PLATELET INHIBITION AND SECONDARY PREVENTION IN CARDIAC SURGERY PATIENTS

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ABSTRACT

Background and objective

Coronary artery bypass grafting (CABG) is the most common cardiac surgery procedure. Dual antiplatelet therapy (DAPT) reduces the risk for ischaemic events in patients with acute coronary syndrome (ACS) but increases the bleeding risk, both for spontaneous bleedings and procedure-related bleedings for the subset of ACS patients undergoing urgent CABG. Statins, beta-blockers, and renin-angiotensin-system (RAS) inhibitors are commonly prescribed after CABG but the scientific evidence for their use after CABG is scarce. The objective of this thesis is to investigate how different aspects of pharmacotherapy are associated with short- and long-term risk for adverse events after CABG.

Methods

Study I: Platelet function before and after cardiac surgery was analysed using impedance aggregometry in patients treated with acetylsalicylic acid and the $P2Y_{12}$-inhibitor ticagrelor. Associations between pre- and postoperative platelet function and risk for severe postoperative bleeding were investigated.

Study II-IV: Individual patient data from the Swedish Cardiac Surgery Registry, the National Patient Register, the Swedish Prescribed Drug Register, LISA register and the Cause of Death Register was merged to obtain data on procedural aspects, baseline comorbidities, adverse events and mortality after CABG. Study II investigated associations between use of statins, beta-blockers, RAS-inhibitors and platelet inhibitors and mortality risk. Study III investigated if the combination of ASA and ticagrelor was associated with improved clinical outcome compared to ASA monotherapy

in patients with acute coronary syndrome undergoing CABG. Study IV investigated the associations between post-discharge major bleeding and myocardial infarction respectively with subsequent mortality risk.

Results

Study I: Postoperative platelet aggregation induced by adenosin diphosphate (ADP) had an area under curve (AUC) of 0.75 (95% CI 0.62-0.87) in predicting severe bleeding. The corresponding value for preoperative testing was AUC of 0.77 (95% CI 0.65-0.89).

Study II: Utilization of secondary prevention medication was high early after CABG but decreased significantly over time. Ongoing use of statins, RAS inhibitors and platelet inhibitors were associated with reduced mortality risk after CABG. Use of beta-blockers was not associated with lower mortality risk.

Study III: The combination of acetylsalicylic acid (ASA) and ticagrelor was not associated with lower risk for ischaemic events but increased the bleeding risk compared with ASA monotherapy.

Study IV: Post-discharge major bleeding was associated with increased mortality risk, comparable to the increase in mortality risk associated with post-discharge myocardial infarction.

Conclusions

Adding a postoperative test of platelet aggregation did not improve accuracy in predicting severe bleeding. Improving long-term utilization of statins, RAS inhibitors and platelet inhibitors poses an opportunity to improve long-term survival after CABG. Prospective, randomized controlled trials are warranted to establish the clinical outcome of DAPT with ticagrelor after CABG in ACS patients, especially considering the increased mortality risk associated with post-discharge major bleeding events.

Keywords: coronary artery bypass grafting, secondary prevention, bleeding complications, impedance aggregometry

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SAMMANFATTNING PÅ SVENSKA

Bakgrund

Kranskärlssjukdom är den vanligaste dödsorsaken, både i Sverige och globalt. Dubbelbehandling med läkemedel som hämmar blodplättarna (trombocyterna) minskar risken för blodproppar vid akut kranskärlssjukdom men ökar blödningsrisken. Detta är dels problematiskt på kort sikt för patienter med utbredd kranskärlsjukdom som genomgår kranskärlsoperation (koronar bypass, CABG) men ökar också risken för spontana blödningar på längre sikt efter kranskärlsoperation. Ett sätt att värdera blödningsrisk inför kranskärlsoperation är att mäta trombocytfunktion före operationen. Trombocytfunktionen påverkas dock under operationen varför det hypotetiskt vore bättre att mäta trombocytfunktionen efter operation. Statiner, beta-blockerare och renin-angiotensin-system (RAS)-inhibitorer är läkemedel som ofta förskrivs efter kranskärlsoperation. Det vetenskapliga underlaget för behandling specifikt i denna population är dock i många fall svagt. Syftet med avhandlingen är att undersöka hur olika aspekter av läkemedelsbehandling påverkar risken för död och sjuklighet på kort och lång sikt efter kranskärlsoperation.

Metoder

I delarbete I mättes trombocytfunktionen före och efter hjärtoperation hos patienter med dubbel trombocythämning. Associationen mellan trombocytfunktion och risk för allvarlig blödning undersöktes.

Delarbete II-IV grundade sig på en databas med sammanslagna patientdata från Hjärtkirurgiregistret, Patientregistret, Läkemedelsregistret och Dödsorsaksregistret. I delarbete II undersöktes association mellan pågående behandling med statiner, betablockerare, RAS-inhibitorer och trombocythämmare med mortalitetsrisk efter kranskärlsoperation. I delarbete III undersöktes om kombinationen av trombocythämmarna acetylsalicylsyra (ASA) och ticagrelor var associerad med förbättrat kliniskt utfall jämfört med endast ASA efter kranskärlsoperation hos patienter med akut kranskärlssjukdom. I delarbete IV undersöktes hur spontana blödningar och hjärtinfarkt efter kranskärlsoperation påverkade efterföljande mortalitetsrisk.

Resultat

Studie I: Låg trombocytfunktion mätt efter kranskärlsoperation predikterade allvarlig blödning med måttlig precision.

Studie II: Användning av statiner, RAS-inhibitorer och trombocythämmare var associerat med lägre mortalitetsrisk. Användning av betablockerare var inte associerad med lägre mortalitetsrisk.

Studie III: Kombinationen ASA och ticagrelor var inte associerad med lägre risk för död, hjärtinfarkt och stroke men ökade blödningsrisken jämfört med enbart ASA.

Studie IV: Både spontan allvarlig blödning och hjärtinfarkt efter kranskärlsoperation var associerade med ökad mortalitetsrisk i liknande omfattning.

Sammanfattning

Postoperativ testning av trombocytfunktion ökade inte precisionen att prediktera allvarlig blödning jämfört med preoperativ testning. Ökad långtidsanvändning av statiner, RAS-inhibitorer och trombocythämmare utgör en möjlighet för att förbättra långtidsöverlevnad efter kranskärlsoperation. Prospektiva, randomiserade och kontrollerade studier behövs för att fastställa den kliniska nyttan av dubbel trombocythämning med ticagrelor efter kranskärlsoperation hos patienter med akut kranskärlssjukdom, särskilt i ljuset av den ökade mortalitetsrisk som är associerad med allvarliga blödningshändelser.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Björklund E, Hansson EC, Romlin BS, Jeppsson A, Malm CJ. Postoperative platelet function is associated with severe bleeding in ticagrelor-treated patients. Interact Cardiovasc Thorac Surg. 2019 May 1;28(5):709-715.

II. Björklund E, Nielsen SJ, Hansson EC, Karlsson M, Wallinder A, Martinsson A, Tygesen H, Romlin BS, Malm CJ, Pivodic A, Jeppsson A. Secondary prevention medications after coronary artery bypass grafting and long-term survival: a population-based longitudinal study from the SWEDEHEART registry. Eur Heart J. 2020 May 1;41(17):1653-1661.

III. Björklund E, Malm CJ, Nielsen SJ, Hansson EC, Tygesen H, Romlin BS, Martinsson A, Omerovic E, Pivodic A, Jeppsson A. Comparison of midterm outcomes associated with aspirin and ticagrelor vs aspirin monotherapy after coronary artery bypass grafting for acute coronary syndrome. JAMA Netw Open. 2021 Aug 2;4(8):e2122597.

IV. Björklund E, Enström P, Nielsen SJ, Tygesen H, Martinsson A, Hansson EC, Lindgren M, Malm CJ, Pivodic A, Jeppson A. Post-discharge major bleeding, myocardial infarction and mortality risk after coronary artery bypass grafting.

Submitted

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ABBREVIATIONS

AA	Arachidonic acid
ACS	Acute coronary syndrome
ADP	Adenosin diphosphate
aHR	adjusted Hazard Ratio
ASA	Acetylsalicylic acid
AUC	Area under curve
CCS	Chronic coronary syndrome
CI	Confidence interval
COX	Cyclooxygenase
CABG	Coronary artery bypass grafting
CURE	Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation
DAPT	Dual antiplatelet therapy
IQR	Interquartile range
ISAR-REACT 5	Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes
ISCHEMIA	The Initial Invasive or Conservative Strategy for Stable Coronary Disease
LIMA	Left internal mammary artery
LDL	Low-density lipoprotein
MACE	Major adverse cardiovascular events
MEA	Multiple-electrode impedance aggregometry

NACE	Net adverse clinical events
NSTE-ACS	Non ST-elevation acute coronary syndrome
PCI	Percutaneous coronary intervention
PLATO	Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes
ROC	Receiver operating characteristic
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
TRAP	Thrombin receptor activating peptide
TRITON-TIMI 38	Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes
UDPB	Universal definition of perioperative bleeding in adult cardiac surgery

1 INTRODUCTION

1.1 ISCHAEMIC HEART DISEASE

Despite improvements in preventive measures, diagnostics and treatment, ischaemic heart disease still is the leading cause of death in both high- and low-income countries.[1,2] The main pathophysiological mechanism is insufficient coronary blood flow, usually caused by atherosclerotic plaque or thrombus, leading to myocardial ischaemia. The cardinal symptom is chest discomfort but, depending on the severity of ischaemia, haemodynamic instability, or in worst case cardiac arrest, may also develop. Ischaemic heart disease is classified as chronic coronary syndrome (CCS) or acute coronary syndrome (ACS). In CCS, symptoms are stable over time whereas ACS is characterized by a sudden debut, or worsening, of symptoms.[3] ACS is further sub-classified according to the degree of ischaemia caused by the coronary obstruction, Figure 1. In non-ST-elevation acute coronary syndrome (NSTE-ACS) there is typically a non-occlusive thrombus or multi-vessel obstructive disease without acute occlusions.[4] This can be further subclassified as unstable angina and non-ST-elevation myocardial infarction, with the difference between the conditions being that evidence of myocardial necrosis, i.e. elevation of cardiac troponin in blood samples, is absent in unstable angina. In ST-elevation myocardial infarction (STEMI), total occlusion of a coronary artery results in the typical ECG pattern of ST-elevation which indicates severe, on-going myocardial ischaemia.[5]

The underlying pathophysiological mechanisms for development of atherosclerotic plaques includes inherent risk factors such as heredity, male sex and age as well as modifiable risk factors such as high levels of cholesterol, arterial hypertension, diabetes and smoking.[6] The transformation from chronic "stable" coronary artery disease to acute coronary syndromes is most often due to rupture or erosion of pre-existing atherosclerotic plaques, exposing platelets and the coagulation system to non-endothelialized tissue which leads to platelet activation and formation of thrombus.[7] Plaque rupture is not unique for the coronary arteries and can result in different clinical manifestations including stroke and lower limb ischaemia. Acute coronary syndrome can thus be viewed as an acute cardiac manifestation of the systemic disease atherosclerosis.

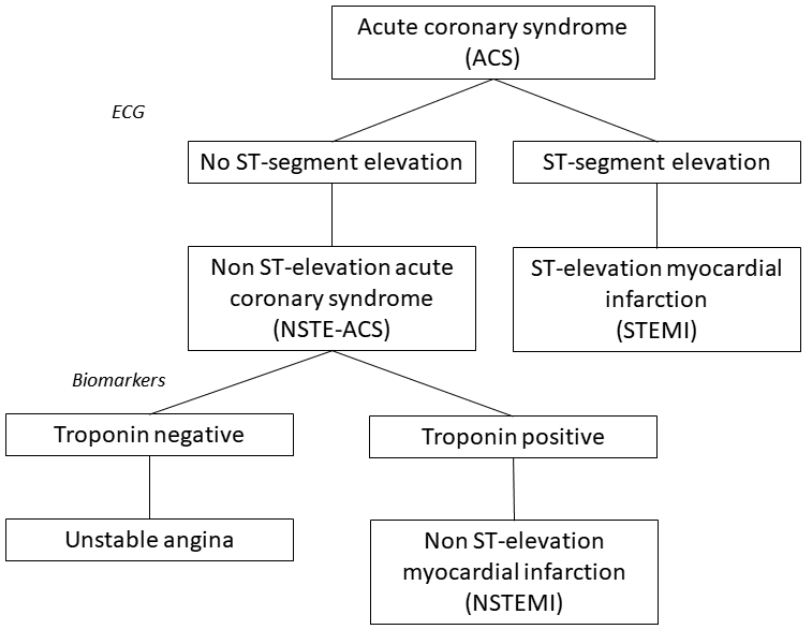

Figure 1. Classification of acute coronary syndrome.

1.1.1 CORONARY ARTERY BYPASS GRAFTING

Various methods of surgical treatment of ischaemic heart disease were experimented with during the 1950s and 1960s, including attaching the pectoral muscle to the myocardium, grafting the internal mammary artery directly to ischaemic myocardium, coronary endarterectomy and patching coronary arteries with vein or pericardial patches. The coronary artery bypass grafting (CABG) procedure as we know it today was developed in the late 1960s by Favaloro and Effler.[8] This technique was made possible by the previous inventions of cardiopulmonary bypass, heparin and coronary angiography.[9,10] In 2017, the last year of follow-up in studies included in this thesis, 2,534 isolated CABG procedures with cardiopulmonary bypass were performed in Sweden.[11] An additional 12 procedures were performed without cardiopulmonary bypass. Left internal mammary artery (LIMA) was used in 96% of cases, vein grafts in 92% and an additional arterial graft in 7%. Mean number of distal anastomoses was 3.2.

1.2 PLATELETS

Platelets in circulating blood are small, anucleate cell fragments with a discoid shape. Once regarded as “cellular dust”, we now know that platelets are

essential for processes such as haemostasis and wound healing and play important roles in various pathophysiological processes, including both bleeding disorders and thrombotic conditions.[12] Platelets originate from mega-karyocytes residing in the bone-marrow and typically circulate 7-10 days before they are cleared from the circulation by phagocytosis in the spleen and liver. Normal concentration is 150-400 x10^9 platelets / L peripheral blood.

1.2.1 PLATELET ACTIVATION

Under physiological conditions, platelets do not adhere to the vessel wall or to other platelets. In case of endothelial disruption, for example due to traumatic injury or rupture of atherosclerotic plaques, membrane receptors on the platelet surface are exposed to agonists such as von Willebrand factor and collagen which leads to platelet adhesion. Once adhered to the damaged vessel wall, the platelet is activated leading to both secretion of dense granules, which contain platelet agonists such as adenosine diphosphate (ADP), and exposure of the glycoprotein complex IIb/IIIa on the platelet surface, resulting in recruitment of circulating platelets. The most important platelet activators are collagen, thrombin, ADP, thromboxane A2 and platelet activating factor, Figure 2.[13]

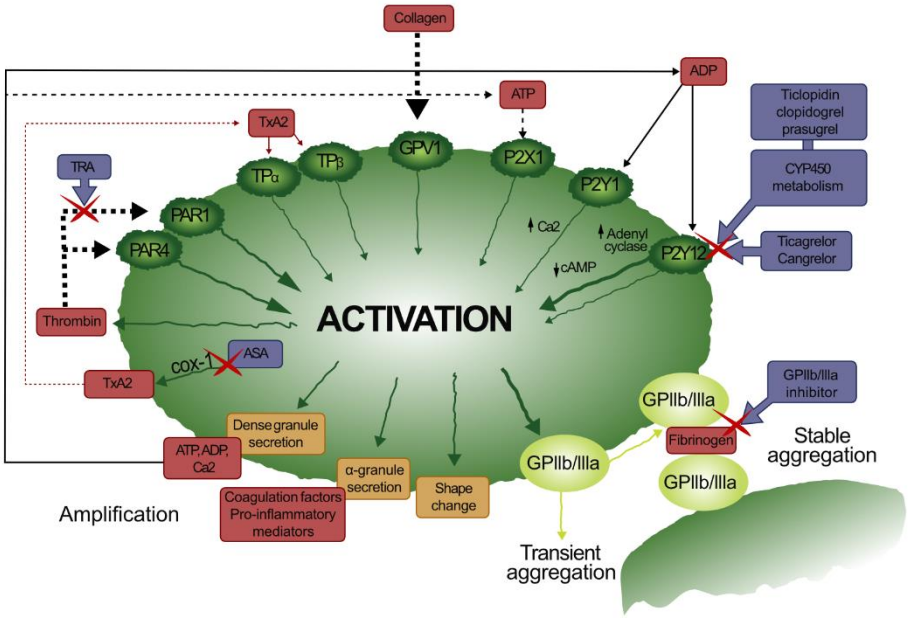

Figure 2. Overview of platelet activation and platelet inhibition. (Modified after Storey RF. Biology and pharmacology of the platelet P2Y12 receptor. Curr Pharm Des 2006;12:1255–1259, with permission)

1.2.2 PLATELET INHIBITION

1.2.2.1 ACETYLSALICYLIC ACID

Acetylsalicylic acid (ASA or aspirin) has been used since the 19th century as an analgesic and antipyretic drug. The increased risk for gastrointestinal bleeding, due to both the inhibiting effect on protective prostaglandins in the gastric mucosa and the antithrombotic effect, was first reported in 1938.[14] A more mechanistic observation of the antithrombotic effect was published in 1967 by Weiss, who demonstrated that ASA inhibited platelet aggregation initiated by connective tissue but not by ADP.[15] It has later been established that ASA irreversibly inhibits the enzymes cyclooxygenase (COX) 1 and 2.[16] COX-1 converts arachidonic acid (AA) to prostaglandins in gastric mucosa and converts arachidonic acid to thromboxane A2 in platelets whereas COX-2 converts AA to prostaglandins in inflammatory activated cells. In turn, prostaglandins both act as inflammatory mediators and exert protective effects in the gastric mucosa while thromboxane A2 promotes platelet aggregation.

Platelet aggregation has long been suspected of having a key role in the formation of coronary thrombi in acute myocardial infarction. In the ISIS-2 trial published 1988 it was demonstrated that platelet inhibition with ASA administered to patients with acute myocardial infarction, both alone and in combination with streptokinase, resulted in lower mortality.[17] Today, ASA is considered a cornerstone in treating coronary artery disease and lifelong treatment with low-dose ASA (75-100 mg) is recommended to all patients without contraindications.[3]

1.2.2.2 P2Y12 INHIBITORS AND DUAL ANTIPLATELET THERAPY

Activation of platelets through ADP are mediated via the $P2Y_1$ and $P2Y_{12}$ receptor.[18] The $P2Y_{12}$ receptor mediates platelet aggregation through activation of the GPIIb/IIIa-receptor. Ticlopidine was the first commercially available $P2Y_{12}$ inhibitor. Originally, ticlopidine was registered in the late 1970s to prevent thrombotic complications where platelets interacted with artificial surfaces, for example in mechanical circulation during cardiac surgery or haemodialysis. It was later demonstrated that the combination of ASA and ticlopidine dramatically reduced the risk for stent thrombosis after coronary stenting and the concept of dual antiplatelet therapy was born.[19,20] Due to adverse side-effects of ticlopidine, including pancytopenia, it was eventually replaced with clopidogrel in the late 1990s.

The thienopyridine clopidogrel is a prodrug requiring a two-step metabolization via CYP450 enzymes in the liver.[21] The active metabolite then binds irreversibly to the $P2Y_{12}$ receptor with maximum platelet inhibition achieved 2-4 hours after a loading dose. The efficacy of dual antiplatelet therapy in ACS was established in the Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation (CURE) trial where DAPT with ASA and clopidogrel was superior to ASA monotherapy, with a reduction of the combined endpoint of cardiovascular death, nonfatal myocardial infarction and stroke from 11.4% to 9.3% over a mean of 9 months of follow-up.[22] A subgroup of the patients included in the CURE trial, 2,072 (16.5%) of in total 12,562 patients, underwent CABG and were included in a post hoc analysis.[23] There was no interaction for treatment effect of clopidogrel in regard to revascularization strategy (CABG, PCI or medical management) and it was thus concluded that the benefits of clopidogrel observed in the original study population were consistent in those undergoing revascularization with CABG. Major bleeding after CABG occurred in 9.6% of patients treated with DAPT vs 7.5% in patients with ASA monotherapy (p=0.095), with the corresponding numbers 3.7% vs 2.7% (p=0.001) for the total population. Clopidogrel became widely adopted and was the second best-selling drug in the world 2010.[19] Despite great commercial success, clopidogrel has some flaws. Being a pro-drug, it is dependent on hepatic metabolization to be converted to the active metabolite, and due to genetic polymorphisms in the enzymes involved, 5-44% of patients have been reported to be non-responders in in-vitro tests.[24] Further, clopidogrel has a relatively slow onset which was considered a problem in the acute setting.[25] This led to the development of the third generation $P2Y_{12}$ inhibitors prasugrel and ticagrelor.

Prasugrel, like clopidogrel, is a thienopyridine and a pro-drug which requires metabolization into its active metabolite before binding irreversibly to the $P2Y_{12}$ receptor. However, the metabolization of prasugrel is simpler than that of clopidogrel, resulting in faster onset and a higher degree of platelet inhibition with few non-responders. In the Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes (TRITON-TIMI 38) study, 13,608 ACS patients scheduled for PCI was included. Treatment with prasugrel reduced the primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke from 12.1 % to 9.9%. Major bleeding, including fatal bleeding, was more common in the prasugrel group. Although primarily designed to study patients scheduled for PCI, a post-hoc analysis of the 346 (2.5%) patients that eventually underwent CABG showed that prasugrel was associated with lower all-cause mortality (2.3% vs 8.7%.,

p=0.025) compared with clopidogrel, despite the almost five-fold risk of CABG-related bleeding (13.4% vs 3.2%, p<0.001).

The triazolopyrimidine ticagrelor is the latest introduced oral $P2Y_{12}$ inhibitor. It differs from the thienopyridines in that it is a direct acting drug that binds reversibly to the $P2Y_{12}$-receptor and acts as an allosteric antagonist.[21] This results in a faster onset, more consistent and more pronounced inhibition of platelet activation compared with clopidogrel.[26] DAPT with ticagrelor vs clopidogrel in ACS patients was investigated in the Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes (PLATO) study.[27] Among 18,624 patients, the primary outcome of death from vascular causes, myocardial infarction or stroke was lower (11.7% vs 9.8%, p<0.001) at 12 months for patients treated with ticagrelor while the rates of bleeding not related to CABG was higher (4.5 %vs 3.8%, p=0.03). The results were consistent in the 1,261 (6.8%) patients that underwent CABG and received study treatment <7 days before surgery, with 10.6% of the ticagrelor group and 13.1% of the clopidogrel group suffering the primary endpoint (p=0.29).[28] There was no significant difference in CABG related bleeding.

DAPT with ticagrelor vs prasugrel in ACS patients have been studied in the open-label Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes (ISAR-REACT 5) trial which included 4,018 patients.[29] The incidence of the primary endpoint of death, myocardial infarction and stroke was significantly lower among patients treated with prasugrel (6.9% vs 9.3%, p=0.006) while there was no difference in major bleeding between the groups. The majority of patients (84.1%) underwent PCI and only 2.1% underwent CABG. Thus ISAR-REACT 5 offers little data on the effect of ticagrelor and prasugrel after CABG.

	Clopidogrel	Prasugrel	Ticagrelor
Prodrug	Yes Hepatic metabolization	Yes Hepatic and intestinal metabolization	No
Non-responders	Up to 30%	Uncommon	Very uncommon
Binding	Irreversible	Irreversible	Reversible
Onset	2-4 hours	30 minutes	30 minutes
Administration	Once daily	Once daily	Twice daily
Effect	3-10 days	7-10 days	3-5 days
Discontinuation before surgery	5 days	7 days	3 days

Table 1. Overview of oral $P2Y_{12}$ inhibitors.

1.2.3 PLATELET FUNCTION TESTING

Early in the 20th century, Duke developed the first platelet function test - the Duke procedure - by inflicting a skin wound and determining the bleeding time.[30] For many years this was the screening test to identify platelet disorders. In the 1950s, accurate platelet count became widespread and in the 1960s Born introduced light transmission aggregometry to test platelet aggregation.[31] In this test platelet-rich plasma, which is naturally turbid, is exposed to platelet agonists leading to platelet aggregation. Platelet aggregation leads to increased light transmission which can be quantified by a photosensitive detector with the light transmission of platelet-poor plasma as the reference. Light transmission aggregometry is still considered the gold standard of platelet function testing, but the need for a specialized laboratory and time-consuming sample preparation makes it unsuitable for routine clinical use, especially in the acute setting. Since the 1980s, several other methods of platelet function tests are available, including platelet electrode aggregometry in whole blood, flow cytometry of activated platelets, assessment of platelet nucleotides and measurements of substances released by activated platelets.

Multiple-electrode impedance aggregometry (MEA; Multiplate®, Roche Diagnostics, Basel, Switzerland) is a platelet function test method that have gained widespread use.[32] The test allows rapid point-of-care assessment of platelet function using whole-blood samples. The test cells have two sets of paired sensor wires and a magnet stirrer. The blood sample is added together with a platelet activator and as platelets adhere to the sensor wires the electrical impedance increases. The increase in impedance (measured in aggregation units) is plotted against time. The area under curve (AUC), aggregation units × time, is a measure of platelet aggregation and is converted to units (U) for simplicity. By adding different platelet activators, different pathways of platelet activation can be studied. Tests include:

- ASPI test: Using arachidonic acid (AA), the substrate for cyclooxygenase dependent formation of the strong platelet activator thromboxane A2. Sensitive for drugs that inhibit cyclooxygenase such as ASA and non-steroid anti-inflammatory drugs.
- ADP-HS test: Using ADP and prostaglandin E1 to activate platelets via the $P2Y_{12}$ receptor. Sensitive for $P2Y_{12}$ inhibitors such as ticagrelor, prasugrel and clopidogrel.
- TRAP test: Thrombin receptor-activating protein-6 (TRAP) activates platelets via the thrombin receptors PAR-1 and PAR-4. Sensitive for GpIIb/IIIa-antagonists.

Clinical implications of MEA include predicting risk for stent thrombosis and bleeding after PCI[33-35] and predicting postoperative major bleeding after CABG in patients on DAPT.[36,37] Using MEA to "guide the decision on the timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors" may be considered according to European guidelines.[38] In the context of cardiac surgery, platelet function using MEA has been shown to not only reflect preoperative antiplatelet therapy, but also effects of the surgical procedure as such, including the surgical trauma and use of cardiopulmonary bypass, with significantly lower ADP- and TRAP-induced platelet aggregation postoperatively.[39]

1.3 BLEEDING COMPLICATIONS AFTER CARDIAC SURGERY

Bleeding after cardiac surgery is always present to some degree and is due to both the surgical trauma and impaired haemostasis. Impaired haemostasis

results from preoperative antiplatelet therapy[40] and peri-operative factors such as haemodilution, exposure to artificial surfaces during extracorporeal circulation and hypothermia.[41] Excessive bleeding after cardiac surgery, including need for multiple transfusions and re-exploration, has been associated with higher mortality and morbidity in several studies.[42-44] Multiple definitions of severe or major bleeding after cardiac surgery have been proposed. Of these, only the universal definition of perioperative bleeding in adult cardiac surgery (UDPB) has been externally validated to predict mortality.[45] It defines severe bleeding as at least one of the following: transfusion of ≥5 units of red blood cells or ≥5 units of fresh frozen plasma during the first 24 hours; chest tube output >1000 mL during the first 12 hours; delayed sternal closure; re-exploration for bleeding within 24 hours; or use of recombinant factor VII to control bleeding.

The use of DAPT after CABG comes with increased risk of spontaneous bleeding.[27,46] Multiple studies have shown a significant increase in mortality risk associated with post-discharge bleeding after PCI and in general ACS populations, but the prognostic impact of late bleeding complications after cardiac surgery, occurring after hospital discharge, is not well described.[47-52]

1.4 SECONDARY PREVENTION AFTER CABG

Secondary prevention is the concept of preventing relapse of ischaemic manifestations or acute events in patients with established atherosclerotic cardiovascular disease. The term is broad and includes both lifestyle interventions, such as smoking cessation and physical exercise, and pharmacotherapy. Given that atherosclerosis is a systemic disease, secondary prevention interventions generally target the whole organism and not only the heart. Although there is wide overlap in recommended secondary prevention after different manifestations of atherosclerotic disease, there are specific considerations depending on the affected organ and potential revascularization procedures. The evidence for secondary prevention after CABG is scarce, with most recommendations based on extrapolation from studies carried out in non-CABG populations, post-hoc or subgroup analysis of randomized controlled trials or expert consensus. There are two main documents, one published by the American Heart Association and one by the European Association for Cardio-Thoracic Surgery, providing advice on secondary prevention specifically after CABG.[53,54] The reported use of secondary prevention after CABG has been surprisingly low[55-57] and lower compared with patients treated with PCI.[58-60] The scope of this doctoral thesis is focusing on four different

classes of medications commonly used after CABG: statins, beta-blockers, renin-angiotensin-system (RAS) inhibitors and antiplatelet therapy.

1.4.1 STATINS

Evidence from genetic studies, Mendelian randomization studies, randomized controlled trials and prospective cohort studies investigating lipid-lowering therapies have established a causative effect from low-density lipoprotein (LDL) cholesterol levels on atherosclerotic cardiovascular disease.[61] In CABG patients, high LDL cholesterol levels have been associated with development of intimal hyperplasia in saphenous vein grafts and progression of atherosclerotic plaques.[62,63] In clinical practice, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, is the main lipid-lowering therapy. HMG-CoA reductase is the rate-limiting step in the biosynthesis of cholesterol in the liver. By inhibiting this enzyme, the intracellular level of cholesterol in hepatocytes decrease which leads to upregulation of LDL-receptors on the cell surface. This, in turn, leads to increased LDL-uptake in the hepatocytes and, consequently, lower plasma levels of LDL cholesterol. The first statin, lovastatin, was introduced in 1987 and since then five additional statins have been introduced, offering gradually more potent LDL-reduction.[64] The reduction in LDL depends both on the dose and choice of statin, with high-intensity treatment defined as an average LDL reduction of >50% and moderate-intensity treatment of 30-50% reduction of LDL.[65] Statins are generally well-tolerated but liver injury and rhabdomyolysis are rare side-effects. Muscle pain is frequently reported, but the incidence of muscle-related symptoms in blinded trials are similar in the placebo and statin allocated groups, and has been attributed to a possible "nocebo" effect.[66] Secondary prevention with high-intensity statins has been showed to decrease mortality and morbidity in clinical trials in general CVD populations[67] as well as preventing vein graft disease and failure after CABG.[68,69] Consequently, statin therapy is recommended to all patients without contraindications after CABG. The target LDL level have gradually been lowered over the years, with the current target of LDL <1.4 mmol/mol and a reduction of ≥50% from baseline.[65]

1.4.2 BETA-BLOCKERS

Inadequate activation of the sympathetic nervous system, both through elevated plasma catecholamine levels and direct sympathetic effect, is an important contributor to the pathophysiology and symptoms of several cardiovascular diseases such as hypertension, heart failure and angina pectoris.[70] The benefit of beta-blockers in ischaemic heart disease was originally established in patients suffering from myocardial infarction in the

early 1980s.[71] Patients undergoing CABG for myocardial infarction were however excluded from these studies and thus the use of beta-blockers after CABG was low. There is only one prospective randomized placebo-controlled trial, published 1995, on long-term beta-blocker therapy after CABG and this study did not demonstrate any benefit in risk for death or adverse cardiac events.[72] Later, observational data however indicated that use of beta-blockers after CABG was associated with lower mortality and together with multiple studies demonstrating a reduction in postoperative atrial fibrillation beta-blockers was introduced as standard secondary prevention after CABG.[73,74] Beta-blocker therapy is generally considered safe in stable patients, but long-term therapy is associated with side effects such as fatigue, weight gain and sexual dysfunction. Although well-established in heart failure, the benefit of routine beta-blocker therapy has recently been questioned in a general coronary artery disease population based on observational data.[75] There is also an ongoing study investigating the routine use of beta-blockers after myocardial infarction with preserved ejection fraction.[76] In summary, long-term beta-blocker therapy after CABG is currently recommended to prevent atrial fibrillation and to patients with prior myocardial infarction or reduced left ventricular ejection fraction ≤35%.[54] It is also frequently used to treat hypertension.

1.4.3 RENIN-ANGIOTENSIN-SYSTEM INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors affects the renin-angiotensin-system by inhibiting conversion from angiotensin I to II and the breakdown of bradykinin.[77] The physiological effects include vasodilation, leading to lowering of the blood pressure and counteracting cardiac remodeling. Although considered beneficial in heart failure, elevated levels of bradykinin also commonly cause severe cough and more rarely angioedema. Direct inhibition of the angiotensin receptor through angiotensin receptor blockers (ARBs) exerts many of the beneficial effects of ACE inhibitors without these side effects. The effects of both ACE inhibitors and ARBs are well documented in heart failure with reduced ejection fraction[78], hypertension[79], after myocardial infarction (STEMI[5] or NSTE-ACS with LVEF<40%, diabetes or chronic kidney disease[4]) and to protect against diabetic kidney disease[80] progression. Commonly, patients are started on ACE inhibitors and then switched to ARBs if they develop cough. Common side effects include hypotension, functional renal insufficiency, and hyperkalemia. Routine use of ACE inhibitors after CABG for patients without other indications for ACE inhibitors has been investigated in one randomized trial.[81] In this low-risk population, ACE inhibitor therapy did not improve clinical outcome and in fact increased adverse events early after surgery. Therefore,

current recommendations advice RAS inhibitors after CABG only when there is a specific indication for this such as reduced left ventricular ejection fraction or hypertension.[54]

1.5 REGISTER-BASED OBSERVATIONAL RESEARCH

The prospective randomized controlled trial is the preferred study design for investigating efficacy and safety of clinical interventions. This design is however expensive, time-consuming and may have ethical considerations making it often impractical or not feasible. Furthermore, issues regarding external validity can be raised in many cases. Observational studies on the other hand are less expensive and have less ethical considerations. The publicly funded health-care system in Sweden together with several population-based mandatory registries and nationwide quality registries provide excellent conditions for register-based research. The personal identification number given to all Swedish residents at birth, or shortly after immigration, makes it possible to merge individual patient data from several registers to provide information on baseline characteristics, exposures of interest, potential confounders, and clinical outcome.[82] The observational design is however hampered by the lack of randomization and selection bias which must be accounted for. Completeness and high validity of data is essential to carry out high-quality register-based research.[83]

The concept of emulating a "target trial" with observational data has been proposed to avoid study design choices resulting in common biases, for example when defining time zero (baseline/start of follow-up).[84,85] In this framework the desired prospective randomized trial – the target trial - is explicitly defined in terms of research question, patient eligibility, treatment assignment, follow-up, outcome and analysis plan and then used as a template to design the observational study. This framework allows the use of observational studies for causal inference, albeit with many methodological considerations along the way.

1.6 RATIONALE

At the start of the thesis project, the research group had published several papers on aspects of platelet function testing using MEA in the context of cardiac surgery, with a special focus on patients treated with ASA + ticagrelor. One study demonstrated the predictive value of preoperative MEA to predict severe bleeding and another demonstrated that cardiac surgery with

cardiopulmonary bypass in itself affects platelet function.[37,39] Thus, from a theoretical point of view, we hypothesized that it would be better to measure platelet function immediately after surgery to more accurately identify patients at high risk for severe bleeding which formed the rationale for Study I.

From there, the focus shifted from investigating impact of preoperative medications on perioperative and early postoperative outcomes to the role of post-operative medications on mid- and long-term clinical outcome. The research group had made a massive effort in gathering a database with data from several nationwide registries which laid the foundation for papers II-IV. Recognizing the low utilization and scarce evidence for secondary prevention specifically after CABG, we designed Study II to describe the utilization of four commonly prescribed classes of secondary prevention medications and the association with mortality risk.

Although a class 1 recommendation, dual antiplatelet therapy with a potent $P2Y_{12}$ inhibitor after CABG has level of evidence C, with the main randomized data of DAPT vs ASA monotherapy dating back to a *post hoc*-analysis of the CURE trial.[23] Considering that current guidelines recommend potent platelet inhibitors rather than clopidogrel, the objective of Study III was to add real-world data on DAPT with ticagrelor and clinical outcome after CABG in patients presenting with ACS.

Having the results from paper III, with no significant reduction in ischaemic events or death but an increase in the risk for major bleeding, we wanted to further investigate the severity of post-discharge major bleeding events in terms of subsequent mortality risk in Study IV.

2 AIMS

The overall aim of the thesis was to increase the knowledge on how different aspects of pharmacotherapy are associated with the risk for adverse events and death in the short and long term after CABG. Specific aims for the individual studies are listed below:

1. To evaluate the association between postoperative platelet function and postoperative bleeding in patients recently treated with DAPT with ticagrelor (Study I).
2. To determine the impact of cardiac surgery with cardio-pulmonary bypass on platelet aggregation capacity in patients with ongoing or recently discontinued DAPT with ticagrelor (Study I).
3. To determine the use of statins, beta-blockers, RAS inhibitors and platelet inhibitors over time after CABG in relation to age and sex (Study II).
4. To investigate associations between ongoing use of statins, beta-blockers, RAS inhibitors and platelet inhibitors and mortality risk (Study II).
5. To determine the utilization of DAPT after CABG in acute coronary syndrome patients in Sweden (Study III).
6. To investigate whether the risk for ischaemic events and major bleeding after CABG in ACS patients differed between patients treated with DAPT with ticagrelor compared with ASA monotherapy (Study III).
7. To investigate the incidence of post-discharge major bleeding after CABG and the association with subsequent mortality risk (Study IV).
8. To compare the incidence and mortality risk associated with post-discharge major bleeding to the incidence and mortality risk associated with post-discharge myocardial infarction (Study IV).

3 PATIENTS AND STUDY DESIGN

This doctoral thesis is based on four studies. Study I is based on patients that underwent surgery at Sahlgrenska University Hospital and Study II-IV are nationwide register-based studies. All studies were conducted in accordance with the Declaration of Helsinki and approved by the Regional Research Ethical Committee in Gothenburg. The need for individual patient consent was waived for all four studies. An overview of basic study design and patient characteristics is presented in Table 2.

	Study I	Study II	Study III	Study IV
Study design	Prospective observational study	Register-based cohort study	Register-based cohort study	Register-based cohort study
Data sources	Locally collected data	Swedish cardiac surgery registry, NPR, CDR, SPDR, TPR	Swedish cardiac surgery registry, NPR, CDR, SPDR, TPR, LISA	Swedish cardiac surgery registry, NPR, CDR, SPDR, TPR, LISA
Inclusion criteria	Acute coronary syndrome with ticagrelor <5 days before cardiac surgery	First time isolated CABG Surviving 6 months after hospital discharge	ACS <6 weeks before surgery, first time isolated CABG Surviving 14 days after hospital discharge Postoperative treatment with ASA or ASA+ticagrelor	First time isolated CABG, Surviving 14 days after hospital discharge
Study participants	74	28,812	6,558	36,633
Age (years)	67±10	67±9	68±9	68±9
Female gender	18 (24%)	5,656 (19.6%)	1,277 (19.5%)	7,206 (19.7%)
Study period	Oct 2012 – Nov 2016	Jan 2006 – Dec 2015	Jan 2012 – Dec 2017	Jan 2006 – Dec 2017

	Study I	Study II	Study III	Study IV
Predictor/ Exposure	Pre- and postoperative platelet function	Statins, Beta-blockers, RAS inhibitors, Platelet inhibitors	Dual antiplatelet therapy with ASA+ticagrelor vs ASA monotherapy	Post-discharge major bleeding and post-discharge myocardial infarction
Length of follow-up	30 days	4.9 (IQR 2.5–7.2) years	2.9 (IQR 1.4-4.4) years	6.0 (IQR 3.0-9.0) years
Outcomes	Severe bleeding Change in platelet function	All-cause mortality	All-cause mortality, myocardial infarction, stroke, major bleeding	All-cause mortality

Table 2. Overview of patients and study design in Study I-IV. CDR, Cause of Death Register; IQR, interquartile range; LISA, The Longitudinal Integration Database for Health Insurance and Labor Market Studies Register; NPR, National Patient Register; SPDR, Swedish Prescribed Drug Register; TPR, Total Population Register

4 METHODS

Study I

Seventy-four patients with ACS treated with DAPT with ticagrelor that underwent cardiac surgery at Sahlgrenska University Hospital within 5 days of ticagrelor administration were included. Seventy-three patients underwent CABG and one patient underwent mitral valve surgery due to acute mitral regurgitation. Platelet function was assessed with MEA (Multiplate®; Roche Diagnostics, Basel, Switzerland) using ASPI, ADP-HS and TRAP tests. Blood was sampled in hirudin tubes at the time of induction of anaesthesia and 2 h after weaning from cardiopulmonary bypass. Data on the surgical procedure, transfusion of blood products, chest tube output, re-exploration for bleeding, use of pro-haemostatic drugs and mortality were collected from hospital records. Severe bleeding was defined according to the UDPB criteria. Change between pre- and post-operative platelet function measurements and the accuracy in predicting severe bleeding were evaluated.

Study II-IV

Study II-IV are register-based cohort studies with individual patient data from several nation-wide mandatory registries. The merging of data was performed by the official authority *Statistics Sweden* and provided to the authors after pseudonymization. Data was obtained from the registers described below.

4.1 REGISTERS

Swedish Cardiac Surgery Registry

This registry is a part of the SWEDEHEART register. Established in 1992, the Swedish Cardiac Surgery Registry holds detailed information on all cardiac surgery procedures in Sweden. It has been validated with a coverage of 98-99% and excellent reliability of included variables.[86] The registry was used to identify the study population and to collect data on procedural aspects, pre-operative status and comorbidities.

National Patient Register

This register has gradually increased in coverage and is considered as complete since 1987. It has full coverage on all hospital admissions including admission date and diagnosis according to International classification of diseases (ICD) 9th and 10th revision, with a validity of 85-95%.[87] Since 2001 it also contains diagnosis from outpatient visits. Data from the National Patient Register was used to identify baseline comorbidities and to identify clinical events during follow-up such as myocardial infarction, stroke or major bleeding.

Cause of Death Register

Contains data on date and cause of death according to ICD. It is electronically available from 1952 and has virtually full coverage, including Swedish residents dying abroad.[88] As cause of death is generally not being confirmed with autopsy, this data is associated with some uncertainty with one study stating that cause of death was correct in 77% of cases.[89] In this thesis, we chose to only include date of death in the studies.

Swedish Prescribed Drug Register

Holds information on prescriptions dispensed from all pharmacies in Sweden from July 2005 according to Anatomical Therapeutic Chemicals (ATC) classification.[90] Exposure status was collected at baseline and updated every third month during follow-up. Patients were considered off treatment if they had no dispensed medication over two consecutive three-month periods. This was based on the typical package size in Sweden covering 90-100 doses and allowing for minor failure to adhere to the treatment as well as irregularities in dispensing intervals.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies Register (LISA)

Originally established in 1990 in response to rising levels of sick leave, the LISA register holds information on education, income and occupation with a completeness of data of 95-100%.[91] Baseline data on income, marital status and education level were collected from this registry.

The Total Population Register

Contains basic demographic information such as date of birth, sex, marital status, date of immigration and emigration and date of death with virtually complete coverage.[92]

4.2 STATISTICAL ANALYSES

Data are presented as mean with standard deviation (SD), median with 25th-75th percentile, median with range or frequency with percent where appropriate. In Study I, normality of data was assessed by visual check of frequency distribution and the Shapiro-Wilk test in order choose the correct statistical tests. Given the large sample sizes in Study II-IV, the assumption of normality was not considered critical as stated by the central limit theorem. Significance was interpreted as a two-tailed p-value of <0.05 in all studies. Missing data was handled as a separate category in studies II-IV.

Study I

Pre- and postoperative platelet aggregation were compared with Wilcoxon signed-rank test and correlation assessed with Spearman's rank-sum test. The effect of peroperative platelet transfusion was investigated by analysing the change in pre- and postoperative platelet function for the groups (patients not receiving transfusions and patients receiving transfusions) in an analysis of covariance (ANCOVA) model adjusted for preoperative baseline level. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was used to evaluate the accuracy of platelet aggregation tests in predicting severe bleeding. Youden's index, J = (sensitivity + specificity - 1), was calculated for all points on the ROC curve. The maximum value for J was then used to determine the theoretically optimal cut-off for the test[93] and sensitivity, specificity, positive and negative predictive values were calculated. The association between postoperative ADP-induced platelet aggregation and the probability of severe bleeding was investigated using univariate logistic regression.

Study II

Patient characteristics and comorbidities were registered at baseline (six months after hospital discharge). This was also the start of follow-up. Exposure was ongoing use of statins, beta-blockers, RAS inhibitors and

platelet inhibitors and was updated every third month during follow-up. Use of medication was defined as a dispensed prescription the last six months. Endpoint was all-cause mortality. The use of medications over time after CABG was reported as crude data with gender and age (≥75 or <75 years) as grouping variables. Differences in use of medication at baseline and 8 years after baseline were analysed using Fishers's exact test. The piecewise linear trend for use of medications was investigated using general estimation equations with the results expressed as relative risk per 1-year increase, where a value of <1 indicated lower use of medication.

The association between time-updated exposure of secondary prevention medications and mortality risk was investigated with Cox proportional hazards models. Model 1 was adjusted for age and sex and model 2 were further adjusted for patient factors at baseline previously shown to influence long-term mortality after CABG.[94] In model 3, considered the main effect model, adjustments for time-updated use of the other categories of secondary prevention medication than the one currently analyzed were added. As a sensitivity analysis, model 3 was applied to consecutive 1-year periods where only patients at risk at the start of a 1-year period were included and exposure status for medication at the start of the year was used to evaluate the association with mortality risk during the 1-year follow-up. The widened timeframe between exposure status and outcome was an attempt to control for "reverse causality" meaning that terminally ill patients stop using medications. The cumulative effects of total exposure time of each medication and mortality risk were also investigated. Interaction analyses were performed for pre-specified subgroups.

Study III

Exposure status was based on a dispensed prescription of ticagrelor within the first 14 days after hospital discharge. Start of follow-up was 15 days after hospital discharge. Co-primary endpoints were major adverse cardiovascular event (MACE, defined as either of all-cause mortality, myocardial infarction or stroke) and major bleeding. Myocardial infarction, stroke and major bleeding were defined as a hospitalization with a primary diagnosis according to ICD-10 of the clinical event. Secondary endpoints were the individual components of the primary endpoint and net adverse clinical events (NACE, defined as either of all-cause mortality, myocardial infarction, stroke, or major bleeding).

Kaplan-Meier estimates were used to compute cumulative incidence of endpoints, with death as competing risk for the individual events of myocardial

infarction, stroke, and major bleeding. The risk for the different endpoints based on exposure status of ticagrelor at the start of follow-up was compared using Cox proportional hazards models. A simple model was adjusted for age and sex and a more complex model, considered the main analysis, was adjusted for 25 baseline covariates and time-updated use of statins, beta-blockers and RAS inhibitors during follow-up. Interaction analyses were performed for pre-specified subgroups. The covariates adjusted for had either been previously shown to affect mortality after CABG or were associated with any of the studied outcomes based on separately performed forward stepwise regression models with $p<0.10$. A propensity score model was developed as a complimentary analysis. Using the same baseline covariates included in the main analysis, a caliper with of 0.005 and matching 1:1 resulted in 1,359 pairs. Time to event was then analyzed with Cox proportional hazards models adjusted for time-updated use of statins, beta-blockers and RAS inhibitors.

Study IV

Start of follow-up was 15 days after hospital discharge. Exposure was major bleeding or myocardial infarction respectively, and endpoint was all-cause mortality. Piecewise Cox proportional hazards models were developed to investigate the impact of major bleeding or myocardial infarction on subsequent mortality risk. Given the strong time-dependence of mortality risk after an adverse event, hazard ratios were calculated for three time periods: <30 days, 30-365 days and >365 days after the event. The models were adjusted for 27 covariates at baseline and for the time-updated use of platelet inhibitors, oral anticoagulants, beta-blockers, RAS inhibitors and statins during follow-up. The covariates adjusted for had either been previously shown to affect mortality after CABG or were associated with mortality based on separately performed stepwise regression models with $p<0.10$. Similar piecewise Cox proportional hazards models were used to estimate mortality risk for different bleeding locations. Due to 287 patients suffering both a major bleeding and a myocardial infarction, a separate analysis including only the first post-discharge event was performed as a sensitivity analysis.

4.3 ETHICAL APPROVALS

The studies were approved by the Regional Research Ethical Committee in Gothenburg. The need for individual patient consent was waived for all studies.

Study I: Ethical approval number EPN 298-11

Study II-IV: Ethical approval number EPN 139-16

5 RESULTS

5.1 PRE- AND POSTOPERATIVE PLATELET FUNCTION IN TICAGRELOR-TREATED PATIENTS

In Study I, platelet aggregation induced by AA was significantly higher postoperatively compared to preoperatively whereas there was no difference in ADP- and TRAP-induced platelet aggregation, Table 3. Pre- and postoperative ADP-induced aggregation had a high correlation (r^2=0.77, p<0.001), AA-induced and TRAP-induced aggregation had a relatively low correlation (r^2=0.24 and r^2=0.21 respectively, both p<0.001). There was no significant increase in ADP- and TRAP-induced aggregation in the 21 patients that received platelet transfusion compared with patients with no platelet transfusion (p=0.79 and p=0.76 respectively); AA-induced aggregation was significantly higher in the patients who received platelet transfusion (median increase 14 U for patients receiving platelet transfusion vs 2 U for patients not receiving platelet transfusion, p<0.001).

	Aggregation capacity (U)	ROC AUC	Cut-off	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
ADP pre	37 (0-117)	0.77	25	63	86	76	78
ADP post	29 (0-145)	0.75	15	68	81	60	86
AA pre	13 (0-66)	0.66	9	46	77	57	69
AA post	20* (0-126)	0.57	8	69	74	36	92
TRAP pre	112 (33-180)	0.76	100	54	82	64	75
TRAP post	116 (11-195)	0.66	119	48	82	76	57

*Table 3. Diagnostic properties of pre- and postoperative platelet aggregation tests. AA, arachidonic acid; ADP, adenosine diphosphate; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; TRAP, thrombin receptor-activating peptide. *P<0.05 vs preoperative value*

5.2 PRE- AND POSTOPERATIVE PLATELET FUNCTION AND BLEEDING RISK

Among the 74 patients included, 25 (34%) developed severe bleeding. Crude 30-day mortality was higher in the group with severe bleeding (5/25 [20%] vs 2/49 [4%], p=0.028). Diagnostic properties of pre- and postoperative platelet function tests are summarized in Table 3. Patients with severe bleeding had lower ADP-induced platelet aggregation capacity both preoperatively [16 (0–104) U vs 49 (4–117) U, P<0.001] and postoperatively [13 (0–80) U vs 37 (0–145) U, P=0.001], Figure 3. The AUC for ROC graphs for ADP-induced aggregation and severe bleeding was 0.77 (95% CI 0.65–0.89) for preoperative measurements and 0.75 (95% CI 0.62–0.87) for postoperative measurements.

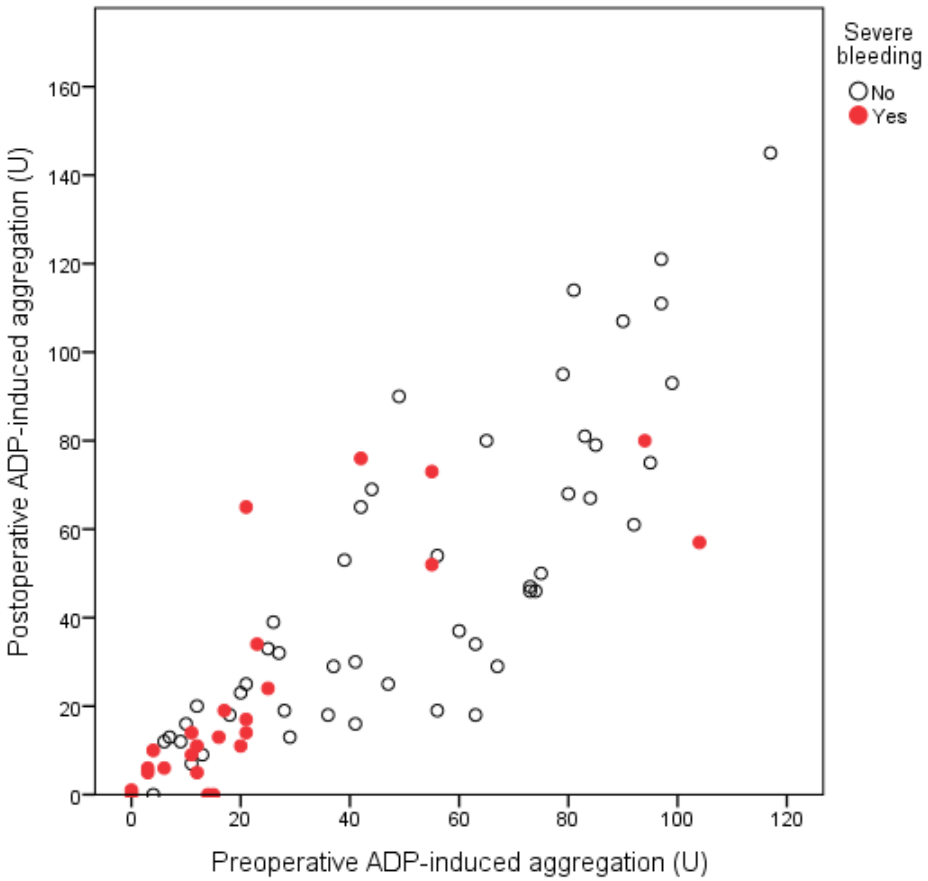

Figure 3. Pre- and postoperative ADP-induced platelet aggregation and severe bleeding.

5.3 UTILIZATION OF SECONDARY PREVENTION AFTER CABG

From 2006 to 2015, the proportion of patients with dispensed prescriptions six months after discharge from CABG of statins, beta-blockers and RAS inhibitors increased from 91.5% to 96.0%, 89.0% to 92.4% and 64.4% to 78.4% respectively (all p<0.001), Study II. During the same time, the proportion with a dispensed prescription of platelet inhibitors decreased from 93.2% to 92.2% (p=0.004). Overall, statins were dispensed to 93.9% at baseline and 77.3% 8 years later, corresponding numbers for beta-blockers were 91.0% and 76.4%, for RAS inhibitors 72.9% and 65.9% and for platelet inhibitors 93.0% and 79.8%. There was a significant trend for yearly reduction of dispensed prescriptions for all four groups of medications over time after surgery, with the steepest decline the first year of follow-up, Figure 4.

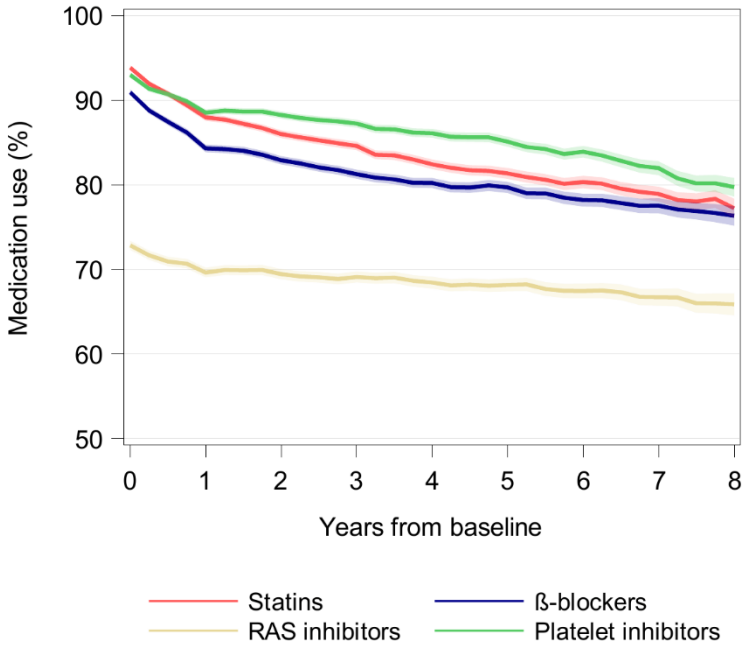

Figure 4. Dispensed prescriptions of secondary prevention medications over time after CABG with start at baseline 6 months after surgery. RAS, renin-angiotensin-system.

Women were dispensed more beta-blockers and RAS inhibitors at baseline. After 8 years of follow-up, women were dispensed more beta-blockers and less statins. Patients ≥75 years were dispensed less statins, beta-blockers, and platelet inhibitors at baseline and after 8 years there were lower rates of dispensation of all four classes of medications to the older group.

In Study III, the utilization of DAPT after CABG in ACS patients increased from 17.4% 2012 to 53.5% 2017 ($p<0.001$). Patients with anticoagulation, ongoing DAPT before the ACS or no dispensed prescriptions of ASA were excluded from this cohort. The use of ticagrelor increased from 4.2% to 49.2% whereas the use of clopidogrel decreased from 13.2% to 4.3% (both $p<0.001$). Prasugrel was only dispensed to 23 patients during the study period.

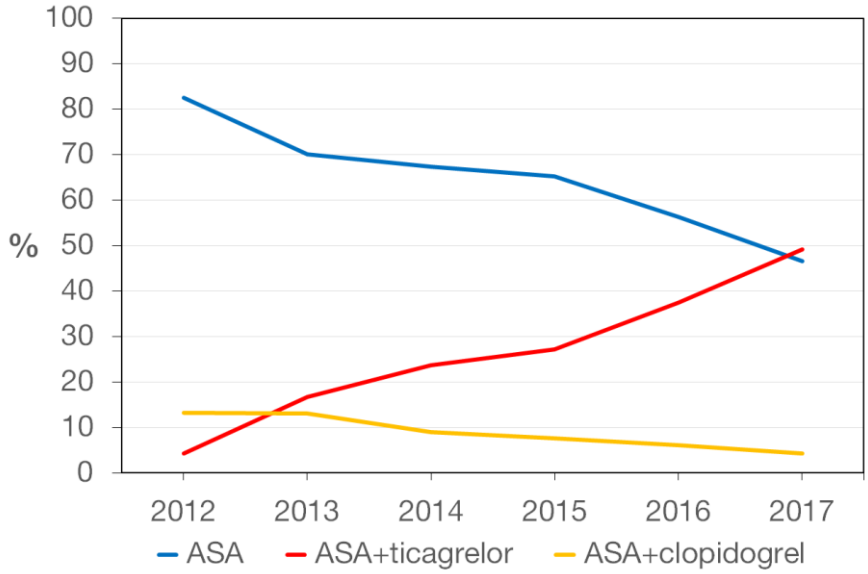

Figure 5. Dispensed prescriptions of platelet inhibitors after CABG for ACS in patients eligible to DAPT in Sweden 2012-2017. ASA, acetylsalicylic acid

5.4 SECONDARY PREVENTION MEDICATIONS AND MORTALITY RISK AFTER CABG

In Study II, 3,787 of 28,812 (13.1%) patients died during a median follow-up of 4.9 years (25^{th}-75^{th} percentile 2.5-7.2 years). In the fully adjusted model, use of statins (aHR 0.56, 95% CI 0.52–0.60), RAS inhibitors (aHR 0.78, 95% CI 0.73–0.84) and platelet inhibitors (aHR 0.74, 95% CI 0.69–0.81) were associated with lower mortality risk, Figure 6. Use of beta-blockers was not associated with lower mortality risk (aHR 0.97, 95% CI 0.90–1.06). There was an association between cumulative medication exposure and lower mortality risk for statins (aHR 0.90, 95% CI 0.88–0.92), RAS inhibitors (aHR 0.98, 95% CI 0.96–1.00) and platelet inhibitors (aHR 0.93, 95% CI 0.91–0.95) per additional year exposed.

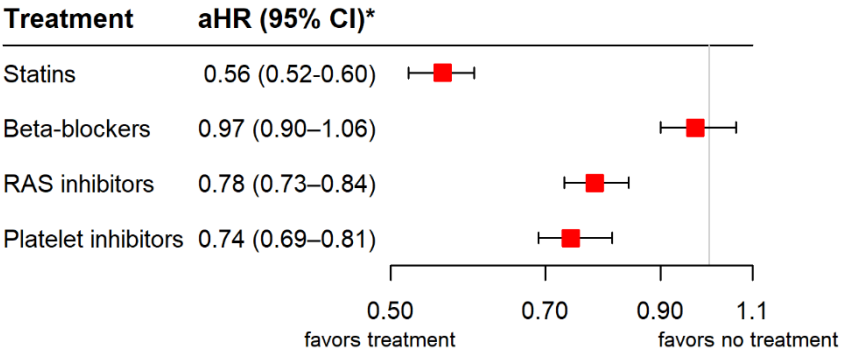

Figure 6. Forest plot describing associations between medication use and mortality risk after CABG.

The association between statin use and lower mortality risk was consistent among all subgroups, with more pronounced reduction in mortality risk in patients without diabetes or clinical heart failure. For RAS inhibitors, there were significant interactions for gender and hypertension with significant reduction in mortality risk only for men and patients with hypertension. There was also an interaction with renal function with more pronounced reduction in mortality risk for patients with eGFR <60 ml/min/1.73m^2. The association between use of platelet inhibitors and lower mortality risk was consistent among all subgroups, with more pronounced reductions in patients with preserved left ventricular ejection fraction (>50%), no clinical heart failure and no atrial fibrillation. There were no interactions for use of beta-blockers and

mortality risk for any of the subgroups, including patients with left ventricular ejection fraction <50%.

In Study III, 366 patients (5.6%) of 6,558 died during a median follow-up of 2.9 years (25th-75th percentile 1.4-4.4 years). There was no association between use of ASA+ticagrelor and lower mortality risk compared with ASA monotherapy (aHR 0.82, 95% CI 0.44-1.51 at 12 months and aHR 0.79, 95% CI 0.57-1.09 at end of follow-up).

5.5 OUTCOME AFTER CABG IN ACS PATIENTS TREATED WITH TICAGRELOR

In Study III, 207 patients (3.2%) suffered a myocardial infarction, 160 patients (2.4%) had a stroke, and 197 patients (3.0%) had a major bleeding. Use of ticagrelor was associated with an increased risk for major bleeding at 12 months (aHR 1.90, 95% CI 1.16-3.13) but not at end of follow-up, Figure 7. There was no association between use of ticagrelor and lower risk for myocardial infarction or stroke, neither at 12 months nor at end of follow-up.

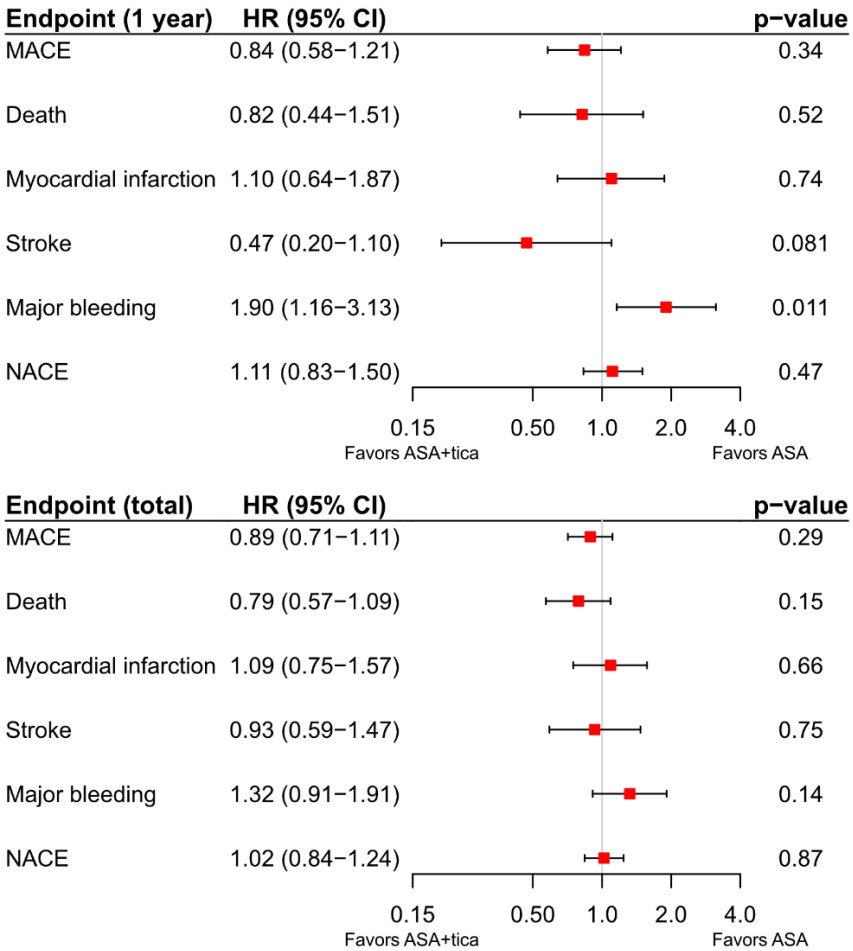

Figure 7. Forest plot describing associations between use of ASA and ticagrelor and clinical events. MACE indicates major adverse cardiovascular events which is a composite of death, myocardial infarction and stroke. NACE indicates net adverse clinical events which is a composite of death, myocardial infarction, stroke or major bleeding.

5.6 POST-DISCHARGE MAJOR BLEEDING, MYOCARDIAL INFARCTION AND SUBSEQUENT MORTALITY AFTER CABG

In Study IV, 36,633 CABG patients were included with a median follow-up of 6.0 years (25^{th}-75^{th} percentile 3.0-9.0 years). During follow-up, 2,429 patients (6.6%) had at least one major bleeding, 2,231 patients (6.1%) had a myocardial infarction and 6,683 patients (18.2%) died. Both major bleeding and myocardial infarction were associated with an increase in subsequent mortality risk. The increase in mortality risk was highest <30 days after the event but remained increased 30-365 days and >365 days after the event for both major bleeding and myocardial infarction. Results of the sensitivity analysis investigating only the first post-discharge event (bleeding or myocardial infarction) were in line with the primary analysis.

Gastrointestinal bleeding was the most common bleeding localization with 1,187 events (49% of bleeding events) and intracranial bleeding occurred in 388 patients (16% of bleeding events). Intracranial bleeding was associated with the largest increase in mortality risk, followed by gastrointestinal bleeding. For detailed results and figures, see Study IV.

6 DISCUSSION

6.1 PLATELET FUNCTION TESTING IN CARDIAC SURGERY

Platelet function testing in cardiac surgery patients may have three major implications: (i) to guide optimal timing of urgent CABG, (ii) to guide transfusion and haemostatic strategies and (iii) to guide optimal postoperative antiplatelet therapy.

Routine administration of dual antiplatelet therapy to ACS patients before coronary anatomy is known leads to the common clinical dilemma of timing of CABG in the approximately 5-10% of patients who are eventually referred for surgery.[95,96] On the one hand the ischaemic risk, with in worst case ongoing ischaemia or – more common – high risk for recurrent ischaemic events and on the other hand the well-documented increase in risk for CABG-related bleeding complications.[40,97] Since there is a high inter-individual variability in recovery of platelet function after drug discontinuation,[98] monitoring of platelet function have been investigated, and proposed in guidelines as a IIb recommendation, to shorten waiting time for urgent surgery, rather than using a fixed number of days since drug-discontinuation.[38] This strategy is however hampered by the moderate accuracy of preoperative platelet function testing in predicting bleeding complications.[36,37]

In Study I, we hypothesized that postoperative platelet function testing, taking in both preoperative antiplatelet therapy and perioperative alterations of platelet function, would predict bleeding complications more accurately compared with preoperative testing. Postoperative testing can, of course, not be used to guide optimal timing of surgery, but could be important to guide postoperative care, especially transfusion and haemostatic strategies. However, the results of Study I did not show any added diagnostic value of postoperative MEA measurements in ticagrelor-treated patients undergoing cardiac surgery. Further, there was no effect of platelet transfusions on ADP-induced platelet aggregation. This is in line with other in-vitro and in-vivo reports of patients treated with ticagrelor receiving platelet transfusions, underscoring the difficulty in treating bleeding diathesis in these patients.[99,100] This difficulty might be about to change with the development of the monoclonal antibody bentracimab. Bentracimab reverses the effect of ticagrelor and a clinical trial evaluating its effect in ticagrelor-treated patients requiring urgent surgery or presenting with major hemorrhage is currently ongoing.[101]

In the 2020 ESC Guidelines for ACS in patients presenting without persistent ST-segment elevation (NSTE-ACS), pre-treatment with $P2Y_{12}$ inhibitors before coronary anatomy is known has been given a class III recommendation.[4] If this recommendation is widely adopted, the need for platelet function testing before or during cardiac surgery could be dramatically reduced. Indeed, pre-treatment with $P2Y_{12}$ inhibitors has been advised against in Västra Götaland county, Sweden, since April 2016. In 2018, less than 15% of ACS patients were pre-treated, with no difference in mortality and stent-thrombosis but a significant lower incidence of bleeding, including reoperation for bleeding after CABG, compared with the preceding time period when routine pre-treatment was administered.[102]

High platelet reactivity despite ongoing treatment with $P2Y_{12}$ inhibitors (especially clopidogrel) have been associated with increased risk for stent thrombosis after PCI.[103] Low platelet reactivity have conversely been linked to higher risk for bleeding complications. This forms the rationale for using platelet function testing to tailor antiplatelet treatment in the individual patient. However, several clinical trials have failed to demonstrate any clinical benefit of platelet function testing to adjust antiplatelet therapy and therefore "routine platelet function testing to adjust antiplatelet therapy before or after elective stenting" has been given a class III, level of evidence A, recommendation.[38] No study on platelet function testing to adjust antiplatelet therapy specifically after CABG has been published.

6.2 UTILIZATION OF SECONDARY PREVENTION AFTER CABG

In Study II, the use of statins, beta-blockers and platelet inhibitors were high at baseline (6 months after discharge) with 93.9%, 91.0% and 93.0% of patients having a dispensed prescription respectively. The use of these three drug classes were stable, with less than 5% change, over the calendar years during the study period. The overall use of RAS inhibitors of 72.9% was lower but increased over the study period from 64.4% 2006 to 78.4% 2015. A similar pattern emerged in Study III, where overall utilization of DAPT increased from 17.4% 2012 to 53.5% 2017, driven by a steep increase in use of ticagrelor from 4.2% to 49.2%. The increase in DAPT due to increased use of ticagrelor is interesting since no new evidence for DAPT vs ASA monotherapy after CABG was presented with the introduction of ticagrelor - ticagrelor is rather a more potent form of DAPT compared with clopidogrel.[27,104] The limited use of

DAPT after CABG in ACS patients in Study III is in line with other studies.[105,106] The reasons for the low adherence to this class I recommendation is not systematically investigated but lack of strong evidence, fear of bleeding complications and a tradition of ASA monotherapy after CABG are possible explanations.

The baseline data from Study II reports similar or higher use of secondary prevention medications as in the latest European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) survey published in 2019.[107] In this study, self-reported use of statins was 80%, beta-blockers 81%, RAS inhibitors 75% and platelet inhibitors 93% in a general CAD population. RAS inhibitors after CABG are typically reserved for patients with reduced left ventricular function, diabetes, hypertension or previous myocardial infarction which may account for the lower use of RAS inhibitors compared to the other medication groups.[53,54] In a study based on largely the same population as Study II, 91.3% of the patients were found to have at least one indication for RAS inhibitors and the use of RAS inhibitors at baseline were higher among patients with indication (77.0%) compared with patients without indication (29.7%).[108] Thus, also in patients with a clear indication, RAS inhibitors were underutilized.

In Study II, there was no major and consistent difference observed between genders in utilization of secondary prevention medication, with only small differences in dispensed prescriptions. In contrast, patients ≥75 years generally dispensed fewer secondary prevention medications than patients <75 years. At the same time, there was no interaction for age ≥75 years for any of the medications, indicating that older patients benefit equally from secondary prevention in terms of mortality risk.

The observed decrease in use of all four classes of medications over time after surgery in Study II is worrisome. Analyses indicated that the benefit of secondary prevention medications was equal, or possibly even greater, over time after surgery with longer accumulated exposure time associated with lower mortality risk. Further, no interaction for follow-up time after surgery was seen for statins, beta-blockers, and platelet inhibitors while the estimated effect for RAS inhibitors increased over time. The decrease in use of secondary prevention medications over time after CABG in Study II is in line with other reports. For example, in a post hoc analysis of the SYNTAX trial, the use of statins, beta-blockers and platelet inhibitors decreased over a five-year period while the use of RAS inhibitors remained stable.[60] The benefits of long-term secondary prevention, including patients ≥75 years, should be emphasized to

maximize the profits from the substantial investment a CABG procedure represents, both from the patient´s and the health care system´s point of view.

Further studies on the causes for the decrease of secondary prevention utilization over time, preferably with qualitative approach, are needed. Principally, causes can be found at patient, physician and health care system level. The sharpest decline in use of medications occurred during the first year of follow-up. In Sweden, patients are typically followed at a cardiology department the first 6-12 months after CABG and then referred to their primary health care centre for continuous follow-up. This fragmentation might be suboptimal for long-term adherence to guideline directed therapies. Use of medications in Study II was defined by dispensed prescriptions during the last 6 months and could thus not differentiate doctors' non-prescription from patients' non-adherence to prescriptions during this transition. Physicians, nurses and physiotherapists in the primary care often have a longstanding relation with their patients, which can be profited from to improve adherence to both secondary prevention medications and lifestyle interventions. Perhaps a more seamless transition from a specialised cardiology department to the primary care, with earlier involvement of primary care professionals and a more active role of cardiologists in the long-term, would serve our patients well. The concept of using a polypill to simplify medication administration has been shown to increase medication adherence and, recently, to improve clinical outcome.[109,110] Nurse-led telephone-based follow-up[111] in addition to standard cardiac rehabilitation and digital health tools are also possibilities in optimizing secondary prevention. Given that many secondary prevention medications are generically available, measures to improve adherence to these existing, inexpensive and well-documented drugs, pose a cost-effective alternative to introducing new therapies in the strive for better long-term survival.

6.3 MEASURING ADHERENCE

There are several methods of measuring adherence, all with advantages and disadvantages. Self-reporting is easy and common in both clinical trials and observational studies but depends on how questions are formulated and have the risk of over-estimation due to patients forgetting non-adherence. In clinical trials, tablet counting, use of electronic monitoring devices and sometimes measurement of drug concentration in body fluids is common and sometimes used together with self-reporting. Tablet counting and monitoring devices may offer more accurate data on adherence, however the external validity of such

data can be questioned since patients may act differently while being monitored. Data on dispensed prescriptions have the advantage of representing a "real-world"-setting but have the limitation of only measuring the dispensation of drugs and not drug intake as such and have a relatively low granularity. This is especially true in medications with a wide span of doses. Several methods of measuring drug persistence in register-based studies have been described.[112] The method used in Study II, where a patient was considered to be on treatment if he/she had a dispensed prescription within the preceding 6 months, only allow for analysis of drug use but not treatment intensity or adherence in terms of proportion-of-days-covered. The rationale for choosing a 6-month period was based on the typical package size in Sweden which covers 90-100 doses and to allow for minor inconsistencies in adherence as well as the possibility of "stock-piling" with subsequent longer gaps between dispensations. This method also has some support in literature.[113] In Study III, the exposure for the studied medication was based on a dispensed prescription at baseline, which represent an "intention-to-treat-like" analysis compared to the approach in Study II which is more "per-protocol-like". Given the fixed dose for ticagrelor and the typical treatment duration of 12 months it was possible to calculate adherence in terms of proportion-of-days-covered. The reason for choosing this approach was because of the relatively short time period of 12 months which ticagrelor typically is prescribed, where the method based on dispensed prescriptions the last 6 months arguably is too crude. The choice of using the intention-to-treat-like approach is also more resembling a "target trial" and aims to answer the clinically more relevant question whether to start ticagrelor or not in ACS patients after CABG, rather than answering if use of ticagrelor after CABG in ACS patients is associated with better outcome.

6.4 SECONDARY PREVENTION OR DISEASE-MODIFYING DRUGS?

Atherosclerosis is typically a chronic pathological process with a long subclinical phase and thus already present before clinical manifestations of angina pectoris or myocardial infarction. Revascularization with CABG and PCI restores the coronary circulation but does not affect the underlying atherosclerotic disease. The term secondary *prevention* may therefore be somewhat misleading. One can argue that atherosclerosis has the characteristics of a chronic, relapsing, and progressive disease. The rate of progression depends on non-modifiable factors such as genetic disposition and

age and modifiable factors such as lifestyle and pharmacotherapy. Thus, secondary prevention medication can be viewed at as disease-modifying drugs whereas revascularization is targeting manifestations of an already established disease. The Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA) trial may serve as an example of this.[114] In this study, 5,179 patients with stable coronary disease and moderate or severe ischaemia were randomized to either medical therapy or medical therapy plus invasive evaluation and treatment (when possible). There was no difference in the primary endpoint consisting of a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest but the invasive group had significantly fewer anginal symptoms.[115] The results underscores the benefits of disease-modifying drugs in treating prognosis in coronary artery disease patients. The patients in ISCHEMIA were indeed well-treated in this regard with 95% using statins and 96% using antithrombotic medications.[116]

After undergoing the major intervention of CABG and, in many cases, experiencing effective relief of symptoms, it is understandable if a patient has the feeling of being "cured". Changing language might help patients understanding the importance of adherence to secondary prevention. Perhaps controversial, one could even use the analogy of anti-retroviral therapy for HIV infection with secondary prevention pharmacotherapy for coronary artery disease. One step in this direction is the introduction of the term "chronic coronary syndrome" instead of stable coronary artery disease, which was adopted in the 2019 ESC guidelines.[3]

6.5 ROLE OF DAPT AFTER CABG

Current European and American guidelines recommend DAPT with a potent $P2Y_{12}$ inhibitor after CABG in patients presenting with ACS and American guidelines also recommend DAPT with clopidogrel to improve vein graft patency after CABG in stable patients.[38,117] Recently, a systematic review and meta-analysis found that DAPT with ticagrelor was associated with a decreased risk for vein graft failure but a higher risk for clinically important bleeding events compared with ASA monotherapy.[118] The evidence for the recommendations in guidelines is however low, reflected in level of evidence C for DAPT to ACS patients and B for DAPT to improve vein graft patency. The results presented in Study III and IV challenge these current recommendations. The main piece of evidence from randomized data on DAPT vs ASA monotherapy after CABG in an ACS setting comes from the

CURE trial, where there was no interaction for revascularization strategy on the benefit of adding clopidogrel to ASA.[23] One observational study, a Danish register-based cohort study published 2011, found an association between ASA+clopidogrel and lower risk for death and MI compared with ASA monotherapy after CABG for patients presenting with myocardial infarction.[119] Ticagrelor after CABG have been studied in the DACAB trial where patients with and without ACS (predominantly unstable angina) were randomised to either ASA monotherapy, ticagrelor monotherapy or DAPT with ASA and ticagrelor.[120] The vein graft patency rate was higher in patients treated with DAPT but there was no significant difference in MACE at 1 year. The TiCAB trial, also including both patients with and without ACS, compared ASA monotherapy and ticagrelor monotherapy after CABG with no difference in MACE at 1 year.[121]

There are important mechanistic differences in the role of DAPT after CABG compared with after PCI or medically treated ACS. One main reason for DAPT after PCI is to prevent stent thrombosis. Stent thrombosis is indeed a catastrophic event with reported mortality up to 50%.[122] The risk for stent thrombosis is highest early after PCI and, with the introduction of modern drug-eluting stents, DAPT as short as 1-3 months in high bleeding risk patients has been reported safe.[123] The remaining time of DAPT (typically 12 months in total for ACS patients) after PCI mainly serves to protect against new plaque ruptures in the remainder of the coronary arterial tree. The corresponding reason for DAPT after CABG is to prevent graft failure. The clinical course of graft failure is however different from stent thrombosis. It has been reported that 3-12 % of saphenous vein grafts are occluded due to thrombosis one month after surgery with a subsequent attrition rate of 1-2 % per year the first 6 years after surgery and 4% per year 6-10 years after surgery.[124] The clinical consequences of graft failure is however not as deleterious as those of stent thrombosis and different studies have reported discordant findings regarding the clinical consequences of graft failure.[124] The variable consequences of graft failure is likely related to the amount of myocardium and the degree of stenosis of the native artery supplied by the failed graft. The role of DAPT in preventing new plaque ruptures is also different after CABG since plaque ruptures in proximal segments might not result in clinical events due to the distally placed grafts. Indeed, the protection against new myocardial infarction by the surgical collateralization after CABG has been proposed as a main driver of the survival benefit associated with CABG.[125]

The abovementioned differences in clinical outcome related to stent thrombosis, graft occlusion and new plaque ruptures after PCI and CABG respectively are examples of why results from ACS studies mainly including

patients treated with PCI cannot be extrapolated to a CABG population. Given the accompanying increase in bleeding risk with DAPT, the risk-benefit equation might differ after CABG compared with other ACS populations. Considering that the CURE trial was carried out 20 years ago, that the benefit of clopidogrel was predominantly seen before surgery, that current recommendations address potent $P2Y_{12}$ inhibitors rather than clopidogrel and the low adherence to recommendations in guidelines, new studies on the subject are much needed. Hopefully, results from the ongoing TACSI trial, a register-randomized open-label trial comparing ASA+ticagrelor for 12 months with ASA monotherapy after CABG in ACS patients, will add important data to the topic.[126] For patients with chronic coronary syndrome, the ODIN trial will compare DAPT with ticagrelor for one month after CABG with ASA monotherapy.[127]

A reasonable approach to the current lack of evidence is to make careful assessment of ischaemic and bleeding risk in the individual patient when deciding on optimal antiplatelet treatment, rather than applying a fixed duration and intensity for all patients. The use of bleeding risk prediction tools such as PRECISE-DAPT, although extrapolated from a PCI population, is one strategy to assess the individual bleeding risk.[128] Also, the differences in baseline criteria in patients with bleeding and myocardial infarction respectively in Study IV might offer some guidance. This approach is in line with the development of antithrombotic strategies after PCI; from the intensification associated with the introduction of the potent $P2Y_{12}$ inhibitors more than a decade ago, to optimization of treatment intensity and duration. Two recent examples of this development are the recommended shortening of the period of triple therapy for ACS patients undergoing PCI with indication for anticoagulation and introducing ticagrelor monotherapy (after an initial 3 months of DAPT) as an alternative to 12 months DAPT in ACS patients treated with PCI.[4]

The prognostic impact of post-discharge bleeding in Study IV challenges the clinical implication of studies and guidelines on dual antiplatelet therapy to improve vein graft patency without a demonstrated benefit in clinical endpoints.[117,120] Further studies, with clinically relevant endpoints including bleeding events, are warranted to estimate the net clinical benefit in this setting.

6.6 RECOGNIZING THE SEVERITY OF POST-DISCHARGE MAJOR BLEEDING

The results from Study IV are consistent with the documented increase in subsequent mortality risk after a post-discharge bleeding event after PCI or in medically managed ACS.[47-52] Interestingly, the similar increase in mortality risk after a bleeding event and a new myocardial infarction in Study IV is also consistent with other coronary artery disease populations.[47-52] It has been proposed that bleeding events and ischaemic events are "prognostically equivalent"[52] in ACS patients receiving DAPT and, given the results in Study IV, this can now be extended to the post-CABG population. These insights are important when interpreting the results from Study III, where an increase in bleeding risk, but no reduction in ischaemic risk, were observed with DAPT. Furthermore, the results from Study IV advocate the use of net adverse clinical events (NACE, a composite of death, myocardial infarction, stroke and major bleeding) as the most appropriate composite endpoint when evaluating anti-thrombotic treatment after CABG. Knowledge of the prognostic impact of post-discharge bleeding is important when deciding on the anti-thrombotic treatment for the individual patient. Interventions to decrease post-discharge bleedings, such as development and systematic use of bleeding prediction tools, routine prescription of proton pump-inhibitors for high-risk patients or screening for Helicobacter pylori, have the potential to increase survival after CABG and poses areas for future research.

6.7 LIMITATIONS AND METHODOLOGICAL ASPECTS

Study I had the limitation of not being blinded to the treating physicians and knowledge of time since discontinuation of ticagrelor and results of platelet function tests, could have influenced decisions on transfusion and re-exploration. A known limitation with MEA is that test results are influenced by low platelet count ($<100x10^9$), however all patients included in the study had a platelet count above this threshold.[129] The choice to use Youden's index to define cut-off values did not account for the clinical consequences of a false negative and false positive result respectively. It was merely chosen to have a consistent method to define a cut-off value to be able to calculate sensitivity, specificity, and predictive values for each test rather than defining clinically relevant cut-off levels.

The observational nature of Study II-IV carries the inherent risk for selection bias. This was addressed by adjusting for variables known to influence outcome after CABG as well as factors associated with the studied outcomes in Study III and IV. In Study III, propensity score matching was also performed. Despite extensive adjustments there is always risk for residual confounding from unmeasured factors or factors not being accounted for. Sophisticated methods to handle residual confounding, such as instrumental variable analysis, were not applied. In Study II, there was no data on smoking which possibly contributed to residual confounding.

The design of Study II, investigating if ongoing treatment with secondary prevention throughout follow-up is associated with lower mortality risk, does not adhere to the "emulating a target trial" framework as you cannot randomize patients to ongoing treatment. Since many of the patients already were on treatment at baseline there is also a risk for prevalent-user bias resulting from prevalent users prior to CABG representing "survivors" not being affected by adverse side effects early after initiation of drug treatment. The objective of the study was however not to inform whether to start or stop secondary prevention after CABG, but to investigate the associations between longitudinal use of secondary prevention medications and long-term mortality, which the study was adequately designed for. This knowledge is valuable as it can guide clinicians in the long-term management of patients after CABG and help to reinforce the positive effect of long-term secondary prevention, which, in turn, could improve adherence.

In Study II, secondary prevention was evaluated by use of medication. In clinical practice however, much effort is spent on achieving target levels such as LDL levels and blood pressure, rather than focusing on medication treatment per se. We recognize this limitation, especially regarding statin treatment, but also the fact that virtually all CABG patients not on lipid lowering therapy have LDL cholesterol levels above the target.[130] Therefore, LDL target levels are more important in determining intensity of treatment rather than the indication per se. There are several other indications for beta-blockers and RAS inhibitors in addition to hypertension and there are currently no platelet function tests recommended to monitor antiplatelet therapy, meaning that studying the use of medication per se for these drug classes is highly relevant.

Despite including all eligible patients in Sweden during six years, Study III has the risk of being underpowered due to low event rates and a limited study population. For comparison, the CURE study included over 12,000 patients with 10% suffering a primary outcome event during 9 months of follow-up

compared with 6,558 patients with 3.4% suffering a MACE during the first year (10.2% during total follow-up) in Study III. The low incidence of adverse events in Study III however indicates that a possible relative risk reduction with DAPT in this population must have a large magnitude to translate into a clinically meaningful reduction in absolute risk, with an accompanying acceptable number needed to treat.

In Study IV the analysis was restricted to patients suffering major bleeding and myocardial infarction not dying before they reached hospital. Analysis of cause of death for patients dying outside of hospital was not performed due to insufficient data quality.[88] It is possible that this could introduce bias in the calculated prognostic impact of major bleeding and myocardial infarction respectively if fatal bleedings or myocardial infarctions are overrepresented in patients dying outside of hospitals.

Defining time zero (baseline/start of follow-up) is essential in observational research to minimize bias. [84,85] In Study II, having time zero six months after hospital discharge was based on the assumption that early mortality after CABG is often related to the procedure itself and less likely to be prevented by secondary prevention medications. It also allowed for secondary prevention medication initiated at follow-up visits the months after surgery to be registered as baseline medication. In Study III, time zero was 15 days after hospital discharge. This was chosen to emulate a target trial where DAPT would be started at hospital discharge but, given the observational nature, 14 days were allowed for treatment assignment (i. e. dispensed prescription of ticagrelor). It also excluded patients dying very early after hospital discharge, which were assumed most probably were related to procedural complications or critical preoperative status (such as the need for cardiopulmonary resuscitation en route to the operating theatre, salvage CABG). In Study IV, time zero was also 15 days after hospital discharge. There was no need for time for treatment assignment in this study as it investigated the mortality risk associated with major bleeding and myocardial infarction but we still wanted to exclude patients dying very early due to procedural complications or critical preoperative status.

7 SUMMARY, CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Study I

- Postoperative ADP-induced platelet aggregation predicts severe bleeding after cardiac surgery with moderate accuracy but was not superior to preoperative platelet function testing.
- The results do not indicate better diagnostic precision by adding postoperative platelet function testing. Preoperative testing should remain standard.
- Evaluation of platelet function testing to guide treatment with bentracimab (an antidote to ticagrelor) poses an interesting future research area.

Study II

- The utilization of secondary prevention medications was high six months after CABG but decreased significantly over the years after surgery. Patients ≥75 years of age received less secondary prevention medications compared with patients <75 years.
- Ongoing treatment with statins, RAS inhibitors and platelet inhibitors, but not beta-blockers, were associated with lower mortality risk after CABG. This benefit was consistent in all age-groups and persisted over the years after surgery.
- Improving long-term utilization of secondary prevention medications, especially in patients ≥75 years, poses an opportunity to improve long-term survival after CABG.
- Further research on the benefit of routine, long-term treatment with beta-blockers is warranted.

Study III

- Utilization of guideline-directed treatment with DAPT after CABG in ACS patients in Sweden increased from 17.4% 2012 to 53.5% 2017 driven by a steep increase in utilization of ticagrelor.
- Treatment with ASA and ticagrelor after CABG in ACS patients was associated with increased bleeding risk but no difference in the risk for ischaemic events compared with ASA monotherapy.
- High-quality clinical trials are needed to establish the clinical outcome of DAPT after CABG in ACS patients, especially considering the increased mortality risk associated with post-discharge major bleeding events.

Study IV

- Post-discharge major bleeding and myocardial infarction after CABG have a similar incidence and were associated with a comparable increase in subsequent mortality risk.
- Careful assessment of bleeding risk and ischaemic risk in the individual patient is imperative when deciding on antithrombotic therapy after CABG.
- Future research on strategies to lower the incidence of post-discharge major bleeding is needed and could potentially translate into improved survival after CABG.

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