs of coagulopathy, and results of standard blood tests. Platelets were transfused for clinical signs of coagulopathy in combination with low PC ( $<100 \times 10^9/\text{L}$ ) or APT continuation prior to surgery. The final decision for blood product transfusion was always at the discretion of the attending physician. The surgeon, anaesthetist and ICU physician were blinded for the results of perioperative platelet function tests.

#### **Statistical analysis**

Sample size calculation was based on a multiple linear regression model including platelet function and three co-variables (power=0.80, alpha=0.05). Aiming at a medium effect size (Cohen's  $f^2 \geq 0.15$ ) the minimum required sample size was 84, allowing for missing data we aimed to include 100 patients.

Continuous data are presented as mean and standard deviation or median and interquartile range (IQR) for normally and non-normally distributed data. Categorical data are described as numbers and percentages. The Student's t-test and the Mann-Whitney U-test were used to compare independent continuous variables between groups for normally and non-normally distributed variables respectively; paired versions were used for within patient comparisons. The Friedman or Tukey test were applied when appropriate for repeated measurements. No adjustment for multiple statistical comparisons was used.

The univariate association between platelet function and postoperative blood loss was explored using linear regression analysis. The following variables were analysed: preoperative creatine, eGFR-MDRD4, APT use, age, gender, weight, body mass index, heparin dose, protamine dose, tranexamic acid dose, salvaged red cell volume reinfused, type of valve surgery, CPB time, RBC transfusion, plasma transfusion, platelet transfusion, and standard blood tests (hematocrit, fibrinogen, hemoglobin, cepho, INR, PT, PC and ACT test results). Multivariate analysis was performed with risk factors for postoperative blood loss ( $P < 0.1$ ). Missing values were not included in the analysis. For statistical analysis IBM SPSS software version 22.0 for Windows was used (IBM Corp., Armonk, NY, USA). A p value  $< 0.05$  was considered statistically significant.

## **Results**

#### *Study population*

A total of 100 patients were eligible for study participation and signed informed consent. One patient was excluded because valve replacement was omitted during surgery and only CABG was performed. The remaining 99 patients were included in the analysis (Table 1). A majority of patients was male and CABG combined with single valve surgery was most commonly performed. Fifty-nine patients (60%) were on antiplatelet therapy (APT) at time of surgery, nine patients with P2Y12i (eight patients with clopidogrel, one patient with ticagrelor) and five patients with dual APT. None of the patients had preoperative anemia and baseline coagulation tests were normal. Postoperative hospital mortality was 3%. In one patient death was the result of bowel ischemia, another patient died from deteriorating low cardiac output syndrome and one patient had a fatal circulatory arrest.

**Table 1.** Baseline characteristics

|                                       | Frequency (n) | missing |
|---------------------------------------|---------------|---------|
| <b>Patient characteristics</b>        |               |         |
| Male gender, n (%)                    | 71 (72 %)     | 0       |
| Age (yr)                              | 73 [67-77]    | 0       |
| Body mass index (kg m <sup>-2</sup> ) | 27 [25-29]    | 1       |
| Diabetes mellitus, n                  | 16            | 1       |
| Hypertension, n                       | 49            | 0       |
| Hypercholesterolemia, n               | 42            | 5       |
| Smoking, n                            | 25            | 0       |
| Acetylsalicylic acid, n               | 55            | 0       |

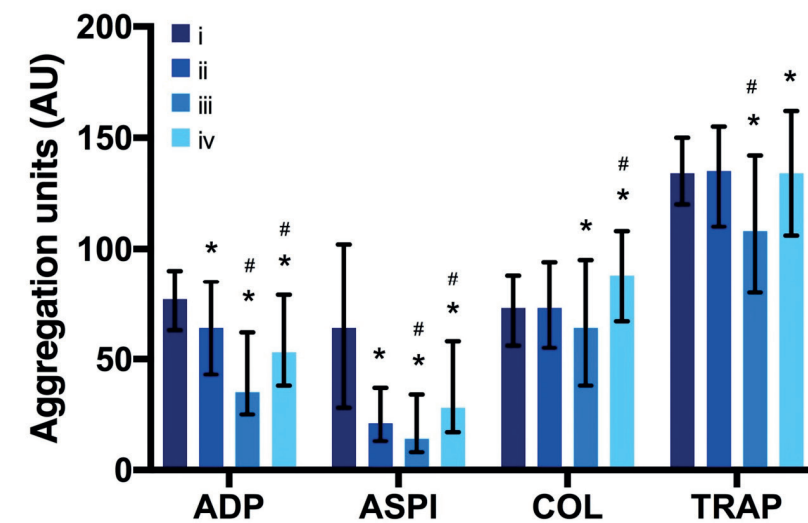
**Table 1.** Baseline characteristics (continued)

|                                         | Frequency (n)    | missing |
|-----------------------------------------|------------------|---------|
| P2Y <sub>12</sub> receptor inhibitor, n | 9                | 0       |
| <b>Type of surgery</b>                  |                  |         |
| CABG + single valve                     | 74               |         |
| CABG + multiple valve                   | 9                |         |
| Multiple valve surgery                  | 16               | 0       |
| number of grafts, median (range)        | 1 (0-4)          | 0       |
| <b>Laboratory</b>                       |                  |         |
| Hemoglobin (mmol/l)                     | 7.6 [6.9-8.1]    | 0       |
| Hematocrit (l/l)                        | 0.36 [0.33-0.38] | 0       |
| Platelet count (x10 <sup>9</sup> /l)    | 193 [162-222]    | 0       |
| PT-INR                                  | 1.1 [1.0-1.3]    | 0       |
| Fibrinogen (g/l)                        | 3.1 [2.7-3.6]    | 0       |
| ADP (AU)                                | 77 [63-90]       | 2       |
| ASPI (AU)                               | 64 [28-102]      | 2       |
| COL (AU)                                | 73 [56-88]       | 3       |
| TRAP (AU)                               | 134 [120-150]    | 2       |
| <b>Procedural characteristics</b>       |                  |         |
| CPB time [min]                          | 150 [119-184]    | 0       |
| Salvaged red cell volume reinfused [ml] | 500 [300-900]    | 8       |
| Lowest body temperature (°C)            | 34.9 [34.2-35.7] | 2       |
| Temperature at ICU arrival (°C)         | 35.9 [35.5-36.2] |         |

Values are median [IQR], (range) or number (percentage) of patients. AU; Aggregation units, CPB; cardiopulmonary bypass.

#### Pre-operative, intra-operative and postoperative platelet function

Perioperative platelet function for all patients is displayed in Figure 1 (and supplementary Table 1). ADP and AA-induced platelet aggregation declined during CPB and after decannulation from CPB, with a maximum decrease of 55% for ADP test (35 vs 77 AU at baseline;  $P<0.001$ ) and 78% for ASPI test (14 vs 64 AU at baseline;  $P<0.001$ ). At the time of ICU arrival, platelet function was partially recovered for both receptors (31% decrease for ADP compared to baseline;  $P<0.001$  and 56% decrease for ASPI compared to baseline;  $P<0.001$ ).

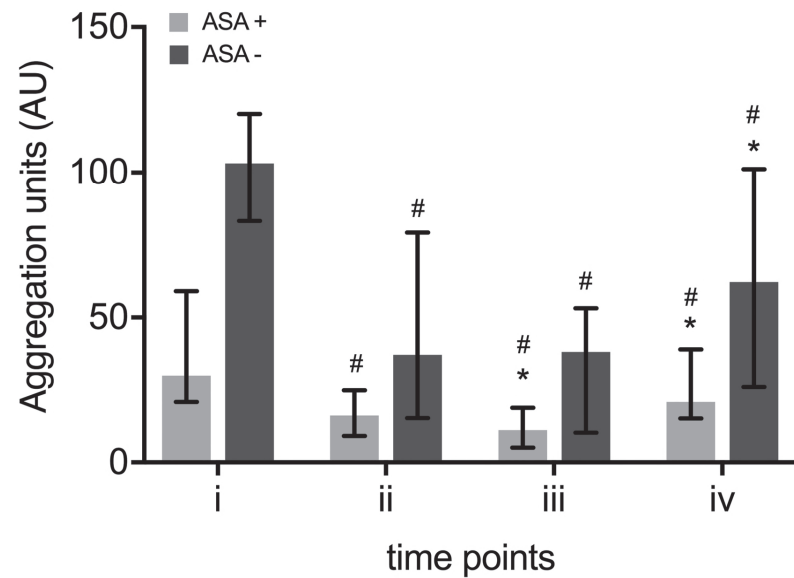
**Figure 1.** Perioperative platelet function.

(\*) significant change compared to previous time point, ( $P<0.05$ ).

(#) significant change compared to baseline, ( $P<0.05$ ). Baseline (i), during CPB (ii), after CPB decannulation and protamine (iii) and arrival at the ICU (iv). Values are median [IQR].

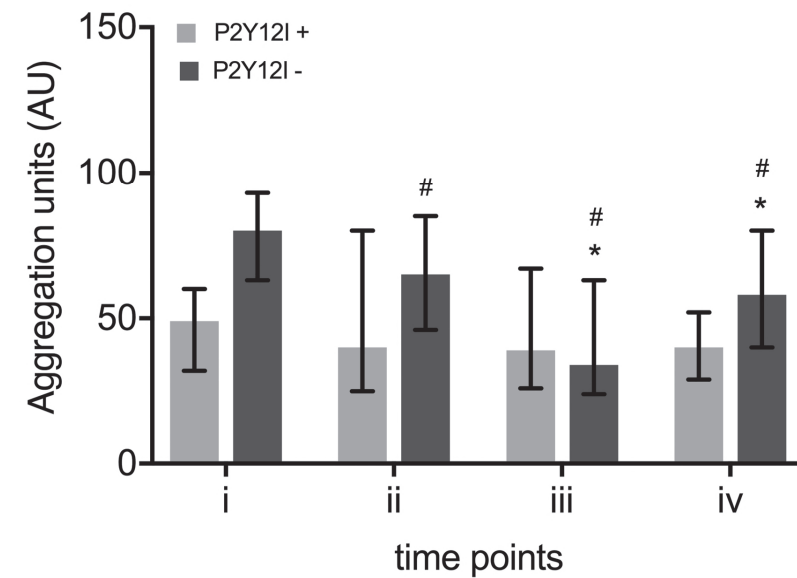
For COL and TRAP, platelet aggregation did not change during CPB and decreased mildly after CPB decannulation, with a maximum of 22% for COL (64 vs 73 AU at baseline;  $P=0.017$ ) and 19% for TRAP (108 vs 134 AU at baseline;  $P<0.001$ ). At the time of ICU arrival platelet function for TRAP and COL was fully recovered. MEA results for ADP, ASPI, COL and TRAP were correlated with PC at all time points (supplementary Table 2).

Figure 2 presents perioperative platelet function stratified according to type of APT use. In patients with aspirin, ASPI-test was lower at all time points compared to patients without aspirin (all timepoints  $P<0.001$ ) (Figure 2). During surgery platelet function in aspirin users declined below baseline with a maximum decrease of 63% after CPB decannulation (11 vs 30 AU at baseline;  $P<0.001$ ). Residual platelet reactivity (RPR), defined as ASPI-induced platelet aggregation  $>40$  AU, was present in 21/54 (39%) patients with aspirin at baseline and in none of the patients with aspirin after CPB decannulation ( $P<0.001$ ).

**Figure 2.** Perioperative platelet function for ASPI, according to ASA use.

(\*) significant change compared to previous time point, ( $P < 0.05$ ). (#) significant change compared to baseline, ( $P < 0.05$ ). Baseline (i), during CPB (ii), after CPB decannulation and protamine (iii) and arrival at the ICU (iv). Patients with ASA ( $n = 49$ ) and without ASA ( $n = 39$ ). Patients with P2Y12I ( $n = 9$ ) were not included in the analysis. Values are median [IQR].

In patients with a P2Y12 inhibitor, ADP-induced platelet aggregation was lower at baseline, during CPB and after arrival at ICU compared to patients without a P2Y12 inhibitor (Figure 3). During surgery platelet function did not change in P2Y12 inhibitor users. Two patients (22%) were non-responders (defined as ADP-induced platelet aggregation  $> 52$  AU).

**Figure 3.** Perioperative platelet function for ADP, according to P2Y12i use.

(\*) significant change compared to previous time point, ( $P < 0.05$ ). (#) significant change compared to baseline, ( $P < 0.05$ ). Baseline (i), during CPB (ii), after CPB decannulation and protamine (iii) and arrival at the ICU (iv). Patients with P2Y12i ( $n = 9$ ) and without P2Y12i ( $n = 88$ ). Values are median [IQR].

#### Postoperative blood loss and transfusions

Median postoperative blood loss was 550 [440-770] ml. None of the patients had massive bleeding class, one patient suffered from severe bleeding (based on surgical re-exploration), fifteen patients had moderate blood loss (801-1000 ml/12h), twelve patients had mild (601-800 ml/12h) and sixty-six patients had insignificant ( $< 600$  ml/12h) postoperative blood loss. Postoperative blood loss was similar between aspirin users and non-users (540 [415-775] ml vs 535 [423-698] ml;  $P = 0.76$ ). Patients with a P2Y12 inhibitor had higher blood loss (770 [595-970] ml vs 540 [430-725] ml for non-users;  $P = 0.017$ ) despite an increased rate of platelet transfusion (67% in P2Y12 inhibitor users vs 18% in non-users;  $P = 0.038$ ).

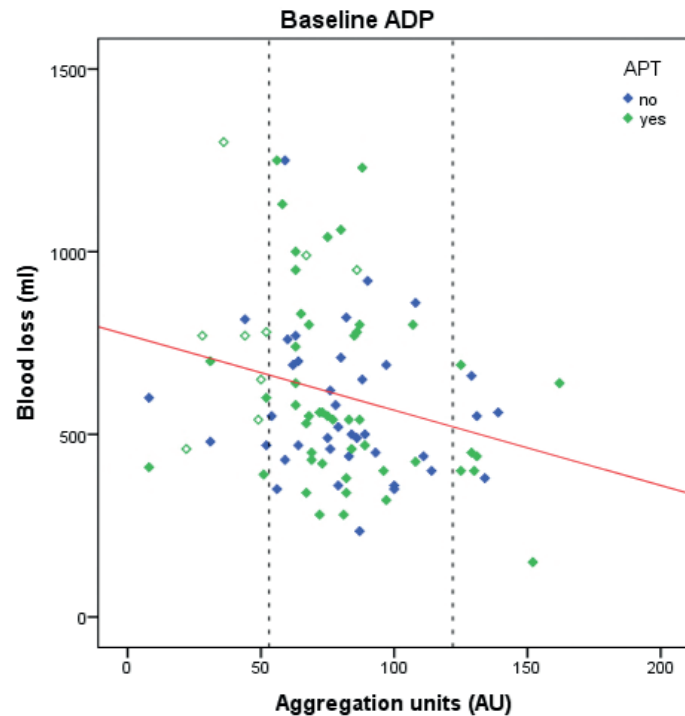
Fifty-seven (58%) patients had at least one blood transfusion. Blood transfusion consisted of EC in 46 patients, plasma in 21 patients and platelets in 30 patients. There was no difference in postoperative blood loss between patients with and without a blood transfusion (550 [435-790] ml vs 550 [450-695] ml respectively;  $P = 0.490$ ). At baseline, ADP levels were associated with platelet transfusion ( $r = -0.298$ ;  $P = 0.003$ ) and plasma transfusion ( $r = -0.246$ ;  $P = 0.015$ ), ASPI levels were associated with EC transfusion

( $r=0.213$ ;  $P=0.036$ ). Platelet count increased significantly after intraoperative platelet transfusion, but platelet function did not (ADP 33 before transfusion versus 39 AU after transfusion,  $P=0.627$ ).

#### Platelet function and postoperative blood loss

A linear relationship was present between ADP-induced platelet aggregometry at baseline and postoperative blood loss ( $r = -0.249$ ;  $P=0.015$ ), meaning that patients with a reduced platelet function prior to surgery had more postoperative blood loss (Figure 4).

**Figure 4.** Relationship between platelet function for ADP at baseline and postoperative blood loss.



Normal values according to manufacturer between dashed lines. APT; green, P2Y12i use; green border and no APT; blue.

This relationship remained present after excluding patients with a P2Y12 inhibitor ( $r = -0.214$  for non-users;  $P=0.047$ ) and after adjustment for multiple risk factors for postoperative bleeding (Table 2). Fibrinogen and hematocrit levels were associated with blood loss at baseline ( $r = -0.225$ ;  $P=0.019$  and  $r = -0.218$ ;  $P=0.032$  respectively). This relationship was lost in multivariable analysis (Table 2).

**Table 2.** Linear regression analyses for postoperative blood loss.

| Factor                                | univariate             |          | multivariate |          |
|---------------------------------------|------------------------|----------|--------------|----------|
|                                       | Regression coefficient | <i>p</i> | Coefficients | <i>p</i> |
| Age (years)                           | 0.091                  | 0.371    |              |          |
| Gender (male)                         | 0.346                  | <0.001   | 0.311        | 0.001    |
| Body mass index (kg m <sup>-2</sup> ) | -0.220                 | 0.030    | - 0.210      | 0.027    |
| Preoperative ADP (AU)                 | -0.249                 | 0.015    | - 0.239      | 0.012    |
| Preoperative hematocrit (l/l)         | 0.218                  | 0.032    |              |          |
| Preoperative fibrinogen (g/l)         | -0.212                 | 0.039    |              |          |
| eGFR-MDRD4 (ml/min)                   | 0.213                  | 0.035    |              |          |

In aspirin users, the maximum decline in ASPI-test between baseline and CPB decannulation was related to postoperative blood loss ( $r = 0.308$ ;  $P = 0.037$ ). However, this relationship was lost in the multivariate analysis. No linear statistical significant relationship was present for COL- and TRAP-induced platelet aggregation and postoperative blood loss at any of the perioperative time points.

## Discussion

This observational cohort study used POC platelet function testing to identify patients at risk for postoperative bleeding in high-risk cardiac surgery patients and reports several new findings. First, a reduced ADP induced platelet aggregation at baseline is associated with increased postoperative blood loss irrespective of dual APT use. Second, during surgery, AA-induced platelet aggregation declines in patients with and without aspirin with more than 50% compared to baseline but this is not associated with increased blood loss after adjustment for other risk factors. Third, patients with P2Y12 inhibitor use have higher postoperative blood loss despite an increased rate of platelet transfusion.

Others have studied the influence of POC platelet function testing with MEA on postoperative blood loss in cardiac surgery patients. Petricevic and colleagues performed preoperative MEA ADP and ASPI testing in 211 CABG patients in a prospective observational study [14]. Patients were divided into four groups according to APT management and characterized as excessive bleeding if postoperative blood loss exceeded the 75th percentile of distribution. Similar to our results a reduced preoperative ADP induced platelet function was associated with postoperative blood loss. Additionally, Petricevic and colleagues showed that preoperative AA induced platelet function was mildly associated with postoperative blood loss ( $r = -0.170$ ;  $P=0.014$ ). However, in their cohort 44% of patients with aspirin had dual APT with increased risk of bleeding, which may explain the correlation between ASPI test and blood loss. Also, multivariate analysis



was not performed. In our cohort, only 5 patients had dual APT and not preoperative ASPI values but the maximum decline in AA-induced platelet function between baseline and CPB decannulation was related to postoperative blood loss ( $r= 0.308$ ;  $P= 0.037$ ). After adjustment for multiple risk factors this association was lost.

Schimmer and others retrospectively analyzed pre- and postoperative ADP, AA and TRAP induced platelet function in 223 patients undergoing various cardiac surgery procedures [15]. MEA results were categorized into abnormal and normal results, based on reference ranges for healthy subjects [16]. In contrast to our findings preoperative abnormal platelet function was not associated with increased postoperative blood loss. However, in Schimmer's study preoperative MEA values were part of platelet transfusion management. Patients with preoperative abnormal ADP induced platelet function had increased platelet transfusion rates and the lack of an association between platelet function and postoperative blood loss is likely the result of early intervention with platelet transfusion in patients with abnormal MEA values.

A recent prospective clinical study by Malm and colleagues in 90 CABG patients with dual APT (aspirin continued and ticagrelor discontinued <5 days) showed that preoperative ADP induced platelet function was lower in subjects with severe postoperative blood loss [17]. Patients with dual APT had an increased risk of bleeding complications. The optimal ADP cut-off value to identify patients at risk of severe bleeding was 22 U (sensitivity 76% and specificity 75%). Although the number of patients with DAPT was small in our study ( $n=5$ ), P2Y12 users had increased postoperative blood loss, despite an increased rate of platelet transfusion.

Cardiopulmonary bypass associated coagulopathy is generally considered an effect of platelet dysfunction and has been linked to adverse outcome [18-20]. The results of our study confirm that platelet dysfunction peaks directly after CPB decannulation. However, no association was found with blood loss after adjustment for other risk factors. This may be explained by the reversibility of CPB induced platelet dysfunction [21]. Poucke and colleagues investigated time-related platelet function in CABG patients with CPB. Platelet function was measured with MEA at baseline, after CPB decannulation and 24 hours postoperatively. Similar to our results, a significant platelet dysfunction was present after CPB that recovered within 24 hours. These findings suggest that platelet transfusion directly after CPB should be reserved for patients with excessive bleeding as early platelet function recovery is likely to contribute to postoperative hemostasis and reduced postoperative bleeding.

Using preoperative laboratory tests to identify patients at increased risk for bleeding offers possibilities to initiate preventive measures. However, the reported correlations in literature for well known risk factors, such as preoperative fibrinogen and hematocrit, are only moderate [22-23]. These results were confirmed in our study (Table 2). Similarly,

the correlation between preoperative ADP measurements and blood loss in our study was moderate. Although this correlation remained present after adjustment for multiple risk factors, these findings indicate that the clinical value of preoperative blood tests to identify patients at risk for bleeding is limited. This is likely the result of several other factors, such as hemodilution due to CPB use and procedural time, that are known to have important impact on postoperative blood loss.

Besides an effect on platelet aggregation several other hematological changes occur during cardiac surgery that influence hemostasis and complicate the diagnosis of perioperative coagulopathy [24]. As a result, the additional value of POC platelet function testing is mainly present during preoperative assessment, which was confirmed in our study. Recently published international guidelines recommend the use of POC platelet function testing for patients with DAPT prior to surgery [25]. Our results show that in high risk cardiac surgery patients reduced ADP induced platelet aggregation at baseline is also a risk factor for postoperative bleeding in patients without dual APT.

Aspirin therapy in CABG patients improves early graft patency and reduces postoperative cardiac events [26]. Despite these benefits, prior reports suggest that RPR is common in preoperative cardiac surgery patients [27]. This is confirmed in our study cohort as more than one-third of patients had RPR prior to surgery. The interpatient variability in platelet function suggests that decision making in postoperative APT management should be personalized according to drug specific platelet function tests to reduce risk of adverse postoperative cardiovascular events. In future studies, the additional value of POC platelet function testing to diagnose preoperative RPR and support optimal postoperative APT should be analysed.

Some limitations have to be taken into account for our study. First, platelet function tests were performed using MEA, which is one of several methods to assess platelet function. Second, subgroup analysis in patients with dual APT was inappropriate because we studied very few patients with dual DAPT due to our policy to discontinue preoperative P2Y12i whenever possible. Third, blood transfusion management was left at the discretion of the attending physician and may have influenced the association between POC MEA results and postoperative blood loss.

In conclusion, reduced ADP induced platelet aggregation at baseline is associated with increased postoperative blood loss in high-risk cardiac surgery patients. Point-of-care platelet function is primarily of additional value prior to surgery to identify patients at risk for bleeding.

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**Supplementary Table 1.** MEA results for ADP, ASPI, COL, TRAP and Platelet (PLT) count

|                                    | Baseline [i]  | CPB [ii]      | postbypass [iii] | ICU [iv]      |
|------------------------------------|---------------|---------------|------------------|---------------|
| ADP [U]                            | 77 [63-90]    | 64 [43-85]    | 35 [25-62]       | 53 [38-79]    |
| ASPI [U]                           | 64 [28-102]   | 21 [13-37]    | 14 [8-34]        | 28 [17-58]    |
| COL [U]                            | 73 [56-88]    | 73 [55-94]    | 64 [38-95]       | 88 [67-108]   |
| TRAP [U]                           | 134 [120-150] | 135 [110-155] | 108 [80-142]     | 134 [106-162] |
| PLT count<br>[x10 <sup>9</sup> /l] | 193 [162-222] | 126 [105-156] | 91 [73-112]      | 113 [92-139]  |

Data are presented as median [IQR]

Time points; baseline (i), during CPB (ii), after CPB decannulation and protamine (iii) and arrival at the ICU (iv).

**Supplementary Table 2.** Association between platelet count and ADP, ASPI, COL and TRAP dependent platelet function test

|     | ADP     | p      | ASPI    | p      | COL     | p      | TRAP    | p      |
|-----|---------|--------|---------|--------|---------|--------|---------|--------|
| I   | r=0.402 | <0.001 | r=0.239 | 0.018  | r=0.255 | 0.012  | r=0.382 | <0.001 |
| ii  | r=0.586 | <0.001 | r=0.434 | <0.001 | r=0.174 | 0.09   | r=0.382 | <0.001 |
| iii | r=0.559 | <0.001 | r=0.533 | <0.001 | r=0.339 | 0.001  | r=0.383 | <0.001 |
| Iv  | r=0.317 | 0.001  | r=0.437 | <0.001 | r=0.353 | <0.001 | r=0.316 | 0.001  |

Time points; baseline (i), during CPB (ii), after CPB decannulation and protamine (iii) and arrival at the ICU (iv).

**Supplementary Table 3.** Correlations between MEA results and blood loss

|     | ADP      | p     | ASPI     | p     | COL      | p     | TRAP     | p     |
|-----|----------|-------|----------|-------|----------|-------|----------|-------|
| I   | r=-0.249 | 0.015 | r=-0.086 | 0.404 | r=-0.141 | 0.173 | r=-0.048 | 0.642 |
| ii  | r=-0.176 | 0.086 | r=-0.116 | 0.262 | r=-0.046 | 0.661 | r=0.015  | 0.881 |
| iii | r=-0.127 | 0.219 | r=-0.080 | 0.438 | r=-0.032 | 0.757 | r=-0.036 | 0.730 |
| Iv  | r=-0.062 | 0.546 | r=-0.051 | 0.618 | r=0.116  | 0.257 | r=0.149  | 0.143 |

Time points; baseline (i), during CPB (ii), after CPB decannulation and protamine (iii) and arrival at the ICU (iv).





# Chapter 4

## Association of plasma fibrinogen and thromboelastography with blood loss in complex cardiac surgery

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## Abstract

Postoperative coagulopathic bleeding is common in cardiac surgery and is associated with increased morbidity and mortality. Ideally, real-time information on in-vivo coagulation should be available. However, up to now it is unclear which perioperative coagulation parameters can be used best to accurately identify patients at increased risk of bleeding.

The present study analyzed the associations of perioperative fibrinogen concentrations and whole blood viscoelastic tests with postoperative bleeding in 89 patients undergoing combined cardiac surgery procedures. Postoperative bleeding was recorded until 24 hours after surgery. Regression analyses were performed to establish associations between blood loss and coagulation parameters after cardiopulmonary bypass including a prediction model with known confounding factors for bleeding.

Coagulation tests show large changes over the perioperative course with the strongest coagulopathic deviations from baseline after cardiopulmonary bypass. After adjustment for multiple confounders, viscoelastic clot strength instead of fibrinogen concentration showed a similar performance for 24 hour blood loss and a better performance for 6 hour blood loss. This makes intraoperative viscoelastic testing a useful tool to strengthen early clinical decision-making with the potential to reduce perioperative blood transfusions.

## Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) is associated with coagulopathy and bleeding<sup>1</sup>. Patients with increased perioperative blood loss are at risk for postoperative morbidity and mortality<sup>2-5</sup>. The etiology of coagulopathy in cardiac surgery patients is multifactorial and varies according to the surgical phase (i.e. preoperative, intraoperative, postoperative). Relevant and immediately available information about perioperative hemostasis is necessary to target interventions that reduce bleeding. Ideally, real-time information on in-vivo coagulation should be available. However, up to now it is unclear which perioperative coagulation parameters can be used to accurately identify patients at increased risk of postoperative bleeding.

Plasma fibrinogen is a key coagulation factor<sup>6</sup> that has been associated with blood loss in cardiac surgery patients<sup>7-9</sup>. The Clauss fibrinogen assay is considered the gold standard to determine the plasma fibrinogen concentration, but the long turn-around time makes this test less suitable for timely clinical decisions. Point of care (POC) viscoelastic tests are available in the operating theatre for real time in-vitro coagulation assessment to guide patient blood management<sup>10-11</sup>. The use of POC viscoelastic testing has been associated with a reduction of inappropriate blood transfusions in cardiac surgery<sup>11-12</sup>. It remains, however, unclear whether this reduction was due to the use of POC viscoelastic testing or other factors such as behavioral changes<sup>13</sup>. Thus, the additional value of POC viscoelastic tests for postoperative bleeding in cardiac surgery patients is still unclear.

The present study aimed to analyze the associations of perioperative fibrinogen concentrations and POC viscoelastic tests with postoperative blood loss in patients undergoing complex cardiac surgery.

## Patients and Methods

### *Study design*

Recently, we studied the effects of perioperative platelet function on postoperative blood loss<sup>14</sup>. This was a prospective observational single center cohort study in patients undergoing elective surgery for combined coronary artery disease (CABG) and valvular heart disease or isolated multiple heart valve disease at a large tertiary hospital for cardiac surgery between april 1<sup>st</sup> 2015 and may 1<sup>st</sup> 2016. Ethical approval was provided by the local ethics committee (Medical Ethics Research Committee United, no. NL51434.100.14). One-hundred patients gave informed consent upon hospital admission. The study was performed in accordance with the Declaration of Helsinki. Now, we analyzed in the same population fibrinogen concentrations and results of viscoelastic testing. In short, routine laboratory coagulation tests and viscoelastic coagulation tests were performed at four perioperative time points with the intention to investigate their

usefulness for the prediction of postoperative blood loss. For detailed information on clinical management and study methods we refer to our recent publication<sup>14</sup>.

#### *Data collection and study procedures*

Data regarding medical history, preoperative drug therapy and perioperative care was collected from electronic medical records by a member of the study team. Blood samples for coagulation tests were collected in all patients at four time points: (i) at baseline after induction of anesthesia, (ii) during CPB after initiation of rewarming from hypothermia, (iii) after CPB decannulation and administration of protamine and (iv) after arrival at the ICU. Routine coagulation assays were performed at the hospital laboratory and included: platelet count (PC), Clauss fibrinogen (STA-R Evolution analyzer, Diagnostica STAGO, Asnières sur Seine, France), prothrombin time (PT), and Cephotest. Cephotest is a heparin-sensitive aPTT and expressed as ratio prolongation compared to a normal pool aPTT. Whole blood for routine coagulation assays was sampled 3.2% sodium citrate tubes (BD Vacutainer). Viscoelastic Point of Care (POC) thromboelastography (TEG) assay (TEG 5000-analyzer, Haemonetics Inc., Braintree, MA, USA) was performed in non-anticoagulated whole blood at the operating theatre by a research professional within 5 minutes after sampling. Viscoelastic assays were performed with plain kaolin activated TEG at time points i, iii, iv and kaolin activated TEG with 2 IU heparinase at time point ii. Plain kaolin activated TEG data were collected as part of the study and were not available for the attending anesthetist or surgeon. Viscoelastic POC parameters included: kaolin initiated clotting time (R; min.), initial clot kinetics with K time (K; min), propagation rate of coagulation (angle; degrees) and clot strength with maximum amplitude (MA; mm).

#### *Blood transfusion and CPB management*

Blood transfusion was performed according to our local transfusion protocol with an intraoperative transfusion trigger for red blood cell (RBC) transfusions (hematocrit <0.20 l/l during CPB or <0.25 l/l after CPB). The RBC transfusion trigger on the intensive care unit (ICU) was a hemoglobin value (Hb) of less than 4.4 mmol/l (7.1 g/dl). Intraoperative transfusion of blood products to treat coagulopathy were based on kaolin-heparinase (ii) TEG parameter R time less than 10 minutes or  $\alpha$ -angle less than 45 ° for plasma and MA less than 45 mm for platelet concentrate. The postoperative decision to transfuse was left to the discretion of the ICU team. Coagulopathy after ICU arrival was defined as bleeding (>300 ml during 1st hour and >150 ml during 2nd-3th hours) in combination with coagulopathy. Postoperative triggers for platelet and/or plasma blood transfusion were low PC (<100x10<sup>9</sup>/l) or extended cephotest (>1.4) with clinical signs of coagulopathy. Coagulation factor concentrates were no part of the hemostasis management during the study period. Intra-operative cell salvage (CS) was routinely used during surgery. The volume of transfused autologous blood was registered as CS reinfused.

During surgery all patients were anticoagulated with 300 IU/kg intravenous unfractionated heparin before CPB to achieve a kaolin activated clotting time (ACT target > 400 s) and patients were cooled to a rectal temperature of 32°C to 34°C. Additional heparin was given when needed to keep ACT above target. After CPB, heparin was reversed with protamine sulfate; 0.75 mg for every 100 U of total heparin dose administered during CPB. Tranexamic acid (1-2 g) was administered to all patients.

#### *Outcomes*

The primary outcome measure was chest tube drainage volume (ml blood loss) at 24 hours after cardiac surgery. Secondary outcome parameters were blood loss after 6 hours, reoperation for bleeding until 24 hours after surgery, and hospital mortality.

#### *Statistical analysis*

As data from a previous study was used<sup>14</sup>, no formal sample size calculation was performed for this study. Normal distribution of variables was assessed with visual inspection of the histograms. Continuous data are presented as mean and standard deviation or median and interquartile range (IQR) for normally and non-normally distributed data. Categorical data are described as numbers and percentages. The Student's t-test and the Mann-Whitney U-test were used to compare independent continuous variables between groups for normally and non-normally distributed variables respectively. No adjustment for multiple testing was performed. Percentage of change for coagulation parameters between baseline and nadir values were calculated.

The correlation between TEG and fibrinogen and the correlation between coagulation parameters and postoperative blood loss were explored using Pearson's correlation coefficient. The association between blood loss and TEG after CPB was explored using linear regression analysis including a multivariable model with a priori selected confounding factors that were based on previously described risk factors for blood loss after cardiac surgery, including gender, body mass index, eGFR-MDRD4 (estimated glomerular filtration rate by modification of diet in renal disease 4 variable equation), baseline hemoglobin and CPB time<sup>15-19</sup>. All analyses were repeated using fibrinogen as the coagulation parameter. No interactions were investigated. To assess the discriminatory ability of coagulation parameters for postoperative blood loss, overall model performance was reported by the coefficient of determination R<sup>2</sup>. R<sup>2</sup> ranges from 0 to 1, with higher values indicating better model performance.

For statistical analysis IBM SPSS software version 24.0 for Windows was used (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant.



## Results

### Study population and outcomes

In the present study ten patients with a P2Y12 inhibitor were excluded, and 1 patient was excluded because information on postoperative blood loss was missing. As a result, 89 patients were included in the analysis. Baseline characteristics of the study population are presented in table 1. Sixty-two (69.7%) patients were male, median age was 73 [68-77] years, and the most commonly performed surgical procedure was CABG combined with single valve surgery. Median postoperative blood loss was 270 [190-400] ml after six hours and 540 [430-730] ml after 24 hours. Forty two patients (47.2%) received one or more allogeneic blood transfusions during surgery (table 2). Postoperative hospital mortality was 3.4% (n=3).

**Table 1.** Baseline patient and surgery characteristics

|                                         | Frequency (n)    | missing |
|-----------------------------------------|------------------|---------|
| <b>Patient characteristics</b>          |                  |         |
| Male gender, n (%)                      | 62 (70)          | 0       |
| Age (yr)                                | 73 [68-77]       | 0       |
| Body mass index (kg m <sup>-2</sup> )   | 26 [25-29]       | 1       |
| Diabetes mellitus, n                    | 13               | 1       |
| Hypertension, n                         | 42               | 0       |
| Hypercholesterolemia, n                 | 36               | 5       |
| Smoking, n                              | 25               | 0       |
| Acetylsalicylic acid, n (%)             | 49 (55)          | 0       |
| <b>Laboratory</b>                       |                  |         |
| Hemoglobin (mmol/l)                     | 7.5 [6.8-8.1]    | 0       |
| eGFR-MDRD4 (ml/min/1.73m <sup>2</sup> ) | 57 ± 7           | 0       |
| <b>Type of surgery</b>                  |                  |         |
| CABG + single valve                     | 66               | 0       |
| CABG + multiple valve                   | 9                | 0       |
| Multiple valve surgery                  | 14               | 0       |
| number of grafts, median (range)        | 1 (4)            | 0       |
| <b>Procedural characteristics</b>       |                  |         |
| Volume CS reinfused (ml)                | 500 [300-790]    | 0       |
| CPB time (min)                          | 150 [120-180]    | 0       |
| Lowest body temperature (°C)            | 34.8 [34.1-35.6] | 2       |
| Temperature at ICU arrival (°C)         | 35.9 [35.5-36.2] | 2       |

Values are median [IQR], mean ± or number (percentage). CABG; coronary artery bypass graft, CPB; cardiopulmonary bypass, CS; cell salvage, eGFR-MDRD4; glomerular filtration rate, ICU; intensive care unit.

**Table 2.** Allogeneic blood transfusions

| Transfusion | Intra-operative |    |              | Post-operative |    |              | Total |    |
|-------------|-----------------|----|--------------|----------------|----|--------------|-------|----|
|             | N               | %  | Median [IQR] | N              | %  | Median [IQR] | N     | %  |
| RBC         | 36              | 40 | 2 [1-2]      | 8              | 9  | 1 [1-1]      | 38    | 43 |
| Plasma      | 13              | 15 | 2 [2-3]      | 4              | 4  | 2 [2-3]      | 16    | 18 |
| TC          | 16              | 18 | 1 [1-1]      | 7              | 8  | 1 [1-1]      | 23    | 26 |
| Total       | 42              | 47 | 2 [1-3]      | 16             | 18 | 1 [1-2]      | 49    | 55 |

RBC; red blood cells, TC; thrombocyte concentrate. With transfusion; N; number of patients, %; percentage of patients and Median number of units in transfused patients.

### Fibrinogen concentrations and TEG results

Perioperative plasma fibrinogen concentrations are presented in table 3. In all patients plasma fibrinogen concentrations were lower during surgery compared to baseline. The maximum relative decrease in fibrinogen concentration was 41 [36-48] % with the lowest fibrinogen concentration occurred after CPB (1.7 [1.5-2.2] g/l). At ICU arrival, the median fibrinogen concentration was 1.8 [1.6-2.3] g/l and below lower reference limit of 2.0 g/l in 56% of patients.

Perioperative POC TEG results are presented in Table 3. TEG values deviated strongest from baseline after CPB. The maximum relative decrease after CPB was 16 [12-21] % for TEG-MA and 8 [0-16] % for TEG-angle. The correlations between fibrinogen and TEG values are presented in supplementary Table A. From all TEG variables, plasma fibrinogen concentrations were best correlated with TEG-MA, with the highest correlations at baseline (r=0.693, P<0.001) and after CPB (r=0.688, P<0.001).

**Table 3.** Results of routine and viscoelastic coagulation assays

|                                      | Baseline      | CPB           | Post-CPB       | ICU           |
|--------------------------------------|---------------|---------------|----------------|---------------|
| <b>Laboratory</b>                    |               |               |                |               |
| Platelet count (x10 <sup>9</sup> /l) | 193 [160-222] | 125 [105-158] | 90 [72-112]    | 112 [93-136]  |
| PT (s)                               | 15 [14-16]    | 23 [21-26]    | 22 [20-24]     | 19 [18-21]    |
| Cephotest                            | 1.0 [1.0-1.0] | 6.0 [6.0-6.0] | 1.3 [1.2-1.4]  | 1.2 [1.1-1.3] |
| Fibrinogen (Clauss; g/l)             | 3.1 [2.7-3.6] | 1.8 [1.6-2.3] | 1.7 [1.5-2.2]  | 1.8 [1.6-2.3] |
| <b>TEG assay</b>                     |               |               |                |               |
| R (min)                              | 7.1 [6.0-8.4] | 7.0 [5.8-8.4] | 7.4 [6.3-10.2] | 6.3 [5.2-7.5] |
| K (min)                              | 1.6 [1.4-1.8] | 1.8 [1.5-2.2] | 2.1 [1.8-2.7]  | 1.9 [1.6-2.2] |
| Angle (°)                            | 67 [63-71]    | 64 [59-69]    | 60 [56-66]     | 63 [58-68]    |
| MA (mm)                              | 70 [67-73]    | 59 [56-63]    | 58 [54-62]     | 60 [57-65]    |

PT; protrombin time, INR international normalized PT ratio, TEG; thromboelastography, R; kaolin initiated clotting time, K; clot kinetics, MA; clot strength with maximum amplitude.

*Coagulation tests and postoperative blood loss*

The correlations between coagulation test results and postoperative blood loss are presented in supplementary table B. At all perioperative time points, the fibrinogen concentration was correlated with 24h blood loss. The strongest correlation was present after ICU arrival ( $r=-0.291$ ,  $P=0.007$ ). The correlation between fibrinogen and 6h blood loss was only significant after ICU arrival. Several TEG values were correlated with postoperative blood loss. After CPB, TEG-MA was correlated with 6h and 24h blood loss ( $r=-0.324$ ,  $P=0.004$  and  $r=-0.267$ ,  $P=0.017$ , respectively). At ICU arrival, TEG MA was no longer associated with postoperative blood loss.

After adjustment for confounders, fibrinogen and TEG-MA after CPB had the strongest association with postoperative blood loss (table 4). Compared to fibrinogen, TEG-MA after CPB showed the best model performance for 6h blood loss ( $R^2=0.345$  compared to 0.278 for fibrinogen). Model performance for 24h blood loss was similar between TEG-MA and fibrinogen ( $R^2=0.268$  compared to 0.271 for fibrinogen).

**Table 4.** Adjusted associations for fibrinogen concentration and clot strength with postoperative blood loss

|                            | Multivariable model |        |        |        |                |        |        |       |
|----------------------------|---------------------|--------|--------|--------|----------------|--------|--------|-------|
|                            | 6h blood loss       |        |        |        | 24h blood loss |        |        |       |
|                            | Fibrinogen          |        | TEG-MA |        | Fibrinogen     |        | TEG-MA |       |
|                            | B                   | P      | B      | P      | B              | P      | B      | P     |
| Gender                     | 120.50              | 0.002  | 115.10 | 0.002  | 175.0          | 0.004  | 147.45 | 0.010 |
| BMI                        | -9.61               | 0.018  | -11.17 | 0.004  | -13.60         | 0.029  | -14.82 | 0.014 |
| eGFR                       | 2.18                | 0.315  | 2.97   | 0.141  | 3.10           | 0.351  | 4.59   | 0.147 |
| Hb                         | 18.50               | 0.331  | 6.38   | 0.760  | 18.93          | 0.516  | 8.10   | 0.805 |
| CPB time                   | -0.27               | 0.413  | -0.19  | 0.532  | -0.31          | 0.532  | -0.30  | 0.537 |
| Fibrinogen Post CPB        | -53.28              | 0.104  |        |        | -107.65        | 0.033  |        |       |
| TEG-MA Post-CPB            |                     |        | -7.43  | 0.005  |                |        | -9.28  | 0.022 |
| <b>R<sup>2</sup> model</b> | 0.278               | <0.001 | 0.345  | <0.001 | 0.271          | <0.001 | 0.268  | 0.001 |

B; unstandardized B, BMI; body mass index, CPB time; cardiopulmonary bypass time (min), eGFR; estimated glomerular filtration rate by modification of diet in renal disease 4 variable equation (ml/min), Hb; hemoglobin at baseline (mmol/l), TEG-MA; thromboelastography maximum clot strength.

**Comment**

This observational study in patients undergoing complex cardiac surgery showed that perioperative fibrinogen concentrations were associated with postoperative blood loss. After adjustment for multiple confounders, the strongest association between blood loss and fibrinogen was present after CPB. A multivariable model that included viscoelastic clot strength instead of fibrinogen concentration after CPB showed a similar performance for 24h blood loss and a better performance for 6h blood loss.

The results of our study including intraoperative coagulation tests before, during and after CPB and postoperative tests after ICU arrival provides a better understanding of the variations in perioperative TEG and fibrinogen levels. We confirmed that perioperative fibrinogen concentrations are associated with blood loss after cardiac surgery<sup>8, 20-21</sup>. In contrast to prior reports, we demonstrated that fibrinogen concentrations in the final surgical phase (after CPB) were best associated with 24 hour blood loss, after adjustment for multiple risk factors for postsurgical bleeding<sup>7, 9, 22-24</sup>. Furthermore, our data illustrated that coagulation test results show large changes over the perioperative course and that the strongest deviations from baseline were present after CPB. As a result, one could advocate to perform multiple coagulation assays to monitor hemostatic conditions after CPB. However, only TEG MA and plasma fibrinogen were significantly correlated with postoperative blood loss. The adjusted value of TEG MA instead of fibrinogen concentration after CPB was higher for 6h blood loss and the performance was similar for 24 h blood loss.

Viscoelastic tests measure multiple components of hemostasis, which allows for a rapid assessment of hemostasis. The results of our study confirmed that TEG MA after CPB was correlated with postoperative blood loss<sup>25-26</sup>. In comparison, another study showed that post CPB rotational thromboelastometry (ROTEM) was best associated with blood loss after including significant covariates (model performance  $R^2$  0.275)<sup>27</sup>. While it is difficult to compare studies due to variations in study design, and although TEG and ROTEM values are not interchangeable, both studies demonstrated that post CPB POC coagulation testing can be used to predict postoperative blood loss. As a result, intraoperative viscoelastic testing is a useful tool to strengthen early clinical decision-making and has the potential to reduce perioperative blood transfusions with consequently blood product cost savings<sup>28-30</sup>.

The following limitations should be considered. The data were prospectively and consecutively collected, but our sample size is limited. Furthermore, our patients had relatively low volumes of blood loss. Although different fibrinogen concentrations were correlated with blood loss, a linear relation cannot be assumed because hemostasis depends on a series of complex interactions between both cellular and protein components of coagulation<sup>31</sup>. Similar to previous literature reports, our models have



rather low  $R^2$  values, suggesting that while adjusted for known confounding risk factors for blood loss, much of the variation in blood loss is related to unobserved characteristics. Each surgical procedure is distinctively unique with several decisions and interventions that influence blood loss.

In conclusion, perioperative fibrinogen concentrations are associated with blood loss after cardiac surgery and a model including viscoelastic clot strength or plasma fibrinogen concentration after CPB can be used to predict postoperative blood loss. However, perioperative coagulopathy is characterized by constantly changing derangements of coagulation that can only be partly assessed with a single coagulation test.

Since TEG became daily routine during cardiac surgery in our hospital, the maximum clot strength after CPB has become the fastest and most useful parameter for guiding our hemostatic management until now. In the future, an improved understanding of the multiple features of coagulation dynamics may lead to new monitoring strategies and ameliorated standardization of global hemostasis assays to further support clinical decision making.

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**Supplementary Table A.** Correlation between fibrinogen and TEG clot kinetics

| TEG        | MA    |        | angle |        | K      |        | R      |       |
|------------|-------|--------|-------|--------|--------|--------|--------|-------|
|            | r     | P      | r     | P      | r      | p      | r      | p     |
| fibrinogen |       |        |       |        |        |        |        |       |
| I          | 0.693 | <0.001 | 0.438 | <0.001 | -0.397 | <0.001 | -0.220 | 0.049 |
| Ii         | 0.477 | <0.001 | 0.180 | 0.103  | -0.157 | 0.164  | 0.007  | 0.951 |
| Iii        | 0.688 | <0.001 | 0.492 | <0.001 | -0.436 | <0.001 | -0.209 | 0.066 |
| iv         | 0.669 | <0.001 | 0.411 | <0.001 | -0.368 | 0.001  | 0.126  | 0.255 |

TEG values R; kaolin initiated clotting time (min.), K; initial clot kinetics with K time (min), angle; propagation rate of coagulation (degrees) and MA; clot strength with maximum amplitude (mm). Timepoints (i) at baseline after induction of anesthesia, (ii) during CPB after initiation of rewarming from hypothermia, (iii) after CPB decanulation and administration of protamine and (iv) after arrival at the ICU.

**Supplementary Table B.** Correlation between coagulation parameters and postoperative blood loss

|                   | 6h Blood loss |       | 24h Blood loss |       |
|-------------------|---------------|-------|----------------|-------|
|                   | r             | P     | r              | P     |
| <b>Laboratory</b> |               |       |                |       |
| Fibrinogen        |               |       |                |       |
| i                 | -0.173        | 0.113 | -0.231         | 0.033 |
| ii                | -0.184        | 0.096 | -0.258         | 0.019 |
| iii               | -0.201        | 0.066 | -0.265         | 0.015 |
| iv                | -0.237        | 0.030 | -0.291         | 0.007 |
| Platelet count    |               |       |                |       |
| i                 | -0.097        | 0.374 | -0.114         | 0.291 |
| ii                | -0.121        | 0.267 | -0.187         | 0.085 |
| iii               | -0.159        | 0.149 | -0.153         | 0.163 |
| iv                | -0.070        | 0.514 | -0.101         | 0.346 |
| PT                |               |       |                |       |
| i                 | -0.055        | 0.612 | -0.099         | 0.360 |
| ii                | 0.080         | 0.468 | 0.045          | 0.681 |
| iii               | 0.055         | 0.620 | 0.013          | 0.908 |
| iv                | 0.054         | 0.659 | 0.075          | 0.536 |
| Cepho test        |               |       |                |       |
| i                 | -0.074        | 0.498 | -0.049         | 0.649 |
| ii                | 0.105         | 0.341 | 0.087          | 0.427 |
| iii               | 0.107         | 0.330 | 0.194          | 0.075 |
| iv                | 0.239         | 0.024 | 0.173          | 0.105 |
| <b>TEG assay</b>  |               |       |                |       |
| R                 |               |       |                |       |
| i                 | 0.128         | 0.246 | 0.172          | 0.117 |
| ii                | -0.016        | 0.886 | -0.061         | 0.579 |
| iii               | -0.023        | 0.839 | 0.035          | 0.755 |
| iv                | -0.138        | 0.203 | -0.235         | 0.028 |
| K                 |               |       |                |       |
| i                 | 0.173         | 0.117 | 0.216          | 0.050 |
| ii                | 0.146         | 0.188 | 0.272          | 0.013 |
| iii               | 0.090         | 0.431 | 0.101          | 0.374 |
| iv                | 0.043         | 0.693 | 0.000          | 0.998 |

**Supplementary Table B.** Correlation between coagulation parameters and postoperative blood loss (continued)

|       | 6h Blood loss |       | 24h Blood loss |       |
|-------|---------------|-------|----------------|-------|
|       | r             | P     | r              | P     |
| Angle |               |       |                |       |
| i     | -0.128        | 0.268 | -0.223         | 0.051 |
| ii    | -0.114        | 0.297 | -0.142         | 0.192 |
| iii   | -0.145        | 0.220 | -0.114         | 0.337 |
| iv    | -0.043        | 0.701 | -0.006         | 0.955 |
| MA    |               |       |                |       |
| i     | -0.217        | 0.048 | -0.216         | 0.050 |
| ii    | -0.171        | 0.119 | -0.183         | 0.096 |
| iii   | -0.324        | 0.004 | -0.267         | 0.017 |
| iv    | -0.110        | 0.317 | -0.094         | 0.393 |

Timepoints (i) at baseline after induction of anesthesia, (ii) during CPB after initiation of rewarming from hypothermia, (iii) after CPB decannulation and administration of protamine and (iv) after arrival at the ICU. PT; protrombin time, INR international normalized PT ratio. TEG values R; kaolin initiated clotting time (min.), K; initial clot kinetics with K time (min), angle; propagation rate of coagulation (degrees) and MA; clot strength with maximum amplitude (mm).

# **Part II**

## **Optimization of Graft Patency**





# Chapter 5

## Expert Analysis Therapies to Improve Vein Graft Patency After CABG

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*<https://www.acc.org/latest-in-cardiology/articles/2021/02/08/19/04/therapies-to-improve-vein-graft-patency-after-cabg>*

## Introduction

CABG is the most commonly performed cardiac surgical procedure worldwide and is preferred over percutaneous coronary intervention in patients with diabetes, reduced left ventricular ejection fraction, and three vessel and complex coronary artery disease.<sup>1</sup> Both arterial and saphenous vein grafts (SVG) can be used as conduits. Grafting the left anterior descending artery with the left internal thoracic artery is the gold standard in CABG because patency rates of this construction surpass SVG,<sup>2</sup> decrease the incidence of coronary reoperation, and improve survival.<sup>3,4</sup> Use of multiple arterial grafts, compared to only a single arterial graft, potentially provides long-term survival benefit in selected patients, but this remains a topic for discussion. As such, SVG remains the most used second conduit. An important and recalcitrant issue with the use of SVG remains vein graft failure. SVG failure rates range from 6% to 26% in the first year and are estimated to be 40-50% at 10 years after CABG.<sup>5,6</sup> Although SVG failure is not one-on-one related with adverse events, it is associated with anginal complaints, myocardial infarction, and long-term mortality after CABG.<sup>7-9</sup> This article discusses therapies to improve vein graft patency after CABG.

## Pathophysiology

SVG failure is a complex, multifactorial process. In the first month after CABG, mechanical factors and endothelial damage after surgery cause thrombotic occlusion.<sup>10</sup> Thereafter, until 1 year after CABG, the predominant process causing failure is intimal hyperplasia. Activated platelets trigger inflammation, causing smooth muscle cell migration from the media to the intima.<sup>11</sup> Both thrombosis and intimal hyperplasia provide the foundation for accelerated atherosclerosis, which is the principal cause of failure beyond the first year after CABG.<sup>12</sup>

## Technical Improvements

Technical improvements in SVG construction during CABG should be taken into account to improve vein graft patency. Regarding SVG harvest and preservation, early studies showed reduced patency rates for endoscopic vein harvesting compared with the conventional open harvest technique,<sup>13</sup> although a recent clinical trial that included 1,150 patients demonstrated no difference in major adverse cardiac events between the endoscopic-harvest group and the open-harvest group at a median follow-up of 2.8 years.<sup>14</sup> A small randomized controlled trial that included 54 patients demonstrated that the “no-touch technique” for SVG harvesting is superior to conventional harvesting and provides long-term patency rates that are comparable with the left internal thoracic artery.<sup>15</sup> SVG preservation in buffered solutions preserves

intimal integrity and can improve patency over grafts preserved in normal saline or blood-based solutions.<sup>16</sup> The appropriate length of the SVG is of importance to avoid both overstretching and kinking<sup>17</sup> and to preserve good target runoff.<sup>18</sup> Measuring intraoperative graft flow potentially identifies technical problems with the anastomoses and outflow targets, thus identifying the need for revision to improve early graft patency.<sup>19</sup> Some studies report sequential grafting providing inferior patency rates compared with single grafts,<sup>20</sup> although as many studies report no difference between both strategies.<sup>21</sup> Additionally, the risk for competitive (native coronary) flow causing reduction or even reversal of graft flow when grafting less than high-grade stenotic coronary arteries is less important in SVG than in arterial grafts and has to be taken in consideration when planning the revascularization.<sup>22</sup> Furthermore, competitive flow presumably has more impact in sequential grafts including Y- or T-constructions. Last, off-pump CABG has been reported to be associated with inferior patency rates,<sup>23</sup> although the current consensus is that in experienced hands, both off-pump and on-pump CABG attain excellent clinical outcomes in most patients.

## Postoperative Therapies

### *Lifestyle*

Lifestyle and behavioral factors are associated with risk for SVG failure. It is established that smoking<sup>18</sup> and hyperlipidaemia<sup>24</sup> are associated with SVG failure. Diabetes and probably hypertension influence graft occlusion after CABG,<sup>25,26</sup> and management of both decreases adverse clinical events.<sup>27,28</sup> Therefore, addressing risk factors by adequate secondary prevention remains the cornerstone of strategies to improve graft patency.

### *Antithrombotic Therapies*

SVG failure is up to five times more frequent in patients who are not treated with aspirin postoperatively,<sup>29</sup> and early postoperative use is associated with a reduced risk of death and ischemic complications, albeit with a slight increase in perioperative bleeding.<sup>30,31</sup> Therefore, guidelines recommend the preoperative or early postoperative use of aspirin.<sup>1,32,33</sup> More potent platelet inhibition could potentially provide better patency after CABG. However, studies investigating additional antithrombotic therapies after CABG have not provided definite conclusions. Addition of dipyridamole does not appear to improve SVG patency<sup>34</sup> and might lead to worse clinical outcomes after CABG<sup>35</sup>; therefore, it is not recommended.<sup>32,33</sup>

The addition of the P2Y<sub>12</sub> inhibitor clopidogrel to aspirin did not improve SVG patency in certain studies,<sup>5</sup> whereas in others it showed better SVG patency.<sup>36</sup> This may be due to 30% of patients having an inadequate inhibitory response to clopidogrel. Nonetheless, addition of the stronger P2Y<sub>12</sub> inhibitor ticagrelor to aspirin does not conclusively render better SVG patency,<sup>37,38</sup> although ticagrelor has hardly any variability in response.

Oral anticoagulation provides no improvement in SVG patency rates compared with aspirin,<sup>39,40</sup> but it causes more bleeding complications.<sup>40</sup> Guidelines therefore advise against routinely administering vitamin K antagonists in patients undergoing CABG without other indications for vitamin K antagonists.<sup>33</sup> There is currently only limited evidence concerning the effect of novel oral anticoagulants after CABG. The recent COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) CABG substudy (n = 1,448 patients) did not show an effect on graft patency of rivaroxaban plus aspirin compared with rivaroxaban monotherapy or aspirin monotherapy.<sup>41</sup>

#### Lipid-Lowering Therapies

Statin therapy reduces SVG occlusion rates as well as adverse events after CABG.<sup>42,43</sup> Guidelines recommend statin therapy in all patients with diagnosed coronary artery disease,<sup>1</sup> and in patients undergoing CABG, statin therapy is to be initiated preoperatively and continued for life.<sup>1</sup> Addition of ezetimibe in patients with prior CABG might amplify the clinical benefits of statin therapy,<sup>44</sup> as might treatment with PCSK9 inhibitors,<sup>45</sup> although more definite conclusions regarding the effect on SVG patency are awaited (NCT03900026, NCT03542110).

#### Other Therapies

Applying external support on the outer surface of the SVG by using an external stent targets factors such as high wall tension and disturbed flow patterns, which could lead to deterioration of the graft. This technique of external stenting is promising for preventing intimal hyperplasia and improving SVG patency.<sup>46</sup> New techniques like immunomodulation<sup>47</sup> and gene therapy<sup>6</sup> are currently being investigated.

## Conclusion

SVG failure is a complex, multifactorial process and is related to adverse outcomes after CABG. SVG occlusion rates are around 11% at 1 year after CABG. Technical factors during surgery and SVG construction are important in optimizing SVG patency. Secondary prevention aimed at preserving SVG patency should address risk factors for SVG failure and include antithrombotic therapy with aspirin and lipid-lowering therapies. Attempts to further improve SVG patency have resulted in the development of promising new targets, such as external stenting of the SVG.

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# Chapter 6

## **A Randomized, Double-Blind, Placebo-Controlled Trial Investigating the Effect Of Ticagrelor On Saphenous Vein Graft Patency In Patients Undergoing Coronary Artery Bypass Grafting Surgery - Rationale and Design of the POPular CABG trial.**

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## Summary

### Rationale

An estimated 15% of saphenous vein grafts (SVGs) occlude in the first year after coronary artery bypass grafting (CABG) despite aspirin therapy. Graft occlusion can result in symptoms, myocardial infarction (MI) and death. SVG occlusion is primarily caused by atherothrombosis, in which platelet activation plays a pivotal role. Evidence regarding the effect of stronger platelet inhibition on SVG patency after CABG is limited. Main objective of the POPular CABG trial is to determine whether dual antiplatelet therapy (DAPT) with aspirin plus ticagrelor improves SVG patency when compared to aspirin alone.

### Study

The POPular CABG is a randomized, double-blind, placebo-controlled, multicenter trial, investigating the effect of adding ticagrelor to standard aspirin therapy on the rate of SVG occlusion. A total of 500 patients undergoing CABG with  $\geq 1$  SVG are randomized to ticagrelor or placebo. The primary endpoint is SVG occlusion rate, assessed with coronary computed tomography angiography (CCTA) at one year. Secondary endpoints are stenoses and occlusions in both SVGs and arterial grafts and SVG failure at one year, defined as a composite of SVG occlusion on CCTA or coronary angiography, SVG revascularization, MI in the territory supplied by a SVG or sudden death. Safety endpoints are bleeding events at 30 days and one year.

### Conclusion

The POPular CABG trial investigates whether adding ticagrelor to standard aspirin after CABG reduces the rate of SVG occlusion at one year.

## Background

Saphenous vein graft (SVG) occlusion is reported in 6.8-26% of grafts in the first year after coronary artery bypass grafting (CABG)(1-3). Graft occlusion is correlated with angina pectoris, myocardial infarction (MI) and long term mortality, whereas reinterventions for SVG occlusions are related with an increased risk for major adverse cardiac events (MACE)(1,4-9). SVG occlusion occurs in three phases. In the first month, occlusion is mostly due to mechanical factors, low flow through the anastomosis (technical, competitive flow or small target vessel) and thrombus formation on the damaged endothelium, where platelet activation plays a pivotal role. Thereafter up until one year, SVG occlusion is caused by intimal hyperplasia, which is partially attributed to thrombocyte mediated factors as well. Accelerated atherosclerosis of the graft is the main cause of occlusion more than one year after CABG(10,11). The use of aspirin after CABG reduces graft occlusion, as well as MI, stroke, renal failure and mortality(12,13). However, not all patients respond to aspirin, and 10-90% of patients (transiently) display aspirin resistance after CABG(12,14,15). The precise mechanisms of aspirin resistance are still unclear, but contributing factors are increased platelet turnover, enhanced platelet reactivity and systemic inflammation(12).

Several studies have been conducted to determine whether outcomes after CABG can be improved with additional antiplatelet therapy. Adding dipyridole to aspirin after CABG was not effective in reducing graft occlusion, MI or death(16,17). Outcomes of several trials suggest positive effects of adding clopidogrel (a P2Y<sub>12</sub> inhibitor) to aspirin on graft patency and even MACCE, but these data are conflicting (18-23). Clopidogrel is associated with a variable response and approximately 25% of treated patients exhibit insufficient platelet inhibition(24,25). This variability in response to clopidogrel may explain the conflicting results of the effect of clopidogrel on SVG patency rates in the aforementioned trials. Better results might be achieved with ticagrelor, a different P2Y<sub>12</sub> inhibitor, since ticagrelor has no interindividual variability in response to the drug, attains full platelet inhibition faster, and is a stronger platelet inhibitor than clopidogrel(26). In patients with acute coronary syndromes (ACS), it is already recommended to continue dual antiplatelet therapy (DAPT) after CABG with a stronger platelet inhibitor, either prasugrel or ticagrelor, being the preferred choice(27). The data from randomized controlled trials evaluating the effect of ticagrelor on SVG patency are not definitive(28,29).

A randomized, double-blind, placebo-controlled trial evaluating the effect of ticagrelor plus aspirin compared to aspirin monotherapy on graft occlusion was performed by Saw et al. (28). The primary endpoint of graft occlusion occurred significantly less in the DAPT group compared to in the aspirin monotherapy group (28.0% vs. 48.3%,  $p=0.044$ ). However, as a result of slow recruitment, the study was terminated prematurely after randomizing only 70 patients. Although SVG occlusion rates were lower in the DAPT group, superiority of DAPT could not be proven. Moreover, graft patency was assessed three months after

CABG, as opposed to one year in our trial, hence not taking into account later graft failure in which thrombocyte mediated factors play a role as well. Zhao et al. randomized 500 patients undergoing CABG to aspirin monotherapy, ticagrelor monotherapy or DAPT with aspirin plus ticagrelor(29). The primary outcome was SVG patency one year after CABG, assessed with coronary computed tomography angiography (CCTA). SVG patency rates at one year were 88.7% in the DAPT group and 76.5% in the aspirin monotherapy group, the difference being statistically significant (absolute risk difference: 12.2% [95%CI, 5.2% to 19.2%];  $p < 0.001$ ). This trial was, in contrast to the POPular CABG trial, not placebo-controlled and conducted in an open-label fashion. Moreover, most patients underwent off-pump CABG, in which technical factors, thrombocyte (dys-) function, transient aspirin resistance and general thrombogenicity differ from conventional on-pump CABG. Therefore, results of the trial might not be generally applicable to patients undergoing CABG in Europe or the US where on-pump CABG is the dominant technique(27,30). Thus, these studies suggest that the postoperative addition of ticagrelor to aspirin after CABG may be associated with better outcomes, but that further studies are needed.

## Methods

### *Study objective*

The primary study objective is to determine whether adding ticagrelor to aspirin after CABG is superior to aspirin monotherapy in reducing SVG occlusions at one year. Various secondary endpoints include significant stenoses and occlusions in both venous and arterial bypass grafts and SVG failure at one year after randomization, defined as a composite of SVG occlusion on CCTA or coronary angiography, SVG revascularization (re-CABG or percutaneous coronary intervention), MI in the myocardial territory supplied by a SVG or sudden death. A secondary objective with regard to safety is to establish the rate of bleeding events at 30 days and one year after randomization. Prespecified subgroups in which the analyses will be performed are: age (<75 vs.  $\geq 75$  years), gender, Diabetes Mellitus, current smoking, left ventricular ejection fraction (good ( $\geq 50\%$ ) vs. moderately impaired (30-49%) vs. severely impaired (<30%)), GFR (<60 ml/min vs.  $\geq 60$  ml/min.), indication for CABG (chronic coronary syndrome (CCS) vs. ACS), previous myocardial infarction, number of grafts anastomoses (<4 vs.  $\geq 4$ ), pump-use (on-pump vs. off-pump) and time of first study drug dose ( $\leq 13$  hours after CABG vs. >13 hours, <24 hours vs.  $\geq 24$  hours and <48 hours vs.  $\geq 48$  hours).

Substudies of the POPular CABG aim to establish the levels of various laboratory markers (platelet reactivity as measured with the VerifyNow Aspirin assay, GDF-15) and their course in the year after CABG, and to establish their use in predicting SVG occlusion.

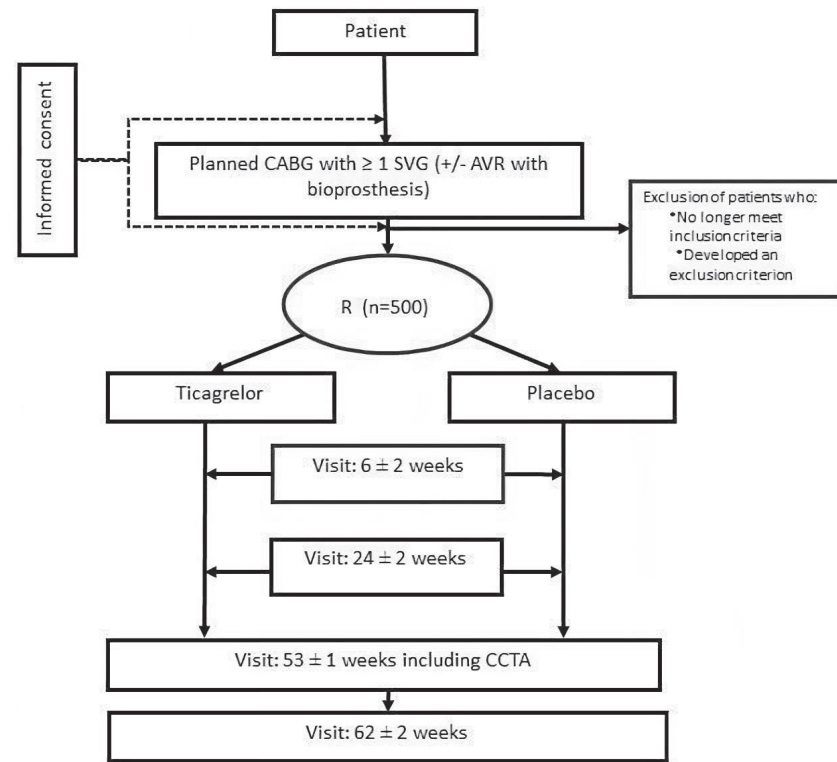
### *Study design, study population and follow-up*

The POPular CABG is a randomized, double-blind, placebo-controlled, multicenter trial. The trial is conducted in six centers in the Netherlands: the St. Antonius Hospital in Nieuwegein, Catharina Hospital in Eindhoven, Erasmus University Medical Center in Rotterdam, the Medical Spectrum Twente in Enschede, the Radboud University Medical Center in Nijmegen and the University Medical Center Groningen in Groningen. The study aims to include 500 patients who have undergone CABG with one or more SVGs. Since April 2018 we also included patients who underwent CABG +/- aortic valve replacement with a bioprosthesis, mainly because of slow recruitment and in an effort to include more patients per month. Patients aged older than 21 are eligible for inclusion when undergoing planned CABG, both for stable CCS and ACS. Major exclusion criteria are, amongst others, use or expected use of oral anticoagulation after CABG, a definite indication for use of a P2Y<sub>12</sub>-inhibitor or other antithrombotic agents after CABG, and contraindication for the use of aspirin or ticagrelor. Detailed in- and exclusion criteria are listed in Appendix A. Informed consent is obtained before undergoing CABG, until one week after CABG. After surgery, the patients undergo a second screening for in- and exclusion criteria (e.g. use of a SVG as a conduit) and only the patients that are still eligible are randomized. Randomization is conducted in a 1:1 allocation of treatment to ticagrelor or placebo with block randomization per study site. A web based, automated, randomization system is used.

Patients are evaluated at 6, 24, 53 and 62 weeks after CABG. Evaluation in week 6 is performed by telephone or through an outpatient hospital visit (patient preference), in week 24 by telephone, week 53 through an outpatient hospital visit, and in week 62 by telephone. A flowchart depicting the study procedures is shown in Figure 1.

Eligible patients are approached for the substudies of the POPular CABG trial. If the patient consents to blood and urine sampling, this is performed three times during the trial: before CABG, 72 hours (48 – 96 hours) after randomization and at one year.



**Figure 1:** Study flowchart of the main study

CABG: coronary artery bypasses grafting surgery  
 SVG: saphenous vein graft  
 CCTA: coronary computed tomography angiography  
 R: randomization  
 AVR: Aortic valve replacement

#### Study drug and concomitant medication

Ticagrelor and the matching placebo are provided by AstraZeneca, and repacked in blisters by the trial pharmacy of the St Antonius Hospital according to GMP guidelines. The study drug is started as early as possible after CABG (preferably within 48 hours), but only when postoperative chest tube drainage does not exceed 50ml/hour in the previous 5 hours and thrombocyte count is  $>100 \times 10^9/L$ . In those patients that have not used DAPT or discontinued DAPT before CABG, a loading dose of study drug (ticagrelor 180mg or placebo) is administered. The patients that receive DAPT until surgery start the use of study medication without receiving a loading dose. Administration of Carbasalate calcium 100mg or aspirin 80-100mg after CABG is started as soon as possible, according to local protocols.

If treatment with oral anticoagulation therapy becomes indicated during the study, the study medication is discontinued. All additional drug treatment is according to local protocols and the opinion of the treating physician.

#### Coronary Computed Tomography Angiography

A high-quality cardiac CT scan is performed in accordance with international (SCCT) guidelines, specified for local practices and available technology(31). Minimal requirements for the CT scanner consisted of a single- or dual-source 64-slice CT or higher. An axial scan mode is preferable over spiral mode and diastolic scans/reconstructions are preferred over systolic phases. The scans are performed by experienced cardiac CT services in the participating centers.

#### Outcome assessment

Per graft, the image quality, anatomy and graft obstruction is assessed. Segments of Y-grafts and jump grafts are considered as separate grafts. A graft is deemed patent when contrast fills the graft conduit and the circuit beyond the anastomosis. Graft stenosis is classified as none, <50%, 50-69%, 70-99% and 100%. A stenosis of 70% or more is considered significantly diseased. Graft occlusion is defined as 100% stenosis. Assessment of each CCTA is performed in a core lab, blinded for the patient's randomization result. Images are analyzed by two independent blinded reviewers. If there is no consensus between both viewers, a third blinded reviewer analyzes the images. The decision of the third reviewer is final. When coronary angiography has already been performed for clinical reasons at 35 - 54 weeks after randomization, the coronary angiography is used to assess patency correspondingly to the assessment of the CCTA and no CCTA is performed.

A blinded clinical endpoint committee (CEC) adjudicates all clinical efficacy and safety endpoints.

#### Study end points

Primary endpoint of the trial is the SVG occlusion rate at one year after randomization, as assessed with CCTA. Secondary efficacy endpoint of the trial is SVG failure at one year after randomization, defined as a composite of SVG occlusion on CCTA or coronary angiography, SVG revascularization, myocardial infarction in the myocardial territory supplied by a SVG or sudden death. Other secondary endpoints are significant SVG stenosis, arterial graft occlusion, and significant arterial graft stenosis as assessed with CCTA at one year after randomization. Safety end points are bleeding events 30 days and one year after randomization, classified according to the BARC-, TIMI- and PLATO-classification. Substudies of the POPular CABG trial intend to determine the levels and cut-off values for aspirin resistance by platelet function testing and GDF-15 during one year after CABG, and define the value of these laboratory markers in predicting SVG occlusions. All study endpoints and definitions are listed in Appendix B.

*Initial sample size*

The mean number of SVGs per patient was 2.4 in 2012 and 2013 in the St. Antonius Hospital in the eligible patient population. SVG occlusion rate was expected to be 15%. The estimated rate of SVG occlusion with the addition of ticagrelor is 10%. To detect a 5% reduction in SVG occlusion with 80% power using a 2-sided  $\chi^2$  test with an  $\alpha$  level of .05, 575 patients need to be randomized (1380 grafts) in this study. We estimated that 20% of the patients would either be lost to follow-up or would not undergo the CCTA. Therefore, our aim was to include 720 randomized patients (with an estimated total of 1728 SVGs) in this study.

*Intermediate adjustment of the sample size*

When became clear the trial would not be able to adjust to affirmed timelines and financial clauses, two options were available for the study team. Firstly, to discontinue the trial prematurely. Since new evidence recently became available(29) that suggested less patients than initially expected might be needed, the second option was to perform a provisional intermediate analysis of the sample size that was based on this new evidence. The study team chose for the second option and the provisional intermediate analysis of the sample size was performed in June 2018. The analysis was based on the expected rate of graft occlusion as mentioned in the recently published article(29), the average number of grafts per patient and the dropout rate in the POPular CABG trial. The analysis was conducted in blinded fashion. Assuming 10% reduction in SVG occlusion with 80% power using a 2-sided  $\chi^2$  test with an  $\alpha$  level of 0.05, with correction of 18% not undergoing CCTA and a mean number of 2.2 SVGs per patient, the sample size was adjusted to a total of 487 patients in this study. Because the incidences of graft occlusion might not be as high in the POPular CABG trial as in the DACAB trial, the Steering Committee decided to randomize a minimum of 487 patients but to extend the inclusion period to the end of the month (which was acceptable with timelines and finances of the trial) in an attempt to forestall lower incidences in the POPular CABG than in the DACAB trial, which was why ultimately 498 patients were randomized. The calculations have been presented to the Steering Committee, which approved the adjustment of the sample size on the 5<sup>th</sup> of September 2018.

*Statistical and analytical plans*

The primary analysis is performed according to the intention-to-treat principle. A secondary per-protocol analysis is performed, in which all patients are included who have received the study medication without interruption for more than 60 days or other major protocol violation, and have had a primary outcome assessment. It is expected that the occlusion of one SVG is correlated with the occlusion of other SVGs, especially with regard to “skip”- or “jump”-grafts. Mixed models are included in our analysis to explore this phenomenon. For secondary endpoints, the event rate curves are estimated using the Kaplan-Meier method. The two study groups are compared with the use of

hazard ratios and two-sided 95% confidence intervals and by using the log-rank test. The analysis is also performed in prespecified subgroups of patients.

*Funding and trial registration*

The POPular CABG trial is registered on ClinicalTrials.gov (NCT02352402) and is approved by the local ethics committee. The trial is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. Integrity of the study is warranted by a Data Safety Monitoring Board, and data will be monitored by an independent monitoring office. The trial is funded by AstraZeneca. AstraZeneca was not involved with study design and study processes, including site selection and management, or data collection and analysis. The authors are solely responsible for the design, data collection and conduct of this study, all study analyses, the drafting and editing of this paper and its final contents.

*Timeline and present status*

The POPular CABG started enrollment on 27 March, 2015. Six centers have recruited patients. On January 1st 2019, enrollment was concluded and 498 patients have been randomized in the trial. Completion of follow-up is expected in March 2020 and publication of results is expected in August 2020.

**Summary**

SVG occlusion occurs frequently and leads to symptoms, MI and death. As SVG occlusion in the first year after CABG is platelet mediated, stronger platelet inhibition during this period may increase graft patency rates. The POPular CABG is a multicenter, randomized, double-blind, placebo-controlled trial, designed to investigate the effect of the addition of ticagrelor on aspirin on SVG patency.

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## Appendix A: Inclusion and exclusion criteria

### Inclusion criteria

1. More than 21 years of age
2. Planned CABG with the use of 1 or more SVGs (+/- AVR with bioprosthesis)

### Exclusion criteria

1. Unable to give informed consent or a life expectancy of less than 1 year
2. Concomitant valve (excluding aortic bioprosthesis), aorta or rhythm surgery during the same session
3. Inability to undergo CCTA, in the investigator's opinion, for instance due to severe claustrophobia or contrast allergy
4. Use of oral anticoagulants (acenocoumarol, fenprocoumon, NOACs) and a contraindication for discontinuation of this medication or the expectation that the patient will have an indication for the use of these drugs after surgery
5. Placement of a drug-eluting stent in a coronary or cerebral artery within 6 months of CABG or placement of a bare-metal stent in a coronary or cerebral artery within 1 month of CABG
6. Use of other antiplatelet drugs than aspirin (clopidogrel, prasugrel, ticagrelor, dipyridamol, etc.) and a contraindication for discontinuation of this medication after CABG, according to the treating physician or the investigator
7. Women who are known to be pregnant, who have given birth within the past 90 days or who are breastfeeding
8. Premenopausal women without adequate contraception
9. Severe renal function impairment requiring dialysis
10. Moderate or severe hepatic impairment
11. Active malignancy with increase in bleeding risk, in the investigator's opinion
12. Use of strong inhibitors of CYP3A4 (e.g. ketaconazole, claritromycin, nefazodone, ritonavir, atazanavir)
13. Clinically significant out of range values for platelet count or haemoglobin at screening, in the investigator's opinion
14. Contraindication for the use of ticagrelor or aspirin (i.e. history of intracranial bleeding, high bleeding risk, previous allergic reaction), in the investigator's opinion



## Appendix B: definitions of end points

**Occlusion** is defined as 100% stenosis of a graft or coronary vessel.

**Significantly diseased** is defined as a stenosis of 70% or more of a graft or coronary vessel.

**SVG failure** is defined as a composite of SVG occlusion on CCTA or coronary angiography, SVG revascularization, myocardial infarction in the myocardial territory supplied by a SVG or sudden death.

**Myocardial infarction in the myocardial territory supplied by a SVG** is defined as any myocardial infarction (for the definition see Myocardial Infarction) without clear electrocardiographic or imaging evidence that the MI is restricted to territories not supplied by the SVG.

**Myocardial infarction** is defined as any of the following, in accordance with the ESC guidelines and the Third Universal Definition of Myocardial Infarction:

- **Spontaneous MI:** A rise and/or fall of cardiac biomarker values (preferably cardiac troponin (cTn)) occurring >48 hours following CABG, with at least two samples with a value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- **CABG-related myocardial infarction** is defined as cTn T or I values >10 x 99th percentile URL or CK-MB level >5 times the URL during the first 48 hours following CABG, occurring from a normal baseline cTn value ( $\leq$ 99th percentile URL). In addition, either (I) new pathological Q waves or new LBBB, or (II) angiographically documented new graft or new native coronary artery occlusion, or (III) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, should be present.

If the pre-CABG CK-MB or cTn T or I level is higher than the URL, one of the additional criteria below is required for the diagnosis of a CABG-related myocardial infarction:

- the demonstration of a falling cTn T or I or CK-MB level prior to the onset of the suspected event
- a subsequent peak of the cardiac biomarker at least 20% above the previous value obtained prior to the onset of the suspected event.

**Target vessel revascularization** is defined as revascularization, with CABG or PCI (balloon inflation with or without stent implantation), of a graft or a coronary vessel that provides blood flow to an artery that was grafted during the index CABG. An intervention in the LM after the index CABG that included a graft on the LAD or RCX counts as target vessel revascularization.

**All-cause mortality** is defined as death from any cause.

**Cardiac death** is defined as death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased

**Cardiovascular death** is defined as sudden death, death from acute myocardial infarction, arrhythmia, heart failure, cardiogenic shock, cerebrovascular event (ischemic stroke, hemorrhagic stroke ischemic stroke with hemorrhagic conversion, or intracranial hemorrhage), pulmonary embolism, peripheral arterial disease, bleeding and any death without another known cause.

### **Bleeding Academic Research Consortium (BARC) bleeding classification:**

Type 0: no evidence of 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. Examples include, but are not limited to, bruising, hematoma, nosebleeds, or haemorrhoidal bleeding for which the patient does not seek medical attention. Type 1 bleeding may include episodes that lead to discontinuation of medications by the patient because of bleeding without visiting a healthcare provider.

Type 2: any clinically overt sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least



one of the following criteria: First, it requires intervention, defined as a healthcare professional-guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (e.g., vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemocult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.

Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

- Bleeding Academic Research Consortium type 3a bleeding
- Any transfusion with overt bleeding
- Overt bleeding plus hemoglobin drop  $\geq 3$  to  $< 5$  g/dL (provided haemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
- Bleeding Academic Research Consortium type 3b bleeding
- Overt bleeding plus hemoglobin drop  $\geq 5$  g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive drugs
- Bleeding Academic Research Consortium type 3c bleeding
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
- Intraocular bleed compromising vision

Type 4: Coronary Artery Bypass Graft-related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of  $\geq 5$  U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output  $\geq 2$  L within a 24-hour period
- Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event

Type 5: Fatal bleeding

- Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:
- Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
- Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.
- The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other

### **TIMI bleeding classification:**

I) Major bleeding is defined as intracranial haemorrhage or a  $\geq 5$  g/dl decrease in the haemoglobin concentration or a  $\geq 15\%$  absolute decrease in the hematocrit.

II) Minor bleeding is defined as:

- Observed blood loss:  $\geq 3$  g/dl decrease in the haemoglobin concentration or  $\geq 10\%$  decrease in the hematocrit.
- No observed blood loss:  $\geq 4$  g/dl decrease in the haemoglobin concentration or  $\geq 12\%$  decrease in the hematocrit.

III) Minimal bleeding is defined as any clinically overt sign of haemorrhage (including imaging) that is associated with a  $< 3$  g/dl decrease in the haemoglobin concentration or  $< 9\%$  decrease in the hematocrit.

All TIMI definitions take into account blood transfusions, so that haemoglobin and hematocrit values are adjusted by 1 g/dl or 3%, respectively, for each unit of blood

transfused. Therefore, the true change in haemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows:  
 $\Delta\text{Hemoglobin} = [\text{baseline Hgb} - \text{post-transfusion Hgb}] + [\text{number of transfused units}]$ ;  
 $\Delta\text{Hematocrit} = [\text{baseline Hct} - \text{post-transfusion Hct}] + [\text{number of transfused units} \times 3]$ .

### **PLATO bleeding classification:**

- Major life-threatening
- Fatal
- Intracranial
- Intrapericardial with cardiac tamponade
- Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
- Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
- Requiring transfusion of  $\geq 4$  U whole blood or PRBCs

#### Other major

- Significantly disabling (eg, intraocular with permanent vision loss)
- Associated drop in hemoglobin of 3 to 5 g/dL
- Requiring transfusion of 2 to 3 U whole blood or PRBCs

#### Any major

Any one of the above criteria

#### Minor

Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)

#### Minimal

All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment



# Chapter 7

## **Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting (POPular CABG). A randomized, double-blind, placebo-controlled trial.**

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## Abstract

### Background

Approximately 15% of saphenous vein grafts (SVGs) occlude during the first year after coronary artery bypass graft surgery (CABG) despite aspirin use. The POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) investigated whether ticagrelor added to standard aspirin improves SVG patency at one year after CABG.

### Methods

In this investigator-initiated, randomized, double-blind, placebo-controlled, multicenter trial, patients with  $\geq 1$  SVGs were randomly assigned (1:1) after CABG to ticagrelor or placebo added to standard aspirin (80mg or 100mg). The primary outcome was SVG occlusion at one year, assessed with coronary computed tomography angiography, in all patients that had primary outcome imaging available. A generalized estimating equation model was used to perform the primary analysis per SVG. The secondary outcome was 1-year SVG failure, which was a composite of SVG occlusion, SVG revascularization, myocardial infarction in myocardial territory supplied by a SVG or sudden death.

### Results

Among 499 randomized patients, the mean age was  $67.9 \pm 8.3$  years, 87.1% were male, the indication for CABG was Acute Coronary Syndrome in 31.3%, and 95.2% of procedures used cardiopulmonary bypass. Primary outcome imaging was available in 219 patients in the ticagrelor group and 224 patients in the placebo group. The SVG occlusion rate in the ticagrelor group was 9.6% (44 of 457 SVGs) versus 10.1% in the placebo group (50 of 497 SVGs), OR 0.87 [95% CI: 0.49 -1.55];  $P=0.64$ . SVG failure occurred in 32 (12.9%) patients in the ticagrelor group versus 32 (13.0%) patients in the placebo group (hazard ratio 1.04, [95% CI: 0.63-1.69]).

### Conclusions

In this randomized, placebo-controlled trial, the addition of ticagrelor to standard aspirin did not reduce SVG occlusion at one year after CABG.

### Registration

ClinicalTrials.gov; : <https://www.clinicaltrials.gov>; registration number NCT02352402.

## Clinical Perspective

### What Is New?

- In this randomized, double-blind, placebo-controlled trial, the addition of ticagrelor to standard aspirin after coronary artery bypass grafting (CABG) did not reduce the rate of saphenous vein graft (SVG) occlusions at one year.
- This conclusion differs from other studies that investigated this research question.

### What are the Clinical Implications?

- This trial provides no reason to routinely start ticagrelor in patients undergoing CABG.
- In patients undergoing CABG for Acute Coronary Syndrome (ACS), ticagrelor is likely to provide antithrombotic and possibly pleiotropic benefits that have no relation to SVG patency.
- Therefore, the POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) does not refute the advice of the guidelines to continue ticagrelor in patients undergoing CABG for ACS.



## Introduction

Revascularization by coronary artery bypass grafting (CABG) can provide significant benefit in survival and quality of life<sup>1,2</sup>, and is favored above percutaneous coronary intervention in patients with diabetes, reduced left ventricular function and extensive multivessel coronary artery disease<sup>3</sup>. Grafting of the left anterior descending artery with the left internal mammary artery has become the standard of care, and better patency has been suggested with a second arterial conduit<sup>4</sup>. Saphenous vein grafts (SVGs) continue to be widely used as second grafts, even though 15% of SVGs occlude within the first year after surgery notwithstanding the use of aspirin<sup>5-7</sup>. SVG occlusion is associated with adverse outcomes such as angina pectoris, myocardial infarction (MI) and long-term mortality<sup>8-10</sup>. Although SVG occlusion is a complex, multifactorial process, platelets likely play an important role<sup>11,12</sup>. Stronger platelet inhibition could improve outcomes after CABG and current guidelines advise to continue both aspirin and a P2Y<sub>12</sub>-inhibitor in patients undergoing CABG for acute coronary syndrome (ACS)<sup>13,14</sup>. Addition of a P2Y<sub>12</sub>-inhibitor to aspirin may improve SVG patency, but prior studies in this area have provided conflicting results<sup>15-19</sup>. This may be partly attributable to the fact that the investigated P2Y<sub>12</sub>-inhibitor was clopidogrel, to which 30% of treated patients have an inadequate inhibitory response, and which is a less potent inhibitor than the currently recommended P2Y<sub>12</sub>-inhibitors (ticagrelor and prasugrel) after ACS<sup>20</sup>. The P2Y<sub>12</sub>-inhibitor ticagrelor is more potent and ensures more consistent response profiles<sup>21</sup>. We performed the randomized, double-blind, placebo-controlled, POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) to investigate the effect of ticagrelor on SVG patency.

## Methods

These (deidentified) clinical trial data, methods used in the analysis, and materials used to conduct the research can be requested by qualified researchers who engage in independent scientific research, and could be provided following review and approval of a research proposal. Data requests can be submitted at any time by contacting the corresponding author.

### Study design

The POPular CABG trial is an investigator-initiated, randomized, double-blind, placebo-controlled trial, performed at 6 Dutch study sites. The study design has been published<sup>22</sup>. The full study protocol can be found in the Data Supplement. The trial was approved by the medical ethics committee and by an institutional review board at each study site. All important changes during the course of the trial were advised upon by the steering committee and the trial was overviewed by a data safety monitoring board. Data monitoring was performed by an independent, external clinical research management company (Research Drive, Norg, The Netherlands).

### Patients

Patients >21 years who underwent planned CABG with ≥1 SVGs were eligible for inclusion. Major exclusion criteria were, among others, use or expected use of oral anticoagulation after CABG or a definite indication for use of a P2Y<sub>12</sub>-inhibitor or other antithrombotic agents other than aspirin after CABG. The inclusion and exclusion criteria are provided in Table I in the Data Supplement. All patients provided written informed consent before or after CABG.

### Randomization and blinding

Patients were randomly assigned, in a 1:1 ratio in a block size of 6 to ticagrelor or matching placebo (identical in appearance). Trial medication was issued by the hospital pharmacy in sequential order according to treatment assignments that were determined by a computer-generated random sequence stratified by center. The study remained blinded to all (patients, investigators, study personnel, outcome assessment teams, and those analyzing data) with the exception of the trial pharmacy, until study completion.

### Procedures

As soon as possible after successful CABG with SVG implantation, treatment with either ticagrelor 90 mg twice daily preceded by a loading dose if P2Y<sub>12</sub>-naïve or placebo was commenced. The first dose of the study medication was given at the time of randomization. The trial medication was continued until 1 year after randomization. Trial regimen included cotreatment with aspirin in a dose of 80 to 100 mg daily. All patients were on maintenance dose of aspirin preoperatively and continued aspirin during the operation. The individual patient who was not on a maintenance dose of aspirin preoperatively started aspirin with a loading dose at least 1 day before surgery. Postoperative aspirin administration was administered according to local protocols and was given for life. Follow-up visits were scheduled at 6, 24, and 53 weeks. Coronary imaging by coronary computed tomography angiography (CCTA) was scheduled at 53 weeks for assessment of the primary outcome. Figure I in the Data Supplement depicts the study design. At each follow-up visit, patients were asked about interim clinical events and the use of cardiovascular medications. Documentation of clinical events was completed with case records from hospital admissions and from general practitioners. Unblinded data were accessible to the first three authors (L.M.W., P.W.A.J., and J.P.), the last author (J.M.t.B.), and the statistical analysis team (J.G.P.T. and J.C.K.) after completion of the trial. The manuscript was drafted by the first 3 authors and the last author (L.M.W., P.W.A.J., J.P., and J.M.t.B.). All authors have reviewed the manuscript. L.M.W. and J.M.t.B. had final responsibility for the decision to submit for publication.

### Outcomes

The primary outcome was (100%) SVG occlusion. Single, sequential, and Y-grafts were individually and, if applicable, per segment adjudicated on CCTA at 1 year. Figure II in the Data Supplement contains a detailed description of graft assessment.



SVGs that were not adequately visualized on CCTA (e.g. because of stair-step artifacts) were adjudicated as patent. In the case of missing CCTA, a coronary angiography could be used if performed between 35 and 53 weeks. The primary outcome was undefined in the absence of outcome imaging by CCTA or coronary angiography. An independent core laboratory whose (3) members were unaware of the trial medication assignment adjudicated the images from CCTA or coronary angiography.

The secondary outcome was SVG failure (a composite of SVG occlusion in any SVG as defined above, SVG revascularization, MI in myocardial territory supplied by an SVG, or sudden death) at 1 year. Additional secondary outcomes were significant ( $\geq 70\%$ ) venous or arterial graft stenosis and any (venous or arterial) graft occlusion at one year. Safety outcomes were bleeding events, classified according to Bleeding Academic Research Consortium (BARC) minor (type 2) and BARC major (type 3,4,5), Thrombolysis in Myocardial Infarction (TIMI), and Platelet Inhibition and Patient Outcomes (PLATO) classifications, 30 days and 1 year after randomization. These clinical events were blindly adjudicated by a clinical events committee. The definitions are provided in Table II in the Data Supplement.

#### *Statistical analysis*

As prespecified, the primary outcome was assessed using a mixed logistic effects model with random intercept for each patient. However, because of lack of measurements per patient ( $\approx 2$  SVGs per patient) this model resulted in an unstable odds ratio (OR) estimate and wide 95% confidence intervals (CIs). Therefore, we used a generalized estimating equation model including terms for treatment to estimate between-group differences to analyze the primary outcome of SVG occlusion. The exchangeable covariance structure was used to model the correlation of SVG occlusion within a patient. The analysis included all SVGs with defined primary outcome, by randomized treatment assignment regardless of its implementation (intention-to-treat). Treatment effects of ticagrelor versus placebo were reported as ORs with 95% CI and *P* values. In a first sensitivity analysis, we assumed that all SVGs that could not be visualized on the outcome images were analyzed as occluded. Second, we added all SVGs of patients who had died of cardiovascular cause as occluded to the dataset. A third, post-hoc sensitivity analysis was performed in which we corrected the primary analysis per center. Fourth, we performed an analysis of the primary outcome on a per protocol basis, by excluding SVGs of patients that had not received the trial medication in accordance with the study protocol. Last, we defined SVG occlusion on a per patient basis if occlusion had occurred in at least 1 SVG. ORs with corresponding 95% CIs were calculated with conventional logistic regression analysis in patients with available outcome imaging. Prespecified subgroup analyses were performed for the primary outcome.

For the (time-to-event) secondary outcomes, hazard ratios (HRs) and corresponding 95% CIs were determined with Cox proportional hazards regression analysis.

Kaplan–Meier curves were used to depict the occurrence of secondary outcomes over time. Follow-up of event-free patients with incomplete clinical follow-up was censored at the last clinical contact. For all secondary outcomes, per protocol (as defined above) analyses were performed as sensitivity analyses.

Continuous variables with normal distribution were expressed as mean with standard deviation and categorical variables were described as frequencies and percentages. A 2-sided *P* value  $< 0.05$  was considered to be statistically significant. No adjustments for multiple comparisons were made for secondary outcomes, which therefore should be considered exploratory. Statistical analyses were performed with R software, version 3.6.1 (R Foundation for Statistical Computing). This trial is registered at <https://www.ClinicalTrials.gov> (Unique identifier: NCT02352402) and EudraCT (2014-002142-50).

#### *Sample size*

The original design assumptions included a reduction of the SVG occlusion rate by ticagrelor from 15% to 10% (based on available literature at the time<sup>5-7,15</sup>) a Yules *Y*-coefficient of 0.1715 per patient, and a mean of 2.4 SVGs per patient. From computer simulations we estimated that inclusion of 575 patients with 1380 evaluable SVGs would provide the trial with 80% power. Considering that 20% of patients would have nonavailable primary outcome imaging, we estimated that 720 patients needed to be included. As recruitment in the trial was slow, the sample size was revised, without knowledge of interim results, when the results of the DACAB trial<sup>23</sup> (Compare the Efficacy of Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery [SVG occlusion rates from 23.5% to 11.2%]) were published. We decided to continue the trial until inclusion of an equal number of evaluable SVGs to the DACAB trial. Corrected for the dropout rate as observed in the interim analysis, we estimated that with 1072 evaluable SVGs in 487 patients (i.e. 2.2 SVGs per patient) the trial would have at least 80% power to statistically detect a reduction of the SVG occlusion rate from 15% to 9% at a two-sided significance level of 0.05.

#### *Retraction original article*

After publication of the original manuscript, we found out that an incorrect randomization list for the patients of 1 participating site (the St Antonius Hospital) was used for the analysis after completion of the study. In all patients, including those in the St Antonius Hospital, randomization to the treatment groups was performed correctly, all patients received study medication according to their right assignment. However, a wrong second randomization list for the St Antonius Hospital alone was used for the analysis, while the correct, first randomization list was used for the other 5 participating centers. This randomization list was erroneously generated 2 years after the start of the study, when randomization lists were generated for 3 new participating centers. Verification of the randomization lists and analyses of the other 5 centers

demonstrated no errors. In consultation with Circulation, we decided to retract the original manuscript and resubmit the article with the corrected analyses.

### Results

#### Trial population

From 27 March 2015 through 1 January 2019, a total of 499 patients were included (Figure 1). Enrollment per study site is presented in Table III in the Data Supplement. After randomization, 3 patients were excluded from the analysis (3 patients withdrew full informed consent), so the study population consisted of 496 patients, of whom 2 patients were lost to follow-up at 12 months.

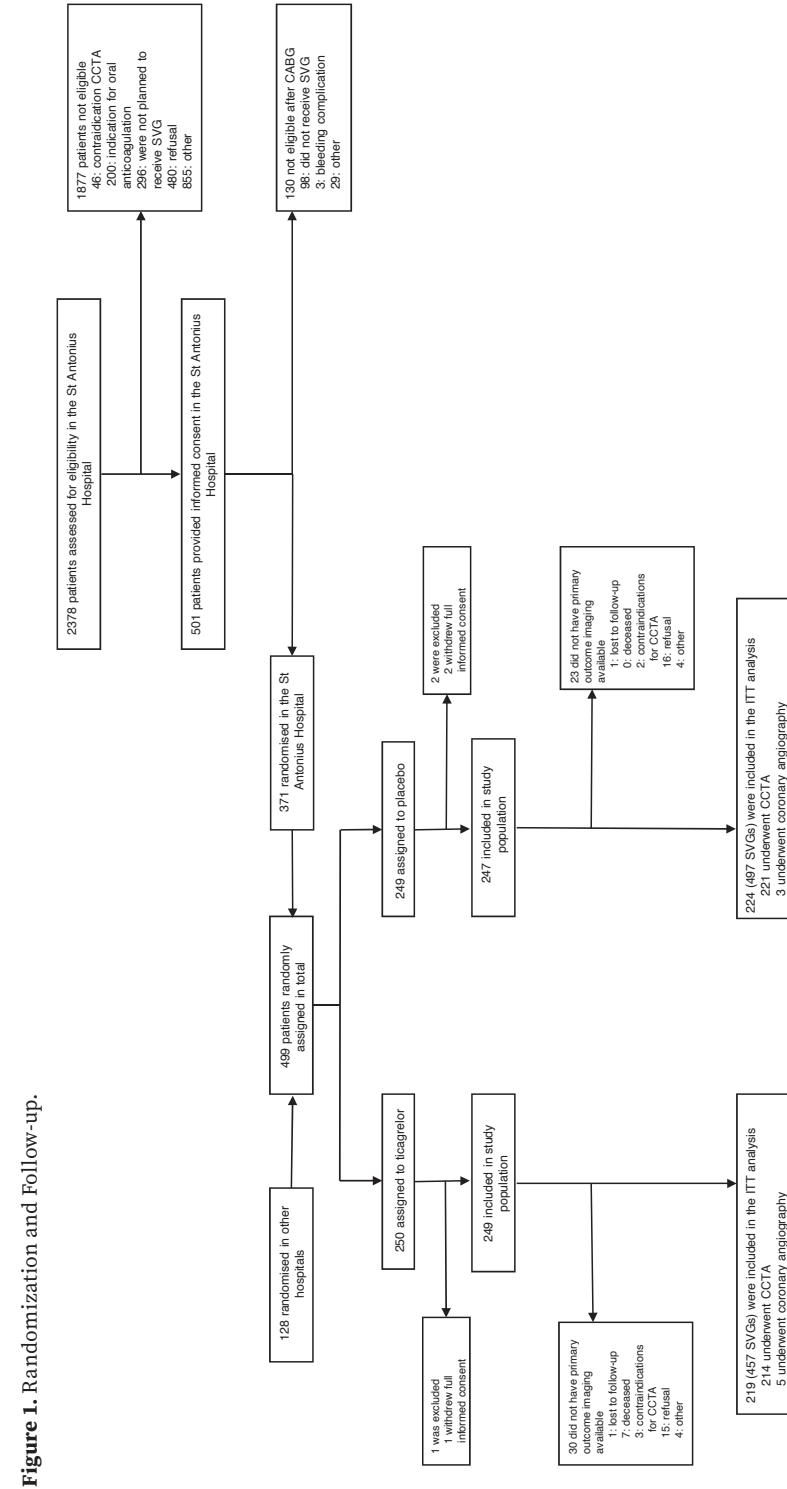


Figure 1. Randomization and Follow-up.

Baseline and procedural characteristics were comparable in both groups (Table 1). Mean age was 67.9±8.3 years, 87.1% were male. Indication for CABG was acute coronary syndrome in 31.3% and cardiopulmonary bypass was used in 95.2% of procedures. At 1 year follow-up, 216 (86.8%) of the patients in the ticagrelor group and 212 (85.8%) of the patients in the placebo group used aspirin. In the ticagrelor group 94 patients (37.8%) and in the placebo group 82 patients (33.2%) had permanently discontinued study medication, most frequently because of oral anticoagulation initiation after CABG (30 patients (12.1%) in the ticagrelor group and 27 (10.9%) patients in the placebo group). Over time, 14 patients (5.6%) in the ticagrelor group and 3 (1.2%) in the placebo group discontinued medication for bleeding. Table IV in the Data Supplement provides an overview of reasons for discontinuing study medication and data regarding medication use at 1 year.

**Table 1.** Characteristics of Included Patients and CABG Procedure at Baseline.

| Characteristics                                                           | Ticagrelor Group (N=249) | Placebo Group (N=247) |
|---------------------------------------------------------------------------|--------------------------|-----------------------|
| Age, y                                                                    | 68.1±8.4                 | 67.7±8.2              |
| Female sex, n (%)                                                         | 29 (11.6)                | 35 (14.2)             |
| Body-mass index*                                                          | 27.7±4.1                 | 28.0±4.2              |
| Race, n (%)                                                               |                          |                       |
| White                                                                     | 242 (97.2)               | 233 (94.3)            |
| Other                                                                     | 4 (1.6)                  | 9 (3.6)               |
| Unknown                                                                   | 3 (1.2)                  | 5 (2.0)               |
| Creatinine clearance ≥ 60 ml/min/1.73m <sup>2</sup> at admission, † n (%) | 202 (82.8)               | 201 (82.7)            |
| Smoker, ‡ n (%)                                                           | 47 (18.9)                | 45 (18.2)             |
| Diabetes, n (%)                                                           | 60 (24.1)                | 68 (27.5)             |
| Hypertension, n (%)                                                       | 152 (61.0)               | 156 (63.2)            |
| Hypercholesterolemia, n (%)§                                              | 248 (99.6)               | 244 (99.6)            |
| Chronic obstructive pulmonary disease, n (%)                              | 27 (10.8)                | 29 (11.7)             |
| Peripheral artery disease, n (%)                                          | 25 (9.7)                 | 25 (10.1)             |
| Previous acute coronary syndrome, n (%)                                   | 36 (14.5)                | 44 (17.9)             |
| Previous percutaneous coronary intervention, n (%)                        | 36 (14.5)                | 42 (17.0)             |
| Previous CABG, n (%)                                                      | 1 (0.4)                  | 2 (0.8)               |
| Previous cerebrovascular accident, n (%)                                  | 2 (0.8)                  | 5 (2.0)               |

**Table 1.** Characteristics of Included Patients and CABG Procedure at Baseline. (continued)

| Characteristics                           | Ticagrelor Group (N=249) | Placebo Group (N=247) |
|-------------------------------------------|--------------------------|-----------------------|
| Prior major bleeding, n (%)               | 12 (4.8)                 | 6 (2.4)               |
| Peptic ulcer in medical history, n (%)    | 15 (6.0)                 | 10 (4.0)              |
| Indication for CABG, n (%)                |                          |                       |
| Chronic coronary syndrome                 | 157 (63.1)               | 162 (65.6)            |
| Acute coronary syndrome                   | 81 (32.5)                | 74 (30.0)             |
| Other                                     | 11 (4.4)                 | 11 (4.5)              |
| Left ventricular ejection fraction, n (%) |                          |                       |
| >50%                                      | 196 (79.4)               | 190 (77.2)            |
| 30-50%                                    | 46 (18.6)                | 48 (19.5)             |
| <30%                                      | 3 (1.2)                  | 8 (3.3)               |
| <sup>  </sup> Additive EuroSCORE          | 3.2±2.1                  | 3.2±2.3               |
| CABG + aortic valve replacement, n (%)    | 7 (2.8)                  | 6 (2.4)               |
| Use of cardiopulmonary bypass, n (%)      | 240 (96.4)               | 232 (93.9)            |
| Graft type, n                             |                          |                       |
| Left internal mammary artery              | 338                      | 316                   |
| Right internal mammary artery             | 57                       | 61                    |
| Radial artery                             | 2                        | 0                     |
| Saphenous vein                            | 526                      | 547                   |
| Mean total grafts/case                    | 3.7±1.0                  | 3.8±1.0               |
| Mean total saphenous vein grafts/case     | 2.1±0.9                  | 2.2±1.0               |
| Sequential grafting of SVG, n (%)         |                          |                       |
| Yes                                       | 181 (72.7)               | 182 (73.7)            |
| No                                        | 67 (26.9)                | 64 (25.9)             |
| Start study drug after CABG, n (%)        |                          |                       |
| <13 hours                                 | 126 (50.6)               | 126 (51.0)            |
| 13-24 hours                               | 29 (11.6)                | 32 (13.0)             |
| 24-48 hours                               | 61 (24.5)                | 58 (23.5)             |
| >48 hours                                 | 33 (13.3)                | 31 (12.6)             |

**Table 1.** Characteristics of Included Patients and CABG Procedure at Baseline. (continued)

| Characteristics                                          | Ticagrelor Group (N=249) | Placebo Group (N=247) |
|----------------------------------------------------------|--------------------------|-----------------------|
| <b>Loading dose study medication administered, n (%)</b> |                          |                       |
| Yes                                                      | 194 (79.5)               | 195 (79.6)            |
| No                                                       | 49 (20.1)                | 50 (20.4)             |

Plus-minus values are means±SD. There were no significant differences between the 2 groups. Percentages may not total 100 because of rounding. CABG denotes coronary artery bypass grafting, and SVG, saphenous vein graft.

\* The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Calculated with the Chronic Kidney Disease Epidemiology Disease Collaboration formula.

‡ Defined as current smoker or quitted smoking <6 months.

§ Defined as low-density lipoprotein >2.5mmol/l at baseline, or use or start of statin or other cholesterol-lowering medication at baseline

|| The additive version of European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a method of calculating predicted operative mortality for patients undergoing cardiac surgery; 0-2 points, low risk; 3-5 points, intermediate risk; ≥6 points, high risk.

#### Primary outcome

A total of 443 patients (89.3%) with a total of 954 SVGs had primary outcome imaging available at 1 year after randomization, 219 patients (457 SVGs) in the ticagrelor group and 224 patients (497 SVGs) in the placebo group. Mean days of randomization after which CCTA was performed was 368 days (±34) in the ticagrelor group, and 372 days (±26) in the placebo group. In the ticagrelor group 10 SVGs (2.2%) and in the placebo group 13 SVGs (2.6%) were not adequately visualized on CCTA. SVG occlusion occurred in 44 of 457 SVGs in the ticagrelor group (9.6%) and in 50 of 497 SVGs (10.1%) in the placebo group (OR 0.87 [95% CI: 0.49–1.55],  $P=0.64$ , Table 2).

When analyzed on a per patient basis, in which subjects were defined as having at least one occluded SVG per patient, 26 patients of the 219 patients in the ticagrelor group had an occluded SVG (11.9%) versus 32 patients of the 224 patients (14.3%) in the placebo group (OR 0.80, [95% CI: 0.46 – 1.41],  $P=0.45$ ). Results for the primary outcome were consistent among different subgroups, including patients whose indication for CABG was ACS (Figure 2).

**Table 2.** Primary Outcome, Secondary Outcomes and Safety Outcomes by Intention-To-Treat analyses.\*

| Outcomes                    | Ticagrelor Group n/total (%) | Placebo Group n/total (%) | Odds Ratio (95% CI) | Hazard Ratio (95% CI) | P Value |
|-----------------------------|------------------------------|---------------------------|---------------------|-----------------------|---------|
| <b>Primary</b>              |                              |                           |                     |                       |         |
| SVG occlusion (per SVG)     | 44/457 (9.6)                 | 50/497 (10.1)             | 0.87 (0.49 – 1.55)  |                       | 0.64    |
| SVG occlusion (per patient) | 26/219 (11.9)                | 32/224 (14.3)             | 0.80 (0.46 – 1.41)  |                       | 0.45    |
| <b>Secondary</b>            |                              |                           |                     |                       |         |
| SVG failure                 | 32/249 (12.9)                | 32/247 (13.0)             |                     | 1.04 (0.63 - 1.69)    | 0.89    |
| 30-day BARC 3-5 bleeding    | 5/249 (2.0)                  | 5/247 (2.0)               |                     | 1.00 (0.29 – 3.44)    | >0.99   |
| 1-year BARC 3-5 bleeding    | 7/249 (2.8)                  | 8/247 (3.2)               |                     | 0.87 (0.32 – 2.40)    | 0.79    |
| 30-day BARC 2-5 bleeding    | 20/249 (8.0)                 | 8/247 (3.2)               |                     | 2.55 (1.12 – 5.79)    | 0.02    |
| 1-year BARC 2-5 bleeding    | 44/249 (17.7)                | 22/247 (8.9)              |                     | 2.09 (1.25 – 3.49)    | 0.004   |

\*All outcomes were confirmed by an independent, blinded adjudication committee or core laboratory. The 95% CIs were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses. BARC indicates Bleeding Academic Research Consortium; and SVG denotes saphenous vein graft.

#### Secondary outcomes

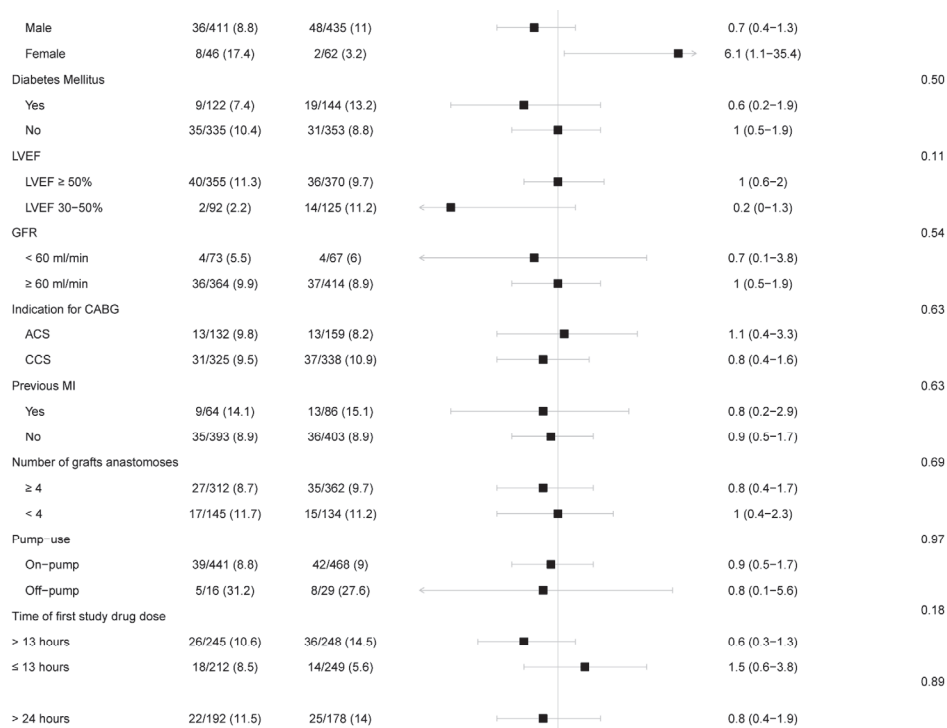
The secondary outcomes of SVG failure occurred in 32 (12.9%) patients in the ticagrelor group and in 32 (13.0%) patients in the placebo group (OR 1.04 [95% CI: 0.63-1.69],  $P=0.89$ , Table 2). Individual components of the outcome SVG failure analyzed on a per patient basis consisted of 26 SVG occlusions in the ticagrelor group versus 32 SVG occlusions in the placebo group, 4 SVG revascularizations in the ticagrelor group versus none in the placebo group, 3 cases of MI in territory of a SVG in the ticagrelor group versus none in the placebo group and one case of sudden death in the ticagrelor group versus none in the placebo group. Stenosis and occlusion rates in arterial grafts and all graft stenosis rates were low (significant stenosis and occlusion rates in arterial grafts 9 of 359 (2.5%) arterial grafts in the ticagrelor group and 10 of 346 (2.9%) grafts in the placebo group; significant stenosis in all grafts: 2 of 816 (0.2%) grafts in the ticagrelor group and 1 of 843 grafts (0.1%) in the placebo group). Incidence of BARC major bleeding at 1 year was 7 (2.8%) in the ticagrelor group and 8 (3.2%) in the placebo group (HR 0.87 [95% CI: 0.32-2.40],  $P=0.79$ , Table 2,



Figure III in the Data Supplement). Incidence of BARC minor bleeding at 1 year was 44 (17.7%) in the ticagrelor group and 22 (8.9%) in the placebo group (HR 2.09 [95% CI: 1.25-3.49],  $P=0.004$ , Table 2). Results of bleeding outcomes remained consistent when analyzed with TIMI and PLATO classifications. Clinical event rates were low in this study (Table 3).

The per protocol analysis and sensitivity analyses rendered consistent results with those of the primary analyses. Results are depicted in Table V and VI in the Data Supplement. Table VII in the Data Supplement provides reasons for exclusion from the intention-to-treat analysis.

**Figure 2.** Subgroup analyses for the primary outcome.



Analyses of the primary outcome SVG occlusion for the 12 prespecified subgroups. Estimates are unadjusted hazard ratios and 95% CIs at 1 year after randomization. ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

**Table 3.** Clinical Event Rates at 1 year after Coronary Artery Bypass Grafting.\*

| Event                                                                       | Ticagrelor Group (N = 249)<br>N (%) | Placebo Group (N = 247)<br>n (%) | Hazard ratio (95% CI) |
|-----------------------------------------------------------------------------|-------------------------------------|----------------------------------|-----------------------|
| Death from any cause                                                        | 7 (2.8)                             | 0 (0)                            | Not available         |
| Cardiovascular death                                                        | 2 (0.8)                             | 0 (0)                            | Not available         |
| Cerebrovascular accident/<br>transient ischemic attack                      | 6 (2.4)                             | 8 (3.2)                          | 0.74 (0.26 - 2.13)    |
| Acute coronary syndrome/<br>myocardial infarction                           | 6 (2.4)                             | 3 (1.2)                          | 2.01 (0.50 - 8.05)    |
| Myocardial infarction in<br>territory supplied by a<br>saphenous vein graft | 3 (1.2)                             | 0 (0)                            | Not available         |
| Revascularization                                                           | 11 (4.4)                            | 4 (1.6)                          | 2.77 (0.88 - 8.70)    |
| Saphenous vein graft<br>revascularization                                   | 4 (1.6)                             | 0 (0)                            | Not available         |

\*All outcomes were confirmed by an independent, blinded adjudication committee. The 95% CIs were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses.

## Discussion

In this investigator-initiated, randomized, double-blind, placebo-controlled, multicenter trial we investigated the potential benefit of adding ticagrelor to standard therapy with aspirin in preventing SVG occlusion 1 year after CABG. The study displayed no effect of ticagrelor on the rate of SVG occlusions or on the composite of SVG occlusions with clinical events.

As previously mentioned, results from studies investigating the effect of the P2Y<sub>12</sub>-inhibitor clopidogrel on SVG patency after CABG showed conflicting results<sup>15-19</sup>. A small, prematurely terminated study showed numerically lower SVG occlusion rates with aspirin and ticagrelor compared with aspirin alone<sup>24</sup>. However, the study evaluated graft patency early (at 3 months) after CABG and was not able to detect statistically significant differences because of the small sample size. The DACAB trial<sup>23</sup> randomly assigned 500 patients undergoing CABG to either aspirin monotherapy, ticagrelor monotherapy or aspirin and ticagrelor. SVG patency rates at 1 year were in favor of the aspirin and ticagrelor group (88.7%) and superior to the aspirin monotherapy group (76.5%, absolute risk difference: 12.2% [95% CI, 5.2% - 19.2%],  $p<0.001$ ). Results from our POPular CABG trial are clearly not in line with the DACAB trial results. First, we found a 1-year SVG occlusion rate of 10.1% in the group of aspirin monotherapy, which was much lower than what was observed in the DACAB trial (23.5%). Second, we could not confirm the reduction in SVG occlusion rate with adding ticagrelor to aspirin, as reported in the DACAB trial. We can only speculate on the reasons why the DACAB

trial found a higher SVG occlusion rate and an effect on patency of adding ticagrelor. In the DACAB trial the majority of patients underwent CABG without cardiopulmonary bypass (75.8%), which may have influenced patency<sup>25-28</sup>, and more patients underwent CABG for ACS (66.4%). The COMPASS-CABG (Cardiovascular Outcomes for People Using Anticoagulation Strategies – CABG)<sup>29</sup> compared the combination of rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone on bypass graft patency. They observed similar low SVG occlusion rates ( $\approx 10\%$ ) as in our trial and concluded that the combination of rivaroxaban and aspirin (and rivaroxaban alone) did not reduce the graft occlusion rates compared with aspirin alone. Explanations for the fact that neither our trial, nor COMPASS-CABG found a reduction of SVG occlusion rates with the use of additional antithrombotic therapy (either ticagrelor or rivaroxaban) remain hypothetical, but both studies suggest that SVG patency may be more dependent on mechanical factors (distal outflow) than thrombotic phenomena<sup>30,31</sup>. Notwithstanding, 2 recent meta-analysis<sup>32,33</sup> concluded that dual antiplatelet therapy with either ticagrelor or clopidogrel and aspirin provided superior SVG patency relative to aspirin alone, although it should be noted that only the 2 studies mentioned in this discussion were included in the analysis investigating dual antiplatelet therapy with aspirin and ticagrelor as compared with aspirin.

In POPular CABG, no discernible effect of adding ticagrelor to aspirin on SVG patency could be found in the ACS subgroup, although the trial was not powered to detect differences in subgroups. Furthermore, it is possible that ticagrelor has not only antithrombotic but also pleiotropic benefits<sup>13</sup> that have no relation to SVG patency. Additional research is needed to determine the most appropriate treatment after CABG, not only to optimize graft patency but also to improve clinical outcomes. Our trial does not refute the advice of the guidelines to continue ticagrelor in patients undergoing CABG for ACS. On the other hand, possible advantages of ticagrelor should be weighed against potential adverse effects, such as dyspnea<sup>34</sup> and an increase in bleeding risk<sup>13</sup>. In our trial, more patients in the ticagrelor group discontinued the study medication for bleeding, and we can establish a significant increase in 30-day and 1-year minor, but not major, bleeding rates in the ticagrelor group. Bleeding rates in our trial were low. This was probably caused by the timing of randomization that was chosen, namely after CABG when the risk of bleeding was minimized.

A notable finding in our trial was the occurrence of more (cardiovascular) death in the ticagrelor group. Two deaths were attributable to cardiovascular causes, 1 death was caused by Amyotrophic Lateral Sclerosis, 1 death was caused by oncologic cause and 3 deaths were caused by detrimental infections after CABG (two mediastinitis and one pneumonia). Based on this verification we think that the difference of mortality rate between the ticagrelor group and the placebo group is attributable to chance. Also, the outcome coming from the subgroup analysis, that ticagrelor is disadvantageous in women, is most probably a chance finding due to small sample size.

Our study has important limitations. First, the trial was powered for the surrogate outcome SVG occlusion, and not for clinical events. Second, the study population consisted predominantly of white men. Third, we had a limited number of study sites only in the Netherlands, most patients were enrolled at only 2 sites. Fourth,  $\approx 75\%$  of patients received sequential SVGs, which are less commonly used in contemporary practice. Fifth, although CCTA appears to be a good method to evaluate SVG occlusion, invasive angiography remains golden standard. It may be difficult to confidently assess SVG patency with CCTA in some patients, and especially with sequential grafts.

In conclusion, in this randomized, placebo-controlled trial, adding ticagrelor to standard aspirin therapy did not reduce SVG occlusion rates 1 year after CABG.

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## SUPPLEMENTAL MATERIAL

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### Study Principal Investigators

### Participating Sites

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## Supplementary Table I: Inclusion and Exclusion Criteria

### Inclusion Criteria\*

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Patients must meet the following criteria to be eligible for inclusion:  
 More than 21 years of age  
 Planned CABG with the use of 1 or more SVGs (+/- AVR with bioprosthesis)\*\*

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### Exclusion Criteria

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Patients are not eligible for trial participation if they meet any of the following exclusion criteria

- Unable to give informed consent or a life expectancy of less than 1 year
- Concomitant valve (excluding aortic bioprosthesis), aorta, or rhythm surgery during the same session
- Inability to undergo CCTA in the investigator's opinion, for instance, due to severe claustrophobia or contrast allergy
- Use of oral anticoagulants (acenocoumarol, phenprocoumon, novel oral anticoagulants) and a contraindication for discontinuation of this medication or the expectation that the patient will have an indication for the use of these drugs after surgery
- Placement of a drug-eluting stent in a coronary or cerebral artery within 6 months of CABG or placement of a bare-metal stent in a coronary or cerebral artery within 1 month of CABG
- Use of other antiplatelet drugs than aspirin (clopidogrel, prasugrel, ticagrelor, dipyridamole, etc) and a contraindication for discontinuation of this medication after CABG, according to the treating physician or the investigator
- Women who are known to be pregnant, who have given birth within the past 90 days, or who are breastfeeding
- Premenopausal women without adequate contraception
- Severe renal function impairment requiring dialysis
- Moderate or severe hepatic impairment
- Active malignancy with increase in bleeding risk in the investigator's opinion
- Use of strong inhibitors of CYP3A4 (eg, ketaconazole, clarithromycin, nefazodone, ritonavir, atazanavir)
- Clinically significant out-of-range values for platelet count or hemoglobin at screening in the investigator's opinion
- Contraindication for the use of ticagrelor or aspirin (ie, history of intracranial bleeding, high bleeding risk, previous allergic reaction) in the investigator's opinion
- Previous randomization in this study

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\* Initially only patients that provided written informed consent pre-CABG were included in the trial. On the 11<sup>th</sup> of April, 2018, it was decided to widen the window for providing informed consent to pre-operative to within 1 week after CABG.

\*\* Initially only patients undergoing an isolated CABG procedure were included. On the 11<sup>th</sup> of April, 2018, it was decided to also include patients who underwent CABG with concomitant bioprosthetic aortic valve replacement (AVR).

**Supplementary Table II: Definitions of Outcomes**

- Occlusion is defined as 100% stenosis of a graft or coronary vessel.
- Significantly diseased is defined as a stenosis of 70% or more of a graft or coronary vessel.
- SVG failure is defined as a composite of SVG occlusion on CCTA or coronary angiography, SVG revascularization, MI in the myocardial territory supplied by an SVG, or sudden death.
- SVG revascularization is defined as revascularization, with CABG or PCI (balloon inflation with or without stent implantation), of a graft or a coronary vessel that provides blood flow to an artery that was grafted with a SVG during the index CABG. An intervention in the LM after the index CABG that included a SVG on the LAD or RCX counts as target vessel revascularization.
- Myocardial infarction in the myocardial territory supplied by a SVG is defined as any myocardial infarction (for the definition see Myocardial Infarction) without clear electrocardiographic or imaging evidence that the MI is restricted to territories not supplied by the SVG.
- Myocardial infarction (MI) is defined as any of the following, in accordance with the ESC guidelines and the Third Universal Definition of Myocardial Infarction:
  - Spontaneous MI: A rise and/or fall of cardiac biomarker values (preferably cardiac troponin (cTn)) occurring >48 hours following CABG, with at least two samples with a value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
- All-cause mortality is defined as death from any cause.
- Cardiovascular death is defined as sudden death, death from acute myocardial infarction, arrhythmia, heart failure, cardiogenic shock, cerebrovascular event (ischemic stroke, hemorrhagic stroke ischemic stroke with hemorrhagic conversion, or intracranial hemorrhage), pulmonary embolism, peripheral arterial disease, bleeding and any death without another known cause.
- Sudden death is defined as an non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event.
- Stroke is defined as an acute new neurological deficit ending in death or lasting >24 hours not due to another readily identifiable cause such as trauma.

- Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.
- Any coronary revascularization is defined as a PCI (balloon inflation with or without stent implantation) or CABG after the initial CABG.
- Target vessel revascularization is defined as revascularization, with CABG or PCI (balloon inflation with or without stent implantation), of a graft or a coronary vessel that provides blood flow to an artery that was grafted during the index CABG. An intervention in the LM after the index CABG that included a graft on the LAD or RCX counts as target vessel revascularization.

For the classification of bleeding complications both the BARC<sup>35</sup>, TIMI<sup>35</sup> and PLATO<sup>13</sup> bleeding classification will be used.

- Bleeding Academic Research Consortium (BARC) bleeding classification:
  - Type 0: no evidence of 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. Examples include, but are not limited to, bruising, hematoma, nosebleeds, or haemorrhoidal bleeding for which the patient does not seek medical attention. Type 1 bleeding may include episodes that lead to discontinuation of medications by the patient because of bleeding without visiting a healthcare provider.
  - Type 2: any clinically overt sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional-guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (e.g., vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemocult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.
  - Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

- Bleeding Academic Research Consortium type 3a bleeding
- Any transfusion with overt bleeding
- Overt bleeding plus hemoglobin drop  $\geq 3$  to  $< 5$  g/dL (provided haemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
- Bleeding Academic Research Consortium type 3b bleeding
  - Overt bleeding plus hemoglobin drop  $\geq 5$  g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive drugs
- Bleeding Academic Research Consortium type 3c bleeding
  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
  - Intraocular bleed compromising vision
- Type 4: Coronary Artery Bypass Graft-related bleeding
  - Perioperative intracranial bleeding within 48 hours
  - Reoperation after closure of sternotomy for the purpose of controlling bleeding
  - Transfusion of  $\geq 5$  U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
  - Chest tube output  $\geq 2$  L within a 24-hour period

Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event

- Type 5: Fatal bleeding
- Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:
  - Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
  - Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.

- The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.
  - TIMI bleeding classification:
    - I) Major bleeding is defined as intracranial hemorrhage or a 5 g/dl decrease in the hemoglobin concentration or a 15% absolute decrease in the hematocrit.
    - II) Minor bleeding is defined as:
      - Observed blood loss: 3 g/dl decrease in the hemoglobin concentration or 10% decrease in the hematocrit.
      - No observed blood loss: 4 g/dl decrease in the hemoglobin concentration or 12% decrease in the hematocrit.
    - III) Requiring medical attention
      - Any overt sign of 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, 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)
    - IV) Minimal bleeding is defined as any clinically overt sign of hemorrhage (including imaging) that is associated with a  $< 3$  g/dl decrease in the hemoglobin concentration or  $< 9\%$  decrease in the hematocrit.
    - V) Bleeding in the setting of CABG
      - Fatal bleeding (bleeding that directly results in death)
      - Perioperative intracranial bleeding
      - Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
      - Transfusion of  $\geq 5$  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
- All TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dl or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows: Hemoglobin = [baseline Hgb - post-transfusion Hgb] + [number of transfused units]; Hematocrit = [baseline Hct - post-transfusion Hct] + [number of transfused units x 3].
- PLATO bleeding classification:
    - Major life-threatening
      - Fatal
      - Intracranial
      - Intrapericardial with cardiac tamponade



- Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
  - Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
  - Requiring transfusion of ≥4 U whole blood or PRBCs
- Other major
- Significantly disabling (eg, intraocular with permanent vision loss)
  - Associated drop in hemoglobin of 3 to 5 g/dL
  - Requiring transfusion of 2 to 3 U whole blood or PRBCs
- Any major
- Any one of the above criteria
- Minor
- Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)
- Minimal
- All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment
- Bleeding not associated with a procedure is categorized as ‘spontaneous’.

**Supplementary Table III:** Enrolment per Study Site

| Study Site              | Ticagrelor | Placebo | Total   |
|-------------------------|------------|---------|---------|
|                         | (N=250)    | (N=249) | (N=499) |
| St Antonius Hospital    | 186        | 185     | 371     |
| Erasmus Medical Center  | 7          | 6       | 13      |
| Catharina Hospital      | 52         | 53      | 105     |
| Radboud UMC             | 1          | 0       | 1       |
| Medisch Spectrum Twente | 3          | 5       | 8       |
| UMC Groningen           | 1          | 0       | 1       |

**Supplementary Table IV:** Data Regarding Medication Use**Table IV:** Data regarding medication use\*

| Characteristics                                          | Ticagrelor  | Placebo     | Missing   |
|----------------------------------------------------------|-------------|-------------|-----------|
|                                                          | (N=249)     | (N=247)     | No. (%)   |
| Total discontinuing study medication – no. (%)           | 94 (37.75)  | 82 (33.20)  | 0 (0)     |
| <i>Indication for oral anticoagulation</i>               | 30 (12.05)  | 27 (10.93)  |           |
| <i>Indication for a P2Y12-inhibitor</i>                  | 15 (6.02)   | 13 (5.26)   |           |
| <i>Surgery or procedure</i>                              | 2 (0.80)    | 3 (1.21)    |           |
| <i>Side effects</i>                                      | 28 (11.24)  | 15 (6.07)   |           |
| <i>Bleeding</i>                                          | 14 (5.62)   | 3 (1.21)    |           |
| <i>Dyspnea</i>                                           | 11 (4.42)   | 4 (1.62)    |           |
| <i>Other</i>                                             | 3 (1.20)    | 8 (3.24)    |           |
| <i>Other</i>                                             | 19 (7.63)   | 24 (9.72)   |           |
| Use of aspirin at 1-year – no. (%)                       | 216 (86.75) | 212 (85.83) | 16 (3.23) |
| Use of statin at 1-year- no. (%)                         | 208 (83.53) | 207 (83.81) | 23 (4.64) |
| Use of other lipid lowering drugs use at 1-year- no. (%) | 37 (14.86)  | 44 (17.81)  | 30 (6.05) |
| Use of PPI at 1-year- no. (%)                            | 177 (71.08) | 160 (64.78) | 23 (4.63) |
| Use of beta blocker at 1-year – no. (%)                  | 142 (57.03) | 137 (55.47) | 24 (4.84) |
| Use of ACE-inhibitor/ARB at 1-year- no. (%)              | 146 (58.63) | 138 (55.87) | 24 (4.84) |
| Use of diuretics at 1-year- no. (%)                      | 49 (19.68)  | 62 (25.10)  | 29 (5.85) |

\* Data regarding medication use are conveyed according to patient reporting by interview, when applicable confirmed with source documentation.

PPI; proton-pump inhibitor, ACE-inhibitor; angiotensin-converting enzyme inhibitor; ARB; angiotensin II receptor blockers.

**Supplementary Table V:** Results from the Per-Protocol\* Analysis**Table V: Results from the per-protocol analysis**

| Outcome (PP analyses)       | Ticagrelor        | Placebo           | Odds ratio<br>(95% CI) | Hazard ratio<br>(95% CI) | P<br>value |
|-----------------------------|-------------------|-------------------|------------------------|--------------------------|------------|
|                             | no./total (%)     | no./total (%)     |                        |                          |            |
| <b>Primary outcome</b>      |                   |                   |                        |                          |            |
| SVG occlusion               | 36/380 (9.47)     | 40/402 (9.95)     | 0.84<br>(0.45 – 1.58)  |                          | 0.591      |
| <b>Secondary outcome</b>    |                   |                   |                        |                          |            |
| SVG failure                 | 26/214<br>(12.15) | 27/203<br>(13.30) |                        | 0.94<br>(0.55 – 1.61)    | 0.817      |
| 30-day BARC 3-5<br>bleeding | 4/214 (1.87)      | 4/203 (1.97)      |                        | 0.95<br>(0.24 – 3.80)    | 0.944      |
| 1-year BARC 3-5<br>bleeding | 6/214 (2.80)      | 6/203 (2.96)      |                        | 0.95<br>(0.31 – 2.94)    | 0.927      |

\* The per-protocol analysis included all patients that received study medication > 60 days or had an endpoint that caused them to discontinue the medication (i.e. a bleeding event or cerebrovascular accident). All endpoints were confirmed by an independent, blinded adjudication committee or core lab. The 95% confidence intervals were not adjusted for multiple comparisons, and no clinical interferences can be made from these analyses. SVG denotes saphenous vein graft, ITT denotes intention-to-treat, BARC denotes Bleeding Academic Research Consortium.

**Supplementary Table VI:** Sensitivity Analyses for the Primary Outcome**Table VI:** Sensitivity Analyses for the Primary Outcome

|                        | Ticagrelor     | Placebo        | Odds ratio<br>(95% Confidence Interval) | P Value |
|------------------------|----------------|----------------|-----------------------------------------|---------|
|                        | no./total(%)   | no./total(%)   |                                         |         |
| <b>Primary outcome</b> |                |                |                                         |         |
| SVG occlusion*         | 54/457 (11.82) | 63/497 (12.68) | 0.90 (0.53 – 1.52)                      | 0.687   |
| SVG occlusion**        | 48/526 (9.13)  | 50/547 (9.14)  | 0.95 (0.55 – 1.66)                      | 0.864   |
| SVG occlusion†         | 44/457 (9.63)  | 50/497 (10.06) | 1.03 (0.49 – 2.17)                      | 0.524   |

\* The sensitivity analysis includes all patients that underwent a primary outcome assessment (CCTA or coronary angiography). All non-assessable SVG were assumed to be occluded.

\*\* The sensitivity analysis includes all patients (also patients who did not undergo primary outcome assessment). All grafts of patients who have died due to a cardiovascular cause, are imputed as occluded grafts, all other missing grafts are assumed to be open.

† This post-hoc sensitivity analysis includes all patients that underwent primary outcome assessment (CCTA or coronary angiography). Results are adjusted for center effect.

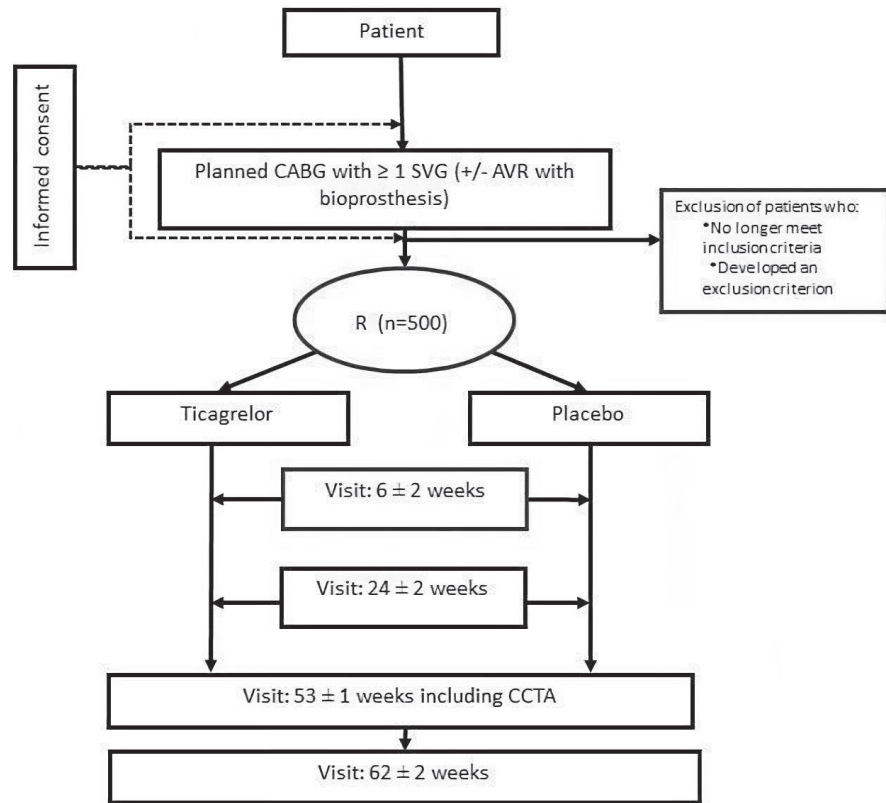
SVG denotes saphenous vein graft, CCTA denotes computed coronary angiography tomography.

**Supplementary Table VII:** Patients excluded from the ITT analysis**Table VII.** Patients and SVGs excluded from the ITT and per protocol\* analyses

| Reasons                                                      | Ticagrelor |     | Placebo |     |
|--------------------------------------------------------------|------------|-----|---------|-----|
|                                                              | N.         |     | N.      |     |
|                                                              | Patient    | SVG | Patient | SVG |
| Study population                                             | 249        | 526 | 247     | 547 |
| No primary outcome assessment<br>(CCTA/coronary angiography) | 30         | 69  | 23      | 50  |
| Included in ITT analysis of primary<br>outcome               | 219        | 457 | 224     | 497 |
| Received study medication < 60 days                          | 32         | 67  | 38      | 80  |
| Other reasons                                                | 3          | 10  | 6       | 15  |
| Included in per protocol analysis of<br>primary outcome      | 184        | 380 | 180     | 402 |
| Included in ITT analyses of secondary<br>outcomes            | 249        |     | 247     |     |
| Received study medication < 60 days                          | 32         |     | 38      |     |
| Other reasons                                                | 3          |     | 6       |     |
| Included in per protocol analyses of<br>secondary outcomes   | 214        |     | 203     |     |

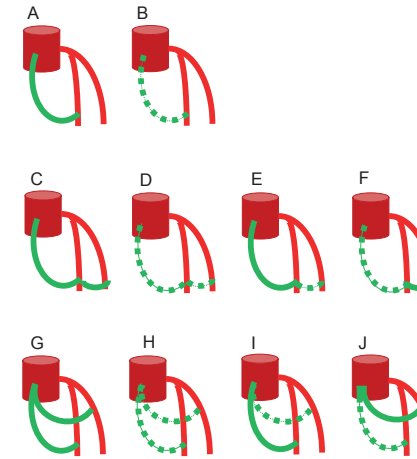
\* The per-protocol analysis included all patients that received study medication > 60 days or had an endpoint that caused them to discontinue the medication (i.e. a bleeding event or cerebrovascular accident). SVG denotes saphenous vein graft, CCTA denotes computed coronary tomography angiography, ITT denotes intention-to-treat.

**Supplementary Figure I: Study Design and Groups**



This figure shows the overall study design and groups of the POPular CABG trial. Patients were randomly assigned to either ticagrelor or placebo for one year. CABG denotes coronary artery bypass grafting, SVG denotes saphenous vein graft, AVR denotes aortic valve replacement, CCTA denotes computed coronary tomography angiography.

**Supplementary Figure II: Description of Graft Assessment**

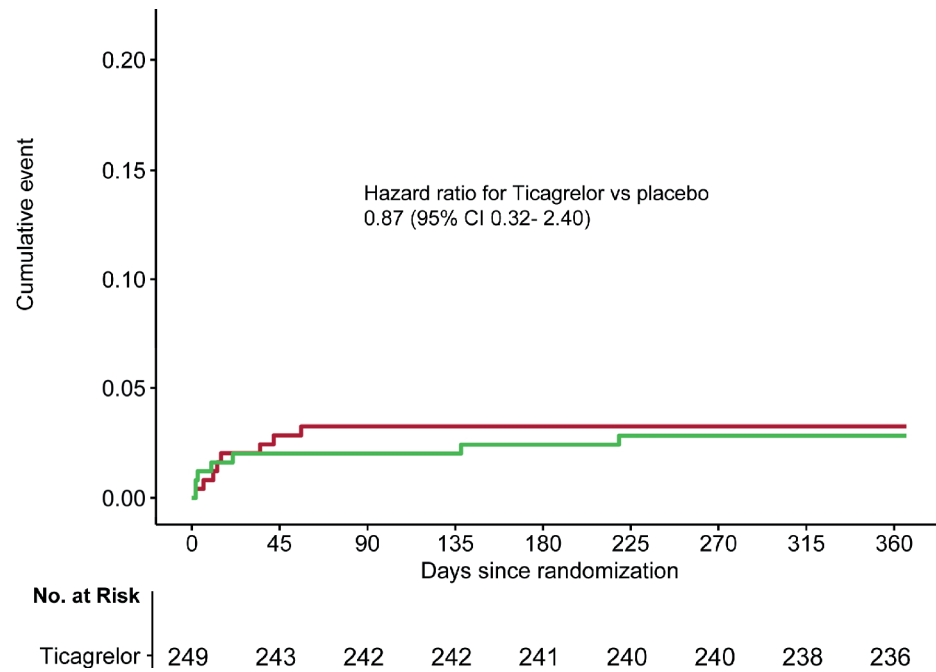


Solid lines depict patent grafts. Dashed lines depict occluded grafts.

- A Single graft configuration, graft patent.
- B Single graft configuration, graft occluded.
- C Sequential (jump) graft configuration, both grafts patent.
- D Sequential (jump) graft configuration, both grafts occluded.
- E Sequential (jump) graft configuration, distal graft occluded.
- F Sequential (jump) graft configuration, proximal graft occluded.
- G Y-graft configuration, both grafts patent.
- H Y-graft configuration, both grafts occluded.
- I Y-graft configuration, one graft occluded.
- J Y-graft configuration, one graft occluded.

In sequential graft configuration, the first graft is defined as patent and second one is occluded if the proximal graft is patent but distal graft is occluded (E). Both grafts are defined as occluded if the proximal part of the graft is occluded but the remain graft beyond the first anastomosis is patent (F).

**Supplementary Figure III:** Secondary Outcome of BARC Major Bleeding at 1 year.



Shown is the time-to-event Kaplan–Meier curve for BARC major (type 3-5) bleeding events at one year. The green line represents the ticagrelor group, the red line the placebo group. The 95% confidence intervals for the secondary outcomes were not adjusted for multiple comparisons, and therefore no clinical inferences can be made. BARC denotes Bleeding academic research consortium, CI denotes confidence interval.





# Chapter 8

## **Analysis of an error in the POPular CABG (Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting) Randomized Controlled Trial**

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*Manuscript in preparation for submission*

## Abstract

### Background

The revised manuscript of the POPular CABG trial (Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting; A Randomized, Double-Blind, Placebo-Controlled Trial; NCT02352402) has recently been presented. After publication of the original version of the article in August 2020, we discovered that an incorrect randomization list for the analysis of one participating site was used, thus affecting the results of the trial and posing the need for revision of the publication. We support transparent research conduct and reporting, and we think other researchers might benefit from sharing our experiences.

### Methods

In order to adequately analyze the origin of the error and prevent a similar error from happening in the future, we thoroughly evaluated and revised our trial procedures.

### Results

While randomization errors of this extent are rare, it is likely more errors of this kind influence trial outcomes. Therefore, we would advocate more detailed and widely available guidelines for trial procedures.

### Conclusions

In this 'Short communication' we would like to elaborate on the error that occurred in our analysis, and share valuable insights we have acquired.

## Introduction

Very recently, the revised version of the article describing the results of the POPular CABG trial (Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting; A Randomized, Double-Blind, Placebo-Controlled Trial) has been published. The POPular CABG was originally published August 31, 2020 and appeared in the November 10, 2020, issue of the journal<sup>1</sup>. The trial was approved by the medical ethics committee and by an institutional review board at each study site, and all participants provided written informed consent. Soon after publication of the manuscript, we discovered that we had used an incorrect randomization list for the analysis of one of the participating sites. In this 'Short communication', we would like to elaborate on this error and share valuable insights we have acquired. We analyze from the perspective of the investigators, meaning the researchers that conducted and analyzed the trial, but were not aware of the randomization allocation during the trial.

The randomization process of the POPular CABG and the error in the process is described in Table 1.

**Table 1.** Randomization process of the POPular CABG and the error in the process.

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### Before start of the trial

1. Investigators requested the head of Research & Innovation to generate randomization lists for three sites who would participate in the POPular CABG trial.
2. These randomization lists were sent to the hospital pharmacy of the St Antonius hospital (site nr. 1), who packed the study medication accordingly. Study medication for the two other sites (site nr. 2 and nr. 3) that participate in the trial is also packed and sent to these sites.

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### Inclusion phase of the trial

3. The three sites were including participants for the trial. All trial participants received study medication according to the randomization lists the hospital pharmacy received in step 2.
4. Two years after the start of inclusion of the trial, it was decided three other centers would participate (site nr. 4, 5, 6). Investigators requested the head of the Research & Innovation to generate three new randomization lists for these centers. When adding these new sites, the original randomization list for only site nr. 1 (the St Antonius hospital) was accidentally overwritten. This went unnoticed.

So, this is where the error originated: the hospital pharmacy packaged study medication according to the original list, and participants were assigned to treatment groups according to the original list. But this original list was erroneously and unknowingly overwritten and preserved in this form by the head of Research & Innovation.

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### After completion of follow-up

5. In order to analyze the results of the trial, the investigators requested the randomization lists of all sites from the head of Research & Innovation for decoding the participants.

6. The head of Research & Innovation sent the randomization lists for all sites to the investigators, including the unknowingly overwritten list for site nr. 1 (St Antonius hospital) mentioned in point 4.

7. The analyses were performed with the incorrect randomization list for site nr. 1, and the manuscript was published.

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#### After publication of the manuscript

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8. As agreed with the trial participants, we informed them of the results from the trial, as well as their randomization allocation. For this, the incorrect randomization list for site nr 1 was used, that was also used for the analysis.

9. The investigators were approached by one participant of the trial. He indicated we informed him that he had used a placebo during his study period, but he still thought this would be highly unlikely because of severe complaints of hematoma during the trial period, that had ceased the day he discontinued the study medication.

10. Although the investigators attributed his notification to the placebo-effect, they decided to verify his unblinding result with the hospital pharmacy.

11. The hospital pharmacy sent their randomization list (the correct list) to the investigators to compare with the randomization list received from the head of the Research & Innovation.

12. It was discovered that the randomization list used for analysis of the trial and informing trial participants differed from the list the hospital pharmacy used to distribute medication to participants.

13. After thoroughly verifying (e.g. with the ledgers for packaging distribution), it was certain that the participants received study medication according to the list of the hospital pharmacy

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## Analysis of the error in the randomization process of the POPular CABG

The conclusion is that we used an incorrect randomization list for the St Antonius Hospital for the analysis of the trial. The incorrect list was used for the analysis only, all participants had received study medication according to their correct treatment group and no participants were reassigned.

It has been stated three types of error can occur in the randomization process, namely 1) bad judgment in type of method, 2) design and programming errors, 3) human error during conduct of the trial<sup>2</sup>. The error in the POPular CABG trial would be classified in the last category. In our opinion, the described procedure of the randomization process of the POPular CABG lacked sufficient checks of trial procedures. Clearly, by the simple act of verifying the randomization list we would have discovered the error before the trial was analyzed.

Of note, had this one participant not contacted the investigators with his suspicion of a mix-up in his allocation (Table 1 step 9), the error would possibly never have been discovered. We think informing participants of study results and randomization

allocation is a right of study participants and thereby a part of respectful study conduct<sup>3-5</sup>. (It goes without saying we informed the study participants of the POPular CABG trial of the analysis error and their correct randomization allocation as well). Notwithstanding, we think assuring the correct study procedures is always the responsibility of the study team. The trial process should be overseen with proper verification procedures of the study itself, and should never be dependent on participants. Needless to say, we are grateful this participant contacted us and thus enabled us to detect this severe error.

Also, the error would not have been discovered had we not followed-up on the notification of the participant. Even though we initially believed his complaints had to be attributable to the placebo-effect, we decided to thoroughly verify his information. Therefore, this case does illustrate, in our opinion, the importance of a non-biased researcher-mindset.

## Earlier occurrence of randomization errors

As it is such a crucial part of the analysis of a Randomized Controlled Trial (RCT), securing the use of the correct randomization list might be considered self-evident. However, we learned the hard way that an error can be easily made, go unnoticed and have major consequences. Furthermore, we discovered that the POPular CABG is not the only trial that dealt with this sort of issues, as some similar errors in randomization procedures have been described before<sup>2</sup>. A computer programming error in one trial affected 71 of 778 patients, assigning them nonrandomly to treatment groups. Investigation of the error required the 60 patients assigned to the placebo group to be unblinded, thus excluding them from further trial participation and the final analysis, extending duration of the trial for three months<sup>2,6</sup>. Meantime, due to a dispensing error, one third of the 323 participants in a phase 3 trial had been given at least one drug bottle of the incorrect allocation assignment. The dispensing error occurred in a non-random subset of participants and the risk of receiving an incorrect study drug dose increased with the length of the time that patients were on the study<sup>7</sup>. The error had a significant impact on the study, causing the need to assess the efficacy of the investigated study drug only in unaffected patients. Therefore, definite conclusions regarding the outcomes of the trial could not be drawn and as a consequence, a second study had to be conducted<sup>8</sup>. Although randomization errors usually do not impact the trial to such an extent, it is suspected they are more common than we conceive<sup>2</sup>. It can be expected that randomization errors often go undiscovered. Moreover, even when they are discovered, such errors are not always reported<sup>2,9</sup>. Concern of creating doubts about the validity of the results of the trial or damage to the reputation of the authors could withhold the reporting of errors, and to date no obligation for reporting of randomization errors exists.



## Guidelines for trial procedures in randomized clinical trials

Without rigorous trial procedures that are focused on preventing procedural errors, mistakes like these are prone to happen. Therefore, transparent and structured trial protocols are vital. Our trial protocol had been developed according to the widely accepted SPIRIT- Guidelines<sup>10</sup>. Yet, more than forty guidelines for the development and conduction of randomized controlled trials (RCTs) exist and the recommendations for the content of a protocol for an RCT vary considerably<sup>11,12</sup>. The blinding process itself has been extensively discussed in literature<sup>13</sup>. All protocols for designing and conducting RCTs include a section on blinding, sometimes including a section that involves emergency unblinding, but no sections on ensuring correct unblinding procedures at the end of the trial can be found in these protocols<sup>10,14,15</sup>.

Guidelines on the reporting of RCTs do not comprise specific recommendations for design and conduct of RCTs, although they affect design and conduct of RCTs indirectly. This includes the CONSORT Statement<sup>16</sup>, to which many journals, including the journal we submitted the manuscript to, request submitted manuscripts of RCTs adhere. In the Explanation and Elaboration document of the CONSORT Statement, an item refers to the method used to generate the randomization sequence and the type of randomization. Another item addresses the mechanism used to implement the random allocation sequence and the steps taken to conceal the sequence until interventions were assigned<sup>17</sup>. It does not, however, include an item on unblinding procedures. Even when individual institutions advise to document the formal process for unblinding procedures at the end of the trial for data analysis<sup>18,19</sup> we could not find a recommended format for this process, or a checklist of items that should be included to guarantee correct unblinding. Because the procedure of unblinding at the end of the trial for data analysis is such an important part of the trial, it qualifies to be captured in Standard Operating Procedures (SOPs). SOPs are defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as “detailed, written instructions to achieve uniformity of the performance of a specific function”<sup>20</sup> and together the SOPs make a complete overview of directions of execution of the RCT. The value of SOPs in RCT conduction has been recognized for a long time<sup>20,21</sup>, but SOPs remain site-specific and no standardized targeted examples of SOPs can be found, though one can imagine composing one focused SOP example for all sorts of research with all different procedures could be a challenge.

We had SOPs developed for creating a randomization list and the process of unblinding at the end of the trial for data analysis, but apparently the SOPs did not sufficiently prevent procedural mistakes.

## What we have changed to avoid randomization errors in the future

To avoid similar mistakes in the future, our SOPs have adapted some changes.

1. Most importantly, to make sure the randomization lists are preserved and can not be modified unintentionally, we have changed the SOP for creating a randomization list for blinded studies and unblinding at the end of the trial for data analysis. The global resume of the old and new SOP for creating a new randomization list can be compared in Table 2 and Table 3. In short, three adaptations are made:
  - When creating a new blinded randomization list for a participating site, we always use a separate file, instead of storing all randomization lists of all sites in one file.
  - The separate files are always stored with a password (that is separately saved in a file in the same location as the randomization lists), so unintentional modification becomes impossible.
  - When a new blinded randomization list is made, this list will be saved as a (in principle) unmodifiable format (e.g. PDF) as well. Before sending the randomization lists for unblinding at the trial for data analysis to the study team in the desired format, the PDF-list will be compared with the randomization list to be uploaded.
2. A second, independent researcher (e.g. the trial monitor, the Data Safety Monitoring Board, or an external research bureau) will verify the randomization after every 100 included participants (block size, stratification, number of cases assigned to the allocation groups). This would not prevent the overwriting of the randomization lists or the analysis with the incorrect randomization list as happened in the POPular CABG trial, but it would prevent randomization errors as mentioned above.
3. Before trial initiation, we will draft a Risk Management Plan, in order to foresee risks, estimate impact of the risks and define a risk strategy that describes responses to risks. Had we done this before initiation of our trial, it would have been more likely we would have identified the risk of overwriting the randomization lists and we could have taken measures to avoid this from happening (for example by modifying the SOP as described in point 1).
4. All changes to the original randomization log will be logged in a destined log-file. Again, this would not have prevented the mistake from happening, but it would encourage diligent handling with the randomization list. Potential errors in the future will be easier and faster identified and analyzed.



**Table 2.** The old standard operating Procedure for creating a randomization list for blinded studies

- 
1. The desired characteristics for the randomization are entered in the online system that creates the randomization list (randomly selected seed number, list of treatments, block size(s), number of cases to be randomized, stratification).
  2. The file is downloaded as CSV-file.
  3. The file contains the randomization list for each participating site on separate tabs. The file is saved with the name of the trial included in the file name.
  4. If required the file can be password protected.
  7. If trial design requires, the randomization list is sent to other parties (such as the hospital pharmacy), in the desired format.
- 

CSV: *comma-separated values*

**Table 3.** The new standard operating procedure for creating a randomization list for blinded studies

- 
1. The desired characteristics for the randomization are entered in the online system that creates the randomization list (randomly selected seed number, list of treatments, block size(s), number of cases to be randomized, stratification).
  2. The file is downloaded as CSV-file.
  3. The randomization list is saved as a separate CSV-file for each participating site, the name of the site and of the trial is included in the file name. The file is always saved with password-protection.
  4. The password is saved in a separate txt-file right next to the CSV file.
  5. The file is saved in a (in principle) unmodifiable format, such as PDF.
  6. Right after saving, both files are compared to verify they contain the same randomization list.
  7. An log-file document is created for this trial, and the creating of the randomization list for Trial X, site X, version 1 is documented.
  8. If trial design requires, the randomization list is sent to other parties (such as the hospital pharmacy), in the desired format. When the randomization list is sent in a modifiable format (such as excel), the PDF-file of the randomization list will always be enclosed.
  9. Every change or addition in the randomization list, will be noted in the log-file.
- 

CSV: *comma-separated values*; PDF: *portable document format*

## Conclusion

In conclusion, in order to make sure RCTs are conducted correctly, defined and clear SOPs in trial design and conduct are necessary. As the POPular CABG illustrates, mistakes are easily made and only by obligating thorough verification we believe these mistakes could be avoided. No complex procedures are required for this, rather simple steps that demand hardly any extra time can achieve this verification. We would therefore encourage researchers and research institutions to make their SOPs widely accessible, or even creating more detailed and targeted examples of SOPs that are publicly available, next to known guidelines for RCT protocol design.

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# Chapter 9

## Perioperative management of antiplatelet treatment in patients undergoing isolated coronary artery bypass grafting in Dutch cardiothoracic centres

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## Abstract

### Background

International guidelines do not provide uniform recommendations regarding the use of antiplatelet treatment in the perioperative period in patients undergoing coronary artery bypass grafting (CABG).

### Methods

A questionnaire was sent to all 16 cardiothoracic centres in the Netherlands to determine which antiplatelet treatment is used in the perioperative setting. Furthermore, a single-centre prospective observational cohort study was performed which included all patients undergoing isolated CABG in July 2014.

### Results

Eleven centres responded to the survey. Acetylsalicylic acid monotherapy was discontinued before surgery in 6 centres. In patients with an acute coronary syndrome receiving dual antiplatelet therapy (DAPT), most centres discontinued the P2Y<sub>12</sub> inhibitor preoperatively. DAPT was restarted after surgery in 4 centres. However, 6 centres continued DAPT in patients who had undergone coronary stenting within one month of surgery. In patients with coronary stents, variation in the management of antiplatelet therapy increased in proportion to the interval between stenting and surgery. A total of 70 patients were included in the registry. Acetylsalicylic acid monotherapy was discontinued in 51% of patients and restarted in all patients. P2Y<sub>12</sub> inhibitor treatment was discontinued before surgery in 70% of patients and re-initiated after CABG in 29%.

### Conclusions

Major differences were observed in the preoperative and postoperative management of antiplatelet treatment between different Dutch cardiothoracic centres and within a single centre. Part of this variation is probably due to lack of evidence and differences between the current guidelines; however, many of the strategies were not in accordance with any of these guidelines.

## Introduction

Most patients scheduled to undergo coronary arterial bypass grafting (CABG) are treated with acetylsalicylic acid (ASA) with or without a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, ticagrelor) before surgery. The current guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA), European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) provide different recommendations regarding the continuation or (temporary) cessation of antiplatelet drugs during the perioperative period[1–4]. In general, it is recommended to continue ASA during and after CABG[1–4]. However, some guidelines state that it can be reasonable to discontinue ASA several days before CABG in patients with stable coronary heart disease[2,3]. The guidelines are consistent in their advice to discontinue P2Y<sub>12</sub> inhibitors before surgery in stable patients without recent coronary stent implantation, although there is no consistency regarding the timing of discontinuation. In high-risk groups, i.e. patients who have recently undergone coronary stent implantation[2] or patients with a high risk for thrombotic events[4], it is recommended not to interrupt dual antiplatelet therapy (DAPT) treatment. Physicians have to decide whether the increased risk of bleeding with continued antiplatelet therapy outweighs the risk of thrombotic events associated with the discontinuation of these drugs before CABG. The use of DAPT after CABG in patients who recently experienced an acute coronary syndrome (ACS) is also a subject of debate[5]. Recent reports have shown that treatment is not re-initiated after surgery in a large portion of patients[6], despite the fact that re-initiation is recommended in the guidelines[3,4].

We aimed to describe the use of antiplatelet treatment in the perioperative period in patients undergoing CABG in contemporary practice in the Netherlands.

## Materials and Methods

First, a survey was sent to all 16 centres in the Netherlands in which CABG surgery is performed. The head of the department of each centre was contacted. The survey consisted of both open and closed questions so that respondents could indicate how predefined groups of patients would be treated in general (i.e. mono antiplatelet therapy versus DAPT, patients after ACS and/or recent stent implantation) and which patients were exempted from standard treatment protocols. The survey is shown online as Electronic Supplementary Material.

Second, we conducted a prospective, observational pilot study in the St. Antonius Hospital in Nieuwegein. All patients undergoing isolated CABG in July 2014 were included in this registry. There were no exclusion criteria. Baseline data, antiplatelet treatment and postoperative complications (with 30 days of follow-up) were registered



in all patients. The study was conducted according to the principles of the Declaration of Helsinki and received approval from the local Human Research Ethics Committee. The local ethics committee provided a waiver for written informed consent, as the study was not associated with any risk.

## Results

### Survey

Between November 2014 and April 2015, 11 out of the 16 Dutch centres in which cardiothoracic surgery is performed, including our own centre, responded to the questionnaire. The other centres are listed in the acknowledgements.

Six out of 11 centres answered that ASA monotherapy was routinely discontinued before CABG, while 5 centres always continued ASA monotherapy (Table 1).

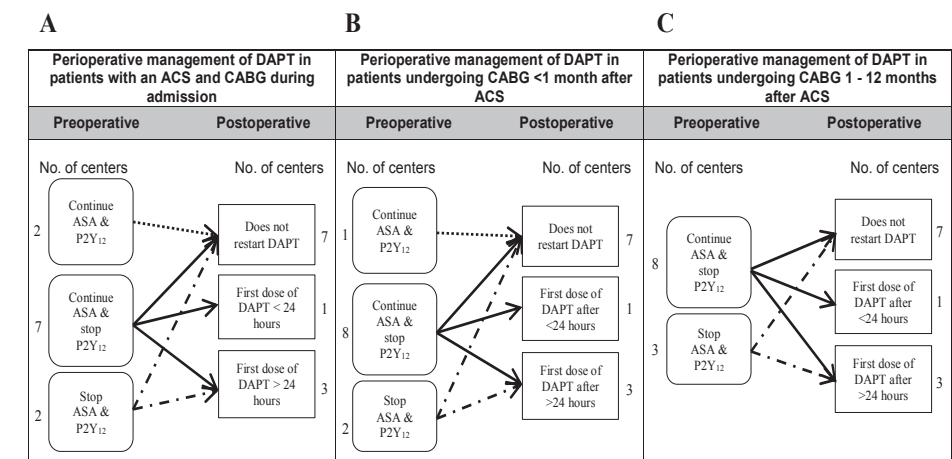
**Table 1.** Preoperative management of antiplatelet therapy

| NUMBER OF CENTRES FOLLOWING EACH STRATEGY |                     |                      |                    |                     |  |
|-------------------------------------------|---------------------|----------------------|--------------------|---------------------|--|
|                                           | ASA monotherapy (N) | DAPT Clopidogrel (N) | DAPT Prasugrel (N) | DAPT Ticagrelor (N) |  |
| CONTINUE:                                 | 5                   | -                    | -                  | -                   |  |
| DISCONTINUE:                              |                     |                      |                    |                     |  |
| - 1 DAY                                   | -                   | -                    | -                  | -                   |  |
| - 2 DAYS                                  | -                   | -                    | -                  | 1                   |  |
| - 3 DAYS                                  | 1                   | -                    | -                  | -                   |  |
| - 4 DAYS                                  | 1                   | 1                    | 1                  | 1                   |  |
| - 3-5 DAYS                                | 1                   | -                    | -                  | -                   |  |
| - 5 DAYS                                  | 2                   | 1                    | 3                  | 5                   |  |
| - 5-7 DAYS                                | -                   | -                    | -                  | 1                   |  |
| - 7 DAYS                                  | -                   | 1                    | 2                  | 1                   |  |
| - 7-10 DAYS                               | 1                   | 6                    | 1                  | -                   |  |

The preoperative management of patients on ASA monotherapy and patients on DAPT with clopidogrel, prasugrel or ticagrelor. ASA: Acetylsalicylic acid, DAPT: dual antiplatelet therapy, N: number of centres.

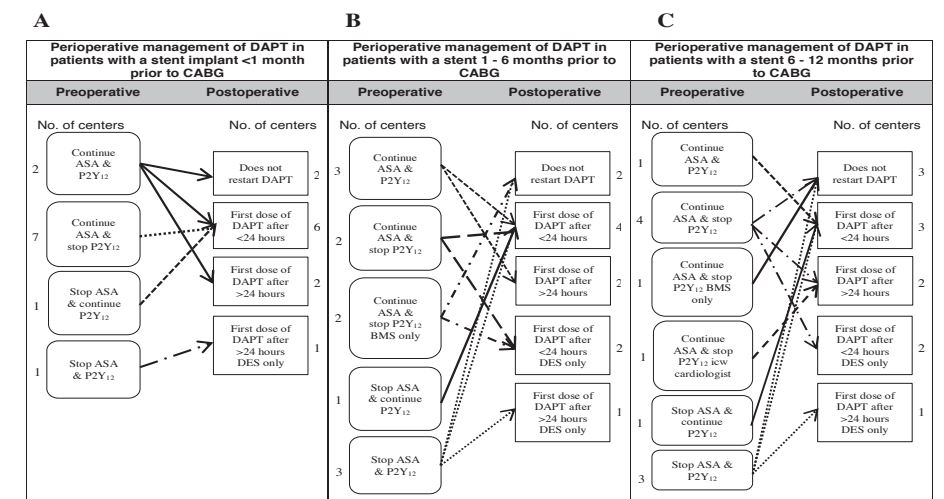
Fig. 1A to 1C show the perioperative management of antiplatelet treatment in patients with ACS undergoing CABG during the index admission, between the index admission and 1 month after the ACS or between 1 month and 12 months after the ACS. Preoperative management differed slightly between centres, but postoperative management was the same for the different groups.

**Figure 1A, 1B and 1C.** Perioperative management of DAPT in patients with ACS and CABG during the same admission, CABG <1 month and CABG 1-12 months after ACS



ACS acute coronary syndrome; ASA acetylsalicylic acid; CABG coronary artery bypass grafting; DAPT dual antiplatelet therapy; No number; P2Y<sub>12</sub> P2Y<sub>12</sub> inhibitor

**Figure 2A, 2B and 2C.** Perioperative management of DAPT in patients undergoing CABG less than 1 month, between 1-6 months and between 6-12 months after stent implantation



ASA acetylsalicylic acid; BMS bare metal stent; CABG coronary artery bypass grafting; DAPT dual antiplatelet therapy; DES drug-eluting stent; ICW in consultation with; No number; P2Y<sub>12</sub> P2Y<sub>12</sub> inhibitor

Fig. 2A to 2C show the perioperative management of antiplatelet treatment in patients undergoing CABG within 1 month, between 1 and 6 months and between 6 and 12 months after coronary stent implantation.

In the 4 centres in which ASA treatment was discontinued before surgery, one centre discontinued ASA 5 days before surgery, a second centre 4 days, a third centre 3 days and the fourth centre 2 days prior to surgery. This discrepancy in the time of discontinuation of treatment also applied to the management of P2Y<sub>12</sub> inhibitor use (Table 1).

**Table 2.** Baseline Characteristics

| Characteristics                               | N = 70<br>N (%) |
|-----------------------------------------------|-----------------|
| <b>Patient characteristics</b>                |                 |
| Male                                          | 57 (81.4)       |
| Age, mean, (SD), y                            | 65.5 ± 10.1     |
| Body mass index, mean, (SD)                   | 28.0 ± 3.2      |
| Current smoker                                | 14 (20.3)       |
| Ex-smoker (>6 weeks)                          | 19 (27.5)       |
| Family history for CAD                        | 8 (12.1)        |
| <b>Medical history</b>                        |                 |
| Hypertension                                  | 58 (82.9)       |
| Diabetes Mellitus                             | 21 (30.0)       |
| Dyslipidaemia                                 | 37 (52.9)       |
| Angina pectoris month prior to surgery*       | 50 (71.4)       |
| TIA/Stroke                                    | 6 (8.6)         |
| COPD                                          | 6 (8.6)         |
| Chronic kidney disease (eGFR MDRD4 <60ml/min) | 3 (4.3)         |
| Peripheral arterial disease                   | 3 (4.3)         |
| Heart failure (NYHA class III or IV)          | 9 (12.9)        |
| ACS                                           | 39 (55.7)       |
| MI                                            | 34 (48.6)       |
| Prior PCI                                     | 18 (26.1)       |
| PCI + Stent                                   | 11 (15.7)       |
| Prior CABG                                    | 0 (0.0)         |

**Table 2.** Baseline Characteristics (continued)

| Characteristics                        | N = 70<br>N (%) |
|----------------------------------------|-----------------|
| <b>Pre-operative medication use</b>    |                 |
| Oral Nitrates                          | 15 (21.4)       |
| Beta-blockers                          | 57 (81.4)       |
| ACE inhibitor                          | 38 (54.3)       |
| AT-II-antagonists                      | 17 (24.3)       |
| Diuretics                              | 18 (25.7)       |
| Statins and other lipid lowering drugs | 67 (95.7)       |
| Oral anti-diabetics                    | 16 (22.9)       |
| Insulin                                | 8 (11.4)        |
| <b>Surgery</b>                         |                 |
| Coronary artery disease                |                 |
| One vessel                             | 10 (14.3)       |
| Two vessel                             | 9 (12.9)        |
| Three vessel                           | 51 (72.9)       |
| Timing:                                |                 |
| Elective/planned                       | 66 (94.3)       |
| Urgent                                 | 2 (2.9)         |
| Emergency                              | 2 (2.9)         |
| EuroScore (SD)                         | 3.2 ± 2.6       |

Data are presented as number and percentage unless otherwise indicated. Denominators to derive percentages are based on available data for each characteristic. \*Any Canadian Cardiovascular Society class angina.

SD: Standard Deviation. y: year. CAD: Coronary Artery Disease. NYHA: New York Heart Association Functional Classification. CVA: Cerebral Vascular Accident. TIA: Transient Ischaemic Attack. COPD: Chronic Obstructive Pulmonary Disease. eGFR MDRD: Estimated Glomerular Filtration Rate according to the Modification of Diet in Renal Disease formula. ACS: Acute Coronary Syndrome. MI: Myocardial Infarction. N: number of patients. PCI: Percutaneous Coronary Intervention. CABG: Coronary Artery Bypass Grafting. (N)OAC: (New) Oral Anticoagulants. LMWH: Low Molecular Weight Heparine.

#### Registry

A total of 70 patients underwent isolated CABG in the St. Antonius Hospital in Nieuwegein in July 2014 and were included in this pilot study. Baseline data are presented in Table 2. Of these 70 patients, 41 were on ASA monotherapy, 28 used a P2Y<sub>12</sub> inhibitor and 1 patient was on ASA plus acenocoumarol treatment before surgery. From the 28 patients using a P2Y<sub>12</sub> inhibitor, 9 were on clopidogrel and 19 were on ticagrelor.

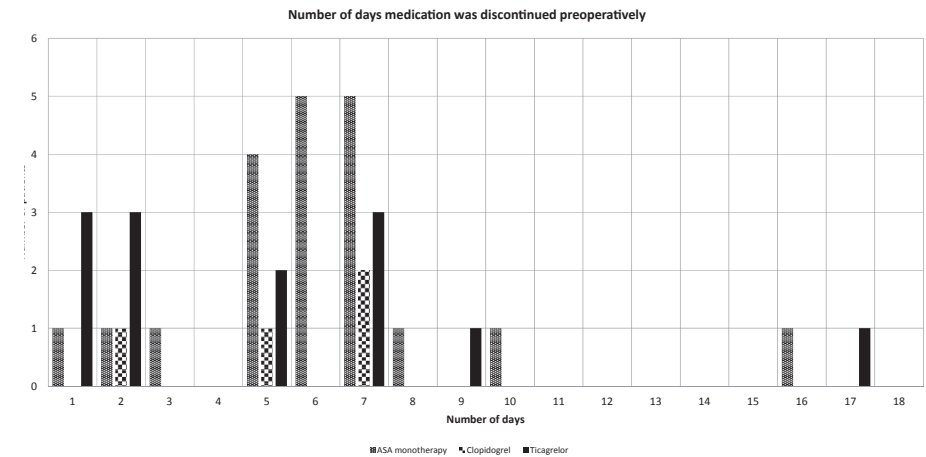
Table 3 shows the preoperative management for patients treated with ASA monotherapy, for patients using clopidogrel as part of DAPT treatment and for patients using ticagrelor as part of DAPT treatment. Of the total of 70 patients, 2 were on clopidogrel due to intolerance for ASA. One of them continued to use clopidogrel. One patient was treated with triple therapy (ASA/clopidogrel/acenocoumarol) and the last patient was treated with clopidogrel and acenocoumarol. The patient on triple therapy continued the acenocoumarol and stopped ASA and clopidogrel. The patient on acenocoumarol plus clopidogrel treatment continued the acenocoumarol and stopped the clopidogrel. Fig. 3 shows the number of days that medication was discontinued preoperatively. In the group of patients who discontinued ticagrelor, 8 patients had experienced an ACS less than 1 month before surgery. In the group that continued ticagrelor, 5 patients had experienced an ACS within 1 month before surgery.

**Table 3.** Preoperative management of patients on ASA monotherapy and of clopidogrel and ticagrelor in patients on DAPT

|                                             | ASA monotherapy | DAPT clopidogrel | DAPT ticagrelor |
|---------------------------------------------|-----------------|------------------|-----------------|
| <b>Preoperative</b>                         |                 |                  |                 |
| Continued                                   | 21              | 1                | 6               |
| Discontinued                                | 20              | 4                | 13              |
| Days discontinued, median (IQR)             | 6 (2)           | 6 (3.5)          | 5 (5.5)         |
| <b>Postoperative</b>                        |                 |                  |                 |
| No restart                                  | 0               | 2                | 10              |
| Restart                                     | 20              | 2                | 3               |
| Days after CABG until restart, median (IQR) | 1 (0)           | 2.5 (3)          | 1 (2)           |

ASA: Acetylsalicylic Acid. DAPT: Dual Antiplatelet Therapy.

**Figure 3.** Number of days ASA was discontinued preoperatively in patients on ASA monotherapy and the number of days clopidogrel and ticagrelor were discontinued in patients on DAPT.

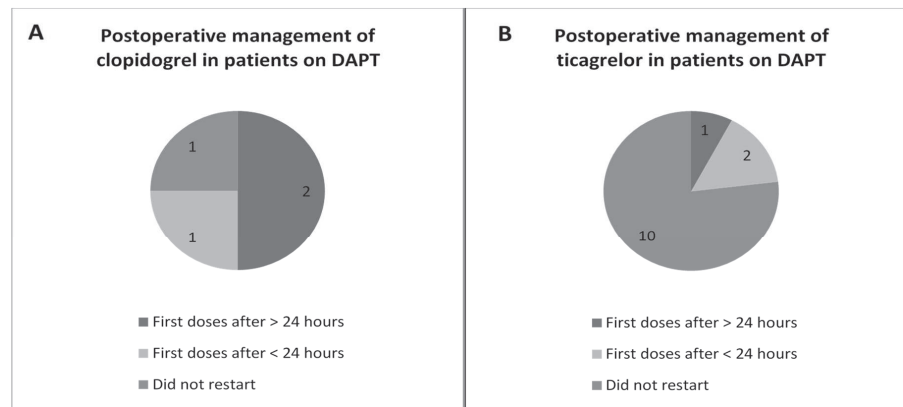


ASA acetylsalicylic acid; DAPT dual antiplatelet therapy

After surgery, 68 out of 70 patients received ASA. Treatment was started the day after surgery in all patients. All these patients received a loading dose of 500 mg intravenously. The two patients who did not receive ASA postoperatively were both preoperatively treated with clopidogrel monotherapy due to ASA intolerance. Both these patients received their first doses of clopidogrel the day after surgery.

Fig. 4 shows the postoperative management of P2Y<sub>12</sub> inhibitors. Patients who received a P2Y<sub>12</sub> inhibitor after CABG did not receive a loading dose, but a regular maintenance dose. There was no apparent relationship between restarting DAPT postoperatively and a preoperative history of ACS or percutaneous coronary intervention (PCI) with stent implantation. The incidence of postoperative complications within 30 days was low. Myocardial infarction (MI), stroke and death were not observed, while Bleeding Academic Research Consortium (BARC) type 4 major bleeding occurred in 3 patients and 2 patients needed surgery for mediastinitis. Due to the small study population with subgroups and low incidence of postoperative complications, we decided not to analyse these postoperative complications in more detail.

**Figure 4A and 4B.** Postoperative management of clopidogrel and ticagrelor in patients preoperatively on DAPT.



DAPT dual antiplatelet therapy

## Discussion

The results from this national survey regarding the perioperative management of antiplatelet treatment in CABG patients show major variability across the different Dutch centres. This variability partly reflects the disparity in recommendations in the different international guidelines[1–4]. A survey regarding antithrombotic treatment in CABG patients conducted in 1989 also showed major differences in antithrombotic treatment between Dutch cardiothoracic centres [7]. Although some treatment strategies that were used at the time (coumarins and dipyridamole) have since been abandoned for routine use in CABG patients, the variability in treatment strategies persists.

### *CABG in patients using ASA monotherapy*

The management of patients with ASA monotherapy differs greatly between centres, both in continuing or discontinuing ASA before surgery and in the timing of discontinuation. Although it might be reasonable to stop ASA in patients with the highest bleeding risk[3,4], the guidelines do not support discontinuation of ASA in the majority of patients, contrary to what appears to be the standard in many cardiothoracic centres who responded to this survey. The differences regarding the preoperative discontinuation of ASA in the guidelines and routine treatment in these centres might be caused by a lack of convincing evidence from randomised clinical trials. A recent meta-analysis including a total of 2399 patients showed that ASA exposure within 7 days before CABG, with or without concomitant surgery, resulted in a 44% reduction in the odds of MI[8]. However, it also resulted in a dose-dependent increase in blood loss, an

increased volume of red cell transfusion and rate of surgical re-exploration without an effect on mortality.

In the largest randomised clinical trial to date regarding the preoperative use of ASA in CABG patients (n=2100), [9] no differences were observed between patients using ASA or placebo with regard to any of the primary outcomes, death, MI, stroke, renal failure, pulmonary embolism and bowel infarction at 30 days after surgery (RR 0.94 95% CI 0.80 – 1.12). There were also no significant differences in the number of reoperations for bleeding or cardiac tamponade. Therefore, there is no clear benefit of ASA treatment before CABG.

The postoperative use of ASA in CABG patients is recommended in all guidelines as it has been proven to increase venous graft patency and reduces the occurrence of ischaemic events during follow-up in all patients regardless of revascularisation strategy[10–13].

### *CABG in patients using DAPT*

Our survey revealed that the discrepancies in treatment strategies between the different centres were even greater in patients who received DAPT. Centres also differed in postoperative antiplatelet management, but the majority of centres stop the P2Y<sub>12</sub> inhibitor without restarting it after surgery. The timing of discontinuation of the P2Y<sub>12</sub> inhibitor varied roughly from 4 to 10 days between centres. A recent study from Hansson et al. shows that it is safe to discontinue ticagrelor 3 days and clopidogrel 5 days prior to CABG [14]. Many guidelines mention the option of preoperative bridging therapy with small molecule GPIIb/IIIa inhibitors (i.e. eptifibatid or tirofiban) or cangrelor after discontinuation of P2Y<sub>12</sub> inhibitors in patients with increased risk for ischaemic events (e.g. with recently implanted drug-eluting stent (DES)), but there is still little clinical evidence for this strategy. None of the respondents mentioned the use of this strategy in their centre.

Not restarting the P2Y<sub>12</sub> inhibitor after surgery is not supported by the guidelines, which recommend restarting DAPT after CABG as soon as it is considered safe and to continue DAPT for at least 12 months following ACS (class I, level A)[3,15]. The ESC guidelines on revascularisation and non-ST-segment elevation ACS (NSTEMI-ACS) were updated after we received answers for our survey, but the 2011 ESC guideline on NSTEMI-ACS also stated that ticagrelor or clopidogrel should be considered to be (re-)started after CABG surgery as soon as considered safe (class IIa, level B)[16]. The recommendations from these guidelines are based on sub-analyses from three large randomised trials in ACS patients: the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study[17], the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction (TRITON-TIMI 38) and the PLATElet inhibition and patient Outcomes (PLATO) study[18,19].



These three trials all showed some benefit of continuation of DAPT after CABG in sub-analyses. However, the trials are underpowered and these post-hoc analyses have many limitations. The reason for the discontinuation of study treatment after surgery in a substantial number of patients is not reported in these trials, so there might be a selection bias. Furthermore, the percentage of patients who underwent CABG was relatively low (16.5% in CURE, 2.5% in TRITON-TIMI 38, and 6.8% in PLATO).

There is still much uncertainty as to how P2Y<sub>12</sub> inhibitor treatment improves clinical outcome in this group and which patients should receive it at which particular moment. Outcomes might be improved due to an increase in vein graft patency with the use of a P2Y<sub>12</sub> inhibitor, as vein graft occlusion occurs in up to 26% of grafts after 1 year in patients using ASA monotherapy[20]. Multiple studies investigating the routine use of P2Y<sub>12</sub> inhibitors in CABG patients are currently recruiting patients, including the The Effect Of Ticagrelor On Saphenous Vein Graft Patency In Patients Undergoing Coronary Artery Bypass Grafting Surgery (POPular CABG) study (clinicaltrials.gov identifier NCT02352402) and the Study Comparing Ticagrelor With Aspirin for Prevention of Vascular Events in Patients Undergoing CABG (TiCAB) study (clinicaltrials.gov identifier NCT01755520). Data from these studies might help us better assess the benefits and risks of antiplatelet therapy in all patients undergoing CABG.

#### **CABG after PCI without prior ACS**

For patients undergoing CABG after PCI without prior ACS it is recommended to continue DAPT for at least 1 month after implantation of a bare metal stent (BMS) (class I, level A) and at least 6 months after a new-generation DES (class I, level B)[4]. However, the guidelines do not specify which postoperative therapy is advised if the target vessel has been bypassed.

The guidelines offer different options for the timing of both preoperative discontinuation and postoperative re-initiation of P2Y<sub>12</sub> inhibitor treatment. It should be considered to withhold clopidogrel and ticagrelor for 5 days and prasugrel for 7 days prior to surgery (class IIA, level C)[1–4]. Postoperatively, DAPT should be restarted within 24 hours if it is deemed safe, with a loading dose of the P2Y<sub>12</sub> inhibitor to optimise vein graft patency (Class IIA, level C)[3,4]. The guideline from the American College of Chest Physicians specifies that when CABG is performed less than 6 weeks after BMS or less than 6 months after DES, DAPT should be continued during surgery to prevent stent thrombosis (Grade 2C)[2].

#### *Registry results*

The results of our registry in the St. Antonius Hospital demonstrate that there are major differences even in a single centre. Generally, the P2Y<sub>12</sub> inhibitor is discontinued for a shorter time period before surgery than is advised by the guidelines. The reasons for this could be that patients were considered to be at higher risk for ischaemic events.

#### *Limitations*

Multiple limitations regarding the survey and registry merit mention. A questionnaire will only result in a general depiction of clinical practice, although we tried to include open questions to gather information regarding treatment of patients who did not fall into standard treatment protocols. However, treatment might actually differ from the answers provided by the responders as individual physicians might deviate from local protocols. Furthermore, only 69% of centres responded to our questionnaire.

The pilot study is limited due to its single-centre nature and the small population size. Another limitation for both studies is that the new ESC guideline regarding non-ST-segment-elevation myocardial infarction was published after the survey and the registry were conducted. Adherence to the guidelines might have increased since.

## **Conclusion**

Dutch cardiothoracic centres are not unified in their perioperative management of antiplatelet therapy in patients undergoing isolated CABG. The lack of evidence from randomised controlled trials could contribute to these differences between centres. More evidence from ongoing trials is essential to better evaluate the benefits and risks of antiplatelet therapy in CABG patients and strengthen the recommendations of the guidelines.

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## Electronic Supplemental Material

### Survey Antiplatelet treatment in CABG patients

Definitions used

ACS= acute coronary syndrome (ST-elevated myocardial infarction, non ST-elevated myocardial infarction or unstable angina pectoris)

ASA = acetylsalicylic acid

BMS = Bare metal stent

DES = Drug eluting stent

P2Y12 inhibitor = antiplatelet agents binding to the P2Y12 protein (clopidogrel (Plavix<sup>®</sup>), Viatorel<sup>®</sup>, Iscover<sup>®</sup>, prasugrel (Efient<sup>®</sup>) or ticagrelor (Brillique<sup>®</sup>)).

PCI = Percutaneous coronary intervention

### Questionnaire

Please answer the following questions about the strategy used in your department. We ask you to answer all questions as completely as possible. We would like to ask you to print out, fill out and sign the questionnaire and then fax, email or mail it back to us. If there are any unclarities concerning the content of the questions, you can always contact us.

1. Does your hospital have a protocol regarding antiplatelet therapy in patients undergoing CABG?

YES / NO\*

If you have answered YES to this question, we would like you to attach a copy of the last version of the protocol to this questionnaire.

### Preoperative phase:

Please specify below how patients are treated on your ward in daily clinical practice in each situation. Circle the most appropriate answer and fill in the entry fields.

2. The patient is treated with ASA monotherapy preoperatively.

2 a. Do you discontinue the ASA?

YES / NO\*

2 b. If you discontinue the ASA, how long do you discontinue it preoperatively?

Comments:

3. The patient uses ASA and a P2Y12 inhibitor after a PCI with a stent placement <1 month prior to CABG.

3 a. Do you discontinue the ASA?

YES / NO\*

3 b. If you answered YES, how long do you discontinue it preoperatively?

3 c. Do you discontinue the P2Y12 inhibitor?

YES / NO\*

3 d. If you answered YES, how long do you discontinue it preoperatively (and does the duration of discontinuation vary based on the specific drug)?

\* Circle the correct answer.

3 e. Are there groups of patients in which you deviate from the treatment described under 3a to 3d (e.g. BMS or DES)?

3 f. Comments:

4. The patient uses ASA and a P2Y12 inhibitor after a PCI with stent placement >1 month and <6 months prior to CABG.

4 a. Do you discontinue ASA?

YES / NO\*

4 b. If you answered YES, how long do you discontinue it preoperatively?

4 c. Do you discontinue the P2Y12 inhibitor?

YES / NO\*

4 d. If you answered YES, how long do you discontinue the drug preoperatively (and does this duration vary based on the specific drug)?

4 e. Are there groups of patients in which you deviate from this (e.g. BMS or DES)?

4 f. Comments:

5. The patient uses ASA and a P2Y12 inhibitor after a PCI with stent placement >6 months and <1 year prior to CABG.

5 a. Do you discontinue ASA?

YES / NO\*

\* Circle the correct answer.

5 b. If you answered YES, how long do you discontinue it preoperatively?

5 c. Do you discontinue the P2Y12 inhibitor?

YES / NO\*

5 d. If YES, how long do you discontinue it preoperatively (and does this duration vary based on the specific drug)?

5 e. Are there groups of patients in which you deviate from the treatment described under 5a to 5d (e.g. BMS or DES)?

5 f. Comments:

6. The patient is admitted for ACS and is treated with ASA and a P2Y12 inhibitor. He or she undergoes a CABG during the same admission (no stent).

6 a. Do you discontinue the ASA?

YES / NO\*

6 b. If you answered YES, how long do you discontinue it preoperatively?

6 c. Do you discontinue the P2Y12 inhibitor?

YES / NO\*

6 d. If YES, how long do you discontinue it preoperatively (and does this duration vary based on the specific drug)?

6 e. Comments:

\* Circle the correct answer.

7. The patient is treated with ASA and a P2Y12 inhibitor preoperatively after an ACS <1 month prior to CABG (no stent).

7 a. Do you discontinue the ASA?

YES / NO\*

7 b. If you answered YES, how long do you discontinue it preoperatively?

7 c. Do you discontinue the P2Y12 inhibitor?

YES / NO\*

7 d. If YES, how long do you discontinue it preoperatively (and does this duration vary based on the specific drug)?

7 e. Comments:

8. The patient uses ASA and a P2Y12 inhibitor preoperatively after an ACS >1 month and <1 year prior to CABG (no stent).

8 a. Do you discontinue the ASA?

YES / NO\*

8 b. If YES, how long do you discontinue it preoperatively (and does this duration vary based on the specific drug)?

8 c. Do you discontinue the P2Y12 inhibitor?

YES / NO\*

8 d. If YES, how long do you discontinue it preoperatively (and does this duration vary based on the specific drug)?

8 e. Comments:

\* Circle the correct answer.

#### Postoperative phase:

The next questions concern the policies after the surgery. Restarting means that the medicine is administered after the surgery. The medicine could have been continued or discontinued prior to the CABG.

9. The patient used ASA and a P2Y12 inhibitor preoperatively because of a PCI with stent <1 month prior to the CABG.

9 a. Do you restart the P2Y12 inhibitor?

YES / NO\*

9 b. If you answered YES, after how long do you restart it?

9 c. Are there groups of patients in which you deviate from the treatment described under 9a and 9b (e.g. BMS or DES)?

9 d. Comments:

10. The patient was treated with ASA and a P2Y12 inhibitor preoperatively after a PCI with stent >1 month and <6 months prior to the CABG.

10 a. Do you restart the P2Y12 inhibitor?

YES / NO\*

10 b. If you answered YES, after how long do you restart it?



10 c. Are there groups of patients in which you deviate from the treatment described under 10a and 10b (e.g. BMS or DES)?

10 d. Comments:

11. The patient was treated with ASA and a P2Y12 inhibitor preoperatively after a PCI with stent >6 months and <1 year prior to the CABG.

11 a. Do you restart the P2Y12 inhibitor?

YES / NO\*

11 b. If you answered YES, after how long do you restart it?

11 c. Are there groups of patients in which you deviate from the treatment described under 11a and 11b (e.g. BMS or DES)?

11 d. Comments:

12. The patient was admitted for an ACS and was treated with ASA and a P2Y12 inhibitor preoperatively. During the same admission he undergoes a CABG.

12 a. Do you restart the P2Y12 inhibitor?

YES / NO\*

12 b. If you answered YES, after how long do you restart it?

12 c. Comments:

13. The patient was treated with ASA and a P2Y12 inhibitor preoperatively for an ACS <1 month prior to surgery (no stent).

13 a. Do you restart the P2Y12 inhibitor?

YES / NO\*

13 b. If you answered YES, after how long do you restart it?

13 c. Comments:

14. The patient was treated with ASA and a P2Y12 inhibitor preoperatively due to an ACS > 1 month and <1 year prior to surgery.

14 a. Do you restart the P2Y12 inhibitor?

YES / NO\*

14 b. If you answered YES, after how long do you restart it?

14 c. Comments:

\* Circle the correct answer.

# **Part III**

## **Optimization of Postoperative Care**



# Chapter 10

## Long-term Follow-Up After Bypass Surgery or Coronary Stenting in Elderly With Multivessel Disease

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## Abstract

### Background

We sought to compare long-term follow-up of coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) in elderly patients with left main (LM) or multivessel disease (MVD), hypothesizing that completeness of revascularization and severity of coronary artery disease (CAD) are predictors of adverse outcomes.

### Methods

Patients aged  $\geq 75$  years with MVD or LM disease who underwent PCI or CABG between 2012-2016 were included in this study. Baseline characteristics from the index procedure were collected. Severity of CAD and completeness of revascularization were assessed. Primary outcome was all cause mortality, in addition we captured major adverse cardiac and cerebral events, bleedings, recurrent angina and new onset atrial fibrillation (AF).

### Results

A total of 597 patients were included. Median follow-up was 4 years (IQR 2.8–5.3 years). At baseline, patients in the PCI-group more often had a previous medical history of CABG and more frequently underwent an urgent procedure compared to patients in the CABG-group. Mortality at 5 year follow-up was significantly higher in patients who underwent PCI compared to CABG (39.9% vs. 25.4%,  $p < 0.001$ ). Furthermore, acute coronary syndrome (ACS), repeat revascularization and recurrent angina occurred more frequently after PCI, while occurrence of bleedings and new onset AF were more frequent after CABG. Neither completeness of revascularization nor severity of CAD was a predictor for any of the outcomes.

### Conclusion

Long-term mortality was higher in elderly patients with MVD undergoing PCI as compared to CABG. In addition, patients undergoing PCI had a higher risk of ACS, repeat revascularization and recurrent angina.

## Background

Coronary artery bypass grafting (CABG) has long been standard of care for patients with left main (LM) or multivessel disease (MVD). However, results of percutaneous coronary intervention (PCI) have been improved by better stents and more potent P2Y<sub>12</sub>-inhibitors. Therefore, the European Society of Cardiology (ESC) guideline for management of myocardial revascularization now recommends either CABG or PCI based on individual decision making by the local heart team, taking into consideration operation risk, complexity of underlying coronary artery disease (CAD), intracardiac and extracardiac factors and local expertise. Furthermore, it is emphasized that achieving complete revascularization is pivotal[1]. The ESC guideline does not advise on which revascularization strategy is preferred in elderly patients as compared to younger patients, probably because the optimal revascularization treatment in elderly is unknown. PCI is less invasive with shorter hospital stay and earlier return to daily activities compared to CABG. This is particularly relevant for elderly, in whom physical recovery after CABG procedures is substantially prolonged compared to younger patients[2]. Several observational studies have been conducted comparing PCI and CABG in the elderly ( $\geq 75$  years) with MVD and/or LM disease[3–6]. These studies found CABG to be associated with significantly lower risk for target vessel revascularization but no significant difference in all-cause death was found. These studies were performed in patients treated with first generation drug-eluting stents (DES) and dual antiplatelet therapy consisting of aspirin with clopidogrel. Also, patients treated with PCI or CABG were not similar with respect to completeness of revascularization and complexity of CAD. Therefore, aim of this study is to compare CABG with PCI in elderly ( $\geq 75$  years) patients with MVD or LM disease, considering completeness of revascularization and severity of coronary artery disease.

## Methods

### Study design

We conducted a retrospective, single-centre cohort study in the St. Antonius hospital, the Netherlands. All patients aged  $\geq 75$  years with MVD or LM disease who underwent revascularization between January 1<sup>st</sup>, 2012 and December 31<sup>st</sup>, 2016 were included. Patients underwent revascularization either by PCI or CABG, which was decided by a multidisciplinary heart team consisting of an interventional cardiologist and a cardiac surgeon. Patients who presented with ST-segment elevation myocardial infarction or who underwent emergency revascularization were excluded. All patients were treated according to the applicable guidelines at that moment. The surgical technique for CABG, the approaches used for stent implantation, and medication regimen post revascularization were left to the discretion of the treating physician. Patients were included if they had at least one year follow-up after the index procedure. Patients



with follow-up in other hospitals were sent a questionnaire inquiring about recurrent revascularization, myocardial infarction (MI), cerebral vascular accident (CVA), bleeding, angina or cardiac hospitalization. Indicated events were verified by assessing patients' medical records. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. A waiver for written informed consent was provided by the local ethics committee.

#### Data collection

Information was obtained from patients' medical records or retrieved from patients' general practitioner. Collected patients' characteristics included sex, age, diabetes mellitus, creatinine (mmol/l), history of CABG, history of atrial fibrillation (AF), location of lesions, completeness of revascularization (determined by location of lesions and revascularized vessels through reviewing the pre-procedural angiogram, procedural angiogram (PCI) and revascularization reports (PCI and CABG) by at least two qualified researchers), type of stent implanted (bare-metal-stent (BMS), second generation DES, bioresorbable vascular scaffold (BVS)), urgency of procedure and Euroscore I. Also, the national mortality register was consulted.

#### Definitions

A stenosis of  $\geq 70\%$  or fractional flow reserve measurement  $< 0.80$  was considered significant in a coronary vessel of  $\geq 2.0$  mm in diameter. A LM stenosis was considered significant when  $\geq 50\%$ . Multivessel disease was presence of a significant stenosis in the LM or at least two major coronary arteries. A procedure was considered elective when it was scheduled and performed on patients with stable coronary artery disease, urgent when it was performed in context of an acute coronary syndrome (ACS) and emergency when it was performed immediately because of the acute nature of the medical condition and increased morbidity or mortality associated with temporary delay in treatment[7]. Completeness of revascularization was determined as treatment of all significant lesions. ACS was defined according to the Fourth Universal Definition of myocardial infarction or unstable angina[8]. CVA was described as acute new neurological deficit by ischemic stroke which lasted  $> 24$  hours or ended in death within 24 hours, excluding haemorrhagic CVA's. Repeat revascularization was defined as revascularization with either PCI or CABG unless index treatment was scheduled as a staged procedure. In the absence of questionnaires, the following outcome measures were chosen to provide an indication of quality of life: recurrent angina, cardiac rehospitalisation and new onset AF. Recurrent angina was classified according to the Canadian Cardiovascular Society of Angina Grading scale. Angina definitely provoked by other causes e.g. anaemia or tachycardia was excluded. Angina was further subdivided into documented ischemia, which included either positive electrocardiogram exercise testing, stress imaging or when adjustment of pharmaceutical therapy for angina relieved the symptoms. Cardiac rehospitalisation was specified as readmission after the procedure for any

cardiac cause, e.g. heart failure or atrial fibrillation. New onset AF was captured when it occurred after the procedure and remained after discharge or presented post-discharge. Bleeding was classified according to Bleeding Academic Research Consortium (BARC) criteria, we captured BARC bleeding type 3 and 5[9].

#### Outcome

Primary outcome was all-cause mortality. We also captured ACS, CVA, recurrent angina, repeat revascularization, cardiac rehospitalisation, new onset AF and bleeding events.

#### Statistical analysis

Baseline characteristics were compared using Students t-test or Mann-Whitney U test for continuous variables and chi-square test for binary variables. Continuous data were expressed as mean  $\pm$  standard deviation (SD). Categorical variables were described as frequencies and percentages. Unadjusted primary and secondary outcomes were presented as Kaplan Meier curves, differences were assessed by using the log-rank test. Risk-adjusted hazard ratios (aHR) with 95% confidence intervals (CI) were estimated by Cox proportional hazard regression. Baseline variables with a p-value  $< 0.100$  in the univariate analysis were included in the multivariate analysis.  $P < 0.05$  was considered statistically significant.

## Results

A total of 597 patients were included, 346 in the PCI group and 251 in the CABG group. Median follow-up period was 4 years (IQR 2.8 - 5.3 years). Baseline characteristics are presented in table 1.

**Table 1.** Baseline characteristics

| Characteristics                                 | PCI (N= 346) | CABG (N=251) | P-value   |
|-------------------------------------------------|--------------|--------------|-----------|
| Male gender - N (%)                             | 225 (65)     | 183 (73)     | 0.041     |
| Age - year mean $\pm$ SD                        | 80 $\pm$ 3.9 | 79 $\pm$ 3.4 | $< 0.001$ |
| Age $\geq 80$ - N (%)                           | 186 (54)     | 98 (39)      | $< 0.001$ |
| Diabetes - N (%)                                | 93 (27)      | 75 (30)      | 0.433     |
| Creatinine $\mu\text{mol/L}$ mean $\pm$ SD      | 109 $\pm$ 85 | 102 $\pm$ 42 | 0.246     |
| Creatinine $\geq 200$ $\mu\text{mol/L}$ - N (%) | 10 (3.2)     | 6 (2.4)      | 0.573     |
| History of CABG - N (%)                         | 71 (21)      | 14 (5.6)     | $< 0.001$ |
| History of AF - N (%)                           | 43 (12)      | 23 (9)       | 0.125     |

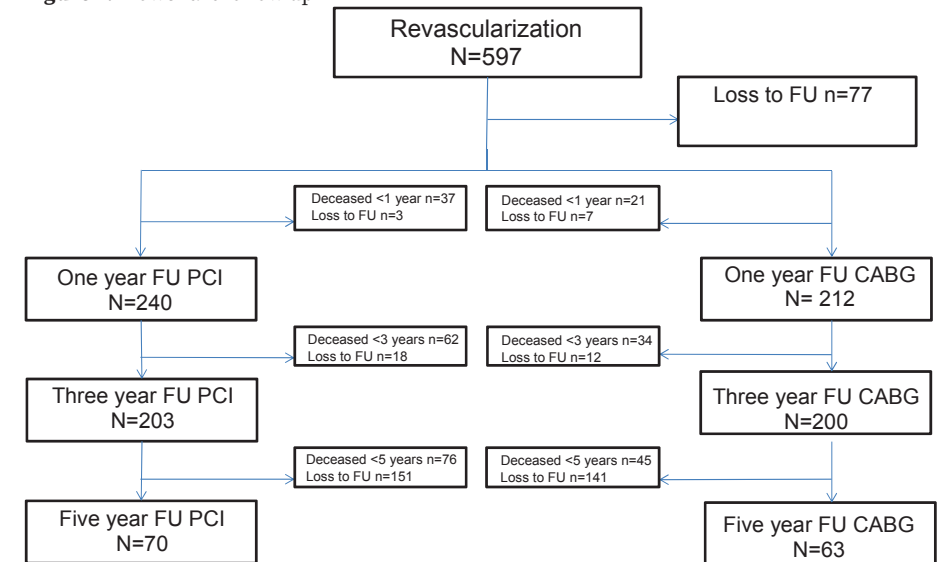
**Table 1.** Baseline characteristics (continued)

| Characteristics                    | PCI (N= 346) | CABG (N=251) | P-value |
|------------------------------------|--------------|--------------|---------|
| Status elective – N (%)            | 260 (75)     | 208 (83)     | 0.024   |
| Status urgent – N (%)              | 86 (25)      | 43 (17)      |         |
| Complete revascularization – N (%) | 102 (30)     | 179 (71)     | <0.001  |
| <b>Coronary artery disease</b>     |              |              |         |
| LAD >70% – N (%)                   | 263 (76)     | 233 (93)     | <0.001  |
| RCx >70% – N (%)                   | 231 (67)     | 192 (77)     | 0.010   |
| RCA >70% – N (%)                   | 236 (68)     | 192 (77)     | 0.027   |
| LM >50% – N (%)                    | 48 (14)      | 70 (28)      | <0.001  |
| Single LM disease – N (%)          | 12 (3.5)     | 3 (1.2)      | 0.080   |
| LM + 1VD – N (%)                   | 20 (5.8)     | 14 (5.6)     | 0.916   |
| LM + 2VD – N (%)                   | 4 (1.2)      | 30 (12)      | <0.001  |
| LM + 3VD – N (%)                   | 12 (3.5)     | 23 (9.2)     | 0.003   |
| 2VD – N (%)                        | 228 (66)     | 69 (28)      | <0.001  |
| 3VD – N (%)                        | 70 (20)      | 112 (45)     | <0.001  |
| <b>PCI characteristics</b>         |              |              |         |
| DES – N (%)                        | 309 (89)     |              |         |
| BMS – N (%)                        | 27 (7.8)     |              |         |
| BVS – N (%)                        | 2 (0.6)      |              |         |
| Balloon – N (%)                    | 81 (23)      |              |         |
| Number of stents mean ± SD         | 1.71 ± 1.0   |              |         |
| <b>CABG characteristics</b>        |              |              |         |
| Euroscore I mean ± SD              |              | 8.6 (7.7)    |         |
| LIMA – N (%)                       |              | 235 (94)     |         |

AF atrial fibrillation; BMS bare metal stent; BVS bioresorbable vascular scaffold; CABG coronary artery bypass grafting; DES drug-eluting stent; LAD left anterior descending artery; LM left main; PCI percutaneous coronary intervention; RCA right coronary artery; RCx ramus circumflex artery; SD standard deviation; VD vessel disease.

Patients who underwent PCI were older; 54% of patients in the PCI group was aged  $\geq 80$  vs. 39% in the CABG group ( $p < 0.001$ ). Patients in the PCI group more frequently had a previous medical history of CABG (21 vs. 5.6%,  $p < 0.01$ ) and more often needed urgent revascularization (25 vs. 17%,  $p = 0.024$ ) compared to patients in the CABG group. Patients who underwent CABG were more often male (73 vs. 65%,  $p = 0.041$ ), had more coronary segments involved, and had LM disease more frequently (28 vs. 14%,  $p < 0.01$ ) compared to patients who underwent PCI. Complete revascularization was more frequently achieved in patients undergoing CABG compared to patients undergoing PCI (71 vs.

30%,  $p < 0.01$ ). Incidence of diabetes mellitus and serum creatinine levels were similar in both groups. Among PCI patients, the majority received DES (89%). Most CABG patients received a left internal mammary artery graft (94%). Mean Euroscore I in the CABG group was 8.6. Loss to follow-up of the study population is presented in figure 1. For the primary outcome we checked the national mortality register, therefore, only 19 patients were loss to follow-up.

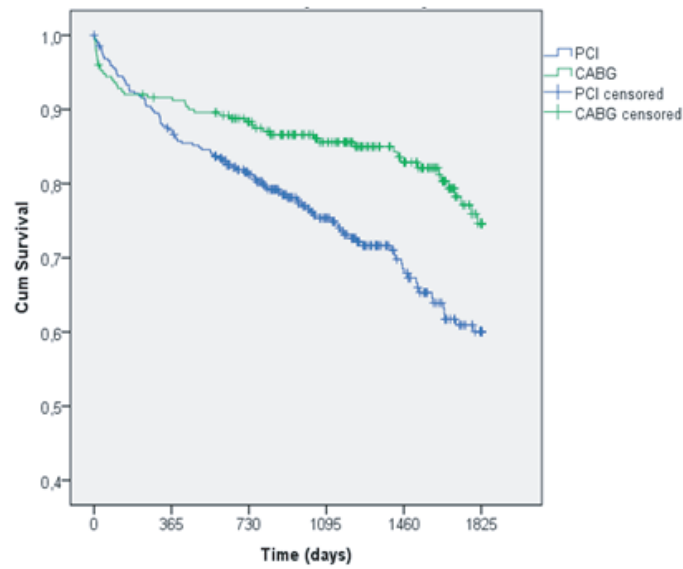
**Figure 1.** Flowchart follow up

CABG coronary artery bypass grafting; FU follow-up; PCI percutaneous coronary intervention.

### Mortality

The unadjusted analyses showed significantly higher long-term mortality rate after PCI compared to after CABG (39.9% vs. 25.4%,  $p = 0.001$ ; figure 2). Cox-regression analysis revealed older age, higher creatinine and LM disease to be independent predictors of long-term mortality. After adjustment for these predictors, 5-year mortality remained significantly higher after PCI (aHR 1.59 [95%CI 1.10-2.28],  $p = 0.013$ ).

**Figure 2.** Kaplan Meier survival curve for primary outcome



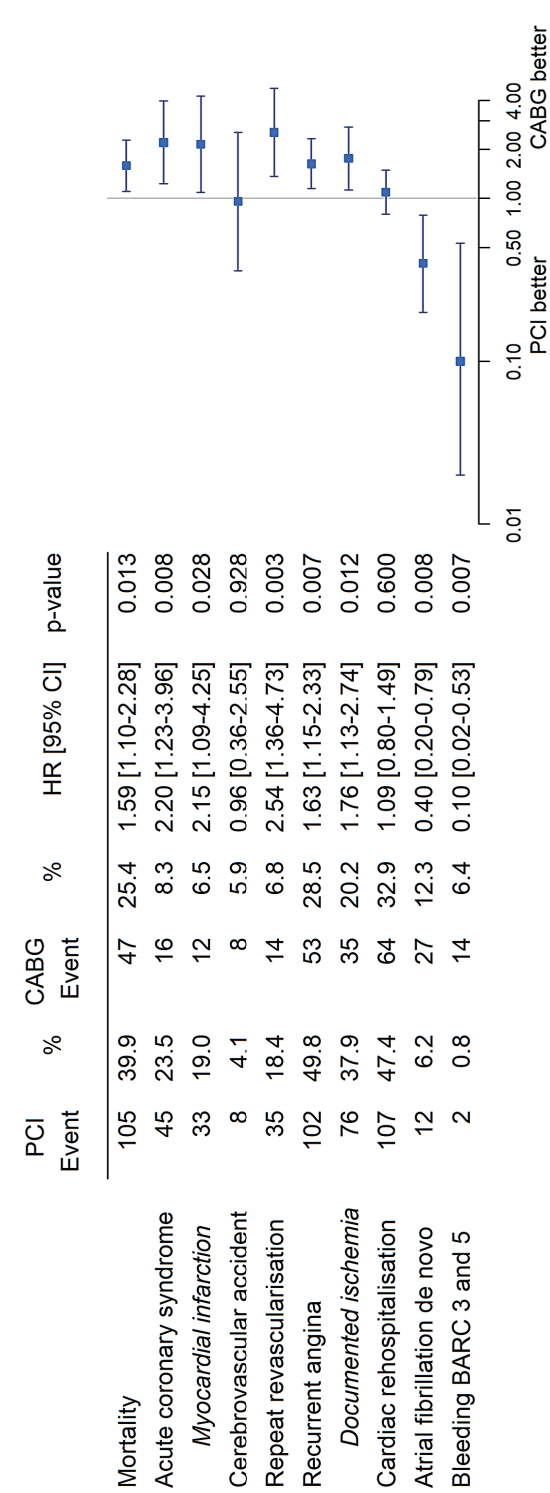
| Day(s)                      | 0   | 365 | 730 | 1095 | 1460 | 1825 |
|-----------------------------|-----|-----|-----|------|------|------|
| Number of patients at risk: |     |     |     |      |      |      |
| PCI:                        | 346 | 299 | 250 | 177  | 109  | 67   |
| CABG:                       | 251 | 227 | 205 | 164  | 116  | 56   |

CABG Coronary artery bypass grafting; PCI Percutaneous coronary intervention.

*Individual outcomes*

After adjustment for the concerning independent predictors, recurrent ACS, consisting of MI in 73% of cases (aHR 2.20 [95%CI 1.23- 3.96], p=0.008), repeat revascularization (aHR 2.54 [95%CI 1.36- 4.73], p=0.003) and recurrent angina (aHR 1.63[ 95%CI 1.15- 2.33], p= 0.007), all occurred more frequently in patients who underwent PCI compared to CABG. On the other hand new onset AF (aHR 0.40 [95%CI 0.20-0.79], p=0.008) and bleeding (aHR 0.10 [95%CI 0.02-0.53], p=0.007) occurred significantly more often in patients who underwent CABG. The incidence of CVA and cardiac rehospitalisation was comparable between both groups (figure 3).

**Figure 3.** Five-year outcomes after PCI and after CABG

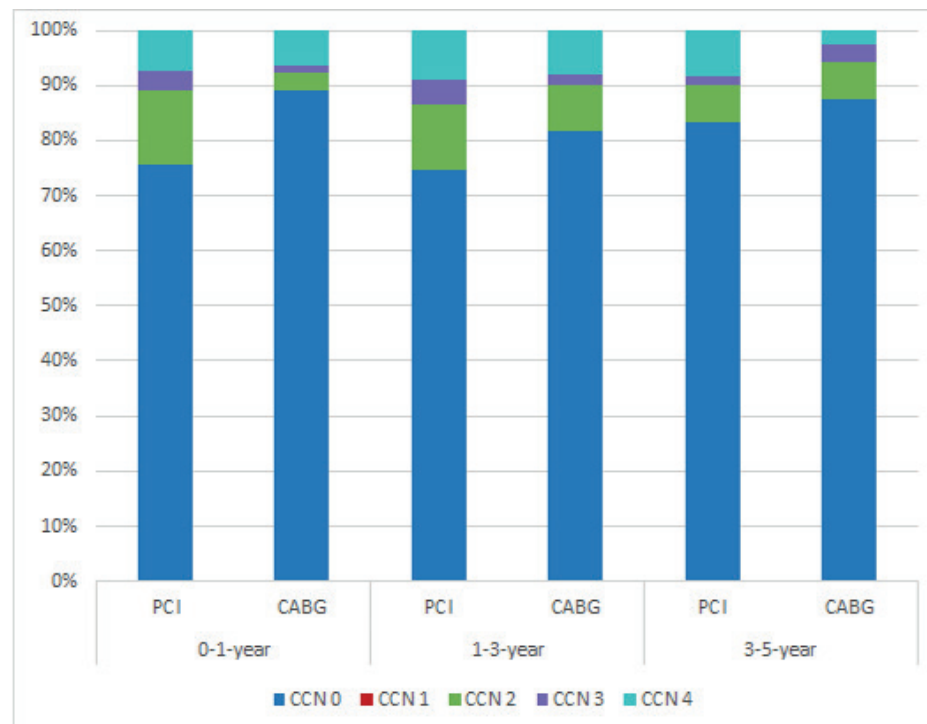


BARC bleeding academic research consortium; CI Confidence Interval, CABG Coronary artery bypass graft; HR Hazard Ratio, PCI Percutaneous coronary intervention.

### Recurrent angina

Recurrent angina during first year after index procedure developed more often in PCI patients compared to in CABG patients (24.4 vs. 9.2%,  $p < 0.001$ ). The difference between the two groups however decreased during follow-up (figure 4). Recurrent angina was caused by documented ischemia in 72% of cases, and differed significantly in favour of CABG (37.9 vs. 20.2%,  $p < 0.012$ ).

**Figure 4.** Recurrent angina classified according to the Canadian Cardiovascular Society of Angina grading scale



Grade 0 asymptomatic/absent angina. Grade I angina only with strenuous exertion. Grade II angina with moderate exertion. Grade III angina with mild exertion. Grade IV angina at rest.

## Discussion

In this large and unselected registry of patients aged 75 years or older with MVD or LM disease treated by PCI or CABG, we identified higher mortality after PCI compared to after CABG. In addition, we found patients undergoing PCI to have higher risk of ACS, recurrent angina, and repeat revascularization during follow-up. We expected to find

completeness of revascularization to be an independent predictor of adverse outcomes. However, in this analysis we could not confirm this hypothesis.

Studies with long-term follow-up of PCI versus CABG in elderly patients are scarce, and outcomes are inconsistent. In our study, mortality appeared to be higher after PCI compared to after CABG. This is in accordance with results from Nicolini et al. who compared PCI to CABG and included 1388 patients of  $\geq 80$  years with MVD and/or LM disease. They also found better survival after CABG compared to after PCI, although this was not statistically significant[6]. On the other hand, Sheridan et al. who included very old patients of  $\geq 85$  years with MVD and presentation with ACS, found significant benefit of CABG compared to PCI already after 2 years[10]. These differences in outcome between the two studies, could have been caused by differences in baseline characteristics, Nicolini included younger patients compared to Sheridan and patients were predominantly treated by BMS while DES were used in the study of Sheridan.

It is, however, debatable whether elderly patients value survival as the most important goal of revascularization. Therefore, we assessed recurrent angina, cardiac rehospitalisation and repeat revascularization after CABG and after PCI. These outcomes occurred significantly less frequent as early as one year following CABG as compared to after PCI. This is consistent with the literature where target vessel revascularization and heart failure hospitalizations occurred significantly less frequently in the CABG group compared to the PCI group[6,11]. This difference in repeat revascularization and hospitalization could be explained by more frequently occurring failure of revascularization (restenosis) after PCI than after CABG (graft failure) or by more complete revascularization after CABG compared to after PCI. The latter is however not corroborated by our study, where incomplete revascularization was not an independent predictor of death or major adverse cardiac and cerebral events.

The 2018 ESC guideline on myocardial revascularization recommends prioritizing completeness of revascularization when deciding between CABG and PCI, based on a meta-analysis of 35 randomized controlled trials and observational studies[12]. Complete revascularization was associated with reduced long-term mortality compared to incomplete revascularization which was observed both after CABG and after PCI. However, evidence concerning revascularization in octogenarians showed conflicting results [13,14]. In these elderly patients, it is suggested that complete revascularization is not necessary to provide good long-term prognosis. This is supported by Généreux et al. who, based on SYNTAX score, identified 70% completeness of revascularization to be sufficient to provide comparable long-term prognosis to 100% completeness of revascularization[15].

A strength of this study is the consistency and uniformity of both procedures during the study period in our centre, e.g. same decision making in the heart team, similar



and contemporary revascularization methods (performed by the same surgeons and cardiologists, and medical treatment after both revascularization methods was according to the same hospital protocols. This suggests that effects found in this study, are truly attributable to the revascularization method, while this may be different in multicentre studies. In addition, all coronary angiograms were reviewed and compared to revascularization reports to ascertain completeness of revascularization.

Some important limitations of this study should also be discussed. First, the retrospective design of the study may have resulted in selection bias allocating patients to one of the two revascularization strategies. By using adjustment through Cox-regression we tried to correct for the differences in baseline variables. However, we should take into account that this still could have had an influence on the results. In addition, in both groups, patients may have been included who had an absolute contraindication for the other revascularization strategy. Second, we were unable to measure quality of life. Quality of life is an important measure, especially at advanced age, and could differ between PCI and CABG patients, as the recovery and rehabilitation period after CABG is longer and more intense compared to after PCI. However, we evaluated recurrent angina and rehospitalisation as substitute outcomes, capturing, in our view, important aspects of quality of life.

To conclude, in this observational study, long-term mortality was higher in elderly patients of 75 years or older with multivessel disease undergoing PCI as compared to CABG. In addition, patients undergoing PCI had higher risk of ACS, repeat revascularization and recurrent angina.

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# Chapter 11

## Platelet Inhibition and Bleeding Risks in Patients Undergoing Non-Cardiac Surgery

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While there have been substantial advances in the use of antiplatelet therapies (APTs) in many conditions such as acute coronary syndrome and coronary interventions (1), the appropriate management of antiplatelet therapy for patients undergoing non-cardiac surgery remains a topic of discussion. With as many as one fifth of the patients requiring non-cardiac surgery within one year after coronary stent implantation (2), weighing the risk of hemorrhagic complications in the perioperative period against the possible ischemic complications, especially stent thrombosis after recent coronary stenting, is a critical decision for every physician involved.

Our current guidelines generally do not recommend the use of aspirin perioperatively (3). The POISE-2 trial randomized over 10,000 patients undergoing non-cardiac surgery to aspirin or placebo before surgery. Rates of myocardial infarction and death were not reduced by use of aspirin 30 days after surgery, whereas major bleeding did increase (4). However, considering only 23% of included patients had known coronary artery disease and all patients undergoing carotid endarterectomy were excluded in the trial, it is possible that patients with low perioperative bleeding risk and high thrombo-embolic risk, might benefit from aspirin perioperatively (3). For patients on dual antiplatelet therapy (DAPT) undergoing surgery, it is indeed recommended to perform surgery without discontinuation of aspirin or P2Y<sub>12</sub> inhibition if surgery is performed within one month after bare-metal stent implantation and three months after drug-eluting stent implantation. If surgery is planned outside these timeframes, current guidelines uphold a universal approach of five days withdrawal for clopidogrel and ticagrelor, and seven days for prasugrel prior to surgery and to continue aspirin (3,5). For all patients who are at especially high risk for stent thrombosis, bridging strategies can be contemplated (3,5).

As it is widely known that individual responses to clopidogrel and platelet function recovery after clopidogrel withdrawal highly vary (6,7), determining the right timing for surgery might be more appropriate with platelet function testing (PFT) that monitors the response of the patient to the withdrawal of clopidogrel exclusively.

In patients undergoing coronary revascularization surgery by coronary artery bypass grafting (CABG), platelet function monitoring is recommended in current guidelines as an option for timing of surgery instead of the standard withdrawal period of five days for clopidogrel (5,8). Assessment of platelet function predicts perioperative bleeding in patients undergoing cardiac surgery, as well as reduces blood transfusions and hence might decrease transfusion related complications, although clinical trials in various settings do not report a beneficial effect on postoperative mortality and surgical re-exploration rates (9–12). In a prospective, single-center non-randomized study, preoperative platelet function testing by thrombelastography in order to determine the timing of CABG in patients treated with clopidogrel, was associated with no excess bleeding when compared to clopidogrel-naïve patients, and led to preoperative

waiting time reduction of 50% as compared to what is recommended in the current guidelines (13). However, although platelet function testing is endorsed as a useful tool to determine appropriate timing of cardiac surgery, more research in this field is urgently needed as there is still much uncertainty about the optimal tests and cut-off values for determining timing of surgery.

In this issue of *Thrombosis and Hemostasis*, Mahla et al. presents the BIANCA study, a prospective study that examines the association between platelet reactivity to ADP and bleeding complications in non-cardiac surgery (14). In cardiac surgery, mechanisms of bleeding involve a complex interaction involving amongst others, hypothermia, excessive fibrinolysis, hemodilution from pump priming and, most importantly, platelet function defects due to cardiopulmonary bypass. While this effect might be absent in non-cardiac surgery, still the assessment of preoperative platelet function may optimize timing of non-cardiac surgery, and therewith minimize both bleeding and thrombotic complications, as Mahla et al suggest in their article.

Of the 197 patients included in this study, 84% underwent surgery within 48 hours after the last clopidogrel dose. Several platelet function tests were used to assess platelet reactivity preoperatively, namely light transmittance aggregometry (LTA), vasodilator stimulated phosphoprotein (VASP) assay, Multiplate analyzer and Innovance PFA200. Of these tests the LTA-assessed platelet reactivity was independently associated with bleeding complications.

The short withdrawal period before surgery and non-adherence to current guidelines is remarkable in itself and probably worthy of further investigation, inasmuch as that the large majority (82% of all patients) underwent elective surgery.

Furthermore, the short withdrawal period ensures preoperative variability in platelet inhibition, showing once again the variable recovery of platelet function and responsiveness to clopidogrel, as the authors stated. Unfortunately, this might have resulted in not being able to state conclusive correlations regarding Multiplate and Innovance PFA200 platelet inhibition testing and bleeding complications. General platelet reactivity even in the third tertile for Multiplate testing was well below the level of “high platelet reactivity”, and made it impossible to set a cut-off value for Innovance PFA200 platelet inhibition closure time in order to reflect normal platelet reactivity.

However, being the first prospective study evaluating the relationship between platelet function and bleeding complications conducted in patients undergoing non-cardiac surgery, the BIANCA study gives us some well-needed direction that maybe the “one size fits all” approach in patients with DAPT undergoing non-cardiac surgery, might not be the best approach.



Furthermore, the concept of platelet function guided timing of surgery, needs deliberation. The test that will eventually be used in clinical practice, will ideally be easily (and quickly) applicable, have low inter- and intra- variability, and will not be too costly. There are also multiple clinical risk scores of varying complexity that have been used to predict bleeding in various clinical settings (15, 16), but such clinical scores will usually have their predictive value improved by biomarkers, such as platelet function tests. Ultimately, more focus on simple assessments and modifiable bleeding risk factors has been advocated (17). These requirements make deciding for the most suitable approach for platelet function guided timing for surgery difficult.

An abundance of potential tests are available that could be used to monitor platelet function. Point of care platelet function test differ in their assay principle, and results are almost impossible to compare. Thus, very little consensus exists on the optimal test on determining platelet function. The classical platelet function test is light transmittance aggregometry (LTA). Notwithstanding, as Mahla et al. indicate, the LTA needs extensive work and expertise and is difficult to reproduce due to lack of standardization. This makes it probably less suitable for the repeated testing that is required in platelet function guided timing of surgery. Of the tests used in this study, the VASP is also time consuming and needs experienced executors. The Innovance PFA200 is easy to learn and semiautomatic, whereas the Multiplate needs some labwork. Another test that might be considered to be used in platelet function guided timing of surgery, is the VerifyNow P2Y12 assay. The VerifyNow P2Y12 assay, is a point-of-care test with results that are rapidly available, has good reproducibility and results of the assay have been shown to correlate well with the LTA (18). Moreover, since sometime it is known that intraoperative platelet function testing in patients undergoing cardiac surgery may lead to costs savings, this effect being especially distinct in patients using ADP-receptor inhibitors (19). Recent evidence appears to indicate that VerifyNow P2Y12 platelet function guided timing of surgery in patients undergoing bypass surgery and/or valve replacement could also cause cost savings by reduced in-hospital waiting time and physician time management, outweighing the costs of the tests (20).

Platelet function guided timing of surgery in non-cardiac surgery patients on DAPT appears to be a promising method. Directing available resources from a “one size fits all” approach, which is still state of the art in both cardiac and non-cardiac surgery, to a more targeted approach, which is far more suitable for the individual patient, it might thereby be possible not only to limit cost-effectiveness of patients scheduled for surgery and after surgery, but, more importantly, also to curtail severe hemorrhagic and ischemic complications for individual patients.

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# Chapter 12

## Summary and Discussion

## Summary

This thesis aimed at researching the optimization of thrombosis and hemostasis in patients undergoing coronary artery bypass surgery (CABG) or heart valve surgery. In part one (chapter 2–4), hemostasis during cardiac surgery is discussed, specifically with regard to bleeding complications.

In chapter 2, we examine the impact of aspirin-responsiveness, as preoperatively measured with the VerifyNow aspirin assay, on 12-hour blood loss after cardiac surgery in patients undergoing coronary artery bypass grafting (CABG). We compared the 12-hour postoperative blood loss in aspirin-sensitive and aspirin-resistant CABG patients, based on a cut-off value of 550 ARU. Mean 12-hour blood loss differed significantly between aspirin-sensitive patients and aspirin-resistant patients, and, in addition, all bleeding events presented in aspirin-sensitive patients.

In chapter 3, we assess platelet function with point-of-care multiple electrode aggregometry (MEA) at four different time points and in response to stimulation with four different receptor agonists, in patients undergoing combined CABG and heart valve surgery. A reduced ADP-induced platelet aggregation at baseline was significantly associated with increased 24-hour postoperative blood loss. The association remained present after adjusting for additional risk factors for postoperative blood loss.

In chapter 4, associations of 24-hour postoperative bleeding and perioperative fibrinogen concentrations and whole-blood viscoelastic tests at four time points are researched in patients undergoing combined CABG and heart valve surgery. Perioperative fibrinogen concentrations were associated with 24-hour blood loss at all time points (the correlation being a negative one), as well as several results from the thromboelastography (TEG) assay. Viscoelastic clot strength (TEG – MA (maximum amplitude)) had the strongest association and could be included in a model to predict postoperative blood loss and help with clinical decision making, for example with regard to perioperative red blood cell (RBC) transfusions.

In part two (chapter 5–9), thrombosis and hemostasis in the perioperative setting is discussed, especially with regard to a common and feared complication after CABG, namely occlusion of the venous grafts. Chapter 5 discusses vein graft patency and therapies to improve this. Chapter 6 introduces the POPular CABG trial and relates the rationale and design of this randomized, placebo-controlled multicenter trial, in which patients who received  $\geq$  one saphenous vein graft (SVG) during CABG were randomized to ticagrelor or placebo added to standard therapy with aspirin. The primary outcome was SVG occlusion at one year, assessed with coronary computed tomography angiography, the secondary outcome was one-year SVG failure, which was a composite of SVG occlusion, SVG revascularization, myocardial infarction in

myocardial territory supplied by a SVG, or sudden death. In chapter 7, the results of this trial are presented. The SVG occlusion did not differ significantly between the ticagrelor group and the placebo group, neither did the rates of SVG failure. Thereby we conclude that the addition of ticagrelor to standard aspirin does not reduce SVG occlusion rates at one year after CABG. Unfortunately, we found out after publication of the article, that an error had been made in the unblinding procedures of the trial, thus resulting in the use of an incorrect randomization list for one participating site, affecting the results of the trial and posing the need for revision of the publication. The revised article is presented in chapter 7, and in chapter 8, we analyze and review the error that had been made, as we think other researchers might benefit from the insights we have acquired. Chapter 9 describes the perioperative management of antiplatelet therapy in patients undergoing CABG.

Part three (chapter 10 and 11) focuses on the optimization of postoperative thrombosis and hemostasis after CABG. In chapter 10, we aim to compare long-term follow-up of elderly patients undergoing CABG or percutaneous coronary intervention (PCI). This retrospective cohort study found that long-term mortality was higher in elderly patients undergoing PCI compared with CABG. In addition, patients undergoing PCI had a higher risk of ACS, repeat revascularization and recurrent angina. Neither completeness of revascularization nor severity of coronary artery disease was a predictor for any of the outcomes. As many patients require non-cardiac surgery someday after a cardiac intervention, chapter 11 summarizes the state of the art on antiplatelet therapy in patients undergoing non-cardiac surgery.

## Discussion

### *Thrombosis and hemostasis during surgery*

Maintaining the balance between thrombosis and hemostasis is a notorious subject for any physician dealing with blood thinning medication – however, in cardiac surgery, physicians walk a very thin line. We know antithrombotic medication is beneficial in the general population (1) and guidelines recommend perioperative aspirin use, however, it most probably increases bleeding complications as well (2), and those come with devastating consequences for individual patients.

For that reason, a hot topic in science remains the search for tests that predict bleeding events in patients undergoing cardiac surgery. As we already explained, a key factor for the usability of these tests is their point-of-care nature, in order to be able to use the results directly to prevent upcoming bleeding events. In this thesis, we have investigated if certain point-of-care tests can be used to predict blood loss (chapter 2,3,4). Indeed, we found that certain platelet-function tests and viscoelastic coagulation tests can predict blood loss, although these results are contradicted by other studies (3,4).

Hemostasis is an extremely complicated and multifactorial process and blood loss is influenced by a lot of factors as for instance, use of cardiopulmonary bypass, cardiopulmonary bypass time, EuroSCORE and perioperative use of a P2Y12-inhibitor (as we again demonstrated in chapter 4 of this thesis) (5,6). Accordingly one can argue the value of preoperative platelet function testing might be limited. Surely, a standardized, point-of-care platelet function test with results that have an indisputable relation to clinical outcome is still lacking. Nevertheless, perhaps the value of point-of-care testing might not lie so much in the test result itself, but rather in the context of the test result in respect to other parameters and patient characteristics, or already designed risk scores and algorithms (7,8), which in combination can facilitate more personalized treatment of the individual patient.

In fact, the 2017 European Society of Cardiology Guidelines on patient blood management for adult cardiac surgery and the 2021 STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management (9,10) recommend perioperative treatment algorithms based on point-of-care testing to guide the number of transfusions and to reduce bleeding (Class IIa, Level B and Class I Level B-R). Needless to say, transfusions can be necessary to correct for anemia during surgery. Nonetheless, intraoperative RBC transfusions have been linked to adverse events, such as infectious disease transmissions, transfusion-related acute lung injury, and mortality (11–13) and by now several randomized controlled trials as well as two meta-analysis (14,15) have concluded that a restrictive perioperative allogeneic RBC transfusion strategy is preferred to a liberal transfusion strategy for perioperative blood conservation, as it reduces both transfusion rate and units of allogeneic RBCs without increased risk for mortality or morbidity (level 1, Class A). Even so, two meta-analysis evaluating the effect of point-of-care platelet function and viscoelastic testing to guide transfusion management confirm that point-of-care testing can reduce transfusions and bleeding, but fail to demonstrate a direct effect on clinical outcomes (16,17), although it can be assumed to be present.

Thereby promising in concept: the use of so many different tests, algorithms and strategies in perioperative point-of-care testing emphasizes another important drawback in the universal implementation of point-of-care testing in cardiac surgery. Results of various tests often correlate poorly with each other and with the gold standard (18,19) and unambiguous cut-off-values for interventions are yet to be determined (9,10,20). Of course, different tests measure different components of platelet function and coagulation, and disagreements between the results of the assays can often be attributed to this, but not singularly. More research is needed to establish definite cut-off values that accurately predict perioperative risk of bleeding (or thrombosis) and transfusion triggers.

Still, as not all intertest variability can be explained by the timing and assay used, it has increasingly been suggested that in order to predict bleeding events reliably, a combination of different platelet function tests and/or viscoelastic assays should be implemented. Whether or not this would be desirable with regard to cost-effectiveness, also remains a topic for future research.

#### *Graft patency*

Preserving graft patency after CABG remains an important long-term target after CABG, as clinical outcomes after CABG are strongly related with (long-term) graft patency (21–23). Although better patency rates have been reported with arterial grafts, and guidelines recommend the use of a second arterial as an adjunct to LIMA-LAD (left internal mammary artery to left anterior descending artery) in suitable patients (24–26). In spite of that, better outcomes with a second arterial graft are not indisputably proven (27,28). The SVG still remains the most commonly used second conduit (29), and also for good reasons: bilateral internal mammary grafting is presented with a higher postoperative complication rates, the procedure is more technically challenging with a steep learning curve, and has a longer operation time (30).

The idea that SVG patency could be improved by extra antithrombotic medication follows quite logically as it is known that 1) SVG occlusion is a (partially) platelet-mediated process, 2) aspirin reduces SVG occlusion after CABG and 3) and 10%-90% of patients (transiently) display aspirin resistance after CABG (31–33). Also, though of course not necessarily comparable with CABG, the results of additional antithrombotic medication in addition to aspirin in the other method of revascularization, namely percutaneous coronary interventions (PCI), are of course extremely positive (34,35). Nonetheless, we were unable to confirm the beneficial effect of stronger antithrombotic therapy on graft patency (chapter 7).

Even so, other studies investigating the effect of additional antiplatelet or anticoagulant therapy after CABG on graft patency present conflicting results as well. It has been known that the addition of dipyridamole to aspirin does not provide any additional benefit (36) and studies disagree on the result of clopidogrel (37–40). Studies that investigated oral anticoagulant therapy suggested that overall oral anticoagulation provided no superior SVG patency rates when compared with aspirin (41–44), and caused more bleeding complications (42). Until present we have only limited evidence concerning novel oral anticoagulants (NOACs) and SVG patency. The COMPASS-CABG substudy concluded that neither rivaroxaban plus aspirin, nor monotherapy with rivaroxaban showed benefit above aspirin monotherapy regarding graft patency, thus being in line with VKA studies regarding SVG patency (45). The authors suggest a reduction in major adverse cardiac and cerebrovascular events (MACCE) in the rivaroxaban plus aspirin group similar to the main study, but it is certain that more research is needed to confirm this statement.



We can only speculate on the causes why we were not able to confirm the hypothesis that additional antithrombotic therapy would improve SVG patency. SVG occlusion might be a less platelet-mediated process than expected, and might be influenced by other variables that have a stronger effect on SVG occlusion than additional antithrombotic medication does not affect. It has indeed been suggested that perhaps these SVG patency rates are 'as good as it gets' (46), and that more aggressive antithrombotic therapy will not improve the one-year occlusion rates up to 16% (47–49), of which the far majority occlude in the first week after CABG (36), most probably due to reasons that have nothing to do with sufficient platelet inhibition, but rather with technical factors such as an impacted outflow or diseased target vessel. Indeed, in our randomized, placebo-controlled trial (chapter 6 and 7), we found lower SVG occlusion rates than we expected (1-year occlusion rate of 10.1% in the aspirin monotherapy group as opposed to an expected 15% when we designed the trial). That may be the case, still, it would be interesting to evaluate the effect of additional antithrombotic therapy to aspirin in the first year on long-term SVG occlusion. Even if the first two phases of SVG occlusion that are directly platelet-mediated mechanisms (thrombotic occlusion and intimal hyperplasia) occur in the first postoperative month up until the first year after CABG, these platelet-mediated processes lay the foundation for the atherosclerosis that causes SVG occlusion on the long term.

The areas in which we can attempt to improve graft patency are vast. Whether other interventions (such as intraoperative flow-assessment, on-pump/off-pump surgery, harvesting and preservation techniques, additional lipid-lowering medication etcetera) or promising future techniques (such as external stenting of the graft, gene therapy or immunomodulation) can definitely improve graft patency and, more importantly, clinical outcomes, is a topic for future research and lies beyond the scope of this thesis.

We would like to emphasize that, even though the evidence for additional P2Y<sub>12</sub>-inhibition for improved SVG patency is not convincing, it does not contradict current guidelines in recommending P2Y<sub>12</sub>-inhibition in patients undergoing CABG for acute coronary syndromes. These patients might benefit more from P2Y<sub>12</sub>-inhibition after CABG, although guidelines' recommendations for resuming P2Y<sub>12</sub>-inhibition in ACS are largely based on expert opinion (24,50). Evidence regarding ticagrelor after CABG is derived from a retrospective analysis from a nonrandomized subgroup of the PLATO trial (34,51), in which the resumption of study medication was late (57% within 7 days after CABG, 84% within 14 days) and at discretion of the treating physician. Still, taking all evidence into account, we think it highly probable that aggressive antithrombotic therapy is advantageous in this high-risk population. For all that, it would surely be desirable to see this presumption confirmed by data from a randomized controlled trial, and needless to say, possible advantages of more potent antithrombotic therapy should always be weighed against possible harmful effects, such as bleeding events.

In that context, one thing to keep in mind when discussing graft patency, is that the aim always should be to treat the patient and not only the graft. Although SVG occlusions are certainly correlated with adverse clinical outcomes, it remains a surrogate outcome and SVG occlusion is not directly causatively related with adverse events that impact the patient (52).

When we put the patient first, it should be remembered that CABG, although an important and excellent procedure for treatment of angina complaints, improving survival and quality of life, remains a palliative treatment and not a cure for coronary artery disease (53). Consequently, at first preventing the need for CABG, and when that is too late, preventing progression of coronary artery disease by promotion of a healthy lifestyle remains paramount and another area in which much can be gained in the future.

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# Appendices



## I. Nederlands Wetenschappelijke Samenvatting

Hart- en vaatziekten zijn de belangrijkste oorzaak van mortaliteit wereldwijd. Operatieve behandeling van hart- en vaatziekten door middel van een CABG ('Coronary Artery Bypass Grafting Surgery' oftewel een omleidingsoperatie) heeft in bepaalde patiëntpopulaties de voorkeur boven een percutane behandeling van hart- en vaatziekten (percutane coronaire interventie; PCI, dotter). Behandeling van coronaire atherosclerose door middel van CABG kan zowel overleving als kwaliteit van leven verbeteren in patiënten met coronaire atherosclerose.

Aangezien de vermindering van het trombotisch risico onvermijdelijk een verhoging van het bloedingsrisico tot gevolg heeft, is het behouden van de optimale balans tussen trombose en hemostase in cardiale chirurgie een grote uitdaging. Zoals bekend hebben patiënten met coronaire atherosclerose (dus patiënten die een CABG ondergaan) groot belang bij een verlaging van hun trombotisch risico, maar de daarmee volgende verhoging van het bloedingsrisico kan vooral tijdens de operatie gevaarlijke complicaties tot gevolg hebben. Daarbij oefenen bepaalde factoren die inherent aan CABGs verbonden zijn invloed uit op het hemostatisch evenwicht (denk bijvoorbeeld aan het gebruik van een hartlongmachine of de veelvoorkomende noodzaak tot bloedtransfusies).

Dit proefschrift richt zich op het optimaliseren van trombose en hemostase in patiënten die cardiale chirurgie ondergaan, in het bijzonder CABG in combinatie met of zonder klepchirurgie.

Deel 1 (hoofdstuk 2 tot en met 4) van dit proefschrift bediscussieert hemostase gedurende of direct na de chirurgie. In deze context is optimalisatie van trombose en hemostase voornamelijk gericht op het voorkomen van bloedingscomplicaties. Een eerste noodzakelijke stap in dit proces is het identificeren van patiënten die een hoog risico hebben op bloedingen. De studies beschreven in hoofdstuk 2 tot en met 4 onderzoeken in hoeverre bepaalde meetbare onderdelen van de coagulatie zich verhouden tot postoperatief bloedverlies.

In hoofdstuk 2 wordt het onderzocht wat het effect is van aspirine-gevoeligheid op bloedverlies na CABG. Aspirine-gevoeligheid is in dit onderzoek bepaald door preoperatief de trombocytreactiviteit (oftewel plaatjesfunctie) te meten met de VerifyNow aspirin assay, waarbij de afkapwaarde van 550 ARU (aspirin reaction units) werd gehanteerd voor aspirine-resistentie. Bloedverlies 12 uur na de operatie werd vergeleken tussen aspirine-gevoelige en aspirine-resistente patiënten, waarbij bleek dat het gemiddelde bloedverlies bij aspirine-gevoelige patiënten significant hoger lag dan bij aspirine-resistente patiënten. Daarbij bleken alle klinisch relevante bloedingen zich te hebben voorgedaan bij aspirine-gevoelige patiënten. Dit onderzoek lijkt te suggereren

dat aspirine-gevoeligheid geassocieerd is met een verhoogde bloedingsneiging tijdens en vlak na de CABG.

Ook hoofdstuk 3 onderzoekt plaatjesfunctie in relatie tot postoperatief bloedverlies. In deze studie is bij patiënten die een CABG met klepvervangende ondergingen de trombocytreactiviteit in reactie tot vier verschillende receptoragonisten (ADP, AA, COL, TRAP) bepaald door de multiple electrode aggregometry (MEA) op vier verschillende perioperatieve tijdstippen (I Baseline, voor anesthesie-inductie, II Tijdens cardiopulmonaire bypass, III Na decannulatie en toediening van protamine, IV bij aankomst op de intensive-care unit). Er kon worden geconcludeerd dat een verminderde ADP-geïnduceerde trombocytengregagatie bij baseline is geassocieerd met een hoger 24-uurs postoperatief bloedverlies.

Hoofdstuk 4 onderzoekt de associatie tussen 24-uurs postoperatief bloedverlies, perioperatieve fibrinogeenconcentraties, en een visco-elastische stollingstest (tromboelastography; TEG) in patiënten die electieve CABG met klepvervangende, of multiple klepvervangende zonder CABG ondergaan. Alle coagulatiestesten (inclusief TEG en fibrinogeen) werden gemeten op vier verschillende perioperatieve tijdstippen (I Baseline, voor anesthesie-inductie, II Tijdens cardiopulmonaire bypass, III Na decannulatie en toediening van protamine, IV bij aankomst op de intensive-care unit). De perioperatieve fibrinogeenconcentraties op elk tijdstip waren negatief geassocieerd met 24-uurs bloedverlies. Ook enkele TEG-uitslagen waren geassocieerd met bloedverlies, waarvan TEG-MA (clot strength) op tijdstip III de sterkste associatie toonde. Deze studie toonde eveneens dat fibrinogeen of TEG-MA op tijdstip 3 geïncorporeerd kon worden in een model dat bloedverlies voorspelde.

Deel 2 (hoofdstuk 5 tot en met 9) van dit proefschrift behandelt trombose en hemostase in de perioperatieve setting en introduceert een veelvoorkomende en gevreesde complicatie na CABG, namelijk occlusie van de veneuze bypass graft.

De houdbaarheid ('patency') van deze veneuze omleidingen en mogelijkheden om deze houdbaarheid te verbeteren zijn het onderwerp van de review in hoofdstuk 5.

De POPular CABG studie vormt hoofdstuk 6 tot en met 8 van dit proefschrift. De POPular CABG studie is een multicenter, placebo-gecontroleerde, dubbelblinde gerandomiseerde gecontroleerde studie, waarin 499 patiënten die een of meer veneuze bypass graft(s) hebben gekregen bij hun CABG werden gerandomiseerd naar standaardtherapie met enkel aspirine of naar dubbele antitrombotische therapie met aspirine en ticagrelor. De primaire uitkomst, namelijk occlusie van de veneuze graft, werd gemeten op CCTA (coronary computed tomography angiography) 1 jaar na CABG. In hoofdstuk 6 wordt de rationale en design van deze studie gepresenteerd.

Hoofdstuk 7 bespreekt de resultaten van de POPular CABG studie. Het aantal veneuze bypass graft occlusies verschilde niet significant tussen de groep patiënten die aspirine monotherapie had gebruikt en de groep die dubbele antitrombotische therapie met aspirine en ticagrelor had gebruikt. Daaruit kon geconcludeerd worden dat het toevoegen van ticagrelor aan de standaardtherapie met aspirine na CABG geen effect heeft op het verminderen van het aantal veneuze graft occlusies na CABG.

Pas na publicatie van de resultaten, ontdekten wij dat er een onfortuinlijke fout was gemaakt in deblinderingsprocedure van de POPular CABG, waardoor er een onjuiste randomisatielijst was gebruikt voor een van de deelnemende centra. De invloed van deze fout op de resultaten van de studie was dusdanig, dat het noodzakelijk was het stuk te reviseren (de gereviseerde versie is gepubliceerd in hoofdstuk 7 van dit proefschrift). Hoofdstuk 8 analyseert hoe deze fout in de deblinderingsprocedure heeft kunnen plaatsvinden, en hoe wij trachten te voorkomen dat deze in de toekomst plaatsvindt, met als idee dat andere onderzoekers mogelijk kunnen leren van deze fout, of anderszins baat zouden kunnen hebben bij de inzichten die wij hebben opgedaan.

In hoofdstuk 9 bestudeert de toenmalige positie van Nederlandse cardiothoracale centra ten opzichte van antitrombotische therapie rondom CABG.

Deel 3 van dit proefschrift (hoofdstuk 10 en 11) focust zich op de optimalisatie van trombose en hemostase op lange termijn na een CABG. Het retrospectieve cohortonderzoek dat in hoofdstuk 10 wordt beschreven had als doelstelling uitkomsten op lange termijn te vergelijken tussen ouderen die een CABG of een PCI hadden ondergaan. Mortaliteit op lange termijn bleek vaker voor te komen bij ouderen die een PCI hadden ondergaan in vergelijking tot ouderen die een CABG hadden ondergaan, ook hadden ouderen die een PCI hadden ondergaan een hoger risico op een nieuw acuut coronair syndroom, een nieuwe revascularisatie en nieuwe anginaklachten.

Aangezien veel patiënten na een coronaire interventie ooit een andersoortige, niet-cardiale, operatie behoeven, worden in hoofdstuk 11 de geldende ideeën omtrent regulatie van antitrombotische therapie en operaties samengevat.

## II. Samenvatting voor Geïnteresseerden

### ACHTERGRONDINFORMATIE MET BETREKKING TOT DIT PROEFSCHRIFT

Dit proefschrift gaat over bloedstolling bij patiënten die hartoperaties ondergaan. Hier zal eerst enige noodzakelijke verduidelijking over de inhoudelijke achtergrond worden gegeven.

#### De bloedstolling

Onze bloedstolling (hemostase) is een magnifiek systeem. Bloedstolling is ongelooflijk complex en bestaat uit talloze onderdelen. Het is een beetje te vergelijken met radertjes in een machine: de verschillende onderdelen van de bloedstolling zijn tandwielletjes die elkaar in werking zetten en elkaar beïnvloeden. Alleen in goede samenwerking zorgen die radertjes voor een lopende machine: een werkende bloedstolling. Het doel van bloedstolling is het voorkomen van bloedverlies bij een beschadiging van een bloedvat, door de vaatwand te dichten. Onze bloedstolling is in te delen in verschillende fasen: vasoconstrictie, de primaire en secundaire hemostase en fibrinolyse (1, 2).

#### *Vasoconstrictie en primaire hemostase*

Bij beschadiging van een bloedvat zal het bloedvat samenknijpen (vasoconstrictie), waardoor er minder bloed naar de wond wordt toegestuurd. Vervolgens vindt de eerste stap in de hemostase plaats: de primaire hemostase, die zelf weer bestaat uit drie stappen. In de primaire hemostase speelt het bloedplaatjessysteem de hoofdrol. De eerste stap in de primaire hemostase is het activeren van de bloedplaatjes (trombocyten) door collageen dat vrijkomt in de beschadigde vaatwand. Door deze activatie komen stoffen vrij die normaal in het bloedplaatje opgeslagen liggen en die zorgen voor nog meer activatie van bloedplaatjes. Stap twee noemen we ‘trombocytenadhesie’ waarin de geactiveerde bloedplaatjes vastplakken aan de beschadigde vaatwand. (Voor degenen die echt geïnteresseerd zijn: door binding aan circulerend Van Willebrand factor, dat de functie van ‘brugmolecuul’ op zich neemt en op zijn beurt weer bindt aan collageen in de vaatwand, of door binding aan fibronectine dat aan collageen bindt). Het bloedplaatje verandert nu ook van vorm, van een simpel ‘bolletje’ in een spin met uitlopers (figuur 1a en b).

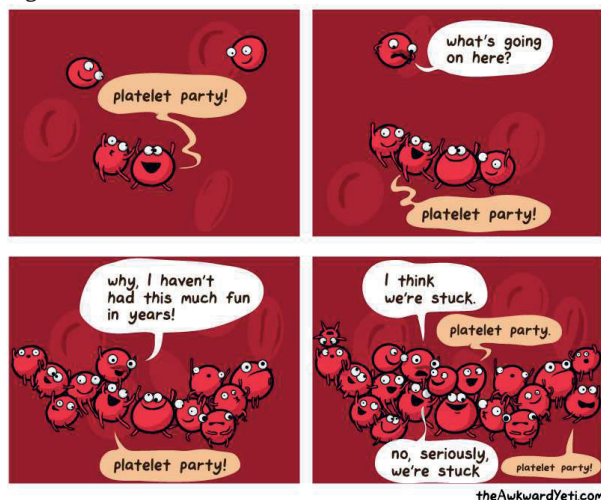
Figuur 1a en b



Niet geactiveerde en geactiveerde bloedplaatjes. Overgenomen van Trombosedienst Leiden (<https://trombosedienst-leiden.nl/trombose-3/trombose/de-bloedstolling/>).

Daarmee is de derde stap, de trombocytenuitbarsting, begonnen. Door deze vormverandering komt een cruciale receptor vrij. Een receptor past precies op een bepaald molecuul, goed te vergelijken met een sleutel en een slot. In dit geval gaat het om de GP-IIb/IIIa-receptor. De GP-IIb/IIIa-receptor kan fibrinogeen (een molecuul) binden, dat een verbinding gaat vormen tussen de bloedplaatjes onderling. De geactiveerde bloedplaatjes zitten zo aan elkaar vast en vormen samen een plug die de beschadiging in de vaatwand dicht (figuur 2, Seluk 2020). De primaire hemostase is daarmee afgerond.

Figuur 2



De derde stap van de hemostase: de trombocytenuitbarsting. Overgenomen van N. Seluk, 2020. The Blood Clot (<https://theawkwardyeti.com/comic/blood-clot/>). © 2020 The Awkward Yeti LLC.

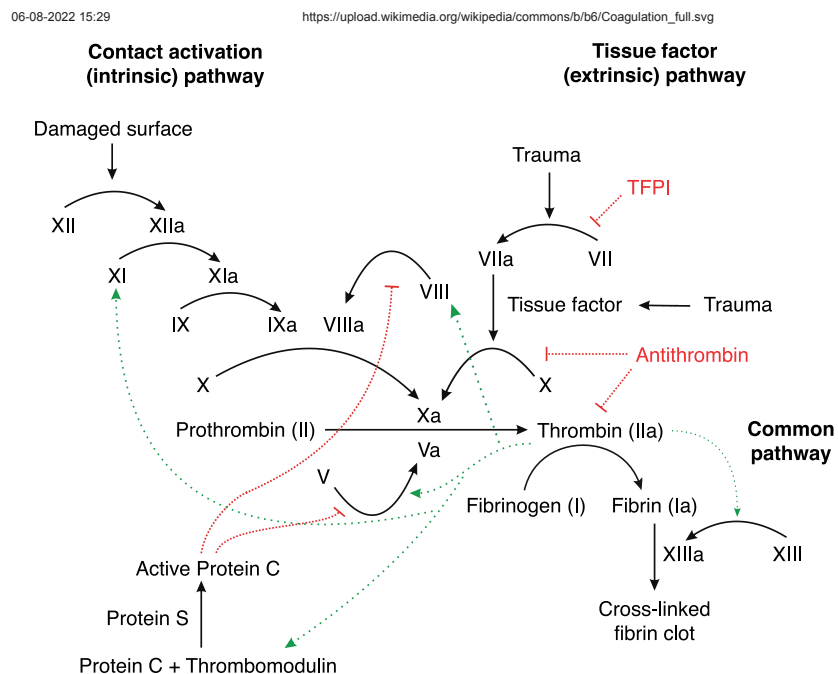
### Secundaire hemostase en fibrinolyse

De secundaire hemostase speelt zich, anders dan de naam doet vermoeden, min of meer tegelijk af met de primaire hemostase (al verloopt de secundaire hemostase veel langzamer). Het is het tweede systeem waarvan onze bloedstolling afhankelijk is, vandaar de term 'secundair'. Het uiteindelijke doel van de secundaire hemostase is het omzetten van de flexibele fibrinogeenmoleculen (de moleculen die de bloedplaatjes in de prop met elkaar verbinden, net ook besproken in de primaire hemostase) in harde, stabiele fibrinedraden die aan elkaar, de verbonden bloedplaatjes en de wondranden hechten. Daarmee komen primaire en secundaire hemostase samen en vormen het bloedstolsel (oftewel het korstje op een wond), eindproduct van de stolling.

Deze secundaire hemostase (ook wel coagulatie genoemd) bestaat uit zo'n twintig (bekende) eiwitten die als enige functie hebben de coagulatie te regelen, ook wel stollingsfactoren genoemd. Onze lever maakt deze stollingsfactoren, die normaal gesproken in inactieve vorm in ons bloed rondzwemmen. Een beschadiging in de vaatwand leidt tot activatie van een stollingsfactor, die een kettingreactie (ook wel coagulatie-cascade genoemd) in gang zet, waarbij activatie van een factor leidt tot activatie van de hele ketting en uiteindelijk ertoe leidt dat fibrinogeenmoleculen worden omgezet in fibrine. Dit is beknopt weergegeven de secundaire hemostase, en in principe voldoende om het systeem te begrijpen. Onderstaande paragraaf waarin de coagulatiecascade in meer detail behandeld wordt kunt u daarom overslaan als u dit verkiest. Mocht u toch graag de gehele inhoud tot u willen nemen, dan zou mijn advies in dit geval zijn onderstaande paragraaf door te nemen en hier vooral uit te distilleren hoe complex onze bloedstolling is.

Ter illustratie van de secundaire hemostase verwijs ik u naar figuur 3. Op het moment dat een vaatwand beschadigd is en stollingsfactor VII (zoals gezegd een eiwit dat in ons bloed circuleert) in aanraking komt met die beschadigde vaatwand, bindt deze factor VII aan moleculen die uit de beschadigde vaatwand vrijkomen (tissue factor).

Figuur 3



De coagulatiede cascade. Overgenomen van Wikimedia Commons, 2007. ([https://commons.wikimedia.org/wiki/File:Coagulation\\_full.svg](https://commons.wikimedia.org/wiki/File:Coagulation_full.svg)). CCo 2007, D, Joe.

Ook treedt er een activatie van factor VII op (die daarna wordt aangeduid met VIIa). De verschillende stollingsfactoren die vervolgens geactiveerd worden, worden numeriek weergegeven, helaas wel op volgorde van ontdekking en niet op volgorde van hun rol in de cascade (tot frustratie van veel geneeskundestudenten). Factor X bindt aan dit complex en wordt op zijn beurt geactiveerd (FXa). Dit supercomplex kan met behulp van stollingsfactor V en het protrombinasecomplex (bestaande uit factor Xa, factor V en factor II) factor II activeren, die in zijn actieve vorm trombine wordt genoemd. Dit is de laatste stap naar het einddoel van de secundaire hemostase: trombine zet fibrinogeen om in fibrine. Naast deze hoofdroute bestaan er twee zijroutes (TF/VIIa activeert factor IX, dat met factor VIII weer FXa kan activeren tot Xa, waarna de rest van de stollingscascade volgt. Daarnaast kan de gevormde trombine ook factor XI activeren, waardoor factor X weer wordt geactiveerd en de rest van de stappen wordt doorlopen.

Bovenstaand systeem is een positief-feedback systeem, waarbij activatie van een onderdeel leidt tot activatie van meer onderdelen. Uiteraard zijn er ook negatieve-feedback systemen in werking, waarbij bij activatie onze stolling geremd wordt.

De officiële laatste fase van de bloedstolling is de fibrinolyse, waarbij het gevormde fibrinestelsel langzaam weer wordt afgebroken.

Het zal u duidelijk zijn waarom ik onze bloedstolling een ongelooflijk complex, maar ook magnifiek systeem noem.

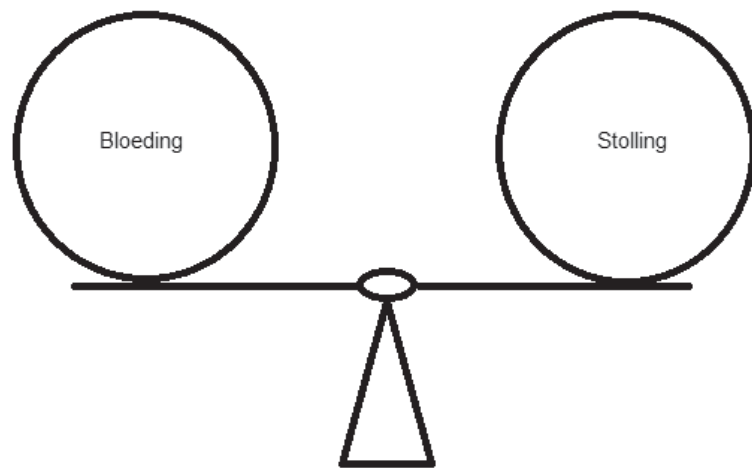
## Een evenwicht

### Stolling en bloeding

Onze bloedstolling is een balans die nauw luistert, bestaand uit de neiging tot stollen enerzijds en de neiging tot bloeden anderzijds. In een gezond systeem zijn bloeding en stolling in evenwicht (figuur 4). Als dit niet het geval is, slaat de balans door naar een van beide kanten. Als de balans uitslaat naar de 'bloedingsgeneigde' kant is er sprake van onvoldoende stollingsvorming. Dit kan dit leiden tot te lang doorbloeden van de wond of buitensporige bloedingen van kleine wondjes. Een bekend voorbeeld hiervan is hemofilie, de erfelijke 'bloederziekte' waaraan diverse mensen van de Europese vorstelijke families leden, en waaraan sommigen ook overleden zijn (3). In 1884 bloedde Leopold, zoon van de Britse koningin Victoria op 31-jarige leeftijd dood aan een knieblessure. Als de balans uitslaat naar de andere kant, de 'stollingsgeneigde' kant, kan een te sterk werkende bloedstolling ook ernstige gevolgen hebben. Als de bloedstolling onvoldoende geremd wordt of als deze te actief is, kan dat leiden tot bloedklonters die gevormd worden op plaatsen waar dit niet de bedoeling is, denk hierbij bijvoorbeeld aan een trombosebeen of een longembolie.



Figuur 4



Onze hemostase is een balans. © L. Willemsen, 2022.

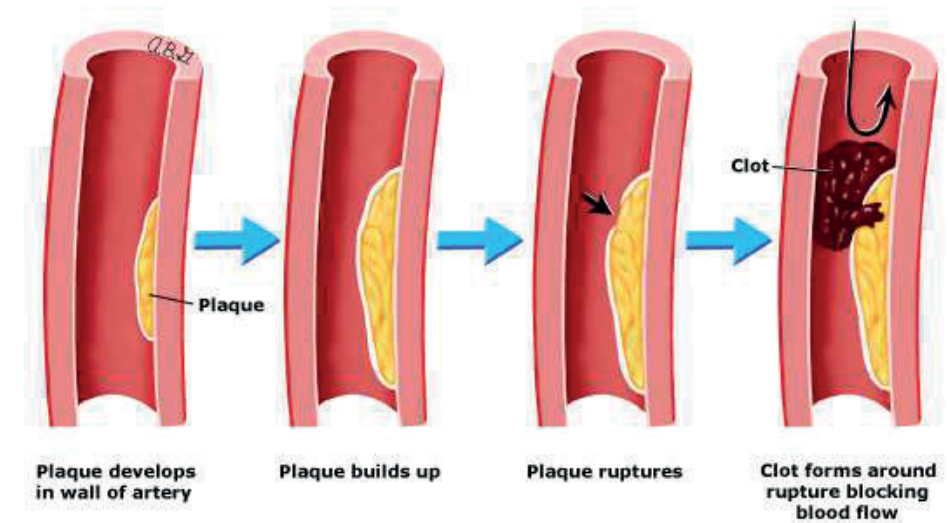
Bloedstolling wordt beïnvloed door allerlei factoren. Dat kunnen vaste, beïnvloedbare factoren zijn (bijvoorbeeld onze leeftijd, of bepaalde genetische factoren die kunnen zorgen voor een neiging naar stollen of juist bloeden) maar ook zeker verworven, of beïnvloedbare factoren. Denk daarbij aan bijvoorbeeld aan ondergaane operaties, overgewicht en gebruik van de anticonceptiepil. Ook aderverkalking zorgt voor een groter risico tot het vormen van bloedstolsels.

#### Aderverkalking

Aderverkalking (atherosclerose) is het dichtslibben van bloedvaten. Het is een langzaam proces waarin cholesterol, ontstekingscellen en kalk zich ophopen in de wand van de bloedvaten. Deze ophopingen in de vaatwand noemen we 'plaques'. Plaquevorming treedt bij iedereen op bij het normale verouderingsproces. Daarentegen, bepaalde factoren versnellen of vergroten de kans op plaquevorming. Dat zijn soms vaste, niet beïnvloedbare factoren, zoals bijvoorbeeld familiale aanleg of het behoren tot het mannelijk geslacht (bij geboorte). Veel factoren zijn echter wel beïnvloedbaar en vaak leefstijl gerelateerd: denk hierbij aan roken, het hebben van suikerziekte, een hoog cholesterolgehalte in het bloed, overgewicht of het hebben van langdurige stress. Uiteindelijk leidt plaquevorming tot aderverkalking, waarbij de opening van het bloedvat waar het bloed doorheen stroomt nauwer wordt. In figuur 5 ziet u dit proces gedetailleerd afgebeeld. Pas als het bloedvat echt vernauwd raakt en de zuurstoftoevoer naar een orgaan in het geding komt, leidt dit tot klachten. Vernauwingen in de kransslagaders (die het hart van zuurstofrijk bloed voorzien) kunnen leiden tot zuurstoftekort in de hartspier. Dit geeft pijn op de borst (angina pectoris), aanvankelijk

alleen als het hart hard moet werken zoals bijvoorbeeld bij inspanning of stress. Als de kransslagaders verder vernauwen en de zuurstoftoevoer instabiel wordt, kan angina pectoris ook optreden in rust.

Figuur 5



Een schematische weergave van atherosclerose en in het laatste stadium, een hartinfarct. Overgenomen van UptoDate, 2022. (<https://www.uptodate.com/contents/coronary-artery-bypass-graft-surgery-beyond-the-basics/print>). © 2022, UptoDate.

Zoals benoemd zorgt aderverkalking voor een verhoogd risico tot het vormen van bloedstolsels. De gevormde plaques kunnen namelijk scheuren, waardoor het bloed in contact komt met de beschadigde vaatwand en de bloedstolling geactiveerd wordt en een bloedstolsel ontstaat. Als zo'n bloedpropje (trombose) in het bloedvat ontstaat en het volledig afsluit, wordt de bloedtoevoer naar een orgaan volledig afgesloten. Dit leidt tot afsterven van het weefsel dat door dat bloedvat van zuurstof wordt voorzien. Dit is wat men een infarct noemt: trombose in een van de slagaders die de hersenen van zuurstof voorzien is een herseninfarct, het afsluiten van de slagader die het hart van zuurstof voorziet (kransslagader) is een hartinfarct (figuur 5).

Volgens de World Health Organization zijn hart- en vaatziekten inmiddels de grootste oorzaak van overlijden ter wereld, verantwoordelijk voor 32% van alle overlijdens in 2019. Daarvan werd 85% veroorzaakt door hart- en herseninfarcten. Hieruit volgt begrijpelijkerwijs dat de behandeling van aderverkalking een zeer belangrijk aandachtsgebied vormt.

## Gevolgen van aderverkalking voorkomen

### Leefstijl

Omdat de oorzaken van aderverkalking vaak leefstijl gerelateerd zijn, bestaat de eerste stap in de behandeling van aderverkalking er altijd uit deze factoren te identificeren en waar nodig aan te pakken. Dat houdt vaak in: stoppen met roken, het reguleren van de bloeddruk en het verlagen van het cholesterolgehalte in het bloed tot een aanvaardbaar niveau, gezond eten en voldoende bewegen et cetera.

### Medicatie

Er zijn ook medicijnen die hierbij kunnen helpen, bijvoorbeeld medicijnen die het cholesterol of de bloeddruk verlagen. Ook bloedverdunners zijn medicijnen die vrijwel altijd worden gegeven bij aderverkalking.

De aanduiding 'bloedverdunners' is bijzonder misleidend: bloedverdunners hebben namelijk helemaal niets te maken met de dikte van het bloed. Ze maken het bloed niet wateriger. Wat ze wel doen is ingrijpen op de bloedstolling, waardoor deze minder geneigd is tot stollen. Onder de term bloedverdunners worden verschillende medicijnen geschaard die op verschillende onderdelen van de bloedstolling ingrijpen en die allemaal tot doel hebben het bloed minder snel te laten stollen. Sintrom bijvoorbeeld, bekend van de opvolging door de trombosedienst, beïnvloedt de stollingscascade. Aspirine en ticagrelor (een bloedverdunner waar u nog meer over zult lezen in dit proefschrift) maken het bloedplaatje minder reactief. Ze worden dan ook gegeven bij patiënten met hart- en vaatziekten om het ontstaan van een bloedstolsel in een bloedvat te voorkomen.

### Dotter

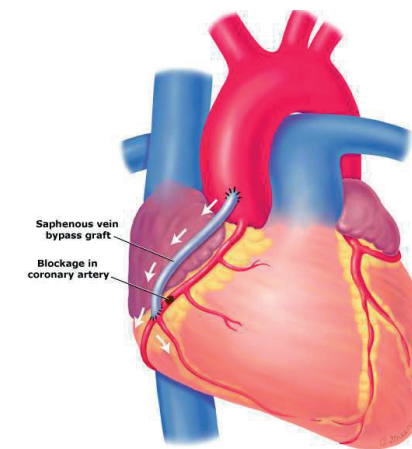
Een afgesloten (of ernstig vernauwd) bloedvat kan behandeld worden door de welbekende dotterprocedure (in de kransslagaders ook wel PCI genoemd; percutaneous coronary intervention). Hierin wordt er een draadje met een onopgeblazen ballonnetje ingebracht in een bloedvat in de arm of de lies, waarna dit helemaal naar het hart wordt geleid. Ter plaatse van de vernauwing of de bloedprop wordt het ballonnetje opgeblazen. Daardoor wordt het bloedvat weer doorgankelijk gemaakt. Vaak wordt er ook een stent geplaatst om het bloedvat open te houden.

### CABG

Een andere mogelijke manier om vernauwde kransslagaders te behandelen is een operatie waarbij er omleidingen langs de vernauwingen in de kransslagaders worden gelegd en het bloed dus via een nieuw aangelegde weg het hart bereikt. Dit is een omleidingsoperatie, oftewel CABG (coronary artery bypass grafting surgery, vaak uitgesproken als het engelse 'cabbage', kool dus), zie figuur 6. Meestal worden er tijdens een CABG meerdere omleidingen (grafts) aangelegd. Deze omleidingen worden gemaakt van slagaders uit de borstkas of de arm, of van aders uit het been.

Een CABG is een open-hart operatie, en hoewel veel invasiever dan een dotterprocedure, is het bij sommige patiënten om diverse redenen een betere keuze (bijvoorbeeld bij patiënten bij wie meerdere vernauwingen in verschillende kransslagaders behandeld moeten worden). CABGs worden dan ook veel uitgevoerd in Nederland, in 2019 7379 keer (4).

**Figuur 6**



Een CABG operatie met een omleiding (graft). U ziet dat er een 'omleiding' wordt gemaakt langs de vernauwing in de kransslagader waardoor het zuurstofrijke bloed de hartspier weer kan bereiken. Overgenomen van UptoDate, 2022. (<https://www.uptodate.com/contents/coronary-artery-bypass-graft-surgery-beyond-the-basics/print>). © 2022 UptoDate .

## WAAROM IS DIT PROEFSCHRIFT RELEVANT

### Bloedstolling bij de cardiologische patiënt

De aderverkalking bij patiënten met hart- en vaatziekten (als ook veel factoren die aderverkalking veroorzaken zoals roken en overgewicht) maken de cardiologische patiënt over het algemeen meer geneigd tot het vormen van stolsels (of infarcten). Als je figuur 4 in gedachten houdt, zou je kunnen zeggen dat hun evenwicht altijd een beetje gekanteld is naar de stollingsgeneigde kant. Juist daarom worden deze patiënten vrijwel altijd behandeld met bloedverdunners, om die infarcten te voorkomen. Daarom is het vinden van het juiste evenwicht tussen bloeden en stollen, het punt waarop die weegschaal in evenwicht is, bij de cardiologische patiënt een extra uitdaging. Dit vormt een onderwerp waaraan veel wetenschappelijke onderzoeken zijn gewijd en op welk gebied nog steeds veel grote ontwikkelingen gaande zijn.

*CABG en bloedstolling tijdens de operatie.*

Het vinden van de juiste balans in de stolling, en daarmee zowel bloedings- als stollingscomplicaties voorkomen, vormt een uitdaging bij patiënten die een CABG ondergaan. De CABG-patiënt is een cardiologische patiënt, met alle boven beschreven uitdagingen. Daarnaast is ondergaan van een operatie een grote risicofactor voor het ontstaan van een bloeding. Tijdens een operatie worden bloedvaten stuk gemaakt, waardoor bloedingen ontstaan. Een CABG is daarin nog gevaarlijker dan de meeste andere operaties, omdat voor een CABG enkele zaken noodzakelijk zijn die de stolling nog meer beïnvloeden. Voorbeelden hiervan zijn het gebruik van bepaalde medicatie tijdens de operatie, de hartlongmachine en de noodzaak tot het koelen van een patiënt. Al die factoren maken dat de patiënt die een CABG ondergaat een hoog risico heeft op een onregelde bloedstolling tijdens de operatie.

*CABG en bloedstolling na de operatie*

Ook na de operatie is de uitdaging nog niet voorbij. Ongeveer 15% van de aangelegde omleidingen slibt binnen een jaar na de operatie dicht. Daarbij is noodzakelijk te vermelden dat niet elke dichtgeslibde omleiding voor problemen zorgt, soms wordt er een omleiding aangelegd die achteraf niet nodig blijkt te zijn omdat de bloedtoevoer uit de eigen kransslagader toch voldoende is. Dan slibt de omleiding langzaam dicht, omdat hij niet gebruikt wordt, vergelijk het met een ongebruikte weg die langzaam overwoekert wordt. Desondanks, de gevolgen van sommige dichtgeslibde omleidingen kunnen ook desastreus zijn, variërend van een hartinfarct of zelfs plotse dood. Het is een proces waarbij veel verschillende factoren betrokken zijn, maar zeker is dat bloedplaatjesactivatie in de eerste fase na de operatie (als reactie op de 'verse' beschadigingen) een belangrijke rol speelt.

Over de optimale behandeling na de CABG is ook nog veel onduidelijk. Met welke behandeling is een patiënt op lange termijn geholpen? Hoe ontwikkelt de stollingsstatus van een patiënt zich jaren na de CABG? In een concrete situatie waar arts en patiënt mee geconfronteerd zouden kunnen worden zou dat bijvoorbeeld kunnen inhouden: Arie Pectoris heeft 10 jaar geleden een CABG ondergaan. Sindsdien heeft hij geen hartklachten meer en lijken alle controles goed te zijn, maar hij gebruikt de bloedverdunners nog steeds, zoals de richtlijnen voorschrijven. Nu moet hij een heupoperatie ondergaan. Wat kunnen we het beste doen met de bloedverdunners van meneer Pectoris, moeten deze gestopt worden rondom de operatie omdat deze een hoog bloedingsrisico geeft, of is dat onverstandig omdat het risico op bloedstolsels en infarcten toch te groot is?

**Dit proefschrift**

'Bloedstolling bij patiënten die een hartoperatie ondergaan' blijft een uitdaging voor elke patiënt en elke arts die ermee in aanraking komen. U begrijpt nu de relevantie van dit proefschrift.

Dit proefschrift is ingedeeld in drie delen. Deel 1 verdiept zich in methoden om bloedingscomplicaties tijdens cardiale chirurgie te voorkomen. In hoofdstuk 2 wordt geëvalueerd of de individuele respons van een patiënt op aspirine (de bloedverdunners die standaard wordt gegeven bij patiënten die een CABG ondergaan) bloedverlies na de operatie kan voorspellen. Hoofdstuk 3 onderzoekt de toegevoegde waarde van bloedplaatjesreactiviteit in het identificeren van patiënten die een hoog risico hebben op bloedingen. Hoofdstuk 4 vervolgens analyseert de relatie tussen de fibrinogeenconcentratie in het bloed, bepaalde stollingstesten en postoperatief bloedverlies.

Deel 2 behandelt in zijn geheel de houdbaarheid van de omleidingen na de CABG. In hoofdstuk 5 wordt de tot op heden bekende informatie over de duurzaamheid van de omleidingen (graft patency) samengevat. De daaropvolgende drie hoofdstukken (6,7,8) behandelen allemaal de placebo-gecontroleerde POPular CABG trial, die onderzoekt of ticagrelor (een andere bloedverdunner) naast de standaard aspirine die patiënten al krijgen na de operatie, ervoor zorgt dat de omleidingen beter open blijven. Hoofdstuk 6 presenteert de opzet van de POPular CABG trial, hoofdstuk 7 de resultaten, en hoofdstuk 8 wijdt uit over de lessen die wij hebben getrokken uit een fout die is gemaakt in de analyse van de trial. Fouten maken hoort erbij in de wetenschap, belangrijk is te evalueren wat ervan geleerd kan worden. Hoofdstuk 9, tot slot van deel 2, analyseert de strategieën van verschillende ziekenhuizen ten opzichte van bloedverdunners in patiënten die CABG ondergaan.

Deel drie, het laatste deel van dit proefschrift, betreft enkele vraagstukken met betrekking tot management op lange termijn van patiënten die een CABG hebben ondergaan. In hoofdstuk 10 worden de uitkomsten van oudere patiënten die een CABG of een PCI hebben ondergaan met elkaar vergeleken. In hoofdstuk 11 wordt gekeken naar patiënten die bloedverdunners gebruiken en een andere, niet-cardiale operatie besproken.

Met betrekking tot bloedstolling bij patiënten die cardiale chirurgie ondergaan is veel nog onzeker en is de juiste handelwijze is vaak nog niet duidelijk. Dit proefschrift heeft op dit gebied een bijdrage willen leveren.

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Figuur 4: Willemsen, L (2022). *Hemostase*. © L. Willemsen, 2022.

Figuur 5: UptoDate (2022). *Plaque formation* [Online afbeelding]. Geraadpleegd 7 augustus 2022 op <https://www.uptodate.com/contents/coronary-artery-bypass-graft-surgery-beyond-the-basics/print>. © 2022 UptoDate .

Figuur 6: UptoDate (2022). *Coronary artery bypass graft surgery* [Online afbeelding]. Geraadpleegd 7 augustus 2022 op <https://www.uptodate.com/contents/coronary-artery-bypass-graft-surgery-beyond-the-basics/print>. © 2022 UptoDate .

## III. Impact Paragraph

This paragraph reflects on the impact of the research presented in this thesis. We will concisely introduce the context of the research performed (1) before we address the research performed itself (2), in order to enable the reader to fully understand the relevance of this research (3) and finally, to whom this research may concern (4).

### 1. Context

As mentioned in the introduction of this thesis, cardiovascular disease remains the leading cause of death worldwide. Surgical treatment of coronary artery disease by coronary artery bypass grafting (CABG) is the most commonly performed cardiac surgery procedure with an incidence of 44 per 100.000 individuals in the modern world, and is still the preferred method of revascularization above percutaneous coronary intervention (PCI) in certain patients.

Retaining the balance between thrombosis and hemostasis in patients undergoing cardiac surgery remains one of the most difficult tasks for treating physicians. Averting both bleeding complications as well as thrombotic complications is vital for we know that the consequences of both are severe. In case of bleeding complications we know that red blood cell transfusions are a risk factor for mortality and that revision for bleeding is associated with mortality. Of course, severe bleeding itself can be fatal. Thrombotic complications include (but are not limited to) postoperative myocardial infarction, stroke, pulmonary embolisms and graft failure. Graft occlusion after CABG on itself presents a whole new set of problems, being associated with new angina complaints, myocardial infarction and long-term survival. Reinterventions for graft failure are associated with morbidity and mortality.

### 2. Research

The main aim of this thesis was to investigate methods to prevent these complications. The first part of this thesis examined the association of certain point-of-care platelet function tests, coagulation parameters and whole blood viscoelastic tests with postoperative blood loss. The second part of this thesis addresses the specific problem of graft failure and the randomized controlled trial we have performed to investigate whether ticagrelor added to the standard aspirin therapy can improve graft patency. The third part of this thesis contains the optimization of long-term postoperative care.

### 3. Relevance

The research presented in the first part of this thesis (prevention of bleeding complications during CABG) was aimed at finding parameters associated with blood loss and bleeding complications, following the notion that the first step towards prevention of postoperative bleeding complications, is predicting in which patients these will occur. Indeed, we were able to identify associations between certain point-of-



care tests and biomarkers. Naturally, the impact of these findings is not yet certain and further investigation is needed to truly determine the use of these tests, but hopefully these findings can provide some foundation for preventing bleeding events in CABG patients.

We conducted the randomized, placebo-controlled POPular CABG trial that is presented in part two of this thesis, in order to answer the question whether the addition of ticagrelor to standard aspirin therapy after CABG could improve graft patency. Although graft occlusion is a surrogate outcome and the trial was not powered for clinical events, we could not establish a discernable effect of the addition of ticagrelor on graft patency. Thereby, based on this trial, we would advise against the standard addition of ticagrelor to aspirin in order to improve graft patency. Ticagrelor is an antithrombotic drug, and can therefore cause bleeding events. The knowledge that it does not improve graft patency can therefore be essential for treating physicians and perhaps prevent some of these bleeding events, and we expect results of this study will be taken into account when international guidelines are composed.

How to deal with the long-term consequences of CABG and thrombosis and hemostasis management is the topic of the last part of this thesis. The finding of the observational study that long-term mortality as well as other adverse events remains higher in elderly patients who undergo PCI as compared with CABG, and the finding that completeness of revascularization was not a predictor of adverse outcomes, might contribute a little to discussion of 'which method of revascularization is best'. It is debatable whether elderly patients value mortality as the most important goal after revascularization, and they are often underrepresented in trials. Therefore, although this study might not provide definite answers to which revascularization method is optimal, it might provide a little more evidence with regard to the elderly.

Lastly, a special mention should be made regarding chapter 7 and 8 of this thesis. No researcher likes to admit mistakes in their research or analysis. However, we hope that by being transparent about these mistakes, we emphasize the importance of wholly and unquestionably ethically conducted research.

#### 4. To whom this research concerns

The research described in this thesis has contributed valuable understandings to the subject of thrombosis and hemostasis in patients undergoing CABG. It can aid physicians in their quest of optimally treating their patients, and lays a possible foundation for further research in order to address the still very much encountered problems of thrombosis and hemostasis during CABG surgery.

## IV. Dankwoord

**“We” is more important than “I”. In medicine, the advances are always the result of many efforts accumulated over the years.’**

- René Favaloro, who performed the first CABG –

*In: Landmarks in the Development of Coronary Artery Bypass Surgery, Circulation. 1998;98:466–478.*

Dit proefschrift heeft alleen tot stand kunnen komen door de steun van velen.

Als allereerste wil ik de echte helden bedanken: de patiënten, of deelnemers aan de onderzoeken in dit proefschrift. Dat jullie bereid zijn geweest het belang van wetenschap mee te laten wegen in een moment van grote persoonlijke zorgen, getuigt naar mijn idee van veel moed. Dank voor het vertrouwen, ik wens jullie het beste.

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dr. Bal), de Steering Committee (prof. dr. Ten Berg, dr. Klein, prof. dr. De Boer opnieuw en prof. dr. Kappetein) en het Core lab (dr. Swaans, dr. Van Es, dr. Rensing) die zich belangeloos hebben ingezet, met name bestaand uit lange vergaderingen en vooral het wegklikken van oneindig veel scans of eindpunten. Veel dank, zonder uw bijdrage was dit onderzoek niet mogelijk geweest.

Martin Swaans, jij verdient naast bovenstaande dankzegging voor de eindeloze uren van het beoordelen van scans, een buitengewone vermelding voor je bijstand in de eeuwige strijd met de computersystemen en alle onderzochte (on)mogelijkheden om scans ergens digitaal te krijgen – iets wat na veel strijd uiteindelijk niet is gelukt en waar we maar omheen hebben gewerkt. Gelukkig is jouw vrolijke enthousiasme niet klein te krijgen en stoom jij onvermoeid door met een guitige glimlach. Superveel dank, ook voor je gezellige invallen met goede verhalen op de onderzoekskamer!

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## V. List of Publications

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## VI. Curriculum Vitae

Laura was born on the 5th of June 1990 in Bonn (Germany) as the first daughter of Hiltrud Moritz and Theodorus Willemsen. She grew up in Maastricht with her sister Saskia. She attended the Porta Mosana College and obtained her gymnasium diploma in 2008, after which she started as a medical student at Utrecht University.



During her medical studies, Laura developed a keen interest in cardiology. After obtaining her medical degree in 2015, Laura started as a PhD-candidate in the St. Antonius Hospital in Nieuwegein, under supervision of J.M. ten Berg and C.M. Hackeng. She was involved in several research projects alongside being coordinating investigator of a placebo-controlled trial, the results of which lay the foundation of this thesis. She presented at a variety of national and international congresses, including the Late-breaking Science Session at the European Congress of Cardiology in 2020.

Laura believes that one of the best ways to prevent morbidity and mortality from cardiovascular disease is to promote a healthy lifestyle. She now works as a physician at the Dutch Obesity Clinic.

In her free time Laura loves being outdoors, enjoying different kind of sports (amongst others boxing, road-cycling, running, hiking), soaking in a warm bath while reading books she just bought in the bookstore next door and most of all having long dinners with family and friends.

"All we have to decide is what to do with the time that is given us." - Gandalf