Technische Universität München
TUM School of Medicine and Health

Novel Aspects of Antiplatelet Drug Therapy in Patients Undergoing Percutaneous Coronary Intervention

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Vollständiger Abdruck der von der TUM School of Medicine and Health der Technischen Universität München zur Erlangung eines

Doctor of Philosophy (Ph.D.)

genehmigten Dissertation.

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Prüfende der Dissertation:

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Die Dissertation wurde am 27.09.2024 bei der TUM School of Medicine and Health der Technischen Universität München eingereicht und durch die TUM School of Medicine and Health am 17.01.2025 angenommen.

ABSTRACT

Dual antiplatelet therapy (DAPT), consisting of aspirin and a $P2Y_{12}$ inhibitor, is the guideline-recommended therapy to prevent ischemic events after percutaneous coronary intervention (PCI). The overarching objective of my thesis was to gain new insights into the optimal antiplatelet treatment for patients with coronary artery disease (CAD) undergoing PCI. More specifically, the thesis assessed the clinical efficacy and safety of the newer $P2Y_{12}$ receptor inhibitors, ticagrelor and prasugrel, in patients with acute coronary syndrome (ACS), and the optimal duration of DAPT after PCI. Furthermore, we tested new strategies aiming to reduce the bleeding risk in patients taking oral anticoagulation (OAC) who undergo PCI. In addition, the role of soluble Glycoprotein VI (sGPVI) in predicting the risk of bleeding or ischemic events in patients with chronic coronary syndrome (CCS) was evaluated. These objectives have been addressed by seven studies summarized in this thesis.

Elderly and/or low-weight patients with ACS represent a group of patients who are at high risk of bleeding and ischemic events after PCI. The antiplatelet drug therapy in these patients should be based on the individual bleeding and ischemic risk. In Chapter 4.1 of this thesis, we showed that in patients 75 years or older or those with a body weight less than 60 kg, a reduced dose of prasugrel (5 mg once daily) is associated with maintained anti-ischemic efficacy while protecting these patients against the excess risk of bleeding. This finding is important as it shows that a reduced dose of prasugrel in elderly or low-weight patients with ACS undergoing PCI is efficacious and safe.

A considerable number of patients presenting with an ACS are on antiplatelet drug therapy at the time of hospital admission. However, data regarding the impact of prior antiplatelet therapy on clinical outcomes of patients admitted with an ACS are lacking. In Chapter 4.2 of this thesis, we found that in patients with ACS, pre-admission therapy with

antiplatelet drugs aspirin and/or clopidogrel did not affect the treatment effect of ticagrelor vs. prasugrel in terms of ischemic or bleeding risk. Therefore, the superiority of prasugrel over ticagrelor in reducing the ischemic risk in patients presenting with an ACS was consistent regardless of prior antiplatelet therapy with aspirin and/or clopidogrel at the time of hospital admission.

The high bleeding risk (HBR) score is often used to identify patients at HBR. In a post hoc analysis of patients recruited in the ISAR-REACT 5 trial, patients considered to be at HBR showed an increased risk of bleeding and ischemic events compared with patients without HBR features. However, HBR status did not significantly interact with the relative treatment effect of ticagrelor vs. prasugrel. The incidence of bleeding events was comparable between patients assigned to ticagrelor and prasugrel regardless of HBR status.

Smoking is an important risk factor for CAD and over one-third of patients undergoing PCI for ACS are smokers. Previous studies have suggested that smokers have better clinical outcomes not only due to younger age, but also due to greater platelet inhibition with clopidogrel compared with nonsmokers. However, the efficacy and safety of ticagrelor and prasugrel according to smoking status have not been studied before. In a prespecified analysis of the ISAR-REACT 5 randomized trial (Chapter 4.4), we found that among patients hospitalized for an ACS and planned to undergo an invasive management strategy, smoking status did not significantly interact with the relative treatment effect of ticagrelor vs. prasugrel.

DAPT following PCI reduces the risk of ischemic events but increases the risk of bleeding. The optimal duration of DAPT and the type of single antiplatelet therapy (SAPT) following DAPT remain to be elucidated. In this thesis (Chapter 4.5), we present the results of a meta-analysis of 9 large randomized clinical trials with 41,864 patients undergoing drug-eluting stent (DES) implantation for both chronic- and acute coronary syndromes. We found

that a short DAPT duration of ≤3 months reduces bleeding without an increase in the risk for stent thrombosis.

The potential value of sGPVI as a marker of ischemic or bleeding risk in patients with CCS undergoing PCI has not been investigated. We studied the association between sGPVI levels and ischemic and bleeding events in 318 patients with CCS undergoing PCI in the setting of a phase 2 randomized clinical trial. Plasma levels of sGPVI did not correlate with ADP- or collagen-induced platelet aggregation. We found that elevated plasma sGPVI levels are associated with a higher incidence of bleeding events but not ischemic complications.

Patients with an indication for OAC undergoing stent implantation have an increased risk of bleeding. In this regard, strategies to reduce bleeding risk in such patients by modifying the duration of DAPT or the type of stent used seem reasonable. A special stent with thromboresistant and pro-healing properties such as the polymer polyzene F-coated (COBRA PzF) stent might allow for a short duration of DAPT in these patients. To address these concerns, the randomized trial of COBRA PzF Stenting to reduce the duration of DAPT in 996 patients on OAC undergoing coronary stenting was conducted. The study could not prove the superiority of the COBRA PzF stent plus 14-day DAPT over Food and Drug Agency (FDA)-approved DES plus 3-6 months of DAPT with respect to bleeding risk in patients with OAC. In addition, the trial could not prove the non-inferiority of the COBRA PzF stent plus 14-day DAPT to FDA-approved DES plus 3-6 months of DAPT regarding thrombo-embolic events at 6 months.

ZUSAMMENFASSUNG

Die duale Thrombozytenaggregationshemmer-Therapie (DAPT), bestehend aus Aspirin und einem $P2Y_{12}$-Hemmer, ist die von den Leitlinien empfohlene Therapie zur Vorbeugung ischämischer Ereignisse nach perkutaner Koronarintervention (PCI). Das übergreifende Ziel meiner Arbeit war es, neue Erkenntnisse über die optimale Thrombozytenaggregationshemmer-Behandlung für Patienten mit koronarer Herzkrankheit (KHK) zu gewinnen, die sich einer PCI unterziehen. Konkret wurden in der Arbeit die klinische Wirksamkeit und Sicherheit der neueren P2Y12-Rezeptor-Inhibitoren Ticagrelor und Prasugrel bei Patienten mit akutem Koronarsyndrom (ACS) sowie die optimale Dauer der DAPT nach PCI untersucht. Darüber hinaus haben wir neue Strategien getestet, die darauf abzielen, das Blutungsrisiko bei Patienten, die eine orale Antikoagulation (OAC) einnehmen und sich einer PCI unterziehen, zu verringern. Außerdem wurde die Rolle des löslichen Glykoproteins VI (sGPVI) bei der Vorhersage des Risikos von Blutungen oder ischämischen Ereignissen bei Patienten mit chronischem Koronarsyndrom (CCS) untersucht. Diese Ziele wurden in sieben Studien verfolgt, die in dieser Arbeit zusammengefasst sind.

Ältere und/oder untergewichtige Patienten mit ACS stellen eine Patientengruppe dar, bei der ein hohes Risiko für Blutungen und ischämische Ereignisse nach PCI besteht. Die Thrombozytenaggregationshemmer-Therapie bei diesen Patienten sollte sich nach dem individuellen Blutungs- und Ischämierisiko richten. In Kapitel 4.1 dieser Arbeit haben wir gezeigt, dass bei Patienten, die 75 Jahre oder älter sind oder ein Körpergewicht von weniger als 60 kg haben, eine reduzierte Dosis von Prasugrel (5 mg einmal täglich) mit einer gleichbleibenden antiischämischen Wirksamkeit verbunden ist und diese Patienten gleichzeitig vor einem erhöhten Blutungsrisiko schützt. Dieses Ergebnis ist wichtig, da es zeigt,

dass eine reduzierte Prasugrel-Dosis bei älteren oder untergewichtigen Patienten mit ACS, die sich einer PCI unterziehen, wirksam und sicher ist.

Eine beträchtliche Anzahl von Patienten, die mit einem ACS eingeliefert werden, nimmt zum Zeitpunkt der stationären Aufnahme Thrombozytenaggregationshemmer ein. Es fehlen jedoch Daten über die Auswirkungen einer vorherigen Thrombozytenaggregationshemmer-Therapie auf die klinischen Ergebnisse von Patienten, die mit einem ACS aufgenommen werden. In Kapitel 4.2 dieser Arbeit haben wir festgestellt, dass bei Patienten mit ACS eine vor der Aufnahme durchgeführte Therapie mit den Thrombozytenaggregationshemmern Aspirin und/oder Clopidogrel keinen Einfluss auf den Behandlungseffekt von Ticagrelor gegenüber Prasugrel in Bezug auf das Ischämie- oder Blutungsrisiko hatte. Die Überlegenheit von Prasugrel gegenüber Ticagrelor bei der Senkung des Ischämierisikos bei Patienten mit einem ACS war also unabhängig von einer bestehenden Thrombozytenaggregationshemmer-Therapie mit Aspirin und/oder Clopidogrel zum Zeitpunkt der stationären Aufnahme gleich.

Der High Bleeding Risk (HBR)-Score wird üblicherweise zur Identifizierung von Patienten mit hohem Blutungsrisiko verwendet. In einer Post-hoc-Analyse von Patienten, die in die ISAR-REACT 5-Studie aufgenommen wurden, wiesen Patienten mit hohem Blutungsrisiko im Vergleich zu Patienten ohne HBR-Merkmale ein erhöhtes Risiko für Blutungen und ischämische Ereignisse auf. Der HBR-Status hatte jedoch keinen signifikanten Einfluss auf den relativen Behandlungseffekt von Ticagrelor gegenüber Prasugrel. Die Inzidenz von Blutungsereignissen war bei Patienten, die Ticagrelor und Prasugrel erhielten, unabhängig vom HBR-Status vergleichbar.

Rauchen ist ein wichtiger Risikofaktor für die koronare Herzkrankheit, und mehr als ein Drittel der Patienten, die sich wegen eines ACS einer PCI unterziehen, sind Raucher. Frühere Studien haben gezeigt, dass Raucher nicht nur aufgrund ihres jüngeren Alters, sondern auch

aufgrund der stärkeren Thrombozytenhemmung durch Clopidogrel im Vergleich zu Nichtrauchern bessere klinische Ergebnisse erzielen. Die Wirksamkeit und Sicherheit von Ticagrelor und Prasugrel in Abhängigkeit vom Raucherstatus wurde jedoch bisher nicht untersucht. In einer vordefinierten Analyse der randomisierten ISAR-REACT 5-Studie (Kapitel 4.4) fanden wir heraus, dass bei Patienten, die wegen eines ACS ins Krankenhaus eingeliefert wurden und bei denen eine invasive Behandlungsstrategie geplant war, der Raucherstatus keinen signifikanten Einfluss auf den relativen Behandlungseffekt von Ticagrelor gegenüber Prasugrel hatte.

Eine DAPT nach PCI verringert das Risiko ischämischer Ereignisse, erhöht aber das Blutungsrisiko. Die optimale Dauer der DAPT und die Art der einzelnen Thrombozytenaggregationshemmer (SAPT) im Anschluss an die DAPT sind noch nicht geklärt. Im Rahmen dieser Arbeit (Kapitel 4.5) stellen wir die Ergebnisse einer Meta-Analyse von 9 großen randomisierten klinischen Studien mit 41,864 Patienten vor, die sich einer Implantation eines medikamentenbeschichteten Stents (DES) sowohl bei chronischer Koronarerkrankung als auch bei ACS unterzogen. Wir fanden heraus, dass eine kurze DAPT-Dauer von ≤3 Monaten, gefolgt von einer SAPT, Blutungen reduziert, ohne das Risiko einer Stentthrombose zu erhöhen.

Der potenzielle Wert von sGPVI als Marker für das Ischämie- oder Blutungsrisiko bei Patienten mit CCS, die sich einer PCI unterziehen, wurde bisher nicht untersucht. Wir untersuchten den Zusammenhang zwischen sGPVI-Spiegeln und ischämischen und blutenden Ereignissen bei 318 Patienten mit CCS, die sich einer PCI im Rahmen einer randomisierten klinischen Phase-2-Studie unterzogen. Die Plasmaspiegel von sGPVI korrelierten nicht mit der ADP- oder Kollagen-induzierten Thrombozytenaggregation. Wir fanden heraus, dass erhöhte

sGPVI-Plasmaspiegel mit einer höheren Inzidenz von Blutungsereignissen, nicht aber von ischämischen Komplikationen verbunden sind.

Patienten mit einer OAK-Indikation, die sich einer Stentimplantation unterziehen, haben ein erhöhtes Blutungsrisiko. In diesem Zusammenhang erscheinen Strategien zur Verringerung des Blutungsrisikos bei diesen Patienten durch Änderung der Dauer der DAPT oder der Art des verwendeten Stents sinnvoll. Ein spezieller Stent mit thromboseresistenten und heilungsfördernden Eigenschaften wie der Polymer-Polyzol-F-beschichtete (COBRA PzF) Stent könnte bei diesen Patienten eine kurze Dauer der DAPT ermöglichen. Um diese Bedenken auszuräumen, wurde die randomisierte Studie COBRA PzF Stenting zur Verkürzung der DAPT bei 996 Patienten mit OAC durchgeführt, die sich einem Koronarstenting unterzogen. Die Studie konnte die Überlegenheit des COBRA PzF-Stents plus 14-tägige DAPT gegenüber den von der Food and Drug Agency (FDA) zugelassenen DES plus 3-6 Monate DAPT in Bezug auf das Blutungsrisiko bei Patienten mit OAC nicht nachweisen. Darüber hinaus konnte die Studie die Nichtunterlegenheit des COBRA PzF-Stents plus 14-tägige DAPT gegenüber FDA-zugelassenen DES plus 3-6-monatige DAPT in Bezug auf thromboembolische Ereignisse nach 6 Monaten nicht nachweisen.

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List of abbreviations

- **ACS** = acute coronary syndrome
- **ADP** = adenosine diphosphate
- **AMI** = acute myocardial infarction
- **ARC** = Academic Research Consortium
- **ARC-HBR** = Academic Research Consortium for High Bleeding Risk
- **BARC** = Bleeding Academic Research Consortium
- **BMI** = body mass index
- **BMS** = bare metal stent
- **CAD** = coronary artery disease
- **CI** = confidence interval
- **CK-MB** = creatine kinase myocardial band
- **CK** = creatine kinase
- **CT** = computer tomography
- **DAPT** = dual antiplatelet therapy
- **DES** = drug-eluting stent
- **DIG** = digoxigenin
- **ECG** = Electrocardiogram, electrocardiographic
- **ESC** = European Society of Cardiology
- **FDA** = Food and Drug Agency
- **HBR** = high bleeding risk
- **HR** = hazard ratio
- **hs-cTnT** = high-sensitivity cardiac troponin T
- **IDI** = integrated discrimination improvement

- **ID-TLR** = ischemia-driven target lesion revascularization
- **LASSO** = least absolute shrinkage and selection operator
- **MACE** = major adverse cardiovascular events
- **MI** = myocardial infarction
- **MRI** = magnetic resonance imaging
- **NSAIDs** = nonsteroidal anti-inflammatory drugs
- **NSTE-ACS** = non-ST elevation acute coronary syndromes
- **NSTEMI** = non-ST elevation myocardial infarction
- **OR** = odds ratio
- **PCI** = percutaneous coronary intervention
- $\mathbf{p_{interaction}}$ = p value for interaction
- **pGPVI** = platelet glycoprotein VI
- **PzF** = polyzene F
- **SAPT** = single antiplatelet therapy
- **sGPVI** = soluble glycoprotein VI
- **ST** = stent thrombosis
- **STEMI** = ST-elevation myocardial infarction
- **TAT** = triple antithrombotic therapy
- **TVR** = target vessel revascularization
- **vWF** = von Willebrand factor
- **UA** = unstable angina
- **URL** = upper reference limit

List of clinical study acronyms

- **ADAPT-DES** = Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents
- **CLASSICS** = The Clopidogrel Aspirin Stent International Cooperative Study
- **CREDO** = Clopidogrel for the Reduction of Events During Observation
- **COBRA-REDUCE** = Randomized Trial of COBRA PzF Stenting to Reduce Duration of Triple Therapy
- **CURE** = Clopidogrel in Unstable Angina to Prevent Recurrent Events
- **ISAR** = Intracoronary Stenting and Antithrombotic Regimen
- **ISAR-REACT 5** = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
- **ISAR-PLASTER** = Intracoronary Stenting and Antithrombotic Regimen: Lesion Platelet Adhesion as Selective Target of Endovenous Revacept
- **MASTER-DAPT** = The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen
- **ONSET/OFFSET** = The Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease
- **One-month DAPT** = One-Month Dual Antiplatelet Therapy Followed by Aspirin Monotherapy After Drug-Eluting Stent Implantation
- **OPTIMIZE** = Three vs Twelve Months of Dual Antiplatelet Therapy after Zotarolimus-Eluting Stents
- **PLATO** = Platelet Inhibition and Clinical Outcomes
- **PRAGUE-18** = Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction
- **RESET** = Real Safety and Efficacy of 3-month DAPT
- **REDUCE** = Randomized Evaluation of Short-Term Dual Antiplatelet Therapy in Patients with Acute Coronary Syndrome Treated with A New Generation Stent

- **GLOBAL-LEADERS** = A Clinical Study Comparing Two Forms of Anti-platelet Therapy after Stent Implantation
- **SOCRATES** = The Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes
- **STOPDAPT-2** = ShorT and Optimal Duration of Dual Antiplatelet Therapy-2-Study
- **TICO** = Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome
- **TRITON–TIMI 38** = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
- **TRILOGY-ACS** = Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes
- **TWILIGHT** = Ticagrelor with or without Aspirin in High-Risk Patients after PCI

List of publications included in this dissertation

The results shown in this thesis have been previously published in the following research articles:

1. **Age- and Weight-Adapted Dose of Prasugrel Versus Standard Dose of Ticagrelor in Patients With Acute Coronary Syndromes: Results From a Randomized Trial**

   Menichelli M, Neumann FJ, Ndrepepa G, Mayer K, Wohrle J, Bernlochner I, Richardt G, Witzenbichler B, Sibbing D, Gewalt S, Angiolillo DJ, **Lahu S**, Hamm CW, Hapfelmeier A, Trenk D, Laugwitz KL, Schunkert H, Schupke S and Kastrati A. **Ann Intern Med**. 2020 Sep 15;173(6):436-444. doi: 10.7326/M20-1806.

2. **Preadmission Antiplatelet Therapy and Treatment Effect of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndromes - A Subgroup Analysis of the ISAR-REACT 5 Trial**

   Lahu S, Ndrepepa G, Neumann FJ, Menichelli M, Bernlochner I, Richardt G, Wohrle J, Witzenbichler B, Hemetsberger R, Mayer K, Akin I, Cassese S, Gewalt S, Xhepa E, Kufner S, Valina C, Sager HB, Joner M, Ibrahim T, Laugwitz KL, Schunkert H, Schupke S and Kastrati A. **Eur Heart J Cardiovasc Pharmacother**. 2022. Sep 29;8(7):687-694. doi: 10.1093/ehjcvp/pvac007.

3. **Ticagrelor or Prasugrel in Patients With Acute Coronary Syndrome and High Bleeding Risk**

   Lahu S, Presch A, Ndrepepa G, Menichelli M, Valina C, Hemetsberger R, Witzenbichler B, Bernlochner I, Joner M, Xhepa E, Hapfelmeier A, Kufner S, Rifatov N, Sager HB, Mayer K, Kessler T, Laugwitz KL, Richardt G, Schunkert H, Neumann FJ, Sibbing D, Angiolillo DJ, Kastrati A, Cassese S. **Circ Cardiovasc Interv**. 2022 Oct;15(10):e012204. doi: 10.1161/CIRCINTERVENTIONS.122.012204. Epub 2022 Oct 18.

4. **Efficacy and Safety of Ticagrelor versus Prasugrel in Smokers and Nonsmokers with Acute Coronary Syndromes**

   Lahu S, Ndrepepa G, Gewalt S, Schupke S, Pellegrini C, Bernlochner I, Aytekin A, Neumann FJ, Menichelli M, Richardt G, Cassese S, Xhepa E, Kufner S, Sager HB, Joner M, Ibrahim T, Fusaro M, Laugwitz KL, Schunkert H, Kastrati A and Mayer K. **Int J Cardiol**. 2021 Sep 1;338:8-13. doi: 10.1016/j.ijcard.2021.06.011. Epub 2021 Jun 11.

5. **Meta-Analysis of Short vs. Prolonged Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation and Role of Continuation with either Aspirin or a P2Y12 Inhibitor Thereafter**

   Lahu S, Bristot P, Gewalt S, Goedel A, Giacoppo D, Schupke S, Schunkert H, Kastrati A and Sarafoff N. Meta-Analysis of Short vs. **J Atheroscler Thromb**. 2022 Jul 1;29(7):1001-1019. doi: 10.5551/jat.63000. Epub 2021 Jul 10.

6. **Plasma Soluble Glycoprotein VI, Platelet Function, Bleeding, and Ischemic Events in Patients Undergoing Elective Percutaneous Coronary Intervention**

   Lahu S, Adler K, Mayer K, Hein-Rothweiler R, Bernlochner I, Ndrepepa G, Schüpke S, Holdenrieder S, Bongiovanni D, Laugwitz KL, Schunkert H, Gawaz M, Massberg S, Kastrati A, Münch G. **Thromb Haemost** 2024 Apr;124(4):297-306. doi: 10.1055/s-0043-1772221. Epub 2023 Aug 17.

7. **A Randomized Trial of COBRA PzF Stenting to Reduce the Duration of Triple Therapy: The COBRA REDUCE Trial**

   Byrne RA, Colleran R, Coughlan JJ, Jauhar R, Maillard L, de Labriolle A, Maeng M, Croft C, Brunner M, Leistner D, Zrenner B, Kollum M, Laugwitz KL, Xhepa E, Mayer K, **Lahu S**, Joner M, Kirtane A, Mehran R, Barakat M, Urban P, Cutlip DE and Kastrati A. **Circ Cardiovasc Interv**. 2024 Oct;17(10):e013735. doi: 10.1161/CIRCINTERVENTIONS.123.013735. Epub 2024 Oct 15.

1 INTRODUCTION

1.1 PHYSIOLOGY OF PLATELETS AND THEIR ROLE IN THROMBOSIS AND HEMOSTASIS

Platelets are disc-shaped, anucleated blood cells with a diameter of 2-4 μm, derived from the megakaryocytes of the bone marrow. The normal platelet count in healthy individuals is between 150-400 $x10^9$/L, and their lifespan is about 7-10 days. They were first discovered in 1882 by the Italian pathologist Giulio Bizzozero in the circulating blood of living animals, and their function was a research subject for many decades (1). The primary function of platelets is hemostasis. Other important functions of platelets include maintenance of vascular integrity, tissue repair and regeneration, and immune response (2,3). Platelets are also involved in the pathophysiology of thrombosis and atherosclerosis. When a blood vessel is damaged, platelets adhere to the exposed collagen and other vascular components at the injury site. They become activated and release chemicals that attract more platelets, forming aggregates that clot the wound. Platelets release substances stored in their granules, such as adenosine diphosphate (ADP), thromboxane A2, and serotonin, which amplify vasoconstriction and platelet aggregation. Human platelets can be activated by numerous agonists such as von Willebrand factor (vWF), collagen, thrombin, and ADP (4,5). ADP acts as an agonist at 2 platelet G-protein coupled receptors, $P2Y_1$ and $P2Y_{12}$. The activation of $P2Y_1$ initiates ADP-induced platelet aggregation and causes a platelet shape change and a limited platelet aggregation (6). On the other hand, the activation of the $P2Y_{12}$ receptor induces a powerful platelet aggregation (7). For this reason, the inhibition of the $P2Y_{12}$ receptor is a major target of antiplatelet therapy in patients undergoing stent implantation (8). The available $P2Y_{12}$ receptor inhibitors are discussed in detail below.

1.2 RATIONALE FOR ANTIPLATELET THERAPY IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

Percutaneous coronary intervention (PCI) is the most commonly performed procedure for myocardial revascularization in patients with coronary artery disease (CAD). The first human percutaneous transluminal coronary angioplasty (PTCA) was performed by Andreas Grüntzig on September 16, 1977 (9). The rationale for using antiplatelet therapy in patients undergoing PCI is primarily to prevent stent thrombosis and reduce the risk of recurrent ischemic events. After a stent is implanted in a coronary artery, there is a risk that platelets will adhere to the stent surface and activate, leading to thrombus formation within the stent. This may result in an abrupt blockage of the artery, which may induce a myocardial infarction (MI) or unexpected cardiac death. The vessel wall damage from stent placement and the presence of the stent itself trigger platelet activation and aggregation as part of the body's natural response to injury (10,11). In this regard, it is crucial to administer medications that inhibit platelet activation and aggregation. Dual antiplatelet therapy (DAPT), discussed below, serves this purpose. **Figure 1** shows the schematic interplay between platelets, coagulation and inflammation in atherothrombosis and the site of action of different antiplatelet agents.

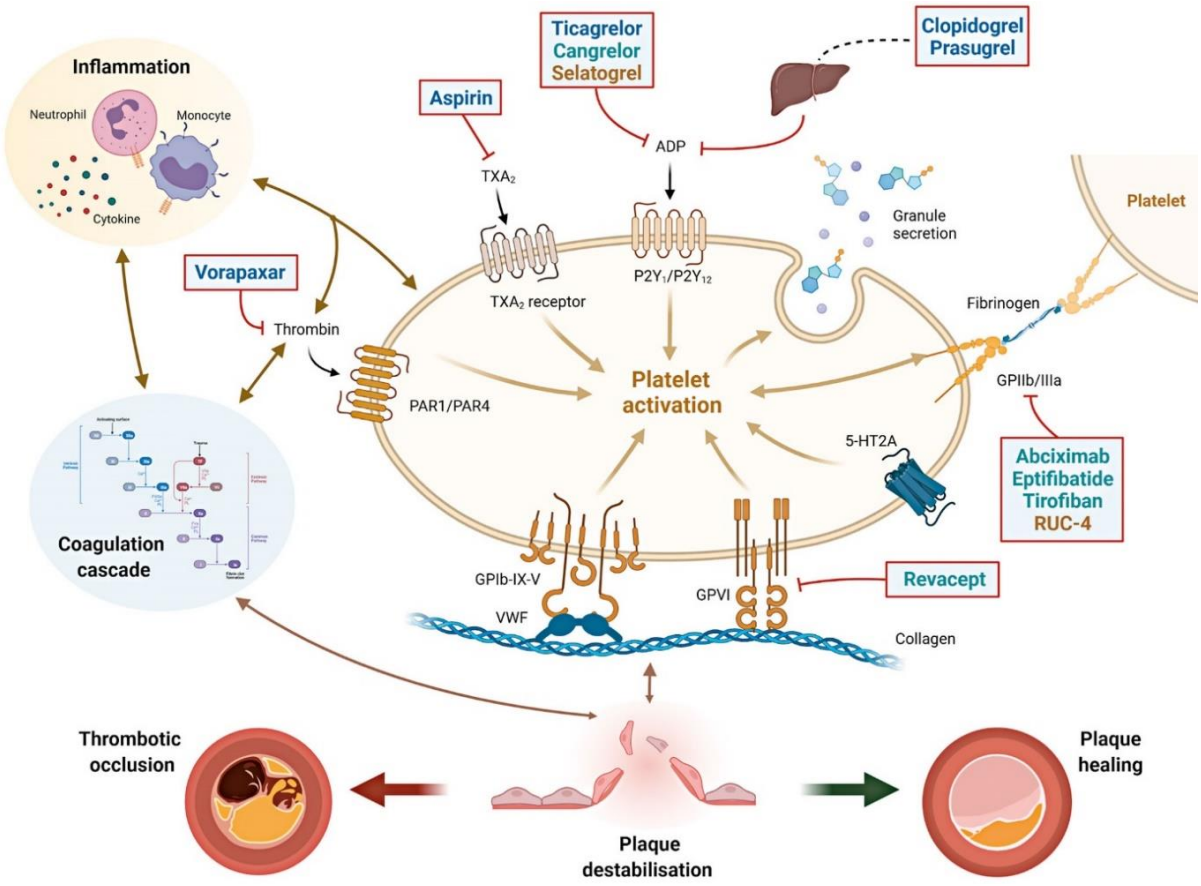

Figure 1. The interplay between platelets, coagulation and inflammation in atherothrombosis and sites of action of antiplatelet agents

Figure reproduced from (12).

1.2.1 Components of dual antiplatelet therapy

DAPT is a combination of aspirin and a $P2Y_{12}$ inhibitor. Currently, three commercial $P2Y_{12}$ receptor inhibitors are in use: clopidogrel, prasugrel, and ticagrelor. Some of the most important characteristics of these antiplatelet agents are provided below.

Aspirin

Aspirin is an acetyl derivative of salicylic acid (13). It acts as an irreversible inhibitor of the cyclooxygenase enzyme (COX), which plays a role in the formation of thromboxane A2 (TXA_2) in platelets. By blocking COX-1, aspirin inhibits the production of TXA_2 and consequently TXA_2-dependent platelet aggregation (14). The inhibition of platelet aggregation lasts for the

lifetime of the platelet (13). Aspirin is absorbed in the upper gastrointestinal tract and exerts a measurable level of antiplatelet effect within as soon as 60 minutes (15). Studies have demonstrated that low-dose aspirin of 75 to 100 mg daily provides adequate inhibition of platelet aggregation with maximal protection from recurrent ischemic events (16-19). Aspirin remains the gold standard of antiplatelet therapy in the long-term prevention of recurrent ischemic events.

Clopidogrel

Clopidogrel is a prodrug of the thienopyridine class, which is metabolized in the liver into an active metabolite. The active metabolite binds to the $P2Y_{12}$ receptor and causes irreversible platelet inhibition (20). Among the CYP enzymes involved in the conversion of clopidogrel into its active form, the CYP1A2, CYP3A4/5, and CYP2C19 isoforms are mostly responsible for the production of the active metabolite of clopidogrel (21,22). The onset of the effect of clopidogrel is between 2 to 6 hours after oral ingestion. The effect of clopidogrel relies on the production of an adequate amount of its active metabolite. Studies have shown that platelet response to clopidogrel shows a large variability, mostly due to genetic variations in the CYP enzymes (23,24). The chemical structure of clopidogrel and the other antiplatelet agents is shown in **Figure 2.**

Prasugrel

Prasugrel is a third-generation oral thienopyridine drug and an irreversible inhibitor of platelet ADP $P2Y_{12}$ receptor (25). Prasugrel is a prodrug that requires two metabolic steps (in the intestine and liver) for conversion into its active form. It is quickly transformed in vivo into an active metabolite (R-138727) that binds specifically and permanently to the platelet $P2Y_{12}$ receptor, thereby blocking ADP-induced platelet activation and aggregation (26). Compared

with clopidogrel, prasugrel provides a faster onset of activity, stronger platelet inhibition, and less response variability (27). Its onset of action is estimated to be between 0.5 and 4 hours.

Ticagrelor

Ticagrelor (AZD6140) is a direct oral, reversible $P2Y_{12}$ inhibitor of the cyclopentyl-triazolopyrimidine class (28). Unlike clopidogrel and prasugrel, ticagrelor does not require hepatic conversion to exert its activity. Ticagrelor directly inhibits the $P2Y_{12}$ receptor on the platelet surface, preventing ADP from binding to this receptor (20). ADP is a key mediator in the platelet activation and aggregation process. With the $P2Y_{12}$ receptor blocked, platelet activation and aggregation are inhibited. The degree of receptor inhibition is dependent on the concentration of ticagrelor (29). Ticagrelor provides greater and more consistent platelet inhibition than clopidogrel (29,30) and has an onset of effect between 0.5 and 2 hours.

Ticlopidine

Although no longer recommended, ticlopidine was the first thienopyridine drug to be used in patients undergoing coronary stenting. It is a prodrug that undergoes metabolization by the hepatic cytochrome P450-1A enzyme system to become active (31) and is an irreversible $P2Y_{12}$ inhibitor. Ticlopidine is quickly absorbed and metabolized following oral administration (32). Due to its unfavorable safety profile, it is no longer used.

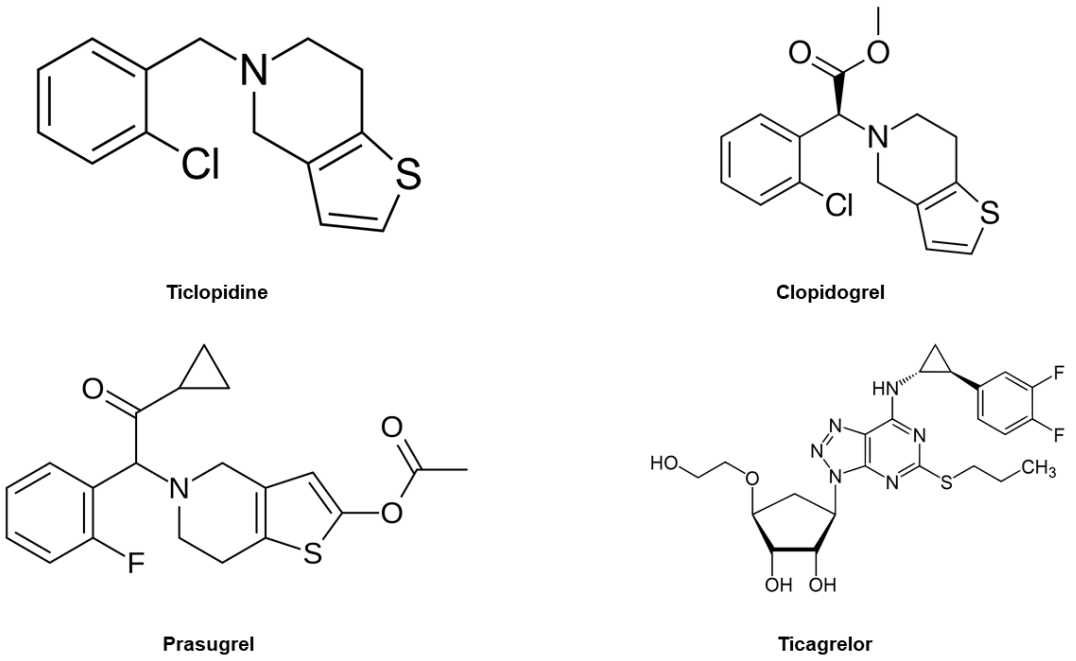

Figure 2. Chemical structures of oral antiplatelet agents

1.2.2 Evolution of antiplatelet therapy

DAPT, consisting of aspirin and a $P2Y_{12}$ inhibitor, is recommended to prevent recurrent thromboembolic events and to improve clinical outcomes in patients undergoing PCI (33,34). With the advancement in coronary device technology, the number of PCI procedures has increased, leading to more patients requiring antiplatelet therapy. The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial was the first randomized clinical trial to compare DAPT (ticlopidine plus aspirin) versus anticoagulant therapy (intravenous heparin, phenprocoumon, and aspirin) after the placement of Palmaz-Schatz coronary-artery stents (35). The 30-day incidence of the primary outcome (a composite of cardiac death, myocardial infarction, aortocoronary bypass surgery, or repeat angioplasty) was 1.6% in patients assigned to DAPT and 6.2% in patients assigned to anticoagulant therapy (relative risk = 0.25, 95% confidence interval [95% CI] 0.06 to 0.77). The 30-day incidence of hemorrhagic and vascular

complications was significantly lower in patients randomized to antiplatelet therapy compared with patients treated with anticoagulation therapy. The trial demonstrated the superiority of antiplatelet therapy over anticoagulation among patients undergoing PCI with BMS (35). Following the publication of the ISAR trial, the combination of aspirin and ticlopidine became the reference antithrombotic regimen after coronary stenting until clopidogrel was developed and introduced into clinical practice. The CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS) trial (36) was the first randomized clinical trial that demonstrated the superiority of clopidogrel plus aspirin over ticlopidine plus aspirin in terms of safety in patients undergoing successful coronary stent implantation. Concerning efficacy, the CLASSICS trial showed a comparable rate of cardiac events with clopidogrel and ticlopidine (36). Both ticlopidine and clopidogrel are prodrugs that require bioactivation to exhibit their antithrombotic effect (31). Due to side effects associated with the use of ticlopidine, such as agranulocytosis, thrombotic thrombocytopenic purpura, and aplastic anemia and the better clinical performance of clopidogrel, the use of ticlopidine was no longer recommended (37,38). This led to the widespread adoption of clopidogrel as the recommended $P2Y_{12}$ inhibitor in combination with aspirin following stent implantation. Clopidogrel is the most widely studied and prescribed $P2Y_{12}$ inhibitor due to its broad spectrum of use. However, there are some drawbacks associated with the use of clopidogrel, especially in patients with ACS. This will be discussed in the next section, which deals with DAPT and the rationale for using newer $P2Y_{12}$ inhibitors in patients with ACS.

1.3 DUAL ANTIPLATELET THERAPY IN PATIENTS WITH ACUTE CORONARY SYNDROME

In this section, we will summarize the evolution of DAPT in patients with ACS and the rationale behind the research conducted in this thesis. The current guidelines recommend a 12-month

DAPT regimen consisting of either prasugrel or ticagrelor in combination with aspirin in patients presenting with ACS (33,34). The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (39) was the first study that investigated the use of a DAPT consisting of clopidogrel and aspirin versus aspirin alone in patients with non-ST elevation acute coronary syndromes (NSTE-ACS). The study demonstrated a beneficial effect of the combination of aspirin plus clopidogrel compared with aspirin alone in terms of reduced adverse cardiovascular events. The CURE trial included 12,562 patients with NSTE-ACS who presented to the hospital within 24 hours of the chest pain onset. Patients were randomized in a double-blinded fashion to either clopidogrel (300 mg loading dose [LD], followed by 75 mg maintenance dose [MD] once daily) or placebo, in addition to treatment with aspirin for 3-12 months. The primary efficacy endpoint was a composite of cardiovascular death, MI, or stroke. The safety endpoint was major bleeding. The authors observed a significant reduction in the ischemic risk and an increase in the bleeding risk associated with clopidogrel compared with placebo. This study is important from a historical perspective as it had an impact on the recommendations concerning DAPT in patients with ACS. The Clopidogrel for the Reduction of Events During Observation (CREDO) trial (40), including 2116 patients scheduled to undergo elective PCI or with a high likelihood of undergoing PCI, later confirmed that a one-year DAPT regimen consisting of aspirin plus clopidogrel is associated with a reduced risk for major cardiovascular events (death, MI, or stroke) compared with only 4 weeks of DAPT (aspirin plus clopidogrel) followed by 11 months of aspirin plus placebo. In the CREDO trial, slightly more than 50% of the patients presented with unstable angina.

1.3.1 The development of the newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor

Although clopidogrel has been widely used in combination with aspirin to prevent ischemic events in patients with ACS undergoing PCI, pharmacodynamic and pharmacokinetic studies have reported some limitations associated with its use, including high interindividual variability in response profiles (41-43), variable transformation to its active metabolite (44), and high on-treatment platelet reactivity with insufficient platelet inhibition (45,46). The inadequate platelet inhibition despite treatment with clopidogrel has been defined as 'clopidogrel non-responsiveness' or 'clopidogrel resistance'. Clopidogrel resistance or non-responsiveness is associated with a higher risk of recurrent ischemic events such as MI or ST (47-51). Concerns raised with the use of clopidogrel have been addressed by the development and clinical testing of the newer $P2Y_{12}$ inhibitors with the hope that they could overcome the limitations of clopidogrel and provide stronger platelet inhibition with less interindividual response variability. The newer $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, appear to have such characteristics. Pharmacodynamic studies have shown that prasugrel and ticagrelor provide a more potent and faster onset of platelet inhibition compared with clopidogrel, with a lower rate of non-responders (30,52-54). Subsequently, pivotal clinical trials performed a head-to-head comparison of these agents with clopidogrel (see sections below).

1.3.2 Head-to-head comparison of prasugrel and clopidogrel

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) trial (55) recruited 13,608 patients with moderate-to-high risk ACS with scheduled PCI to receive prasugrel (LD of 60 mg followed by a 10 mg MD once daily) or clopidogrel (300 mg LD, followed by a 75 mg MD) for 6-15 months. The primary endpoint of the trial was a composite of cardiovascular

death, nonfatal MI, or nonfatal stroke. The key safety endpoint was non-CABG-related TIMI major bleeding. The incidence of the primary endpoint was 9.9% in the prasugrel group and 12.1% in the clopidogrel group (hazard ratio [HR]=0.81; 95% CI, 0.73 to 0.90). The incidence of TIMI major bleeding was higher in the prasugrel group than in the clopidogrel group (2.4% vs. 1.8%; HR=1.32; 95% CI, 1.03 to 1.68). The TRITON-TIMI 38 trial showed that in patients with ACS undergoing PCI, prasugrel is associated with significantly reduced rates of ischemic events but with an increased risk of bleeding, including fatal bleeding.

1.3.3 Head-to-head comparison of ticagrelor and clopidogrel

The Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndrome (PLATO) trial was a randomized, double-blinded clinical trial that compared ticagrelor and clopidogrel in patients with ACS (56). The PLATO trial randomized 18,624 patients with ACS to receive ticagrelor or clopidogrel. Patients in the ticagrelor group were given a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Patients in the clopidogrel group received a loading dose of 300 mg, followed by a maintenance dose of 75 mg once daily. In this trial, 61% of patients underwent PCI, and most were treated with bare metal stents (BMS). The primary endpoint was a composite of death from vascular causes, MI, or stroke at 1-year follow-up. Treatment with ticagrelor was associated with a significant reduction of the ischemic risk (cumulative incidences, 9.8% in the ticagrelor group vs. 11.7% in the clopidogrel group; HR=0.84; 95% CI, 0.77 to 0.92). Concerning major bleeding, there was no significant difference in the rates of TIMI major bleeding between the groups (7.9% in the ticagrelor group versus 7.7% in the clopidogrel group), although, in the ticagrelor arm, a higher rate of non-CABG-related major bleeding was observed (4.5% vs. 3.8%, P=0.03). The PLATO trial showed that in patients with ACS, ticagrelor significantly reduced the risk of death from

vascular causes, MI, or stroke at the expense of an increase in the rate of non-procedure-related bleeding.

The two abovementioned trials, TRITON-TIMI 38 and PLATO, led to changes in guideline recommendations on DAPT use in patients with ACS, which strongly recommended the replacement of clopidogrel with the more powerful platelet inhibitors prasugrel and ticagrelor.

1.3.4 Head-to-head comparison of ticagrelor and prasugrel

So far, only 2 clinical trials have performed a randomized head-to-head comparison of prasugrel and ticagrelor in patients with ACS undergoing PCI. The PRAGUE-18 (57) (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) trial randomized 1230 patients with acute myocardial infarction (AMI) (95% with ST-elevation myocardial infarction [STEMI]) undergoing primary or immediate PCI to either prasugrel or ticagrelor. The 7-day composite of all-cause death, reinfarction, stroke, serious bleeding requiring transfusion or prolonging hospitalization, or urgent target vessel revascularization (4.0% versus 4.1% for prasugrel vs. ticagrelor, respectively; odds ratio (OR)= 0.98; 95%CI, 0.55 to 1.73), the 30-day composite of cardiovascular death, nonfatal myocardial infarction, or stroke (2.7% vs. 2.5% for prasugrel vs. ticagrelor, respectively; OR=1.06, 95%CI, 0.53 to 2.15) and the 1-year composite of cardiovascular death, nonfatal myocardial infarction, or stroke (6.6% vs. 5.7% for prasugrel vs. ticagrelor, respectively; HR=1.17, 95%CI 0.74 to 1.83) or major bleeding (10.9% vs.11.1% for prasugrel vs. ticagrelor, respectively; HR=0.99, 95%CI, 0.70 to 1.38) did not differ between patients assigned to prasugrel and those assigned to ticagrelor (57,58). However, the premature trial termination and high rates of switching to clopidogrel impede a true comparison between the drugs.

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial (59) showed the superiority of prasugrel over ticagrelor in reducing the 1-year incidence of ischemic events, with no significant excess in bleeding risk in a randomized head-to-head comparison of ticagrelor and prasugrel in patients with ACS planned to undergo an invasive management strategy. The detailed methodology and study protocol are provided in the Methods section of this thesis, and the primary publication (59). Briefly, 4018 patients with ACS were randomized to either ticagrelor or prasugrel therapy in a 1:1 ratio. The primary endpoint of the study was the composite of all-cause death, MI, or stroke at 12 months. The key safety endpoint was the Bleeding Academic Research Consortium (BARC) 3 to 5 bleeding at one year. The study showed that the incidence of death, MI, or stroke was significantly lower with prasugrel compared with ticagrelor, whereas the incidence of major bleeding was not significantly different between the 2 treatment groups (59). Based on the findings of the ISAR REACT 5 trial, the 2020 European Society of Cardiology (ESC) guidelines on the management of patients with NSTE-ACS recommend prasugrel as the preferred $P2Y_{12}$ receptor inhibitor for NSTE-ACS patients who proceed to PCI (60). The 2023 ESC Guidelines on the management of patients with ACS recommend prasugrel as the preferred $P2Y_{12}$ inhibitor in $P2Y_{12}$ inhibitor-näive patients proceeding to PCI, as well (Class I recommendation, level of evidence B) (34).

1.3.5 Optimal antiplatelet therapy in specific groups of patients with acute coronary syndrome

Elderly and/or low body weight patients

Approximately one-third of patients undergoing PCI are ≥75 years old (61). Elderly patients with ACS are at a higher risk for subsequent ischemic and bleeding complications after invasive

or conservative therapy (55,62). Therefore, it is of paramount importance to optimize the antiplatelet therapy by taking into account an increased ischemic and bleeding risk in this specific group of patients. The newer antiplatelet drugs ticagrelor and prasugrel provide more potent and consistent platelet inhibition compared with clopidogrel (63,64), and both drugs have proven to be superior to clopidogrel in reducing the risk for ischemic events in patients with ACS undergoing PCI (55,56). In the TRITON-TIMI 38 trial (55), patients aged ≥75 years had no net clinical benefit from prasugrel, owing to increased risk for intracranial and fatal bleeding. Additionally, an increased risk of bleeding was also observed in patients younger than 75 years of age who weighed less than 60 kg. Based on these findings, the United States Food and Drug Agency (US FDA) issued a warning about an excess risk of bleeding with prasugrel in these two subgroups of patients. Subsequently, a reduced dose of prasugrel (5 mg) was recommended for these patients. Our group investigated the effect of an age- and weight-adapted dose of prasugrel versus a standard dose of ticagrelor in patients with ACS (65), and the main results of this study are included in this thesis.

Patients on pre-admission antiplatelet therapy

A considerable number of patients are on antiplatelet therapy with aspirin and/or a $P2Y_{12}$ inhibitor upon hospital admission for an ACS. Studies on patients with NSTE-ACS have shown that patients on prior antiplatelet therapy with aspirin and/or clopidogrel experience worse clinical outcomes compared with those not on such therapy (66-68). Differences in the baseline risk profile and hyporesponsiveness to aspirin or clopidogrel may be held accountable for the differences observed in clinical outcomes (64,69-71). The authors of the PLATO trial (56) found that the treatment effect of ticagrelor vs. clopidogrel was not influenced by prior antiplatelet treatment status in terms of efficacy or safety. The TRITON TIMI 38 trial (55)

excluded patients using any thienopyridine within 5 days before enrollment and data concerning the impact of prior aspirin use on the efficacy and safety of prasugrel vs. clopidogrel were not reported. The effect of prior antiplatelet therapy on the efficacy and safety of the newer $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, is addressed in Chapter 4.2 of this thesis.

Patients at high bleeding risk

The use of antiplatelet therapy following PCI increases the risk of bleeding complications, which are associated with a similar risk of mortality as ischemic events (72). This is especially true for patients with high bleeding risk (HBR) features undergoing PCI, in whom a balance between the benefits and risks of antithrombotic therapy is crucial. A consensus document from the Academic Research Consortium (ARC) has standardized the definition of HBR in patients undergoing PCI by identifying twenty clinical criteria associated with an increased risk of bleeding at 1 year (73). In this thesis, we assessed the treatment effect of the potent $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, according to HBR status defined by ARC-HBR criteria, in patients with ACS undergoing PCI.

Smokers

It is estimated that approximately 30% of patients hospitalized for ACS are smokers. Smoking is a potent risk factor for the development of CAD, associated with significant morbidity and mortality (74). Previous studies (75,76) have reported better outcomes after thrombolysis or PCI among smokers with myocardial infarction, a phenomenon known as the smoker's paradox (75). Smokers might have a greater clinical benefit from clopidogrel (77-80) owing to greater platelet inhibition and lower rates of on-treatment platelet reactivity, as well as younger age compared with nonsmokers (81-83). The greater platelet inhibition by clopidogrel in smokers has been attributed to a smoking-related increase in the clopidogrel

biotransformation via induction of hepatic cytochrome P450 (CYP) 1A2AC isoenzyme activity – the predominant isoenzyme responsible for conversion of clopidogrel into its active metabolite (84,85). The impact of smoking on the efficacy and safety of ticagrelor and prasugrel in patients with ACS undergoing PCI remains poorly investigated and has been addressed in this thesis.

1.4 Antiplatelet therapy in chronic coronary syndrome

The guideline-recommended DAPT in patients with chronic coronary syndrome (CCS) undergoing PCI consists of the combination of aspirin plus clopidogrel for 6 months, irrespective of the stent type (Class I recommendation, Level A of evidence) (33). Although there are no studies directly comparing different durations of DAPT in patients with CCS, in patients considered to be at high ischemic risk, a prolongation of DAPT >6 months may be considered (Class IIb recommendation, Level A of evidence), whereas in patients at high bleeding risk, shortening of DAPT to 3 months should be considered (Class IIa recommendation, Level B of evidence) (33). These recommendations were derived mainly from subgroup analyses of related randomized controlled trials (86,87). The newer antiplatelet agents, prasugrel and ticagrelor, have not sufficiently been tested in patients with CCS undergoing PCI.

1.5 Optimal duration of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention

As previously mentioned, DAPT is recommended for 12 months in patients with ACS (34,60) and 6 months in patients with CCS (33) undergoing PCI. Although DAPT significantly reduces the risk of ischemic events following PCI, it unavoidably increases the risk of bleeding, which may lead to adverse clinical outcomes (88). The risk of stent thrombosis (ST) is usually highest

in the early phase following PCI and decreases over time (89), whereas the bleeding risk increases with the duration of therapy. Ideally, the duration of DAPT should be tailored based on the patient's individual ischemic and bleeding risk. In this regard, several trials have evaluated very short DAPT durations (≤3 months) with the aim of reducing bleeding risk. However, whether a short DAPT duration sufficiently protects patients from ischemic events is still unclear. The optimal duration of DAPT and the type of single antiplatelet therapy (SAPT) following DAPT in patients undergoing PCI is still a matter of debate. The role of aspirin as the traditionally recommended antiplatelet agent following DAPT has been recently challenged by the concept that a $P2Y_{12}$ inhibitor monotherapy may provide superior antithrombotic efficacy and lower bleeding rates compared with aspirin (90,91). To assess the outcomes with short vs. prolonged DAPT duration in patients with CAD undergoing PCI, we performed a meta-analysis and its results are reported in Chapter 4.5 of the thesis.

1.6 The role of soluble glycoprotein VI in predicting the ischemic and bleeding risk in patients with chronic coronary syndrome undergoing Percutaneous coronary intervention

Glycoprotein VI (GPVI) is a platelet membrane glycoprotein of the immunoglobulin family, described as the major platelet-specific collagen receptor (92-94). GPVI plays a crucial role in the initiation of thrombus formation in pathological thrombotic events such as myocardial infarction and stroke. Platelet activation by collagen leads to increased expression of GPVI (platelet GPVI [pGPVI]). GPVI shedding with the generation of soluble GPVI (sGPVI) is an endogenous feedback mechanism preventing platelet overstimulation. pGPVI is increased in patients with ACS as compared to patients with CCS (95,96), and an inverse relationship has been reported between sGPVI and pGPVI plasma levels in patients with CAD (97). The sGPVI has not been investigated in patients with CCS undergoing PCI, especially regarding its

potential value as a predictor of ischemic and bleeding risk. In Chapter 4.6 of this thesis, we assessed the correlates of plasma levels of sGPVI, the association between sGPVI level and platelet reactivity after standard peri-procedural antiplatelet treatment, and the ability of sGPVI to predict early post-procedural ischemic and bleeding events in patients with CCS undergoing PCI.

1.7 ANTIPLATELET THERAPY IN PATIENTS ON ORAL ANTICOAGULATION

Current guidelines recommend DAPT for 12 months after PCI with DES implantation to prevent ischemic events, such as stent thrombosis, in patients with ACS (33). Up to 10% of patients undergoing PCI for CAD have an indication for oral anticoagulation (OAC) for the prevention of ischemic stroke and systemic embolism (98). These patients require a combination of OAC and DAPT, referred to as triple antithrombotic therapy (TAT). TAT consists of aspirin, a $P2Y_{12}$ inhibitor, and an oral anticoagulant (OAC). Treatment with OAC is associated with a high bleeding risk, and the concomitant use of DAPT further increases this risk (99,100). Extra caution should be taken when treating these patients to minimize the bleeding risk. Randomized clinical trials that included patients undergoing PCI for CAD who had an indication for long-term OAC have found that double antithrombotic therapy (DAT) with an OAC and a $P2Y_{12}$ inhibitor is associated with a reduced risk of bleeding compared with TAT (101-104).

European and US Guidelines on DAPT for patients with an indication for OAC undergoing PCI recommend that the duration of TAT should be kept as short as possible, and preference should be given to DAT (105,106). In this regard, DAT with a novel oral anticoagulant (NOAC) at the approved dose for stroke prevention and a $P2Y_{12}$ inhibitor (usually clopidogrel) is recommended for up to 12 months as the default strategy (after 1 week of TAT) in ACS patients with an indication for OAC who undergo PCI (34). In patients considered to be at high ischemic

risk, the duration of TAT can be prolonged up to a maximum of one month following PCI. In patients with mechanical heart valves or contraindications to NOACs, Vitamin K antagonists are recommended instead (107-109).

1.7.1 The role of special inactive stent coating in shortening the duration of dual antiplatelet therapy in patients on oral anticoagulation

DESs are associated with improved clinical outcomes in comparison to uncoated stents, but they have been associated with delayed vascular healing, especially in patients presenting with ACS (110,111). A polymer-coated non-DES that could combine an accelerated vascular healing profile with a performance efficacy similar to DES might be useful for patients with an indication for OAC (112). The COBRA Polyzene-F (COBRA PzF, Celonova BioSciences Inc. San Antonio, TX) stent is a thin strut cobalt-chromium alloy stent coated with a nano-thin layer (≤ 0.05 μm) of Polyzene-F, a durable inorganic polymer, with no elution of anti-restenotic drug (113). The use of a coronary stent with thromboresistant and pro-healing properties, such as the COBRA PzF stent (110-112), could facilitate an abbreviated duration of DAPT in patients with an indication for OAC undergoing PCI. From this perspective, we conducted the Randomized Trial of COBRA PzF Stenting to REDUCE Duration of Triple Therapy (COBRA-REDUCE) to compare the clinical safety and efficacy of the COBRA PzF stent in combination with 14 days of clopidogrel therapy with US FDA-approved drug-eluting stents (DES) in combination with 3-6 months of clopidogrel therapy, in patients taking OAC and aspirin (summarized in Chapter 4.7 of this thesis).

2 OBJECTIVES OF THE THESIS

The main objective of this thesis was to provide new insights into the optimal antiplatelet therapy in patients with CAD undergoing PCI, with a special emphasis on the use of the third-generation $P2Y_{12}$ inhibitors – ticagrelor and prasugrel – in specific groups of patients with ACS undergoing an invasive management strategy. In addition, the thesis aimed to assess the optimal duration of antiplatelet therapy in patients undergoing PCI, to test new strategies to reduce the bleeding risk in patients taking OAC and undergoing PCI, and to identify markers of ischemic and bleeding risk in patients with CCS who undergo PCI. The thesis includes seven studies to address the following specific objectives:

1. *to assess the effect of age- and weight-adapted dose of prasugrel vs. standard dose of ticagrelor on ischemic and bleeding risk in patients with ACS undergoing PCI;*
2. *to investigate the impact of pre-admission antiplatelet therapy on the efficacy and safety of ticagrelor and prasugrel in patients with ACS undergoing PCI;*
3. *to assess the comparative efficacy and safety of ticagrelor and prasugrel in patients with ACS and HBR undergoing PCI;*
4. *to evaluate the influence of smoking on the efficacy and safety of ticagrelor and prasugrel in patients with ACS undergoing PCI;*
5. *to compare clinical outcomes of short vs. control DAPT duration in patients undergoing PCI;*
6. *to study the association between plasma levels of sGPVI and platelet function, bleeding and ischemic events in patients with CCS undergoing PCI; and*
7. *to investigate whether COBRA PzF stent plus 14 days of DAPT reduces bleeding compared with standard FDA-approved DES plus 3-6 months of DAPT while maintaining the anti-ischemic efficacy in patients on OAC undergoing PCI.*

3 METHODS AND MATERIALS

3.1 HEAD-TO-HEAD COMPARISON OF TICAGRELOR AND PRASUGREL IN PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION – THE STUDY PROTOCOL

Study population

Patients presenting with an ACS (unstable angina pectoris, non-ST-elevation myocardial infarction [NSTEMI], or STEMI), planned to undergo an invasive strategy were randomized in the setting of the ISAR-REACT 5 trial. The study protocol and results have been previously published (59,114). The trial was conducted in accordance with the Declaration of Helsinki, and the local ethics committee of each participating center approved the study protocol. All patients provided full, written, informed consent.

Inclusion and exclusion criteria

- **Inclusion criteria**: [1] informed written consent; [2] patients ≥18 years of age; [3] patients with an ACS planned to undergo an invasive evaluation strategy.
- **Exclusion criteria**: [1] intolerance or allergy to ticagrelor or prasugrel; [2] history of any stroke, transient ischemic attack (TIA), or intracranial bleeding; [3] known intracranial neoplasm, intracranial arteriovenous malformation, or intracranial aneurysm; [4] active bleeding or clinical findings associated with an increased risk of bleeding; [5] fibrin-specific fibrinolytic therapy <24 hours before randomization; [6] known platelet count <100.000/µL at the time of screening; [7] known anemia with a hemoglobin value of <10 g/dL at the time of screening; [8] concomitant therapy with oral anticoagulants; [9] INR value greater than 1.5 at the time of screening; [10] chronic renal failure requiring dialysis; [11] moderate or severe hepatic dysfunction (Child Pugh class B or C); [12] bradycardia; [13] the index event is an acute complication (<30 days)

of PCI; [14] life expectancy <1 year; [15] concomitant therapy with CYP3A inhibitors, CYP3A inducers, or CYP3A substrates with narrow therapeutic indices; [16] therapy with ticagrelor or prasugrel within 5 days before randomization; [17] lack of informed consent; [18] nonadherence to study protocol; [19] participation in another investigational study; [20] women of childbearing potential not agreeing to use a reliable birth control method; [21] pregnancy, giving birth within the last 90 days, or lactation. The detailed inclusion and exclusion criteria have been previously published by Schüpke et al. (59).

Randomization and study drugs

Patients were randomized in a 1:1 fashion to either ticagrelor or prasugrel treatment strategy. Patients randomized to ticagrelor received a loading dose of 180 mg as soon as possible after randomization, followed by a maintenance dose of 90 mg twice daily. In patients with NSTEMI or unstable angina, a loading dose of 60 mg of prasugrel was given only after coronary anatomy was known (i.e., after diagnostic coronary angiography). The maintenance dose of prasugrel was 10 mg once daily. For patients ≥75 years old or with a body weight <60 kg, a reduced dose of 5 mg prasugrel was recommended. The specific details of the methodology applied in subgroup analyses are provided in the respective parts of the thesis.

Study endpoints and definitions

- ***The primary (efficacy) endpoint*** of the trial was the composite of all-cause death, myocardial infarction, or stroke at 12 months after randomization.
- ***The main secondary (safety) endpoint*** was the incidence of Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding at 12 months after randomization.

- ***Individual endpoints of the primary outcome*** (death, MI, stroke) and stent thrombosis (definite and probable) were also analyzed.

Deaths were classified as of cardiac and noncardiac origin.

Myocardial infarction was defined according to the Third Universal Definition of Myocardial Infarction (115). Cardiac troponin was used as the preferred biomarker. CK-MB (and CK) values were also assessed and used in the case of missing troponin measurements. MI is subclassified according to the Third Universal Definition of Myocardial Infarction (115) into the following types:

Type of myocardial infarction	Definition
Type 1: Spontaneous myocardial infarction	Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type 2: Myocardial infarction secondary to an ischemic imbalance	In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, anemia, hypotension etc.
Type 3: Myocardial infarction resulting in death when biomarker values are unavailable	Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiographic (ECG) changes or new left bundle branch block, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to PCI	MI associated with PCI is defined by elevation of cardiac troponin values 5 x 99th percentile upper reference limit (URL) in patients with normal baseline values (<99th percentile URL) or a rise of >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new left bundle branch block, or

	(iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis	MI associated with ST is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)	MI associated with CABG is arbitrarily defined by the elevation of cardiac biomarker values > 10 x 99th percentile URL in patients with normal baseline cardiac troponin values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

ST-segment elevation myocardial infarction

ST-segment elevation myocardial infarction was defined as chest discomfort suggestive of ischemia of ≥ 20 minutes at rest, within 24 h prior to randomization with one of the following ECG features:

- ST-segment elevation ≥ 1 mm in ≥ 2 contiguous ECG leads or
- New or presumably new left bundle branch block (LBBB)

Non-ST-segment elevation acute coronary syndrome (unstable angina or NSTEMI)

Chest discomfort suggestive of cardiac ischemia for ≥10 minutes at rest within 48 h prior to randomization plus one of the following criteria (59):

- ST-segment depression ≥ 1 mm in ≥ 1 or 2 contiguous ECG leads or
- Troponin T or I or CK-MB >upper limit of normal (ULN), or
- Two of the following criteria:
    - age ≥ 60 years

- ≥ 3 risk factors for CAD (arterial hypertension, hypercholesterolemia, family history, diabetes mellitus, current smoker)
- diabetes mellitus
- aspirin use in the past 7 days
- severe angina (≥ 2 episodes within the last 24 hours)
- chronic renal dysfunction
- prior MI or CABG
- known CAD with ≥ 50% stenosis in ≥ 2 vessels
- carotid stenosis ≥ 50% or cerebral revascularization
- peripheral artery disease

Stroke was defined as the new onset of focal or global neurologic deficit caused by ischemia or hemorrhage within or around the brain lasting for more than 24 hours or leading to death. The diagnosis of stroke had to be confirmed by CT, MRI, or autopsy (59).

Stent thrombosis was defined as per Academic Research Consortium Criteria (ARC) (116) and was subclassified into the following categories:

- ***Definite*** Presence of an ACS with angiographic or autopsy evidence of thrombus or occlusion
- ***Probable*** Unexplained deaths within 30 days after the procedure or AMI involving the target-vessel territory without angiographic confirmation
- ***Possible*** All unexplained deaths occurring at least 30 days after the procedure

Bleeding was defined according to the BARC criteria (117). BARC type 3 to 5 bleeding events (major bleeding) were considered for the study. The detailed definition of bleeding according to the BARC criteria is as follows:

Type 1	bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional
Type 2	any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a health care professional; (2) leading to hospitalization or increased level of care; or (3) prompting evaluation
Type 3a	overt bleeding plus a hemoglobin drop of 3 to 5 g/dL* (provided the hemoglobin drop is related to bleed); any transfusion with overt bleeding
Type 3b	overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoids); bleeding requiring intravenous vasoactive agents
Type 3c	intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period
Type 5a	probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation

*Corrected for transfusion (1 Unit packed red blood cells or 1 Unit whole blood=1 g/dL)

Follow-up and monitoring

The follow-up was scheduled at 30 (±10) days, 6 (±1) months, and 12 (±1) months. Patients were contacted by telephone, hospital or outpatient visit (10%), or structured follow-up letter (7%) to collect information about possible adverse events and adherence to study drug and concomitant medications. In case of endpoint-related adverse events, source data were solicited. All serious adverse events and primary and secondary endpoints in the ISAR-REACT 5 trial were monitored on-site.

3.1.1 The efficacy and safety of age- and weight-adapted dose of prasugrel versus standard dose of ticagrelor

Study design and patients

The current study is a pre-specified analysis of the ISAR-REACT 5 trial. As previously described, patients were eligible for enrollment if they were hospitalized for an ACS (STEMI, NSTEMI, or unstable angina) and planned to undergo diagnostic coronary angiography and PCI if needed. Patients were randomized in a 1:1 ratio to receive either ticagrelor or prasugrel.

For the present analysis, patients with available body weight data were considered. Body weight data were missing for 27 of the 4018 patients enrolled in the primary trial. Six patients with missing body weight were aged 75 years or older, and these patients were included in the analysis as only the age or weight criterion was required to include patients in the group aged 75 years or older or with body weight below 60 kg. Twenty-one patients with missing body weight were younger than 75 years, and these patients were excluded, leaving 3997 patients for the current study. Based on age and weight, patients were categorized into 2 groups: “the elderly or low-weight” group comprising those aged 75 years or older or with

body weight less than 60 kg (1099 patients), and “the neither elderly nor low-weight” group comprising those younger than 75 years and with a body weight of ≥ 60 kg (2898 patients).

Study outcomes

The efficacy endpoint of the study was the composite of all-cause death, myocardial infarction, or stroke at 12 months after randomization. The safety endpoint was BARC type 3 to 5 bleeding. BARC type 1 to 5 bleeding was also assessed to increase the sensitivity of the analysis. Other endpoints analyzed were the incidence of the individual components of the efficacy endpoint and the incidence of stent thrombosis at 12 months (definite or probable).

Statistical analysis

Continuous data are presented as means with standard deviations (SDs) or medians (25th and 75th percentiles). Categorical variables were presented as counts and proportions (percentages) and were compared using the Chi-squared test. The cumulative incidence of the efficacy endpoint was computed using the Kaplan-Meier estimates of event-free survival. For endpoints that did not include all-cause mortality, cumulative incidence functions were calculated to adjust for competing risks. The participating center and stratification according to clinical presentation (ACS with or without ST-segment elevation) were entered into the Cox proportional hazards model as covariates along with the study treatment group. The primary efficacy endpoint was assessed using the intention-to-treat (ITT) population, meaning all randomized patients were included regardless of the actual treatment received. The safety endpoint was evaluated in a modified intention-to-treat (mITT) population, which comprised patients who received at least one dose of the study drug and were monitored for bleeding events for up to one week after drug discontinuation. Patients were analyzed from randomization until death, withdrawal of consent, or last contact date. The statistical analysis

was performed using the R 3.6.0 Statistical Software (The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided P value less than 0.05 was considered statistically significant (65).

3.1.2 Pre-admission antiplatelet therapy and the comparative efficacy and safety of ticagrelor versus prasugrel

Study population and design

This part of the thesis represents a post hoc analysis of the ISAR-REACT 5 trial. Based on pre-admission antiplatelet drug therapy, patients were classified into two groups: the group on therapy with aspirin and/or clopidogrel at the time of admission (pre-admission aspirin and/or clopidogrel group) and the group not on therapy with aspirin or clopidogrel at admission (no pre-admission aspirin or clopidogrel group). Pre-admission therapy with aspirin and/or clopidogrel was defined as aspirin or clopidogrel use for >7 days before admission.

Clinical endpoints

The primary endpoint was a composite of all-cause death, myocardial infarction, or stroke at 12 months after randomization. The secondary safety endpoint was the one-year incidence of BARC type 3 to 5 bleeding. A detailed description of the study endpoint definitions has been published previously (59,114).

Follow-up

In this study, follow-up was performed at 30 (±10) days, 6 (±1) months, and 12 (±1) months.

Statistical analysis

This analysis was not prespecified in the protocol of the primary trial. Continuous data are presented as means (±SD) or medians with interquartile ranges (IQR). Hypothesis tests for group differences were performed using either the Student's t-test or the Wilcoxon rank sum

test, depending on the data distribution. Categorical data are presented as counts and proportions (%) and were compared using the Chi-squared test. Cumulative incidences for the primary endpoint and all-cause death were calculated using the Kaplan-Meier method. Other events are presented as cumulative incidence(s) after accounting for the competing risk of death. This was done with the use of the R-package 'cmprsk' (118,119). The comparison between the groups was performed using a Cox proportional hazards model after checking for fulfillment of the proportional hazards assumption according to the Grambsch and Therneau method (120). To assess the interaction between the treatment arm and antiplatelet therapy with aspirin and/or clopidogrel status on admission for the study endpoints, an interaction term was entered into the Cox proportional hazards model. Risk estimates are presented as HRs with inherent 95% CIs. The primary endpoint was analyzed in the ITT population (i.e., including all patients as initially assigned, regardless of the treatment received). The secondary safety endpoint was analyzed in the mITT population (i.e., including all patients who received at least one dose of the study drug, with bleeding assessed for up to 7 days after study drug discontinuation). Statistical analysis was performed using the R 3.6.0 Statistical Software (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value of <0.05 was taken to confer statistical significance (121).

3.1.3 High bleeding risk status and the efficacy and safety of ticagrelor versus prasugrel

Study population and treatment groups

The present study is a post hoc analysis of the ISAR-REACT 5 trial, including all patients who underwent PCI. For the purpose of this analysis, patients were grouped into two categories based on the HBR status. The HBR status was defined according to the Academic Research Consortium-High Bleeding Risk (ARC-HBR) consensus (73).

Definition of HBR

Patients were considered at HBR if they met at least one major or two minor criteria for HBR as defined by the ARC-HBR consensus (122). Major ARC-HBR criteria available for the present study were estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 (excluding chronic renal insufficiency requiring dialysis) and hemoglobin <11g/dL (but not <10g/dL at the time of screening). A platelet count <100 x 10^9/L, another major ARC-HBR feature, represented an exclusion criterion in the primary trial but some patients with this condition were enrolled and, therefore, were considered for the present analysis. Minor ARC-HBR criteria available for the present study were the following: age ≥75 years, eGFR 30 to 59 mL/min, hemoglobin 11 to 12.9 g/dL for men and 11 to 11.9g/dL for women, and long-term use of oral nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids. Exclusion criteria of the ISAR-REACT 5 trial and major and minor HBR criteria definitions provided in the original ARC-HBR consensus document are presented in **Table A1** in the Appendix to this thesis. Baseline laboratory values were recorded during the screening process in the setting of the primary trial. Patients undergoing PCI were divided into 2 groups: with HBR and without HBR.

Clinical outcomes

The primary endpoint was the composite of all-cause death, myocardial infarction, or stroke, analyzed in the ITT population. The secondary safety endpoint was the incidence of BARC type 3 to 5 bleeding. Both endpoints were assessed at 12 months after randomization. BARC type 3 to 5 bleeding was assessed in the ITT population in the subgroups according to HBR status. The mITT population served to compare ticagrelor and prasugrel within both the HBR and non-HBR groups. Detailed definitions of the study endpoints are shown in Section 3.1 of the thesis.

Statistical analysis

The analysis of outcomes according to HBR status and assigned antiplatelet therapy was not specified in the study protocol. Continuous data are reported as means (±SD) or medians and IQR and were compared between groups using the t-test or the Wilcoxon rank sum test when appropriate. Categorical variables are reported as counts and proportions. The Chi-squared test or Fisher's exact tests were used to assess group differences in categorical variables. The primary endpoint and all-cause death are displayed as cumulative incidence and were estimated using the Kaplan-Meier method. All other endpoints were calculated after accounting for the competing risk of death. The comparison between the groups was performed using the Cox proportional hazards model, with the participating center and clinical presentation (ACS with or without ST-segment elevation) entered into the model as covariates along with the treatment arm. We provided HRs with 95% CI by using a Cox proportional hazards model after checking for fulfillment of the proportional hazards assumption according to the Grambsch and Therneau method (120). A landmark analysis to assess the risk of early and late outcomes (primary and secondary endpoints) using the 30-day time point as a landmark was performed. The treatment allocation-by-HBR status interaction was assessed by entering an interaction term in the Cox proportional hazards model and P for interaction (Pint) was calculated. Finally, we generated a point-based HBR score relying on ARC-HBR definitions for major and minor HBR criteria. We assigned 2 points to each major criterion and 1 point to each minor criterion, given their relative weight in defining HBR. The C statistic was calculated to assess the discriminatory power of the HBR score to predict the primary efficacy and safety endpoints. The statistical analysis was performed using the R 3.6.0 Statistical

Software (The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided P<0.05 was considered to indicate statistical significance (123).

3.1.4 Smoking and the relative efficacy and safety of ticagrelor versus prasugrel

Study population and enrollment criteria

This study is a pre-specified analysis of the ISAR-REACT 5 trial (59). For the present analysis, patients were categorized into 2 groups according to smoking status: smokers – patients who have been smoking any tobacco product, either daily or occasionally, in the prior 6 months, and nonsmokers – patients who did not smoke regularly or occasionally within the prior 6 months before randomization. Information on smoking was available in 4001 of 4018 patients of the ISAR-REACT 5 trial.

Study endpoints and definitions

The primary (efficacy) endpoint was a composite of death, myocardial infarction, or stroke at 12 months after randomization. The secondary safety endpoint was the 12-month incidence of BARC type 3 to 5 bleeding. Individual components of the primary endpoint, cardiovascular death, and stent thrombosis (definite or probable) were analyzed as additional endpoints. Detailed definitions of the study outcomes are reported in the primary publication (59).

Follow-up and monitoring

In the ISAR-REACT 5 trial, patients were followed up at 30(±10) days, 6(±1) months, and 12(±1) months.

Statistical analysis

The analysis of outcomes according to smoking status was pre-specified in the trial protocol. Continuous variables are presented as mean±standard deviation or median with 25th–75th

percentiles and were compared using the Student's t-test or the Wilcoxon rank sum test. Categorical data are presented as counts and proportions (%) and were compared using the Chi-squared test. The primary endpoint and all-cause death were presented as cumulative incidence(s) and were calculated using the Kaplan-Meier estimates. All other endpoints were presented as cumulative incidence(s) after accounting for competing risk. The comparison between the groups was performed using the Cox proportional hazards model after the participating center and stratification according to clinical presentation (ACS with or without ST-segment elevation) was entered into the model as covariates along with the study treatment group. To estimate the interaction between the treatment arm and smoking status for the study endpoints, an interaction term was entered into the Cox proportional hazards model. Risk estimates are presented as hazard ratios with 95% confidence intervals. The primary (efficacy) endpoint was analyzed in the ITT population (i.e., including all patients as initially assigned, irrespective of the actual treatment received). The secondary safety endpoint was analyzed in the mITT population (i.e., including all patients with at least one application of the study drug, with bleeding assessed for up to 1 week after study drug discontinuation). The statistical analysis was performed using the R 3.6.0 Statistical Software (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided $P < 0.05$ was considered to indicate statistical significance (124).

3.2 Comparison of ≤3 months with ≥6 months of dual antiplatelet therapy in patients undergoing drug-eluting stent implantation — A Meta-analysis of randomized trials

Search strategy and study selection

We searched PubMed, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), proceedings of international meetings, and relevant websites without restricting

language or publication status. Search terms included the keywords and the corresponding Medical Subject Headings for: “dual antiplatelet therapy,” “drug-eluting stent,” and “randomized clinical trial.” We included reports fulfilling the following criteria: (i) randomized clinical trial; (ii) total number of participants >1000; (iii) DAPT duration ≤3 months in the experimental arm; (iv) DAPT duration ≥6 months in the control arm; and (v) implantation of DES. Clinical trials investigating outcomes in patients treated with BMS were ineligible for inclusion.

We independently assessed publications for eligibility at the title and/or abstract level. Divergences were resolved by consensus. Studies that met the inclusion criteria were selected for further analysis. The risk of bias was independently evaluated for each study in accordance with the Cochrane Collaboration method (125).

Endpoints

The primary endpoint of the analysis was definite or probable stent thrombosis. The co-primary endpoint was bleeding. The definition of bleeding differed between the trials. A detailed definition of clinical outcomes according to the trial protocols is provided in **Table A2** in the Appendix. The secondary endpoints were mortality, cardiac death, myocardial infarction, and stroke. All endpoints were evaluated in the ITT population up to 1 year, in conformity with definitions reported in the original study protocols.

Data synthesis and analysis

We summarized the distribution of patient characteristics in individual trials by calculating means (continuous variables) and proportions (categorical variables). We used the HRs and corresponding 95% CIs reported in individual trials. In the two trials in which no HRs were reported (126,127), the absolute number of events and the provided log-rank p-value were used to calculate HRs with 95% CIs according to the method of Parmar et al. (128). In one trial

(129), neither HRs nor log-rank p-value for cardiac death were provided; in this case, the absolute number of events was used to calculate ORs with 95% CIs. We obtained pooled HRs from the inverse variance random-effects model. The heterogeneity across trials was estimated using the I^2 statistic, with values around 25%, 50%, and 75% indicating low, moderate, or high heterogeneity, respectively (130). The between-study variance was calculated according to the DerSimonian–Laird method. Risk estimates from random and fixed model effects are displayed in the figures, while results from the random-effects model are only reported in the text. We also assessed whether the treatment effect of monotherapy following DAPT depended on its type—aspirin or $P2Y_{12}$ inhibitor. For this purpose, we performed separate analyses by pooling the 4 studies that continued with aspirin monotherapy after an initial short DAPT duration and the 5 studies that continued with $P2Y_{12}$ inhibitor monotherapy after a short DAPT duration. The pooled HRs obtained by these 2 separate analyses were checked for significant heterogeneity. All analyses were performed using R (version 3.6.3; The R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant. This meta-analysis was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (131). The meta-analysis was registered with PROSPERO (132).

3.3 Plasma soluble glycoprotein VI, a specific marker of bleeding risk in patients undergoing elective percutaneous coronary intervention

Study design and population

This study included 318 of the 334 patients enrolled in the Intracoronary Stenting and Antithrombotic Regimen: Lesion Platelet Adhesion as Selective Target of Endovenous Revacept in Patients With Chronic Coronary Syndrome (ISAR-PLASTER) trial (133), in whom sGPVI levels were assessed. Sixteen patients were excluded because data on baseline sGPVI levels were not available.

The design and outcomes of the ISAR-PLASTER trial (Rev/CAD/02 EudraCT Number: 2015-000686-32) have previously been reported (133,134). Briefly, ISAR PLASTER was a phase II, multicenter, randomized, double-blind, placebo-controlled, 3-arm trial that enrolled patients with CCS undergoing PCI. The inclusion criteria of the ISAR-PLASTER consisted of age ≥ 18 years, presentation with CCS, normal high-sensitivity cardiac troponin T (hsTnT) levels on admission, and angiographic evidence of CAD with an indication for PCI. The enrolled patients were randomly assigned to 2 different doses of Revacept, a recombinant dimeric GPVI-Fc fusion protein (either 80 mg or 160 mg) (135), or placebo. The assigned drug was administered as an infusion before the start of the PCI procedure. Periprocedural antithrombotic therapy consisting of clopidogrel, aspirin, and heparin (or bivalirudin) was administered in all patients as recommended by current guidelines (136). The study conformed to the Declaration of Helsinki, and its protocol was approved by the ethics committee at each participating site. All patients provided their written informed consent before enrollment.

The primary endpoint of the ISAR-PLASTER trial was the composite of death or myocardial injury, defined as the increase in hsTnT value to at least 5 times the ULN within 48 hours from randomization.

The safety endpoint of the ISAR-PLASTER trial was the BARC type 2 or higher at 30 days post-randomization.

For the present analysis, we included patients of the ISAR-PLASTER trial in whom sGPVI levels were measured.

Soluble GPVI measurements

Blood samples were drawn at baseline before the study drug infusion and PCI in all patients. Because the sGPVI ELISA detects both endogenous GPVI and the administered GPVI-Fc drug Revacept, at day 2, the sGPVI concentrations were determined only in the placebo group. A validated sandwich ELISA assay was established, in which soluble GPVI is detected with two monoclonal rat antibodies 1A5 and 4C9 that are specific for different epitopes of the extracellular domain of GPVI. The 1A5 was used as a coating antibody, and 4C9 conjugated with digoxigenin (DIG) was used as a detection antibody, followed by an anti-DIG antibody coupled to peroxidase. GPVI concentrations were visualized by 3,3',5,5'-tetramethylbenzidine (TMB) substrate addition and measured in an ELISA reader. Samples were quantified by a defined standard curve of recombinant sGPVI covering concentrations from 1.56 to 100 ng/ml. The mean accuracy of quality control samples ranged from 95% to 97%, and sGPVI could be determined with a threshold of 1.56 ng/ml.

Assessment of platelet function

In vitro platelet aggregation tests were performed with whole blood multiple electrode aggregometry (Multiplate Analyzer, Roche Diagnostics, Basel, Switzerland). Hirudinized blood samples collected before angiography and study drug administration as well as at day 2 after randomization were subjected to platelet aggregation using ADP at a concentration of 200 µM as well as three different concentrations of rabbit aortic collagen (31 µg/mL, 93 µg/mL, and 253 µg/mL, respectively) as described before (135). According to the study plan, 2

participating centers were selected for the assessment of platelet function: Deutsches Herzzentrum München, Munich (both collagen- and ADP-induced platelet aggregation in 157 patients) and Klinikum rechts der Isar, Munich (ADP-induced platelet aggregation in 35 patients). The results of the tests were quantified as the area under the curve (AUC) of aggregation units (AU): AUC = AU × min.

Clinical outcomes and definitions

Two co-primary endpoints were chosen for this specific study: ***the composite of death or myocardial injury***, defined as an increase in hsTnT to at least 5 times the ULN within 48 hours from randomization, and ***the bleeding endpoint*** defined as BARC type 1 to 5 bleeding at 30 days post-randomization. Major adverse cardiovascular events (MACE), a composite of death, myocardial infarction, definite stent thrombosis, or urgent coronary revascularization at 30 days were also assessed. Detailed definitions of the clinical outcomes have been previously reported (133,134). The hsTnT was measured using a high-sensitivity assay (Roche Diagnostics, Basel, Switzerland) on a cobas e 411 immunoanalyzer (Roche Diagnostics). The 99th upper reference limit (URL) is 14 ng/L.

Statistical analysis

Continuous variables are presented as median [25th, 75th percentiles] or mean ±SD and were compared using the Wilcoxon rank sum test or the Student's t-test as appropriate**.** Categorical variables are presented as counts and proportions (%) and were compared using the Chi-squared test. Correlates of plasma sGPVI levels were assessed by the multivariable linear regression model. The rate of the bleeding endpoint was determined from cumulative incidence functions, taking mortality as a competing risk into account. The adjusted risk associated with sGPVI levels was assessed using logistic regression analysis for the co-primary ischemic endpoint and the Cox proportional hazards model for the co-primary bleeding

endpoint. The Least Absolute Shrinkage and Selection Operator (LASSO) regression method (R-package "glmnet") was used to select variables to be entered into the multivariable models. To assess the discriminatory power of sGPVI regarding the ischemic risk (primary endpoint) or bleeding, receiver operating characteristic (ROC) curve analysis was performed. Areas under the ROC curve (AUC) are presented with 95% CI. If AUC was significantly different from 0.5, we assessed the added discrimination ability for prediction of the endpoint in the multivariable model, including sGPVI, as compared with the multivariable model without sGPVI, by calculating the C statistic and the integrated discrimination improvement (IDI). The bootstrapping method (2000 samples) was used to calculate the confidence interval of the C statistic and IDI and to enable the comparison of the C statistic and IDI of the models with and without sGPVI. The statistical analysis was performed using the R 4.1.0 Statistical Software (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided $P<0.05$ was considered to indicate statistical significance (137).

3.4 Role of special inactive stent coating in shortening the duration of dual antiplatelet therapy in patients on oral anticoagulation

Study design and trial population

The Randomized Trial of COBRA PzF Stenting to Reduce Duration of Triple Therapy ***(COBRA-REDUCE)*** was a multicenter, randomized, prospective, parallel-group, open-label, assessor-blinded clinical trial conducted at 63 sites in the United States and Europe. The design and rationale of the trial has been published previously (112). The trial protocol was written by the principal and co-investigators, in association with the steering committee. The trial was sponsored and financed by CeloNova BioSciences Inc. San Antonio, TX, USA. The study sponsor

had no role in data collection, analysis, or interpretation. The data coordinating center was the ISAResearch Center, Deutsches Herzzentrum München, Munich, Germany.

Patients (n= 996) older than 18 years of age with symptoms (stable or unstable angina or ACS without thrombosis of the target lesion on coronary angiography) or objective evidence of myocardial ischemia and ≥50% *de novo* stenosis located in a native coronary vessel (maximum of 2 lesions in a maximum of 2 vessels) with an indication for long-term OAC with a coumadin-derivative or a NOAC were eligible for inclusion.

The **inclusion criteria** included:

- patients ≥18 years with ischemic symptoms (stable or unstable angina or NSTEMI without thrombosis of the target lesion on coronary angiography) or evidence of myocardial ischemia in the presence of ≥50% *de novo* stenosis located in native coronary vessels (max. 2 lesions in one or 2 separate vessels).
- patients receiving or with an indication for new treatment with long-term oral anticoagulation with coumadin derivatives or non-vitamin K oral anticoagulants.
- written, informed consent by the patient for participation in the study.

The full list of **exclusion criteria** consisted of:

- cardiogenic shock
- target lesion located in the left main trunk
- bifurcation interventions with a planned 2-stent strategy
- vessel size too small for implantation of a 2.5 mm stent by visual estimation
- patients requiring staging PCI procedure within 6 months after the index procedure
- patients requiring DAPT for more than 2 weeks after the index procedure

- contraindications or allergy to cobalt, chromium, platinum, Polyzene-F, Everolimus, Zotarolimus or the inability to take triple therapy for at least 6 months
- platelet count <$100x10^9$ cells/L or >$600x10^9$ cells/L
- active bleeding; bleeding diathesis; recent trauma or major surgery in the last month; history of intracranial bleeding or structural abnormalities; suspected aortic dissection
- malignancies or other co-morbid conditions with life expectancy of less than 12 months
- pregnancy; present, suspected or planned, breastfeeding
- known allergy or intolerance to study medications: aspirin, clopidogrel, coumadin, and its derivatives
- patient's inability to fully cooperate with the study protocol

Randomization

Eligible patients were randomized in a 1:1 treatment ratio to either a COBRA PzF stent plus 14 days of DAPT or an FDA-approved DES plus 3-6 months of DAPT in the order in which they qualified. In each participating center, allocation to treatment was performed using the electronic case report form (eCRF) system. Random sequence generation in permuted blocks was performed using a computerized random number generator. Randomization was performed by study personnel at each participating site immediately after the lesion was crossed with a guidewire. Time zero was defined as the time of randomization. Patients who met all of the inclusion criteria and none of the exclusion criteria were stratified and randomized in the order that they qualified. Treatment allocation was stratified according to participating center and treatment with coumadin derivatives or NOAC by means of a computer-generated list pre-generated in permuted blocks for each site and therapy

stratification. In the event that the treating physician was planning to switch the OAC (e.g., from a coumadin derivative to NOAC at the same time as PCI/enrolment), then the patient was stratified to the new OAC (i.e., in the case above, NOAC). If the decision to switch the patient was not final at the time of enrolment, then the patient remained by default in the stratum according to medication at enrollment. All patients provided informed written consent prior to any study-related procedure.

Study devices

The trial investigational device was the COBRA Polyzene-F (COBRA PzF, *CeloNova BioSciences Inc. San Antonio, TX*) stent. The COBRA stent is a balloon-expandable cobalt-chromium alloy BMS. The alloy has a very low strut-thickness (71µ) and is treated with the nano-thin PzF, which is an inorganic polymer with high biocompatibility and very low thickness (≤0.05µ). This device is *conformité européenne* (CE)-marked for use in Europe and received FDA approval for use in February 2017. The stents used in the control group had to be FDA-approved new generation DES (e.g., Xience/Promus, Resolute or Synergy), the choice of which was at the operator's discretion. This could include DES from the same family used under a different name in Europe (e.g., Xience PRO).

Trial procedure

All patients underwent coronary angiography. In addition, left ventricular angiography or echocardiography was performed according to standard practices if not performed within the previous 6 months. PCI was performed according to institutional guidelines and standards. The decision to use single or multiple coronary stents and to perform single or two-vessel interventions was left to the operator’s discretion. The same randomly assigned stent had to be implanted in all lesions treated. The placement of more than one stent per lesion was permitted. Blood samples were drawn 12-24 hours after the procedure to assess cardiac

biomarkers and blood cell counts (including hemoglobin, hematocrit, platelet count, and white blood cell count). An electrocardiogram was performed directly following and 12-24 hours after the index procedure.

Antithrombotic therapy

All patients received a loading dose of 600 mg of clopidogrel before catheterization or immediately after the index procedure. The loading dose of clopidogrel was administered at the treating physician's discretion for patients who had already been taking the daily maintenance dose of clopidogrel or another $P2Y_{12}$ inhibitor during the week prior to randomization. Following the decision to stent, patients were given aspirin (if they had not received it within the previous 12 hours), and intra-arterial or intravenous (i.v.) unfractionated heparin (70-100U/kg body weight) or bivalirudin (i.v. bolus of 0.75mg/kg prior to the start of the intervention, followed by an infusion of 1.75mg/kg per hour for the duration of the procedure), with activated clotting time guidance at the operator's discretion.

After the intervention, the recommencement of oral anticoagulation within 24 hours was recommended. All patients were recommended to continue their oral anticoagulation and aspirin (75–200 mg/day) for the duration of the trial. In addition to aspirin and OAC, patients received clopidogrel 75 mg/day for 14 days after COBRA PzF implantation or for a total of 3-6 months after FDA-approved DES implantation. In patients taking coumadin derivatives, the recommended target INR for the duration of triple therapy was 2.0 for atrial fibrillation and 2.5 for mechanical heart valves. After clopidogrel discontinuation, the recommended INR was according to standard guidelines. Treatment with a NOAC was recommended according to current guidelines, and the dosing of NOAC was at the discretion of the treating physician. Proton pump inhibitor (PPI) therapy was recommended for all patients.

Trial hypothesis and endpoints

The trial hypothesis was that in patients on OAC undergoing coronary stenting, treatment with the COBRA PzF stent plus 14 days of DAPT would be superior to standard FDA-approved DES plus 3-6 months of DAPT with respect to bleeding events at 6 months and non-inferior with respect to thrombo-embolic events at 6 months. The trial had two co-primary endpoints. The **bleeding co-primary endpoin**t was BARC class ≥2 bleeding beyond 14 days (or after hospital discharge, whichever was later) up to 6 months post-randomization. The **thromboembolic co-primary endpoint** was the composite of all-cause death, myocardial infarction, definite or probable ST, or ischemic stroke from the time of the procedure until 6 months post-randomization. Since both groups received the same antithrombotic regimen during the first 14 days following the procedure, bleeding events that occurred within this time were not considered for the bleeding co-primary endpoint. Thromboembolic events within 14 days of the procedure were considered in the thromboembolic co-primary endpoint as these events may have been influenced by the stent type used, which differed between the treatment groups. Detailed definitions of the study endpoints are provided in **Table A3** in the Appendix to this thesis. All primary and secondary endpoints were adjudicated and classified according to source data by members of the event adjudication committee, who were blinded to treatment allocation.

Follow-up and monitoring

Patients were followed up at 14 days (±2 days), 30 days (±7days), 6 months (±14 days), and 12 months (±28 days) either by office visit, telephone, or follow-up letter. Source data were solicited in case of potential endpoint–related adverse events. Throughout the study period patients were monitored for the occurrence of the following clinical events: death, myocardial

infarction, stent thrombosis, TLR (PCI or CABG) and stroke. In addition, they were monitored for the occurrence of bleeding or the need for transfusion of blood products.

Statistical analysis

Sample size calculation

To calculate the sample size for the bleeding co-primary endpoint at 6 months, BARC ≥2 bleeding incidences of 5.6% in patients assigned to DES plus 3-6 months DAPT and 2.1% in patients assigned to the COBRA PzF plus 14 days DAPT were assumed. Based on the reported bleeding events in the triple therapy group of the WOEST trial, a reduction of 15-20% was expected in the assumed incidence of bleeding beyond 14 days between the control group patients receiving 6-month DAPT (6%) and the control group patients receiving 3-month DAPT (5%) and it was expected that 60% of patients would be selected to receive 6 months of DAPT (101). Based on these assumptions, it was calculated that a sample size of 948 patients (474 in each treatment arm) would provide 80% power to reject the null hypothesis at a two-sided α-error level of 0.05, signifying that the treatment strategy utilizing COBRA PzF is superior to the use of an FDA-approved DES-based strategy with respect to BARC ≥2 bleeding. A total of 996 subjects were planned for enrollment to account for loss to follow-up, which was estimated to be approximately 5%. The null hypothesis for the bleeding co-primary endpoint stated that the COBRA PzF-based strategy is associated with a BARC class ≥2 bleeding rate equal to the DES-based strategy.

For the thromboembolic co-primary endpoint, a rate of 8.0% at 6 months was assumed in both groups. In the WOEST trial, the 12-month outcome of the thromboembolic events including target vessel revascularization (TVR) in the triple therapy arm was 17.6% or 14.8% without TVR. 32 (11.3%) events including TVR occurred at 6 months (101). Therefore, an assumption

of a thrombo-embolic event rate (death, myocardial infarction, definite and probable stent thrombosis, or ischemic stroke) of 8% at 6 months was considered appropriate. The assumption of a 5% non-inferiority margin was felt to be clinically meaningful and in keeping with the overall feasibility of trial conduct. The null hypothesis for the thromboembolic co-primary endpoint states that the rate of this endpoint in the COBRA PzF group exceeds that in the DES group by ≥ 5.0%. Assuming the true rate of the thromboembolic co-primary endpoint was 8.0% in both treatment groups, an evaluable sample size of 948 (474:474) was calculated to provide 88% power to reject the null hypothesis at a one-sided α-error level of 0.05, accounting for an estimated loss to follow-up of 5%. The minimum detectable margin with a sample size of 948 (474:474) patients, providing 80% power and a one-sided α-error level of 0.05, was calculated to be 4.4%.

Categorical variables are presented as counts and percentages and differences between groups were compared using Chi-squared or Fisher's exact test, as appropriate. Continuous variables are presented as means ±SD or medians (with 25^{th}-75^{th} percentiles) and differences between groups were compared using asymptotic or non-parametric methods, depending on the distribution of the analyzed variable. Analysis of the co-primary endpoints, the individual components of the co-primary endpoints and the secondary endpoints was performed according to the ITT principle: all subjects who signed the written informed consent and were randomized were included according to the treatment to which they were allocated, irrespective of protocol violations or continued participation in the study. A patient was considered to have adequate follow-up if they had an event or follow-up of ≥166 days, allowing for a visit window of 6 months ± 14 days. Analysis was also performed on the per-

protocol population, which was defined as subjects with procedural success and no major protocol violations.

For the bleeding co-primary endpoint, an assessment of the null and alternative hypotheses was carried out using the z-test for two binomial proportions at the one-sided 0.025 level of significance on the ITT subjects. The null hypothesis was rejected if the significance level of the z-test with pooled variance and no continuity correction was ≤0.025 and the bleeding rate in the COBRA-PzF arm was lower than in the DES arm. For the thromboembolic co-primary endpoint, an assessment of the null and alternative hypotheses was carried out using the Farrington and Manning test of non-inferiority for two binomial proportions with an additive non-inferiority margin of 5.0% at the 0.05 level of significance on the ITT subjects. The null hypothesis was rejected if the p-value of the Farrington and Manning one-sided test of non-inferiority was ≤0.05 and the composite endpoint rate in the COBRA-PzF arm was non-inferior to that in the DES arm. For the co-primary bleeding endpoint, the endpoint was reported starting from the day after discharge or 14 whichever is later, and for all patients with events to 180 days or follow-up of at least 166 days.

For the co-primary ischemic endpoint, the endpoint was reported for patients with at least 166 days of follow-up following the index procedure or with the study endpoint within 180 days post index procedure. Trial success was declared if the null hypotheses for both co-primary endpoints were rejected. The analysis of the co-primary endpoints described above was also repeated in the per-protocol population. The assessment of the two hypotheses was also carried out on all ITT patients by comparing time to each of the co-primary endpoints in the two study groups using the Kaplan-Meier method and the significance level of a log-rank test.

Pre-specified subgroup analysis for both the bleeding and thrombo-embolic co-primary endpoints was performed according to age, gender, diabetes status, history of stroke, history of bleeding, clinical presentation, indication for OAC, ejection fraction, proton pump inhibitor treatment, access site, renal function, treatment with coumadin derivatives or NOAC and number of major bleeding risk criteria as defined by the ARC-HBR consensus. For subgroup analyses, cox proportional hazards model were used and hazard ratios were calculated after accounting for center clustering effect.

4 RESULTS

4.1 THE EFFICACY AND SAFETY OF AGE- AND WEIGHT-ADAPTED DOSE OF PRASUGREL VERSUS STANDARD DOSE OF TICAGRELOR

This pre-specified analysis included 3997 patients of the ISAR-REACT 5 trial, of whom 1099 were aged 75 years or older or weighed less than 60 kg (elderly or low-weight group), and 2898 were younger than 75 years and weighed 60 kg or more (neither elderly nor low-weight group). Baseline clinical characteristics were well-matched between patients in the prasugrel and ticagrelor groups in both groups (**Table A4** in the Appendix to this thesis). Angiographic and procedural characteristics are presented in **Table A5**.

Clinical outcomes according to age and weight group

The efficacy endpoint (a composite of all-cause death, myocardial infarction, or stroke at 12 months after randomization) occurred in 148 patients in the elderly or low-weight group and 172 patients in the neither elderly nor low-weight group (Kaplan–Meier estimates of the efficacy endpoint, 13.7% and 6.0%, respectively; hazard ratio [HR]=2.37 [95% CI, 1.90–2.96]; $P < 0.001$). BARC type 3 to 5 bleeding occurred in 81 patients in the elderly or low-weight group and 93 patients in the neither elderly nor low-weight group (cumulative incidence accounting for competing risk, 9.4% and 3.8%, respectively; HR=2.82 [95%CI, 2.08–3.82]; $P < 0.001$). These data are presented in **Figure 3.**

Primary endpoint according to the study treatment group

Clinical outcomes according to the study drug among the 2 groups are shown in **Table 1.** In the elderly or low-weight group, the primary (efficacy) endpoint occurred in 68 patients assigned to prasugrel and 80 patients assigned to ticagrelor (cumulative incidence, 12.7% and 14.6%, respectively; HR=0.82 [95%CI, 0.60–1.14]; $P > 0.2$) (**Figure 4**). In the neither elderly nor

low-weight group, the primary endpoint occurred in 68 patients assigned to receive prasugrel and 104 patients assigned to receive ticagrelor (cumulative incidence, 4.8%, and 7.3%, respectively; HR=0.65 [95%CI, 0.48–0.88]; P = 0.006) **(Figure 4)**. No significant treatment effect-by-study group interaction with respect to the efficacy endpoint (*P* for interaction > 0.2) was observed.

Bleeding events according to the study treatment group

In the elderly or low-weight group, the safety endpoint of BARC type 3 to 5 bleeding occurred in 34 of 466 patients (8.1%) in the prasugrel group and 47 of 548 patients (10.6%) in the ticagrelor group (HR=0.72 [95%CI, 0.46–1.12]; *P* = 0.15; **Figure 5**). In the neither elderly nor low-weight group, BARC type 3 to 5 bleeding occurred in 45 of 1294 patients (3.7%) in the prasugrel group and 48 of 1433 patients (3.8%) in the ticagrelor group (HR=0.98 [95%CI, 0.65–1.47]; *P* > 0.2) (**Table 1** and **Figure 5**). There was no significant treatment effect-by-study group interaction with respect to the occurrence of BARC type 3 to 5 bleeding (*P* for interaction > 0.2).

BARC type 1 to 5 bleeding occurred in 124 patients assigned to receive prasugrel and 145 patients assigned to receive ticagrelor in the elderly or low-weight group (cumulative incidence accounting for competing risk, 29.5% and 32.9%, respectively; HR=0.81 [95%CI, 0.64–1.04]; *P* = 0.095). In the neither elderly nor low-weight group, the safety endpoint occurred in 239 patients in the prasugrel group and 201 patients in the ticagrelor group (cumulative incidence accounting for competing risk, 19.8% and 16.5%, respectively; HR=1.27 [95%CI, 1.05–1.53]; *P* =0.013). These data are shown in the Appendix, **Figure A1**. There was a significant treatment effect-by-study group interaction concerning the occurrence of BARC type 1 to 5 bleeding (*P* for interaction = 0.004).

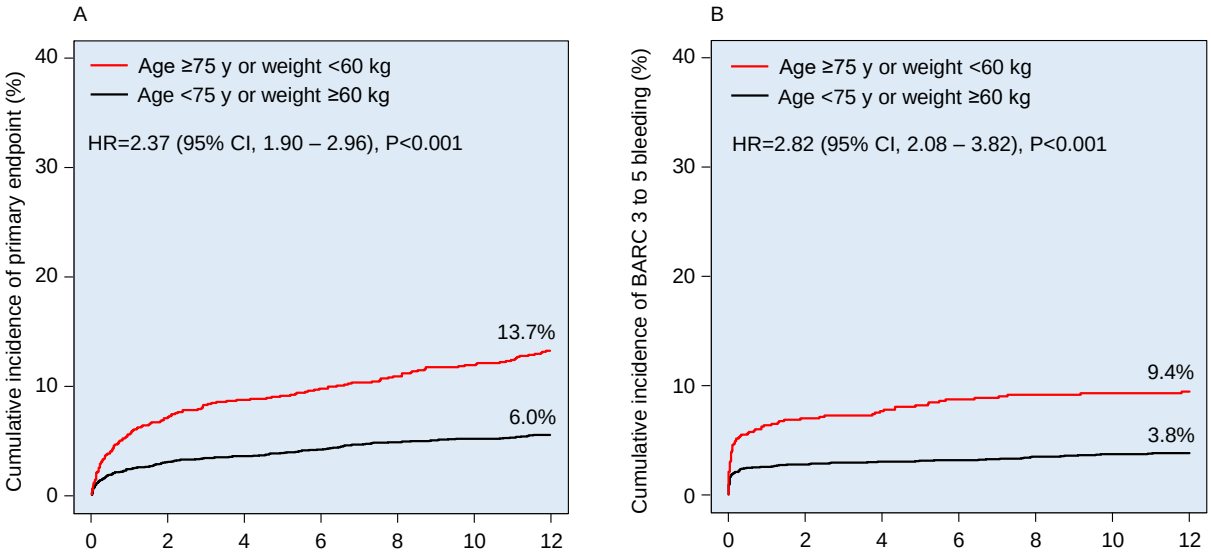

Figure 3. One-year cumulative incidence of the primary endpoint and the safety endpoint in the elderly or low-weight group and the neither elderly nor low-weight group

Left panel. Time-to-event curves of the primary endpoint (death, myocardial infarction, or stroke).

Right Panel. Time-to-event curves of the safety endpoint (BARC type 3 to 5 bleeding). BARC, Bleeding Academic Research Consortium; HR, hazard ratio. Figure adapted from (65).

Table 1. Clinical outcomes according to study drug and age and weight group

Characteristic	Elderly or Low-Weight (n=1099)				Neither Elderly nor Low-Weight (n=2898)			
	Prasugrel, 5mg (n=544)	**Ticagrelor, 180 mg** (n=555)	**Hazard Ratio [95% CI]**	*P* value	**Prasugrel, 10 mg** (n=1449)	**Ticagrelor, 180 mg** (n=1449)	**Hazard Ratio [95% CI]**	*P* value
Primary endpoint, n (%)								
Death, myocardial infarction, or stroke*	68 (12.7)	80 (14.6)	0.82 [0.60-1.14]	>0.2	68 (4.8)	104 (7.3)	0.65 [0.48-0.88]	0.006
Death*								
Overall	47 (8.8)	50 (9.2)	0.89 [0.60-1.33]	>0.2	25 (1.7)	40 (2.8)	0.64 [0.39-1.05]	0.079
Cardiovascular	36	33			22	30		
Non-cardiovascular	11	17			3	10		
Myocardial infarction†								
Overall	22 (4.0)	33 (6.0)	0.66 [0.38-1.13]	0.132	38 (2.7)	63 (4.4)	0.59 [0.40-0.89]	0.011
STEMI	6	10			8	21		
Stroke†								
Overall	7 (1.3)	10 (1.8)	0.70 [0.26-1.85]	>0.2	12 (0.8)	12 (0.8)	0.99 [0.44-2.21]	>0.2
Stent thrombosis, n/N (%)†								
Definite or probable	10 (1.8)	6 (1.1)	1.71 [0.62-4.72]	0.30	10 (0.7)	20 (1.4)	0.50 [0.23-1.06]	0.072
Definite	5 (0.9)	4 (0.7)	1.29 [0.34-4.82]	>0.2	7 (0.5)	18 (1.2)	0.38 [0.16-0.92]	0.032
Safety endpoint, n/N (%)								
BARC type 3-5 bleeding†‡	34/466 (8.1)	47/548 (10.6)	0.72 [0.46-1.12]	0.15	45/1294 (3.7)	48/1433 (3.8)	0.98 [0.65-1.47]	>0.2
BARC type 1-5 bleeding†‡	124/473 (29.5)	145/550 (32.9)	0.81 [0.64-1.04]	0.095	239/1303(19.8)	201/1433(16.5)	1.27 [1.05-1.53]	0.013
Type 1	59	61			137	99		
Type 2	31	37			57	54		
Type 3a	18	24			23	23		
Type 3b	12	15			18	17		
Type 3c	0	3			2	1		
Type 4	2	4			0	4		
Type 5a	0	1			0	0		
Type 5b	2	0			2	3		

BARC indicates Bleeding Academic Research Consortium; STEMI, ST-segment elevation myocardial infarction.

* One-year cumulative incidence (%). † One-year cumulative incidence accounting for competing risk.

‡ Analyzed in a modified intention-to-treat population, which included patients with at least 1 application of the study drug. Patients were assessed for up to 1 week after drug discontinuation. Table adapted from (65).

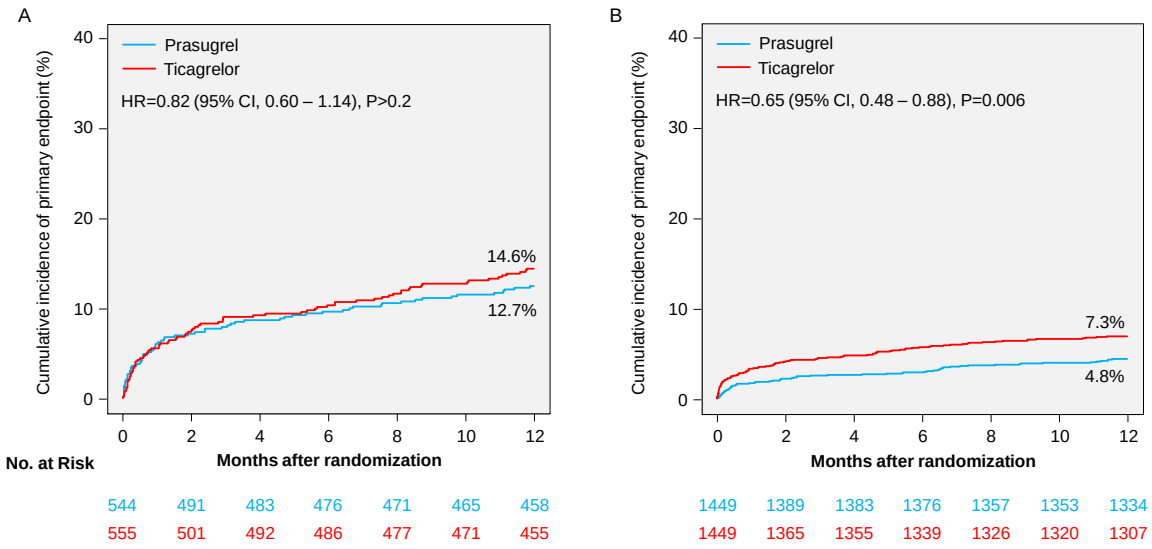

Figure 4. One-year cumulative incidence of the primary endpoint according to study drug in the elderly or low-weight group, and the neither elderly nor low-weight group

Panel A. Time-to-event curves of the primary endpoint in the elderly or low-weight group. **Panel B**. Time-to-event curves of the primary endpoint in the neither elderly nor low-weight group. HR indicates hazard ratio; 95% CI, confidence interval. Adapted from (65).

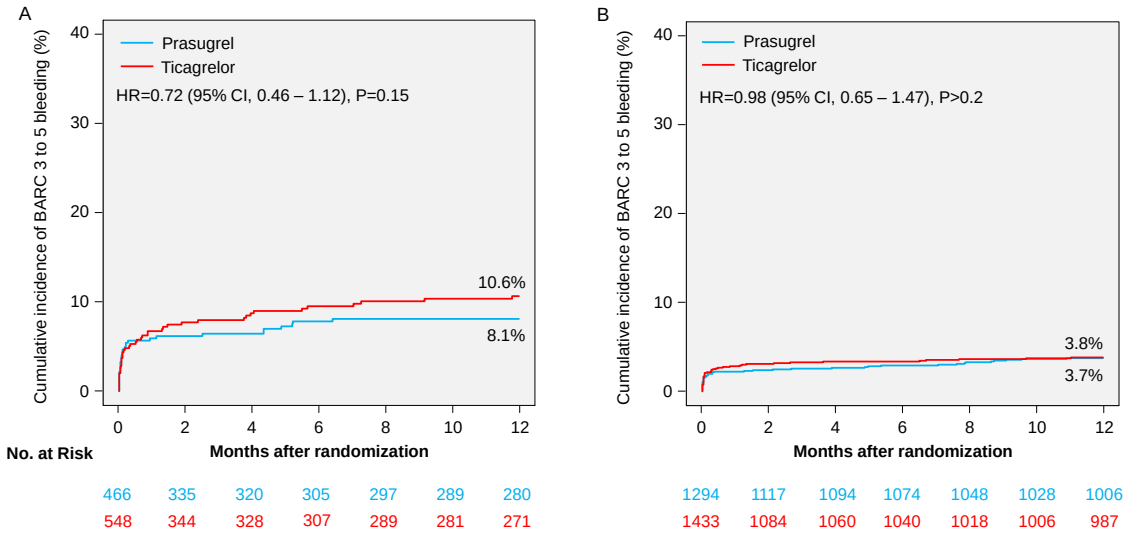

Figure 5. One-year cumulative incidence of the safety endpoint according to study drug in the elderly or low-weight group, and the neither elderly nor low-weight group

Panel A. Time-to-event curves of the safety endpoint in the elderly or low-weight group. **Panel B.** Time-to-event curves of the safety endpoint in the neither elderly nor low-weight group. HR indicates hazard ratio; 95% CI, confidence interval. Adapted from (65).

4.2 PRE-ADMISSION ANTIPLATELET THERAPY AND THE EFFICACY AND SAFETY OF TICAGRELOR VS. PRASUGREL

This study included all patients enrolled in the ISAR-REACT 5 trial (n=4018). Patients were divided into two groups: the group with pre-admission aspirin and/or clopidogrel (*n* = 1455) and the group with no pre-admission aspirin or clopidogrel (*n* = 2563). The study flowchart is displayed in **Figure A2**.

Baseline data and outcomes according to pre-admission antiplatelet therapy

In the group on pre-admission aspirin and/or clopidogrel, 1413 patients were on aspirin (1260 patients on aspirin only), 195 patients were on clopidogrel (42 patients on clopidogrel only), and 153 patients were on both drugs in the pre-admission period. Baseline data of patient groups according to pre-admission antiplatelet therapy status are shown in **Table A6**. Patients in the pre-admission aspirin and/or clopidogrel group were older and had a worse cardiovascular risk profile. Specifically, they were more likely to have diabetes mellitus, arterial hypertension, and prior revascularization procedures. With regard to diagnosis at admission, patients of the pre-admission aspirin and/or clopidogrel group presented less often with STEMI and underwent less often PCI compared with patients of the no pre-admission aspirin or clopidogrel group.

The primary endpoint (death, MI, or stroke) at 12 months after randomization occurred in 150 patients in the pre-admission aspirin and/or clopidogrel group and 171 patients in the no pre-admission aspirin or clopidogrel group (cumulative incidence 10.5% and 6.7%, respectively; HR=1.58 [95% CI, 1.27–1.96]; **Figure 6A**). BARC type 3–5 bleeding occurred in 82 patients in the pre-admission aspirin and/or clopidogrel group and 144 patients in the no pre-admission aspirin or clopidogrel group (cumulative incidence accounting for competing risk 5.7% and 5.7%; HR=1.01 [95% CI, 0.77–1.33]; **Figure 6B**).

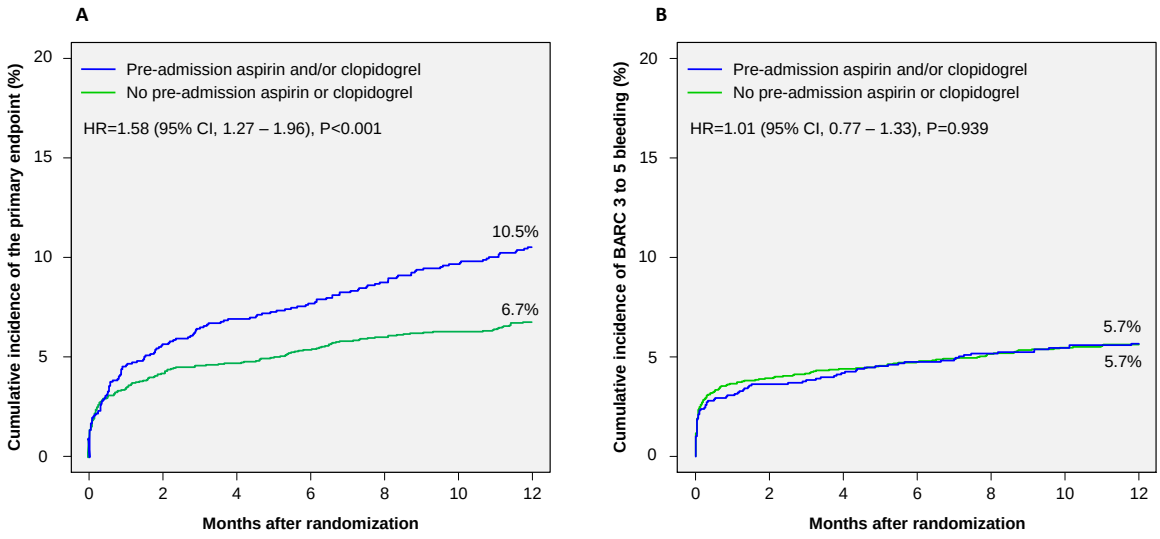

Figure 6. Cumulative incidence of the primary endpoint (*A*) and safety endpoint (*B*) at 1 year according to pre-admission therapy with aspirin and/or clopidogrel

The cumulative incidence of the primary endpoint—a composite of death, myocardial infarction, or stroke—was evaluated in the intention-to-treat population. The cumulative incidence of the secondary safety endpoint was assessed in the intention-to-treat population after accounting for the competing risk of death. BARC, Bleeding Academic Research Consortium type 3–5 bleeding; CI, confidence interval; and HR, hazard ratio (121).

Baseline data according to study drugs

In the pre-admission aspirin and/or clopidogrel group, 717 patients were randomized to ticagrelor and 738 patients to prasugrel. In the no preadmission aspirin or clopidogrel group, 1295 patients were randomized to ticagrelor and 1268 patients to prasugrel. Baseline data according to the study drug are presented in **Table 2**. Data were well-balanced between patients assigned to ticagrelor and prasugrel in either group.

Angiographic and procedural data according to study drugs

Angiographic and procedural characteristics are shown in **Table A7**. No significant differences in terms of access site, number of diseased coronary arteries, or left ventricular ejection fraction were observed between ticagrelor- and prasugrel-assigned patients in either of the groups. Drug therapy at discharge is shown in **Table A8**. In the no pre-admission aspirin or

clopidogrel group, patients in the prasugrel group were more often discharged on clopidogrel (*P*=0.028) and oral anticoagulant drugs (*P*=0.038) compared with patients in the ticagrelor group.

Clinical outcomes according to study drugs

Clinical outcomes are shown in **Table 3**. In the pre-admission aspirin and/or clopidogrel group, the **primary endpoint** occurred in 81 patients (11.5%) in the ticagrelor group and 69 patients (9.5%) in the prasugrel group (HR=1.23 [95%CI, 0.89–1.69]; **Figure 7A**). In the no pre-admission aspirin or clopidogrel group, the **primary endpoint** occurred in 103 patients (8.0%) in the ticagrelor group and 68 patients (5.4%) in the prasugrel group (HR=1.50 [95% CI, 1.10–2.03]; **Figure 7B**). There was no significant treatment-arm-by-pre-admission antiplatelet therapy interaction regarding the primary endpoint (*P* for interaction = 0.38).

In the pre-admission aspirin and/or clopidogrel group, **BARC type 3–5 bleeding** occurred in 35 patients assigned to ticagrelor and 26 patients assigned to prasugrel (cumulative incidence accounting for competing risk 6.2% and 4.5%, respectively; HR=1.30 [95% CI, 0.79–2.17]). In the no pre-admission aspirin or clopidogrel group, **BARC type 3–5 bleeding** occurred in 60 patients in the ticagrelor group and 54 patients in the prasugrel group (cumulative incidence accounting for competing risk 5.3% and 5.1%, respectively; HR=1.07 [95%CI, 0.74–1.55]). Kaplan–Meier curves are presented in **Figure 8**. No significant treatment-arm-by-pre-admission antiplatelet therapy interaction was found regarding the secondary (safety) endpoint (*P* for interaction = 0.54).

Table 2. Baseline characteristics according to study drug and pre-admission antiplatelet therapy

Characteristic	Pre-admission aspirin and/or clopidogrel (n=1455)			No pre-admission aspirin or clopidogrel (n=2563)		
	Ticagrelor (n=717)	**Prasugrel** (n=738)	P value	**Ticagrelor** (n=1295)	**Prasugrel** (n=1268)	P value
Age (years)	70.0 [61.0-77.0]	70.0 [61.0-78.0]	0.40	62.0 [53.0-72.0]	61.0 [54.0-71.0]	0.60
Sex			>0.99			0.98
Female, no. (%)	162 (22.6)	167 (22.6)		316 (24.4)	311 (24.5)	
Diabetes, no. (%)	242 (33.8)	219/737 (29.7)	0.11	221/1294 (17.1)	210 (16.6)	0.77
Smoking, no. (%)	178/714 (24.9)	184 (25.0)	>0.99	504/1288 (39.1)	483/1264 (38.2)	0.66
Arterial hypertension, no. (%)	637 (88.8)	639/737 (86.7)	0.24	795/1291 (61.6)	745/1266 (58.8)	0.17
Hypercholesterolemia, no. (%)	562 (78.4)	570/737 (77.3)	0.68	616/1290 (47.8)	593/1266 (46.8)	0.67
Prior myocardial infarction, no. (%)	265/716 (37.0)	274 (37.1)	>0.99	46/1294 (3.6)	46/1267 (3.6)	>0.99
Prior PCI, no. (%)	405 (56.5)	415/736 (56.4)	>0.99	48/1294 (3.7)	48 (3.8)	>0.99
Prior CABG, no. (%)	99 (13.8)	110/737 (14.9)	0.59	16/1294 (1.2)	20 (1.6)	0.57
Cardiogenic shock, no. (%)	10 (1.4)	14 (1.9)	0.59	21 (1.6)	20 (1.6)	>0.99
Systolic blood pressure (mmHg)	142 [129-160]	140 [125-160]	0.27	140 [127-160]	140 [126-160]	0.81
Diastolic blood pressure (mmHg)	80.0 [70.0-87.8]	80.0 [70.0-89.0]	0.87	80.0 [75.0-91.0]	80.0 [75.0-90.0]	0.77
Heart rate (beats/min)	73.0 [65.0-84.0]	73.0 [64.0-82.0]	0.32	76.0 [67.0-88.0]	75.0 [67.0-86.0]	0.23
Body mass index (kg/m²)	27.4 [24.8-30.1]	27.6 [25.1-30.4]	0.35	27.1 [24.7-30.0]	27.0 [24.7-29.8]	0.70
Weight <60 kg, no. (%)	40/714 (5.6)	34/733 (4.6)	0.48	68/1289 (5.3)	60/1255 (4.8)	0.63
Creatinine (µmol/L)	86.6 [72.5-105]	88.4 [74.3-106]	0.33	81.3 [70.7-95.0]	79.6 [69.8-93.7]	0.25
Diagnosis at admission			0.20			0.29
Unstable angina, no. (%)	160 (22.3)	190 (25.7)		89 (6.9)	71 (5.6)	
NSTEMI, no. (%)	377 (52.6)	356 (48.2)		553 (42.7)	569 (44.9)	
STEMI, no. (%)	180 (25.1)	192 (26.0)		653 (50.4)	628 (49.5)	
Coronary angiography, no. (%)	714 (99.6)	734 (99.5)	>0.99	1289 (99.5)	1267 (99.9)	0.13
Treatment strategy, no.(%)			0.72			0.38
PCI	573/715 (80.1)	597/737 (81.0)		1103/1293 (85.3)	1104 (87.1)	

CABG	19/715 (2.7)	15/737 (2.0)		28/1293 (2.2)	21 (1.7)
Conservative	123/715 (17.2)	125/737 (17.0)		162/1293 (12.5)	143 (11.3)
Aspirin on admission	698 (97.4)	715 (96.9)	0.71	0	0
Clopidogrel on admission	100 (13.9)	95 (12.9)	0.60	0	0

Data are shown as counts [proportion (%)] or median with 25th-75th percentiles.

Missing continuous data:

Pre-admission aspirin and/or clopidogrel: diastolic blood pressure, 6 patients (3 in each group); body mass index, 8 patients (3 in the ticagrelor group, 5 in the prasugrel group).

No pre-admission aspirin or clopidogrel: systolic blood pressure, 3 patients (1 in the ticagrelor group, 2 in the prasugrel group); diastolic blood pressure, 10 patients (4 in the ticagrelor group, 6 in the prasugrel group); heart rate, 2 patients (1 in each group), body mass index, 23 patients (9 in the ticagrelor group, 14 in the prasugrel group).

The remaining continuous data were complete. CABG, coronary artery bypass grafting; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. Adapted from (121).

Table 3. Clinical outcomes according to study drug and pre-admission antiplatelet therapy

Outcome	**Pre-admission aspirin and/or clopidogrel** (n=1455)			**No pre-admission aspirin or clopidogrel** (n=2563)			P for interaction
	Ticagrelor (n=717)	**Prasugrel** (n=738)	**HR (95% CI)**	**Ticagrelor** (n=1295)	**Prasugrel** (n=1268)	**HR (95% CI)**	
Primary endpoint – (death, MI, or stroke)	81 (11.5)	69 (9.5)	1.23 (0.89-1.69)	103 (8.0)	68 (5.4)	1.50 (1.10-2.03)	0.38
Death	39 (5.6)	35 (4.8)	1.16 (0.73-1.83)	51 (4.0)	38 (3.0)	1.31 (0.86-2.00)	0.69
Myocardial infarction	44 (6.3)	32 (4.4)	1.44 (0.92-2.28)	52 (4.0)	28 (2.2)	1.83 (1.16-2.90)	0.47
Stroke	6 (0.9)	9 (1.2)	0.69 (0.25-1.93)	16 (1.2)	10 (0.8)	1.57 (0.71-3.45)	0.22
Definite or probable stent thrombosis	5 (0.7)	9 (1.2)	0.57 (0.19-1.71)	21 (1.6)	11 (0.9)	1.87 (0.90-3.88)	0.078
Definite stent thrombosis	5 (0.7)	6 (0.8)	0.86 (0.26-2.82)	17 (1.3)	6 (0.5)	2.78 (1.09-7.05)	0.13
BARC type 3 to 5 bleeding	35/706 (6.2)	26/631 (4.5)	1.30 (0.79-2.17)	60/1283 (5.3)	54/1142 (5.1)	1.07 (0.74-1.55)	0.54

Data are numbers of events with Kaplan-Meier estimates (%) for the primary endpoint and death or cumulative incidence (%) after accounting for the competing risk of death for the remaining endpoints.

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction. Adapted from (121).

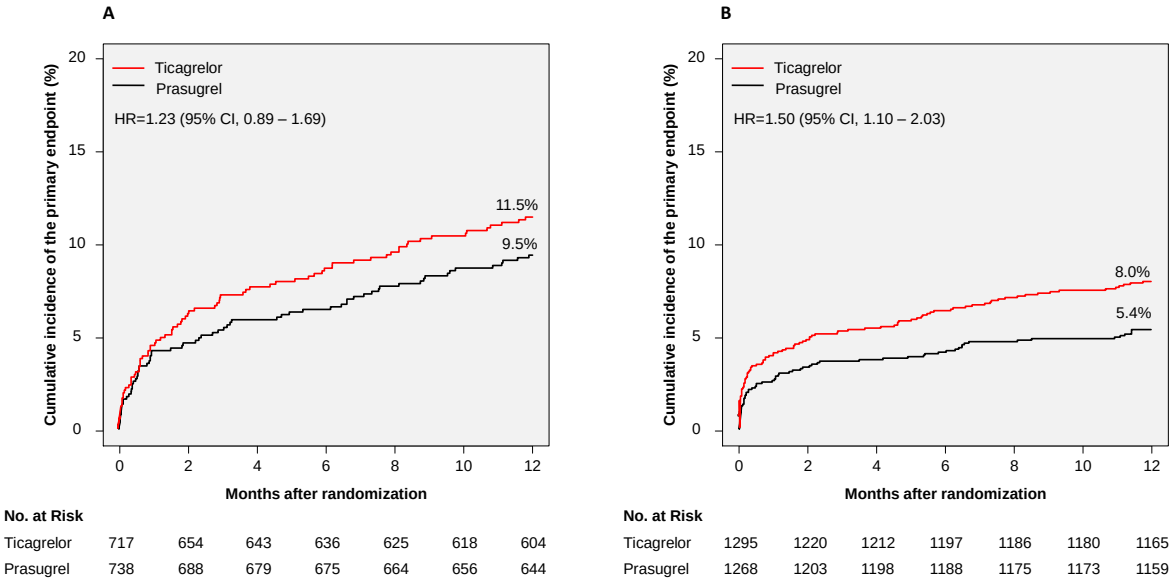

Figure 7. Cumulative incidence of the primary endpoint at 1 year according to study drug and pre-admission antiplatelet therapy

The Kaplan-Meier curves show the one-year cumulative incidence of the primary endpoint (composite of death, myocardial infarction, or stroke) in the ticagrelor and prasugrel groups in **(A)** pre-admission aspirin and/or clopidogrel group and **(B)** no pre-admission aspirin or clopidogrel group. The primary endpoint was evaluated in the intention-to-treat population (121).

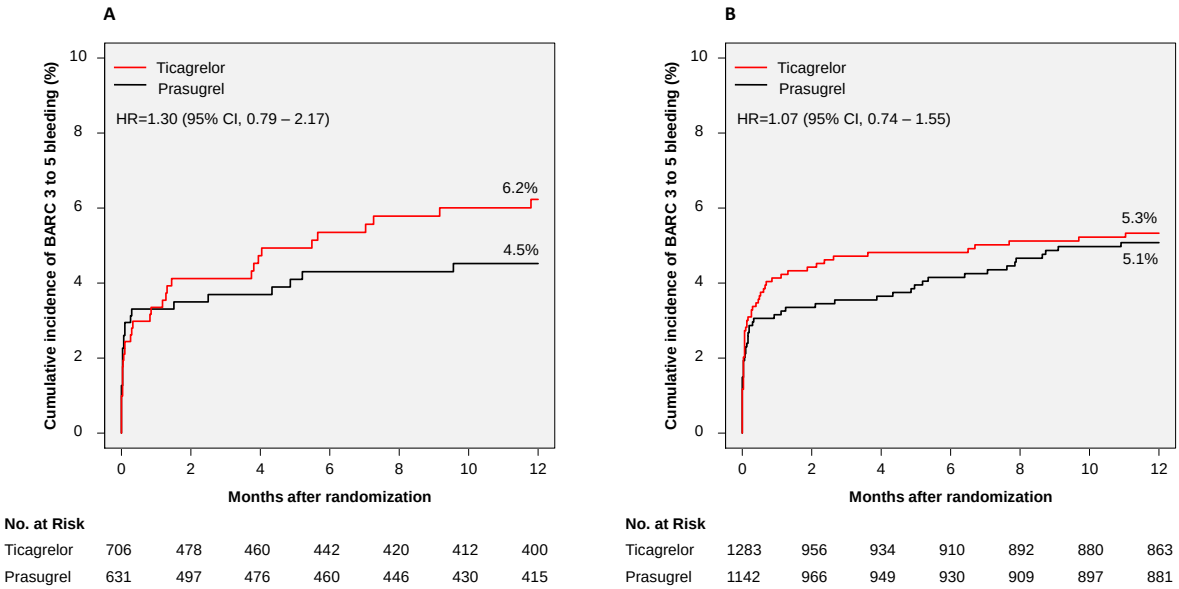

Figure 8. Cumulative incidence of the safety endpoint at 1 year according to study drug and pre-admission antiplatelet therapy

The Kaplan-Meier curves show the cumulative incidence of the safety endpoint BARC type 3-5 bleeding in the ticagrelor and prasugrel groups in **(A)** pre-admission aspirin and/or clopidogrel group and **B)** no pre-admission aspirin or clopidogrel group. BARC type 3-5 bleeding was evaluated in the modified intention-to-treat population after accounting for the competing risk of death. BARC, Bleeding Academic Research Consortium; CI, confidence interval; and HR, hazard ratio (121).

4.3 HIGH BLEEDING RISK STATUS AND THE EFFICACY AND SAFETY OF TICAGRELOR VERSUS PRASUGREL

This analysis included 3239 patients who underwent PCI in the ISAR-REACT 5 trial (80.6% of the overall trial population). Patients were divided into the HBR group (n=486) and the non-HBR group (n=2753) based on the fulfillment of ARC-HBR criteria.

Baseline, angiographic, and procedural characteristics according to HBR status

Patients in the HBR group were significantly older, more frequently women, and more likely to have cardiovascular risk factors such as diabetes mellitus, history of prior MI, or prior coronary revascularization. In addition, they were more likely to have worse renal function and a history of cardiogenic shock. With regard to diagnosis at admission, patients in the HBR group presented more frequently with unstable angina and NSTEMI compared with patients in the non-HBR group. Baseline data are presented in **Table 4.** Additionally, patients with HBR were more likely to have complex CAD and reduced left ventricular ejection fraction compared with patients without HBR. Angiographic, procedural data, and drug therapy at discharge are displayed in **Tables A9 and A10** in the Appendix to this thesis.

Clinical outcomes according to HBR status

The composite of death, myocardial infarction, or stroke occurred in 99 of 486 patients in the HBR group and 171 of 2753 patients in the non-HBR group (cumulative incidence: 20.6% vs. 6.3%, respectively; HR=3.57 [95% CI, 2.79–4.57], p<0.001; **Figure A3**). BARC type 3 to 5 bleeding at 12 months occurred in 61 of 486 patients in the HBR group and 127 of 2753 patients in the non-HBR group (cumulative incidence after accounting for the competing risk of death: 12.7% vs. 4.6%, respectively; HR=2.94 [95%CI, 2.17–3.99], p<0.001; **Figure A4**). The one-year incidence of MI was significantly higher in the HBR group compared with the non-HBR group (cumulative incidence after accounting for the competing risk of

death: 7.7% vs. 3.6%, respectively; HR=2.30 [95%CI, 1.57–3.35], p<0.001; **Table 5)**. The full list of the endpoints is presented in **Table 5.**

Table 4. Baseline characteristics according to HBR status

Characteristic	HBR (N=486)	Non-HBR (N=2753)	*P* value
Age, y	79.0 [75.0-83.0]	62.0 [54.0-70.0]	<0.001
Sex			<0.001
Female, n (%)	162 (33.3)	518 (18.8)	
Male, n (%)	324 (66.7)	2235 (81.2)	
Diabetes, n (%)	160/485 (33.0)	558 (20.3)	<0.001
Smoking, n (%)	60/481 (12.5)	1072/2745 (39.1)	<0.001
Arterial hypertension, n (%)	409/484 (84.5)	1836/2750 (66.8)	<0.001
Hypercholesterolemia, n (%)	318/484 (65.7)	1568/2750 (57.0)	<0.001
Prior myocardial infarction, n (%)	120 (24.7)	389/2751 (14.1)	<0.001
Prior PCI, n (%)	170/485 (35.1)	562/2751 (20.4)	<0.001
Prior CABG, n (%)	62 (12.8)	137/2751 (5.0)	<0.001
Cardiogenic shock, n (%)	23 (4.7)	39 (1.4)	<0.001
Systolic blood pressure, mmHg	140 [124-160]	140 [127-160]	0.49
Diastolic blood pressure, mmHg	79.0 [70.0-85.0]	80.0 [74.0-90.0]	<0.001
Heart rate, beats/min	73.0 [65.0-84.0]	75.0 [66.0-85.0]	0.073
Body mass index, kg/m²	26.6 [24.2-29.4]	27.3 [24.9-30.0]	0.001
Weight <60 kg, n (%)	28/482 (5.8)	114/2733 (4.2)	0.14
Creatinine, µmol/L	111 [90.4-133]	79.6 [70.7-92.8]	<0.001
Diagnosis at admission			<0.001
Unstable angina, n (%)	56 (11.5)	217 (7.9)	
NSTEMI, n (%)	261 (53.7)	1258 (45.7)	
STEMI, n (%)	169 (34.8)	1278 (46.4)	
Aspirin on admission	263 (54.1)	845 (30.7)	<0.001
Clopidogrel on admission	42 (8.6)	100 (3.6)	<0.001
Hemoglobin on admission, g/dL	12.8 [11.7-14.2]	14.7 [13.8-15.6]	<0.001
Thrombocyte count, x 10^9/L	216 [176-261]	224 [189-265]	0.001
eGFR, ml/min/1.73 m²	50.5 [41.0-58.1]	84.6 [71.5-95.1]	<0.001
ARC-HBR criteria			
Major criteria			
eGFR <30 ml/min/1.73 m²	54 (11.1)	-	<0.001
Hemoglobin <11 g/dL*	67 (13.9)	-	<0.001
Thrombocyte count <100 x 10^9/L, n (%)	17 (3.5)	-	<0.001
Minor criteria			
Age ≥75 y	403 (82.9)	385 (14.0)	<0.001
eGFR 30-59 ml/min/1.73 m²	321 (66.0)	202 (7.3)	<0.001
Hemoglobin, (g/dL) 11-12.9 for men,	124/481 (25.8) for men	102 (3.7) for men	<0.001
11-11.9 for women	41 (8.4) for women	21 (0.8) for women	<0.001
Long-term use of NSAIDs or steroids	6 (1.2)	7 (0.3)	0.007

Data are median with 25th–75th percentiles or counts (%). Missing continuous data: HBR group: systolic blood pressure, 1 patient; diastolic blood pressure, 2 patients; heart rate, 1 patient; body mass index, 4 patients. Non-HBR group: systolic blood pressure, 2 patients; diastolic blood pressure, 9 patients; heart rate, 1 patient; and body mass index, 24 patients. ARC indicates Academic Research Consortium; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; non-HBR, non-high bleeding risk; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction. *Patients with hemoglobin values <10 g/dL were excluded from the primary trial at the time of screening of patients for inclusion in the study. Table adapted from (123).

Table 5. Clinical outcomes according to HBR status

Outcome	HBR (N=486)	Non-HBR (N=2753)	HR [95% CI]	*P* value
Primary endpoint (death, MI, or stroke)	99 (20.6)	171 (6.3)	3.57 [2.79–4.57]	<0.001
Death	64 (13.3)	74 (2.7)	5.22 [3.73–7.29]	<0.001
Myocardial infarction	37 (7.7)	99 (3.6)	2.30 [1.57–3.35]	<0.001
Stroke	7 (1.5)	21 (0.8)	1.98 [0.84–4.65]	0.12
Definite or probable stent thrombosis	11 (2.3)	32 (1.2)	2.02 [1.02–4.02]	0.044
Definite stent thrombosis	7 (1.4)	25 (0.9)	1.64 [0.71–3.80]	0.25
BARC type 3-5 bleeding*	61 (12.7)	127 (4.6)	2.94 [2.17–3.99]	<0.001

Data are number of events with Kaplan-Meier estimates (%) for the primary endpoint and death, or cumulative incidence (%) after accounting for the competing risk of death for the remaining endpoints.

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio; MI, myocardial infarction; Non-HBR, non-high bleeding risk. *BARC type 3 to 5 bleeding was analyzed in the intention-to-treat population. Table adapted from (123).

Landmark analysis

To assess the risk of early and late outcomes (efficacy and safety outcomes), we performed a landmark analysis using the 30-day time point as a landmark. There was a consistent increase in the risk for the primary (efficacy) endpoint within the first 30 days (HR=3.89 [95%CI, 2.73–5.55]) and from 30 days to 12 months (HR=3.29 [95%CI, 2.32–4.65]) (**Figure A5, left panel**) and the risk for the secondary (safety) endpoint within the first 30 days (HR=2.89 [95%CI, 1.96–4.27]) and from 30 days to one year (HR=3.02 [95%CI, 1.85–4.96]) (**Figure A5, right panel**) in patients with HBR compared with patients without HBR.

Baseline characteristics according to study drug and HBR status

In the HBR group, 230 patients were randomized to ticagrelor, and 256 patients to prasugrel. In the non-HBR group, 1375 patients were randomized to ticagrelor and 1378 patients to prasugrel. Baseline clinical features, angiographic and procedural data according to HBR status and assigned study drug are displayed in **Tables A11 and A12**, respectively. Clinical and demographic data and angiographic/procedural characteristics were well-balanced between patients assigned to ticagrelor and prasugrel within the HBR and non-HBR groups.

Clinical outcomes according to study drug in patients with and without HBR

Primary (efficacy) endpoint

In patients in the HBR group, the composite of death, myocardial infarction, or stroke (primary efficacy endpoint) occurred in 49/230 patients assigned to ticagrelor and 50/256 patients assigned to prasugrel (cumulative incidence: 21.5% vs. 19.8%, respectively; HR=1.09 [95%CI, 0.73–1.62]; **Figure 9A**). ***In patients in the non-HBR group***, the primary endpoint occurred in 105/1375 patients assigned to ticagrelor and 66/1378 patients assigned to prasugrel (cumulative incidence: 7.7% vs. 4.9%, respectively; HR=1.62 [95%CI, 1.19–2.20]; **Figure 9B**).

Secondary (safety) endpoint

In patients in the HBR group, BARC type 3-5 bleeding occurred in 25/229 patients assigned to ticagrelor and 23/245 patients assigned to prasugrel (cumulative incidences: 12.1% vs. 10.3%, respectively; HR=1.18 [95% CI, 0.67–2.08]; **Figure 10A**). ***In patients in the non-HBR group***, BARC type 3-5 bleeding occurred in 56/1373 patients assigned to ticagrelor and 52/1368 patients assigned to prasugrel (cumulative incidences: 4.3% vs. 4.0%, respectively; HR=1.08 [95%CI, 0.74–1.58]; **Figure 10B**). No significant interaction between the treatment arm and HBR status with respect to the primary (*P* for interaction=0.12) or secondary (*P* for interaction =0.80) endpoints was found.

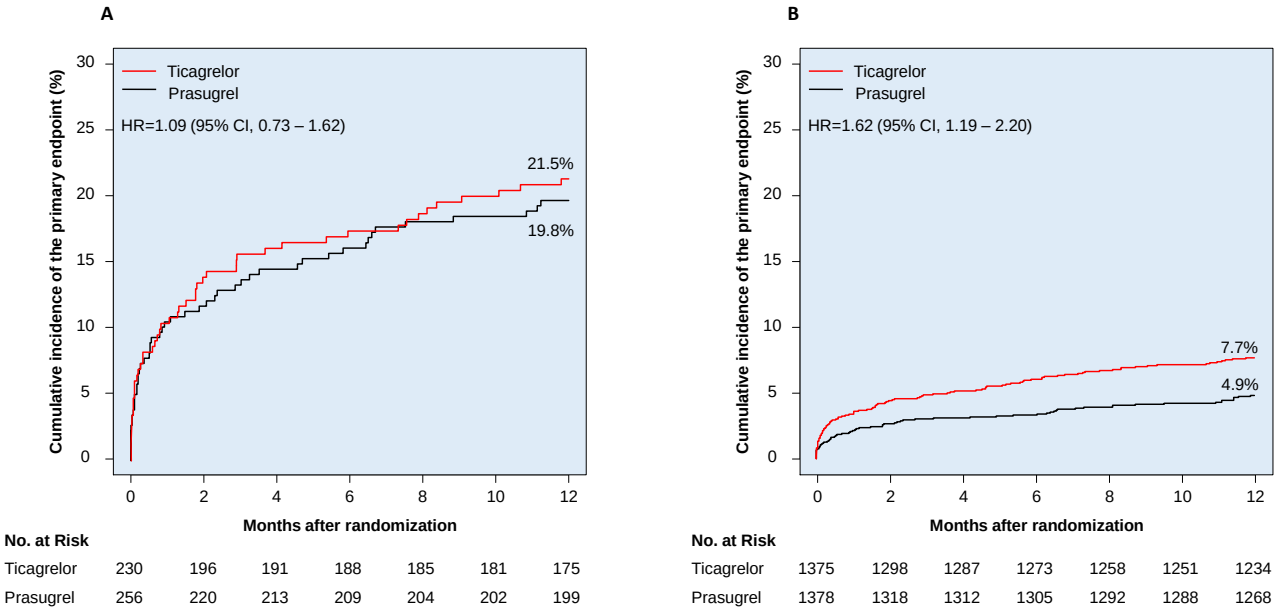

Figure 9. One-year cumulative incidence of the primary endpoint according to study group and high bleeding risk status

Panel A. Time-to-event curves of the primary endpoint in the group with high bleeding risk (HBR). **Panel B.** Time-to-event curves of the primary endpoint in the non-HBR group. The primary endpoint was assessed in the intention-to-treat population. HR indicates hazard ratio. Figure adapted from (123).

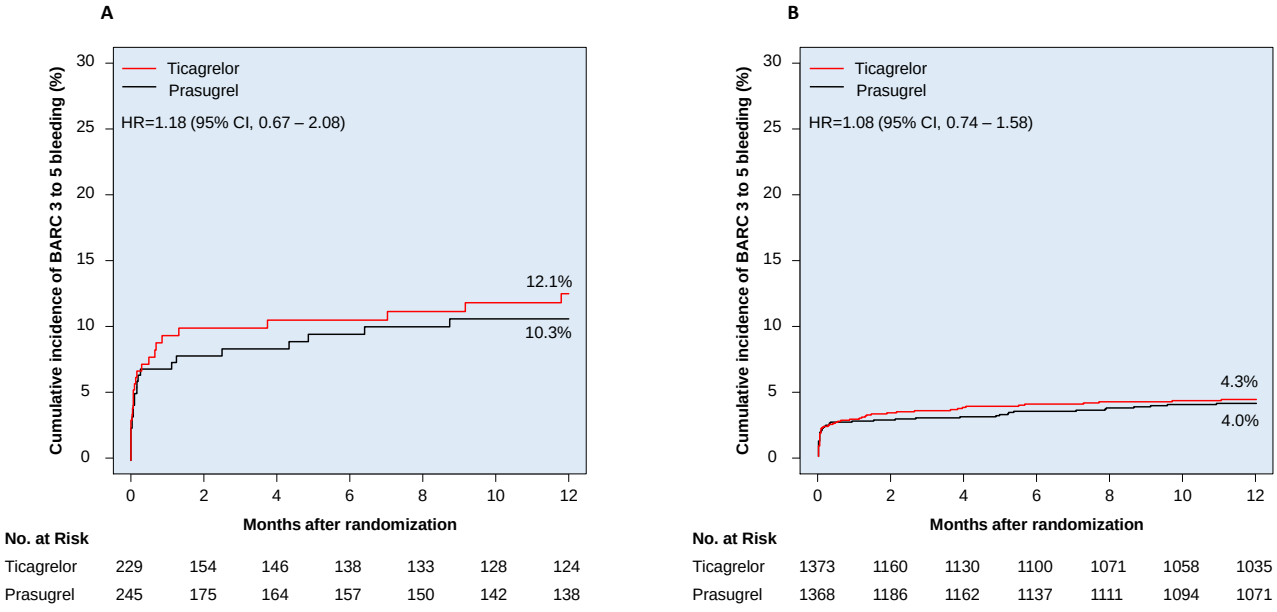

Figure 10. One-year cumulative incidence of the safety endpoint according to study group and high bleeding risk status

Panel A. Time-to-event curves of the safety endpoint in the group with high bleeding risk (HBR). **Panel B.** Time-to-event curves of the safety endpoint in the non-HBR group. Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding was evaluated in the modified intention-to-treat population after accounting for the competing risk of death. HR indicates hazard ratio. Figure adapted from (123).

ARC-HBR Score

The average ARC-HBR score was 2.35±0.59 in the HBR group and 0.26±0.44 in the non-HBR group (P<0.001). The C statistic, calculated to assess the discriminatory power of the HBR score for the primary efficacy endpoint was 0.614, while the C statistic for the secondary safety endpoint was 0.592.

A visual summary of the main findings of this analysis is presented in **Figure 11.**

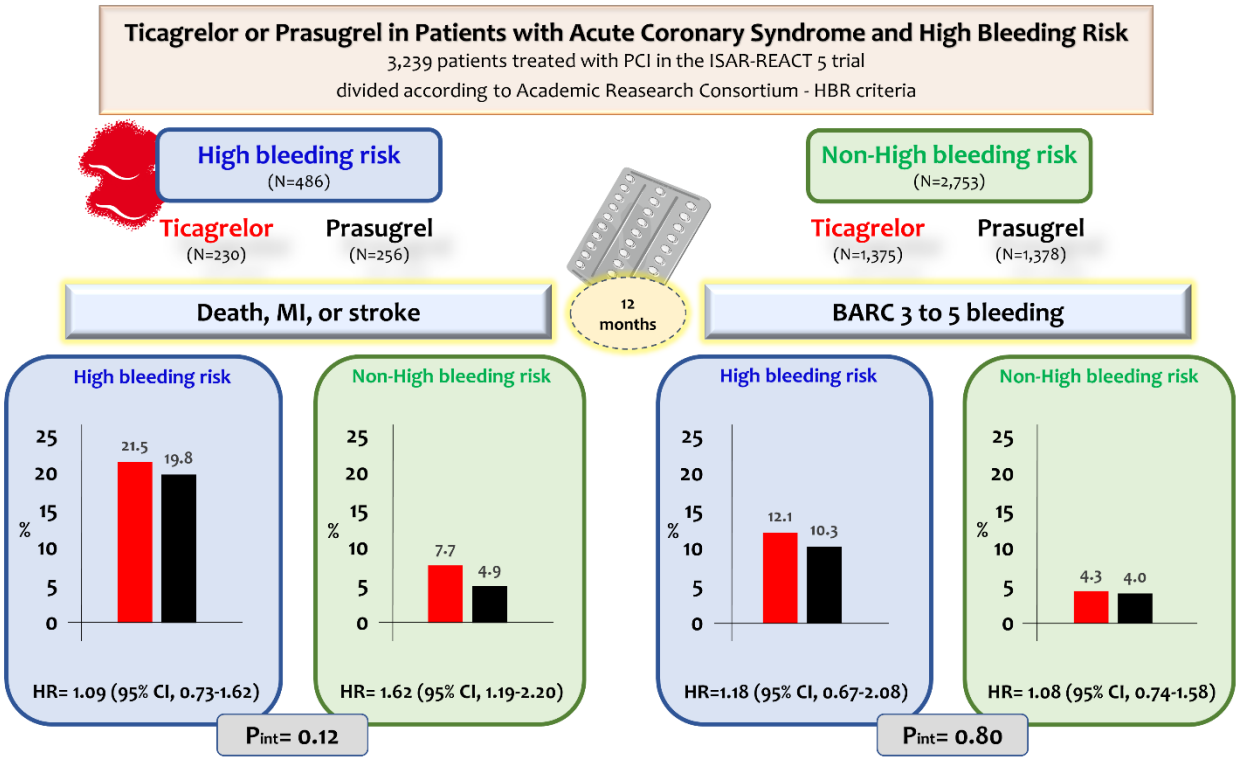

Figure 11. Study flowchart and the 12-month incidence of the primary (efficacy) and secondary (safety) endpoints according to study drug and high bleeding risk status

Figure adapted from (123).

4.4 THE EFFICACY AND SAFETY OF TICAGRELOR VERSUS PRASUGREL ACCORDING TO SMOKING STATUS

This part of the thesis represents a subgroup analysis pre-specified in the ISAR-REACT 5 trial protocol. This analysis included 4001 patients with available smoking status data. Patients were categorized into smokers (N=1349) and nonsmokers (N=2652).

Baseline and outcome data according to smoking status

Baseline, angiographic, and procedural data in smokers and nonsmokers are shown in **Tables A13 and A14**, respectively. In the smokers' group, **the primary endpoint** (composite of all-cause death, stroke, or myocardial infarction) at one year after randomization occurred in 88 patients, whereas in the non-smokers' group in 227 patients (cumulative incidence 6.6% and 8.7%, respectively; HR=0.76 [95%CI, 0.59–0.97]; *P*=0.029). **BARC type 3 to 5 bleeding** occurred in 60 patients in the group of smokers and 112 patients in the group of nonsmokers (cumulative incidence accounting for competing risk, 5.5% and 5.7%, respectively; HR=0.98 [95%CI, 0.74–1.31]; *P*=0.913). One-year clinical outcomes according to smoking status are shown in **Figure A6** in the Appendix.

Baseline, angiographic and procedural data according to study drugs

Among the smokers' group, 682 patients were randomized to ticagrelor and 667 patients to prasugrel. Among the nonsmokers' group, 1320 patients were randomized to ticagrelor and 1332 patients to prasugrel. The baseline characteristics between patients assigned to ticagrelor and those assigned to prasugrel in the group of smokers were well-matched except for the proportion of patients with arterial hypertension, which was higher among ticagrelor-assigned patients. Slight but significant differences were also observed regarding the heart rate and treatment strategy between ticagrelor- and prasugrel-assigned patients in the smokers' group. In the nonsmokers' group, there were no significant differences in baseline

characteristics between ticagrelor-assigned and prasugrel-assigned patients. The baseline data are presented in **Table 6**.

Table 6. Baseline data according to study drug in smokers and nonsmokers

Characteristic	Smokers (N=1349)			Nonsmokers (N=2652)		
	Ticagrelor (N=682)	Prasugrel (N=667)	*P* value	Ticagrelor (N=1320)	Prasugrel (N=1332)	*P* value
Age – years	57.7±10.4	57.4±10.2	0.658	68.0±11.3	68.2±11.3	0.614
Gender			0.634			0.855
Female– no. (%)	129 (18.9)	134 (20.1)		345 (26.1)	343 (25.8)	
Diabetes – no. (%)	117 (17.2)	95 (14.2)	0.163	342 (25.9)	330 (24.8)	0.531
Arterial hypertension – no. (%)	428/681 (62.8)	381/666 (57.2)	0.040	999 (75.7)	999 (75.0)	0.717
Hypercholesterolemia – no. (%)	365 (53.5)	332/666 (49.8)	0.196	811/1318 (61.5)	825/1331 (62.0)	0.842
Prior myocardial infarction – no. (%)	93 (13.6)	92 (13.8)	0.996	218/1319 (16.5)	226 (17.0)	0.802
Prior PCI – no. (%)	119 (17.4)	114 (17.1)	0.919	333 (25.2)	347/1331 (26.1)	0.651
Prior CABG – no. (%)	19 (2.8)	18 (2.7)	>0.999	96 (7.3)	112 (8.4)	0.310
Cardiogenic shock – no. (%)	12 (1.8)	16 (2.4)	0.527	16 (1.2)	15 (1.1)	0.980
Systolic blood pressure – (mmHg)	141±24.2	139±24.1	0.143	145±25.3	145±24.4	0.871
Diastolic blood pressure – (mmHg)	83.0±14.4	82.3±14.0	0.328	81.5±14.6	81.6±13.7	0.870
Heart rate – (beats/min)	78.7±16.9	76.5±15.7	0.012	76.0±15.3	75.7±15.1	0.599
Body mass index – (kg/m^2)	27.8±4.9	27.4±4.6	0.191	27.8±4.5	28.0±4.3	0.217
Weight < 60 kg – no. (%)	34/679 (5.0)	28/662 (4.2)	0.584	73/1314 (5.6)	65/1319 (4.9)	0.525
Creatinine – (µmol/L)	82.4±24.5	83.2±25.5	0.578	90.2±27.8	90.5±31.9	0.791
Diagnosis at admission			0.960			0.768
Unstable angina – no. (%)	60 (8.8)	58 (8.7)		188 (14.2)	203 (15.2)	
NSTEMI – no. (%)	277 (40.6)	276 (41.4)		650 (49.3)	647 (48.6)	
STEMI – no. (%)	345 (50.6)	333 (49.9)		482 (36.5)	482 (36.2)	
Coronary angiography – no. (%)	675 (99.0)	665 (99.7)	0.178	1318 (99.8)	1329 (99.8)	>0.999
Treatment strategy – no. (%)			0.019			0.905
PCI	584 (85.9)	605 (90.7)		1085 (82.3)	1089 (81.8)	
CABG	19 (2.8)	10 (1.5)		27 (2.1)	26 (2.0)	
Conservative	77 (11.3)	52 (7.8)		206 (15.6)	216 (16.2)	

Data are mean ± standard deviation or counts (%). CABG, coronary artery bypass grafting; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Missing continuous data: Smokers group: systolic blood pressure, 2 patients in the prasugrel group; diastolic blood pressure, 8 patients (4 in each group); heart rate, 1 patient in the prasugrel group; body mass index, 10 patients (4 in the ticagrelor group, 6 in the prasugrel group).

Nonsmokers group: systolic blood pressure, 1 patient in the ticagrelor group; diastolic blood pressure, 8 patients (3 patients in the ticagrelor group, 5 patients in the prasugrel group); heart rate, 1 patient in the ticagrelor group; body mass index, 21 patents (8 in the ticagrelor group, 13 in the prasugrel group). The remaining continuous data were complete. Table adapted from (124).

Angiographic and procedural data according to the assigned study drug are presented in **Table A15** in the Appendix to this thesis. Data concerning access site, number of narrowed coronary arteries, or left ventricular ejection fraction were well-balanced between the 2 treatment groups in both smokers and nonsmokers.

One-year clinical outcome

The full list of one-year clinical outcomes according to study drugs in smokers and nonsmokers is shown in **Table 7.**

Primary endpoint

In the group of smokers, the primary endpoint (a composite of all-cause death, myocardial infarction, or stroke) occurred in 47 patients (7.0%) in the ticagrelor group and 41 patients (6.2%) in the prasugrel group (HR=1.15 [95%CI, 0.76–1.75]; *P*=0.510; **Figure 12, left panel**). In the group of nonsmokers, the primary endpoint occurred in 133 patients (10.2%) in the ticagrelor group and 94 patients (7.2%) in the prasugrel group (HR=1.44 [95%CI, 1.10–1.87]; *P*=0.007; **Figure 12, right panel**). No significant interaction between the treatment arm and smoking status regarding the primary endpoint was observed (*P* for interaction =0.378).

Secondary safety endpoint

Bleeding events are shown in **Table 7.** In the group of smokers, BARC type 3 to 5 bleeding (safety endpoint) occurred in 27 patients in the ticagrelor group and 33 patients in the prasugrel group (cumulative incidence accounting for competing risk, 4.6% and 5.6%, respectively; HR=0.81 [95%CI, 0.49–1.35]; *P*=0.412). In the group of nonsmokers, BARC type 3 to 5 bleeding occurred in 66 patients assigned to ticagrelor and 46 patients assigned to prasugrel (cumulative incidence accounting for competing risk 6.0% and 4.4%, respectively; HR=1.38 [95%CI, 0.94–2.01]; *P*=0.097). Time-to-event curves are shown in **Figure 13**. There

was no significant interaction between the treatment arm and smoking status regarding the secondary safety endpoint (*P* for interaction =0.099).

Table 7. **Clinical outcomes according to the study drug in smokers and nonsmokers**

Outcome	Smokers (N=1349)				Nonsmokers (N=2652)			
	Ticagrelor (N=682)	**Prasugrel** (N=667)	**HR [95% CI]**	***P* value**	**Ticagrelor** (N=1320**)**	**Prasugrel** (N=1332)	**HR [95% CI]**	***P* value**
Primary endpoint – (death, MI, or stroke) – no. (%)	47 (7.0)	41 (6.2)	1.15 [0.76-1.75]	0.510	133 (10.2)	94 (7.2)	1.44 [1.10-1.87]	0.007
Death	26 (3.9)	21 (3.2)	1.22 [0.69-2.17]	0.501	60 (4.6)	50 (3.8)	1.21 [0.83-1.77]	0.314
Cardiovascular	18	20			41	37		
Non-cardiovascular	8	1			19	13		
Myocardial Infarction	23 (3.4)	21 (3.2)	1.12 [0.62- 2.03]	0.699	72 (5.5)	39 (3.0)	1.87 [1.26- 2.76]	0.002
Stroke	8 (1.2)	3 (0.5)	2.60 [0.69-9.83]	0.158	14 (1.1)	16 (1.2)	0.89 [0.44-1.83]	0.758
Ischemic	6	2			10	15		
Hemorrhagic	2	1			4	1		
Definite or probable stent thrombosis	8 (1.2)	7(1.1)	1.17 [0.42- 3.23]	0.761	17 (1.3)	13 (1.0)	1.29 [0.63-2.65]	0.492
Definite stent thrombosis	7 (1.0)	5 (0.8)	1.40 [0.44-4.41]	0.568	14 (1.1)	7 (0.5)	2.01 [0.81-4.97]	0.133
BARC type 3 to 5 bleeding[a]	27/676 (4.6)	33/622 (5.6)	0.81 [0.49- 1.35]	0.412	66/1304 (6.0)	46/1144 (4.4)	1.38 [0.94-2.01]	0.097

Data are numbers of events with Kaplan-Meier estimates (%) for the primary endpoint and death, or cumulative incidence (%) after accounting for competing risk for the remaining endpoints.

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

[a] BARC type 3 to 5 bleeding was analyzed according to the modified intention-to-treat principle.

Kaplan-Meier estimates or cumulative incidence of the events and risk estimates are obtained from the Cox proportional hazards model after adjustment for the participating center and stratification according to the clinical presentation (acute coronary syndrome with or without ST-segment elevation). Table adapted from (124).

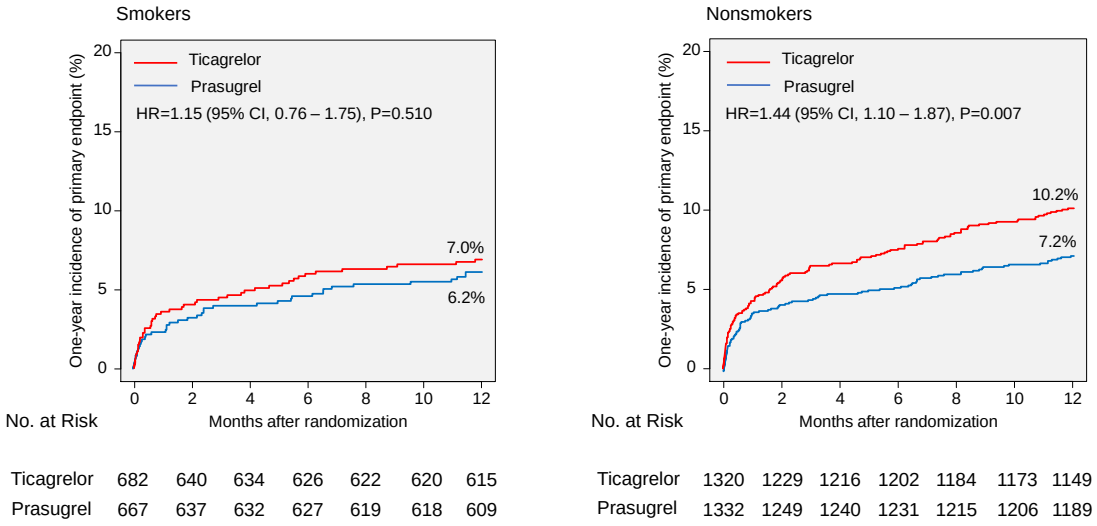

Figure 12. Cumulative incidence of the primary endpoint (one-year incidence of all-cause death, myocardial infarction, or stroke) according to study drug and smoking status

CI, confidence interval; HR, hazard ratio. The primary endpoint was evaluated in the intention-to-treat population. Figure adapted from (124).

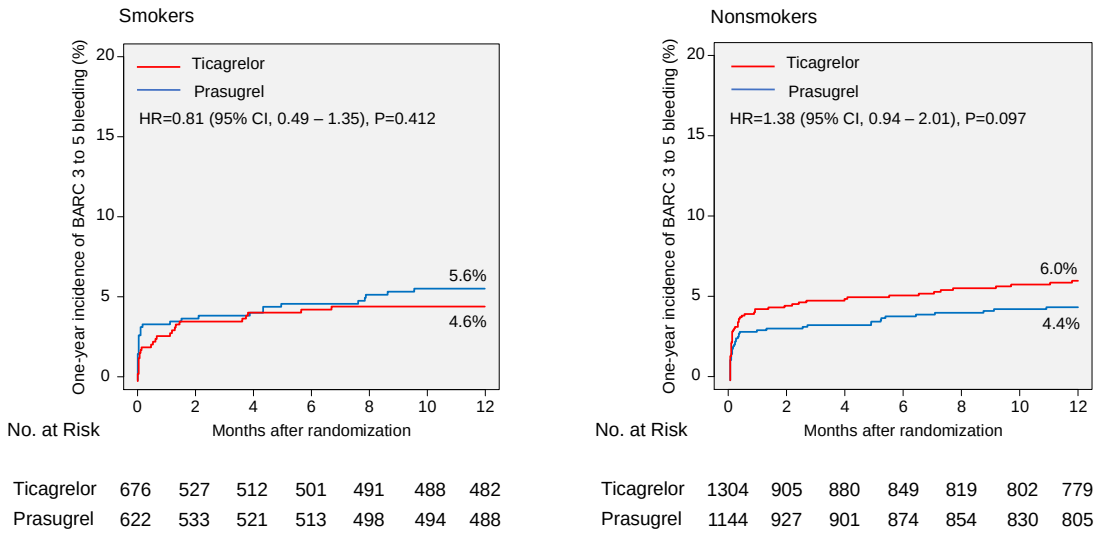

Figure 13. Cumulative incidence of the secondary (safety) endpoint according to study drug and smoking status

Left Panel. Kaplan-Meier curves of the safety endpoint in smokers. **Right Panel.** Kaplan-Meier curves of the safety endpoint in nonsmokers. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio. BARC type 3 to 5 bleeding was evaluated in the modified intention-to-treat population after accounting for the competing risk of death. Figure adapted from (124).

4.5 Comparison of ≤3 months with ≥6 months of dual antiplatelet therapy in patients undergoing drug-eluting stent implantation – A meta-analysis of randomized clinical trials

Included studies and patient characteristics

After merging independent searches, we identified 9 randomized clinical trials to include in this analysis: 8 trials published as full-length manuscripts (126,127,129,138-142) and one trial as a meeting presentation at the time when the analysis was performed (143). All were randomized, multi-center, open-label trials, except for the TWILIGHT trial, which was double-blinded (140). In these trials, patients with CAD undergoing stent implantation were randomized to either short or control (standard) DAPT duration. In total, 41,864 patients were included in the present analysis; 20,915 patients were allocated to short DAPT duration (≤3 months) and 20,949 patients to control DAPT duration (≥6 months). The main patient and trial characteristics are presented in **Table 8** and **Table A16**, respectively.

Seven trials included patients with stable and unstable CAD, whereas two trials included only patients with ACS (129,139). Short DAPT was given for three months in six trials and one month in three trials (127,142,143). Control DAPT was given for 6-12 months in one trial (143), for 12 months in seven trials and 15 months (3+12 months) in one trial (140). After short DAPT therapy, patients continued with aspirin monotherapy in four trials (126,138,139,143), and $P2Y_{12}$ inhibitor monotherapy in five trials (127,129,140-142).

Clinical features of the included patients were well-balanced among the two treatment arms in all trials. The mean age of patients ranged from 61 to 69 years in different trials. The percentage of women ranged from 20 to 37%.

Table 8. Main characteristics of patients enrolled in the trials included in the meta-analysis

Trial	GLOBAL LEADERS	One-Month DAPT	OPTIMIZE	REDUCE	RESET	SMART-CHOICE	STOPDAPT-2	TICO	TWILIGHT
Patients	15968	3020	3119	1496	2117	2993	3009	3056	7119
Age – years (mean)	64.5	67.0	61.6	60.5	62.4	64.5	68.6	61.0	65.1
Women – no.(%)	3714 (23.3)	933 (31)	1145 (36.7)	300 (20.1)	770 (36.4)	795 (26.6)	672 (22.3)	628 (20.5)	23.8
BMI (kg/m^2)	28.2	NA	NA	NA	25.0	24.6	24.3	24.9	28.5
Diabetes – no.(%)	4038/15957 (25.3)	1135 (37.6)	1103 35.4	307/1494 (20.5)	621 (29.3)	1122 (37.5)	1159 (38.5)	835 (27.3)	36.8
Arterial hypertension – no. (%)	11715/15914 (73.6)	2009 (66.5)	2721 (87.2)	754/1488 (50.7)	1310 (61.9)	1840 (61.5)	2221 (73.8)	1541 (50.4)	5154/7118 (72.4)
Dyslipidemia – no. (%)	10768/15465 (69.6)	2454 (81.3)	1905 (61.1)	679/1490 (45.6)	1245 (58.8)	1352 (45.2)	2244 (74.6)	1846 (60.4)	4303 (60.4)
Current smoker– no (%)	4169 (26.1)	NA	559 (17.9)	627/1480 (42.4)	508 (24.0)	791 (26.4)	710 (23.6)	1142 (37.4)	1548/7115 (21.8)
Ejection fraction, %	NA	63	NA	NA	64.1	60.0	59.8	NA	NA
Previous PCI – no. (%)	5221/15954 (32.7)	521 (17.3)	624 (20.0)	161 (10.8)	69 (3.3)	NA	1032 (34.3)	262 (8.6)	2998 (42.1)
Prior CABG – no. (%)	943/15955 (5.9)	44/3020 (1.5)	239/3119 (7.7)	42 (2.8)	8 (0.4)	NA	59 (2.0)	18 (0.6)	710/7118 (10.0)
Stable CAD – no. (%)	8481 (53.1)	1828/3020 (60.5)	2123 (68.1)	0	961 (45.4)	1250 (41.8)	1861 (61.9)	0	2503/7117 (35.2)
Multivessel disease – no. (%)	NA	1745 (57.8)[*]	809[†] (25.9)	523/1495 (35.0)	910 (43.0)[*]	1483 (49.5)	NA	1703 (55.7)	4466/7119 (62.7)
Lesion Type B2/C – no. (%)	NA	NA	1526/4120 (37.0)[‡]	NA	1842/2687 (68.6)	NA	490/638 (76.8)[§]	NA	NA

Number of treated lesions	20841	3604	4120	NA	2687	3734	NA	3779	NA
LAD treated (%)	8666/20841 (41.6)	2001/3604 (55.5)	1946/4120 (47.2)	689/1495 (46.1)	1429/2687 (53.2)	1853/3734 (49.6)	1682/3009 (55.9)	1821/3779 (48.2)	4003/7119 (56.2)
Stent/lesion	1.2	1.3‖	1.2	NA	NA	NA	1.3	1.1	NA
Stent length/lesion (mm)	24.8	31‖	32.7‖	23.0#	22.8	37.9‖	30.4#	35‖	NA
$P2Y_{12}$ Inhibitor, LD	Ticagrelor 180 mg or Clopidogrel 600 mg	NA	300 to 600 mg Clopidogrel	Ticagrelor 180 mg or Prasugrel 60 mg or Clopidogrel at least 300 mg.**	300 mg Clopidogrel	300- or 600 mg Clopidogrel (In ACS patients 60 mg prasugrel or 180 mg ticagrelor)	NA	180 mg Ticagrelor	NA
Aspirin, LD	325 mg	NA	300 to 500 mg	At least 300 mg	At least 75 mg	300 mg	As in clinical practice	300 mg	NA
Type of DES used	Biolimus A9-eluting stent	BioFreedom (experimental arm) Biomatrix or Ultimaster (control arm)	Endeavor zotarolimus-eluting stent	Combo	Endeavor zotarolimus (experimental arm) Cypher, Xience, Resolute (control arm)	Cobalt chromium EES (Xience); platinum-chromium EES (Promus, Synergy); SES (Orsiro, Biotronik)	Cobalt-chromium everolimus eluting stent (Xience, Abbott vascular)	Bioresorbable polymer sirolimus-eluting stent (Orsiro, Biotronik AG)	Second generation DES

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug-eluting stent; EES, everolimus-eluting stent; LAD, left anterior descending; LD, loading dose; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent.

* Including ≥ 2-vessel disease

† Multivessel PCI

‡ Lesion type C

§ Only 638 lesions analyzed

‖Indicates stent per patient, not per lesion

Total stent length

** Ticagrelor and prasugrel were preferred over clopidogrel. Table adapted from (132).

Co-Primary endpoints: Stent thrombosis; Bleeding

The co-primary endpoint of definite or probable ST occurred in 212 patients (0.5%). The risk of ST at 1-year follow-up was similar with short and control DAPT (0.5% vs. 0.5%; HR=1.17 [95%CI, 0.89–1.54]; p=0.26; **Figure 14A**).

The co-primary endpoint of bleeding occurred in 1,029 patients (2.5%). The risk of bleeding was significantly reduced with short DAPT compared with control DAPT (1.9% vs. 3.0%; HR=0.65 [95% CI, 0.54–0.77]; p<0.001; **Figure 14B**).

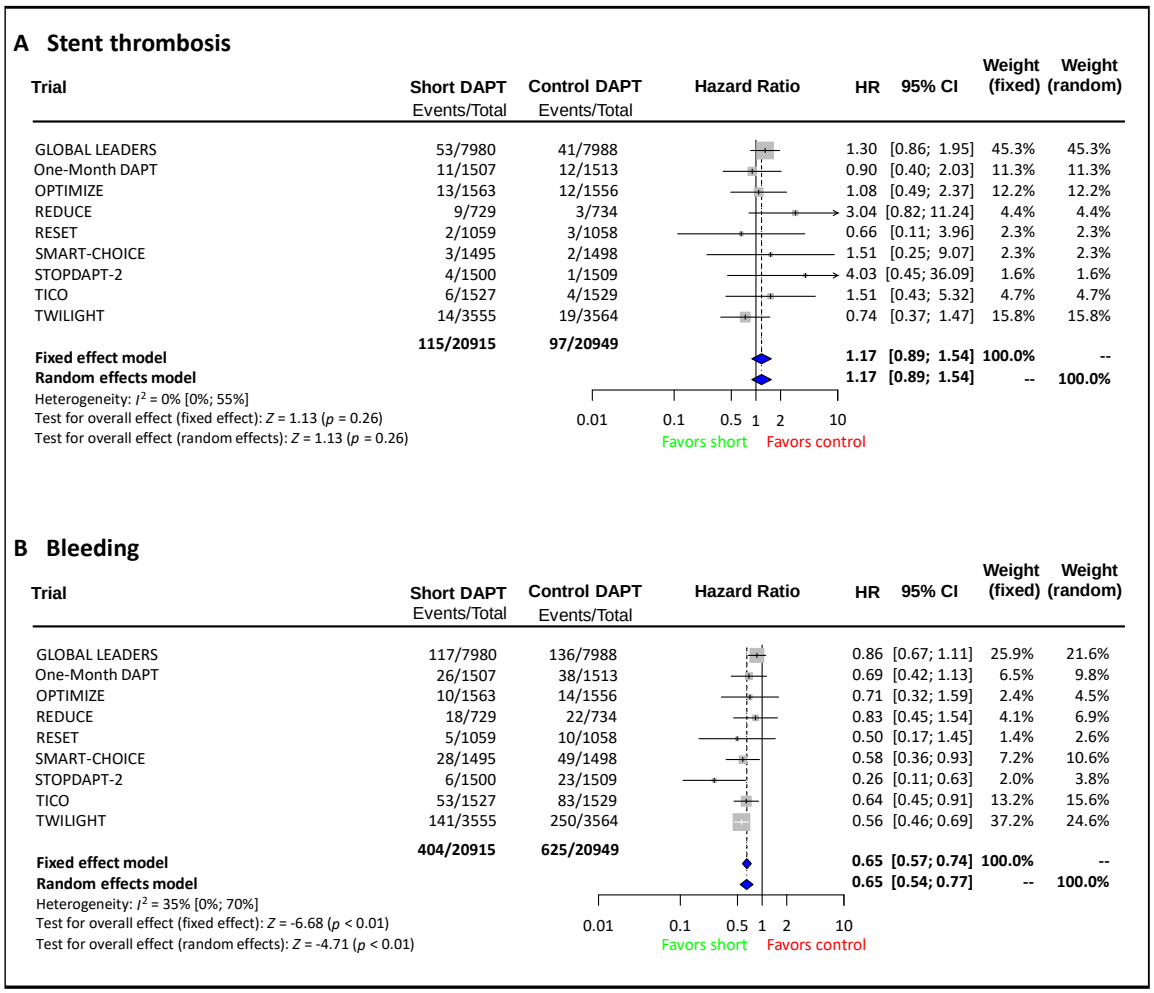

Figure 14. Forest plots of the primary endpoints for short DAPT vs. control DAPT

A) Definite or probable stent thrombosis, and **B)** Bleeding.

The squares indicate the point estimate [hazard ratio (HR)] and the lines represent the 95% confidence intervals. The size of each square is proportional to the statistical weight of a trial in the meta-analysis; the diamond indicates the effect estimate derived from the meta-analysis. The arrow indicates a CI value beyond the shown axis limit. DAPT, dual antiplatelet therapy. Figure adapted from (132).

Secondary endpoints: death, myocardial infarction, stroke

All-cause death occurred in 589 patients (1.4%). The risk for all-cause death was similar between short and control DAPT durations (1.3% vs. 1.5%, respectively; HR=0.88 [95% CI, 0.74–1.04]; p=0.13; **Figure 15**). A total of 275 deaths occurred in the short DAPT group, and 314 occurred in the control DAPT group. Cardiac death occurred in 220 patients (0.5%). The risk of cardiac death was comparable between short and control DAPT durations (0.5% vs. 0.6%, respectively; HR=0.80 [95% CI, 0.61–1.04]; p=0.10; **Figure A7**). Myocardial infarction occurred in 763 patients (1.8%). The risk of MI was similar between short and control DAPT durations (1.9% vs. 1.8%, respectively; HR=1.05 [95% CI, 0.91–1.21]; p=0.53; **Figure A7**). Stroke occurred in 240 patients (0.6%). The risk of stroke was similar between short and control DAPT durations (0.6% vs. 0.6%; HR=1.01 [95% CI, 0.77–1.33]; p=0.94; **Figure A7**).

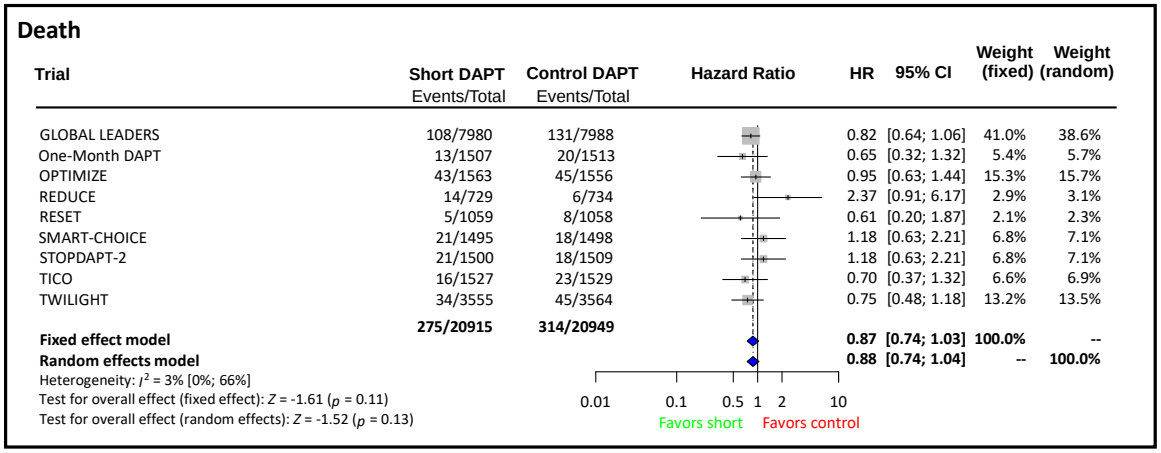

Figure 15. All-cause mortality in patients with short vs. control DAPT after percutaneous coronary intervention

The squares indicate the point estimate [hazard ratio (HR)], and the lines represent the 95% confidence intervals. The size of each square is proportional to the statistical weight of a trial in the meta-analysis; the diamond indicates the effect estimate derived from the meta-analysis. DAPT, dual antiplatelet therapy. Figure adapted from (132).

Clinical outcomes in the aspirin- and $P2Y_{12}$ inhibitor monotherapy studies

We also separately compared the primary and secondary endpoints between the short and control DAPT duration arms in the 4 studies that continued with aspirin monotherapy and the 5 studies that continued with $P2Y_{12}$ inhibitor monotherapy after short therapy with DAPT.

The aspirin monotherapy studies included 9,719 patients with a median DAPT duration of 1.8 vs. 10.9 months for the short vs. control group, respectively. The $P2Y_{12}$ inhibitor monotherapy studies included 32,145 patients, with a DAPT duration of 1.4 vs. 12.6 months for the short vs. control DAPT group.

The risk of stent thrombosis was not significantly different between the short and control DAPT groups in both the aspirin monotherapy (0.7% vs. 0.6% for short vs. control DAPT, respectively; HR=1.13 [0.69–1.86]; p=0.63) and $P2Y_{12}$ inhibitor monotherapy studies (0.5% vs.0.4% for short vs. control DAPT, respectively; HR=1.19 [0.86–1.65]; p=0.30, **Figure 16**). No heterogeneity between the aspirin monotherapy and $P2Y_{12}$ inhibitor monotherapy groups was detected (p=0.861) concerning stent thrombosis.

Bleeding was significantly reduced with short vs. control DAPT duration in the aspirin monotherapy studies (1.2% vs.1.7%, respectively; 0.71 [0.51–0.99]; p=0.04) as well as in the $P2Y_{12}$ inhibitor monotherapy studies (2.1% vs. 3.4%, for short vs. control DAPT, respectively; 0.62 [0.47–0.80]; p<0.001, **Figure 16**). No heterogeneity between aspirin- and $P2Y_{12}$ inhibitor-monotherapy groups concerning bleeding events was detected (p=0.515). Additionally, there were no significant differences in all-cause mortality or ischemic events such as cardiac death, myocardial infarction, or stroke between these groups, as shown in **Table 9**. The analysis showed no heterogeneity between the aspirin and $P2Y_{12}$ inhibitor monotherapy groups for these endpoints.

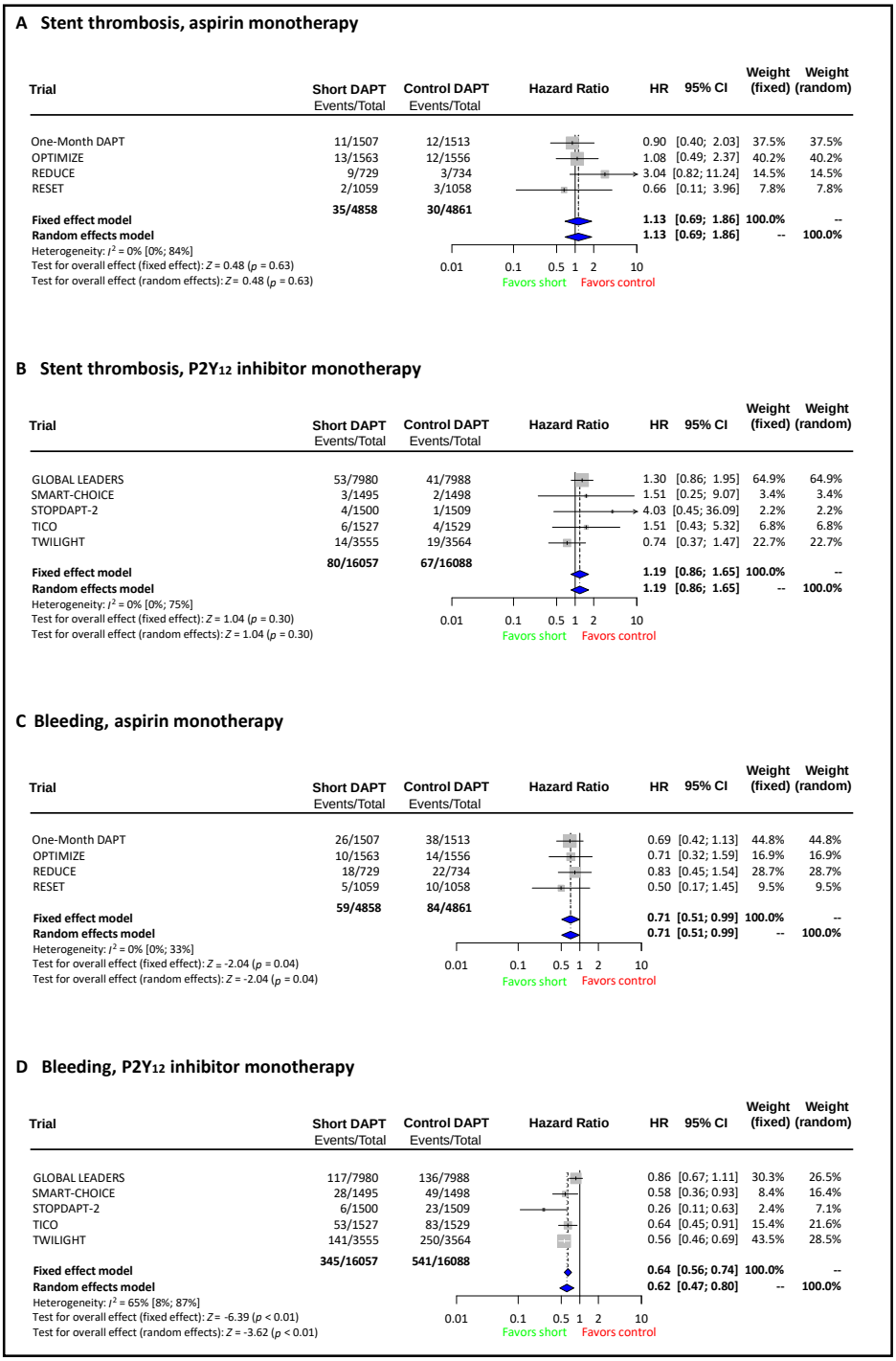

Figure 16. Outcomes of patients with short DAPT vs. control DAPT in the ASS- and $P2Y_{12}$ inhibitor monotherapy studies

A) Stent thrombosis in trials with aspirin monotherapy after short DAPT; B) Stent thrombosis in trials with $P2Y_{12}$ inhibitor monotherapy after short DAPT; C) Bleeding in trials with aspirin monotherapy after short DAPT; D) Bleeding in trials with $P2Y_{12}$ inhibitor monotherapy after short DAPT. The squares indicate the point estimate [hazard ratio (HR)], and the lines represent the 95% confidence intervals (CI). The size of each square is proportional to the statistical weight of a trial in the meta-analysis. DAPT, dual antiplatelet therapy. Figure adapted from (132).

Table 9. Clinical endpoints according to aspirin- and $P2Y_{12}$ inhibitor monotherapy groups

Endpoints	Aspirin mono* HR [95% CI]	$P2Y_{12}$ inhibitor mono HR [95% CI]	p for heterogeneity
Stent thrombosis	1.13 [0.69-1.86]	1.19 [0.86-1.65]	0.861
Bleeding	0.71 [0.51-0.99]	0.62 [0.47-0.80]	0.515
Death	0.95 [0.59-1.54]	0.85 [0.71-1.03]	0.681
Cardiovascular death	0.91 [0.53-1.54]	0.72 [0.51-1.04]	0.496
Myocardial infarction	1.04 [0.77-1.42]	1.05 [0.89-1.23]	0.988
Stroke	0.86 [0.51-1.46]	1.08 [0.67-1.74]	0.528

* Mono, monotherapy; CI, confidence interval; HR, hazard ratio. Table adapted from (132).

4.6 Plasma soluble glycoprotein VI, a specific marker of bleeding risk in patients undergoing elective percutaneous coronary intervention

Baseline characteristics

This analysis included 318 patients with available sGPVI measurements. The sGPVI values ranged from 2.6 ng/ml to 351.0 ng/ml. Patients were categorized into 3 groups according to tertiles of sGPVI: lower tertile (sGPVI: 2.6 to <9.5 ng/mL; 106 patients); middle tertile (sGPVI: 9.5 to <16.2 ng/mL; 106 patients); and upper tertile of sGPVI (sGPVI: 16.2 to 351.0 ng/mL; 106 patients). Baseline characteristics are shown in **Table 10.** The baseline characteristics differed little between tertiles of sGPVI, apart from platelet count, which showed a significant difference across the sGPVI tertiles. There were no significant differences between tertiles of sGPVI with respect to drug therapy (**Table A17**)**.** Particularly, the proportion of patients on aspirin and clopidogrel at admission was not significantly different across the tertiles of sGPVI. Additionally, there was no significant

difference in the total dose of administered peri-interventional heparin across the sGPVI tertiles. Angiographic and procedural characteristics are presented in **Table A18.**

The LASSO regression (see Statistical analysis in Section 3.3) identified three variables (hypercholesterolemia, multivessel disease, and platelet count) to be entered in the multivariable linear regression model applied to identify the independent correlates of plasma sGPVI levels. Platelet count was the strongest correlate of sGPVI level (regression coefficient=0.15, p<0.001); multivessel disease showed a significant but marginal association with sGPVI level (regression coefficient=–12.56, p=0.047) with the regression coefficient showing the change in sGPVI level per unit change in baseline variable and minus sign showing an inverse association.

The sGPVI in the placebo group

In the placebo group (93 patients), there was no significant difference between sGPVI levels measured at baseline (12.4 [8.5–20.9] ng/mL) and 48 hours after randomization (11.6 [8.8–18.8] ng/mL, P=0.23; **Figure A8**).

sGPVI and platelet function

In the measurements performed at baseline in all 3 study drug groups, there was no significant correlation between sGPVI and platelet response to ADP or each of the 3 collagen concentrations (R≤0.06, P≥0.20), **Figure 17A** and **Figure 17B**. In the measurements performed at day 2 in the placebo group, there was no significant correlation between sGPVI and platelet response to ADP or each of the 3 collagen concentrations (R≤0.14, P≥0.29), **Figure 17C** and **Figure 17D**.

Table 10. Baseline patient characteristics according to the tertiles of sGPVI

Characteristic	Plasma soluble glycoprotein VI level			P value
	Lower tertile (N=106)	**Middle tertile (n=106)**	**Upper tertile (n=106)**	
Treatment group				
Placebo	29 (27.4)	35 (33.0)		0.58
Revacept 80 mg	39 (36.8)	31 (29.2)	42 (39.6)	
Revacept 160 mg	38 (35.8)	40 (37.7)	35 (33.0)	
Age, y	66.1 [60.4-75.0]	67.9 [61.6-74.5]	68.7 [59.9-75.6]	0.78
Sex				
Female	26 (24.5)	29 (27.4)	23 (21.7)	0.63
Male	80 (75.5)	77 (72.6)	83 (78.3)	
Cardiovascular risk factors				
Diabetes	26 (24.5)	27 (25.5)	33 (31.1)	0.50
Current smoker	18 (17.0)	22 (20.8)	23 (21.7)	0.50
Arterial hypertension	98 (92.5)	95 (89.6)	89 (84.0)	0.14
Hypercholesterolemia	98 (92.5)	95 (89.6)	89 (84.0)	0.14
Myocardial infarction	23 (21.7)	27 (25.5)	20 (18.9)	0.51
Percutaneous coronary intervention	64 (60.4)	62 (58.5)	55 (51.9)	0.42
CABG	10 (9.4)	10 (9.4)	6 (5.7)	0.51
Stroke	2 (1.9)	3 (2.8)	3 (2.8)	>0.99
Peripheral arterial occlusive disease	10 (9.4)	8 (7.6)	8 (7.6)	0.85
Chronic obstructive pulmonary disease	6 (5.7)	4 (3.8)	5 (4.7)	0.81
Chronic kidney disease	8 (7.6)	12 (11.3)	10 (9.4)	0.64
Family history of premature coronary artery disease[a]	52/105 (49.5)	39/104 (37.5)	42 (39.6)	0.17
Body mass index, kg/m^2	27.3 [24.6-30.2]	26.5 [23.7-28.9]	27.8 [24.7-30.5]	0.091
Heart rate, bpm	64.0 [57.0-71.8]	64.5 [59.0-70.8]	67.0 [59.2-74.0]	0.24
Multivessel disease	90 (84.9)	87 (82.1)	86 (81.1)	0.75
Creatinine, mg/dL	0.9 [0.8-1.1]	1.0 [0.8-1.1]	1.0 [0.8-1.1]	0.53
C- reactive protein, mg/L[b]	1.0 [0.6-2.5]	1.0 [0.6-2.7]	1.2 [1.0-3.0]	0.03
Hemoglobin, g/dL	14.3 [13.3-15.4]	14.4 [13.5-15.3]	14.3 [13.4-15.0]	0.60
Platelet count, 10^9/L	210 [168-242]	226 [192-252]	237 [211-270]	0.001
High sensitivity troponin T, ng/L	12 [9.0-13.0]	11 [7.0-13.0]	10.5 [8.0-13.0]	0.21

Number of patients (%) or median [25th–75th percentiles] is shown.

[a] Family disposition of premature coronary artery disease not available in 3 patients (1 in the lower sGPVI tertile, 2 in the middle sGPVI tertile).

[b] C-reactive protein not available in one patient in the middle sGPVI tertile. Table adapted from (137).

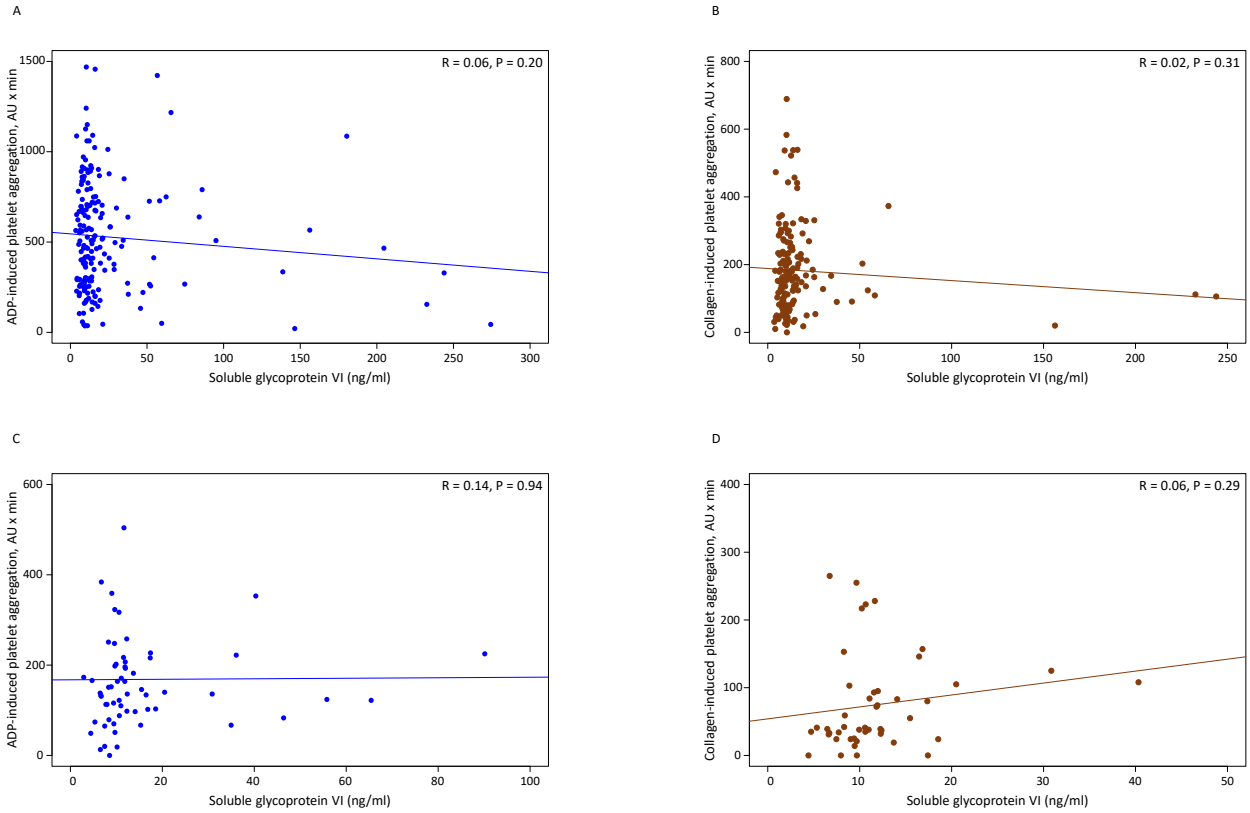

Figure 17. Correlation between soluble glycoprotein VI level and platelet function

(A) Correlation between soluble glycoprotein VI level and ADP-induced platelet aggregation both measured at baseline. (B) Correlation between soluble glycoprotein VI level and collagen-induced platelet aggregation both measured at baseline. (C) Correlation between soluble glycoprotein VI level and ADP-induced platelet aggregation, both measured at 48 hours after PCI. (D) Correlation between soluble glycoprotein VI level and collagen-induced platelet aggregation, both measured at 48 hours after PCI. Collagen was used in the 253 µg/mL concentration. ADP, adenosine diphosphate; PCI, percutaneous coronary intervention. (B, D) shows only platelet response to the 253 µg/mL collagen concentration. Figure adapted from (137).

sGPVI and clinical outcomes

Peak postprocedural hsTnT measurements were available in 314 patients. The incidence of the **co-primary ischemic endpoint** at 48 hours was 25.0% in the lower sGPVI tertile, 22.9% in the middle sGPVI tertile, and 26.7% in the upper sGPVI tertile (p=0.82). There was no sGPVI tertile-by-revacept interaction with respect to the co-primary ischemic endpoint (P for interaction=0.78). Given that there was only one death within the 30-day period, the myocardial injury component practically constituted the ischemic endpoint. The peak hsTnT values (median [25th-75th percentiles]) at 48 hours were 34.5

[9-1,460] ng/L in patients of the lower sGPVI tertile, 30.0 [3-997]ng/L in patients of the middle sGPVI tertile, and 27.0 [4-3,750]ng/L in patients of the upper sGPVI tertile (p=0.67). To assess the discriminatory power of sGPVI in predicting the risk of the co-primary ischemic endpoint, we performed the ROC curve analysis (**Figure 18**). The AUC was 0.50 (95%CI: 0.43–0.58), indicating a lack of predictive ability of the sGPVI with respect to this endpoint.

The LASSO regression identified sGPVI, sex, age, hypercholesterolemia, active smoking, diabetes, a family history of premature CAD, a history of MI, CABG or PCI, peripheral arterial disease, chronic obstructive pulmonary disease, multivessel disease, heart rate, baseline platelet count, hemoglobin level, and hsTnT, as well as the use of femoral artery access for PCI to be eligibile for the multivariable logistic regression model, which sought to identify the independent correlates of the ischemic risk. The model showed no significant association between sGPVI and the ischemic endpoint (adjusted p=0.78). Independent correlates of a higher risk for the ischemic endpoint were female sex (p=0.014), multivessel disease (p=0.010), a high heart rate (p=0.002), and low haemoglobin level (p=0.002). The lack of independent association between sGPVI and ischemic endpoint was also seen for sGPVI entered as a continuous variable (p=0.32).

The composite endpoint of 30-day MACE occurred in 8 of 318 patients: 4 of the 106 patients (3.8%) in the lower sGPVI tertile, 1 of the 106 patients (0.9%) in the middle sGPVI tertile, and 3 of the 106 patients (2.8%) in the upper sGPVI tertile (p=0.54) (**Table A19** in the Appendix). There were no significant differences in sGPVI levels in patients with MACE versus those without MACE (12.3 [7.5–30.0] ng/mL vs. 12.2 [8.5-20.8] ng/mL; p=0.98).

Overall, 53 patients experienced **bleeding** events at 30 days: 12 patients (11.8%) in the lower sGPVI tertile, 13 patients (12.6%) in the middle sGPVI tertile, and 28 patients (26.4%) in the upper sGPVI tertile (p=0.006) (**Figure 19A**). BARC type 2 to 5 bleeding events occurred in 5 patients in the lower sGPVI tertile group, 6 patients in the middle sGPVI tertile group, and 10 patients in the higher sGPVI tertile group. BARC 3a bleeding occurred in 3 patients in the middle sGPVI tertile and BARC 3b in 1 patient in the lower sGPVI tertile. There were no BARC type 4 or 5 bleeding events among tertiles. The AUC of sGPVI for bleeding was 0.62 [0.54–0.71], showing a significant but modest discrimination for bleeding by sGPVI. There was no sGPVI tertile-by-revacept interaction with respect to bleeding (P for interaction=0.74). There was a nonlinear relation between plasma sGPVI levels and the risk of bleeding (**Figure 19B**)**.** Patients who experienced bleeding had significantly higher sGPVI levels compared to those who did not (17.9 [10.4–35.4] ng/mL vs. 11.6 [8.4–18.3] ng/mL; p= 0.004).

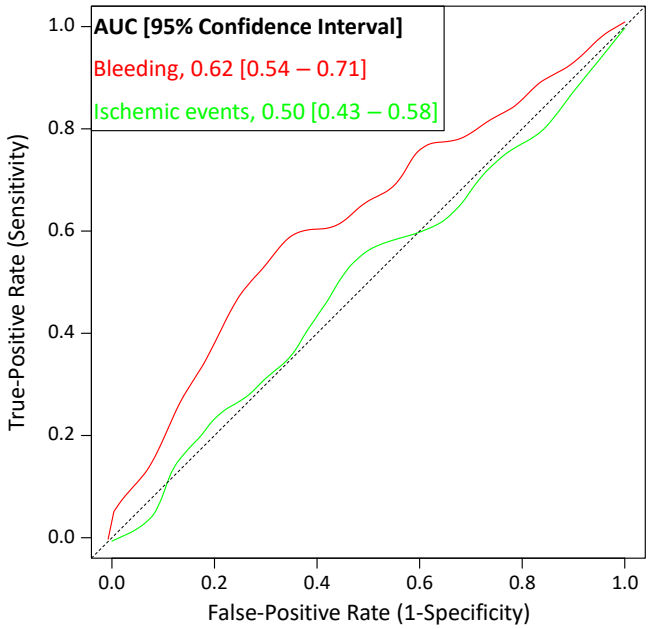

Figure 18. Receiver operating characteristic (ROC) curve analysis showing areas under the ROC curve (AUC) of soluble glycoprotein VI for ischemic and bleeding complications

Figure adapted from (137).

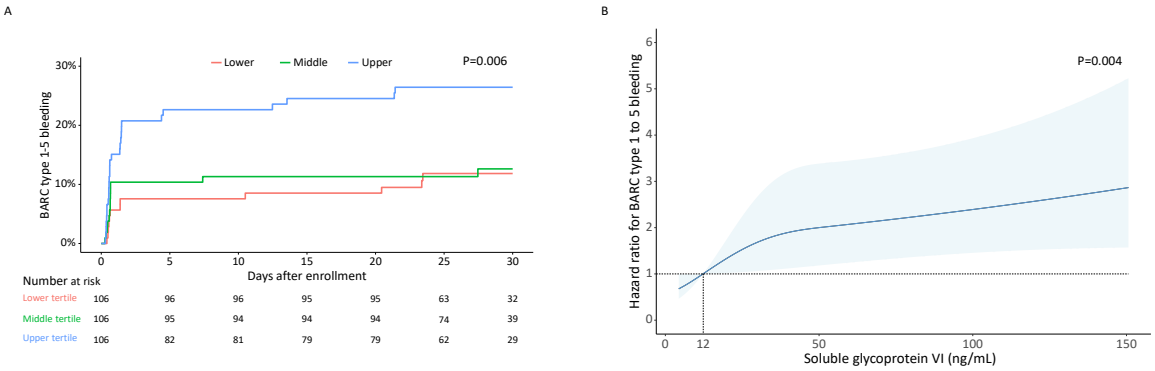

Figure 19. Soluble glycoprotein VI and Bleeding Academic Research Consortium (BARC) type 1 to 5 bleeding

(A) Cumulative incidence of BARC type 1 to 5 bleeding according to soluble glycoprotein VI tertiles. (B) Restricted cubic spline regression curve showing the nonlinear relation between plasma levels of soluble glycoprotein VI and the risk of bleeding. Plasma levels above 12 ng/mL (marked on the graph) are associated with a significantly increased risk of bleeding. Figure adapted from (137).

Correlates of the bleeding risk

The LASSO regression model identified the following variables: sGPVI, arterial hypertension, a history of stroke or PCI, multivessel disease, body mass index, hemoglobin, C-reactive protein levels, and the use of femoral artery for vascular access during the PCI procedure to be eligible for the multivariable Cox proportional hazards model aimed at identifying the independent correlates of the bleeding risk. Patients in the upper tertile of sGPVI experienced a higher risk of bleeding compared with patients in the lower tertile (adjusted HR=2.54 [95% CI, 1.27–5.10]; p=0.009) or middle tertile (adjusted HR=2.56 [95% CI, 1.30–5.07]; p=0.007). The risk of bleeding differed little between patients in the middle sGPVI tertile and those in the lower sGPVI tertile (p=0.98). Additional factors that were independently associated with an increased bleeding risk were: arterial hypertension (p=0.036), no history of PCI (p=0.040), single vessel disease (p=0.037), low body mass index (p <0.001), and the use of femoral artery access for PCI (p=0.011). In a separate analysis, platelet count was also forced into the

multivariable model for bleeding and did neither correlate with it (p=0.70) nor modify the association between sGPVI and bleeding.

The multivariable model for bleeding that included sGPVI yielded a C-statistic of 0.77 [0.71-0.83] and an IDI of 0.18 [0.09-0.28], showing a significant improvement in discrimination over the respective values of the multivariable model without sGPVI: C-statistic: 0.74 [0.68-0.79] (p=0.03), and IDI: 0.14 [0.07-0.22] (p=0.005).

The mechanism of release of the sGPVI and a visual summary of the findings are shown in **Figure 20.**

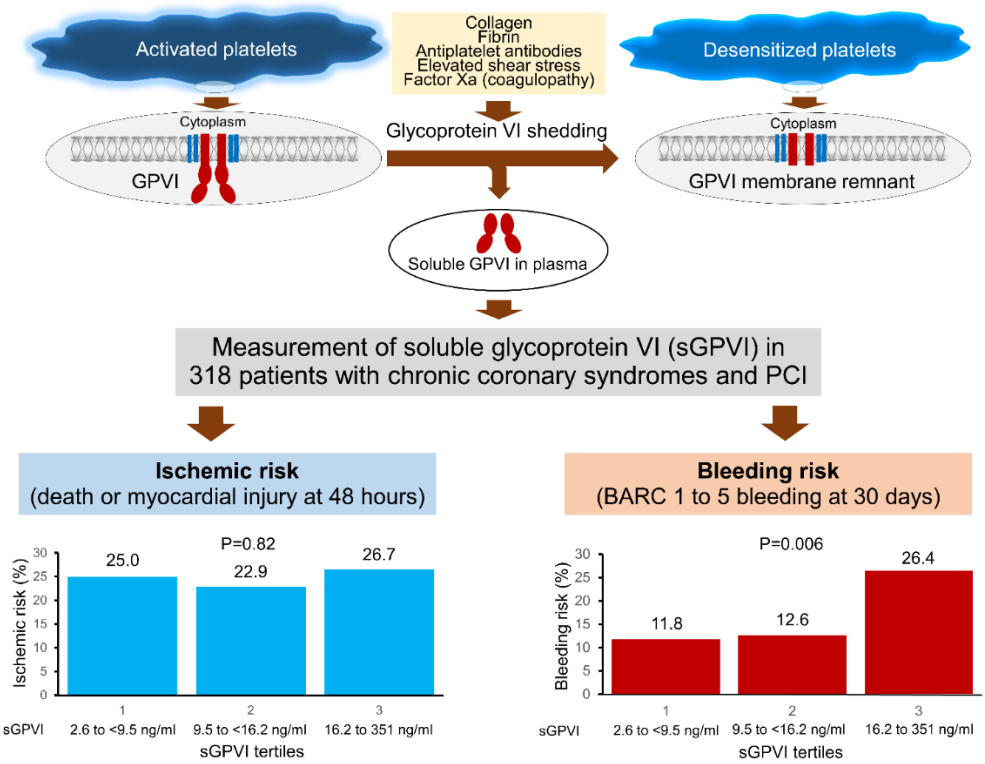

Figure 20. Mechanism of release of the soluble glycoprotein VI (sGPVI) from platelets and the association between sGPVI and ischemic and bleeding outcomes

Glycoprotein VI shedding from the platelets (as a mechanism to mitigate the platelet overstimulation) is associated with increased levels of sGPVI and the generation of desensitized or exhausted platelets, which may reduce the platelet ability to respond to collagen at the site of vascular trauma (lesions) leading to an increased risk of bleeding. Figure adapted from (137).

4.7 Role of special inactive stent coating in shortening the duration of dual antiplatelet therapy in patients on oral anticoagulation

Between February 2016 and May 2020, a total of 996 patients were enrolled across 63 clinical sites, in the United States of America and Europe. Of those, 495 patients were assigned to the COBRA PzF group and 501 patients were assigned to the control group (144). Of the 996 patients enrolled, 982 (98.6%) had sufficient follow up for analysis of the co-primary endpoints at 180 days. Overall, 845 patients were included in the per-protocol (PP) analysis and 783 in the mITT analysis.

Baseline characteristics

Baseline patient data were well-balanced for both groups (**Table 11**). The mean age at enrollment was 74.8 years in the COBRA PzF group and 74.0 years in the control group (p=0.17). The most common indication for OAC in both groups was atrial fibrillation and the indication for PCI in the majority of patients was CCS.

ARC-HBR criteria

All patients enrolled in the trial were considered to be at high bleeding risk as they were all taking OAC, a major ARC-HBR criterion for defining high bleeding risk. Specifically, 41% of patients in the COBRA PzF group and 43% of patients in the control group met ≥2 ARC-HBR major criteria and 7% of patients in both groups met ≥3 ARC-HBR major criteria.

Angiographic and procedural characteristics

Angiographic and procedural characteristics for both groups are summarized in **Table 12**. The stent types used in both groups are summarized in **Table 13.** Procedural success was achieved in 98.5% of cases in the COBRA PzF group and 99.5% of cases in the control group (p=0.09).

Table 11. Baseline patient characteristics in the COBRA and Control groups

Baseline Patient Characteristics	COBRA PzF Group (n=495)	Control Group (n=501)	P value
Age (years)	74.8 ± 8.7	74.0 ± 8.7	0.17
Male	358 (72.3%)	368 (73.5%)	0.72
Diabetes mellitus	178 (36.0%)	181/498 (36.4%)	0.95
Hypertension	450 (90.9%)	450/501 (89.8%)	0.59
Current smoker	42 (8.5%)	52 (10.4%)	0.90
Alcohol consumption >8 drinks per day	20/474 (4.2%)	14/483 (2.9%)	0.30
BMI (kg/m^2)	29.9 ± 6.3	29.5 ± 7.1	0.29
Family history of coronary artery disease	161/409 (39.4%)	160/420 (38.1%)	0.72
History of dyslipidemia	387/491 (78.8%)	385/495 (77.8%)	0.70
Known heart failure	134/487 (27.5%)	135/496 (27.2%)	0.94
Previous myocardial infarction	69/490 (14.1%)	88/496 (17.7%)	0.12
Previous stroke	63/494 (12.8%)	56/500 (11.2%)	0.49
History of peripheral vascular disease	65/486 (13.4%)	68/494 (13.8%)	0.93
Known severe renal insufficiency	30/494 (6.1%)	37 (7.4%)	0.45
Known liver disease	3 (0.6%)	10/500 (2.0%)	0.09
History of major bleeding or bleeding disposition	14/493 (2.8%)	15/499 (3.0%)	>0.99
Labile INR	18/399 (4.5%)	25/418 (6.0%)	0.43
History of CABG	52 (10.5%)	46 (9.2%)	0.52
History of PCI	178/491 (36.3%)	179/499 (35.9%)	0.95
Ejection fraction (%)	51.6 ± 12.4	51.8 ± 12.3	0.88
No. of diseased coronary vessels			0.17
1	278 (56.2%)	297 (59.3%)	
2	126 (25.4%)	134 (26.7%)	
3	91 (18.4%)	14 (2.8%)	
Left main coronary artery disease	21 (4.2%)	14 (2.8%)	0.23
Clinical presentation			0.28
CCS	361 (72.9%)	342 (68.3%)	
ACS	134 (27.1%)	159 (31.7%)	
Indication for oral anticoagulation therapy			0.16
Atrial fibrillation	446 (90.3%)	441 (88.2%)	
Mechanical valve	8 (1.6%)	6 (1.2%)	
Pulmonary embolism	12 (2.4%)	11 (2.2%)	
Deep venous thrombosis	7 (1.4%)	20 (4.0%)	
Other	21 (4.3%)	22 (4.4%)	
No. of ARC-HBR Major Criteria			
≥ 1	495/495 (100%)	501/501 (100%)	> 0.99
≥ 2	203/495 (41%)	215/501 (43%)	0.54
≥ 3	35/495 (7%)	35/501 (7%)	0.96

Data regarding the indication for oral anticoagulation therapy were available for 494 patients in the COBRA PzF group and 500 patients in the Control group.

ARC-HBR, Academic Research Consortium for High Bleeding Risk; BMI, body mass index; INR, international normalized ratio. Adapted from (144).

Table 12. Procedural and angiographic characteristics

	COBRA PzF Group (N=495 patients, 610 lesions)	Control Group (N=501 patients, 622 lesions)	P value
Angiographic characteristics			
Target lesion location			
Left main coronary artery	1 (0.2%)	0 (0.0%)	0.50
Left anterior descending coronary artery	280 (45.9%)	275 (44.2%)	0.57
Left circumflex coronary artery	142 (23.3%)	143 (23.0%)	0.95
Right coronary artery	184 (30.2%)	199 (32.0%)	0.50
Lesion Complexity B2/C (ACC/AHA)	403/596 (67.6%)	385/605 (63.6%)	0.11
Pre-Procedure TIMI Flow			0.44
0	8/596 (1.3%)	6/605 (1.0%)	
1	2/596 (0.3%)	1/605 (0.2%)	
2	10/596 (1.7%)	9/605 (1.5%)	
3	576/596 (96.6%)	589/605 (97.4%)	
Thrombus	7/596 (1.2%)	11/605 (1.8%)	0.48
Calcification Score			0.61
0	186/596 (31.2%)	175/605 (28.9%)	
1	159/596 (26.7%)	170/605 (28.1%)	
2	180/596 (30.2%)	189/605 (31.2%)	
3	71/596 (11.9%)	71/605 (11.7%)	
Ostial lesion	57/596 (9.6%)	54/605 (8.9%)	0.77
Bifurcation lesion	120/596 (20.1%)	93/605 (15.4%)	0.03
Chronic total occlusion	5/596 (0.8%)	2/605 (0.3%)	0.28
Procedural characteristics			
Access site			0.31
Radial	337 (68.1%)	326 (65.1%)	
Femoral	158 (31.9%)	175 (34.9%)	
Pre-procedural reference vessel diameter (mm)	2.89±0.50	2.89±0.52	> 0.99
Pre-procedural minimal lumen diameter (mm)	1.05±0.41	1.10±0.41	0.05
Pre-procedural diameter stenosis (%)	63.8±11.7	62.2±11.5	0.02
Lesion length (mm)	15.0±9.0	14.5±8.1	0.29
Post-procedural minimal lumen diameter (mm)	2.65±0.45	2.67±0.47	0.49
Post-procedural in-segment stenosis (%)	21.2±9.9	19.9±8.8	0.05
Post-procedural in-stent stenosis (%)	11.3±6.2	10.7±5.5	0.31
Acute gain (%)	52.4±12.7	51.4±12.1	0.19
Procedural success (%)	590/599 (98.5%)	613/616 (99.5%)	0.09

TIMI, Thrombolysis in Myocardial Infarction. Adapted from (144).

Table 13. Stent characteristics

	COBRA PzF Group (N=495 patients, 599 lesions, 696 stents)	Control Group (N=501 patients, 616 lesions, 692 stents)	P value
Stent characteristics			
No. of Stents per lesion			0.22
0	5/599 (0.8%)	5/616 (0.8%)	
1	509/599 (85.0%)	539/616 (87.5%)	
2+	85/599 (14.2%)	72/616 (11.7%)	
Stent Type			
COBRA	679/696 (97.6%)	2/692 (0.3%)	
DP-EES	2/696 (0.3%)	365/692 (52.8%)	
BP-SES	5/696 (0.7%)	10/692 (1.5%)	
DP-ZES	8/696 (1.2%)	133/692 (19.2%)	
DP-RES	0/696 (0.0%)	4/692 (0.6%)	
BP-EES	2/696 (0.3%)	167/692 (24.1%)	
Other	0/696 (0.0%)	11/692 (1.6%)	
Mean stent length (mm)	19.9 ± 6.8	20.0 ± 7.7	0.50
Mean stent diameter (mm)	3.1 ± 0.5	3.1 ± 0.5	0.40
Pre-dilatation performed	421/599 (70.3%)	420/616 (68.2%)	0.46
Max balloon diameter (mm)	2.6 ± 0.4	2.6 ± 0.5	0.96
Post-dilatation performed	277/599 (46.2%)	272/616 (44.2%)	0.49
Max balloon diameter (mm)	3.3 ± 0.6	3.3 ± 0.6	0.81

DP, durable polymer; BP, biodegradable polymer; EES, everolimus eluting stent; RES, ridaforolimus eluting stent; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent. Adapted from (144).

Antithrombotic therapy

Information on DAPT was documented throughout the post-procedure period for both the ITT and PP populations. In the first 2 weeks following the procedure, 96.1% of patients in the COBRA PzF group and 97.6% of patients in the control group were on DAPT in the ITT population. From day 15 to day 90 after the PCI procedure, 2.5% of the COBRA PzF group and 85.2% of the control group were on DAPT (ITT population). In the PP COBRA PzF group, only 0.7% of patients continued DAPT beyond 14 days. The proportion of ITT patients on DAPT dropped further during the 91-180 days post procedure. During this period, 2.1% of patients in the COBRA PzF group and 37.7% of patients in the control group were on DAPT.

On the day of discharge, 97.2% of patients in the ITT COBRA PzF group were taking OAC therapy (27.5% were taking coumadin derivatives, 69.7% NOACs). In the control group, 96.2% of patients were taking OAC therapy (27.2% taking coumadin derivatives, 69.1% NOACs). A reduced dose of NOAC was used in 46% of patients in the COBRA PzF group and 56% of patients in the control group (p=0.006).

Clinical outcomes

Co-primary endpoints: outcomes at 6 months in the ITT analysis

The outcomes for both the bleeding and thromboembolic co-primary endpoints in the COBRA PzF and control groups are summarized in **Table 14.**

Bleeding co-primary endpoint

The bleeding co-primary endpoint, BARC ≥2 bleeding at 6 months, occurred in 37 of 475 patients (7.8%) in the COBRA PzF group and 47 of 482 patients (9.8%) in the control group (Difference, -2.0; 95% CI, -5.6-1.6, p-value for superiority=0.14; **Figure 21**).

Thromboembolic co-primary endpoint

The thrombo-embolic co-primary endpoint, a composite of all-cause death, myocardial infarction, definite or probable ST, or ischemic stroke occurred in 37 of 492 patients (7.5%) in the COBRA PzF group and 24 of 490 patients (4.9%) in the control group (difference, 2.6%; upper limit of one-sided 95% CI of the difference, 5.2%, p value for non-inferiority= 0.07; **Figure 22**). Further data regarding the individual components of the thrombo-embolic co-primary endpoint are shown in **Table 14.**

Table 14. Co-primary endpoints to 180 days (Intention-to-treat population)

Co-Primary bleeding endpoint*	COBRA PzF Group (N=495)	Control Group (N=501)	Difference	(95% Confidence interval)	P value
BARC ≥2 Bleeding	37/475 (7.8%)	47/482 (9.8%)	-2.0%	(-5.6 to 1.6)	0.14

Co-Primary thrombo-embolic endpoint**	COBRA PzF Group (N=495)	Control Group (N=501)	Difference	Upper limit of the one-sided 95% CI of the difference	P value for non-inferiority
Composite of all-cause death, myocardial infarction, definite and probable stent thrombosis, or ischemic stroke	37/492 (7.5%)	24/490 (4.9%)	2.6%	5.2%	0.07

Individual components of the co-primary thrombo-embolic endpoint	COBRA PzF Group (N=495)	Control Group (N=501)
All cause death	21/492 (4.3%)	14/490 (2.9%)
Myocardial infarction	13/473 (2.8%)	8/476 (1.7%)
Definite stent thrombosis	2/472 (0.4%)	3/477 (0.6%)
Probable stent thrombosis	0/472 (0.0%)	0/476 (0.0%)
Ischemic stroke	5/473 (1.1%)	3/477 (0.6%)

*The endpoint is reported starting from the day after discharge or 14 days after randomization whichever is later, and for all patients with events to 180 days or follow-up of at least 166 days. **At 6 months post-randomization. The endpoint is reported for patients with at least 166 days of follow-up following the index procedure or with the study endpoint within 180 days post-index procedure.

n/N (%): n=number of events, N=number of patients, %=percentage

BARC, Bleeding Academic Research Consortium

Adapted from (144).

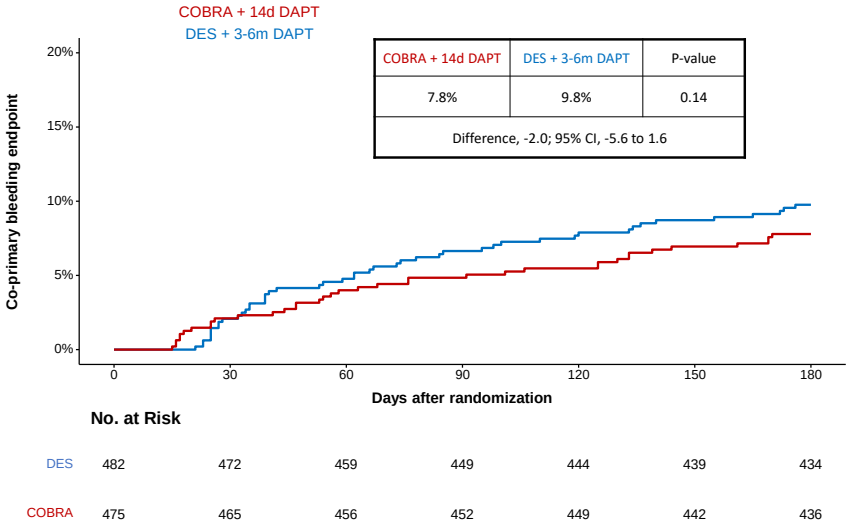

Figure 21. Bleeding co-primary endpoint (Bleeding Academic Research Consortium type 2-5 bleeding) from 14 to 180 days after PCI

DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

Adapted from (144).

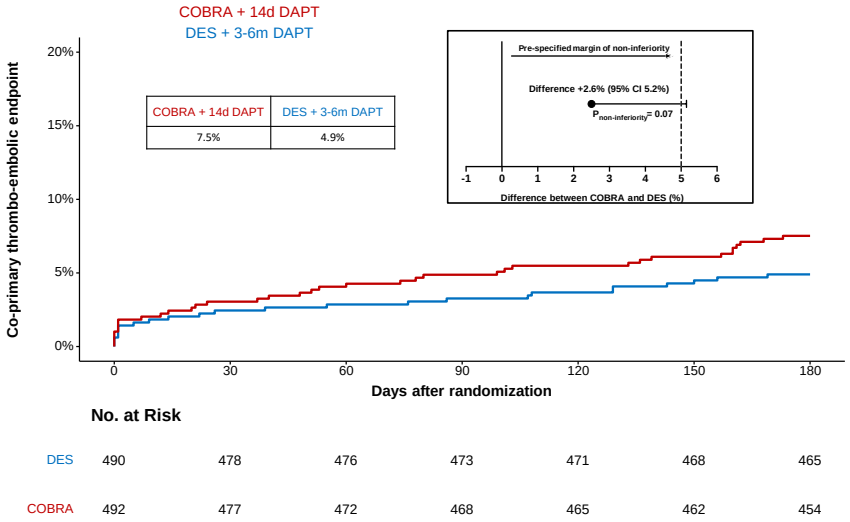

Figure 22. Thrombo-embolic co-primary endpoint (death, myocardial infarction, stent thrombosis, or ischemic stroke) from 0 to 180 days after PCI

DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

Adapted from (144).

Per protocol and modified intention-to-treat analysis

In both the PP and mITT, the COBRA PzF group was not found to be superior to the control group with respect to the co-primary bleeding endpoint and was not non-inferior to the control group with respect to the co-primary thromboembolic endpoint.

Subgroup analyses

A pre-specified subgroup analysis was performed for both of the co-primary endpoints (**Figure A9** and **Figure A10**). With regard to the co-primary bleeding endpoint, no statistically significant treatment effect interactions were observed. With regard to the co-primary thromboembolic endpoint, the most relevant interaction was between sex and type of stent (p=0.03).

Survival analysis

Kaplan Meier (KM) plots were used to display survival analysis for the co-primary endpoints (**Figure A11** and **Figure A12**). The treatment effects for the bleeding co-primary endpoint (7.8% vs. 9.8%, HR=0.79 [95% CI, 0.53–1.18]; p=0.25) and thromboembolic co-primary endpoint (7.5% vs. 4.9%, HR=1.55 [95%CI, 0.92–2.62]; p=0.10) were broadly consistent using this methodology. Hazard ratios and their associated 95% confidence intervals for the co-primary endpoints are shown in **Figures A11 and A12** in the Appendix.

Secondary endpoints

The secondary endpoints (to 180 days post-randomization for the secondary bleeding endpoints and to 360 days post-randomization for the secondary thromboembolic endpoints) are summarized in **Table 15.**

Secondary bleeding endpoints

BARC 3 to 5 bleeding at 180 days post-randomization occurred in 18/474 patients in the COBRA PzF group and 22/481 patients in the control group (3.8% vs. 4.6%, p=0.63). TIMI

Major and Minor Bleeding were also comparable between the two groups at 180 days post randomization (**Table 15**).

Secondary thromboembolic endpoints

The composite endpoint of all-cause death, myocardial infarction, definite and probable ST, ischemia-driven target lesion revascularization (ID-TLR), or ischemic stroke at 360 days post-randomization occurred in 64 of 488 patients (13.1%) in the COBRA PzF group and 42 of 485 patients (8.7%) in the control group (p=0.03). ID-TLR occurred in 24 of 460 patients (5.2%) in the COBRA PzF group and 10 of 465 (2.1%) patients in the control group (p=0.01). The remaining secondary thrombo-embolic endpoints: cardiac death or myocardial infarction (5.3% vs. 4.6%, p=0.66), definite or probable ST (0.4% vs. 0.6%, p>0.99), and ischemic stroke (1.3% vs. 0.6%, p=0.34) were comparable between the two groups at 360 days post randomization.

Table 15. Secondary endpoints (Intention-to-treat population)

Secondary bleeding endpoints (to 180 days post randomization)					
Secondary bleeding endpoints*	**COBRA PzF Group (N=495)**	**Control Group (N=501)**	**Difference**	**(95% CI of the difference Wilson Method)**	**P value**
BARC 3-5 Bleeding	18/474 (3.8%)	22/481 (4.6%)	-0.8%	-3.4% to 1.8%	0.63
TIMI Major or Minor Bleeding	17/474 (3.6%)	19/481 (4.0%)	-0.4%	-2.9% to 2.2%	0.87
TIMI Major Bleeding	8/473 (1.7%)	12/481 (2.5%)	-0.8%	-2.8% to 1.1%	0.50
TIMI Minor Bleeding	9/473 (1.9%)	8/477 (1.7%)	0.2%	-1.6% to 2.1%	0.81
Secondary thrombo-embolic endpoints (to 360 days post randomization)					
Secondary thrombo-embolic endpoints**	**COBRA PzF Group (N=495)**	**Control Group (N=501)**	**Difference**	**(95% CI of the difference Wilson Method)**	**P value**
All cause death, MI, definite or probable ST, IDTLR, or ischemic stroke	64/488 (13.1%)	42/485 (8.7%)	4.5%	0.5% to 8.4%	0.03
Cardiac death or MI	25/470 (5.3%)	22/473 (4.6%)	0.7%	-2.2% to 3.5%	0.66
Ischemia-driven target lesion revascularization	24/460 (5.2%)	10/465 (2.1%)	3.1%	0.6% to 5.7%	0.01
Definite or probable stent thrombosis	2/459 (0.4%)	3/464 (0.6%)	-0.2%	-1.5% to 1.0%	>0.99
Ischemic stroke	6/460 (1.3%)	3/465 (0.6%)	0.7%	-0.8% to 2.2%	0.34

*The secondary bleeding endpoints are reported for after the discharge or beyond 14 days post index procedure, whichever is later.

**The secondary thrombo-embolic endpoints are reported for all patients with events to 360 days or follow-up of at least 330 days following the index procedure.

n/N (%): n=number of events, N=number of patients, %=percentage

BARC, Bleeding Academic Research Consortium; CI, confidence interval; IDTLR, ischemia-driven target lesion revascularization; MI, myocardial infarction; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

5 DISCUSSION

The main objective of this thesis was to provide insights into the optimal antiplatelet therapy in patients with CAD undergoing PCI. Specifically, the thesis focused on the use of the third-generation $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, in specific groups of patients with ACS undergoing an invasive management strategy. In addition, the thesis aimed to assess the optimal duration of antiplatelet therapy in patients undergoing PCI, to test new strategies to reduce the bleeding risk in patients taking OAC and undergoing PCI, and to identify markers of ischemic and bleeding risk in patients with CCS undergoing PCI. These objectives were addressed by the 7 studies included in this thesis. The main findings of this thesis are discussed below.

5.1 THE EFFICACY AND SAFETY OF AGE- AND WEIGHT-ADAPTED DOSE OF PRASUGREL VERSUS STANDARD DOSE OF TICAGRELOR

The main findings of this part of the thesis may be summarized as follows:

- In patients aged ≥75 years or those with a body weight <60 kg, a reduced dose of prasugrel was associated with similar efficacy to a standard dose of ticagrelor in terms of ischemic complications (all-cause death, myocardial infarction, or stroke);
- In patients aged <75 years weighing 60 kg or more, the 10 mg maintenance dose of prasugrel was associated with a significantly lower risk of ischemic events compared with the standard dose of ticagrelor;
- The reduced maintenance dose of prasugrel in patients aged 75 or older or with a body weight less than 60 kg appears to mitigate the excess risk of bleeding previously observed with the full dose of prasugrel in this group of patients.

To the best of our knowledge, this is the first study to compare the efficacy and safety of a reduced dose of prasugrel with a standard dose of ticagrelor in elderly patients (aged ≥75 years) or patients with low body weight (<60 kg). In this study, we found that a reduced dose of prasugrel versus the standard dose of ticagrelor in elderly or low-weight patients with ACS is associated with a maintained anti-ischemic efficacy without increasing the risk of bleeding. In line with the results of the primary trial (59), in patients aged <75 years with a body weight ≥60 kg, prasugrel at a maintenance dose of 10 mg was associated with a significantly lower risk of ischemic complications compared with ticagrelor at 1-year follow-up. With regard to all bleeding events, we found a treatment effect-by-study group interaction, suggesting that the reduced dose of prasugrel prevented the excess risk for bleeding previously observed with the full dose of prasugrel in patients aged 75 years or older or with a body weight less than 60 kg (55). In light of this, age- and weight-based dose adaptation of prasugrel may at least partially explain why prasugrel did not raise the risk of bleeding in the whole population of the ISAR-REACT 5 trial, despite significantly reducing ischemic complications compared with ticagrelor. Another explanation for this could be that, in contrast to ticagrelor, which was usually given as preloading, the loading dose of prasugrel was given after diagnostic angiography in the majority of trial participants. This might have impacted early postprocedural bleeding, which is a major contributor to the overall incidence of bleeding.

The increased risk of serious bleeding associated with the full dose of prasugrel (10 mg) in elderly patients and those with low body weight, as documented in the TRITON-TIMI 38 trial (55), is the basis for using a lower dose of prasugrel (5mg) in this group of patients. Further investigations on platelet inhibition showed that a 5-mg dose of prasugrel in patients who were 75 years of age or older or who weighed less than 60 kg was not less effective than a 10-

mg dose in individuals who were younger or weighed 60 kg or more (145,146). Additionally, research on platelet function revealed that in individuals receiving conservative treatment for NSTE-ACS (62) or in elderly patients receiving aspirin for stable CAD (145), a 5-mg dose of prasugrel exhibited a higher degree of platelet inhibition than clopidogrel, 75 mg. In a study of elderly patients with ACS undergoing PCI and exhibiting high platelet reactivity while receiving clopidogrel, prasugrel, 5 mg/d, significantly reduced platelet reactivity and the proportion of patients with high platelet reactivity compared with clopidogrel, 150 mg/d (147). Research has demonstrated that in elderly patients, a lower dosage of prasugrel is equivalent to clopidogrel. In a subgroup analysis of the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Manage Acute Coronary Syndromes) study, which included patients with NSTE-ACS treated conservatively, the rates of TIMI major bleeding and ischemic complications were similar with reduced-dose prasugrel and clopidogrel in elderly patients (62).

With respect to ticagrelor use in elderly patients, the PLATO trial found that the efficacy and safety of ticagrelor did not depend on age (56). Registry data have produced contradictory findings with respect to the efficacy or safety of ticagrelor in the elderly. In one registry of patients aged ≥80 undergoing successful PCI for NSTE-ACS, ticagrelor and clopidogrel were associated with equal rates of ischemic events (148). In this study, therapy with ticagrelor was associated with higher rates of relevant bleeding (148). Another registry of elderly patients (aged ≥ 75 years) presenting with STEMI and treated with primary PCI showed the superiority of ticagrelor over clopidogrel in reducing major adverse cardiac and cerebrovascular events, with no significant difference in mortality or bleeding at 1 year (149).

In summary, this part of the thesis showed that in ACS patients 75 years or older, or those with a body weight of less than 60 kg, a reduced dose of prasugrel (5 mg/day) was associated with maintained antiischemic efficacy and a reduction in excess bleeding risk compared to the standard dose of ticagrelor (180 mg/day) up to one year after PCI.

5.2 PRE-ADMISSION ANTIPLATELET THERAPY AND EFFICACY AND SAFETY OF TICAGRELOR VS. PRASUGREL

The key findings of the analysis that assessed the efficacy and safety of ticagrelor versus prasugrel according to pre-admission antiplatelet therapy status in patients presenting with ACS planned to undergo an invasive management strategy were as follows:

- Patients on pre-admission therapy with aspirin and/or clopidogrel had a higher risk of ischemic events but a similar risk of bleeding to patients not on pre-admission therapy with aspirin or clopidogrel;
- Pre-admission therapy with aspirin and/or clopidogrel had no significant influence on the treatment effect of ticagrelor vs. prasugrel in terms of efficacy. Thus, the advantage of prasugrel over ticagrelor in reducing the one-year ischemic risk was consistent irrespective of pre-admission use of antiplatelet drug therapy, albeit with different risk estimates;
- The relative safety (bleeding risk) of ticagrelor and prasugrel was not influenced by pre-admission antiplatelet drug therapy.

There is limited evidence on the efficacy and safety of ticagrelor vs. prasugrel according to pre-admission antiplatelet treatment status. In the PLATO trial, the efficacy and safety of ticagrelor vs. clopidogrel were not affected by prior antiplatelet therapy (56). In this study, the incidence of ischemic events was numerically lower with ticagrelor than clopidogrel, regardless of prior treatment with aspirin and/or clopidogrel. Bleeding events were

comparable between the two treatment groups, irrespective of prior antiplatelet treatment status. A subgroup analysis of the Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial (150), which investigated the effectiveness and safety of ticagrelor versus aspirin in patients presenting with acute ischemic stroke or transient ischemic attack and on aspirin therapy within the preceding 7 days before randomization, revealed a lower incidence of primary endpoint events (including time to stroke, myocardial infarction, or death) among patients treated with ticagrelor compared with those treated with aspirin. However, there was no statistically significant interaction observed between treatment and prior aspirin use (150). The incidence of bleeding events was comparable between ticagrelor- and aspirin- assigned patients, irrespective of prior aspirin use. The Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease (ONSET/OFFSET) study, which assessed platelet inhibition with ticagrelor vs. high-loading dose clopidogrel in patients with stable CAD on prior aspirin therapy (75–100 mg/day), found a more rapid and greater platelet inhibition with ticagrelor compared with clopidogrel and a higher rate of bleeding-related events in the ticagrelor arm (64).

The available evidence regarding the impact of prior therapy with aspirin and/or clopidogrel on the efficacy and safety of prasugrel in patients with ACS is rather limited. A subgroup analysis of the TRILOGY ACS trial, assessing the influence of prior clopidogrel use on clinical outcomes of patients with ACS treated medically, found that prior clopidogrel use did not affect the treatment effect of prasugrel vs. clopidogrel (P for interaction >0.05)(151).

In the present study, we found that patients on pre-admission therapy with aspirin and/or clopidogrel had a significantly higher ischemic risk and a similar bleeding risk to patients in

the no pre-admission aspirin and/or clopidogrel. Previous studies have reported similar findings in patients with NSTE-ACS (66-68,151). We found that patients on pre-admission aspirin and/or clopidogrel had a worse cardiovascular risk profile compared with patients not on pre-admission therapy with aspirin or clopidogrel. Specifically, patients in the pre-admission aspirin and/or clopidogrel group were older and more likely to have diabetes mellitus, arterial hypertension, hypercholesterolemia, and prior revascularization procedures. Additionally, they presented more often with NSTE-ACS, a subgroup of patients with ACS known to have a particularly worse cardiovascular risk profile (152). The worse cardiovascular risk profile of patients being on antiplatelet drug therapy before admission may explain the higher incidence of ischaemic events in these patients. Along the same lines, a study by Rich *et al.* (153) found that in patients with ACS, prior aspirin use was associated with a higher risk of recurrent cardiovascular events. As anticipated, individuals with previous aspirin use in this study exhibited a higher baseline risk profile and presented with less severe clinical symptoms. In a study conducted by Regev *et al*. (69), it was found that patients with prior clopidogrel therapy who presented with acute MI demonstrated higher ADP-induced platelet aggregation and a diminished response to clopidogrel compared to matched clopidogrel-naïve patients. This observation may suggest a potential involvement of clopidogrel hyporesponsiveness in the pathogenesis of acute MI in these individuals. In this regard, it may be postulated that besides the worse cardiovascular risk profile in patients receiving antiplatelet drugs before admission for an ACS, the occurrence of an ACS while on antiplatelet therapy may indicate a poor response to this therapy, potentially related to a higher probability of resistance to aspirin or clopidogrel among these patients. However, it remains speculative whether hyporesponsiveness to aspirin or clopidogrel contributed to the

occurrence of ACS in our patients who were on antiplatelet therapy before admission. In patients with acute MI, similar ischemic and bleeding risks between patients with and without prior aspirin therapy have been reported (154). Likewise, another study in patients with acute MI reported a similar bleeding risk in patients on antiplatelet therapy compared with those not on antiplatelet treatment at the time of presentation (155). However, despite having a worse cardiovascular baseline risk profile, patients on pre-admission antiplatelet therapy had a smaller infarct size compared with patients not on antiplatelet therapy (155). A previous study showed that the degree of platelet inhibition from a 600 mg loading dose of clopidogrel did not depend on whether the patient was on chronic clopidogrel therapy (156). In this regard, our findings are reassuring with respect to the use of a loading dose of ticagrelor or prasugrel in patients with ACS regardless of pre-admission antiplatelet drug therapy with aspirin and/or clopidogrel.

5.3 HIGH BLEEDING RISK AND THE EFFICACY AND SAFETY OF TICAGRELOR VERSUS PRASUGREL

This part of the thesis addressed the efficacy and safety of ticagrelor versus prasugrel according to bleeding risk in patients with ACS undergoing an invasive management strategy. This analysis and the source study (123) represent the first comparison of the efficacy and safety of ticagrelor vs. prasugrel according to bleeding risk in a contemporary cohort of ACS patients undergoing PCI. The principal findings may be summarized as follows:

- Patients with ACS and HBR features (as defined by the ARC-HBR consensus), had an increased risk of ischemic and bleeding events after PCI compared with patients without HBR;
- Therapy with ticagrelor and prasugrel was associated with a comparable bleeding risk regardless of HBR status;

- The superior efficacy of prasugrel over ticagrelor was more evident in non-HBR patients, albeit without significant interaction between HBR status and the treatment effect of these drugs.

This analysis has some unique features. Firstly, we studied the efficacy and safety of the more potent $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, according to HBR status in patients with ACS undergoing PCI. Patients at HBR treated with either ticagrelor or prasugrel showed a 3-fold higher risk of major bleeding at 12 months compared with non-HBR patients. Interestingly, in patients in the non-HBR group, the incidence of major bleeding after 1 year exceeded the 4% threshold defining the HBR status, as per ARC definition. This suggests that ACS foretells an inherent risk of bleeding regardless of ARC-HBR criteria, even though the percentage of HBR patients included in our analysis was small in absolute terms (15.0% of all PCI patients with available data). This is likely attributable to the more aggressive antithrombotic therapies and the hemostatic dysregulation secondary to the pro-inflammatory state of unstable CAD (157).

Secondly, as per the ISAR-REACT 5 trial protocol, participants were randomized to either ticagrelor or prasugrel strategy at the time of invasive evaluation, implying that patients at high risk for early adverse events were not excluded. The landmark analysis performed here gives support to a constant risk of ischemic and bleeding events out to 1 year after PCI. A pre-specified subgroup analysis of the Ticagrelor with or without Aspirin in High-Risk Patients after PCI (TWILIGHT) trial performed in HBR patients undergoing PCI for stable CAD, unstable angina, or NSTEMI, who completed 3-month of DAPT without adverse events, showed that ticagrelor monotherapy significantly reduced bleeding without increasing ischemic events, compared with ticagrelor-based DAPT for 12 months (158). However, the

overall event rates in this trial were lower than expected, likely due to the exclusion of patients experiencing adverse events within 3 months after PCI.

Thirdly, in previous observations of patients undergoing PCI according to HBR status, DAPT regimens diverged to various extents from current guidelines recommendations in terms of both composition and duration (158,159). Furthermore, investigations on the clinical efficacy and safety of prasugrel in patients undergoing PCI with HBR have yet to be performed. In this respect, the present analysis provides novel insights into the contemporary management of patients with ACS and HBR features undergoing PCI and treated with ticagrelor or prasugrel — the guideline-recommended $P2Y_{12}$ inhibitors for patients with ACS not requiring long-term oral anticoagulation. We found no significant antiplatelet treatment-by-HBR status interaction regarding the bleeding risk. This may imply that the superior antithrombotic potency of prasugrel is not about trading off benefits against the increased risk of bleeding. This is of paramount importance because HBR patients are at increased risk for bleeding and thrombotic events owing to their poor cardiovascular risk profile (160,161). Consistently, in this study, patients in the HBR group were more likely to have diabetes mellitus, arterial hypertension, hypercholesterolemia, and a history of CAD, and a two-fold increase in the risk of MI and definite or probable ST after 12 months as compared with non-HBR patients.

Our study showed that the anti-ischemic efficacy of ticagrelor and prasugrel did not differ significantly in HBR patients. In contrast, prasugrel significantly reduced the primary ischemic endpoint compared with ticagrelor in non-HBR patients, albeit without significant treatment effect-by-HBR status interaction. Although the difference in the anti-ischemic efficacy of ticagrelor versus prasugrel according to HBR status is not fully understood, the

imbalance in baseline characteristics between the groups with and without HBR features may offer some explanations. Specifically, the HBR group had a higher proportion of patients ≥75 years, women, and patients with diabetes mellitus compared with the non-HBR group. Previous analyses of the ISAR-REACT 5 trial reported no significant differences in the anti-ischemic efficacy of ticagrelor and prasugrel in these subgroups (65,162,163). Furthermore, better adherence to assigned drugs in the non-HBR group compared with the HBR group could have played a role in the observed HBR status-related differences in the efficacy of the drugs. With regard to the safety endpoint, we found that prasugrel did not increase the risk of bleeding in either the HBR or non-HBR group. Patients ≥75 years, present in a higher proportion in the HBR group, received by protocol a reduced dose of prasugrel. This may partly explain the lack of increased bleeding with prasugrel in this group.

Finally, the proportion and the distribution of HBR criteria partially differed from previous analyses of HBR patients treated with PCI (158,159) and ARC-HBR validation studies (164-166). On the one side, the need for lifelong oral anticoagulation, a previous cerebrovascular accident, and a bleeding diathesis were among the key exclusion criteria of the ISAR-REACT 5 trial. For this reason, these conditions were not represented in the present cohort in which minor criteria such as age ≥75 years and moderate chronic kidney disease were mostly prevalent. On the other side, beyond a different risk profile due to ethnicity (159), previous investigations included predominantly HBR patients treated with PCI due to stable CAD (158,159), with recognized differences in baseline characteristics compared with ACS patients (167). Although the current analysis confirms the concomitant risk of ischemic and bleeding events in patients with HBR undergoing PCI due to ACS, it also documented a modest discriminatory power of HBR risk score in predicting future adverse events.

5.4 THE EFFICACY AND SAFETY OF TICAGRELOR VS. PRASUGREL ACCORDING TO SMOKING STATUS

In this part of the thesis and the source study (124), the efficacy and safety of ticagrelor versus prasugrel according to smoking status in patients with ACS were assessed. The main finding of this analysis was that there was no significant interaction between smoking status and the treatment effect of ticagrelor versus prasugrel with respect to both ischemic and bleeding complications in patients with ACS undergoing an invasive treatment strategy.

There is limited and conflicting evidence regarding the influence of smoking status on the efficacy and safety of ticagrelor or prasugrel in patients with ACS undergoing PCI. The Influence of Smoking Status on the Pharmacodynamics of Prasugrel and Clopidogrel (PARADOX) study found that on-prasugrel treatment platelet reactivity was not different between smokers and nonsmokers (83). Contrary to these findings, several studies reported higher ADP-induced platelet reactivity on prasugrel treatment in smokers compared with nonsmokers (168-170). A subgroup analysis of the TRILOGY ACS trial that included patients <75 years of age showed that smokers had lower platelet reactivity in both prasugrel and clopidogrel groups. Importantly, a significant reduction in the incidence of ischemic events (cardiovascular death, myocardial infarction, or stroke) by prasugrel compared to clopidogrel was observed in smokers but not nonsmokers through 30 months of follow-up, with a significant treatment-by-smoking status interaction (171). The authors suggested that mechanisms beyond platelet reactivity may influence the response to therapy in this population.

A post-hoc analysis of the PLATO trial showed that the treatment effect of ticagrelor compared with clopidogrel was consistent for all outcomes regardless of smoking status, with no treatment-by-smoking status interaction for any of the outcomes investigated (172).

However, smoking was associated with a higher incidence of definite stent thrombosis, even after adjustment for imbalances in the baseline data. A pharmacokinetic study in patients with ACS showed that habitual smoking decreased apparent ticagrelor clearance by 22%, simultaneously increasing apparent clearance of ticagrelor active metabolite, AR-C124910XX (173). Another recent pharmacokinetic study suggested that smoking may increase the degree of ticagrelor transformation in patients with ACS, based on the area under the plasma concentration-time curve for AR-C124910XX (AUC_M) to AUC for ticagrelor (AUC_T) ratio (174). However, at present, the clinical significance of these findings remains unclear. A 2013 meta-analysis that included 9 randomized trials with 74,489 patients, of whom 21,717 were smokers, concluded that the newer antiplatelet drugs, prasugrel and ticagrelor, appear to be more efficacious in smokers and marginally more efficacious in nonsmokers compared with clopidogrel (175). However, it is important to mention that usually smokers are younger than nonsmokers at the time of hospital admission for CAD. In indirect comparisons, the relative risk for the composite outcome of cardiovascular death, myocardial infarction, or stroke was 15% lower for prasugrel versus ticagrelor in smokers and only 3% higher (prasugrel vs ticagrelor) in nonsmokers, both under the level of statistical significance (175). Notably, due to the lack of head-to-head comparisons between prasugrel and ticagrelor, the question of whether there is a differentiated effect of smoking on the efficacy or safety of these drugs remains unanswered. A recent retrospective cohort analysis suggested lower ischemic and bleeding risks with ticagrelor versus prasugrel; however, an analysis of the efficacy or safety of these drugs according to smoking status was not performed (176).

5.5 Comparison of ≤3 months with ≥6 months of dual antiplatelet therapy in patients undergoing drug-eluting stent implantation — A meta-analysis of randomized trials

This meta-analysis (132) included 9 randomized controlled trials (126,127,129,138-143) with a total of 41,864 patients with DES implantation receiving either short or standard DAPT duration. The main findings were:

- Short DAPT duration was not associated with an increase in the rate of ST, all-cause death, cardiac death, MI, and stroke;
- Bleeding rates were higher with longer DAPT duration;
- Short DAPT was associated with reduced bleeding rates in patients receiving aspirin- as well as $P2Y_{12}$ inhibitor- monotherapy after initial DAPT.

The optimal duration of DAPT following PCI remains a matter of debate. An early meta-analysis comparing 6 months vs. 1 year vs. longer than 1-year DAPT durations found that DAPT duration beyond one year reduced MI and ST but was associated with increased mortality, while 6 months DAPT vs. 12 months DAPT had similar rates of ischemic events including mortality, MI, and ST but was associated with lower rates of major bleeding (177). Several studies have therefore evaluated an even shorter duration of DAPT of ≤ 3 months compared with ≥ 6 months of DAPT, and these are included in the present study. None of the included 9 trials showed increased ischemic events with the shorter DAPT duration; however, these trials were not adequately powered to assess rare events such as ST properly. In our meta-analysis, we could show that ST and ischemic events such as cardiac death, MI, or stroke are not increased with a DAPT duration of ≤ 3 months. Moreover, this result was consistent in patients who continued with aspirin monotherapy (126,138,139,143) as well as in those who continued with $P2Y_{12}$ inhibitor monotherapy (127,129,140-142).

Our analysis confirms and extends the findings of previous meta-analyses (178,179), which have also assessed short DAPT with subsequent SAPT with either aspirin or a $P2Y_{12}$ inhibitor. These analyses have also found that the incidence of ischemic events was not increased with short DAPT. While these analyses primarily found a bleeding reduction with short DAPT and subsequent $P2Y_{12}$ inhibitor therapy, our analysis also showed that patients who continued with aspirin monotherapy were also at a significantly lower risk for bleeding. This may be attributed to the fact that they had different inclusion criteria (179), different studies were included (178,179), and different bleeding definitions were applied compared with our analysis.

It is interesting that bleeding rates were numerically higher in the $P2Y_{12}$ inhibitor monotherapy trials than in the aspirin monotherapy ones. However, it is difficult to compare these numbers because patient populations, the used $P2Y_{12}$ inhibitor, and bleeding definitions between trials differed. The results of our meta-analysis neither favor aspirin nor $P2Y_{12}$ inhibitor monotherapy because both strategies reduced bleeding events without an increase in ischemic events. In the SOCRATES trial, ticagrelor monotherapy was compared with aspirin monotherapy in patients with acute ischemic stroke or TIA, and no significant difference in the rate of major bleeding (180) or ischemic (181) events between the two groups was found. In the multicentric HOST-Extended Antiplatelet Monotherapy (HOST-EXAM) trial, clopidogrel monotherapy was reported to significantly lower the risk of both ischemic and bleeding events throughout the chronic maintenance phase following PCI with DES when compared with aspirin monotherapy in Asian populations (182).

It was speculated that patients with ACS may benefit from longer DAPT duration because of systemic antithrombotic properties, which are effective beyond the implanted

stent. In the present study, we did not specifically analyze ACS patients, but in the two included trials who included only ACS patients (129,139), 3-month DAPT was not associated with an increase in ischemic events. One explanation may come from the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) registry, which observed that ST risk in patients with MI was greatest in the first 30 days post-PCI and was observed predominantly among those with increased high platelet reactivity on clopidogrel (183). The other seven trials from our meta-analysis reported subgroup analyses on ACS patients regarding the primary combined endpoint. However, the primary combined endpoint varied among those trials and a meaningful comparison was therefore not feasible.

Several meta-analyses have found that longer than 12 months of DAPT duration leads to a reduction in ischemic events such as MI and ST (179,184). However, this effect is offset by higher bleeding rates, and some analyses have even found higher rates of non-cardiac death (184) with a longer duration of DAPT. We, therefore, believe that DAPT durations beyond 12 months should be reserved for patients with a high ischemic risk, such as those with recurrent ischemic events who tolerate DAPT well.

5.6 Plasma soluble glycoprotein VI, a specific marker of bleeding risk in patients undergoing elective percutaneous coronary intervention

In this analysis (137), we assessed the relationship between sGPVI levels, platelet function, bleeding and ischemic events in patients with CCS undergoing PCI. The key findings were:

- Plasma levels of sGPVI were stable and not influenced by elective PCI and peri-procedural antithrombotic therapy;

- Plasma levels of sGPVI did not correlate with ADP- or collagen-induced platelet aggregation at baseline and at day 2 after PCI;
- Patients with higher baseline plasma levels of sGPVI had a higher risk of bleeding but no excess risk of ischemic events within 30 days after PCI.

Our study showed that plasma levels of sGPVI remained stable and were not influenced by PCI and/or antithrombotic therapy loading. In addition, plasma levels of sGPVI were relatively independent of patients' baseline characteristics or drug therapy on admission. The strongest correlate of plasma sGPVI levels was platelet count. Although this relationship is mechanistically plausible because a higher platelet count provides more substrate for shedding, it is at variance with a previous study that showed no association between sGPVI and platelet count in patients with ACS (185). Differences between CCS and ACS patients are a likely explanation for the discrepancy between studies with the enhanced platelet activation and GPVI expression contributing more to plasma sGPVI in patients with ACS than platelet count.

We found no significant correlation between sGPVI and ADP- or collagen-induced platelet aggregation. This correlation has not been investigated before. The lack of correlation between sGPVI and ADP- or collagen-induced platelet aggregation remains poorly understood. However, shear-induced GPVI shedding, independent of platelet activation/aggregation, has been suggested as a mechanism for sGPVI level modulation in patients with CAD (186). Our findings suggest that ADP- and collagen-induced platelet aggregation testing cannot be used to assess the status or significance of sGPVI in patients with CCS.

Elevated plasma levels of sGPVI have been reported in patients with ACS and atrial fibrillation (187) and in patients with acute ischemic stroke (188). Our study showed that baseline plasma sGPVI levels of patients with CCS undergoing PCI failed to predict ischemic events at 48 hours and at 30 days after the procedure. The clinical significance of this finding is difficult to interpret. The main component of the ischemic endpoint of the study was myocardial injury, defined as a 5-time increase of hsTnT above the ULN within 48 hours after PCI. Although hsTnT is a very sensitive marker of procedure-related myocardial injury, it has a limited prognostic value in patients with CCS (189). In addition, the number of ischemic events at 30 days was low, and thus, the study is underpowered to assess the impact of sGPVI on MACE.

The most interesting finding of the present study is the association between plasma levels of sGPVI and bleeding. The sGPVI improved the discrimination for bleeding when added alongside baseline variables in the risk estimation models. This finding is novel and has not been reported before in patients with atherosclerotic disease, let alone in patients with CCS undergoing PCI. An association between sGPVI and bleeding has been reported in patients with suspected heparin-induced thrombocytopenia (190), or after implantation of left ventricular assist devices (191). However, the specific nature of these clinical conditions may not help to explain our findings. As already mentioned, we did not find an association between sGPVI and platelet function before and after administration of the loading dose of clopidogrel that could have driven the sGPVI-bleeding association. However, the predictive value of platelet function is less established for bleeding than it is for ischemic complications (192). It is difficult to attribute the association between sGPVI and bleeding to a specific mechanism, especially in the light of suggestions that sGPVI is essential for thrombosis but

not for hemostasis (193). A plausible hypothesis to explain our findings is that the reduced number of GPVI in platelets because of shedding may lead to desensitized or exhausted platelets and reduce their ability to respond adequately to collagen. Moreover, elevated levels of sGPVI – the ectodomain of GPVI responsible for platelet binding to collagen – may bind to exposed vascular collagen, hampering the platelet-collagen interaction, which may predispose to bleeding.

Prevention of bleeding after PCI in patients with CAD has become the focus of intensive work because of the relevance of bleeding as a prognostic factor (194,195). Identification of patients who benefit from bleeding reduction strategies without increasing their risk of ischemic complications remains challenging. Therefore, several high-bleeding risk scores have been proposed (122,196). A general limitation of existing clinical scores is that they poorly discriminate between ischemic and bleeding risk. In this regard, the identification of specific markers of bleeding risk may offer new valuable tools for guiding antithrombotic therapy in patients with CAD after PCI. As shown in the current study, sGPVI appears to be a specific marker candidate for bleeding in patients with CAD undergoing PCI. Nevertheless, this finding requires confirmation by larger prospective studies.

5.7 Role of special inactive stent coating in shortening the duration of dual antiplatelet therapy in patients on oral anticoagulation

In the first randomized clinical trial comparing the clinical safety and efficacy of the COBRA PzF stent in combination with 14 days of clopidogrel therapy with US FDA-approved DES in combination with 3-6 months of clopidogrel therapy, in patients taking OAC and aspirin, the key findings were:

- In patients with an indication for OAC undergoing PCI, treatment with the COBRA PzF stent plus 14 days of DAPT was not superior to treatment with a standard FDA-approved DES plus 3-6 months of DAPT with regard to the co-primary bleeding endpoint, BARC ≥2 bleeding, at 6 months.
- Treatment with the COBRA PzF stent plus 14 days of DAPT was not non-inferior to treatment with a standard FDA-approved DES plus 3-6 months of DAPT with regard to the co-primary thromboembolic endpoint, a composite of all-cause death, myocardial infarction, definite or probable ST or ischemic stroke, at 6 months.
- Patients in the COBRA PzF stent plus 14 days DAPT group also had a higher incidence of both the secondary composite thrombo-embolic endpoint and ID-TLR at 360 days.

These data do not support the initial study hypothesis that the use of the COBRA PzF stent plus 14 days of DAPT would demonstrate net clinical benefit in comparison to an FDA-approved DES and 3-6 months of DAPT in patients with an indication for OAC undergoing PCI. However, the design of this study, with differing ATT regimens in the COBRA PzF and control arms, means that it is not possible to determine the relative contribution of the different stent types and differing ATT regimens to the observed outcomes. Concerning the bleeding outcomes observed in the trial, a number of findings warrant further discussion. Firstly, despite the shorter duration of DAPT in the COBRA PzF arm, the bleeding co-primary endpoint was comparable in both study arms. This finding should be interpreted in light of the fact that this was an open-label study and decisions regarding NOAC dosing were left to the discretion of the treating physicians. A reduced dose of NOAC was used more frequently in patients in the control group, which may suggest an attempt by the treating physicians to minimize the totality of the bleeding risk in patients in the control group assigned to the longer duration

DAPT regimen. Although this may reflect clinical practice, this may have also reduced the ability to detect a difference in bleeding between the treatment groups. Second, by design, the bleeding co-primary endpoint did not include events during the first 14 days after the procedure as treatments during this time period were identical in the two arms. This is relevant when interpreting the data in the context of routine clinical practice, as the immediate and early post-procedural period is the highest risk time for bleeding events in patients undergoing PCI (197). Thirdly, in relation to the protocol-defined duration of antithrombotic therapy in patients in the control group treated with FDA-approved DES of 3-6 months, recent randomized clinical trial data from The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen (MASTER-DAPT) trial (198) investigating optimal antiplatelet therapy duration in patients at high bleeding risk, in which one-third of the randomized HBR patients were taking OAC, suggest that a shorter one-month duration of TAT improves outcomes compared with ≥3 months. Another possibility in this study is that any advantages conferred by the changes in DAPT duration may have been relatively minor in the context of an increased bleeding risk due to the use of OAC in an elderly patient population.

In addition to failing to demonstrate a benefit in terms of a reduction of bleeding events, the COBRA PzF arm did not meet the criteria for non-inferiority in comparison to the control arm with respect to the thromboembolic co-primary endpoint through to 6 months. However, at 1 year follow-up, the incidence of both the secondary thrombo-embolic composite endpoint and ID-TLR were higher in patients assigned to the COBRA PzF group. The difference in the incidence of the secondary ischemic endpoint at 360 days was driven primarily by TLR. Given the design of the COBRA PzF stent, the recognized increased risk of

restenosis with BMS compared with DES may be relevant with respect to this finding. However, differences in the antithrombotic regimens in the two randomized arms may have also contributed to this increased risk. Despite this, it is notable that the COBRA PzF stent was associated with a low incidence of definite or probable ST despite treatment with a DAPT duration of only 14 days.

Current guidelines and expert consensus documents recommend that patients with an indication for OAC undergoing PCI should receive a short period of TAT followed by DAT, consisting of OAC and SAPT (60,199). Meta-analyses of non-vitamin K antagonist oral anticoagulant (NOAC) based clinical trials have reported that while DAT is associated with a clear reduction in bleeding compared with TAT, this benefit may be counterbalanced by an increased risk of cardiac ischemic events, including ST (200,201). Consequently, there has been some debate regarding the optimal time for transition from TAT to DAT after PCI, with some authors suggesting that this should be individualized based on the clinical situation and the patient's bleeding and thrombotic risk profile (199,202).

In this study, all patients were taking OAC and aspirin, with only the duration of clopidogrel therapy differing between the two randomized treatment arms. However, an alternative strategy for these patients could be to drop aspirin after the initial period of TAT and use a clopidogrel and OAC-based DAT regimen thereafter. Some evidence for this approach after 1 month is provided by the MASTER-DAPT trial in which one-third of the randomized HBR patients were taking OAC (203). The combination of clopidogrel and OAC may strike a better balance with regard to ischemic and bleeding risk, particularly in patients

with ACS, and further studies to assess if this approach is useful in patients undergoing PCI with an indication for OAC may be useful.

6 CONCLUSIONS

This thesis summarized the results of 7 studies (65,121,123,124,132,137,144) with the main objective of providing new insights into the optimal antiplatelet treatment of patients with CAD undergoing PCI. The specific objectives of the thesis were:

1. to assess the effect of age- and weight-adapted dose of prasugrel vs. standard dose of ticagrelor on ischemic and bleeding risk in patients with ACS undergoing PCI;
2. to investigate the impact of pre-admission antiplatelet therapy on the efficacy and safety of ticagrelor and prasugrel in patients with ACS undergoing PCI;
3. to assess the comparative efficacy and safety of ticagrelor and prasugrel in patients with ACS and HBR undergoing PCI;
4. to evaluate the influence of smoking on the efficacy and safety of ticagrelor and prasugrel in patients with ACS undergoing PCI;
5. to compare clinical outcomes of short vs. standard DAPT duration in patients undergoing PCI;
6. to study the association between plasma levels of sGPVI and platelet function, bleeding and ischemic events in patients with CCS undergoing PCI; and
7. to investigate whether COBRA PzF stent plus 14 days of DAPT reduces bleeding compared with standard FDA-approved DES plus 3-6-months of DAPT while maintaining the anti-ischemic efficacy in patients on OAC undergoing PCI.

Based on the results outlined in this thesis, the main findings with respect to thesis objectives are as follows:

1. In ACS patients aged 75 years or older and/or those with a body weight of less than

60 kg, a reduced dose of prasugrel (5 mg) showed similar efficacy to the standard dose of ticagrelor in terms of ischemic risk (all-cause death, myocardial infarction, or stroke) after PCI. In patients <75 years or those with a body weight of 60 kg or more, prasugrel (10 mg) was associated with a reduced risk of ischemic events compared with ticagrelor. The reduced dose of prasugrel used in patients ≥75 years of age or those with a body weight <60 kg protected these patients from the excess risk of bleeding previously observed with the full dose of prasugrel.

2. Patients with ACS who were on antiplatelet therapy with aspirin and/or clopidogrel upon hospital admission had a higher risk of ischemic events but a similar risk of bleeding to patients not on such therapy, at one-year after randomization. In patients with ACS, the advantage of prasugrel over ticagrelor in reducing the one-year ischemic risk was consistent regardless of pre-admission use of antiplatelet therapy, albeit with different risk estimates. With regard to bleeding risk, the relative safety of ticagrelor and prasugrel was not influenced by pre-admission antiplatelet drug therapy.

3. Patients with ACS and HBR features experienced more ischemic and bleeding events after PCI compared with patients without HBR features. The relative safety of ticagrelor and prasugrel was not dependent on HBR status. With respect to the efficacy of the drugs, we found that the superiority of prasugrel over ticagrelor was more evident in non-HBR patients, albeit without significant treatment effect-by-HBR status interaction.

4. In patients with ACS undergoing an invasive management strategy, smoking status did not significantly interact with the relative treatment effect of ticagrelor vs.

prasugrel. Prasugrel numerically reduced the one-year ischemic risk compared with ticagrelor regardless of smoking status. The incidence of bleeding events was comparable between patients assigned to ticagrelor and prasugrel, irrespective of smoking status.

5. In a meta-analysis of study-level data from 9 randomized clinical trials assessing the benefits and risks of a short vs. standard DAPT duration, we found that in patients with CAD undergoing DES implantation, short DAPT duration (≤3 months) reduces bleeding and is not associated with an increased risk of ST, mortality, or other ischemic events. The reduction in bleeding with short DAPT is consistent regardless of the SAPT type (aspirin or $P2Y_{12}$ inhibitor) used following short DAPT.

6. In patients with CCS undergoing PCI, plasma levels of sGPVI did not correlate with ADP- and collagen-induced platelet aggregation. Patients with higher baseline plasma levels of sGPVI had a higher risk of bleeding but no excess risk of ischemic events within 30 days after PCI. Plasma sGPVI may be a specific marker of the bleeding risk in patients undergoing elective PCI.

7. In patients undergoing PCI while on therapy with OAC and aspirin, treatment with the COBRA PzF stent plus 14 days of clopidogrel was not superior with respect to bleeding events and was not non-inferior with respect to thrombo-embolic events at 6 months compared to treatment with standard FDA-approved DES plus 3-6 months of clopidogrel. Our data indicate that the use of the COBRA PzF stent plus 14 days of DAPT is not clinically beneficial compared to an FDA-approved DES plus 3-6 months of DAPT in patients with an indication for OAC undergoing PCI.

Appendix

Table A1. Exclusion criteria of the ISAR-REACT 5 trial and the original definitions from the ARC-HBR consensus document

ARC-HBR Criteria	ARC-HBR Criteria [1]	ISAR-REACT 5 Exclusion Criteria
Major Criteria		
Anticoagulation	Anticipated use of long-term oral anticoagulation	Yes
Severe/end-stage CKD	eGFR <30 mL/min	No
Moderate/severe anemia	Hemoglobin <11 g/dL	No*
Thrombocytopenia	Platelet count <100x10^9/L	Yes
Liver disease	Liver cirrhosis with portal hypertension	No
Prior major bleeding	Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Yes†
	Non-deferrable major surgery on dual antiplatelet therapy	Yes†
	Chronic bleeding diathesis	Yes†
	Previous spontaneous ICH; traumatic ICH within the past 12 months; presence of brain arteriovenous malformations; ischemic stroke within the past 6 months	Yes
	Recent major surgery or major trauma within 30 days before PCI	Yes†
	Active malignancy within the past 12 months	Yes
Minor Criteria		
Age 75+	Age ≥75 years	No
Moderate CKD	eGFR 30–59 mL/min	No
Mild anemia	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	No
Long-term use of oral NSAIDs	Long-term use of oral NSAIDs or steroids	No
	Spontaneous bleeding within the past 12 months not meeting the major criterion	Yes†
	Any ischemic stroke at any time not meeting the major criterion	Yes

*Hemoglobin < 10 g/dL was an exclusion criterion of the ISAR-REACT 5 trial.

†It refers to the criterion "active bleeding, clinical findings, that in the judgement of the investigator are associated with an increased risk of bleeding" reported in the exclusion criteria list of the ISAR REACT 5 trial. ARC-HBR, Academic Research Consortium for High Bleeding Risk; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICH, intracranial hemorrhage; NSAIDs, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention.

[1] Definitions adapted from Urban P. et al., Circulation 2019;140:240-261

Table A2. Definitions of clinical endpoints according to protocols of trials included in the meta-analysis

Trial/Endpoint	Cardiovascular death	Myocardial Infarction	Stent thrombosis	Stroke	Bleeding
GLOBAL LEADERS	Cardiovascular mortality includes unclear causes of death (204)	According to the Third Universal Definition of MI (115)	Stent thrombosis was defined as definite or probable stent thrombosis according to the ARC criteria (116)	Any ischemic and hemorrhagic stroke	According to BARC definition (BARC 3 or 5) (117)
One-Month DAPT	All deaths are considered cardiovascular deaths unless a definite non-cardiovascular cause can be established.	According to the Third Universal Definition of MI (115)	According to ARC criteria (116)	NA	According to STEEPLE criteria (205)
OPTIMIZE	Any unknown cause of death or death that cannot be clearly attributed to a non-cardiac cause will be considered cardiac.	According to the extended WHO definition (206)	According to ARC criteria (116)	Classified as hemorrhagic or ischemic. Defined as acute neurological event with duration ≥ 24 hours with confirmation by CT or MRI or pathological confirmation.	Modified REPLACE-2 and GUSTO criteria
REDUCE	NA	Based on the Third Universal Definition of MI (115)	According to ARC criteria (116)	NA	According to BARC criteria (BARC 2,3,5)(117)
RESET	All deaths are considered cardiovascular deaths unless a definite non-cardiovascular cause can be established.	According to the Third Universal Definition of MI (115)	According to ARC criteria (116)	NA	According to TIMI criteria (TIMI major or minor)
SMART-CHOICE	All deaths were considered cardiac unless a definite non-cardiac cause could be established	Defined as elevated cardiac enzyme levels (cardiac troponin or myocardial band fraction of creatine kinase)	According to the ARC criteria (116)	Stroke was defined as any nonconvulsive focal or global neurologic deficit of abrupt onset lasting for more than 24 hours or leading to death, which was caused by ischemia or hemorrhage	According to BARC definition (BARC 2-5) (117)

				within the brain.	
STOPDAPT-2	According to ARC criteria (116)	According to ARC criteria (116)	According to ARC criteria (116)	Acute onset of a neurological deficit that persists for at least 24 hours and is the result of a disturbance of the cerebral circulation due to ischemia or hemorrhage.	According to TIMI criteria (TIMI major or minor)
TICO	Cardiac death was defined as death due to MI, cardiac perforation or pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or related to the procedure; death due to a procedural complication; or any cause of death in which a cardiac cause was not excluded.	According to the Third Universal Definition of MI (115) Defined as symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatinine kinase MB fraction above the upper normal limits of a troponin T or I level greater than the 99th percentile of the upper normal limit.	According to ARC criteria (116)	Defined as an acute cerebrovascular event that caused death, a neurological deficit lasting more than 24 hours, or an acute infarction shown by imaging studies.	According to TIMI criteria (TIMI major or minor)
TWILIGHT	Cardiovascular death includes unwitnessed death and death of unknown cause.	According to Third Universal definition of MI (115)	According to ARC criteria (116)	Defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture.	According to BARC definition (117) (2,3 or 5)

ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; WHO, World Health Organization. Table adapted from (132).

Table A3. Endpoint definitions in the COBRA-REDUCE trial

Endpoint	Definition
Death	The secondary end point includes death from any cause. In addition, the cause of death will be adjudicated.
Cardiac death	Cardiac death is defined as death due to any of the following: • Acute myocardial infarction • Cardiac perforation/pericardial tamponade • Arrhythmia or conduction abnormality • Stroke within 30 days of the procedure or stroke suspected of being related to the procedure • Death due to complications of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery • Any death in which a cardiac cause cannot be excluded
Noncardiac death	Non cardiac death is defined as a death not due to cardiac causes (as defined above)
Canadian Cardiovascular Society Classification of Angina	
Class I	Ordinary physical activity (such as walking and climbing stairs) does not cause angina. Angina with strenuous, rapid or prolonged exertion at work or recreation
Class II	Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in the cold, in wind or under emotional stress, or only during the few hours after awakening. Angina if walking more than two blocks on a level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Walking one to two blocks on a level and climbing one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.
Acute coronary syndrome	Unstable angina pectoris, or non-ST-segment elevation MI, or recent but non-acute ST-segment elevation MI.
Unstable angina pectoris at enrollment	History of chest pain with an accelerating pattern or prolonged (>20 minutes) or recurrent episodes at rest or with minimal effort or of new onset within the preceding 48 hours.
Acute myocardial infarction	According to the Third Universal Definition of Myocardial Infarction (115)
Prior myocardial infarction	Must fulfill one of the following criteria: • Prior medical record clearly states the patient has had an MI • Q-wave ≥0.04 sec in duration are present in 2 contiguous leads • History of acute ischemic pain followed by a hospitalization where the patient was clearly told

	that they had suffered a heart attack
Stent thrombosis	Defined according to the ARC criteria (116)
Stroke	Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation
Hemorrhagic stroke	Including intraparenchymal, subarachnoid hemorrhage and subdural hematomas
Ischemic stroke	
Unknown case	In which case there was no brain imaging or autopsy
Transient ischemic neurological attack	Presence of focal neurological or retinal symptoms lasting more than 30 seconds and resolving in less than 24 hours.
Urgent revascularization	Any PCI or bypass surgery that occurs because of: • Unstable angina (CCS class III-IV) • Documentation of new ST-segments shifts ≥0.5 mV on 12 lead ECG or lasting >20 minutes on ambulatory ECG monitoring • An episode of acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic on origin • A recurrent MI
Target lesion revascularization	TLR is defined as any ischemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. Ischemia-driven TLR is considered: • diameter stenosis ≥50% (“in-segment” QCA-analysis) at follow-up angiography and the patient had a positive functional study corresponding to the area served by the target lesion, and ischemic symptoms and ECG changes at rest referable to the target lesion. • diameter stenosis <50% at follow-up angiography but a markedly positive functional study or ECG changes corresponding to the territory supplied by target vessel. • diameter stenosis ≥70% at follow-up angiography in absence of documented clinical or functional ischemia.
Target vessel revascularization	TVR as any ischemia-driven (as defined by TLR) repeat PCI or bypass surgery of the target vessel. The target vessel consists of target lesion(s) and any additional lesions in the main epicardial coronary artery or branches containing the target lesion.
Bleeding	As per Bleeding Academic Research Consortium criteria (117)

Table A4. Baseline characteristics

Characteristic	Elderly or Low-Weight (n=1099)*		Neither Elderly nor Low-Weight (n=2898)	
	Prasugrel, 5 mg (n=544)	Ticagrelor, 180 mg (n=555)	Prasugrel, 10 mg (n=1449)	Ticagrelor, 180 mg (n=1449)
Mean age (SD), y	78.4 (7.1)	77.9 (6.5)	59.5 (9.1)	59.4 (9.4)
Women, n/N (%)	211/544 (38.8)	222/555 (40.0)	264/1449 (18.2)	254/1449 (17.5)
Diabetes, n/N (%)	141/544 (25.9)	137/555 (24.7)	283/1448 (19.5)	323/1448 (22.3)
Current smoker, n/N (%)	62/540 (11.5)	72/551 (13.1)	600/1446 (41.5)	607/1443 (42.1)
Arterial hypertension, n/N (%)	423/543 (77.9)	441/553 (79.7)	951/1447 (65.7)	986/1447 (68.1)
Hypercholesterolemia, n/N (%)	337/544 (61.9)	337/554 (60.8)	818/1446 (56.6)	835/1445 (57.8)
Prior myocardial infarction, n/N (%)	112/544 (20.6)	91/554 (16.4)	206/1448 (14.2)	219/1448 (15.1)
Prior PCI, n/N (%)	160/542 (29.5)	145/555 (26.1)	301/1449 (20.8)	307/1448 (21.2)
Prior CABG, n/N (%)	50/543 (9.2)	53/555 (9.6)	78/1449 (5.4)	61/1448 (4.2)
Cardiogenic shock, n/N (%)	18/544 (3.3)	11/555 (2.0)	16/1449 (1.1)	20/1449 (1.4)
Body weight <60 kg, n/N (%)	94/544 (17.4)	108/555 (19.5)	0	0
Mean body mass index (SD), kg/m^2	26.4 (4.3)	25.9 (4.4)	28.3 (4.4)	28.5 (4.5)
Mean creatinine concentration (SD), mg/dL	1.1 (0.4)	1.0 (0.4)	1.0 (0.3)	1.0 (0.3)
Diagnosis at admission, n/N (%)				
Unstable angina	88/544 (16.2)	82/555 (14.8)	173/1449 (11.9)	167/1449 (11.5)
NSTEMI	269/544 (49.4)	298/555 (53.7)	652/1449 (45.0)	627/1449 (43.3)
STEMI	187/544 (34.4)	175/555 (31.5)	624/1449 (43.1)	655/1449 (45.2)
Coronary angiography, n/N (%)	543/544 (99.8)	553/555 (99.6)	1445/1449 (99.7)	1442/1449 (99.5)
Treatment strategy, n/N (%)				
PCI	449/544 (82.5)	448/555 (80.7)	1239/1449 (85.6)	1221/1445 (84.5)
CABG	12/544 (2.2)	13/555 (2.3)	24/1449 (1.7)	34/1445 (2.4)
Conservative	83/544 (15.3)	94/555 (16.9)	185/1449 (12.8)	190/1445 (13.1)

CABG, coronary artery bypass grafting; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

* Patients in this group were aged 75 years or older or had a body weight less than 60 kg. Table adapted from (65).

Table A5. Angiographic and procedural data

Angiographic characteristics				
Characteristic	**Elderly or Low-Weight (n=1096)**		**Neither Elderly nor Low-Weight (n=2887)**	
	Prasugrel, 5 mg (n=543)	**Ticagrelor, 180 mg** (n=553)	**Prasugrel, 10 mg** (n=1445)	**Ticagrelor, 180 mg** (n=1442)
Access site, n (%)				
Femoral artery	372 (68.5)	348 (62.9)	884 (61.2)	897 (62.2)
Radial artery	167 (30.8)	201 (36.3)	555 (38.4)	539 (37.4)
Other	4 (0.7)	4 (0.7)	6 (0.4)	6 (0.4)
Number of diseased coronary arteries, n (%)				
No obstructive CAD	44 (8.1)	51 (9.2)	120 (8.3)	118 (8.1)
One-vessel disease	124 (22.8)	132 (23.9)	455 (31.5)	468 (32.5)
Two-vessel disease	138 (25.4)	132 (23.9)	413 (28.6)	386 (26.8)
Three-vessel disease	237 (43.6)	238 (43.0)	457 (31.6)	470 (32.6)
Mean LVEF (SD), % *	50.6 (11.8)	50.6 (11.9)	52.6 (10.9)	51.9 (11.1)
Procedural characteristics				
Characteristic	**Elderly or Low-Weight (n=897)**		**Neither Elderly nor Low-Weight (n=2460)**	
	Prasugrel, 5 mg (n=449)	**Ticagrelor, 180 mg** (n=448)	**Prasugrel, 10 mg** (n=1239)	**Ticagrelor, 180 mg** (n=1221)
Target vessel, n (%)				
Left main coronary artery	18 (4.0)	16 (3.6)	20 (1.6)	20 (1.6)
LAD coronary artery	196 (43.7)	209 (46.7)	518 (41.8)	535 (43.8)
Left circumflex coronary artery	93 (20.7)	86 (19.2)	251 (20.3)	259 (21.2)
Right coronary artery	129 (28.7)	124 (27.7)	432 (34.9)	393 (32.2)
Bypass graft	13 (2.9)	13 (2.9)	18 (1.4)	14 (1.2)
Complex lesion (type B2/C), n (%)	306 (68.2)	284 (63.4)	694 (56.0)	690 (56.5)
≥ 1 lesion treated, n (%)	189 (42.1)	155 (34.6)	411 (33.2)	413 (33.8)
TIMI flow grade before the intervention, n (%)				
0	122 (27.2)	130 (29.0)	461 (37.2)	460 (37.7)
1	37 (8.2)	24 (5.4)	115 (9.3)	102 (8.4)
2	117 (26.1)	99 (22.1)	262 (21.1)	258 (21.1)
3	173 (38.5)	195 (43.5)	401 (32.4)	401 (32.8)
TIMI flow grade after the intervention, n (%)				
0	8 (1.8)	4 (0.8)	8 (0.7)	13 (1.0)
1	3 (0.7)	1 (0.2)	4 (0.3)	8 (0.7)
2	12 (2.7)	18 (4.0)	25 (2.0)	32 (2.6)
3	426 (94.9)	425 (94.9)	1202 (97.0)	1168 (95.7)
Type of intervention, n (%)				
Drug-eluting stent	423 (94.2)	425 (94.9)	1121 (90.5)	1077 (88.2)
Bare-metal stent	5 (1.1)	0	3 (0.2)	4 (0.3)
Bioresorbable vascular scaffold	9 (2.0)	13 (2.9)	85 (6.9)	86 (7.0)
Drug-eluting balloon	9 (2.0)	13 (2.9)	17 (1.4)	23 (1.9)
Plain balloon angioplasty	21 (4.7)	14 (3.1)	24 (1.9)	43 (3.5)
Maximal stent diameter, mm	3.1 ± 0.5	3.1 ± 0.5	3.2 ± 0.5	3.2 ± 0.5

Total stented length, mm	29.5 ± 16.9	30.6 ± 17.1	30.5 ± 17.0	30.8 ± 16.7
Successful PCI, n (%)	433 (96.4)	439 (98.0)	1216 (98.1)	1194 (97.8)

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

*unavailable in 59 patients. Table adapted from (65).

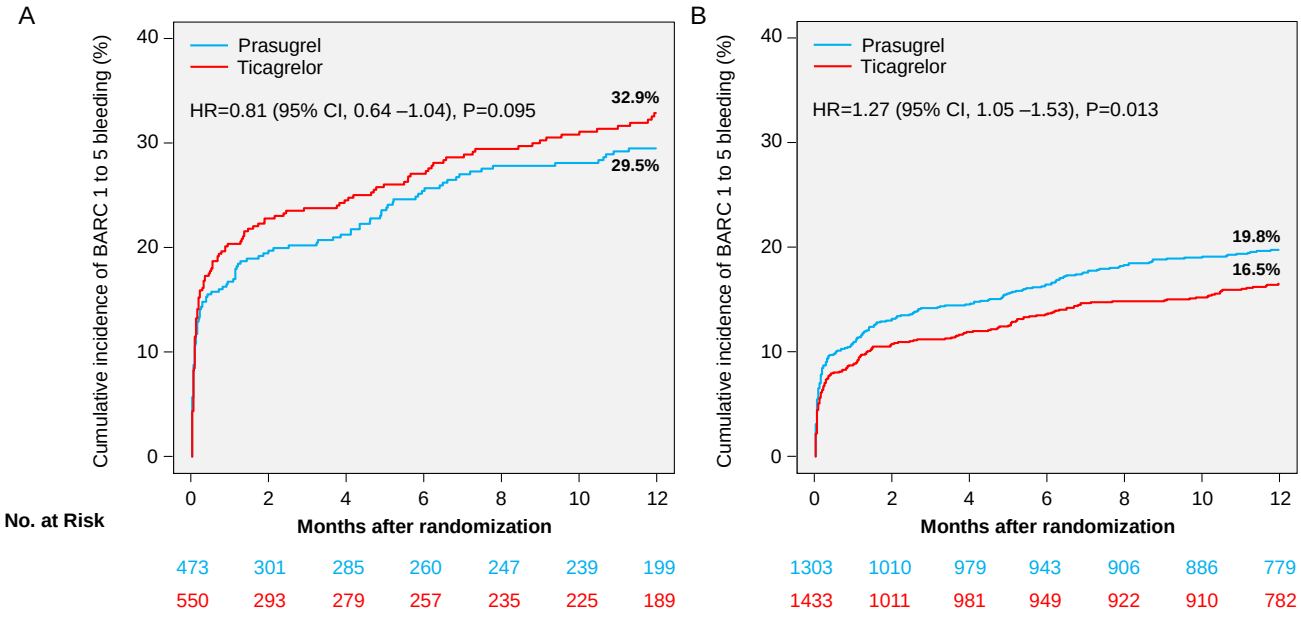

Figure A1. One-year cumulative incidence of BARC type 1 to 5 bleeding among patients assigned to receive prasugrel and those assigned to receive ticagrelor in the elderly or low-weight group (left) **and the neither elderly nor low-weight group** (right)

Adapted from (65).

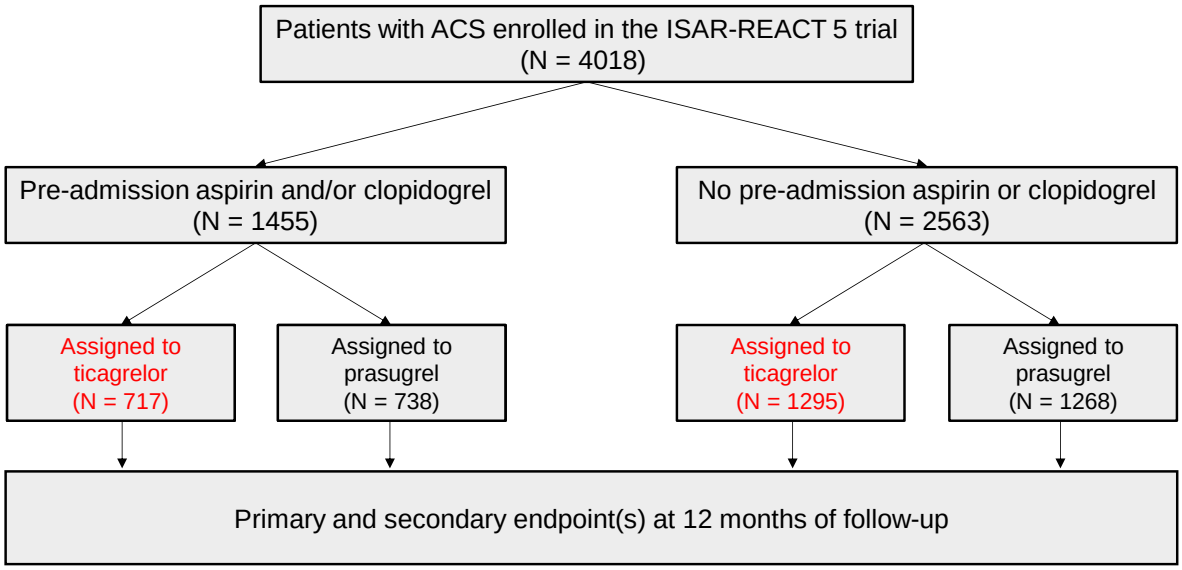

Figure A2. Study flowchart

ACS = acute coronary syndrome. Figure adapted from (121).

Table A6. Baseline characteristics according to pre-admission antiplatelet therapy status

Characteristic	Pre-admission aspirin and/or clopidogrel (N=1455)	No pre-admission aspirin or clopidogrel (N=2563)	*P* value
Age – years	70.0 [61.0-77.0]	62.0 [53.0-71.0]	<0.001
Sex			0.20
Female – no. (%)	329 (22.6)	627 (24.5)	
Diabetes – no. (%)	461/1454 (31.7)	431/2562 (16.8)	<0.001
Insulin-treated – no. (%)	176/1454 (12.1)	104/2562 (4.1)	<0.001
Smoking – no. (%)	362/1449 (25.0)	987/2552 (38.7)	<0.001
Arterial hypertension – no. (%)	1276/1454 (87.8)	1540/2557 (60.2)	<0.001
Hypercholesterolemia – no. (%)	1132/1454 (77.9)	1209/2556 (47.3)	<0.001
Prior myocardial infarction – no. (%)	539/1454 (37.1)	92/2561 (3.6)	<0.001
Prior PCI – no. (%)	820/1453 (56.4)	96/2562 (3.8)	<0.001
Prior CABG – no. (%)	209/1454 (14.4)	36/2562 (1.4)	<0.001
Cardiogenic shock – no. (%)	24/1455 (1.7)	41 (1.6)	>0.999
Systolic blood pressure – (mmHg)	141 [127-160]	140 [127-160]	0.46
Diastolic blood pressure – (mmHg)	80.0 [70.0-88.0]	80.0 [75.0-90.0]	<0.001
Heart rate – (beats/min)	73.0 [64.0-83.0]	76.0 [67.0-87.0]	<0.001
Body mass index – (kg/m²)	27.5 [24.9-30.3]	27.0 [24.7-29.9]	0.036
Weight < 60 kg – no. (%)	74/1447 (5.1)	128/2544 (5.0)	0.97
Creatinine – (µmol/L)	88.4 [73.4-106]	80.4 [70.7-94.6]	<0.001
Diagnosis at admission			<0.001
Unstable angina – no. (%)	350 (24.1)	160 (6.2)	
NSTEMI – no. (%)	733 (50.4)	1122 (43.8)	
STEMI – no. (%)	372 (25.6)	1281 (50.0)	
Coronary angiography – no. (%)	1448 (99.5)	2556 (99.7)	0.43
Treatment strategy – no. (%)			<0.001
PCI	1170 (80.6)	2207 (86.2)	
CABG	34 (2.3)	49 (1.9)	
Conservative	248 (17.1)	305 (11.9)	
Aspirin on admission	1413 (97.1)	0 (0.0)	<0.001
Clopidogrel on admission	195 (13.4)	0 (0.0)	<0.001

Data are median with 25th-75th percentiles or counts (%).

CABG, coronary artery bypass grafting; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Missing continuous data:

Pre-admission aspirin and/or clopidogrel: diastolic blood pressure, 6 patients; body mass index, 8 patients. The remaining continuous data were complete.

No pre-admission aspirin or clopidogrel: systolic blood pressure, 3 patients; diastolic blood pressure, 10 patients; heart rate, 2 patients; body mass index, 23 patients.

Table adapted from (121).

Table A7. Angiographic and procedural data*

Angiographic characteristics						
Characteristic	**Pre-admission aspirin and/or clopidogrel** (N=1448)			**No pre-admission aspirin or clopidogrel** (N=2556)		
	Ticagrelor (N=714)	**Prasugrel** (N=734)	***P* value**	**Ticagrelor** (N=1289)	**Prasugrel** (N=1267)	***P* value**
Access site, n (%)			0.46			0.66
Femoral artery	460 (64.4)	483 (65.8)		785 (60.9)	777 (61.3)	
Radial artery	249 (34.9)	249 (33.9)		499 (38.7)	482 (38.0)	
Other	5 (0.7)	2 (0.3)		5 (0.4)	8 (0.6)	
Number of diseased coronary arteries, n (%)			0.23			0.79
No obstructive CAD	38 (5.3)	43 (5.9)		132 (10.2)	121 (9.6)	
One-vessel disease	151 (21.1)	127 (17.3)		450 (34.9)	455 (35.9)	
Two-vessel disease	174 (24.4)	202 (27.5)		347 (26.9)	353 (27.9)	
Three-vessel disease	351 (49.2)	362 (49.3)		360 (27.9)	338 (26.7)	
Multivessel disease	525 (73.5)	564 (76.8)	0.16	707 (54.8)	691 (54.5)	0.91
Mean LVEF (SD), % †	50.5 (11.7)	51.6 (11.7)	0.09	52.2 (11.0)	52.3 (10.9)	0.84
Procedural characteristics						
Characteristic	**Pre-admission aspirin and/or clopidogrel** (N=1445)			**No pre-admission aspirin or clopidogrel** (N=2563)		
	Ticagrelor (N=717)	**Prasugrel** (N=738)	***P* value**	**Ticagrelor** (N=1295)	**Prasugrel** (N=1268)	***P* value**
Target vessel, n (%)			0.85			0.15
Left main coronary artery	23 (4.0)	17 (2.9)		13 (1.2)	21 (1.9)	
LAD coronary artery	201 (35.1)	218 (36.5)		545 (49.4)	501 (45.3)	
Left circumflex coronary artery	124 (21.6)	127 (21.3)		222 (20.1)	218 (19.7)	
Right coronary artery	198 (34.6)	206 (34.5)		322 (29.2)	363 (32.9)	
Bypass graft	27 (4.7)	29 (4.9)		1 (0.1)	2 (0.2)	
Complex lesion (type B2/C), n (%)	369 (64.4)	368 (61.6)	0.36	610 (55.3)	641 (58.0)	0.21
≥ 1 lesion treated, n (%)	197 (27.5)	226 (30.6)	0.21	372 (28.7)	378 (29.8)	0.58
TIMI flow grade before the intervention, n (%)			0.19			0.82
0	159 (27.7)	157 (26.3)		433 (39.2)	428 (38.7)	
1	29 (5.1)	45 (7.5)		98 (8.9)	110 (9.9)	
2	128 (22.3)	149 (25.0)		233 (21.1)	237 (21.4)	
3	257 (44.9)	246 (41.2)		340 (30.8)	330 (29.9)	
TIMI flow grade after the intervention, n (%)			0.96			0.19
0	8 (1.4)	7 (1.2)		9 (0.8)	9 (0.8)	
1	4 (0.7)	4 (0.7)		5 (0.5)	3 (0.3)	
2	12 (2.1)	15 (2.5)		38 (3.4)	22 (2.0)	
3	549 (95.8)	571 (95.6)		1052 (95.3)	1071 (96.9)	
Type of intervention, n (%)						
Drug-eluting stent	492 (85.9)	522 (87.4)	0.48	1005 (91.0)	1021 (92.4)	0.28

Bare-metal stent	3 (0.5)	6 (1.0)	0.51	1 (0.1)	2 (0.2)	>0.999
Bioresorbable vascular scaffold	26 (4.5)	30 (5.0)	0.80	73 (6.6)	66 (6.0)	0.60
Drug-eluting balloon	30 (5.2)	22 (3.7)	0.25	6 (0.5)	5 (0.5)	0.999
Plain balloon angioplasty	32 (5.6)	28 (4.7)	0.58	25 (2.3)	18 (1.6)	0.35
Maximal stent diameter, mm	3.2 ± 0.5	3.2 ± 0.5	0.54	3.2 ± 0.5	3.2 ± 0.5	0.19
Total stented length, mm	31.6 ±17.6	29.4 ±16.8	0.04	30.3 ±16.4	30.8 ±17.1	0.55
Successful PCI, n (%)	557 (97.2)	578 (96.8)	0.83	1083 (98.2)	1084 (98.2)	>0.999

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

*Angiographic data were not available for 7 patients in the Pre-admission aspirin and/or clopidogrel group (3 in the ticagrelor group and 4 in the prasugrel group) and 7 patients in the No pre-admission aspirin or clopidogrel group (6 in the ticagrelor group and 1 in the prasugrel group) and [†]Left ventricular ejection fraction was not available in 68 patients in the Pre-admission aspirin and/or clopidogrel group (36 in the ticagrelor group and 32 in the prasugrel group) and 156 patients in the No pre-admission aspirin or clopidogrel group (74 in the ticagrelor group and 82 in the prasugrel group). Table adapted from (121).

Table A8. Diagnosis and drug therapy at discharge

Characteristic	**Pre-admission aspirin and/or clopidogrel** (N=1430)			**No pre-admission aspirin or clopidogrel** (N=2523)		
	Ticagrelor (N=713)	**Prasugrel** (N=737)	**P value**	**Ticagrelor** (N=1293)	**Prasugrel** (N=1267)	**P value**
Final diagnosis of ACS, n (%)	654 (91.7)	654 (88.7)	0.07	1176 (91.0)	1159 (91.5)	0.69
Unstable angina	130/654 (19.9)	126/654 (19.3)		59/1176 (5.0)	47/1159 (4.1)	
NSTEMI	347/654 (53.1)	341/654 (52.1)		487/1176 (41.4)	486/1159 (41.9)	
STEMI	177/654 (27.1)	187/654 (28.6)		630/1176 (53.6)	626/1159 (54.0)	
Therapy at discharge, n (%)*						
Aspirin	684/703 (97.3)	708/727 (97.4)	>0.999	1182/1272 (92.9)	1170/1251 (93.5)	0.60
Ticagrelor	559/703 (79.5)	8/727 (1.1)	<0.001	1043/1272 (82.0)	6/1251 (0.5)	<0.001
Prasugrel	5/703 (0.7)	558/727 (76.8)	<0.001	16/1272 (1.3)	1038/1251 (83.0)	<0.001
Clopidogrel	44/703 (6.3)	48/727 (6.6)	0.88	46/1272 (3.6)	69/1251 (5.5)	0.03
Oral anticoagulant drugs	34/703 (4.8)	30/727 (4.1)	0.60	48/1272 (3.8)	70/1251 (5.6)	0.04
Beta blocking agents	601/703 (85.5)	601/727 (82.7)	0.17	1040/1272 (81.8)	1044/1251 (83.5)	0.29
ACE Inhibitor/ARB	607/703 (86.3)	625/727 (86.0)	0.90	1052/1272 (82.7)	1065/1251 (85.1)	0.11
Statin	659/703 (93.7)	683/727 (93.9)	0.96	1151/1272 (90.5)	1148/1251 (91.8)	0.29

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

*Shown for patients discharged alive, not available for patients who withdrew consent before discharge.

Table adapted from (121).

Table A9. Angiographic and procedural characteristics according to HBR status

Angiographic characteristics			
Characteristic	**HBR** (N=486)	**Non-HBR** (N=2753)	**P value**
Access site, n (%)			0.12
Femoral artery	328 (67.5)	1734 (63.0)	
Radial artery	155 (31.9)	1007 (36.6)	
Other	3 (0.6)	12 (0.4)	
Number of diseased coronary arteries, n (%)			<0.001
No obstructive CAD	1 (0.2)	3 (0.1)	
One-vessel disease	96 (19.8)	947 (34.4)	
Two-vessel disease	139 (28.6)	824 (29.9)	
Three-vessel disease	250 (51.4)	979 (35.6)	
Multivessel disease	389 (80.0)	1803 (65.5)	<0.001
Mean LVEF (SD), % *	48.9 ± 12.3	51.6 ± 11.0	<0.001
Procedural characteristics			
	HBR (N=486)	**Non-HBR** (N=2753)	**P value**
Target vessel, n (%)			<0.001
Left main coronary artery	23 (4.7)	49 (1.8)	
LAD coronary artery	201 (41.4)	1204 (43.7)	
Left circumflex coronary artery	89 (18.3)	577 (21.0)	
Right coronary artery	154 (31.7)	885 (32.1)	
Bypass graft	19 (3.9)	38 (1.4)	
Complex lesion (type B2/C), n (%)	339 (69.8)	1578 (57.3)	<0.001
≥ 1 lesion treated, n (%)	181 (37.2)	952 (34.6)	0.28
TIMI flow grade before the intervention, n (%)			0.003
0	135 (27.8)	978 (35.5)	
1	35 (7.2)	235 (8.5)	
2	121 (24.9)	596 (21.6)	
3	195 (40.1)	944 (34.3)	
TIMI flow grade after the intervention, n (%)			0.022
0	11 (2.3)	21 (0.8)	
1	3 (0.6)	12 (0.4)	
2	13 (2.7)	67 (2.4)	
3	459 (94.4)	2653 (96.4)	
Type of intervention, n (%)			
Drug-eluting stent	432 (88.9)	2483 (90.2)	0.42
Bare-metal stent	3 (0.6)	9 (0.3)	0.42
Bioresorbable vascular scaffold	18 (3.7)	168 (6.1)	0.047
Drug-eluting balloon	14 (2.9)	47 (1.7)	0.12

Plain balloon angioplasty	22 (4.5)	76 (2.8)	0.051
Maximal stent diameter, mm	3.1 ± 0.5	3.2 ± 0.5	0.022
Total stented length, mm	31.6 ± 18.9	30.5 ± 16.6	0.28
Successful PCI, n (%)	467 (96.1)	2,704 (98.2)	0.004
Periprocedural antithrombotic medication			
Aspirin	422 (86.8)	2488 (90.4)	0.021
Unfractionated heparin	465 (95.7)	2574 (93.5)	0.082
Low molecular weight heparin	17 (3.5)	117 (4.3)	0.520
Bivalirudin	33 (6.8)	233 (8.5)	0.250
GPIIb/IIIa inhibitor	46 (9.5)	322 (11.7)	0.177

Data are shown as counts (proportion; %) or mean ± standard deviation. CAD, coronary artery disease; GPIIb/IIIa, glycoprotein IIb/IIIa; HBR, high bleeding risk; LAD, left anterior descending; Non-HBR, non-high bleeding risk; LVEF, left ventricular ejection fraction; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

*unavailable in 35 patients in the HBR group and 148 patients in the Non-HBR group.

Table adapted from (123).

Table A10. Diagnosis and drug therapy at discharge according to HBR status

Characteristic	HBR (N=485)	Non-HBR (N=2749)	P value
Final diagnosis of ACS, n (%)	483 (99.6)	2744 (99.8)	0.60
Unstable angina	47/483 (9.7)	209/2744 (7.6)	
NSTEMI	258/483 (53.4)	1237/2744 (45.1)	
STEMI	178/483 (36.9)	1298/2744 (47.3)	
Therapy at discharge, n (%)*			
Aspirin	440/455 (96.7)	2685/2726 (98.5)	0.012
Ticagrelor	188/455 (41.3)	1282/2726 (47.0)	0.027
Prasugrel	205/455 (45.1)	1293/2726 (47.4)	0.37
Clopidogrel	51/455 (11.2)	130/2726 (4.8)	<0.001
Oral anticoagulant drugs	35/455 (7.7)	107/2726 (3.9)	0.001
Beta blocking agents	388/455 (85.3)	2366/2726 (86.8)	0.42
ACE inhibitor/ARB	395/455 (86.8)	2370/2726 (86.9)	>0.99
Statins	419/455 (92.1)	2610/2726 (95.7)	0.001

Data are shown as counts (proportions; %).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HBR, high bleeding risk; Non-HBR, non-high bleeding risk; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

*Shown for patients discharged alive, not available for patients who withdrew consent before discharge.

Table adapted from (123).

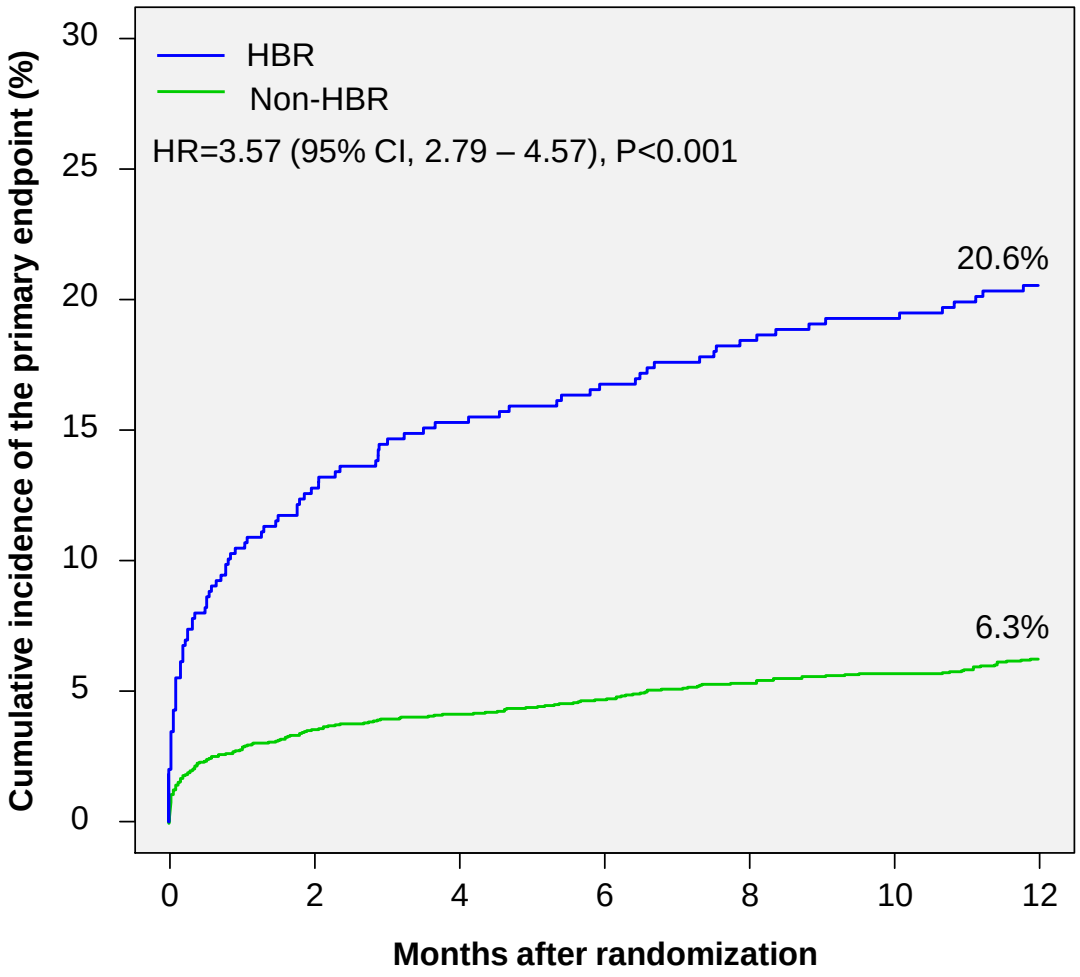

Figure A3. Cumulative incidence of the primary efficacy endpoint at 1 year according to HBR status

The cumulative incidence of the primary endpoint — a composite of death, myocardial infarction, or stroke — was evaluated according to the intention-to-treat principle. CI, confidence interval; HR, hazard ratio; HBR, high bleeding risk; Non-HBR, non-high bleeding risk (123).

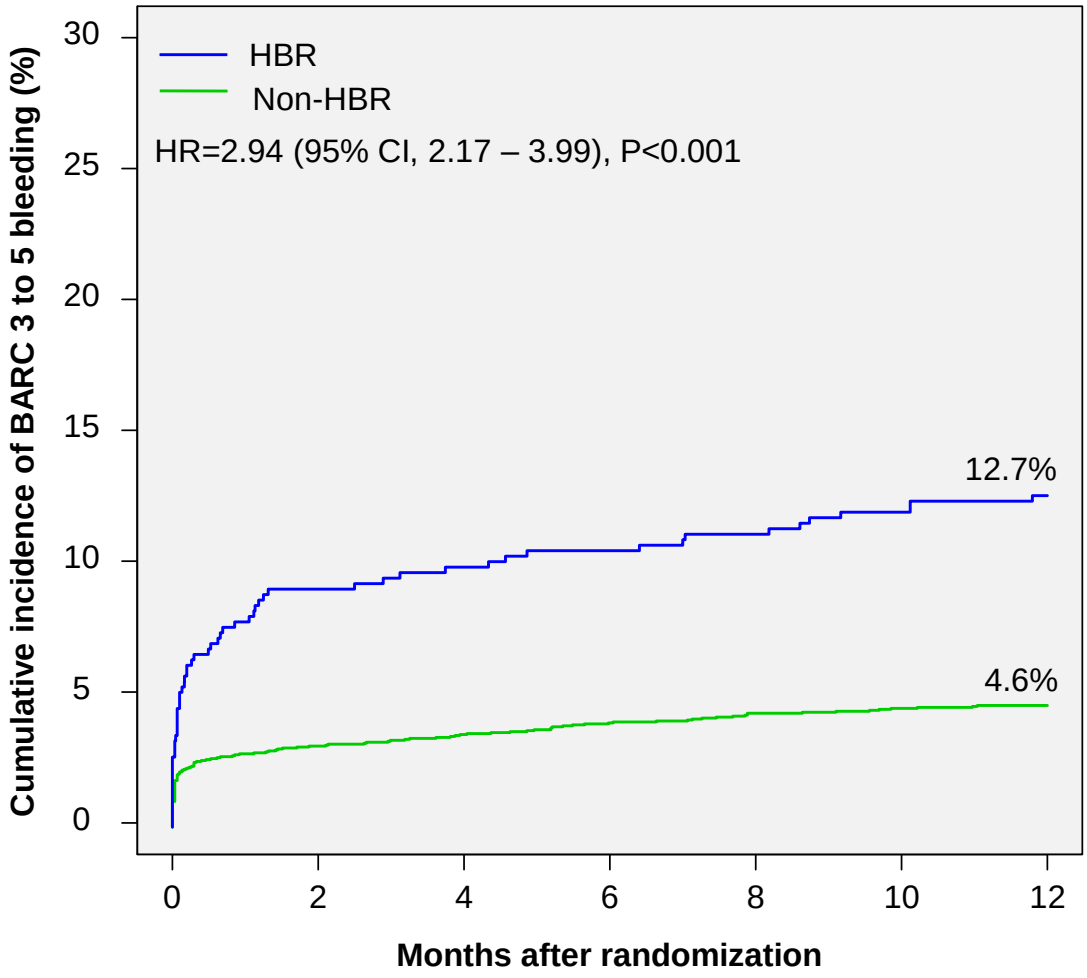

Figure A4. Cumulative incidence of the safety endpoint at 1 year according to HBR status

The cumulative incidence of the safety endpoint (BARC 3 to 5 bleeding) was assessed in the intention-to-treat population after accounting for the competing risk of death.

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; HBR, high bleeding risk; Non-HBR, non-high bleeding risk. Figure adapted from (123).

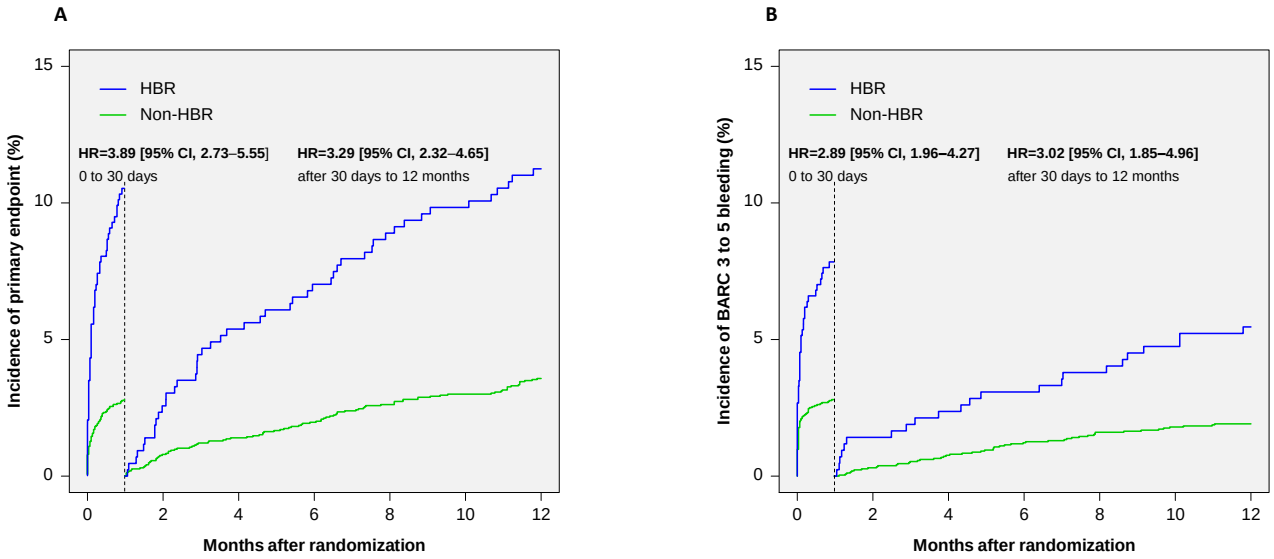

Figure A5. Incidence of the primary (efficacy) and secondary (safety) endpoints at 30-day landmark analysis according to HBR status

The incidence of the primary efficacy endpoint (**panel A**) and secondary endpoint (**panel B**) according to HBR status was assessed with a time-point landmark at 30-day follow-up.

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; HBR, high bleeding risk; Non-HBR, non-high bleeding risk. Figure adapted from (123).

Table A11. Baseline characteristics according to assigned therapy in the HBR and non-HBR groups

Characteristic	HBR (N=486)			Non-HBR (N=2753)		
	Ticagrelor (N=230)	**Prasugrel** (N=256)	***P value***	**Ticagrelor** (N=1375)	**Prasugrel** (N=1378)	***P* value**
Age, y	79.0 [75.2-82.0]	79.0 [75.0-83.0]	0.83	63.0 [54.0-71.0]	62.0 [55.0-70.0]	0.95
Sex			0.26			0.61
Female, n (%)	83 (36.1)	79 (30.9)		253 (18.4)	265 (19.2)	
Male, n (%)	147 (63.9)	177 (69.1)		1122 (81.6)	1113 (80.8)	
Diabetes, n (%)	70 (30.4)	90/255 (35.3)	0.30	290 (21.1)	268 (19.4)	0.31
Insulin treated, n (%)	34 (14.8)	34/255 (13.3)	0.74	78 (5.7)	81 (5.9)	0.88
Smoking, n (%)	26/228 (11.4)	34/253 (13.4)	0.59	531/1371 (38.7)	541/1374 (39.4)	0.76
Arterial hypertension, n (%)	189/229 (82.5)	220/255 (86.3)	0.31	946/1373 (68.9)	890/1377 (64.6)	0.020
Hypercholesterolemia, n (%)	151/229 (65.9)	167/255 (65.5)	0.99	798/1373 (58.1)	770/1377 (55.9)	0.26
Prior myocardial infarction, n (%)	54 (23.5)	66 (25.8)	0.63	201/1374 (14.6)	188/1377 (13.7)	0.50
Prior PCI, n (%)	81 (35.2)	89/255 (34.9)	>0.99	286/1374 (20.8)	276/1377 (20.0)	0.65
Prior CABG, n (%)	29 (12.6)	33 (12.9)	>0.99	65/1374 (4.7)	72/1377 (5.2)	0.61
Cardiogenic shock, n (%)	7 (3.0)	16 (6.3)	0.15	22 (1.6)	17 (1.2)	0.51
Systolic blood pressure, mmHg	140 [125-160]	140 [122-160]	0.88	140 [127-160]	141 [128-160]	0.68
Diastolic blood pressure, mmHg	80.0 [70.0-90.0]	78.0 [70.0-82.5]	0.28	80.0 [74.0-90.0]	80.0 [75.0-90.0]	0.62
Heart rate, beats/min	72.0 [65.0-83.0]	74.5 [64.0-84.0]	0.53	75.0 [66.0-86.0]	75.0 [65.0-85.0]	0.088
Body mass index, kg/m²	26.3 [23.9-29.0]	26.9 [24.5-30.2]	0.050	27.4 [24.9-30.1]	27.2 [24.9-29.9]	0.55
Weight <60 kg, n (%)	19/229 (8.3)	9 (3.6)	0.043	58/1368 (4.2)	56/1365 (4.1)	0.93
Creatinine, µmol/L	110 [89.1-133]	111 [91.7-130]	0.82	80.0 [70.7-94.0]	79.6 [70.7-91.9]	0.56
Diagnosis at admission			0.053			0.48
Unstable angina, n (%)	18 (7.8)	38 (14.8)		117 (8.5)	100 (7.3)	
NSTEMI, n (%)	128 (55.7)	133 (52.0)		624 (45.4)	634 (46.0)	
STEMI, n (%)	84 (36.5)	85 (33.2)		634 (46.1)	644 (46.7)	
Aspirin on admission	119 (51.7)	144 (56.2)	0.365	426 (31.0)	419 (30.4)	0.78
Clopidogrel on admission	16 (7.0)	26 (10.2)	0.275	56 (4.1)	44 (3.2)	0.26
Hemoglobin on admission, g/dL	12.8 [11.9-14.1]	12.8 [11.6-14.2]	0.991	14.7 [13.8-15.6]	14.8 [13.9-15.6]	0.65
Thrombocyte count, x 10^9/L	221 [182-267]	212 [172-254]	0.030	223 [189-266]	224 [188-264]	0.89

eGFR, ml/min/1.73 m^2	50.2 [41.0-57.1]	51.2 [41.0-59.4]	0.605	84.6 [71.3-95.1]	84.4 [71.6-95.0]	0.72

Data are shown as counts (proportion; %) or median with 25th-75th percentiles.

Missing continuous data:

HBR group: systolic blood pressure, 1 patient in the ticagrelor group; diastolic blood pressure, 2 patients in the ticagrelor group; heart rate, 1 patient in the ticagrelor group; body mass index, 4 patients (1 in the ticagrelor group, 3 in the prasugrel group).

Non-HBR group: systolic blood pressure, 2 patients in the prasugrel group; diastolic blood pressure, 9 patients (2 in the ticagrelor group, 7 in the prasugrel group); heart rate, 1 patient in the prasugrel group; body mass index, 24 patients (10 in the ticagrelor group, 14 in the prasugrel group).

CABG indicates coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; Non-HBR, non-high bleeding risk; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. Table adapted from (123).

Table A12. Angiographic and procedural data

Angiographic characteristics						
Characteristic	**HBR** (N=486)			**Non-HBR** (N=2753)		
	Ticagrelor (N=230)	**Prasugrel** (N=256)	***P* value**	**Ticagrelor** (N=1375)	**Prasugrel** (N=1378)	***P* value**
Access site, n (%)			0.41			0.51
Femoral artery	149 (64.8)	179 (69.9)		868 (63.1)	866 (62.8)	
Radial artery	80 (34.8)	75 (29.3)		503 (36.6)	504 (36.6)	
Other	1 (0.4)	2 (0.8)		4 (0.3)	8 (0.6)	
Number of diseased coronary arteries, n (%)			0.11			0.98
No obstructive CAD	0 (0.0)	1 (0.4)		1 (0.1)	2 (0.2)	
One-vessel disease	53 (23.0)	43 (16.8)		476 (34.6)	471 (34.2)	
Two-vessel disease	57 (24.8)	82 (32.0)		412 (30.0)	412 (29.9)	
Three-vessel disease	120 (52.2)	130 (50.8)		486 (35.3)	493 (35.8)	
Multivessel disease	177 (77.0)	212 (82.8)	0.13	898 (65.3)	905 (65.7)	0.87
Mean LVEF (SD), %	48.2 ± 12.0	49.5 ± 12.5	0.23	51.5 ± 11.1	51.6 ± 10.9	0.78
Procedural characteristics						
Characteristic	**HBR** (N=486)			**Non-HBR** (N=2753)		
	Ticagrelor (N=230)	**Prasugrel** (N=256)	***P* value**	**Ticagrelor** (N=1375)	**Prasugrel** (N=1378)	***P* value**
Target vessel, n (%)			0.68			0.69
Left main coronary artery	11 (4.8)	12 (4.7)		25 (1.8)	24 (1.7)	
LAD coronary artery	102 (44.3)	99 (38.7)		614 (44.7)	590 (42.8)	
Left circumflex coronary artery	39 (17.0)	50 (19.5)		292 (21.2)	285 (20.7)	
Right coronary artery	71 (30.9)	83 (32.4)		424 (30.8)	461 (33.5)	
Bypass graft	7 (3.0)	12 (4.7)		20 (1.5)	18 (1.3)	
Complex lesion (type B2/C), n (%)	161 (70.0)	178 (69.5)	0.99	783 (56.9)	795 (57.7)	0.72
≥ 1 lesion treated, n (%)	76 (33.0)	105 (41.0)	0.085	474 (34.5)	478 (34.7)	0.94
TIMI flow grade before the intervention, n (%)			0.19			0.33
0	74 (32.2)	61 (23.8)		484 (35.2)	494 (35.8)	
1	14 (6.1)	21 (8.2)		106 (7.7)	129 (9.4)	
2	52 (22.6)	69 (27.0)		297 (21.6)	299 (21.7)	
3	90 (39.1)	105 (41.0)		488 (35.5)	456 (33.1)	
TIMI flow grade after the intervention, n (%)			0.40			0.39
0	4 (1.7)	7 (2.7)		13 (0.9)	8 (0.6)	
1	1 (0.4)	2 (0.8)		8 (0.6)	4 (0.3)	
2	9 (3.9)	4 (1.6)		36 (2.6)	31 (2.3)	
3	216 (93.9)	243 (94.9)		1318 (95.9)	1335 (96.9)	
Type of intervention, n (%)						
Drug-eluting stent	203 (88.3)	229 (89.5)	0.79	1229 (89.4)	1254 (91.0)	0.17
Bare-metal stent	0 (0.0)	3 (1.2)	0.28	4 (0.3)	5 (0.4)	>0.99

Bioresorbable vascular scaffold	10 (4.4)	8 (3.1)	0.64	85 (6.2)	83 (6.0)	0.93
Drug-eluting balloon	9 (3.9)	5 (1.9)	0.31	26 (1.9)	21 (1.5)	0.55
Plain balloon angioplasty	10 (4.4)	12 (4.7)	>0.99	45 (3.3)	31 (2.3)	0.13
Maximal stent diameter, mm	3.1 ± 0.5	3.2 ± 0.5	0.55	3.2 ± 0.5	3.2 ± 0.5	0.43
Total stented length, mm	32.6 ± 19.4	30.6 ± 18.5	0.25	30.6 ± 16.5	30.5 ± 16.8	0.89
Successful PCI, n (%)	222 (96.5)	245 (95.7)	0.82	1,348 (98.0)	1,356 (98.4)	0.56
Periprocedural antithrombotic medication						
Aspirin	197 (85.7)	225 (87.9)	0.55	1239 (90.1)	1249 (90.6)	0.68
Unfractionated heparin	220 (95.7)	245 (95.7)	>0.99	1290 (93.8)	1284 (93.2)	0.55
LMWH	10 (4.4)	7 (2.7)	0.47	61 (4.4)	56 (4.1)	0.70
Bivalirudin	13 (5.7)	20 (7.8)	0.44	112 (8.2)	121 (8.8)	0.60
GPIIb/IIIa inhibitor	25 (10.9)	21 (8.2)	0.40	168 (12.2)	154 (11.2)	0.43

CAD, coronary artery disease; GPIIb/IIIa, glycoprotein IIb/IIIa; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction. Table adapted from (123).

Table A13. Baseline characteristics according to smoking status

Characteristic	Smokers (N=1349)	Nonsmokers (N=2652)	*P* value
Age – years	57.6 ± 10.3	68.1 ± 11.3	<0.001
Sex			<0.001
Female – no. (%)	263 (19.5)	688 (25.9)	
Diabetes – no. (%)	212 (15.7)	672 (25.3)	<0.001
Insulin-treated – no. (%)	57 (4.2)	218 (8.2)	<0.001
Arterial hypertension – no. (%)	809/1347 (60.1)	1998 (75.3)	<0.001
Hypercholesterolemia – no. (%)	697/1348 (51.7)	1636/2649 (61.8)	<0.001
Prior myocardial infarction – no. (%)	185 (13.7)	444/2651 (16.7)	0.014
Prior PCI – no. (%)	233 (17.3)	680/2651 (25.7)	<0.001
Prior CABG – no. (%)	37 (2.7)	208 (7.8)	<0.001
Cardiogenic shock – no. (%)	28 (2.1)	31 (1.2)	0.035
Systolic blood pressure – (mmHg)	140 ± 24.1	145 ± 24.8	<0.001
Diastolic blood pressure – (mmHg)	82.7 ± 14.2	81.6 ± 14.2	0.024
Heart rate – (beats/min)	77.6 ± 16.4	75.9 ± 15.2	0.001
Body mass index – (kg/m²)	27.6 ± 4.8	27.9 ± 4.4	0.073
Weight < 60 kg – no. (%)	62/1341 (4.6)	138/2633 (5.2)	0.444
Creatinine – (µmol/L)	82.8 ± 25.0	90.3 ± 29.9	<0.001
Diagnosis at admission			<0.001
Unstable angina – no. (%)	118 (8.7)	391 (14.8)	
NSTEMI – no. (%)	553 (41.0)	1297 (48.9)	
STEMI – no. (%)	678 (50.3)	964 (36.3)	
Coronary angiography – no. (%)	1340 (99.3)	2647 (99.8)	0.022
Treatment strategy – no. (%)			<0.001
PCI	1189/1347 (88.3)	2174/2649 (82.1)	
CABG	29/1347 (2.1)	53/2649 (2.0)	
Conservative	129/1347 (9.6)	422/2649 (15.9)	

Data are mean ± standard deviation or counts (%).

CABG, coronary artery bypass grafting; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Missing continuous data:

Smokers group: systolic blood pressure, 2 patients; diastolic blood pressure, 8 patients; heart rate, 1 patient; body mass index, 10 patients

Nonsmokers group: systolic blood pressure, 1 patient; diastolic blood pressure, 8 patients; heart rate, 1 patient; body mass index, 21 patients.

The remaining continuous data were complete.

Table adapted from (124).

Table A14. Angiographic and procedural data in smokers and nonsmokers

Angiographic characteristics[a]			
Characteristic	**Smokers** (N=1340)	**Nonsmokers** (N=2647)	**P value**
Access site, n (%)			0.991
Femoral artery	838 (62.5)	1655 (62.5)	
Radial artery	495 (37.0)	979 (37.0)	
Other	7 (0.5)	13 (0.5)	
Number of diseased coronary arteries, n (%)			<0.001
No obstructive CAD	83 (6.2)	250 (9.4)	
One-vessel disease	462 (34.5)	716 (27.1)	
Two-vessel disease	376 (28.0)	696 (26.3)	
Three-vessel disease	419 (31.3)	985 (37.2)	
Mean LVEF (SD), % [b]	51.2 ± 11.3	52.1 ± 11.2	0.014
Procedural characteristics			
	Smokers (N=1189)	**Nonsmokers** (N=2174)	**P value**
Target vessel, n (%)			0.067
Left main coronary artery	26 (2.2)	47 (2.2)	
LAD coronary artery	497 (41.8)	960 (44.1)	
Left circumflex coronary artery	250 (21.0)	440 (20.2)	
Right coronary artery	404 (34.0)	680 (31.3)	
Bypass graft	12 (1.0)	47 (2.2)	
Complex lesion (type B2/C), n (%)	654 (55.0)	1321 (60.8)	0.001
≥ 1 lesion treated, n (%)	396 (33.3)	771 (35.5)	0.223
TIMI flow grade before the intervention, n (%)			<0.001
0	452 (38.0)	716 (32.9)	
1	118 (9.9)	163 (7.5)	
2	240 (20.2)	506 (23.3)	
3	379 (31.9)	789 (36.3)	
TIMI flow grade after the intervention, n (%)			0.030
0	6 (0.5)	26 (1.2)	
1	2 (0.2)	14 (0.6)	
2	26 (2.2)	61 (2.8)	
3	1155 (97.1)	2073 (95.4)	
Type of intervention, n (%)			
Drug-eluting stent	1068 (89.8)	1960 (90.2)	0.804
Bare-metal stent	4 (0.3)	8 (0.4)	>0.999
Bioresorbable vascular scaffold	94 (7.9)	101 (4.7)	<0.001
Drug-eluting balloon	11 (0.9)	52 (2.4)	0.004
Plain balloon angioplasty	24 (2.0)	77 (3.5)	0.018

Maximal stent diameter, mm	3.22 ± 0.5	3.17 ± 0.5	0.027
Total stented length, mm	30.8 ± 16.2	30.3 ± 17.2	0.376
Successful PCI, n (%)	1174 (98.7)	2116 (97.3)	0.011
Periprocedural antithrombotic medication			
Aspirin	1086 (91.3)	1935 (89.0)	0.038
Unfractionated heparin	1091 (91.8)	2074 (95.4)	<0.001
Low molecular weight heparin	49 (4.1)	89 (4.1)	>0.999
Bivalirudin	117 (9.8)	149 (6.9)	0.003
GPIIb/IIIa inhibitor	152 (12.8)	261 (12.0)	0.547

Data are shown as counts (proportion; %) or mean ± standard deviation. CAD, coronary artery disease; GPIIb/IIIa, glycoprotein IIb/IIIa; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

[a] Angiographic data were not available for 9 patients in the smokers group and 5 patients in the nonsmokers group.

[b] Left ventricular ejection fraction was not available in 83 patients in the smokers group and 136 patients in the nonsmokers group. Table adapted from (124).

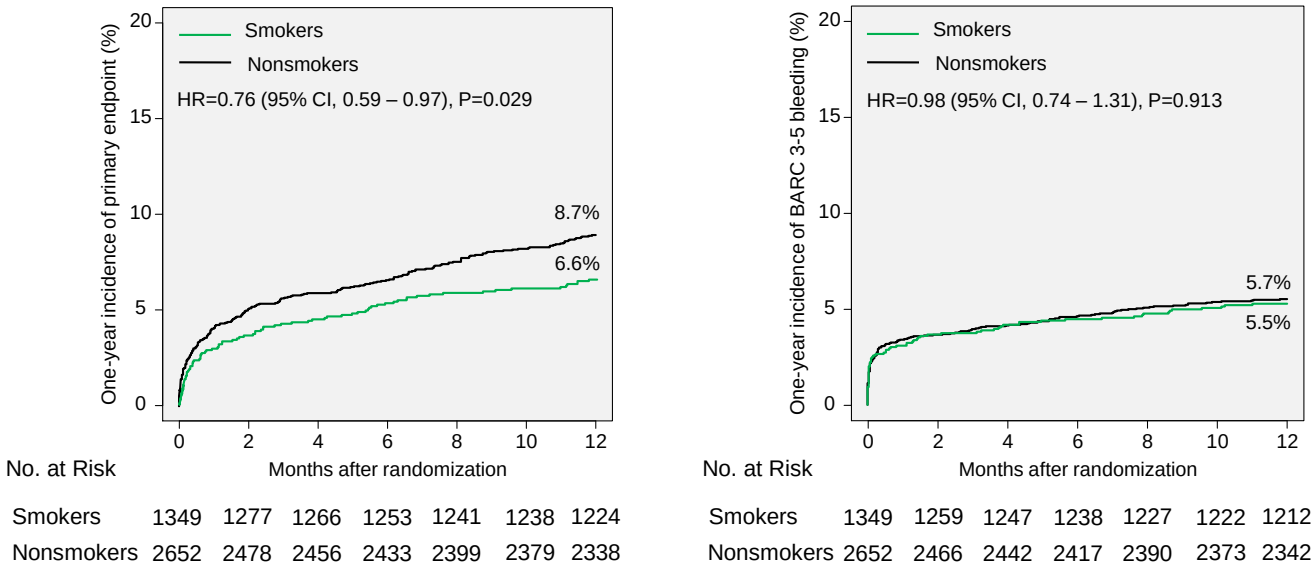

Figure A6. Cumulative incidence of the primary (one-year incidence of death, myocardial infarction, or stroke) and secondary (BARC type 3 to 5 bleeding) endpoints in smokers and nonsmokers

Bleeding was analyzed according to the intention-to-treat principle. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio. Figure adapted from (124).

Table A15. Angiographic and procedural data

Angiographic characteristics*						
Characteristic	**Smokers** (N=1340)			**Nonsmokers** (N=2647)		
	Ticagrelor (N=675)	**Prasugrel** (N=665)	P value	**Ticagrelor** (N=1318)	**Prasugrel** (N=1329)	P value
Access site, n (%)			0.392			0.311
Femoral artery	428 (63.4)	410 (61.7)		809 (61.4)	846 (63.7)	
Radial artery	242 (35.9)	253 (38.0)		504 (38.2)	475 (35.7)	
Other	5 (0.7)	2 (0.3)		5 (0.4)	8 (0.6)	
Number of diseased coronary arteries, n (%)			0.408			0.262
No obstructive CAD	49 (7.3)	34 (5.1)		120 (9.1)	130 (9.8)	
One-vessel disease	226 (33.5)	236 (35.5)		373 (28.3)	343 (25.8)	
Two-vessel disease	190 (28.1)	186 (28.0)		328 (24.9)	368 (27.7)	
Three-vessel disease	210 (31.1)	209 (31.4)		497 (37.7)	488 (36.7)	
Mean LVEF (SD), % †	51.1 ± 11.0	51.2 ± 11.6	0.912	51.8 ± 11.4	52.5 ± 10.9	0.156
Procedural characteristics						
Characteristic	**Smokers** (N=1189)			**Nonsmokers** (N=2174)		
	Ticagrelor (N=584)	**Prasugrel** (N=605)	P value	**Ticagrelor** (N=1085)	**Prasugrel** (N=1089)	P value
Target vessel, n (%)			0.305			0.793
Left main coronary artery	10 (1.7)	16 (2.7)		25 (2.3)	22 (2.0)	
LAD coronary artery	259 (44.4)	238 (39.3)		485 (44.7)	475 (43.6)	
Left circumflex coronary artery	120 (20.5)	130 (21.5)		225 (20.7)	215 (19.8)	
Right coronary artery	191 (32.7)	213 (35.2)		326 (30.1)	354 (32.5)	
Bypass graft	4 (0.7)	8 (1.3)		24 (2.2)	23 (2.1)	
Complex lesion (type B2/C), n (%)	324 (55.5)	330 (54.5)	0.791	649 (59.8)	672 (61.7)	0.390
≥ 1 lesion treated, n (%)	192 (32.9)	204 (33.7)	0.805	375 (34.6)	396 (36.4)	0.405
TIMI flow grade before the intervention, n (%)			0.759			0.121
0	228 (39.0)	224 (37.0)		361 (33.3)	355 (32.6)	
1	55 (9.4)	63 (10.4)		71 (6.5)	92 (8.5)	
2	121 (20.7)	119 (19.7)		240 (22.1)	266 (24.4)	
3	180 (30.9)	199 (32.9)		413 (38.1)	376 (34.5)	
TIMI flow grade after the intervention, n (%)			0.092			0.830
0	5 (0.8)	1 (0.2)		12 (1.1)	14 (1.3)	
1	1 (0.2)	1 (0.2)		8 (0.7)	6 (0.5)	
2	17 (2.9)	9 (1.5)		33 (3.1)	28 (2.6)	
3	561 (96.1)	594 (98.1)		1032 (95.1)	1041 (95.6)	
Type of intervention, n (%)						
Drug-eluting stent	518 (88.7)	550 (90.9)	0.244	973 (89.7)	987 (90.6)	0.499
Bare-metal stent	2 (0.3)	2 (0.3)	>0.999	2 (0.2)	6 (0.6)	0.288
Bioresorbable vascular scaffold	48 (8.2)	46 (7.6)	0.775	51 (4.7)	50 (4.6)	0.985
Drug-eluting balloon	4 (0.7)	7 (1.2)	0.584	32 (2.9)	20 (1.8)	0.119

Plain balloon angioplasty	16 (2.7)	8 (1.3)	0.126	40 (3.7)	37 (3.4)	0.804
Maximal stent diameter, mm	3.20 ± 0.5	3.23 ± 0.5	0.312	3.17 ± 0.5	3.18 ± 0.5	0.897
Total stented length, mm	31.1 ± 16.3	30.5 ± 16.0	0.537	30.5 ± 17.1	30.1 ± 17.4	0.585
Successful PCI, n (%)	577 (98.8)	597 (98.7)	>0.999	1057 (97.4)	1059 (97.2)	0.905

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

* Angiographic data were not available for 9 patients in the smokers group (7 in the ticagrelor group and 2 in the prasugrel group) and 5 patients in the nonsmokers group (2 in the ticagrelor group and 3 in the prasugrel group).

† Left ventricular ejection fraction was not available in 83 patients in the smokers group (39 in the ticagrelor group and 44 in the prasugrel group) and 136 patients in the nonsmokers group (66 in the ticagrelor group and 70 in the prasugrel group). Table adapted from (124).

Table A16. Main characteristics of the trials included in the meta-analysis

Trial	*Study design*	*Time to randomization*	*Stratification*	*Assigned therapies*	*Key inclusion criteria*	*Key exclusion criteria*	*Primary endpoints*	*Secondary endpoints*
GLOBAL LEADERS	Randomized, open-label, multicenter trial	After coronary angiography but before PCI	By center and clinical presentation (stable CAD vs. ACS)	75-100 mg/d ASA+ 90 mg Ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy vs. standard DAPT with 75-100 mg ASA + either 75 mg/d clopidogrel or 2x 90 mg ticagrelor for 12 months, followed by aspirin monotherapy for 12 months	• Age ≥18; • any clinical indication for PCI (stable CAD or ACS)	• Intolerance to aspirin, $P2Y_{12}$ inhibitors, bivalirudin, stainless steel or biolimus; • intake of a strong CYP3A4 inhibitor; • need for OAC; • overt major bleeding	Composite of all-cause death or non-fatal new Q-wave MI at 24 months	• BARC type 3 to 5 bleeding • the individual components of the primary endpoint (a composite of all-cause death, new Q-wave MI, or stroke; MI; stroke; any revascularization; and definite ST).
One-Month DAPT	Randomized, open-label, noninferiority multicenter trial	At PCI		1-month DAPT followed by aspirin monotherapy vs. 6-12 months DAPT followed by aspirin monotherapy	• Patients undergoing PCI for stable or unstable IHD • ≥ 19 years of age • significant de novo coronary lesion	• acute MI • complex lesion • cardiogenic shock or previous cardiopulmonary resuscitation	Composite of cardiac death, nonfatal MI, TVR, stroke, or major bleeding	• all-cause death • cardiac death • nonfatal MI • TVR • stent thrombosis • stroke • major bleeding
OPTIMIZE	Multicenter, open-label, active-controlled, randomized clinical trial	At PCI	By the presence of diabetes mellitus	Aspirin 100-200 mg daily + clopidogrel 75 mg daily for 3 months, followed by therapy with aspirin alone vs. aspirin 100-200 mg daily + clopidogrel	• > 18 years of age • clinical indication for PCI • lesion located in a native major epicardial vessel or a major side branch ≥ 2.50	• STEMI presenting for primary PCI • PCI with BMS in nontarget lesions <6 months prior to the index procedure	A composite of all-cause death, MI, stroke, or major bleeding	• stent thrombosis, • TLR and TVR • MACE (including death from any cause, MI, emergent CABG or TLR) • any bleeding

				75 mg daily for 12 months.	• mm (by visual estimation) or arterial conduit. • at least one stenosis ≥ 50% (by visual estimation)	• previous treatment with any DES • scheduled elective surgery within 12 months after the index procedure • hypersensitivity to aspirin and/or clopidogrel • lesion located in a saphenous vein graft • ISR of a DES.			
REDUCE	Prospective, open-label, multicenter, randomized, investigator-initiated study	At index PCI (before discharge)	By site	3-month DAPT with ASA 75 mg + either ticagrelor 90 mg twice daily or prasugrel 10 mg daily* or clopidogrel 75 mg daily vs. 12-month DAPT (ASA 75 mg + either ticagrelor 90 mg twice daily or prasugrel 10 mg daily or clopidogrel 75 mg daily).	• patients older than 18 years • patients with ACS • successful COMBO stent implantation	• patients presenting with cardiogenic shock • major bleeding complications or contraindication to DAPT • patients who have been treated with another DES	composite of all-cause death, myocardial infarction, stent thrombosis, stroke, target vessel revascularization or bleeding (BARC 2, 3, 5) at 12 months.	• bleeding (BARC 2,3,5) at 12 months • all-cause mortality, MI, ST, stroke, TVR, bleeding at 24 months • mortality at 12 months and 24 months • any MI at 12 and 24 months etc.
RESET	Prospective, open-label, randomized trial	At PCI	By participating center and 4 clinical or lesion characteristics:diabetes mellitus; acute coronary syndrome; treatment of a short lesion (stent length ≤ 24mm); and treatment of a long lesion (≥28 mm)	E-ZES with 3-month DAPT (ASA 100 mg daily + 75 mg Clopidogrel) vs. other DES with 12-month DAPT (ASA 100 mg daily + 75 mg Clopidogrel)	• CAD including stable angina, unstable angina and acute MI • age 20 years or older • significant coronary artery stenosis (>50% by visual estimation)	• Contraindication to antiplatelet agents & bleeding history within prior 3 months • prior history of cerebral vascular accidents, peripheral artery occlusive	composite of death from cardiovascular causes, MI, ST, ischemia-driven target-vessel revascularization, or bleeding at 1-year post-procedure.	• Individual components of the primary endpoint • the composite of all-cause death, MI or ST.

						disease, thrombo-embolic disease, ST • LVEF <40% • cardiogenic shock • severe renal or hepatic dysfunction		
SMART-CHOICE	Investigator-initiated, multicenter, open-label, noninferiority, randomized study.	At index procedure or at a follow-up visit within 3 months after the index procedure.	• By clinical presentation (stable ischemic heart disease or acute coronary syndrome), • enrolling center, • type of $P2Y_{12}$ inhibitor used (clopidogrel, prasugrel, or ticagrelor) and • type of stent used	Aspirin 100 mg daily + either clopidogrel 75 mg daily, or prasugrel 10 mg daily, or ticagrelor 90 mg twice daily for 3 months, followed by the respective $P2Y_{12}$ inhibitor monotherapy for 6 or 12 months vs. aspirin 100 mg daily + 1 $P2Y_{12}$ inhibitor (either clopidogrel, prasugrel, or ticagrelor) for 12 months.	• age at least 20 • written informed consent • successful PCI with DES for SIHD or ACS • one or more coronary stenosis of 50% or more in a native coronary artery.	• hypersensitivity or contraindication to any of the following:´ Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Everolimus, Sirolimus • hemodynamic instability or cardiogenic shock • active pathological bleeding including GI or genitourinary bleeding • DES implantation within 12 months before index PCI.	Composite of all-cause death, myocardial infarction, or stroke at 12 months after the index procedure.	• individual components of the primary end point at 12-months • cardiac death at 12-month, • target lesion revascularization, • any revascularization at 12 months, • stent thrombosis at 12 months, • BARC bleeding type 2 to 5, • each component of primary and secondary end points at 2 and 3 years.
STOPDAPT- 2	Multicenter, open-label, randomized trial	Before hospital discharge, after index PCI	By participating center	either aspirin 81- 200 mg/d and clopidogrel 75 mg/d (in 62% of patients) **or** aspirin 81-200 mg/d and prasugrel 3,75 mg/d (in 38% of patients)	• PCI with a cobalt chromium everolimus-eluting stent • no plan for staged PCI	• need for OAC or antiplatelet therapy other than aspirin and $P2Y_{12}$ inhibitors,	composite of CV death, MI, ischemic or hemorrhagic stroke, definite ST, and TIMI major or	• composite of CV death, MI, ischemic or hemorrhagic stroke, or definite ST

				for 1 month, followed by monotherapy with the respective $P2Y_{12}$ inhibitor alone for 5 years vs. aspirin + clopidogrel for 12 months.		• history of intracranial bleeding, and • known intolerance to clopidogrel	minor bleeding at 12 months.	• TIMI major or minor bleeding
TICO	Randomized, investigator-initiated, multicenter, unblinded trial	After PCI	According to the presence of diabetes and STEMI	Aspirin 100 mg/d + 90 mg ticagrelor twice daily for 3 months, followed by ticagrelor monotherapy vs. aspirin 100 mg daily + ticagrelor 90 mg twice daily for 12 months.	• Age ≥ 19 • Patients who received bioresorbable polymer sirolimus-eluting stent • Provision of informed consent	• age > 80 years • increased risk of bleeding • need for OAC • life expectancy <1 year	Composite of major bleeding and major adverse cardiac and cerebrovascular events (death, MI, ST, stroke, or TVR)	• Each component of the primary outcome • cardiac or non-cardiac death • stent thrombosis • any bleeding (TIMI minor or major)

TWILIGHT	Randomized, double-blind placebo-controlled, multicenter trial	After 3 months	According to site	90 mg ticagrelor twice daily + aspirin 81-100 mg daily for 3 months, followed by ticagrelor + placebo for 12 months vs. 90 mg ticagrelor twice daily + aspirin 81-100 mg daily for 3+12 months.	High risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration	• <18 years of age • contraindication to aspirin or ticagrelor • planned surgery within 90 days • planned coronary revascularization within 90 days • need for chronic OAC • prior stroke • life expectancy <1 year	BARC type 2, 3, or 5 bleeding	• First occurrence of death from any cause, nonfatal MI, or nonfatal stroke • Secondary bleeding endpoints: BARC type 3 or 5 bleeding; TIMI major or minor bleeding; GUSTO moderate, severe, or life-threatening bleeding; or major ISTH bleeding

ASA, aspirin; ACS, acute coronary syndrome; ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; BMS, bare-metal stent; CAD, coronary artery disease; CV, cardiovascular; CYP3A4, cytochrome P450 3A4; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; E-ZES, endeavor zotarolimus-eluting stent; GI, gastrointestinal; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; IC, Informed consent; IHD, ischemic heart disease; ISTH, International Society on Thrombosis and Haemostasis; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

*(5 mg if >75 years, or < 60 kg) (REDUCE Study)

Official titles and acronyms: **GLOBAL LEADERS**: Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs.aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent; **One-month DAPT**: One-month dual antiplatelet therapy followed by aspirin monotherapy vs. 6-12 months DAPT followed by aspirin monotherapy after drug-eluting stent implantation; **OPTIMIZE:** Three vs. Twelve Months of Dual Antiplatelet Therapy After Zotarolimus-Eluting Stents; **REDUCE:** The Randomised Evaluation of short-term DUal antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual-therapy stEnt; **RESET:** REal Safety and Efficacy of 3- month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; **SMART-CHOICE:** Effect of P2Y12 Inhibitor Monotherapy vs. Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention; **STOPDAPT-2:** Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs. 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI; **TICO:** Effect of Ticagrelor Monotherapy vs. Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome; **TWILIGHT:** Ticagrelor with or without Aspirin in High-Risk Patients after PCI. Table adapted from (132).

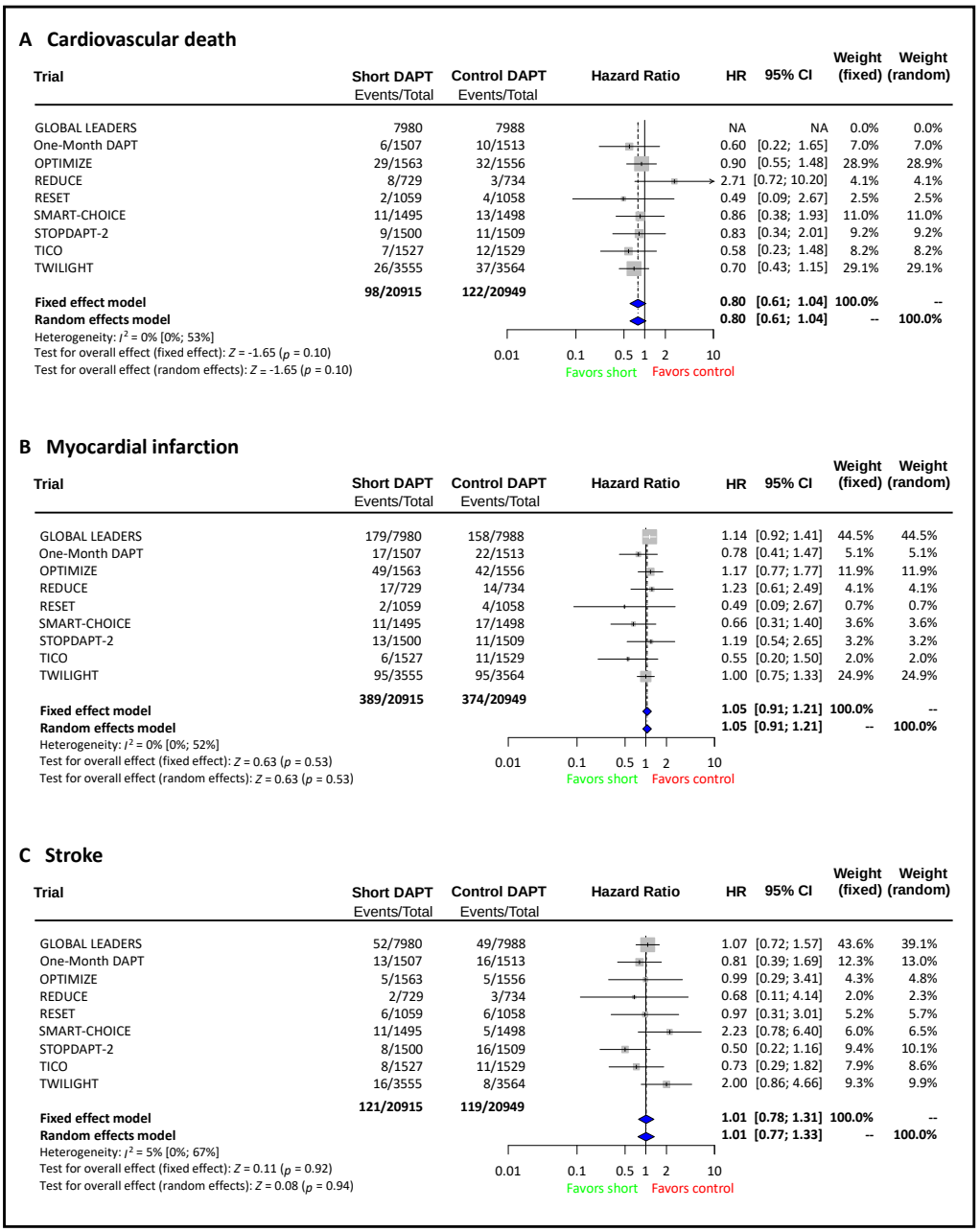

Figure A7. Secondary outcomes of patients with short vs. control DAPT after PCI

Panel A. Cardiac death**; Panel B.** Myocardial infarction; **Panel C.** Stroke

The squares indicate the point estimate [hazard ratio (HR)] and the lines represent the 95% confidence intervals. The size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis. The arrow indicates a CI value beyond the shown axis limit. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention (132).

Table A17. Concomitant medication according to the tertiles of soluble glycoprotein VI

Characteristic	Plasma soluble glycoprotein VI level			*P* value
	Lower tertile (n=106)	Middle tertile (n=106)	Upper tertile (n=106)	
Drug therapy at baseline				
Aspirin	94 (88.7)	99 (93.4)	95 (89.6)	0.46
Clopidogrel	58 (54.7)	60 (56.6)	55 (51.9)	0.79
Statin	98 (92.5)	95 (89.6)	93 (87.7)	0.52
Betablocker	53 (50.0)	58 (54.7)	57 (53.8)	0.77
ACE inhibitor/ARB	80 (75.5)	82 (77.4)	78 (73.6)	0.82
Periprocedural antithrombotic medication				
Aspirin loading[a]	78 (73.6)	81 (76.4)	68 (64.2)	0.12
Clopidogrel loading[a]	83 (78.3)	85 (80.2)	92 (86.8)	0.24
Unfractionated heparin	106 (100)	106 (100)	106 (100)	>0.99
Total heparin dose[b]	7250 [6000;9000]	7000 [6000;8000]	7000 [6000;8000]	0.46
Drug therapy at discharge				
Aspirin	106 (100)	106 (100)	104 (98.1)	0.33
Clopidogrel	106 (100)	106 (100)	106 (100)	
Statin	103 (97.2)	101 (95.3)	104 (98.1)	0.62
Betablocker	56 (52.8)	66 (62.3)	71 (67.0)	0.10
ACE inhibitor/ARB	82 (77.4)	87 (82.1)	92 (86.8)	0.20

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; sGPVI, soluble glycoprotein VI. Number of patients (%) is shown.

[a] Aspirin loading was administered immediately prior to percutaneous coronary intervention and clopidogrel loading on an average of 3.7 hours prior to percutaneous coronary intervention. Patients who did not receive loading were on chronic antiplatelet therapy on admission.

[b] Median [IQR], IU is shown. IU, International units. Table adapted from (137).

Table A18. Angiographic and procedural characteristics according to tertiles of soluble glycoprotein VI

Characteristic	Plasma soluble glycoprotein VI level			*P* value
	Lower tertile (n=152)	Middle tertile (n=170)	Upper tertile (n=170)	
Target vessel				0.67
Left main coronary artery	10 (6.6)	11 (6.5)	7 (4.1)	
Left anterior descending coronary artery	65 (42.8)	71 (41.8)	66 (38.8)	
Left circumflex coronary artery	41 (27.0)	40 (23.5)	45 (26.5)	
Right coronary artery	34 (22.4)	48 (28.2)	51 (30.0)	
Bypass graft	2 (1.3)	0	1 (0.6)	
Complex lesion (type B2/C)	93 (61.2)	123 (72.4)	103 (60.6)	0.04
Chronic total occlusion	3 (2.0)	11 (6.5)	11 (6.5)	0.11
TIMI flow grade before the intervention				0.006
0	2 (1.3)	9 (5.3)	6 (3.6)	
1	0	3 (1.8)	7 (4.1)	
2	1 (0.7)	7 (4.1)	8 (4.7)	
3	149 (98.0)	151 (88.8)	148 (87.6)	
Type of intervention				
Drug eluting stent	139 (91.4)	157 (92.4)	161 (94.7)	0.50
Drug eluting balloon	11 (7.2)	7 (4.1)	4 (2.4)	0.10
PTCA only	11 (7.2)	11 (6.5)	8 (4.7)	0.62
Total stented length, mm[a]	23.0 [18.0-32.0]	23.0 [18.0-33.0]	24.0 [18.0-38.0]	0.12
Maximum stent diameter, mm[a]	3.0 [3.0-3.5]	3.5 [3.0-3.5]	3.0 [2.8-3.5]	0.02
Maximum balloon diameter, mm[b]	3.0 [2.8-3.5]	3.5 [3.0-4.0]	3.0 [2.8-3.5]	0.17
Maximum balloon pressure, atm[c]	14.0 [12.0-16.0]	16.0 [12.0-18.0]	14.0 [12.0-16.0]	0.009
TIMI flow grade after the intervention[d]				>0.99
0	1 (0.7)	1 (0.6)	2 (1.2)	
1	1 (0.7)	2 (1.2)	1 (0.6)	
2	0	0	0	
3	151 (99.3)	166 (97.6)	166 (98.2)	

PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TIMI, Thrombolysis in Myocardial Infarction. Number of lesions (%) or median [25th-75th percentiles] is shown.

[a] Total stent length and maximal stent diameter refer only to lesions treated with stent(s). Maximum stent diameter not available in 35 patients (13 in the lower sGPVI tertile, 13 in the middle sGPVI, and 9 in the upper sGPVI tertile).

[b] Maximum balloon diameter not available in 5 patients (2 in the middle sGPVI tertile, and 3 in the upper sGPVI tertile).

[c] Maximum balloon pressure not available in 6 patients (3 in the middle sGPVI tertile, and 3 in the upper sGPVI tertile).

[d] For a patient in the upper sGPVI tertile, TIMI flow after the intervention could not be assessed. Table adapted from (137).

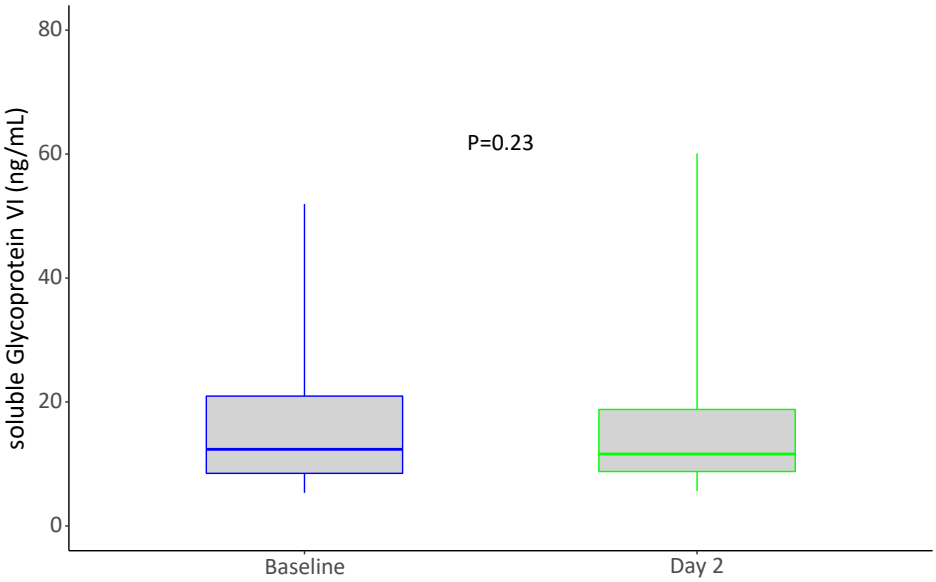

Figure A8. Plasma sGPVI at baseline and day 2 in patients of the placebo group

Medians, 25th and 75th percentiles, as well as 95% confidence intervals, are shown. sGPVI, soluble glycoprotein VI. Figure adapted from (137).

Table A19. Efficacy endpoints at 30 days according to the tertiles of sGPVI

Characteristic	Plasma soluble glycoprotein VI level		
	Lower tertile (n=106)	**Middle tertile** (n=106)	**Upper tertile** (n=106)
All-cause mortality	0	0	1
Myocardial infarction	3	1	3
Type 3	0	0	1
Type 4a	3	1	2
Definite stent thrombosis	0	0	0
Urgent coronary revascularization	1	0	0
Major adverse cardiovascular events	4	1	3[b]

sGPVI, soluble glycoprotein VI. Number of patients is shown.

[a] Major adverse cardiovascular events include death, myocardial infarction, stroke, or urgent coronary revascularization.

[b] A patient of the upper sGPVI tertile experienced two events, death and myocardial infarction. Table adapted from (137).

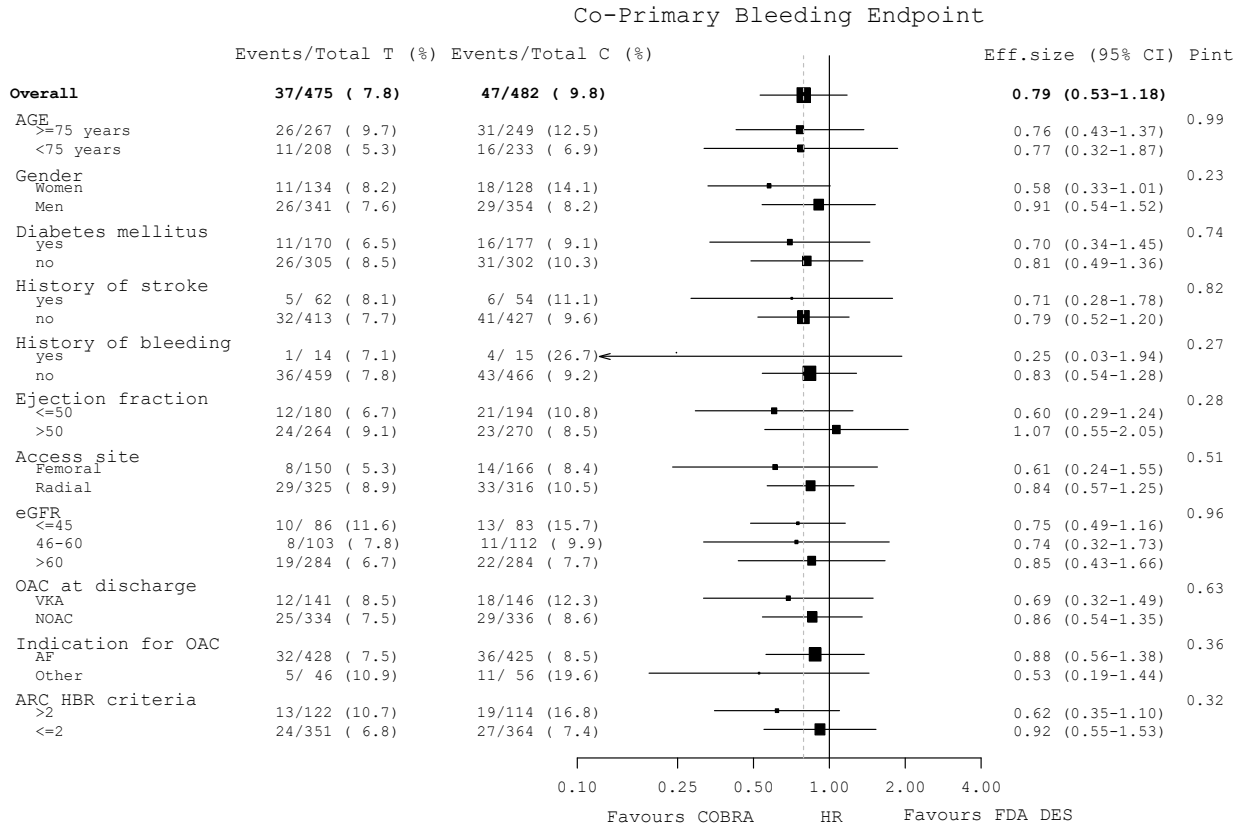

Figure A9. Subgroup analysis of the co-primary bleeding endpoint

Cumulative incidences were calculated for the co-primary endpoint of bleeding after accounting for the competing risk of death.

FDA-DES: Food and Drug Agency - Drug-eluting stent; HR: hazard ratio. Figure adapted from (144).

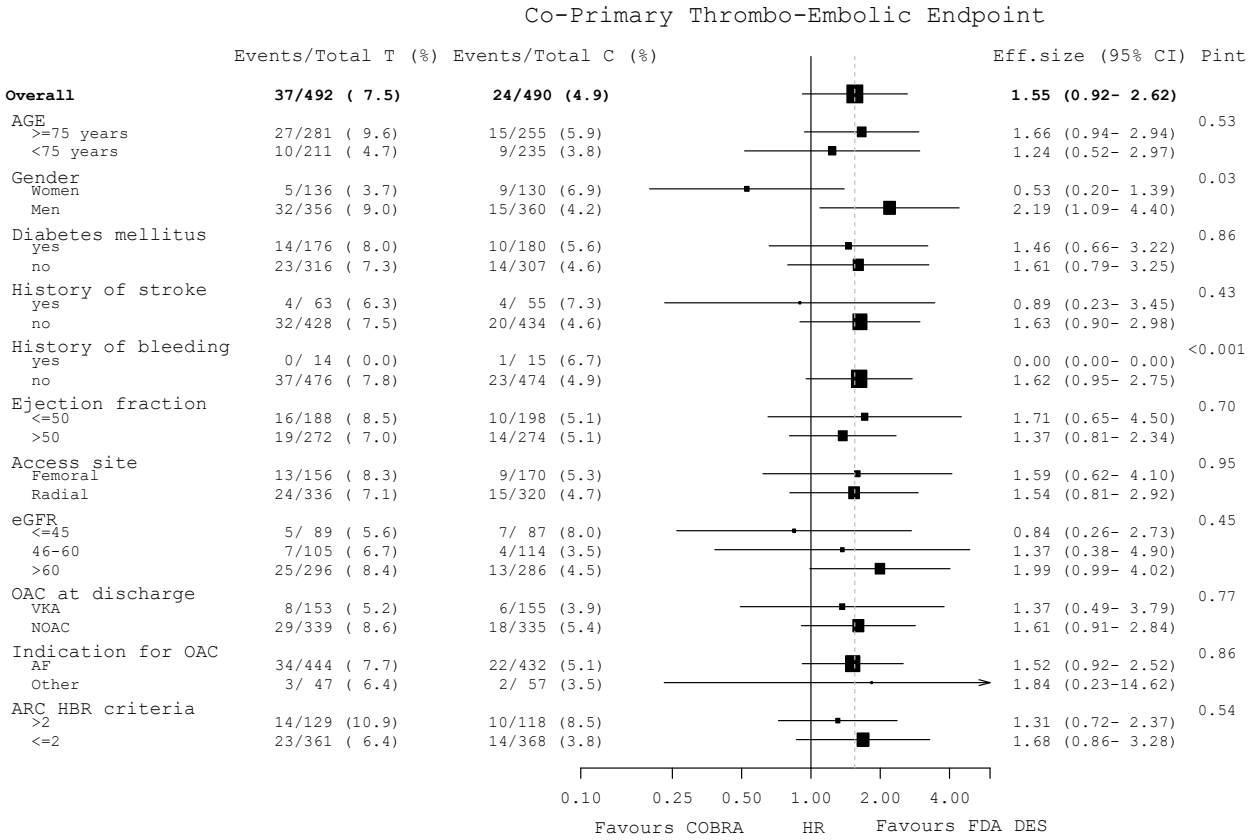

Figure A10. Subgroup analysis of the co-primary thrombo-embolic endpoint

Cumulative incidences for the thrombo-embolic co-primary endpoint were calculated using Kaplan-Meier estimates.

ARC-HBR: Academic Research Consortium-High Bleeding Risk; FDA-DES: Food and Drug Agency - Drug-eluting stent; HR: hazard ratio. Figure adapted from (144).

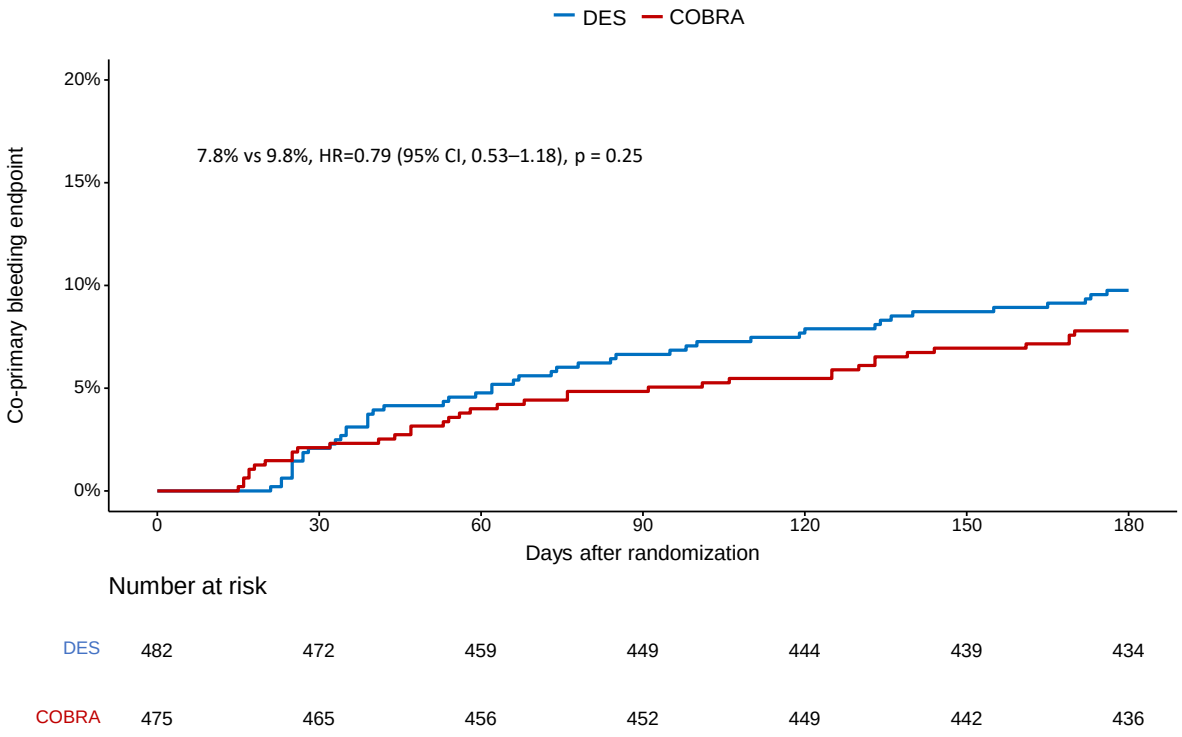

Figure A11. Survival analysis of bleeding co-primary endpoint (BARC ≥2 bleeding) – ITT population

BARC, Bleeding Academic Research Consortium; DES, drug-eluting stent; ITT, intention-to-treat.

Figure adapted from (144).

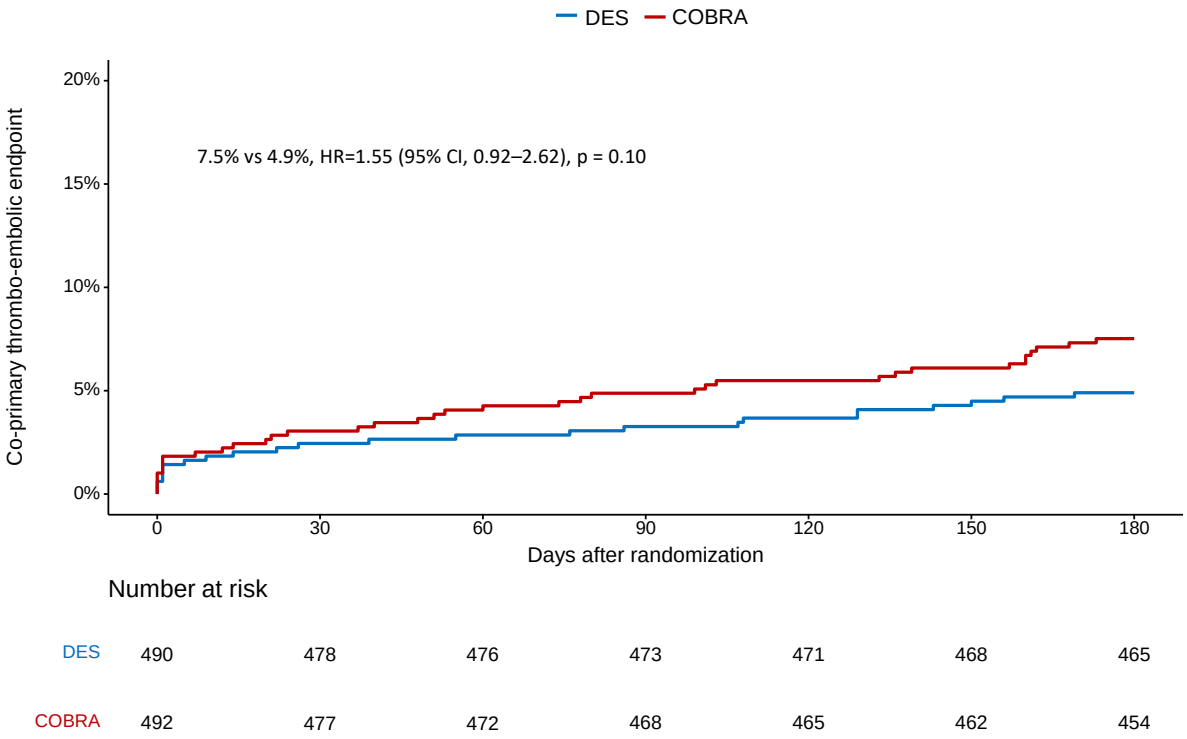

Figure A12. Survival analysis of the thrombo-embolic co-primary endpoint (a composite of all-cause death, myocardial infarction, definite or probable stent thrombosis or ischemic stroke) – ITT Population

DES, drug-eluting stent; ITT, intention-to-treat. Figure adapted from (144).

Acknowledgements

Completing my Ph.D. research was an immensely rewarding experience that would have not been possible without the support and encouragement of many different people.

I would firstly like to express my deepest gratitude and appreciation to my Ph.D. advisor Prof. Dr. Adnan Kastrati for the opportunity to join his research group and for the immeasurable level of mentorship during my Ph.D. studies. His creative scientific mind, good-humored disposition, as well as his enthusiasm for research inspired me and generated a continual drive to further evolve my scientific understanding. I feel privileged to have benefited and learned from his deep insight into clinical trial design, statistical analysis, critical appraisal of the literature, and scientific writing. Dear Professor Kastrati, I am forever grateful for the support and opportunities you have given me in my career!

I would also like to thank my Ph.D. mentors Prof. Dr. Sebastian Kufner and Prof. Dr. Isabell Bernlochner for their support and scientific expertise, along with the fruitful collaborations we have shared. It was a pleasure to work with you!

Special thanks are due to Prof. Dr. Gjin Ndrepepa for his sincere guidance and endless support through all stages of my Ph.D. research. He was the person who introduced me to the world of scientific writing and statistical analysis and was always ready to help me. Forever grateful to you for your support and mentorship, Professor Ndrepepa!

I would also like to extend my thanks to Dr. Salvatore Cassese for his good-humored encouragement and support during my Ph.D.

Further, I would like to thank my colleagues from the ISAResearch Center especially Nonni Rifatov, Susanne Pinieck, Prof. Katharina Mayer, Barbara Merzljak, Monika Neumeyer, and Dr. Marion Janisch

for their friendship and close collegial work. I would also like to thank Raphaela Blum and Bettina Kratzer for their assistance during the course of this Ph.D. program.

Last, but not least, I would like to thank my parents, Xhyla Lahu and Prof. Ali Lahu, for their love, unwavering support, and encouragement in everything I do, and for the many sacrifices they have made for my education. This work is dedicated to them. I am also grateful to my siblings Marigona, Vendenis, and Doruntina for their love, endless support, and encouragement to follow my dreams. *Faleminderit!*

Sources of funding

The studies and the research included in this work were predominantly investigator-initiated and industry-independent studies. There was no remuneration for investigators or subjects. The study analyses and design were predominantly performed by Deutsches Herzzentrum München-Klinik der Technischen Universität München.

The ISAR-REACT 5 trial was supported by a grant (FKZ 81X1600501) from the German Center for Cardiovascular Research and the Deutsches Herzzentrum München, Germany.

The ISAR-PLASTER trial was supported by a grant from the German Center for Cardiovascular Research, Deutsches Herzzentrum München, Federal Ministry of Education and Research (BMBF), and advanceCOR GmbH (the manufacturer of revacept). The funding sources had no role in the design and conduct of the study, collection, management, or interpretation of the data.

The COBRA-REDUCE trial was sponsored and financed by CeloNova BioSciences Inc. San Antonio, TX, USA. The data coordinating center was the ISAResearch Center, Deutsches Herzzentrum München, Munich, Germany. The trial sponsor had no role in data collection, analysis, or interpretation.

REFERENCES

1. Ribatti D, Crivellato E. Giulio Bizzozero and the discovery of platelets. Leuk Res 2007;31:1339-41.
2. Gremmel T, Frelinger AL, 3rd, Michelson AD. Platelet Physiology. Semin Thromb Hemost 2016;42:191-204.
3. Ghoshal K, Bhattacharyya M. Overview of platelet physiology: its hemostatic and nonhemostatic role in disease pathogenesis. ScientificWorldJournal 2014;2014:781857.
4. Jennings LK. Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis. Thromb Haemost 2009;102:248-57.
5. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 1962;194:927-9.
6. Jin J, Daniel JL, Kunapuli SP. Molecular basis for ADP-induced platelet activation. II. The P2Y1 receptor mediates ADP-induced intracellular calcium mobilization and shape change in platelets. J Biol Chem 1998;273:2030-4.
7. Jin J, Kunapuli SP. Coactivation of two different G protein-coupled receptors is essential for ADP-induced platelet aggregation. Proc Natl Acad Sci U S A 1998;95:8070-4.
8. Cattaneo M. P2Y12 receptor antagonists: a rapidly expanding group of antiplatelet agents. Eur Heart J 2006;27:1010-2.
9. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1:263.
10. Kereiakes DJ, Choo JK, Young JJ, Broderick TM. Thrombosis and drug-eluting stents: a critical appraisal. Rev Cardiovasc Med 2004;5:9-15.
11. Luscher TF, Steffel J, Eberli FR et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 2007;115:1051-8.
12. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. EuroIntervention 2022;17:e1371-e1396.
13. Awtry EH, Loscalzo J. Aspirin. Circulation 2000;101:1206-18.
14. FitzGerald GA, Oates JA, Hawiger J et al. Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. J Clin Invest 1983;71:676-88.
15. Jimenez AH, Stubbs ME, Tofler GH, Winther K, Williams GH, Muller JE. Rapidity and duration of platelet suppression by enteric-coated aspirin in healthy young men. Am J Cardiol 1992;69:258-62.
16. Lorenz RL, Schacky CV, Weber M et al. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily). Effects on platelet aggregation and thromboxane formation. Lancet 1984;1:1261-4.
17. Peters RJ, Mehta SR, Fox KA et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108:1682-7.
18. Serebruany VL, Steinhubl SR, Berger PB et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol 2005;95:1218-22.
19. Jolly SS, Pogue J, Haladyn K et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study. Eur Heart J 2009;30:900-7.
20. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J 2009;30:1964-77.
21. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. Drug Metab Dispos 2003;31:53-9.

22. Farid NA, Payne CD, Small DS et al. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. Clin Pharmacol Ther 2007;81:735-41.
23. Hulot JS, Bura A, Villard E et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 2006;108:2244-7.
24. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E et al. Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. Arterioscler Thromb Vasc Biol 2006;26:1895-900.
25. Angiolillo DJ, Suryadevara S, Capranzano P, Bass TA. Prasugrel: a novel platelet ADP P2Y12 receptor antagonist. A review on its mechanism of action and clinical development. Expert Opin Pharmacother 2008;9:2893-900.
26. Jakubowski JA, Winters KJ, Naganuma H, Wallentin L. Prasugrel: a novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. Cardiovasc Drug Rev 2007;25:357-74.
27. Niitsu Y, Jakubowski JA, Sugidachi A, Asai F. Pharmacology of CS-747 (prasugrel, LY640315), a novel, potent antiplatelet agent with in vivo P2Y12 receptor antagonist activity. Semin Thromb Hemost 2005;31:184-94.
28. Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. Pharmacotherapy 2014;34:1077-90.
29. Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. Cardiovasc Ther 2009;27:259-74.
30. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;27:1038-47.
31. Savi P, Combalbert J, Gaich C et al. The antiaggregating activity of clopidogrel is due to a metabolic activation by the hepatic cytochrome P450-1A. Thromb Haemost 1994;72:313-7.
32. Desager JP. Clinical pharmacokinetics of ticlopidine. Clin Pharmacokinet 1994;26:347-55.
33. Valgimigli M, Bueno H, Byrne RA et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-260.
34. Byrne RA, Rossello X, Coughlan JJ et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720-3826.
35. Schomig A, Neumann FJ, Kastrati A et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084-9.
36. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators C. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102:624-9.
37. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999;100:1667-72.
38. Bennett CL, Davidson CJ, Raisch DW, Weinberg PD, Bennett RH, Feldman MD. Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. Arch Intern Med 1999;159:2524-8.
39. Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
40. Steinhubl SR, Berger PB, Mann JT, 3rd et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20.

41. Schror K, Weber AA, Hohlfeld T. Clopidogrel "resistance" and statin cotreatment - significant for cardiocoronary prevention in real life? Thromb Haemost 2005;94:235-7.
42. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908-13.
43. Jaremo P, Lindahl TL, Fransson SG, Richter A. Individual variations of platelet inhibition after loading doses of clopidogrel. J Intern Med 2002;252:233-8.
44. Kuliczkowski W, Witkowski A, Polonski L et al. Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2009;30:426-35.
45. Gurbel PA, Antonino MJ, Bliden KP et al. Platelet reactivity to adenosine diphosphate and long-term ischemic event occurrence following percutaneous coronary intervention: a potential antiplatelet therapeutic target. Platelets 2008;19:595-604.
46. Cuisset T, Frere C, Quilici J et al. High post-treatment platelet reactivity is associated with a high incidence of myonecrosis after stenting for non-ST elevation acute coronary syndromes. Thromb Haemost 2007;97:282-7.
47. Matetzky S, Shenkman B, Guetta V et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171-5.
48. Gurbel PA, Bliden KP, Samara W et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. J Am Coll Cardiol 2005;46:1827-32.
49. Sibbing D, Braun S, Morath T et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009;53:849-56.
50. Buonamici P, Marcucci R, Migliorini A et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. J Am Coll Cardiol 2007;49:2312-7.
51. Migliorini A, Valenti R, Marcucci R et al. High residual platelet reactivity after clopidogrel loading and long-term clinical outcome after drug-eluting stenting for unprotected left main coronary disease. Circulation 2009;120:2214-21.
52. Jernberg T, Payne CD, Winters KJ et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J 2006;27:1166-73.
53. Wallentin L, Varenhorst C, James S et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. Eur Heart J 2008;29:21-30.
54. Storey RF, Husted S, Harrington RA et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852-6.
55. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
56. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
57. Motovska Z, Hlinomaz O, Miklik R et al. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation 2016;134:1603-1612.
58. Motovska Z, Hlinomaz O, Kala P et al. 1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated With Prasugrel Versus Ticagrelor. J Am Coll Cardiol 2018;71:371-381.

59. Schupke S, Neumann FJ, Menichelli M et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. N Engl J Med 2019;381:1524-1534.
60. Collet JP, Thiele H, Barbato E et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289-1367.
61. Alexander KP, Roe MT, Chen AY et al. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol 2005;46:1479-87.
62. Roe MT, Goodman SG, Ohman EM et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. Circulation 2013;128:823-33.
63. Brandt JT, Payne CD, Wiviott SD et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. Am Heart J 2007;153:66 e9-16.
64. Gurbel PA, Bliden KP, Butler K et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;120:2577-85.
65. Menichelli M, Neumann FJ, Ndrepepa G et al. Age- and Weight-Adapted Dose of Prasugrel Versus Standard Dose of Ticagrelor in Patients With Acute Coronary Syndromes : Results From a Randomized Trial. Ann Intern Med 2020;173:436-444.
66. Alexander JH, Harrington RA, Tuttle RH et al. Prior aspirin use predicts worse outcomes in patients with non-ST-elevation acute coronary syndromes. PURSUIT Investigators. Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy. Am J Cardiol 1999;83:1147-51.
67. Santopinto J, Gurfinkel EP, Torres V et al. Prior aspirin users with acute non-ST-elevation coronary syndromes are at increased risk of cardiac events and benefit from enoxaparin. Am Heart J 2001;141:566-72.
68. Ambrosio G, Steinhubl S, Gresele P et al. Impact of chronic antiplatelet therapy before hospitalization on ischemic and bleeding events in invasively managed patients with acute coronary syndromes: the ACUITY trial. Eur J Cardiovasc Prev Rehabil 2011;18:121-8.
69. Regev E, Asher E, Fefer P et al. Acute myocardial infarction occurring while on chronic clopidogrel therapy ('clopidogrel failure') is associated with high incidence of clopidogrel poor responsiveness and stent thrombosis. PLoS One 2018;13:e0195504.
70. Angiolillo DJ, Jakubowski JA, Ferreiro JL et al. Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. J Am Coll Cardiol 2014;64:1005-14.
71. Collet JP, Montalescot G, Blanchet B et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110:2361-7.
72. Piccolo R, Oliva A, Avvedimento M et al. Mortality after bleeding versus myocardial infarction in coronary artery disease: a systematic review and meta-analysis. EuroIntervention 2021;17:550-560.
73. Urban P, Mehran R, Colleran R et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. Circulation 2019;140:240-261.
74. Carter BD, Freedman ND, Jacobs EJ. Smoking and mortality--beyond established causes. N Engl J Med 2015;372:2170.
75. Barbash GI, Reiner J, White HD et al. Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995;26:1222-9.

76. Gupta T, Kolte D, Khera S et al. Smoker's Paradox in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. J Am Heart Assoc 2016;5.
77. Desai NR, Mega JL, Jiang S, Cannon CP, Sabatine MS. Interaction between cigarette smoking and clinical benefit of clopidogrel. J Am Coll Cardiol 2009;53:1273-8.
78. Berger JS, Bhatt DL, Steinhubl SR et al. Smoking, clopidogrel, and mortality in patients with established cardiovascular disease. Circulation 2009;120:2337-44.
79. Mehta SR, Tanguay JF, Eikelboom JW et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233-43.
80. Ferreiro JL, Bhatt DL, Ueno M, Bauer D, Angiolillo DJ. Impact of smoking on long-term outcomes in patients with atherosclerotic vascular disease treated with aspirin or clopidogrel: insights from the CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events). J Am Coll Cardiol 2014;63:769-77.
81. Bliden KP, Dichiara J, Lawal L et al. The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. J Am Coll Cardiol 2008;52:531-3.
82. Park KW, Kang SH, Kang J et al. Enhanced clopidogrel response in smokers is reversed after discontinuation as assessed by VerifyNow assay: additional evidence for the concept of 'smokers' paradox'. Heart 2012;98:1000-6.
83. Gurbel PA, Bliden KP, Logan DK et al. The influence of smoking status on the pharmacokinetics and pharmacodynamics of clopidogrel and prasugrel: the PARADOX study. J Am Coll Cardiol 2013;62:505-12.
84. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Ther 2004;76:178-84.
85. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-drug interactions. J Am Coll Cardiol 2011;57:1251-63.
86. Costa F, Vranckx P, Leonardi S et al. Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. Eur Heart J 2015;36:1242-51.
87. Yeh RW, Kereiakes DJ, Steg PG et al. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. J Am Coll Cardiol 2015;65:2211-21.
88. Ndrepepa G, Schuster T, Hadamitzky M et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012;125:1424-31.
89. Schulz S, Schuster T, Mehilli J et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J 2009;30:2714-21.
90. Capodanno D, Mehran R, Valgimigli M et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018;15:480-496.
91. Capodanno D, Baber U, Bhatt DL et al. P2Y(12) inhibitor monotherapy in patients undergoing percutaneous coronary intervention. Nat Rev Cardiol 2022;19:829-844.
92. Moroi M, Jung SM, Okuma M, Shinmyozu K. A patient with platelets deficient in glycoprotein VI that lack both collagen-induced aggregation and adhesion. J Clin Invest 1989;84:1440-5.
93. Nieswandt B, Watson SP. Platelet-collagen interaction: is GPVI the central receptor? Blood 2003;102:449-61.

94. Sugiyama T, Okuma M, Ushikubi F, Sensaki S, Kanaji K, Uchino H. A novel platelet aggregating factor found in a patient with defective collagen-induced platelet aggregation and autoimmune thrombocytopenia. Blood 1987;69:1712-20.
95. Bigalke B, Geisler T, Stellos K et al. Platelet collagen receptor glycoprotein VI as a possible novel indicator for the acute coronary syndrome. Am Heart J 2008;156:193-200.
96. Bigalke B, Lindemann S, Ehlers R et al. Expression of platelet collagen receptor glycoprotein VI is associated with acute coronary syndrome. Eur Heart J 2006;27:2165-9.
97. Bigalke B, Stellos K, Geisler T, Lindemann S, May AE, Gawaz M. Glycoprotein VI as a prognostic biomarker for cardiovascular death in patients with symptomatic coronary artery disease. Clin Res Cardiol 2010;99:227-33.
98. Secemsky EA, Butala NM, Kartoun U et al. Use of Chronic Oral Anticoagulation and Associated Outcomes Among Patients Undergoing Percutaneous Coronary Intervention. J Am Heart Assoc 2016;5.
99. Sorensen R, Hansen ML, Abildstrom SZ et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-74.
100. Dans AL, Connolly SJ, Wallentin L et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013;127:634-40.
101. Dewilde WJ, Oirbans T, Verheugt FW et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381:1107-15.
102. Gibson CM, Mehran R, Bode C et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med 2016;375:2423-2434.
103. Cannon CP, Bhatt DL, Oldgren J et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med 2017;377:1513-1524.
104. Lopes RD, Heizer G, Aronson R et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019;380:1509-1524.
105. Hindricks G, Potpara T, Dagres N et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
106. Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.
107. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635-41.
108. Mok CK, Boey J, Wang R et al. Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial. Circulation 1985;72:1059-63.
109. Vahanian A, Beyersdorf F, Praz F et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561-632.
110. Chaabane C, Otsuka F, Virmani R, Bochaton-Piallat ML. Biological responses in stented arteries. Cardiovasc Res 2013;99:353-63.
111. Nakazawa G, Finn AV, Joner M et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138-45.

112. Colleran R, Joner M, Cutlip D et al. Design and Rationale of a Randomized Trial of COBRA PzF Stenting to REDUCE Duration of Triple Therapy (COBRA-REDUCE). Cardiovasc Revasc Med 2022;34:17-24.
113. Mori H, Jinnouchi H, Diljon C et al. A new category stent with novel polyphosphazene surface modification. Future Cardiol 2018;14:225-235.
114. Schulz S, Angiolillo DJ, Antoniucci D et al. Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy--design and rationale of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial. J Cardiovasc Transl Res 2014;7:91-100.
115. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
116. Cutlip DE, Windecker S, Mehran R et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
117. Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
118. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 1999;94:496-509.
119. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics 1988;16:1141-1154.
120. GRAMBSCH PM, THERNEAU TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-526.
121. Lahu S, Ndrepepa G, Neumann FJ et al. Preadmission antiplatelet therapy and treatment effect of ticagrelor versus prasugrel in patients with acute coronary syndromes - a subgroup analysis of the ISAR-REACT 5 trial. Eur Heart J Cardiovasc Pharmacother 2022.
122. Urban P, Mehran R, Colleran R et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J 2019;40:2632-2653.
123. Lahu S, Presch A, Ndrepepa G et al. Ticagrelor or Prasugrel in Patients With Acute Coronary Syndrome and High Bleeding Risk. Circ Cardiovasc Interv 2022;15:e012204.
124. Lahu S, Ndrepepa G, Gewalt S et al. Efficacy and safety of ticagrelor versus prasugrel in smokers and nonsmokers with acute coronary syndromes. Int J Cardiol 2021;338:8-13.
125. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
126. Kim BK, Hong MK, Shin DH et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol 2012;60:1340-8.
127. Vranckx P, Valgimigli M, Juni P et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940-949.
128. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.
129. Kim BK, Hong SJ, Cho YH et al. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. JAMA 2020;323:2407-2416.
130. Higgins JP, Altman DG, Gotzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
131. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

132. Lahu S, Bristot P, Gewalt S et al. Meta-Analysis of Short vs. Prolonged Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation and Role of Continuation with either Aspirin or a P2Y(12) Inhibitor Thereafter. J Atheroscler Thromb 2022;29:1001-1019.
133. Mayer K, Hein-Rothweiler R, Schupke S et al. Efficacy and Safety of Revacept, a Novel Lesion-Directed Competitive Antagonist to Platelet Glycoprotein VI, in Patients Undergoing Elective Percutaneous Coronary Intervention for Stable Ischemic Heart Disease: The Randomized, Double-blind, Placebo-Controlled ISAR-PLASTER Phase 2 Trial. JAMA Cardiol 2021;6:753-761.
134. Schupke S, Hein-Rothweiler R, Mayer K et al. Revacept, a Novel Inhibitor of Platelet Adhesion, in Patients Undergoing Elective PCI-Design and Rationale of the Randomized ISAR-PLASTER Trial. Thromb Haemost 2019;119:1539-1545.
135. Ungerer M, Rosport K, Bultmann A et al. Novel antiplatelet drug revacept (Dimeric Glycoprotein VI-Fc) specifically and efficiently inhibited collagen-induced platelet aggregation without affecting general hemostasis in humans. Circulation 2011;123:1891-9.
136. Neumann FJ, Sousa-Uva M, Ahlsson A et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
137. Lahu S, Adler K, Mayer K et al. Plasma Soluble Glycoprotein VI, Platelet Function, Bleeding, and Ischemic Events in Patients Undergoing Elective Percutaneous Coronary Intervention. Thromb Haemost 2024;124:297-306.
138. Feres F, Costa RA, Abizaid A et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA 2013;310:2510-22.
139. De Luca G, Damen SA, Camaro C et al. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). EuroIntervention 2019;15:e990-e998.
140. Mehran R, Baber U, Sharma SK et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019;381:2032-2042.
141. Hahn JY, Song YB, Oh JH et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA 2019;321:2428-2437.
142. Watanabe H, Domei T, Morimoto T et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA 2019;321:2414-2427.
143. Hong SJ, Kim JS, Hong SJ et al. 1-Month Dual-Antiplatelet Therapy Followed by Aspirin Monotherapy After Polymer-Free Drug-Coated Stent Implantation: One-Month DAPT Trial. JACC Cardiovasc Interv 2021;14:1801-1811.
144. Byrne RA, Colleran R, Coughlan JJ et al. Randomized Trial of COBRA PzF Stenting to Reduce the Duration of Triple Therapy: The COBRA-REDUCE Trial. Circ Cardiovasc Interv 2024;17:e013735.
145. Erlinge D, Gurbel PA, James S et al. Prasugrel 5 mg in the very elderly attenuates platelet inhibition but maintains noninferiority to prasugrel 10 mg in nonelderly patients: the GENERATIONS trial, a pharmacodynamic and pharmacokinetic study in stable coronary artery disease patients. J Am Coll Cardiol 2013;62:577-83.
146. Erlinge D, Ten Berg J, Foley D et al. Reduction in platelet reactivity with prasugrel 5 mg in low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. J Am Coll Cardiol 2012;60:2032-40.
147. Alexopoulos D, Xanthopoulou I, Plakomyti TE et al. Pharmacodynamic effect of prasugrel 5 mg vs clopidogrel 150 mg in elderly patients with high on-clopidogrel platelet reactivity. Am Heart J 2013;165:73-9.
148. De Luca L, De Servi S, Musumeci G, Bolognese L. Is ticagrelor safe in octogenarian patients with non-ST elevation acute coronary syndromes? Eur Heart J Cardiovasc Pharmacother 2018;4:12-14.

149. Schmucker J, Fach A, Mata Marin LA et al. Efficacy and Safety of Ticagrelor in Comparison to Clopidogrel in Elderly Patients With ST-Segment-Elevation Myocardial Infarctions. J Am Heart Assoc 2019;8:e012530.
150. Wong KSL, Amarenco P, Albers GW et al. Efficacy and Safety of Ticagrelor in Relation to Aspirin Use Within the Week Before Randomization in the SOCRATES Trial. Stroke 2018;49:1678-1685.
151. Chin CT, Boden WE, Roe MT et al. Effect of prior clopidogrel use on outcomes in medically managed acute coronary syndrome patients. Heart 2016;102:1221-9.
152. Ndrepepa G, Mehilli J, Schulz S et al. Patterns of presentation and outcomes of patients with acute coronary syndromes. Cardiology 2009;113:198-206.
153. Rich JD, Cannon CP, Murphy SA, Qin J, Giugliano RP, Braunwald E. Prior aspirin use and outcomes in acute coronary syndromes. J Am Coll Cardiol 2010;56:1376-85.
154. Enhos A, Karacop E. Impact of Antecedent Aspirin Use on Infarct Size, Bleeding and Composite Endpoint in Patients with de Novo Acute Myocardial Infarction. Ther Clin Risk Manag 2021;17:441-452.
155. Campodonico J, Cosentino N, Milazzo V et al. Impact of Chronic Antiplatelet Therapy on Infarct Size and Bleeding in Patients With Acute Myocardial Infarction. J Cardiovasc Pharmacol Ther 2018;23:407-413.
156. Kastrati A, von Beckerath N, Joost A, Pogatsa-Murray G, Gorchakova O, Schomig A. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. Circulation 2004;110:1916-9.
157. Tomaniak M, Katagiri Y, Modolo R et al. Vulnerable plaques and patients: state-of-the-art. Eur Heart J 2020;41:2997-3004.
158. Escaned J, Cao D, Baber U et al. Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR. Eur Heart J 2021;42:4624-4634.
159. Watanabe H, Domei T, Morimoto T et al. Very Short Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Patients With High Bleeding Risk: Insight From the STOPDAPT-2 Trial. Circulation 2019;140:1957-1959.
160. Urban P, Gregson J, Owen R et al. Assessing the Risks of Bleeding vs Thrombotic Events in Patients at High Bleeding Risk After Coronary Stent Implantation: The ARC-High Bleeding Risk Trade-off Model. JAMA Cardiol 2021;6:410-419.
161. Valgimigli M, Costa F, Lokhnygina Y et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 2017;38:804-810.
162. Gewalt S, Lahu S, Ndrepepa G et al. Efficacy and Safety of Ticagrelor Versus Prasugrel in Women and Men with Acute Coronary Syndrome: A Pre-specified, Sex-Specific Analysis of the ISAR-REACT 5 Trial. J Atheroscler Thromb 2022;29:747-761.
163. Ndrepepa G, Kastrati A, Menichelli M et al. Ticagrelor or Prasugrel in Patients With Acute Coronary Syndromes and Diabetes Mellitus. JACC Cardiovasc Interv 2020;13:2238-2247.
164. Corpataux N, Spirito A, Gragnano F et al. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. Eur Heart J 2020;41:3743-3749.
165. Cao D, Mehran R, Dangas G et al. Validation of the Academic Research Consortium High Bleeding Risk Definition in Contemporary PCI Patients. J Am Coll Cardiol 2020;75:2711-2722.
166. Nicolas J, Beerkens F, Cao D et al. Performance of the academic research consortium high-bleeding risk criteria in patients undergoing PCI for acute myocardial infarction. J Thromb Thrombolysis 2022;53:20-29.

167. Alcock RF, Yong AS, Ng AC et al. Acute coronary syndrome and stable coronary artery disease: are they so different? Long-term outcomes in a contemporary PCI cohort. Int J Cardiol 2013;167:1343-6.
168. Hochholzer W, Trenk D, Mega JL et al. Impact of smoking on antiplatelet effect of clopidogrel and prasugrel after loading dose and on maintenance therapy. Am Heart J 2011;162:518-26 e5.
169. Patti G, Polacco M, Taurino E, Gaudio C, Greco C. Effects of cigarette smoking on platelet reactivity during P2Y12 inhibition in patients with myocardial infarction undergoing drug-eluting stent implantation: results from the prospective cigarette smoking on platelet reactivity (COPTER) study. J Thromb Thrombolysis 2016;41:648-53.
170. Orban M, Trenk D, Geisler T et al. Smoking and outcomes following guided de-escalation of antiplatelet treatment in acute coronary syndrome patients: a substudy from the randomized TROPICAL-ACS trial. Eur Heart J Cardiovasc Pharmacother 2020;6:372-381.
171. Cornel JH, Ohman EM, Neely B et al. Impact of smoking status on platelet function and clinical outcomes with prasugrel vs. clopidogrel in patients with acute coronary syndromes managed without revascularization: Insights from the TRILOGY ACS trial. Am Heart J 2014;168:76-87 e1.
172. Cornel JH, Becker RC, Goodman SG et al. Prior smoking status, clinical outcomes, and the comparison of ticagrelor with clopidogrel in acute coronary syndromes-insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2012;164:334-342 e1.
173. Li J, Tang W, Storey RF, Husted S, Teng R. Population pharmacokinetics of ticagrelor in patients with acute coronary syndromes. Int J Clin Pharmacol Ther 2016;54:666-74.
174. Adamski P, Buszko K, Sikora J et al. Metabolism of ticagrelor in patients with acute coronary syndromes. Sci Rep 2018;8:11746.
175. Gagne JJ, Bykov K, Choudhry NK, Toomey TJ, Connolly JG, Avorn J. Effect of smoking on comparative efficacy of antiplatelet agents: systematic review, meta-analysis, and indirect comparison. BMJ 2013;347:f5307.
176. Dawwas GK, Dietrich E, Winchester DE, Winterstein AG, Segal R, Park H. Comparative Effectiveness and Safety of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome: A Retrospective Cohort Analysis. Pharmacotherapy 2019;39:912-920.
177. Palmerini T, Benedetto U, Bacchi-Reggiani L et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet 2015;385:2371-82.
178. Giacoppo D, Matsuda Y, Fovino LN et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J 2021;42:308-319.
179. Khan SU, Singh M, Valavoor S et al. Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents: A Systematic Review and Network Meta-Analysis. Circulation 2020;142:1425-1436.
180. Easton JD, Aunes M, Albers GW et al. Risk for Major Bleeding in Patients Receiving Ticagrelor Compared With Aspirin After Transient Ischemic Attack or Acute Ischemic Stroke in the SOCRATES Study (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes). Circulation 2017;136:907-916.
181. Johnston SC, Amarenco P, Albers GW et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med 2016;375:35-43.
182. Koo BK, Kang J, Park KW et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;397:2487-2496.
183. Chau KH, Kirtane AJ, Easterwood RM et al. Stent Thrombosis Risk Over Time on the Basis of Clinical Presentation and Platelet Reactivity: Analysis From ADAPT-DES. JACC Cardiovasc Interv 2021;14:417-427.

184. Yin SH, Xu P, Wang B et al. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis. BMJ 2019;365:l2222.
185. Bigalke B, Stellos K, Stakos D et al. Influence of platelet count on the expression of platelet collagen receptor glycoprotein VI (GPVI) in patients with acute coronary syndrome. Thromb Haemost 2009;101:911-5.
186. Al-Tamimi M, Tan CW, Qiao J et al. Pathologic shear triggers shedding of vascular receptors: a novel mechanism for down-regulation of platelet glycoprotein VI in stenosed coronary vessels. Blood 2012;119:4311-20.
187. Bigalke B, Stellos K, Weig HJ et al. Regulation of platelet glycoprotein VI (GPVI) surface expression and of soluble GPVI in patients with atrial fibrillation (AF) and acute coronary syndrome (ACS). Basic Res Cardiol 2009;104:352-7.
188. Al-Tamimi M, Gardiner EE, Thom JY et al. Soluble glycoprotein VI is raised in the plasma of patients with acute ischemic stroke. Stroke 2011;42:498-500.
189. Ndrepepa G, Colleran R, Braun S et al. High-Sensitivity Troponin T and Mortality After Elective Percutaneous Coronary Intervention. J Am Coll Cardiol 2016;68:2259-2268.
190. Pishko AM, Andrews RK, Gardiner EE, Lefler DS, Cuker A. Soluble glycoprotein VI is a predictor of major bleeding in patients with suspected heparin-induced thrombocytopenia. Blood Adv 2020;4:4327-4332.
191. Muthiah K, Connor D, Ly K et al. Longitudinal changes in hemostatic parameters and reduced pulsatility contribute to non-surgical bleeding in patients with centrifugal continuous-flow left ventricular assist devices. J Heart Lung Transplant 2016;35:743-51.
192. Tantry US, Bonello L, Aradi D et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261-73.
193. Chatterjee M, Gawaz M. Clinical significance of receptor shedding-platelet GPVI as an emerging diagnostic and therapeutic tool. Platelets 2017;28:362-371.
194. Ndrepepa G, Berger PB, Mehilli J et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690-7.
195. Ndrepepa G, Stephan T, Fiedler KA, Guerra E, Kufner S, Kastrati A. Procedure-related bleeding in elective percutaneous coronary interventions. Eur J Clin Invest 2015;45:263-73.
196. Costa F, van Klaveren D, James S et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025-1034.
197. Valle JA, Shetterly S, Maddox TM et al. Postdischarge Bleeding After Percutaneous Coronary Intervention and Subsequent Mortality and Myocardial Infarction: Insights From the HMO Research Network-Stent Registry. Circ Cardiovasc Interv 2016;9.
198. Valgimigli M, Frigoli E, Heg D et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med 2021;385:1643-1655.
199. Angiolillo DJ, Bhatt DL, Cannon CP et al. Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention: A North American Perspective: 2021 Update. Circulation 2021;143:583-596.
200. Gargiulo G, Cannon CP, Gibson CM et al. Safety and efficacy of double vs. triple antithrombotic therapy in patients with atrial fibrillation with or without acute coronary syndrome undergoing percutaneous coronary intervention: a collaborative meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J Cardiovasc Pharmacother 2021;7:f50-f60.
201. Gargiulo G, Goette A, Tijssen J et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary

intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J 2019;40:3757-3767.
202. De Caterina R, Agewall S, Andreotti F et al. Great Debate: Triple antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting should be limited to 1 week. Eur Heart J 2022.
203. Valgimigli M, Frigoli E, Heg D et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med 2021;385:1643-1655.
204. Hicks KA, Mahaffey KW, Mehran R et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021-1034.
205. White HD, Gallo R, Cohen M et al. The use of intravenous enoxaparin in elective percutaneous coronary intervention in patients with renal impairment: results from the SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation (STEEPLE) trial. Am Heart J 2009;157:125-31.
206. Vranckx P, Cutlip DE, Mehran R et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871-4.

List of publications

First-author publications

1. **Lahu S*,** Adler K*, Mayer K, Hein-Rothweiler R, Bernlochner I, Ndrepepa G, Schüpke S, Holdenrieder S, Bongiovanni D, Laugwitz KL, Schunkert H, Gawaz M, Massberg S, Kastrati A, Münch G. *Plasma Soluble Glycoprotein VI, Platelet Function, Bleeding, and Ischemic Events in Patients Undergoing Elective Percutaneous Coronary Intervention*. Thromb Haemost. 2024 Apr;124(4):297-306. doi: 10.1055/s-0043-1772221. Epub 2023 Aug 17. PMID: 37591289.

2. **Lahu S***, Scalamogna M*, Ndrepepa G, Menichelli M, Valina C, Hemetsberger R, Witzenbichler B, Bernlochner I, Joner M, Xhepa E, Hapfelmeier A, Kufner S, Sager HB, Mayer K, Kessler T, Laugwitz KL, Richardt G, Schunkert H, Neumann FJ, Kastrati A, Cassese S. *Prior Myocardial Infarction and Treatment Effect of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndromes - A Post-hoc Analysis of the ISAR-REACT 5 Trial*. J Am Heart Assoc. 2022 Dec 20;11(24):e027257. doi: 10.1161/JAHA.122.027257. Epub 2022 Dec 14. PMID: 36515247; PMCID: PMC9798807.

3. **Lahu S***, Presch A*, Ndrepepa G, Menichelli M, Valina C, Hemetsberger R, Witzenbichler B, Bernlochner I, Joner M, Xhepa E, Hapfelmeier A, Kufner S, Rifatov N, Sager HB, Mayer K, Kessler T, Laugwitz KL, Richardt G, Schunkert H, Neumann FJ, Sibbing D, Angiolillo DJ, Kastrati A, Cassese S. *Ticagrelor or Prasugrel in Patients With Acute Coronary Syndrome and High Bleeding Risk.* Circ Cardiovasc Interv. 2022 Oct;15(10):e012204. doi: 10.1161/CIRCINTERVENTIONS.122.012204. Epub 2022 Oct 18. PMID: 36256695.

4. **Lahu S**, Ndrepepa G, Neumann FJ, Menichelli M, Bernlochner I, Richardt G, Wohrle J, Witzenbichler B, Hemetsberger R, Mayer K, Akin I, Cassese S, Gewalt S, Xhepa E, Kufner S, Valina C, Sager HB, Joner M, Ibrahim T, Laugwitz KL, Schunkert H, Schupke S and Kastrati A. *Pre-admission antiplatelet therapy and treatment effect of ticagrelor vs. prasugrel in patients with acute coronary syndromes-a subgroup analysis of the ISAR-REACT 5 trial*. Eur Heart J Cardiovasc Pharmacother. 2022 Sep 29;8(7):687-694. doi: 10.1093/ehjcvp/pvac007. PMID: 35191982.

5. **Lahu S**, Bristot P, Gewalt S, Goedel A, Giacoppo D, Schupke S, Schunkert H, Kastrati A and Sarafoff N. *Meta-Analysis of Short vs. Prolonged Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation and Role of Continuation with either Aspirin or a $P2Y_{12}$ Inhibitor Thereafter*. J Atheroscler Thromb. 2022 Jul 1;29(7):1001-1019. doi: 10.5551/jat.63000. Epub 2021 Jul 10. PMID: 34248087; PMCID: PMC9252616.

6. **Lahu S**, Behnes M, Ndrepepa G, Neumann FJ, Sibbing D, Bernlochner I, Menichelli M, Mayer K, Richardt G, Gewalt S, Angiolillo DJ, Coughlan JJ, Aytekin A, Witzenbichler B, Hochholzer W, Cassese S, Kufner S, Xhepa E, Sager HB, Joner M, Fusaro M, Laugwitz KL, Schunkert H, Schupke S, Kastrati A and Akin I. *Body mass index and efficacy and safety of ticagrelor versus prasugrel in patients with acute coronary syndromes*. Rev Esp Cardiol (Engl Ed). 2022 Sep;75(9):747-755. English, Spanish. doi: 10.1016/j.rec.2021.11.007. Epub 2021 Dec 24. PMID: 34961732.

7. **Lahu S**, Ndrepepa G, Gewalt S, Schupke S, Pellegrini C, Bernlochner I, Aytekin A, Neumann FJ, Menichelli M, Richardt G, Cassese S, Xhepa E, Kufner S, Sager HB, Joner M, Ibrahim T, Fusaro M, Laugwitz KL, Schunkert H, Kastrati A and Mayer K. *Efficacy and safety of ticagrelor versus prasugrel in smokers and nonsmokers with acute coronary syndromes*. Int J Cardiol. 2021 Sep 1;338:8-13. doi: 10.1016/j.ijcard.2021.06.011. Epub 2021 Jun 11. PMID: 34126130.

8. Behnes M*, **Lahu S***, Ndrepepa G, Menichelli M, Mayer K, Wohrle J, Bernlochner I, Gewalt S, Witzenbichler B, Hochholzer W, Sibbing D, Cassese S, Angiolillo DJ, Hemetsberger R, Valina C, Müller A, Kufner S, Hamm CW, Xhepa E, Hapfelmeier A, Sager HB, Joner M, Fussaro M, Mankerious N, Liebetrau C, Bernlochner I, Hamm CW, Allali A, Joner M, Fusaro M, Richardt G, Laugwitz KL, Neumann FJ, Schunkert H, Schüpke S, Kastrati A, Akin I. *Ticagrelor or prasugrel in patients with acute coronary*

syndrome with off-hour versus on-hour presentation: a subgroup analysis of the ISAR-REACT 5 trial. Clin Res Cardiol. 2023 Apr;112(4):518-528. doi: 10.1007/s00392-022-02040-z. Epub 2022 Jul 5. PMID: 35789430; PMCID: PMC10050020.

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Co-authored publications

1. Byrne RA, Colleran R, Coughlan JJ, Jauhar R, Maillard L, de Labriolle A, Maeng M, Croft C, Brunner M, Leistner D, Zrenner B, Kollum M, Laugwitz KL, Xhepa E, Mayer K, **Lahu S**, Joner M, Kirtane A, Mehran R, Barakat M, Urban P, Cutlip DE and Kastrati A. *A Randomized Trial of COBRA PzF Stenting to Reduce the Duration of Triple Therapy: The COBRA REDUCE Trial*. Circ Cardiovasc Interv. 2024 Oct;17(10):e013735. doi: 10.1161/CIRCINTERVENTIONS.123.013735. Epub 2024 Oct 15.

2. Ndrepepa G, Cassese S, Scalamogna M, **Lahu S**, Aytekin A, Xhepa E, Schunkert H, Kastrati A. *Association of De Ritis Ratio with Prognosis in Patients with Coronary Artery Disease and Aminotransferase Activity within and outside the Healthy Values of Reference Range*. J Clin Med 2023; 12(9).

3. Aytekin A, Scalamogna M, Coughlan JJ, **Lahu S**, Ndrepepa G, Menichelli M, Mayer K, Wöhrle J, Bernlochner I, Witzenbichler B, Hochholzer W, Sibbing D, Angiolillo DJ, Hemetsberger R, Tölg R, Valina C, Müller A, Kufner S, Liebetrau C, Xhepa E, Hapfelmeier A, Sager HB, Joner M, Richardt G, Laugwitz KL, Neumann FJ, Schunkert H, Schüpke S, Kastrati A, Cassese S. *Incidence and pattern of urgent revascularization in acute coronary syndromes treated with ticagrelor or prasugrel*. Clin Res Cardiol. 2024 Jul;113(7):1060-1069. doi: 10.1007/s00392-024-02454-x. Epub 2024 May 13. PMID: 38740722; PMCID: PMC11219404.

4. Scalamogna M, Kuna C, Voll F, Aytekin A, **Lahu S**, Kessler T, Kufner S, Rheude T, Sager HB, Xhepa E, Wiebe J, Joner M, Ndrepepa G, Kastrati A, Cassese S. *Modified balloons to prepare severely calcified coronary lesions before stent implantation: a systematic review and meta-analysis of randomized trials*. Clin Res Cardiol 2023.

5. Aytekin A, Coughlan JJ, Ndrepepa G, Cassese S, **Lahu S**, Kufner S, Mayer K, Xhepa E, Gewalt S, Joner M, Hapfelmeier A, Angiolillo DJ, Menichelli M, Richardt G, Neumann FJ, Schunkert H, Kastrati A. *The effect of a Prasugrel- vs. a Ticagrelor-based strategy on total ischaemic and bleeding events in patients with acute coronary syndromes*. Eur Heart J Cardiovasc Pharmacother. 2023 Apr 10;9(3):231-239. doi: 10.1093/ehjcvp/pvac067. PMID: 36434779.

6. Koch T, **Lahu S,** Coughlan JJ, Cassese S, Voll F, Ndrepepa G, Menichelli M, Valina C, Hemetsberger R, Witzenbichler B, Bernlochner I, Joner M, Xhepa E, Mayer K, Kessler T, Laugwitz KL, Richardt G, Schunkert H, Angiolillo DJ, Sibbing D, Kastrati A, Kufner S. *Association between Platelet Count and Treatment Effect of Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes*. Thromb Haemost. 2023 Apr;123(4):464-477. doi: 10.1055/a-1988-5047. Epub 2022 Nov 28. PMID: 36442805; PMCID: PMC10060058.

7. Coughlan JJ, Aytekin A, **Lahu S**, Scalamogna M, Wiebe J, Pinieck S, Kufner S, Xhepa E, Joner M, Kuna C, Voll F, Laugwitz KL, Schunkert H, Kastrati A, Cassese S. *Derivation and validation of the ISAR score to predict the risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent restenosis.* EuroIntervention. 2023 Apr 3;18(16):e1328-e1338. doi: 10.4244/EIJ-D-22-00860. PMID: 36785947; PMCID: PMC10068863.

8. Ndrepepa G, **Lahu S**, Aytekin A, Scalamogna M, Coughlan JJ, Gewalt S, Pellegrini C, Mayer K and Kastrati A. *One-Year Ischemic and Bleeding Events According to Renal Function in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes Treated With Percutaneous Coronary Intervention and Third-Generation Antiplatelet Drugs*. Am J Cardiol. 2022.

9. Hemetsberger R, Richardt G, **Lahu S**, Valina C, Menichelli M, Abdelghani M, Wohrle J, Toelg R, Witzenbichler B, Mankerious N, Liebetrau C, Bernlochner I, Hamm CW, Allali A, Joner M, Fusaro M, Xhepa E, Hapfelmeier A, Kufner S, Sager HB, Schupke S, Laugwitz KL, Schunkert H, Neumann FJ, Kastrati A and Cassese S. *Access route and clinical outcomes after ticagrelor versus prasugrel in patients with acute coronary syndrome undergoing invasive treatment strategy.* Cardiovasc Revasc Med. 2022.

10. Ndrepepa G, Holdenrieder S, Xhepa E, Cassese S, **Lahu S**, Kufner S and Kastrati A. *Alkaline Phosphatase and Prognosis in Patients with Diabetes Mellitus and Ischemic Heart Disease*. Clin Chim Acta. 2022.

11. Ndrepepa G, Neumann FJ, Menichelli M, Richardt G, Cassese S, Xhepa E, Kufner S, **Lahu S**, Aytekin A, Sager HB, Joner M, Ibrahim T, Muller A, Fusaro M, Hapfelmeier A, Laugwitz KL, Schunkert H, Kastrati A and Kasel M. *Prediction of risk for bleeding, myocardial infarction and mortality after percutaneous coronary intervention in patients with acute coronary syndromes.* Coron Artery Dis. 2022;33:213-221.

12. Nano N, Aytekin A, Ndrepepa G, Seguchi M, Bresha J, Alvarez Covarrubias HA, Nicol P, Lenz T, **Lahu S**, Gewalt S, Voll F, Rheude T, Wiebe J, Schunkert H, Kufner S, Cassese S, Joner M, Kastrati A and Xhepa E. *Periprocedural myocardial injury according to optical characteristics of neointima and treatment modality of in-stent restenosis*. *Clin Res Cardiol*. 2022.

13. Wohrle J, Seeger J, **Lahu S,** Mayer K, Bernlochner I, Gewalt S, Menichelli M, Witzenbichler B, Hochholzer W, Sibbing D, Cassese S, Angiolillo DJ, Hemetsberger R, Valina C, Kufner S, Xhepa E, Hapfelmeier A, Sager HB, Joner M, Richardt G, Laugwitz KL, Neumann FJ, Schunkert H, Schupke S, Kastrati A and Ndrepepa G. *Ticagrelor or Prasugrel in Patients With Acute Coronary Syndrome in Relation to Estimated Glomerular Filtration Rate*. JACC Cardiovasc Interv. 2021;14:1857-1866.

14. Gewalt S, **Lahu S**, Ndrepepa G, Pellegrini C, Bernlochner I, Neumann FJ, Menichelli M, Morath T, Witzenbichler B, Wohrle J, Hoppe K, Richardt G, Laugwitz KL, Schunkert H, Kastrati A, Schupke S and Mayer K. *Efficacy and Safety of Ticagrelor Versus Prasugrel in Women and Men with Acute Coronary Syndrome: A Pre-specified, Sex-Specific Analysis of the ISAR-REACT 5 Trial*. J Atheroscler Thromb. 2021.

15. Ndrepepa G, Holdenrieder S, Neumann FJ, **Lahu S**, Cassese S, Joner M, Xhepa E, Kufner S, Wiebe J, Laugwitz KL, Gewalt S, Schunkert H and Kastrati A. *Prognostic value of glomerular function estimated by Cockcroft-Gault creatinine clearance, MDRD-4, CKD-EPI and European Kidney Function Consortium equations in patients with acute coronary syndromes*. Clin Chim Acta. 2021;523:106-113.

16. Menichelli M, Neumann FJ, Ndrepepa G, Mayer K, Wohrle J, Bernlochner I, Richardt G, Witzenbichler B, Sibbing D, Gewalt S, Angiolillo DJ, **Lahu S**, Hamm CW, Hapfelmeier A, Trenk D, Laugwitz KL, Schunkert H, Schupke S and Kastrati A. *Age- and Weight-Adapted Dose of Prasugrel Versus Standard Dose of Ticagrelor in Patients With Acute Coronary Syndromes : Results From a Randomized Trial.* Ann Intern Med. 2020;173:436-444.

17. Coughlan JJ, Aytekin A, **Lahu S**, Ndrepepa G, Menichelli M, Mayer K, Wohrle J, Bernlochner I, Gewalt S, Witzenbichler B, Hochholzer W, Sibbing D, Cassese S, Angiolillo DJ, Hemetsberger R, Valina C, Muller A, Kufner S, Liebetrau C, Xhepa E, Hapfelmeier A, Sager HB, Joner M, Fusaro M, Richardt G, Laugwitz KL, Neumann FJ, Schunkert H, Schupke S and Kastrati A. *Ticagrelor or Prasugrel for Patients With Acute Coronary Syndrome Treated With Percutaneous Coronary Intervention: A Prespecified Subgroup Analysis of a Randomized Clinical Trial*. JAMA Cardiol. 2021;6:1121-1129.

18. Aytekin A, Ndrepepa G, Neumann FJ, Menichelli M, Mayer K, Wohrle J, Bernlochner I, **Lahu S**, Richardt G, Witzenbichler B, Sibbing D, Cassese S, Angiolillo DJ, Valina C, Kufner S, Liebetrau C, Hamm CW, Xhepa E, Hapfelmeier A, Sager HB, Wustrow I, Joner M, Trenk D, Fusaro M, Laugwitz KL, Schunkert H, Schupke S and Kastrati A. *Ticagrelor or Prasugrel in Patients With ST-Segment-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention*. Circulation. 2020;142:2329-2337.