Department of Clinical Sciences, Danderyd Hospital
Karolinska Institutet, Stockholm, Sweden

BLEEDING COMPLICATIONS FOLLOWING ACUTE MYOCARDIAL INFARCTION: TIME TRENDS, RISK ASSESSMENT AND ASSOCIATED PROGNOSIS

Moa Simonsson

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”That´s a giant leap for me, one small step for mankind.”

Adapted from Neil Armstrong 21 July 1969

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Bleeding complications following acute myocardial infarction: time trends, risk assessment and associated prognosis

THESIS FOR DOCTORAL DEGREE (Ph.D)

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By

Moa Simonsson

Principal Supervisor:
Professor Tomas Jernberg
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital
Division of Cardiology

Co-supervisor(s):
Associate Professor Karolina Szummer
Karolinska Institutet
Department of Medicine, Huddinge
Karolinska University Hospital

Associate Professor Joakim Alfredsson
Linköping University
Department of Health, Medicine
and Caring Sciences
Division of Cardiology

Assistant Professor Peter Ueda
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Epidemiology

Opponent:
Associate Professor Ziad Hijazi
Uppsala University
Department of Medical Sciences
Division of Cardiology

Examination Board:
Professor Rebecka Hultgren
Karolinska Institutet
Department of Molecular Medicine and Surgery
Department of Vascular Surgery
Karolinska University Hospital

Docent Gustaf Edgren
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology

Professor Lennart Bergfeldt
University of Gothenburg
Sahlgrenska Academy
Department of Molecular and Clinical Medicine

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ABSTRACT

Background:
In patients with acute myocardial infarction (MI), bleeding complications are common and associated with worse prognosis. This thesis aimed to investigate the epidemiology, risk assessment and associated outcomes of bleeding complications in patients with acute MI.

Methods and results:
Study I: Patients with acute MI enrolled in the SWEDEHEART registry from 1995–2018 were included (n=371 431). The incidence of in-hospital and out-of-hospital bleeding at one-year was investigated parallel to treatment changes and ischemic outcomes. From 1995 to 2018, in-hospital bleeding increased from 0.5% to 1.3% and out-of-hospital bleeding increased from 2.5% to 4.8% along with increased use of invasive revascularisation and more efficient antithrombotic treatment. Meanwhile in-hospital and out-of-hospital ischemic outcomes decreased from 12.1% to 5.6% and 27.5% to 15.1%, respectively.

Study II: Patients with acute MI enrolled in the SWEDEHEART registry from 2009–2014 were included (n=97 597). A prediction model for in-hospital bleeding was created using logistic regression and the performance was compared to that of the CRUSADE and ACTION scores. Due to miscalibration, the CRUSADE and ACTION scores were recalibrated. The SWEDEHEART score, consisting of five baseline variables (haemoglobin, age, sex, creatinine, and C-reactive protein) plus one interaction term (haemoglobin and sex) had a C-index of 0.80 as compared with 0.72 and 0.73 for the recalibrated CRUSADE and ACTION scores, respectively.

Study III: Patients with acute MI enrolled in the SWEDEHEART registry from 2007–2016 and discharged alive on any antithrombotic treatment were included (n=149 447). The incidence, associated outcomes and predictors of upper gastrointestinal bleeding (UGIB) was investigated. The incidence of UGIB within one year after discharge was 1.5% and experiencing UGIB was associated with increased risk of mortality and stroke, but not significantly associated with MI. Using both logistic regression and machine-learning models, new potential predictors of UGIB were found, such as smoking status and blood glucose.

Study IV: Patients with acute MI enrolled in the SWEDEHEART registry and discharged alive on any antithrombotic treatment from 2012–2017 were included (n=86 736). The incidence and associated mortality risk of ischemic (MI or ischemic stroke) and bleeding events was investigated. Within one year after discharge, the incidence rate of ischemic and bleeding events was 5.7/100 person years and 4.8/100 person years, respectively. Both ischemic and bleeding events were associated with higher risk of mortality as compared with no event, with adjusted hazard ratios (HR)s of 4.16 (95% CI 3.91 to 4.43) and 3.43 (95% CI 3.17 to 3.71), respectively. In a direct comparison of ischemic vs bleeding event, the adjusted HR was 1.27 (95% CI 1.15 to 1.40.)

Conclusion:
In the past two decades, the incidence of both short- and long-term bleeding events has nearly doubled in patients with acute MI. The five-item SWEDEHEART score predicts in-hospital bleeding in patients with acute MI more accurately than the recalibrated CRUSADE and ACTION scores. Among patients with a recent MI, upper gastrointestinal bleeding is common and associated with poorer prognosis. Beyond the known risk factors for bleeding, other predictors for upper gastrointestinal bleeding may be present. In patients discharged after an acute MI, ischemic events were more common and associated with higher risk of mortality than bleeding events.

SAMMANFATTNING

Bakgrund:
Blödningskomplikationer efter akut hjärtinfarkt är vanliga och associerade med sämre prognos. Den här avhandlingens syfte var att undersöka epidemiologi, riskbedömning och associerad prognos vid blödningskomplikationer hos patienter med akut hjärtinfarkt.

Metoder och resultat:
Studie I: Patienter med akut hjärtinfarkt registrerade i SWEDEHEART registret från 1995 - 2018 inkluderades (n=371 431). Incidensen av blödningar under vårdtiden samt vid ett år undersöktes parallellt med förändringar i behandling och ischemiska händelser. Från 1995 till 2018 ökade förekomsten av blödningar under vårdtiden från 0.5% till 1.3% och blödningar vid ett år ökade från 2.5% till 4.8% parallellt med ökad användning av invasiv revaskularisering och mer effektiv antitrombotisk behandling. Samtidigt minskade ischemiska händelser under vårdtiden från 12.1% till 5.6 och vid ett år från 27.5% till 15.1%.

Studie II: Patienter med akut hjärtinfarkt registrerade i SWEDEHEART registret från 2009 – 2014 inkluderades (n=97 597). En prediktionsmodell för blödning under vårdtiden skapades med hjälp av logistisk regression. Den nya modellens prediktionsförmåga och kalibrering jämfördes med CRUSADE och ACTION modellerna som pga. miskalibrering rekalibrerades. SWEDEHEART modellen bestående av fem variabler (hemoglobin, ålder, kön, kreatinin och C-reaktivt protein) samt en interaktions term (hemoglobin och kön) hade en C-statistika på 0.80 jämfört med 0.72 och 0.73 för de rekalibrerade CRUSADE och ACTION modellerna.

Studie III: Patienter med akut hjärtinfarkt registrerade i SWEDEHEART registret från 2007 – 2016, utskrivna vid liv med antitrombotisk behandling inkluderades (n=149 447). Incidensen, associerade utfall och prediktorer för övre gastrointestinal blödning (ÖGIB) undersöktes. Incidensen av (ÖGIB) vid ett år var 1.5% och ÖGIB var associerad med ökad risk för död och stroke men var ej signifikant associerad med återinsjuknande i hjärtinfarkt. Med hjälp av både logistisk regression och maskininlärnings modeller identifierades nya potentiella prediktorer för ÖGIB såsom rökning och blodsocker.

Studie IV: Patienter med akut hjärtinfarkt registrerade i SWEDEHEART registret, utskrivna vid liv med antitrombotisk behandling från 2012 – 2017 inkluderades (n=86 736). Incidensen och den associerade risken för död efter en ischemisk (hjärtinfarkt eller ischemisk stroke) eller blödningshändelse analyserades. Inom ett år efter utskrivning var incidensen av ischemisk- och blödningshändelse 5.7/100 personår och 4.8/100 personår. Jämfört med ingen händelse var både ischemisk- och blödningshändelse associerad med ökad risk för död, justerade hazardkvoter (HR)s 4.16 (95% CI 3.91 to 4.43) and 3.43 (95% CI 3.17 to 3.71). I en direkt jämförelse mellan ischemisk vs blödningshändelse var den justerade HR 1.27 (95% CI 1.15 to 1.40).

Konklusion:
Under de två senaste decennierna har incidensen av blödningar under vårdtiden samt vid ett år nästan dubblerats hos patienter med akut hjärtinfarkt. SWEDEHEART modellen bestående av fem variabler predicerar blödning under vårdtiden mer exakt än de rekalibrerade CRUSADE och ACTION modellerna. Hos patienter med akut hjärtinfarkt är ÖGIB vanligt och associerat med sämre prognos. Utöver kända riskfaktorer för blödning finns det möjligen andra faktorer som predikterar ÖGIB. Hos patienter med en nylig hjärtinfarkt var en ny ischemisk händelse både vanligare och associerad med större risk för död jämfört med en blödningshändelse.

LIST OF SCIENTIFIC PAPERS

I. Simonsson M, Wallentin L, Alfredsson J, Erlinge D, Hellström Ängerud K, Hofmann R, Kellerth T, Lindhagen L, Ravn-Fischer A, Szummer K, Ueda P, Yndigegn T, Jernberg T. Temporal trends in bleeding events in acute myocardial infarction: insights from the SWEDEHEART registry
Eur Heart J. 2020 Feb 14;41(7):833-843.

II. Simonsson M, Winell H, Olsson H, Szummer K, Joakim Alfredsson, Hall M, Dondo TB, Gale CP, Jernberg T. Development and Validation of a Novel Risk Score for In-Hospital Major Bleeding in Acute Myocardial Infarction:-The SWEDEHEART Score
J Am Heart Assoc. Mar 5 2019;8(5):e012157.

III. Sarajlic P, Simonsson M, Jernberg T, Bäck M, Hofmann R. Incidence, associated outcomes, and predictors of upper gastrointestinal bleeding following acute myocardial infarction: a SWEDEHEART-based nationwide cohort study
Eur Heart J Cardiovasc Pharmacother. Aug 23 2021;doi:10.1093/ehjcvp / pvab059

IV. Simonsson M, Alfredsson J, Szummer K, Jernberg T, Ueda P. Associations of ischemic and bleeding event with mortality among patients with recent myocardial infarction taking antithrombotic therapy
Manuscript submitted

LIST OF ABBREVIATIONS

ACS:	Acute coronary syndrome
ARC-HBR:	Academic Research Consortium for High Bleeding Risk
BARC:	Bleeding Academic Research Consortium
CABG:	Coronary artery bypass grafting
CI:	Confidence interval
COPD:	Chronic obstructive pulmonary disease
COX:	Cyclooxygenase
CRP:	C-reactive protein
DAPT:	Dual antiplatelet therapy
ESC:	European Society of Cardiology
eGFR:	Estimated glomerular filtration
GP IIb/IIIa:	Glycoprotein IIb/IIIa
GUSTO:	Global Utilization Of Streptokinase And Tpa For Occluded Arteries
HF:	Heart failure
HR:	Hazard ratio
ICD:	International Classification of Diseases and Related Health Problems
LMWH:	Low molecular weight heparin
LEAD:	Lower extremity artery disease
MACE:	Major adverse cardiovascular event
MI:	Myocardial infarction
NOAC:	Non-Vitamin K oral anticoagulant
NSAID:	Non-steroidal anti-inflammatory drug
NSTEMI:	Non-ST-elevation myocardial infarction
OAC:	Oral anticoagulant
PAD:	Peripheral artery disease
PCI:	Percutaneous Coronary Intervention
PPI:	Protonpump inhibitors
RCT:	Randomised clinical trial
ROC:	Reciever operating characteristics
SAPT:	Single antiplatelet therapy
STEMI:	ST-elevation myocardial infarction
TAVI:	Transcateter aortic valve intervention
TIMI:	Thrombolysis In Myocardial Infarction
TXA2:	Thromboxane-A_2
UCR:	Uppsala research center
UGIB:	Upper gastrointestinal bleeding
vWF:	von Willebrand Factor

1 BACKGROUND

Acute myocardial infarction (MI) is a leading cause of death in the developed world, causing approximately 3 million deaths globally per year[1] and more than 5 000 deaths in Sweden annually.[2] In the past two decades, reperfusion therapy, more efficient antithrombotic treatment and improved secondary prevention have led to a substantial improvement in MI outcomes, nearly halving the one-year mortality following acute MI in Sweden.[3,4]

1.1 Antithrombotic treatment is essential for patients with acute MI

The pathophysiology of acute MI is rupture of a coronary artery plaque followed by activation of platelets and the coagulation system, resulting in partial or complete occlusion of the coronary vessel and subsequent ischemia in the myocardium supplied by the culprit vessel (Figure 1). Reperfusion by percutaneous coronary intervention (PCI) with balloon dilatation and stenting of the lesion (Figure 2) in combination with antithrombotic treatment is the preferred strategy to restore blood flow in the compromised vessel. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is recommended for all patients with acute MI, irrespective of invasive or conservative treatment, to avoid stent thrombosis (in case PCI was performed) and to reduce new non-stent-related ischemic events.[5-7] In addition to DAPT, patients with acute MI receive anticoagulant treatment pre- and peri-procedural during coronary intervention, or when waiting for subacute coronary artery bypass grafting (CABG). Furthermore, approximately 10–15% of patients with MI have concomitant indication for oral anticoagulation (OAC) due to atrial fibrillation/flutter, mechanical heart valves, left ventricular thrombi, venous thromboembolism or other rare indications. These patients are treated with either triple therapy, with DAPT and OAC, or dual therapy with single antiplatelet and OAC for up to one year and thereafter only OAC.[7,8]

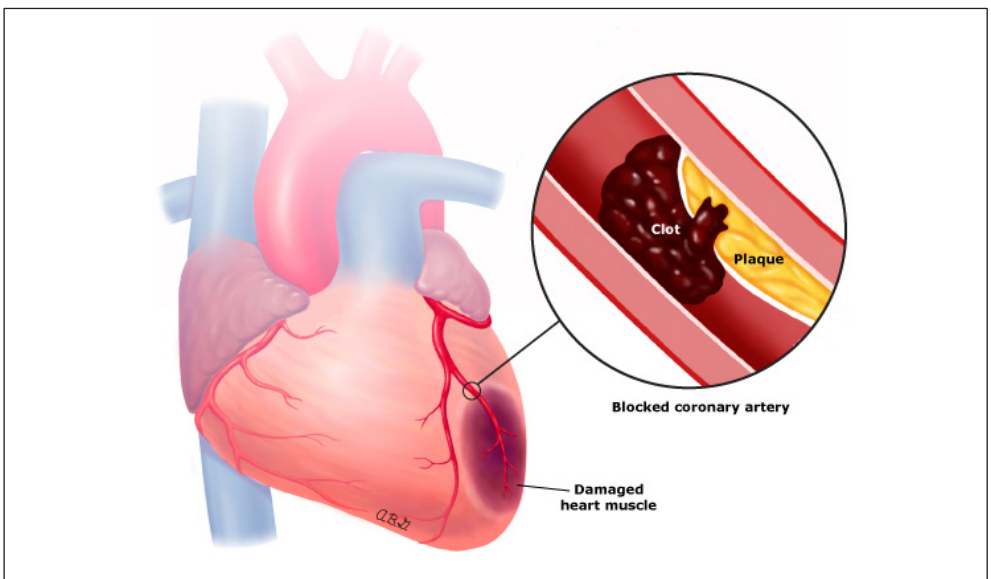


Figure 1. Acute myocardial infarction caused by rupture of a coronary artery plaque and thrombus formation with subsequent ischemia in the area of myocardium supplied by the affected vessel
With permission from uptodate.inc

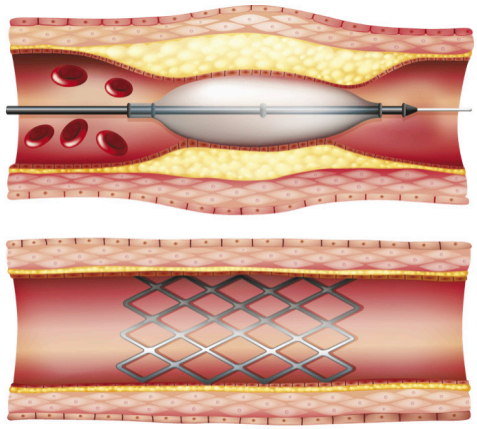


Figure 2. Percutaneous coronary intervention (PCI) with balloon dilatation (upper panel) and delivery of a coronary stent that is left in the vessel wall to hold the artery open (lower panel)
With permission: Adrian Banning thecardiologist.co.uk

1.2 Basic concepts of haemostasis and thrombosis

Haemostasis is the physiological process by which blood cells, mainly platelets, and plasma components interact to seal an injured blood vessel wall to prevent blood loss, i.e., bleeding. Arterial thrombosis is when the haemostatic process develops uncontrolled and can lead to partial or total occlusion of the blood vessel. Thrombosis can also occur in the venous system triggered by factors such as immobilisation or stasis, hypercoagulability, or endothelial injury. In this thesis, thrombosis will refer to arterial thrombosis unless stated otherwise. There is a close interplay between haemostasis and thrombosis, with the main actors being the endothelial wall, platelets, the coagulation system and the fibrinolysis system[9].

1.3 Endothelium

Quiescent endothelium has antithrombotic properties. Endothelial cells release nitric oxide (NO) and prostaglandins while the endothelial membrane expresses ADPase, thrombomodulin and heparan. When inflamed or injured, the endothelium switches to prothrombotic properties; adhesion molecules are expressed and factors that activate platelets and the coagulation system (von Willebrand factor (vWF), tissue factor, plasminogen activator inhibitor 1 (PAI-1)), as well as chemokines that attract monocytes, are released. The endothelium also functions as a barrier, when injured subendothelial extracellular matrix components are exposed, which activates both platelets and coagulation factors[9].

1.4 Platelets

Platelets are anucleate discoid small blood cells, synthesised from megakaryocytes in the bone marrow, with a median size of 2–3 x 0.5 micrometres and a lifespan of approximately 7–10 days. They express several adhesion molecules and membrane receptors and store granules with molecules and enzymes . Platelets play the main role in primary haemostasis, patrolling the vessel walls and, in case of injury, they adhere and become activated, releasing thromboxane-A_2 (TXA_2) and ADP, which stimulate platelet aggregation, as well as thrombin, which activates both platelets and the coagulation system, finally creating a haemostatic plug at the site of injury.[10] (Figure 3)

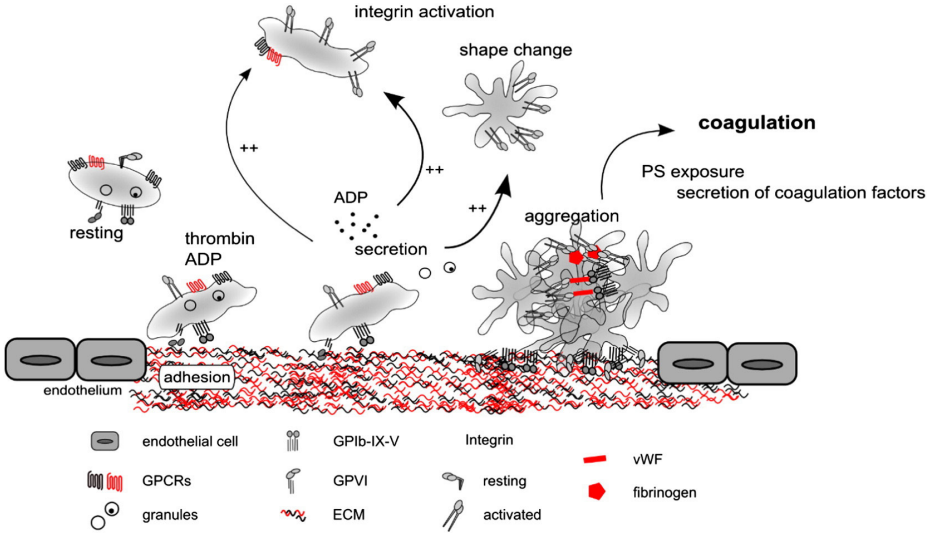


Figure 3. A resting platelet patrols the vessel wall. In contact with injured endothelium the platelet adheres and gets activated releasing molecules that activates more platelets and the coagulation system. The activated platelet changes shape from smooth discoid to irregular with increased contact surface which facilitates adhesion and aggregation. Finally, a hemostatic plug is formed.

E.M. Golebiewska, A.W. Poole / Blood Reviews 29 (2015) 153–162
Creative common licenses

1.5 The coagulation system

The coagulation system consists of clotting factors with procoagulant or anticoagulant properties. Most clotting factors are precursors of proteolytic enzymes that circulate in an inactivate form. Upon activation, a chainlike reaction starts, the coagulation cascade, in which each factor gets activated by the previous factor. The coagulation cascade can be activated through two pathways, the contact pathway, formerly intrinsic, or the cellular pathway, formerly extrinsic, which both converge on factor X. Activated factor X then activates factor V, which in turn activates factor II to generate thrombin, which turns fibrinogen into fibrin and finally a clot is formed (Figure 4). In parallel, the anticoagulant and the fibrinolytic system work to terminate clot formation. When the coagulant and anticoagulant systems are imbalanced, thrombosis or bleeding occurs.[9]

The platelets and the coagulation system are not two separate systems; there is a close interplay between them. For example, thrombin is a strong activator of platelets, vWF activates platelets by interaction with FVIII, and TF activates both platelets and the coagulation system.

1.6 Antithrombotic agents - antiplatelets

Antithrombotic agents can be divided into antiplatelets and anticoagulants. The targets of the different antiplatelets and anticoagulants are shown in Figure 5a and 5b.

Aspirin or acetylic salicylic acid belongs to the non-steroidal anti-inflammatory drugs (NSAID)s and exerts its effect by irreversible inhibition of the cyclooxygenase-1 (COX-1) enzyme which inhibits generation of TXA_2.[11] TXA_2 is produced by platelets in response to stimuli (thrombin, ADP and collagen) and it induces platelet aggregation and vasoconstriction.

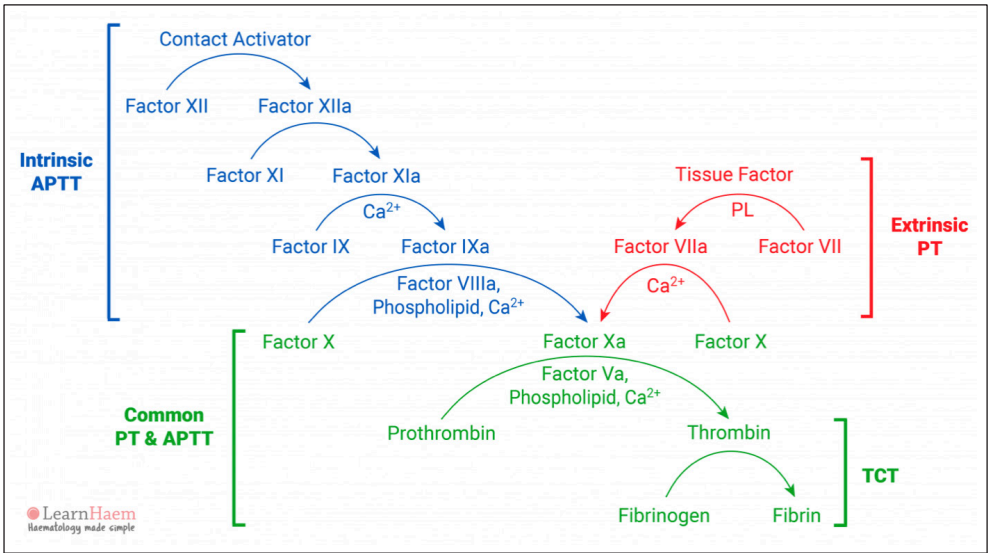


Figure 4. The coagulation cascade can get activated through the contact pathway (former intrinsic) or the tissue factor pathway (former extrinsic) which both converge on factor X. In the final common pathway activated factor X activates Factor II (prothrombin) to activated factor II (thrombin) which turns fibrinogen to fibrin.

With permission from: learnheam.com

Aspirin also inhibits the synthesis of prostaglandins which have negative effects on the gastric mucosa and some effect on the endothelium, even though at low dose aspirin seems to inhibit platelet COX more than endothelial COX.[12,13]

Clopidogrel, prasugrel and ticagrelor block the platelet activation mediated by ADP through irreversible competitive (clopidogrel and prasugrel) or reversible non-competitive (ticagrelor) binding to the ADP receptor ($P2Y_{12}$ receptor).[11,14] The thienopyridines, clopidogrel and prasugrel are prodrugs that need metabolization in the intestine (prasugrel) and by liver enzymes (clopidogrel and prasugrel) to their active forms. Metabolization of clopidogrel to its active form is dependent mainly on CYP2C19 while prasugrel seems less dependent on any specific enzyme. Ticagrelor is a cyclopentyltriazolopyrimidine and does not require any activation but has an active metabolite, AR-C124910XX. While clopidogrel response is highly individual depending mainly on CYP2C19 activity, both prasugrel and ticagrelor result in more reliable and more potent antiplatelet effect.[11,14]

1.7 Antithrombotic agents - anticoagulants

Oral anticoagulants can be divided into vitamin K antagonists and non-vitamin K antagonists (NOAC)s, also called direct acting oral anticoagulants (DOAC)s. Vitamin K antagonists inhibit the K-vitamin dependent coagulation factors II, VII, IX and X. The NOACs apixaban, rivaroxaban and edoxaban are factor Xa inhibitors while dabigatran is a direct thrombin (factor II) inhibitor.

Heparin binds both antithrombin III and thrombin enabling them to interact and thus both factor Xa and thrombin are inactivated, resulting in fast onset. Low molecular weight heparins (LMWH)s are smaller fragments of heparin which also bind and activate antithrombin III, in turn inactivating factor Xa but without a direct effect on thrombin. Bivalirudin is a direct thrombin inhibitor. Fondaparinux is a synthetic factor Xa inhibitor.

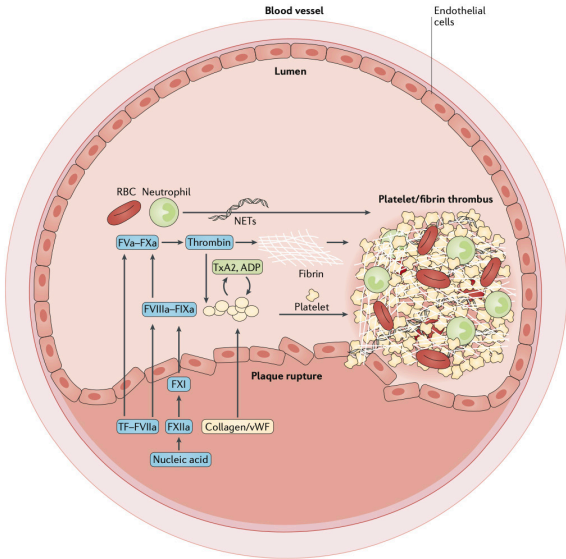
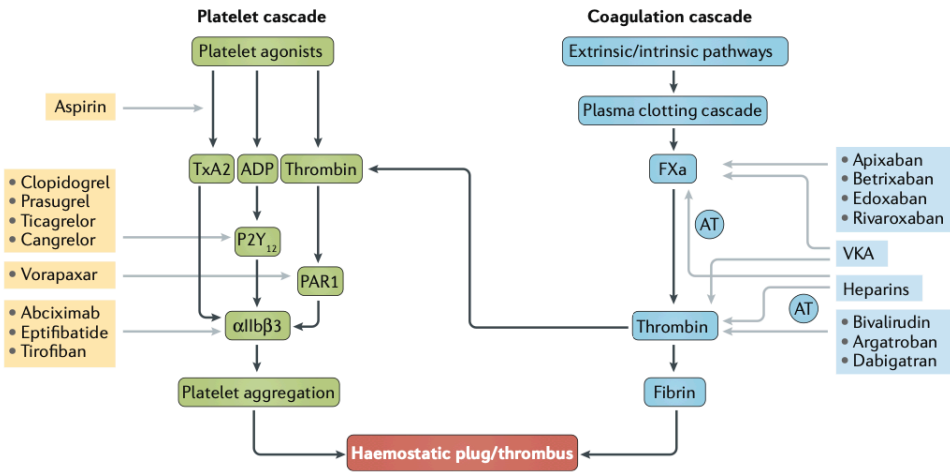


Figure 5a. Thrombus formation is driven by activation and interplay between platelets and the coagulation system



5b. Antiplatelets: Aspirin irreversibly blocks the cyclooxygenase-1 (COX-1) pathway and inhibits formation of Thromboxane A_2 (TXA_2). Clopidogrel, prasugrel, ticagrelor, cangrelor and selatogrel* block the ADP ($P2Y_{12}$) receptor and thus inhibit the activation of platelets mediated by ADP. Voraxapar blocks the thrombin receptor, proetase-activated-receptor-1 (PAR-1). Abciximab, eptifibatide and tirofiban are glycoprotein (GP) IIb/IIIa receptor blockers. The GPIIb/IIIa receptor binds fibrinogen vWF and other adhesion molecules and enables the final common step of platelet aggregation. GPIIb/IIIa blockers are currently the strongest platelet inhibitors available.

Anticoagulants: Apixaban, rivaroxaban and edoxaban are factor Xa inhibitors. Dabigatran, bivalirudin and argatroban are direct thrombin inhibitors. Unfractionated heparins inhibit both factor Xa and thrombin while low weight molecular heparins (LMWH)s mostly inhibit factor Xa with only little effect on thrombin. Warfarin (VKA) inhibits the K-vitamin dependent coagulations factors, II, VII, IX and X.

*selatogrel is a novel subcutaneous P2Y12 inhibitor currently tested in an ongoing Phase III study

With permission. Mackman, N et al. Nat rev Drug Discov 19, 333-352 (2020)

1.8 Antithrombotic treatment and bleeding events

While antithrombotic treatment is essential for patients with acute MI, the ischemic risk reduction conferred by decreasing thrombosis inevitably comes at the expense of an increased risk of bleeding due to its simultaneous negative effect on haemostasis. Thus, bleeding events are common in patients following acute MI (Table 1). Along with the implementation of invasive treatment and more potent antithrombotic therapy in the past two decades, the incidence of bleeding events may have increased. Still, data on bleeding event trends in this time-period are scarce.

1.9 Definition of bleeding events

The definition of bleeding severity is unlike the definition of ischemic outcomes heterogenous. While most bleeding definitions combine laboratory (i.e., haemoglobin changes) and clinical (including blood transfusion) variables, the GUSTO (Global Utilization of Streptokinase and Tpa for Occluded Arteries) definition[27] is based entirely on clinical variables. Blood transfusion is included in all bleeding definitions except for the TIMI (Thrombolysis in Myocardial Infarction) definition, but here decreases in haemoglobin indirectly account for blood transfusion, since each unit of transfused blood corresponds to a decrease of haemoglobin by 1g/dL.[28-30] (Table 2). The lack of standardisation makes interpretation and comparison between studies complicated. To overcome this, the Bleeding Academy Research Consortium (BARC) developed a standardised bleeding definition, the BARC bleeding definition[33]. The BARC bleeding definition has been externally validated showing increasing one-year mortality risk with higher BARC bleeding scale in patients with ACS or following PCI.[38-40] Still, there is wide-spread use of different bleeding definitions in clinical trials. For example, the TIMI and GUSTO bleeding definitions are often used despite being derived in the thrombolysis era of the 1990s. Observational register studies may be limited by the information available in the register and standardised bleeding definitions cannot always be used.

1.10 Bleeding incidence

Interpretation and comparison of bleeding incidence is difficult since the incidence of bleeding events varies depending on; i) bleeding definition used, ii) population studied iii) time-period studied and duration of follow-up, iv) antithrombotic treatment used, v) type of follow-up and completeness of reporting of bleeding events, and vi) blood transfusion strategy. The magnitude of this variation, mainly due to definition used, antithrombotic treatment and duration of follow-up, can be illustrated in the randomised clinical trials (RCT)s of combination therapy, in which patients were treated with different combinations and different durations of antiplatelets and OACs. For example, in the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) study[18] the primary outcome was any TIMI bleeding, while in the RE-DUAL-PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention)[20] and the AUGUSTUS (An open-Label, 2 × 2 Factorial, Randomized Controlled Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention) studies[21] the primary outcome was ISTH CRNM (International Society on Thrombosis and Haemostasis Clinically Relevant Non-Major) bleeding resulting in a bleeding incidence of 44% at one year in the WOEST study, 26% at 14 months in the RE-DUAL-PCI study and 16% at six months in the AUGUSTS study in the triple treatment arms. Other major definitions were

Table 1. Bleeding incidence in landmark clinical studies and in register studies

	N	Follow up in months	Age year	Population	Antithrombotic treatment	Bleeding definition	Bleeding incidence	Ischemic outcome: MI + stroke + CV death
DAPT vs SAPT								
CURE [15] 1998-2000	12 562	12 m	64.2 y	ACS without ST-elevation	aspirin + clopidogrel vs aspirin	Major (fatal, requiring transfusion of 2U or more, or surgical intervention, or inotropic agents) haemorrhagic stroke,	3.7% vs 2.7%	9.3% vs 11.4%
POTENT DAPT vs DAPT								
TRITON-TIMI 38 [16] 2004-2007	13 608	14.5 m	61 y	ASC with planned PCI	aspirin + prasugrel vs aspirin + clopidogrel	TIMI major (non-CABG related)	2.4% vs 1.8%	9.9% vs 12.1%
PLATO [17] 2006 -2008	18 624	12 m	62 y	ACS	Aspirin + ticagrelor vs aspirin + clopidogrel	PLATO major non-CABG related* TIMI major non-CABG related	4.5% vs 3.8% 2.8% vs 2.2%	9.8% vs 11.7%
COMBINATION THERAPY (APT+OAC)								
WOEST[18] 2008-2011	573	12 m	70 y	Patients with indication for OAC (69% AF, 10% mechanical valve, 20% other) and indication for PCI	warfarin + clopidogrel vs warfarin + clopidogrel + aspirin	Any TIMI bleeding TIMI major	44.4% vs 19.4% 3.2% vs 5.6% **	(death, MI, stroke TVR and ST) 11.1% vs 17.6%***
PIONEER-AF[19] 2013-2014	2 124	12 m	70 y	Patients with atrial fibrillation undergoing PCI.	rivaroxaban 15 mg + $P2Y_{12}$ rivaroxaban 2.5 + aspirin + $P2Y_{12}$ warfarin + aspirin + $P2Y_{12}$	TIMI minor + major	16.8% and 18.0% vs 26.7%	6.5%, 5.6% vs 6.0%**, ***
RE-DUAL PCI[20] 2014-2016	2 725	14 m	70.8 y	Patients with atrial fibrillation undergoing PCI	dabigatran 110mg bid + $P2Y_{12}$[a] dabigatran 150 mg bid + $P2Y_{12}$[b] warfarin + aspirin + $P2Y_{1}$	ISTH CRNM TIMI major	15.4% vs 26.9%[a] 20.2% vs 25.7%[b] 1.4% vs 3.8%[a] 2.1% vs 3.9%[b]	(death, MI, stroke, SSE, unplanned revascularisation) 15.2% vs 13.4%[a] 11.8% vs 12.8%[b]

AUGUSTUS[21] 2015-2018	4 614	6 m	70.7 y	Patients with atrial fibrillation and undergoing PCI or with ACS planned use of $P2Y_{12}$ inhibitor	2:2 factorial design apixaban or warfarin [a] + $P2Y_{12}$ + aspirin or placebo [b]	ISTH CRNM TIMI major	10.5% vs 14.7%[a] 16.1% vs 9.0%[b] 1.3% vs 2.4% dual vs triple	(death, MI, stroke, ST, urgent revascularisation) 14.3% vs 15.3%[a] 13.9% vs 15.7%[b]
ENTRUST[22] 2017-2018	1 506	12 m	69.5 y		edoxaban + $P2Y_{12\ vs}$ warfarin + $P2Y_{12}$ + aspirin	ISTH CRNM	17% vs 20%****	(CV death, stroke, SSE, MI or ST) 7% vs 6%***
REGISTRIES								
REACH[23] 2003-2004	64 589	24 m	68.6 y	45 years, with established CVD, CAD, PAD, or with at least three atherosclerosis risk factors		Serious bleeding: non-fatal haemorrhagic stroke or bleeding leading to both hospitalisation and transfusion.	1.4%	
PARIS [24] 2009-2010	4 190	24 m	64 y	Patients undergoing PCI (62.5 % CCS) with DES stent and discharged on DAPT	DAPT triple therapy 5%	BARC 3 and 5	3.2%	(Coronary thrombotic event: MI or ST) 3.6%
BleeMACS[25] 2003-2014	15 401	12 m		Patients with ACS undergoing PCI discharged alive with follow-up data for 1 year			3.2 /100 person years	
Spanish registry (two tertiary hospitals) 2012-2015[26]	4 229	15 m	67 y	ACS undergoing PCI (review of medical records)	DAPT 84.8 % OAC 11.3 %	BARC 2 and 3 BARC 2 BARC 3a BARC 3b BARC 3c	7.7/100 person years 8.5% 1.4% 1.2% 0.7%	MI 3.1/100 person years

ACS: acute coronary syndrome, AF: atrial fibrillation, APT: antiplatelet therapy, BARC: Bleeding Academic Research Consortium, CABG: coronary artery bypass grafting, CAD: coronary artery disease, CCS: chronic coronary syndrome, CRNM: clinically relevant non major bleeding, CV: cardiovascular, CVD: cardiovascular disease, DAPT: dual antiplatelet therapy, DES: drug eluting stent, ISTH:International Society on Thrombosis and Haemostasis, MI: myocardial infarction, OAC: oral anticoagulant, PAD: peripheral arterial disease, PCI: percutaneous coronary intervention, SAP: single antiplatelet therapy, SSE: stroke or systemic embolism, ST: stent thrombosis, TIMI: thrombolysis in myocardial infarction, TVR: target vessel revascularization

*PLATO bleeding definition see Table 3
** not statistically significant
***underpowered
**** significant for non-inferiority but not superiority

Table 2. Bleeding definitions		
GUSTO[27]	**Severe or life-threatening**	Intracerebral haemorrhage Resulting in substantial hemodynamic compromise requiring treatment
	Moderate	Requiring blood transfusion
	Mild	Bleeding that does not meet the severe or moderate criteria
TIMI[28-30]	**Major (Non-CABG related)**	Any intracranial (excluding microhaemorrhages < 10 mm on gradient-echo MRI) Hb drop ≥ 5 g/dL and clinical overt bleeding Fatal bleeding (within 7 days)
	Minor	Hb drop 3 to < 5 g/dL and clinical overt bleeding
	Requiring medical attention	Any clinically overt bleeding that meets one of the following and does not meet the major or minor criteria 1. Requiring intervention (medical or surgical intervention including temporary or permanent change in medication) 2. Leading to or prolonging hospitalisation 3. Prompting evaluation (leading to unscheduled visit, testing, laboratory or imaging)
	Minimal	Overt clinical bleeding that does not meet the criteria above
ISTH[31-32]	**Major Non-Surgical patients**	Fatal Symptomatic bleeding in critical area or organ, intracranial, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular with compartment Hb drop ≥ 2g/dL Blood transfusion of two or more units of whole blood or red cells
	Clinically relevant non-major	Any clinically over bleeding that does not meet the criteria for major meets at least one of the following 1. Requiring intervention (medical or surgical intervention including temporary or permanent change in medication) 2. Leading to or prolonging hospitalisation 3. Prompting evaluation (leading to unscheduled visit, testing, laboratory or imaging)
	Minor non clinically relevant	All other minor bleeds that do not meet the clinically relevant criteria
BARC[33]	**Type 0**	No bleeding
	Type 1	Nonactionable and no unscheduled visits, hospitalisations, or testing May include self-discontinuation of medical therapy without consulting a health care professional
	Type 2	Overt bleeding (including bleeding found by imaging) that does not meet criteria 3, 4 or 5 but does meet at least one of the following 1. Requiring non-surgical medical intervention by health care professional 2. Leading to hospitalisation or increased level of care 3. Prompting evaluation

	Type 3a	Hb drop of 3 to < 5 g/dL and overt bleeding Any transfusion and overt bleeding
	Type 3b	Hb drop ≥ 5g/dL and overt bleeding Cardiac tamponade Requiring surgical intervention for control (excluding dental, nasal, skin, hemorrhoid) Requiring vasoactive agents
	Type 3c	Intracranial haemorrhage including intraspinal (excluding microbleeds or haemorrhagic transformation) Subcategories confirmed by autopsy, imaging or lumbar punction Intraocular compromising vision
	Type 4 CABG related	Perioperative intracranial bleeding (within 48h) Reoperation after closure of sternotomy for bleeding Blood transfusion ≥ 5 units whole blood or packed red blood cells within 48 h Chest tube output ≥ 2L within 24 h period
	Type 5a	Probable fatal bleeding; no autopsy or imaging but clinically suspicious
	Type 5b	Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation
CRUSADE[34]	**Major**	Intracranial Documented retroperitoneal Hematocrit drop ≥ 12% Any red blood cell transfusion when hematocrit was ≥ 28% Any red blood cell transfusion when hematocrit was < 28% with witnessed bleed
ACUITY[35]/ **HORIZONS**[36,37]	**Major**	Intracranial or intraocular haemorrhage Access site haemorrhage requiring intervention Hematoma ≥ 5 cm Retroperitoneal Hb drop ≥ 4 g/dL without overt source of bleeding Hb drop ≥ 3g/dL with an overt source of bleeding Reoperation for bleeding Use of any blood product transfusion
BleeMACS[25]	**Serious spontaneous bleeding**	Intracranial Leading to hospitalisation And/or red blood cell transfusion ≥ 1U
PLATO[17]	**Major life threatening**	Fatal bleeding Intracranial bleeding Intrapericardial bleeding with cardiac tamponade Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery Hb drop of ≥ 5.0 g / dL Transfusion ≥ 4 units of red cells.
	Other major	Leading to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) bleeding either associated with a Hb drop of 3.0-5.0 g / dL or requiring transfusion of 2 to 3 units of red cells.

also reported and the corresponding incidence of TIMI major bleeding was 5.6 % in WOEST, 3.8% in RE-DUAL-PCI and 2.4 % in AUGUSTUS in the triple treatment arms (Table 1).

1.11 Bleeding localities

Procedure-related bleeding is most common at the puncture site of the femoral or radial artery, i.e., access-site bleeding, but it can also manifest as cardiac tamponade. Access-site bleeding from the femoral artery can cause life-threatening situations when blood can leak back into the retroperitoneal space. Intracranial bleeding is rare but still the most feared bleeding complication. Of the non-procedure related or spontaneous non-CABG related bleedings, the most common locality is bleeding from the gastrointestinal tract.[41-43] Bleeding from an unknown source is problematic since it cannot be resolved and, if antithrombotic treatment is stopped, clinicians may be hesitant to resume treatment again. Bleeding can also occur in the airways, oropharyngeal mucosa, ear, eye and perhaps more commonly in the nose (epistaxis).

1.12 Aspirin, NOACS and gastrointestinal bleedings

Aspirin increases the risk of upper gastrointestinal bleeding through a toxic effect on the gastric mucosa by inhibition of prostaglandin production. While NOACs have shown superior safety as compared with warfarin regarding intracranial bleeding they may increase the risk of gastrointestinal bleeding.[44] Whether there are specific properties of the four different NOACs regarding both efficacy and safety is unclear since randomised head-to-head comparisons are lacking. From the pivotal trials,[45-48] apixaban seems to have equal risk of GI bleeding while dabigatran (the 150 mg dose), rivaroxaban and edoxaban (the 60 mg dose) seem to increase the risk of GI bleeding compared with warfarin. Observational data have shown that rivaroxaban[49] and dabigatran[50] were associated with higher risk of GI bleeding, although this must be interpreted with caution given the non-randomised comparisons. A higher risk of gastrointestinal bleeding with edoxaban compared with warfarin has also been shown in elderly patients with aortic stenosis undergoing transcatheter aortic valve intervention (TAVI).[51] The use of NOACs is believed to increase as the population grows older and more patients are diagnosed with atrial fibrillation. Among patients hospitalised with acute MI in Sweden, approximately 10–15% have concomitant indication for OAC, mainly due to atrial fibrillation, and the proportion of patients with acute MI treated with OAC plus antiplatelet increases every year.[52] It is thus likely that the incidence of gastrointestinal bleedings will increase and any measure to decrease the risk of GI bleeding is warranted.

Upper gastrointestinal bleeding (UGIB) is of specific interest since there are prophylactic measures to reduce this with proton-pump inhibitors (PPI)s[53] and aspirin-free strategies. Helicobacter pylori screening and subsequent eradication is also being tested in an ongoing cluster randomised study.[54] Predictors and the prognostic associations of UGIB are not sufficiently understood. In addition, most previous studies in patients with acute MI have included bleeding of both upper and lower origin[55-58], and/or had small[55] and selected[59] study populations.

1.13 Bleeding events as prognostically important outcomes

In the early aspirin studies of the 1980s, bleeding events were either not mentioned[60] or reported as side-effects rather than separate outcomes.[61-63] In the late 1990s, concerns were raised regarding bleeding complications due to use of GPIIb/IIIa blockers and methods to reduce these complications were proposed.[64] One of the first studies investigating the associated prognosis of bleeding events was published in 2003, showing that bleeding events

were associated with increased mortality.[65] Thereafter, several studies have replicated these results in different settings, showing that after adjustment for confounders, major bleeding was strongly associated with increased mortality in a dose-dependent fashion.[66-68] Since then, bleeding events as prognostically important outcomes have gained increasing interest[69] and strategies to reduce these events were introduced. Use of fondaparinux in the OASIS-5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial was among the first to show that reduction of bleeding events was associated with reduced mortality.[70] Similar findings for radial access were shown in the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial[71] but not in other radial- versus femoral-access trials.[72,73] Bleeding avoidance strategies such as radial access, decreased use of GP blockers and vascular closure devices are now the default strategies in most countries. In the past decade, bleeding avoidance strategies have expanded to include antithrombotic strategies[74] such as shorter DAPT[75-77], aspirin-free regimens[78-81] or de-escalation, either un-guided, [82,83] or guided by platelet-function[84] or genotype testing[85] (Figure 6). The concept of a so-called trade-off between ischemic reduction and bleeding has become generally accepted, resulting in a shift of focus to more extensive reporting of bleeding. Thus, in four decades, bleeding events have gone from being underreported to figuring as the primary outcome in several large multicentre randomised clinical trials.[19-22,86]

1.14 Possible mechanisms linking bleeding with mortality

The mechanisms linking bleeding with mortality are multifactorial and complex. While the most severe bleeding directly causes life-threatening situations, the consequences of less severe bleeding are indirect. For example, intracranial or massive bleeding can cause brain damage or hemodynamic collapse resulting in death. Blood transfusion may exert indirect effects by causing systemic inflammation with a prothrombotic state[87], increased oxidative stress and paradoxical decreased oxygen delivery[88] which all could contribute to worse outcome. Even mild bleeding not requiring blood transfusion may lead to discontinuation of antithrombotic treatment and thus indirectly influence prognosis. Finally, despite statistical adjustments, the association of bleeding events with mortality may be biased from residual confounding, i.e., the same factors are related to both a higher risk of bleeding and mortality (Table 3 and Figure 7).

1.15 Bleeding risk assessment

Assessment of bleeding risk is essential to guide antithrombotic treatment based on individual ischemic and bleeding risk.[7] Several bleeding risk scores for patients with acute coronary syndrome or patients undergoing PCI have been developed. These include the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines)[34] and ACTION (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines)[89] scores for assessment of in-hospital bleeding risk, the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY)[90] score for bleeding risk at 30 days, the DAPT[91] score for assessment of both ischemic and bleeding risk at one year, the BleeMACs (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome)[25], and the PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy)[92] scores for bleeding risk at one year and the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients)[24] and the REACH (Reduction of Atherothrombosis for Continued Health)[23] scores

General measurements
Correct indication
Correct dosing
Avoid other treatments that increase or potentiate bleeding risk of antithrombotics ($NSAID_S$, concomitant long-term steroid treatment)
PPI
HP eradication (?)
Alcohol intake?

Procedural aspects
Radial access
Vascular closure device
Less use of GPIIb/IIIa blocker
Avoid loading with $P2Y_{12}$ inhibitor before coronary angiography

Antithrombotic strategies

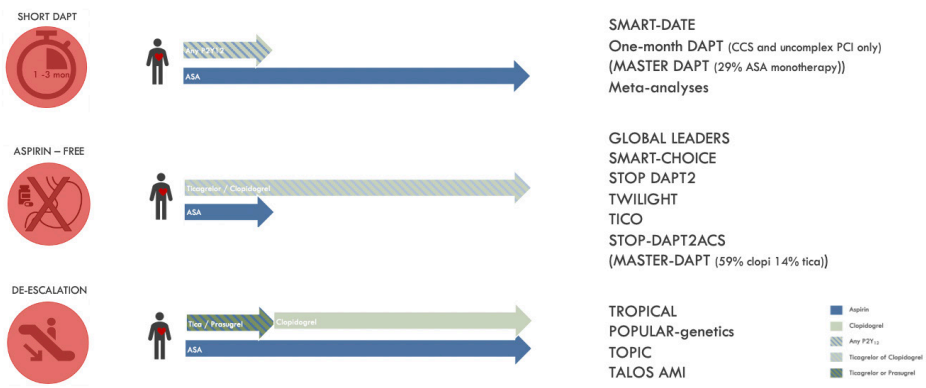


Figure 6. Bleeding avoidance strategies
CCS: chronic coronary syndrome, HP: helicobacter pylori, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor

for bleeding risk at two years. (Table 4) The most recent European guidelines[5,7] highlight the DAPT score for assessment of ischemic risk and the PRECISE-DAPT score or ARC-HBR (Academic Research Consortium for High Bleeding Risk) criteria[93] (Table 5 and Figure 8) for assessment of bleeding risk.
The ARC-HBR criteria were developed as a consensus definition of patients at high bleeding risk undergoing PCI. ARC-HBR consists of 20 clinical criteria identified as either major or minor. High bleeding risk is defined as at least one major or two minor criteria and should correspond to a one-year risk of BARC 3 or 5 bleeding ≥4% or a one-year risk of intracranial bleeding ≥1%. The ARC-HBR criteria have been validated in both ACS and PCI populations[94,95] showing a stepwise increase of bleeding risk across increasing numbers of high bleeding risk criteria met.

Table 3. Possible mechanisms linking bleeding with mortality

Mechanism	Effect
Fatal haemorrhage	Fatal injury to vital organs such as the brain
Cardiocirculatory collapse	Hypotension, ischemia, arrhythmias and general impairment of tissue oxygenation
Blood Transfusion	Generalized systemic inflammation, increased oxidative stress, prothrombotic state
Discontinuation of antiplatelet therapy	Increased risk of ischemic complications and stent thrombosis
Discontinuation of anticoagulant therapy	Increased risk of stroke or systemic embolism
Discontinuation of other cardioprotective drugs	Lower cardiac protection
Residual confounding	Patients at high risk of bleeding have higher mortality risk independent from bleeding events

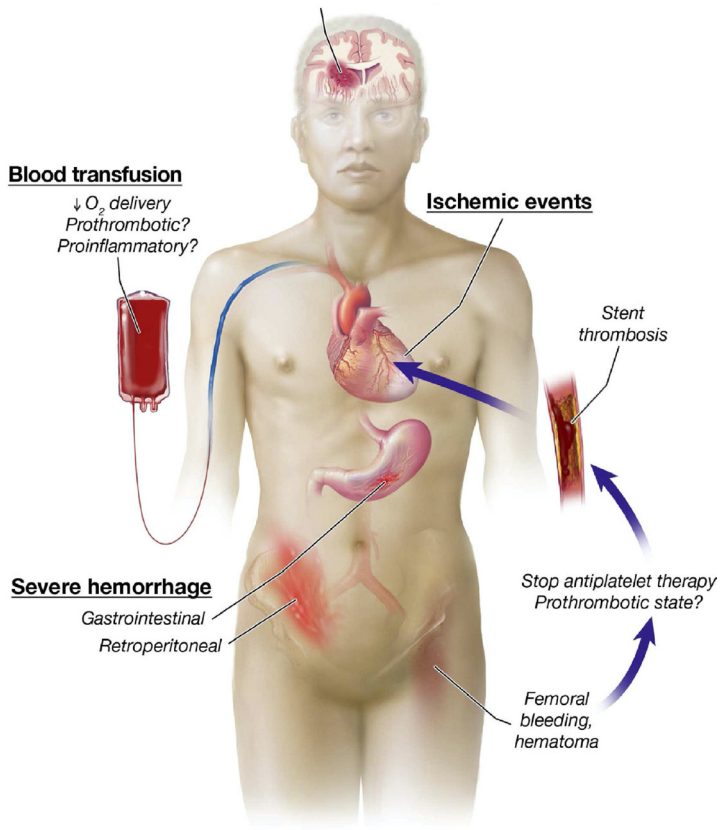


Figure 7. Possible mechanisms linking bleeding with mortality

With permission: Doyle et al, J Am Coll Cardiol 2009;53:2019-27

Table 4. Bleeding risk scores for patients with coronary artery disease

	Derivation cohort	Validation cohort	Bleeding definition	Bleeding incidence or incidence rate	C-statistics D: V:
CRUSADE[34]	n = 71 277 of 89 134 NSTEMI 2003-2006 CRUSADE registry	Internal random split n = 17 857 of 89 134 2003-2006	CRUSADE definition	9.6% in-hospital	D: 0.72 V: 0.71
ACTION[89]	n = 72 313 of 103 890 NSTEMI+STEMI 2007-2008 ACTION registry -GWTG	Internal random split n = 17 969 of 103 890 2007-2008	ACTION definition	10.8% in-hospital	D: 0.73 V: 0.71
ACUITY[90]	n = 17 421 STEMI+NSTEMI+UAP ACUITY and HORIZONS-AMI RCTs	N/A	ACUITY and HORIZONS-AMI definition	7.3% at 30 days	D: 0.74
BleeMACS[25]	n = 15 401 ACS undergoing PCI 2003-2014 Cohort study	External n = 96 321 PCI n = 93 150 no PCI SWEDEHEART registry 2003-2012	BleeMACS definition	3.2 /100 person years at 1 year	D: 0.71 V: 0.65
PRECISE-DAPT[92]	n = 14 936 post PCI Pooled from 8 RCTs	External n = 8 595 PLATO 2006-2008 n = 6 172 Bern PCI registry 2009-2014	TIMI minor and major definition	12.5 resp 6.9/ 1000 person years minor/ major at 1 year	D: 0.73 V: 0.7 and 0.66
DAPT[91]	n = 11 648 Post PCI event-free at 1-y 2009-2014 DAPT study	External n = 8 136 PROTECT 2007-2014 PCI	GUSTO moderate or severe	D: 1.8 % at 18 months V 0.5% at	D: 0.68 V: 0.64
PARIS[24]	n = 4 190 PCI with stent 2009-2010 PARIS registry	External n = 8 130 ADAPT-DES Registry 2008-2010	BARC 3 or 5	D: 3.3% at 2 years	D: 0.72 V: 0.64
REACH[23]	n = 56 6716 Stable /risk of CAD 2003-2004 REACH registry	External n = 15 603 CHARISMA 2002-2003	D: REACH definition V: GUSTO moderate or severe	D: 1.4% at 2 years V: 3.1 at 2 years	D: 0.68 V: 0.64

ACS: acute coronary syndrome, BARC: Bleeding Academic Research Consortium, CABG: coronary artery bypass grafting CAD: coronary artery disease, D: derivation, DAPT: dual antiplatelet therapy, NSTEMI: non-ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction, V: validation

Common variables in the PRECISE-DAPT score, ARC-HBR criteria and most other bleeding risk scores are haemoglobin, renal function, age and previous bleeding. When available, a biomarker may be useful and is represented by white blood cell count in the PRECISE-DAPT score, (Table 6) and growth differentiation factor 15 (GDF-15) in the ABC (age, biomarkers, clinical history) bleeding risk score[96] for patients with atrial fibrillation.

1.16 The CRUSADE score

The CRUSADE score is the most established score to assess in-hospital bleeding risk. It consists of 8 baseline variables which can be entered in an online calculator to give the CRUSADE score points and corresponding estimated bleeding risk in per cent. Clinical studies often report CRUSADE score as a measure of population characteristics similar to how studies on atrial fibrillation report CHA_2DS_2VASc score.[97] The CRUSADE score has been externally validated showing moderate to good discrimination in patients undergoing coronary angiography[98] but it has shown limited discrimination in patients treated conservatively, i.e., not undergoing coronary angiography,[98] in elderly patients,[99-101] in patients with reduced renal function[101] or on OAC treatment.[98] Moreover, the CRUSADE score was derived in a cohort of NSTEMI patients from 2003–2006. During this time, femoral access without vascular closure devices was predominantly used and GPIIb/IIIa blockers were used more frequently, resulting in a very high incidence of in-hospital bleeding and limiting the external validity of the CRUSADE score in a contemporary population.

1.17 Guideline recommendations

Use of bleeding risk scores has a class IIb ('may be considered') recommendation limited to patients undergoing coronary angiography in recent European guidelines.[7] Use of specific scores to guide DAPT duration, such as the PRECISE-DAPT and DAPT scores, also has a class IIb recommendation and, in that setting, the focus is on long-term post-discharge thrombotic and bleeding risk.[5,7] This rather weak class of recommendation is partly due to the lack of prospective evaluation of the use of scores in clinical trials. So far, evidence is scarce regarding whether use of scores is superior to clinical evaluation to risk-stratify patients.

1.18 Association of ischemic and bleeding events with mortality

The concept of individualised antithrombotic strategies, in which ischemic and bleeding risk are weighed against each other, assumes that the prognostic importance of these events is equal. While several studies have shown that the relative mortality risk of an MI and bleeding event[102 26,43,103-108] is equal,[109] few studies have compared ischemic events, including ischemic stroke, versus bleeding events[110,111] (Table 7). Inclusion of ischemic stroke in the ischemic outcome may be relevant since the risk of ischemic stroke can also be modified by antithrombotic treatment. The few studies on ischemic vs bleeding events[110,111] were based on randomised clinical trials, and one only assessed events beyond one year after PCI with stenting, resulting in a very selected low-risk population with an overall one-year-mortality rate of less than 1–2 %[110] and thus limited external validity. Large-scale data comparing the relative mortality risk of ischemic vs bleeding events from non-selected populations are lacking.

Table 5. ARC HBR criteria

Major Criteria	Minor Criteria
• Haemoglobin <11 g/dL • Severe or end-stage CKD (eGFR < 30ml/min) • Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent • Moderate or severe thrombocytopenia (platelet count < 100 x 10^9/L) • Liver cirrhosis with portalhypertension • Chronic bleeding diathesis • Previous spontaneous ICH (at any time) • Previous traumatic ICH within the past 12 mo • Presence of bAVM • Moderate or severe ischemic stroke within the past 6 months • Active malignancy • Anticipated use of long-term anticoagulation • Nondeferrable major surgery on DAPT • Recent surgery or major trauma within 30 d before PCI	• Age≥ 75 y • Haemoglobin 11-12.9 g/dl • Moderate CKD (eGFR 30–59 ml/min) • Spontaneous bleeding requiring hospitalisation or transfusion in the past 12 months, not meeting the major criteria • Any ischemic stroke at any time not meeting the major criteria • Long-term use of NSAIDs or steroids

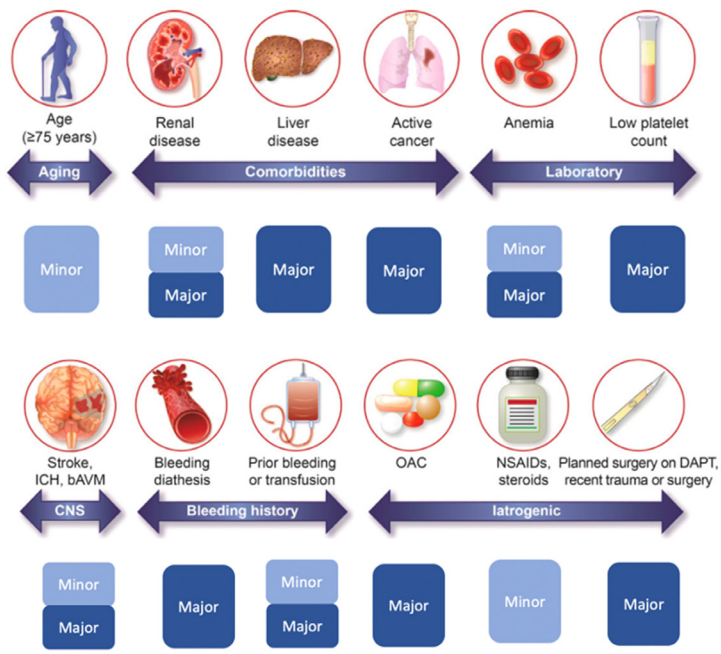


Figure 8. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria. High bleeding risk is defined as at least one major or two minor criteria and should correspond to a one-year risk of BARC 3 or 5 bleeding of ≥ 4% or one-year risk of intracranial bleeding ≥ 1%.

bAVM: brain arteriovenous malformation, CKD: chronic kidney disease, DAPT: dual antiplatelet therapy, eGFR: estimated glomerular filtration, ICH: intracranial haemorrhage, NSAIDs: non-steroidal anti-inflammatory drug, OAC: oral anticoagulant, PCI: percutaneous coronary intervention

Adapted from Urban et al, European Heart Journal (2019) 40, 2632–2653
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Table 6. Predictors in bleeding risk scores for patient with acute or chronic coronary artery disease								
	CRUSADE	**ACTION**	**ACUITY**	**BleeMACS**	**PRECISE-DAPT**	**DAPT**	**PARIS**	**REACH**
Variables (N)	**8**	**12**	**7**	**7**	**5**	**1**	**6**	**9**
Age		+	+	+	+	+	+	+
Sex	+	+	+					
Weight/BMI		+					+	
Previous bleeding				+	+			
Hemoglobin	+	+	+	+	+		+	
Renal function	+	+	+	+	+		+	
"Biomarker"			WBC		WBC			
Type of MI			+					
ECG changes		+						
HF/shock	+	+						+
Smoking							+	+
Hypertension				+				+
Diabetes	+	+						+
Hypercholesterolemia								+
Previous PAD/VD	+	+		+				+
Previous Cancer				+				
Systolic Blood pressure	+	+						
Heart Rate	+	+						
Antithrombotic treatment								
Hep+ GPIIb/IIIa vs Hep			+					
Triple treatment							+	
Warfarin		+						
OAC								+
APT								+

APT: antiplatelet therapy, BMI: body mass index, ECG: electrocardiogram, Hep: heparin, HF: heart failure, MI: myocardial infarction OAC: oral anticoagulant, PAD: peripheral artery disease, VD: vascular disease, WBC: white blood cell count

Table 7. Studies on mortality following MI or ischemic events (in bold) vs bleeding events

	Type of study Year of inclusion	**Study population**	**N**	**Follow up in m**	**Age**	**Comparison**	**Bleeding definition**	**Exposure event n/(%)**	**N died at FU**	**Adjusted HR**	**Comment**
Mehran[102] 2009	RCT ACUITY 2003-2005	PCI 56.4 NSTEMI 100%	13 819	12		MI vs bleeding 30 days	ACUITY Periprocedural	MI 705 (5.1%) Major Bleed 645 (4.7%) Event and dead at the same day	524 (3.8%)	MI 3.1 Bleed 3.5 BloodTX 4.5	Hematomas included periprocedural
KIM[103] 2011	Registry 2003-2006	PCI 100% ACS 14%	3 148	36	60	MI vs bleed Periprocedural + 3 year	STEEPLE major and minor	Bleed 207 MB 123 MI 204	134	MI 2.5 Bleed 5.8	Both in-hospital and out-of hospital
Kikkert[112] 2013	Registry 2003-2008	PCI 100% STEMI 100%	2 002	48	62	MI vs bleed one year	GUSTO severe	MI 149 (8%) Bleed 85 (4.4%) Unclear	366 (18.4%)	MI 4.16 Bleed 1.46 (0.99-2.15)	Unclear 1 year bleeding including in-hospital probably
Kazi[104]	Registry 1996-2008	PCI 100% ACS 14%%	32 906	53	64	MI vs bleed 7-365 days Post-discharge	ICD-9 codes primary for MI and IC bleed primary + secondary for EC bleed	Bleed 530 MI 991 No fatal events?	4 048	MI 1.91 Bleed 1.61 CIs overlap	Only spontaneous
Genereux[43]	Registry ADAPT-DES 2008-2010	PCI 100% 2008-2010 ACS 50%	8 577	24	64	MI vs bleed Post discharge	TIMI major + minor, ACUITY major, GUSTO sev + mod Any bleed requiring medical attention	MI 387 PDB 535 TIMI major och		MI 1.92 Bleed 5.03	Only spontaneous
Baber[105]	Registry PARIS 2009-2010	PCI 100% ACS 41%	5 018	24	63.5	CTE (MI + ST) vs bleed	BARC 2,3 (Actionable bleed)	CTE 289 Bleed 391	227 (4.7%)	CTE 3.3 Bleed 3.5	Included periprocedural events 340 (6.8) were lost to FU

Garot[106]	RCT Leaders free 2012-2014	PCI 100% HBR 100% ACS 27%	2 466	24	75.7	CTE (MI+ST vs bleed) 2 year	BARC 3, 4 or 5	CTE 219 9.4% Bleed 210 9.1%		CTE 4.43 Bleed 3.43 CIs overlap	Both in-hospital and out-of hospital?
Valgimigli[107]	RCT TRACER 2007-2010	NSTEMI 58,7% PCI	12 707	16	64	MI vs bleed 30-365 days	BARC 1, 2, or 3	MI 718 (5.6%) BARC 1, 2 ,3 999 BARC 1 878 (6.9%) BARC 2 712 (5.6%) BARC 3 346 (2.7%)	500 (3.9%)	MI 5.36 BARC 3 5.73	Grading BARC 3a, b c
Secemsky[110]	**RCT DAPT 2009-2011**	**PCI 100% ACS 31%**	**11 648**	**21**	**61**	**Ischemic (MI + ST + stroke) vs bleeding Between 12-33 months after PCI**	**GUSTO mod + sev TIMI BARC 3, 4, 5**	**MI 478 (4.1%) Bleed 275 (2.0%) 15 pat had BARC5 88 pat had CV death that was not MI, ST or stroke**		**Ischemic 12.6 Bleed 18.1**	**Only spontaneous**
Caneiro-Queija[26]	Registry 2012-2015	PCI 73.5% ACS 100%	4 229	15	67	MI vs bleed post-discharge	BARC 2-3	MI 204 Bleed 500 BARC 3 141	355	MI 5.8 Bleed 5.1	Same conclusion as Valgimigli Graded according to BARC status
Hara[108]	RCT Global leaders 2013-2015	PCI 100% ACS 47%	15 968	24	64.5	MI vs bleed Periprocedural included	BARC 2, 3 & 5	MI 498 (3.12%) Bleed 1061 (6.64%)	477 (2.99%)	MI 5.06 Bleed 5.97	
Ducrocq[111]	**RCT PLATO 2006-2008**	**ACS PCI**	**18 624**	**12**	**62**	**Ischemic (MI + stroke) vs bleed**	**PLATO major TIMI major GUSTO severe**	**Ischemic 822 (4.4%) Bleed 485 (2.6%)**	**905**	**Short term isch vs TIMI bleed:1.26 Longterm isch vs TIMI bleed: 1.19 CI overlap**	**Overall similar associated prognosis**

ACS: acute coronary syndrome, BARC: Bleeding Academic Research Consortium, CI: confidence interval, CRNM: clinically relevant non major bleeding, CTE: coronary thrombotic event, DAPT: dual antiplatelet therapy, DES: drug eluting stent, EC, extracranial, HBR: high bleeding risk, IC: intracranial, MI: myocardial infarction, NSTEMI: non ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, PDB: post discharge bleeding, RCT: randomized clinical trial, ST: stent thrombosis, STEMI: ST-elevation myocardial infarction, TIMI: thrombolysis in myocardial infarction

2 RESEARCH AIMS

This thesis aimed to investigate in depth different aspects of bleeding complications in patients with acute myocardial infarction.

STUDY I: BLEEDING TRENDS

To describe the time trends of in-hospital and out-of-hospital bleeding events following acute myocardial infarction over the past two decades parallel to the development of antithrombotic and invasive treatment, and ischemic outcomes

STUDY II: BLEEDING RISK SCORE

To develop and validate a new in-hospital bleeding risk score for patients with acute MI that could overcome the shortcomings of previous scores

STUDY III: UPPER GASTROINTESTINAL BLEEDINGS

To determine the incidence, associated outcomes and predictors of UGIB

STUDY IV: ASSOCIATED MORTALITY OF ISCHEMIC VS BLEEDING EVENTS

To compare the association of ischemic and bleeding events with mortality in patients with recent myocardial infarction

To examine whether the relative mortality risk of ischemic versus bleeding events had changed over the past two decades

3 MATERIALS AND METHODS

3.1 THE SWEDISH NATIONAL REGISTERS

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry[113] is a nationwide cardiac quality register. It was created in 2009 by merging the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry and the National Registry of Secondary Prevention (SEPHIA). Recently, the Swedish Transcatheter Cardiac Intervention Registry (SWENTRY) and Swedish National Cardiogenetic Registry have also been added. SWEDEHEART has nearly complete coverage regarding patients hospitalised with acute MI in Sweden. It collects information on baseline characteristics, in-hospital course and treatment, and medication on arrival and at discharge. Regular monitoring has showed on average 96% agreement between the registry and electronic medical records. According to Swedish law, no informed consent is required but all patients are informed about their inclusion in the registry, and they have the right to opt out.

The National Patient Register[114] holds information on International statistical Classification of Diseases and Related Health Problems (ICD) codes for all hospital admissions since 1987 as well as outpatient specialist visits, excluding general practitioners, since 2001. Since 1997 and onwards it uses the tenth version, ICD-10. Before 1997 the ninth version, ICD-9, was used.

The Swedish Population Registers[115] hold information on major life events such as birth, death, immigration and marital status with close to complete coverage of all births and deaths in Sweden.

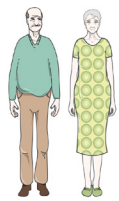
The Cause of Death Register[116] holds complete information on all deaths in Sweden since 1952 and since 1961 it is updated annually. Like the National Patient Register, it uses ICD-10 since 1997.

The Swedish Drug Prescription Register[117] registers all dispensed drugs and includes information about dosages, prescription, and dispensation date from pharmacies across the country.

3.2 STUDY POPULATIONS

Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

National Patient Register
Swedish Population Registers
Cause of Death Register (only Study I)
Drug Prescription Register (only Study III)



Patients with MI aged ≥18 years

Inclusion	Exclusion
Study I Enrolled January 1995 – May 2018 MI definition ICD-10 code I21 n = 407 366	Readmission during each 2-year block (first admission included) n = 35 955
Study II Enrolled January 2009 – October 2014 (first MI definition ICD-10 code I21 n = 109 714	Readmission during study period (first admission included) Missing on bleeding outcome n = 180
Study III Enrolled January 2007 – June 2016 MI definition ICD-10 I21 or I22 First admission during study period Discharged alive n = 149 708	Discharged without antithrombotic treatment n = 216
Study IV Discharged January 2012–December 2017 Discharged alive One random admission during study period n = 88 840	Missing on antithrombotic treatment n = 82 Discharged without antithrombotic treatment n = 1885 Missing on any of the variables in the Cox models n = 137

Final study populations

Study I: n = 371 431
Study II: n = 97 597
Study III: n = 149 447
Study IV: n = 86 736

3.3 OUTCOMES AND STATISTICAL ANALYSIS

3.3.1 STUDY I: BLEEDING TRENDS

Outcome definitions

In-hospital bleeding was defined as fatal, intracranial or bleeding requiring blood transfusion or surgery, as registered in the SWEDEHEART registry. Out-of-hospital bleeding was defined as rehospitalisation with bleeding ICD-9 or ICD-10 code (Table 8) in the National Patient Register within one year of discharge through 31 December 2017.

In-hospital re-infarction was defined as registered in the SWEDEHEART registry. Out-of-hospital MI was defined as rehospitalisation with diagnosis of MI in the SWEDEHEART registry (day 2–30) or rehospitalisation with ICD-10 diagnosis of MI (I21 or I22) in the National Patient Register (day 31–365). Both in-hospital and out-of-hospital MI were registered from 1 January 1997 through 31 December 2016. Ischemic stroke was defined as hospitalisation with ICD-code (433, 434, I63, I64 or G45) in the National Patient Register at least 1 day and within one year after discharge from January 1995 through December 2016.

Cardiovascular death was defined as death within one year after discharge with ICD-codes I00-I99 as underlying cause of death in the Cause of Death Register from 1 January 1995 through 31 December 2016.

Missing data and outcome standardisation

Missing data were handled by multiple imputation of five sets. The study period from January 1995–May 2018 was divided into two-year periods. All in-hospital and out-of-hospital bleeding and ischemic outcomes were standardised using logistic regression models with data from the whole study period and two-year period as predictor together with possible confounders. The models were adjusted adding confounders stepwise from crude (only two-year block), age and sex, baseline characteristics, and finally in-hospital treatment for in-hospital outcomes or out-of-hospital treatment for out-of-hospital outcomes. Predicted probabilities of the outcome in all two-year periods were calculated for patients from the last two-year period using the fitted models. These analyses were performed in all imputed data sets and the final standardised outcome was the average over the 5 imputations.

All analyses were performed in all patients and in the subgroups of NSTEMI and STEMI.

All statistical analyses were performed using R version 3.5.0 (2018-04-23).

3.3.2 STUDY II: BLEEDING RISK SCORE

Outcome definitions

In-hospital major bleeding was defined as fatal, intracranial or bleeding requiring blood transfusion or surgery as registered in the SWEDEHEART registry. For patients undergoing CABG during hospital stay, bleeding was only registered if it occurred before surgery.

Model derivation and validation

First, a full model was created using logistic regression of 23 predictor variables (age, sex, body weight, hypertension, diabetes mellitus, previous myocardial infarction, previous PCI, previous CABG surgery, previous stroke, peripheral artery disease (PAD), chronic heart failure, previous bleeding, single aspirin therapy, DAPT, OAC therapy, cardiopulmonary resuscitation (CPR) before hospital, atrial fibrillation at hospitalisation, cardiogenic shock, heart failure at hospitalisation, ST-elevation myocardial infarction (STEMI), serum creatinine, C-reactive protein (CRP) and haemoglobin), selected based on clinical relevance and previous

Table 8. Bleeding ICD-codes: ICD-9 until 1996, ICD-10 from 1997 and onwards; ICD-10 codes of upper gastrointestinal bleeding used in Study III in the last column

ICD-9 code	ICD-10 code	Bleeding locality	ICD-10 code of upper gastrointestinal bleeding
430	I60	Subarachnoidal bleeding	
431	I61	Intracerebral bleeding	
432	I62	Other intracranial bleeding	
285B	D629	Anemia after acute larger bleeding	
	D500	Iron deficiency anemia secondary to chronic blood loss	
	H356	Retinal bleeding	
	H431	Vitreous bleeding	
	H450	Vitreous bleeding	
	H922	Bleeding from the ear	
456 A	I850	Esophageal varices with bleeding	I850
530H	K226	Gastro-esophageal ulcer with bleeding, Mallory Weiss	K226
531A	K250	Ulcus ventriculi acute with bleeding	K250
531C	K252	Ulcus ventriculi acute with bleeding and perforation	K252
531E	K254	Ulcus ventriculi chronic or unspecified with bleeding	K254
531G	K256	Ulcus ventriculi chronic or unspecified with bleeding and perforation	K256
532A	K260	Ulcus duodeni with bleeding acute with bleeding	K260
532C	K262	Ulcus duodeni with acute with bleeding and perforation	K262
532E	K264	Ulcus duodeni chronic or unspecified with bleeding	K264
532G	K266	Ulcus duodeni chronic or unspecified with bleeding and perforation	K266
533A	K270	Ulcus ventriculi or duodeni acute with bleeding	K270
533C	K272	Ulcus ventriculi or duodeni acute with bleeding or perforation	K272
533E	K274	Ulcus ventriculi or duodeni chronic or unspecified with bleeding	K274
533G	K276	Ulcus ventriculi or duodeni chronic or unspecified with bleeding and perforation	K276
534A	K280	Reccurence of bleeding ulcer	K280
534C	K282	Reccurence of bleeding ulcer with perforation	K282
534E	K284	Reccurence of chronic or unspecified bleeding ulcer	K284
534G	K286	Reccurence of chronic or unspecified bleeding ulcer with perforation	K286
	K290	Acute haemorrhagic gastritis	K290
569D	K625	Bleeding in anus or rectum	
578	K920	Hematesis	
578	K921	Melena	
578	K922	GI-bleeding unspecified	K922
602B	N421	Prostate bleeding	
	N938	Bleeding from uterus or vagina	
	N939	Bleeding from uterus or vagina	
627B	N950	Bleeding after menopause	
784W	R041	Bleeding from pharynx	
786D	R048	Bleeding from the airways	
	R049	Bleeding from the airways	
599H	R319	Hematuria	
998B	T810	Bleeding complicating a procedure	
	N501A	Bleeding from male genitalia	

knowledge, and 8 interaction terms (age and sex, age and diabetes, age and serum creatinine, age and haemoglobin, sex and body weight, sex and diabetes, sex and serum creatinine, and sex and haemoglobin). In this model, continuous variables were handled in restricted cubic splines and skewed variables were log transformed. The full model was then approximated using the stepdown method[118] by a smaller model of five predictors and one interaction term, termed the SWEDEHEART score. Five risk classes were created according to predicted bleeding risk of < 0.5%, 0.5-1%, 1-2%, 3-4% and > 4%. Calibration and discrimination were assessed and compared with the CRUSADE and ACTION scores. The CRUSADE and ACTION scores were poorly calibrated in the derivation cohort and were therefore recalibrated. The SWEDEHEART, CRUSADE and ACTION scores were internally validated using 200 bootstrap samples. The SWEDEHEART score was also validated temporally by internal-external cross validation[119] in which each admission year was omitted in turn. Clinical utility was assessed using decision curve analysis.[120] The reporting was in agreement with the TRIPOD statement.[121,122]

Missing data

The proportion of missing data varied from 0–12% across the predictors and was highest for the laboratory variables. Assuming a missing-at-random mechanism, multiple imputation by chained equations (MICE)[123,124] was performed, creating 25 imputed data sets. The logistic regression models were then fitted to the imputed data sets and the estimates were combined into an average estimate.

All statistical analyses were performed with R (version 3.4.3; The R Foundation for Statistical Computing, Vienna, Austria) using the add-on packages mice (version 2.44) and rms (version 5.1-1).

3.3.3. STUDY III: UPPER GASTROINTESTINAL BLEEDING

Outcome definitions

Upper gastrointestinal bleeding (UGIB) was defined as rehospitalisation with an ICD-10 code of UGIB (Table 8) as primary or secondary diagnosis in the National Patient Register.

Major Adverse Cardiovascular Event (MACE) at one year was defined as a composite of all-cause death, MI and ischemic stroke. All-cause death was captured from the Swedish Population Register. MI was defined as rehospitalisation with diagnosis of MI in the SWEDEHEART registry (day 2–30) or rehospitalisation with ICD-10 code I21 as primary or secondary diagnosis in the National Patient Register (day 31-365). Ischemic stroke was defined as rehospitalisation with ICD-10 code I63 as primary or secondary diagnosis in the National Patient Register (day 1–365).

Statistical analysis

A logistic regression model was fitted with UGIB as the outcome and 25 predictor variables, including demographics (age, sex, weight, STEMI, smoking status), medical history (hypertension, diabetes, previous MI, previous PCI, previous CABG, previous stroke, previous HF, previous lower extremity artery disease (LEAD), previous UGIB, previous cancer, chronic obstructive pulmonary disease (COPD)), laboratory variables (haemoglobin, creatinine, CRP) and discharge medical treatment (gastroprotective treatment, corticosteroid treatment, NSAID treatment and antithrombotic treatment [single antiplatelet therapy (SAPT), DAPT with clopidogrel, DAPT with ticagrelor, OAC alone, combination therapy]), which were selected based on previous knowledge and clinical relevance. Predictor importance was assessed by ranking of the Wald χ^2. Cox proportional hazards regression with UGIB as

a time-dependent predictor and MACE as well as the individual MACE components as the outcome was used to estimate crude and adjusted hazard ratios (HR)s with 95% confidence intervals (CI)s of UGIB and associated outcomes. The Cox models were adjusted for baseline characteristics, in-hospital treatment, and medication at discharge (using the same variables as the predictor variables in the logistic regression). The continuous variables (age, weight, haemoglobin, creatinine and CRP) were handled in restricted cubic splines in the regression models.
Four machine-learning models were also trained and validated to predict UGIB using 105 predictor variables. Variable importance, presented as weights, was calculated for the best performing model. Model performance of the logistic regression model and the machine-learning models was assessed through comparison of receiver operating characteristics (ROC) curves.

Missing data
The proportion of missing data was zero or low for most variables except for laboratory variables, smoking status and weight. Assuming a missing-at-random mechanism, missing data were handled by k-nearest neighbour (k-NN) imputation.
All statistical analyses were performed in R version 4.0.3. except for the machine-learning modelling, which was performed using RapidMiner Studio 9.8 (RapidMiner, Inc 2020).

3.3.4 STUDY IV: ASSOCIATED MORTALITY OF ISCHEMIC VS BLEEDING EVENTS

Outcome definitions
Ischemic event was defined as the composite of MI or ischemic stroke. MI was defined as rehospitalisation with diagnosis of MI registered in the SWEDEHEART registry (day 2–30) or rehospitalisation with ICD-10 code I21 as primary diagnosis in the National Patient Register (day 31–365). Ischemic stroke was defined as rehospitalisation with ICD-code I63 as primary or secondary diagnosis in the National Patient Register (day 1–365). Bleeding was defined as rehospitalisation with an ICD-10 code of bleeding as primary or secondary diagnosis (Table 8) in the National Patient Register (day 1–365). For patients with more than one event, only the first event was considered. If both types of events occurred on the same day, the ischemic event was considered. All-cause death was captured from the Swedish Population Register.

Statistical analysis
The incidence (presented as incidence rate per 100 person years) of ischemic and bleeding events was described using Kaplan Meier methods; patients were followed for up to 365 days after discharge until event, death or end of study period (31 December 2017). Two primary analyses were made to assess the association of ischemic and bleeding events with mortality.

First, Cox proportional hazards regression with exposure event as a time-dependent categorical variable with three mutually exclusive categories (no-event, ischemic event or bleeding event) was used to estimate crude and adjusted HRs for mortality associated with an ischemic or bleeding event vs no event. In this analysis, patients were censored at death, 730 days after discharge, 365 days after an ischemic or bleeding event, if their first ischemic or bleeding event occurred after 365 but before 730 days after discharge, or at the end of study period (31 December 2017). The model was adjusted for age (restricted cubic splines), sex, year of discharge, STEMI, medical history (hypertension, diabetes, previous MI, previous PCI, previous CABG, previous stroke, previous bleeding, previous HF, previous cancer,

previous LEAD, COPD, previous renal failure), in-hospital invasive treatment (coronary angiography, PCI or CABG), antithrombotic treatment strategy at discharge (SAPT, DAPT, dual, triple) and discharge medication (beta blocker, calcium blocker, digoxin, diuretics and statins).
Next, the analysis was restricted to patients experiencing an ischemic or bleeding event within 365 days after discharge. Cox regression was used to estimate crude and adjusted HRs for mortality associated with an ischemic vs bleeding event. In this analysis, patients were censored at death, 365 days after an ischemic or bleeding event or at the end of study period (31 December 2017). The model was adjusted for the same variables as in the first primary analysis described above, with the addition of the variable 'time-to-ischemic-or-bleeding-event'.

To assess whether the relative mortality risk of an ischemic vs bleeding event had changed over the past two decades, data from January 1997 through December 2017 were used. Three time-periods representing different treatment paradigms were created: 1997–2000 (before routine PCI and DAPT), 2001–2011 (when routine PCI and DAPT were implemented) and 2012 –2017 (contemporary period with more frequent use of the potent $P2Y_{12}$ inhibitors). Cox regression was used to estimate crude and adjusted HRs for mortality associated with ischemic vs bleeding events among patients who experienced an ischemic or bleeding event within 365 days after discharge. This model was adjusted for the same variables as in the first primary analysis described above, including the variable 'time-to-ischemic-or-bleeding-event'. Effect modification by time-period was assessed using an interaction term between time-period and event.

Missing data
In the primary analysis population of patients discharged from 2012–2017, the proportion of missing data for variables included in the Cox model was negligible and, according to the inclusion criteria, patients missing any of these variables were excluded (zero missing for all variables but STEMI (n=1/<0.1%) and discharge medication (n=16-51/< 0.1 %).
The proportion of missing data was higher for laboratory variables (haemoglobin and eGFR) and smoking status, neither of which were included in the Cox models.

Sensitivity analysis
To investigate the potential influence of haemoglobin, estimated glomerular filtration rate (eGFR) and smoking status on the aHRs, a sensitivity analysis was performed in which only patients with data available on these additional variables were included. In this complete case population, the primary analyses were performed with and without additional adjustment for these variables.

All statistical analyses were performed in STATA version 15 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

3.4 ETHICAL CONSIDERATIONS

Studies I–IV were approved by the Regional Ethics Committee in Stockholm (2012/60-13/2). According to Swedish law no informed consent is needed for large scale registry-based cohort studies. All patients are informed that they are included in a national quality register and that they have the right to opt out. Potential harm to the participant includes the risk of integrity breach, but given our pseudonymised data, large study sample sizes and the low-granularity data of the registers, any participant's identity is unlikely to be revealed.

4 RESULTS

4.1 STUDY I: BLEEDING TRENDS

From January 1995 to May 2018, 371 431 patients were enrolled with maximum one admission per two-year period. The median interquartile range (IQR) age was 73 (63-80) years, 35.8% were female, 33.9% presented with STEMI, 24.7 % with diabetes mellitus and 5.8% with previous bleeding. Over the study period, only minor fluctuations were observed regarding age and sex. Due to a new definition of MI in 2001, the proportion of STEMI changed from approximately 40% in the first three two-year periods (1995-2000) to 33–34% in the remaining two-year periods (2001-2018). Hypertension and previous bleeding doubled from 35.3% to 66.9% and 3.6% to 6.5%, respectively, previous cancer within 3 years more than doubled from 1.5% to 3.4% and previous PCI increased from 2.5% to 20.7%. Pulmonary rales on admission decreased from 36.8% to 8.9%. Antithrombotic treatment on admission changed from 33.6% SAPT with aspirin and 4.5% OAC with warfarin to 29.9% SAPT, 3.5% DAPT and 9.8% OAC whereof 5.2% NOAC. Treatment with statins and RAAS blockade on admission increased from 4.5% to 32.7% and 13.3% to 41% respectively, while betablocker treatment increased only slightly from 31.7% to 37.3% (Table 9).

In-hospital treatment and antithrombotic treatment at discharge

There were major changes in in-hospital treatment during the study period. Invasive treatment with coronary angiography and PCI increased from 5–6% in 1995–1996 to 85.5% and 71% in 2017–2018, respectively. In patients with STEMI, thrombolysis was replaced by primary PCI and the rate of any reperfusion for STEMI increased from 65% to 85% over the study period. Treatment with GPIIb/IIIa blocker first increased to a peak of 30% in 2005–2006 then declined to <5% from 2015 and onwards. Radial access started to increase in 2005 and reached over 70% in 2018. Dual antiplatelet therapy at discharge increased rapidly from 1999–2000 to a plateau at nearly 80% from 2011 and onwards. Combination therapy with antiplatelet and oral anticoagulant increased in the last three two-year periods, from 2013–2018, and seemingly continues to increase.

Bleeding trends in relation to in-hospital treatment.

In-hospital bleeding increased from 0.5% to a peak of 2% in 2005/2006 and then declined to a plateau around 1.3 % from 2011 to 2018. The increase of in-hospital bleeding in the first decade was seen in parallel with increased use of invasive treatment and GP IIb/IIIa blockers and the decrease in the last decade was seen in parallel with implementation of bleeding avoidance strategies, namely decreased use of GP IIb/IIIa blockers and transition to radial access (Figure 9a).

Out-of-hospital bleeding increased in a stepwise fashion from 2.5% to 3.5% in 2005/2006 and then to 4.8% in 2016. The increase was seen in parallel with increased use of DAPT in the first decade and increased use of potent $P2Y_{12}$ inhibitors and combination therapy in the last decade (Figure 9b).

Table 9. Baseline Characteristics (Study I)

	N=13979 1995-1996	N=23476 1997-1998	N=30021 1999-2000	N=34595 2001-2002	N=35393 2003-2004	N=35236 2005-2006	N= 36640 2007-2008	N=34889 2009-2010	N=36030 2011-2012	N=34448 2013-2014	N=34236 2015-2016	N=22488 2017-2018
Age	72 (63-79)	73(63-79)	73 (63-80)	74 (64-81)	74 (63-81)	74 (63-82)	73(62-81)	72 (63-81)	72(63-81)	72(63-81)	72(63-81)	72 (63-80)
Female	34.5%	35.2%	36.2%	37,4%%	37.2%	36.8%	36.8%	35.5%	35.6%	34.9%	34.3%	33.0%
Hypertension	35.3%	36.7%	38.8%	42.2%	46.3%	50.6%	56.2%	59.2%	62.2%	63.8%	64.9%	66.9%
Diabetes	21.7%	22.1%	22.9%	24.0%	24.0%	24.5%	24.8%	24.8%	25.4%	26.3%	26.9%	27.2%
Previous MI	29.4%	29.6%	28.6%	29.6%	29.2%	28.3%	27.7%	27.9%	27.2%	26.8%	27.4%	26.9%
Previous PCI	2.5%	3.5%	4.3%	5.6%	7.1%	9.4%	11.9%	14.9%	16.1%	17.7%	19.8%	20.7%
Previous CABG	4.2%	5.0%	6.0%	7.2%	7.9%	8.7%	8.8%	9.6%	9.4%	9.2%	8.4%	7.8%
Previous HF	27.1%	26.1%	25.9%	27.5%	26.7%	25.8%	23.4%	22.6%	21.9%	20.6%	20.0%	18.6%
Previous Stroke	10.0%	11.1%	11.8%	12.8%	12.7%	15.1%	14.5%	14.0%	14.1%	13.3%	12.9%	12.2%
Previous LEAD	5.6%	5.7%	5.9%	6.4%	6.4%	6.3%	6.1%	6.1%	6.4%	6.7%	6.3%	6.2%
Previous Bleeding	3.6%	4.3%	4.5%	5.3%	5.6%	6.1%	6.1%	6.3%	6.7%	6.6%	6.7%	6.5%
Previous COPD	3.8%	4.3%	5.1%	6.1%	6.1%	6.8%	7.1%	7.6%	7.8%	8.2%	8.3%	7.3%
Cancer (within 3 years)	1.5%	1.6%	1.7%	1.9%	2.1%	2.4%	2.7%	3.2%	3.5%	3.9%	3.7%	3.4%
Atrial fibrillation on admission	11.2%	12.0%	12.4%	13.4%	12.8%	12.8%	12.2%	11.3%	11.1%	10.8%	10.3%	9.5%
STEMI	39.8%	40.3%	38.2%	33.7%	32.4%	32.0%	31.7%	33.2%	32.0%	32.5%	32.8%	34.7%
Pulmonary rales on admission	36.8%	32.3%	29.5%	27.2%	23.2%	18.1%	15.2%	12.8%	11.3%	10.1%	10.0%	8.9%
SAPT on admission	33.6%	38.0%	40.2%	42.6%	40.6%	39.5%	37.9%	37.1%	36.1%	34.9%	32.6%	29.9%
DAPT on admission	0.0%	0.1%	0.3%	1.2%	3.3%	4.5%	4.9%	4.9%	4.8%	4.3%	3.8%	3.5%
OAC on admssion	4.5%	4.5%	4.6%	5.3%	5.2%	5.3%	5.6%	5.4%	5.6%	6.9%	8.7%	9.8%
Warfarin on admission	4.5%	4.5%	4.6%	5.3%	5.2%	5.3%	5.6%	5.4%	5.5%	6.4%	6.2%	4.6%
NOAC on admission	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.5%	2.6%	5.2%
Betablocker on admission	31.7%	32.9%	35.9%	39.3%	40.8%	41.0%	41.0%	40.0%	39.5%	38.9%	38.2%	37.3%
ACEi/ARB on admission	13.3%	15.9%	17.0%	21.2%	24.5%	28.5%	33.0%	35.4%	37.5%	38.9%	40.2%	41.0%
Statin on admission	4.5%	7.8%	11.8%	17.4%	20.8%	24.6%	28.4%	31.0%	31.8%	30.8%	31.5%	32.7%
eGFR ml/min	0.0%	0.0%	0.0%	65 (48-80)	67 (49-84)	71 (52-87)	73(53-89)	74 (54-89)	75 (55-90)	75 (55-90)	76(56-90)	76 (57-90)
eGFR<60ml/min	0.0%	0.0%	0.0%	43.5%	39.3%	35.1%	32.5%	31.6%	30.2%	30.4%	29.3%	28.0%

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, DAPT: dual antiplatelet therapy, eGFR: estimated glomerular filtration rate, HF: heart failure, IQR: interquartile range, LEAD: lower extremity artery disease MI: myocardial infarction, NOAC: non-vitamin K antagonist oral anticoagulant, OAC: oral anticoagulant, PCI: percutaneous coronary intervention, SAPT: single antiplatelet therapy, STEMI: ST-segment elevation myocardial infarction

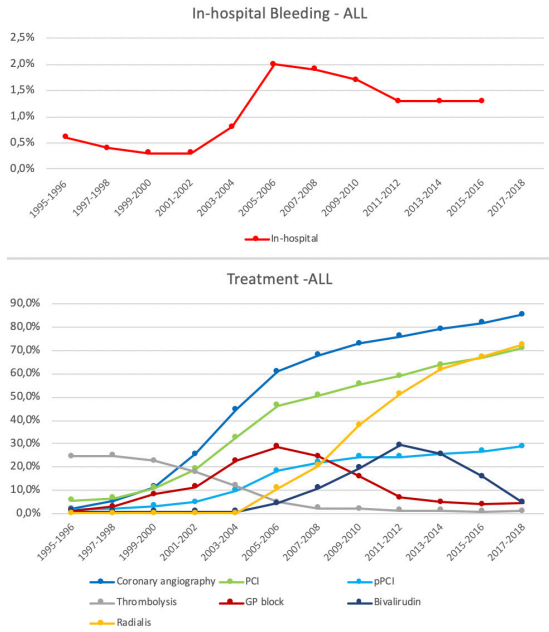


Figure 9a. In-hospital bleeding (upper panel in red) parallel to invasive and intravenous antithrombotic treatment (lower panel)
GP block: glycoprotein IIb/IIIa blocker, PCI: percutaneous coronary intervention, pPCI primary percutaneous coronary intervention

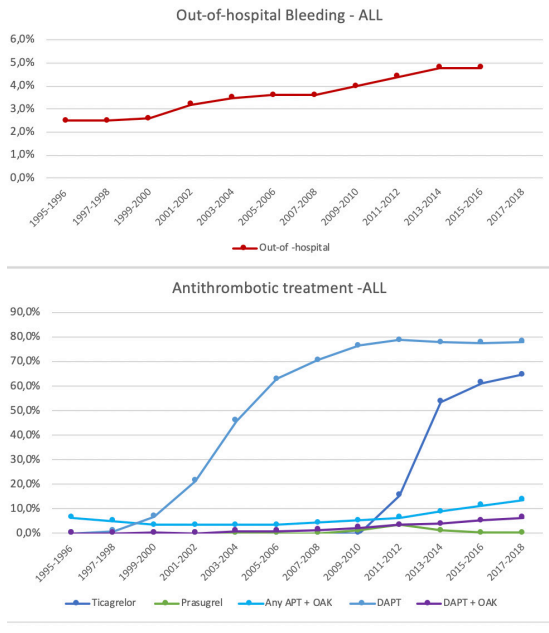


Figure 9b. Out-of-hospital bleeding (upper panel in dark red) and oral antithrombotic treatment (lower panel)
APT: antiplatelet therapy, DAPT: dual antiplatelet therapy, OAC: oral anticoagulant

Bleeding trends in relation to ischemic outcomes

While in-hospital bleeding increased by 0.8% per cent units (from 0.5% to 1.3%) from 1995–2016, in-hospital MI decreased by 2.2 % per cent units (from 2.8% to 0.6%) from 1997–2016. Out-of-hospital bleeding increased by 2.3% per cent units (from 2.5% to 4.8%) from 1995–2016, out-of-hospital MI decreased by 5.5% per cent units (from 12.6% to 7.1%) 1997–2016. MI, stroke and CV death events added decreased by 12.4 per cent units (from 27.5% to 15.1%). (Figure 10)

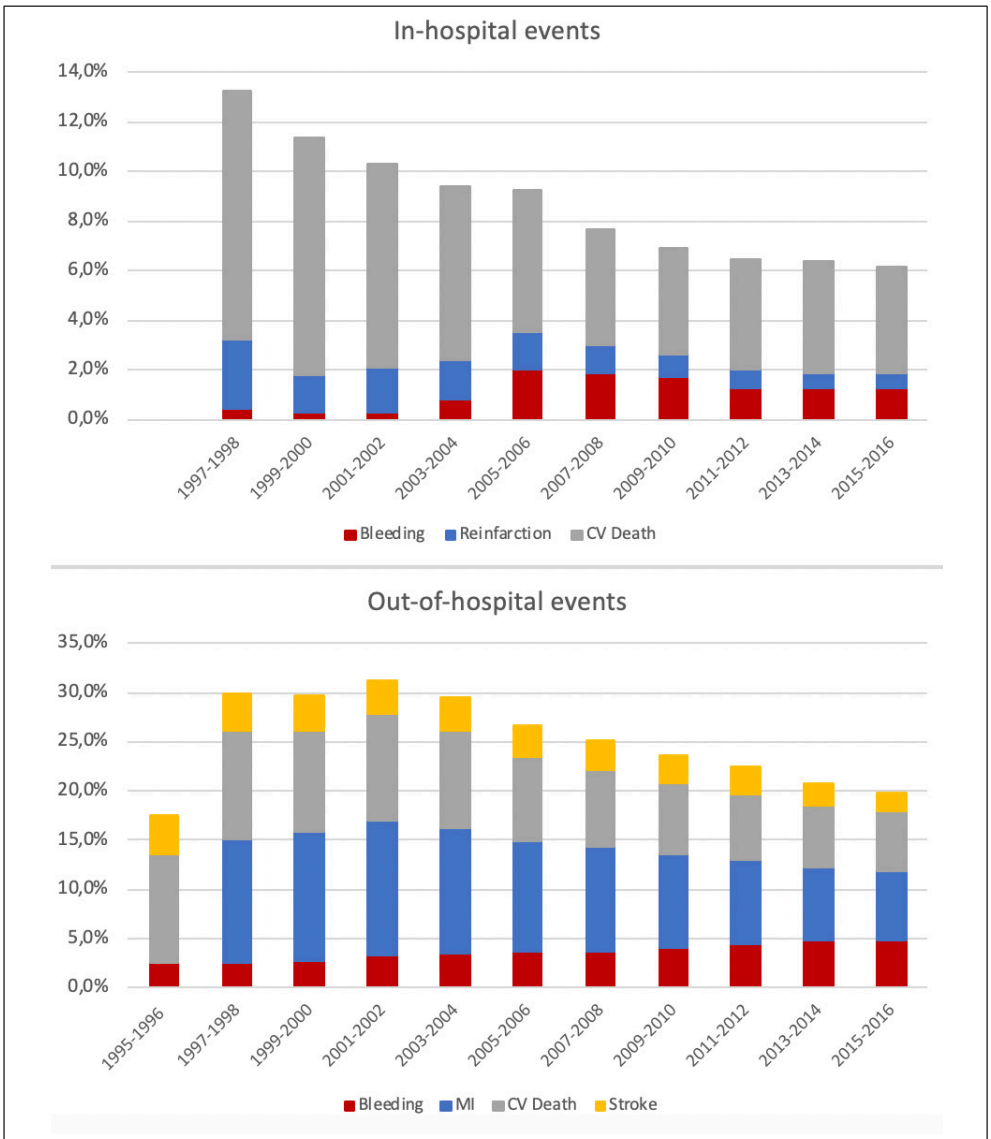


Figure 10. In-hospital events, bleeding, reinfarction and cardiovascular (CV) death added (upper panel). Out-of-hospital events, bleeding, recurrent myocardial infarction (MI), CV death and stroke added (lower panel).

4.2 STUDY II: BLEEDING RISK SCORE

From January 2009 to October 2014, 97 597 patients with first-admission MI enrolled in the SWEDEHEART registry were included. Major bleeding occurred in 1 356 (1.4%) patients, whereof 50 (0.1%) were fatal, 114 (0.1%) were intracerebral and 1 192 (1.2%) were bleeding events requiring surgery or blood transfusion. Compared with patients without bleeding events, patients with bleeding events were older (77 vs 72 years), more often female (46% vs 36%), had a higher burden of comorbidities and were more often on antithrombotic treatment on admission (Table 10). Patients with a bleeding event were less likely to receive invasive treatment (coronary angiography 56.9% vs 77.2% and PCI 43.9% vs 60.3%) and more likely to experience in-hospital complications, with a three-fold incidence of new onset atrial fibrillation, cardiac arrest and death, and a four- to five-fold incidence of re-infarction and cardiogenic shock in-hospital.

The full model with 23 predictors and 8 interaction terms had a C-index of 0.81 (95% confidence interval (CI) 0.80-0.82). The approximated model, the SWEDEHEART score, with 5 variables (haemoglobin, age, sex, creatinine and C-reactive protein) and one interaction term (haemoglobin and sex), represented 92.7% of the full model and had a C-index of 0.80 (95% CI:0.79-0.81). Internal-external temporal validation yielded a similar C-index indicating temporal stability. Due to poor calibration, the ACTION and CRUSADE scores were recalibrated. The SWEDEHEART score and the recalibrated ACTION and CRUSADE scores showed similar good calibration between bleeding probabilities of 1–4%. Below 1% and above 4% the SWEDEHEART score was superior. The recalibrated ACTION and CRUSADE scores had a *C*-index of 0.73 (95% CI: 0.72-0.74) and 0.72 (95% CI 0.71-0.74) respectively. In the subgroups of female, elderly (>75 years), STEMI/NSTEMI, non-invasively managed, patients treated with OAC or with chronic kidney disease (CKD) (eGFR < 60 ml/min), the SWEDEHEART score achieved consistently higher C-index than the recalibrated ACTION and CRUSADE scores. The recalibrated CRUSADE score performed especially poorly in the subgroup of patients managed non-invasively with a C-index of 0.59 (95% CI 0.57-0.62) (Table 11).

4.3 STUDY III: UPPER GASTROINTESTINAL BLEEDING

Between January 2007 and June 2016, 149 447 patients with acute MI discharged alive on antithrombotic treatment were included. During 365 days of follow up, UGIB occurred in 2 230 patients (cumulative incidence 1.5 % and incidence rate 1 492/100 000 person years). As compared with patients without an UGIB, patients with an UGIB event were older (77 vs 71 years), more often female (38.6% vs 34.8%), more often previous or current smokers (59.5% vs 54.5%) and had more comorbidities including more frequent previous UGIB (7.6% vs 2.0%) and more frequent treatment with OAC (12.9% vs 8.5%), steroids (6.1% vs 3.5%), NSAIDs (2.2% vs 1.7%) and gastroprotective treatment (41.0% vs 28.3%) (Table 12). Experiencing an UGIB was associated with an increased risk of MACE (adjusted HR 2.00, 95% CI 21.81-2.20), all-cause death (adjusted HR 2.86, 95% CI 2.58-3-16) and stroke (adjusted HR 1.80, 95% CI 1.32-2.45) but was not significantly associated with MI (adjusted HR 1.17, 95% CI 0.97-1.42). The top six predictors of UGIB in the logistic regression model were haemoglobin, age, previous UGIB, smoking status, antithrombotic treatment and gastroprotective treatment. Smoking status included three categories, never, former, and active smoker. With never smoking as reference, former and active smoker were associated

with increased risk of UGIB. Antithrombotic treatment included five categories, SAPT, OAC alone, DAPT with clopidogrel, DAPT with ticagrelor/prasugrel and combination therapy (APT+OAC). With SAPT as reference, combination therapy, DAPT with ticagrelor/prasugrel and OAC alone were associated with increased risk of UGIB while there was no significant association for DAPT with clopidogrel (Table 13). The top six predictors of UGIB identified by the best performing ML model (random forest) were haemoglobin, age, systolic blood pressure, blood glucose, gastroprotective treatment and corticosteroid treatment (Figure 11).

Table 10. Baseline Characteristics (Study II)

	No major bleed (n = 96241)	**Major Bleed** (n = 1356)
Demography		
Age (years)	72 (63-81)	77 (69-83)
Weight (kg)	78 (69-90)	74 (64-85)
Female %	33779 (35.1)	621 (45.8)
Medical History		
Hypertension %	54923 (57.1)	916 (67.6)
Diabetes Mellitus	23172 (24.1%)	411 (30.3%)
Previous MI	23268 (24.2%)	398 (29.4%)
Previous PCI	13295 (13.8%)	200 (14.7%)
Previous CABG	8286 (8.6%)	145 (10.7%)
Previous PAD	5641 (5.9%)	157 (11.6%)
Previous Stroke	11498 (11.9%)	259 (19.1%)
Chronic Heart Failure	13647 (14.2%)	337 (24.9%)
Previous bleeding	5918 (6.1%)	170 (12.5%)
COPD	6986 (7.3%)	142 (10.5%)
Previous cancer	3176 (3.3%)	91 (6.7%)
Medication on admission		
Betablocker	35771 (37.2%)	633 (46.7%)
RAS blockade	59934 (62.3)	739 (54.5)
Calcium antagonist	18368 (19.1%)	324 (23.9%)
Digoxin	2052 (2.1%)	48 (3.5%)
Statins	28056 (29.2%)	481 (35.5%)
Diuretics	23301 (24.2%)	500 (36.9%)
Aspirin	35389 (36.8%)	602 (44.4%)
DAPT	3933 (4.1%)	86 (6.3%)
OAC	5417 (5.6%)	108 (8.0%)
Presentation		
CPR before hospital	1708 (1.8%)	37 (2.7%)
Atrial fibrillation	10262 (10.7%)	213 (15.7%)
Heartrate (beats per min)	79 (66-93)	86 (70-100)
Systolic blood pressure (mmHg)	147 (130-167)	140 (120-160)
Symptoms or signs of HF	11312 (11.8%)	288 (21.2%)
Shock	1214 (1.3%)	36 (2.7%)
ST-elevation	31991 (33.2%)	457 (33.7%)
Laboratory data on admission		
Hemoglobin (g/L)	139 (127-149)	116 (101-131)
Anemia WHO definition	19729 (20.5%)	818 (60.3%)
Creatinine (mmol/l)	84 (70-103)	99 (77-137)
eGFR by CKD-EPI (ml/min)	74 (55-89)	56 (37-76)
CRP	5 (3-15)	17 (5-66)

Values are median with IQR or n %.

CABG: coronary artery bypass graft, CPR: Cardiopulmonary resuscitation CRP: C-Reactive protein, COPD: chronic obstructive pulmonary disease, DAPT: dual antiplatelet therapy, HF: heart failure, MI: myocardial infarction, OAC: Oral anticoagulant, PCI: percutaneous coronary intervention, RAS: renin angiotensin system

Table 11. C-index (Study II)

				C-index		
		N	Bleeds	ACTION	CRUSADE	SWEDEHEART
Overall		97597	1356	0.73 (0.72-0.74)	0.72 (0.71-0.74)	0.80 (0.79-0.81) [0.80]
Sex	Female	34400	621	0.68 (0.66-0.70)	0.66 (0.64-0.68)	0.74 (0.72-0.76) [0.74]
	Male	63197	735	0.76 (0.74-0.78)	0.76 (0.74-0.77)	0.83 (0.81-0.84) [0.82]
	Missing	0				
Age	< 75	56002	572	0.77 (0.75-0.79)	0.76 (0.74-0.78)	0.81 (0.80-0.83) [0.81]
	≥ 75	41594	784	0.67 (0.65-0.69)	0.65 (0.64-0.67)	0.76 (0.75-0.78) [0.76]
	Missing	1				
Anticoagulation	No	91204	1228	0.73 (0.72-0.75)	0.72 (0.71-0.74)	0.80 (0.79-0.81) [0.80]
	Yes	5525	108	0.71 (0.67-0.76)	0.70 (0.65-0.74)	0.77 (0.73-0.82) [0.77]
	Missing	868				
Angiography	No	22541	584	0.63 (0.61-0.65)	0.59 (0.57-0.62)	0.76 (0.74-0.79) [0.76]
	Yes	75056	772	0.75 (0.73-0.77)	0.74 (0.73-0.76)	0.79 (0.78-0.81) [0.79]
	Missing	0				
STEMI	No	64730	896	0.74 (0.73-0.76)	0.72 (0.71-0.74)	0.82 (0.80-0.83) [0.81]
	Yes	31304	447	0.74 (0.72-0.76)	0.73 (0.71-0.75)	0.77 (0.75-0.79) [0.77]
	Missing	1563				
eGFR	< 60	28236	715	0.66 (0.65-0.68)	0.65 (0.63-0.67)	0.75 (0.73-0.77) [0.75]
	≥ 60	63999	578	0.73 (0.71-0.75)	0.71 (0.69-0.73)	0.79 (0.77-0.81) [0.78]
	Missing	5362				

eGFR: estimated glomerular filtration rate, STEMI: ST-elevation myocardial infarction

Table 12. Baseline Characteristics divided by UGIB status (Study III)

	No UGIB n = 147 217	**UGIB n = 2230**
Demographics		
Age year median (IQR)	71 (62 - 80)	77 (68 - 83)
Female Sex n (%)	51 292 (34.8)	861 (38.6)
Weight kg median (IQR)	78 (69 - 89)	76 (65 - 86)
STEMI n (%)	48 973 (33.3)	662 (29.7)
Smoking status: never n (%)	66 998 (45.5)	904 (40.5)
Former n (%)	49 590 (33.7)	825 (37.0)
Active n (%)	30 629 (20.8)	501 (22.5)
Medical history		
Hypertension n (%)	82 397 (56.0)	1495 (67.0)
Diabetes n (%)	35 769 (24.3)	617 (27.7)
Previous MI n (%)	32 783 (22.3)	536 (24.0)
Previous PCI n (%)	17 707 (12.0)	265 (11.9)
Previous CABG n (%)	11 824 (8.0)	185 (8.3)
Previous HF n (%)	14 802 (10.1)	354 (15.9)
Previous stroke n (%)	17 070 (11.6)	340 (15.2)
Previous LEAD n (%)	8117 (5.5)	211 (9.5)
Previous UGIB n (%)	2951 (2.0)	170 (7.6)
Previous Cancer n (%)	4381 (3.0)	126 (5.7)
Previous COPD n (%)	10 688 (7.3)	276 (12.4)
Laboratory parameters		
Haemoglobin g/L median (IQR)	138 (126 - 149)	129.0 (117 - 142)
Creatinine mmol/L median (IQR)	84.0 (70.0 – 102.0)	90.0 (73.0 – 117.6)
CRP mg/L median (IQR)	6.0 (3.0 – 17.9)	9.0 (4.0 – 29.0)
Invasive treatment in-hospital		
PCI n (%)	90 630 (61.6)	1252 (56.1)
CABG n (%)	6093 (4.1)	73 (3.3)
Medication at discharge		
Gastroprotective treatment n (%)	41 617 (28.3)	914 (41.0)
Corticosteroid n (%)	5182 (3.5)	137 (6.1)
NSAID n (%)	2499 (1.7)	49 (2.2)
Antithrombotic treatment		
SAPT n (%)	24 180 (16.6)	421 (19.2)
OAC alone n (%)	3137 (2.2)	80 (3.6)
DAPT clopidogrel n (%)	73 730 (50.6)	940 (42.8)
DAPT ticagrelor/prasugrel n (%)	35 381 (24.3)	552 (25.1)
Combination therapy (APT+OAC) n (%)	9229 (6.3)	205 (9.3)

APT: antiplatelet therapy, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, DAPT: dual antiplatelet therapy, DM: diabetes mellitus, HF: heart failure, IQR: interquartile range, LEAD: lower extremity artery disease MI: myocardial infarction, NSAID: non-steroidal anti-inflammatory drug, OAC: oral anticoagulant, PCI: percutaneous coronary intervention, SAPT: single antiplatelet therapy, STEMI: ST-segment elevation myocardial infarction, UGIB: upper gastrointestinal bleeding.

Table 13. Logistic regression top predictors of upper gastrointestinal bleeding

Predictor	Odds ratio	Wald χ^2	Significance
Haemoglobin	NA*	241	0.000
Age	NA*	122.3	0.000
Previous UGIB	2.58	117.6	0.000
Smoking status		90.8	
Never	ref		
Active	1.84		0.000
Former	1.29		0.000
Antithrombotic treatment		61.0	
SAPT	ref		
Combination therapy (APT+OAC)	1.56		0.000
OAC alone	1.52		0.001
DAPT ticagrelor/prasugrel	1.41		0.000
DAPT clopidogrel	1.03		0.711
Gastro protective treatment	1.33	37.4	0.000

APT antiplatelet therapy, DAPT: dual antiplatelet therapy, OAC: oral anticoagulant, SAPT single antiplatelet therapy, UGIB: upper gastrointestinal bleeding

The six most important predictors of UGIB with corresponding Wald χ^2 values, odds ratios and p-values. Smoking status has three categories and antithrombotic treatment has five categories.
*continuous variables in restricted cubic splines therefore no single OR is given

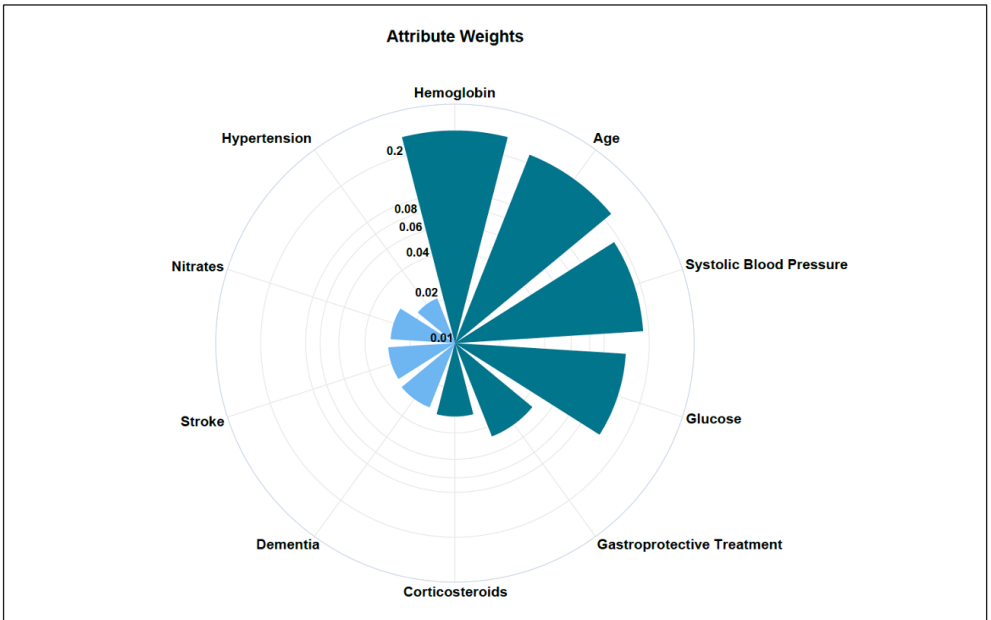


Figure 11. For each of the 10 variables, a variable importance weight measure is presented, which is proportional to the increase in the misclassification rate of the random forest, if the variable was removed from the model. Higher importance weights indicate that the variable is more important when predicting UGIB events.

4.4 STUDY IV: ASSOCIATED MORTALITY OF ISCHEMIC VS BLEEDING EVENTS

Among 86 736 patients with MI discharged alive on antithrombotic treatment between January 2012 and December 2017 (4 039 patients experienced a first ischemic event (incidence rate 5.7/100 person years) and 3 399 patients experienced a first bleeding event (incidence rate 4.8/100 person years). 2 863 of the ischemic events were recurrent MI and 1 176 were ischemic stroke. The median (IQR) time to first ischemic and bleeding event was 102 days (38 to 124) and 95 days (30 to 207), respectively.
Patients with an ischemic or bleeding event were older (79 or 76 vs 70 years), had more comorbidities and were more often treated with OAC and less often treated with DAPT and ticagrelor that patients without any event. Patients with ischemic event were older (79 vs 76 years) and had more cardiovascular risk factors than patients with bleeding event while those with bleeding events were more likely to have experienced a previous bleeding event (11.7% vs 9.6%) and were more often treated with triple therapy (6.4% vs 4.4%) and potent $P2Y_{12}$ inhibitors (52% vs 36%) than patients with ischemic events (Table 14).

In the analyses comparing the risk of mortality after an ischemic and bleeding event vs no event, 9 671 patients died during follow-up. 1 292 died after a first ischemic event (incidence rate 46.2 deaths/100 person years), 715 died after a first bleeding event (incidence rate 27.1 deaths/100 person years) and 7 664 died after no event (incidence rate 6.2 deaths /100 person years). As compared with no event, both ischemic adjusted HR (95% CI) 4.16 (3.91 to 4.43) and bleeding events adjusted HR (95% CI) 3.43 (3.17 to 3.71) were associated with increased risk of death.

When the analysis was restricted to patients experiencing a first ischemic or bleeding event, ischemic event was associated with higher risk of death adjusted HR (95% CI) 1.27 (1.15 to 1.40) (Table 15).

In the analysis of relative mortality risk over three time-periods between 1997 and 2017, the incidence rate of ischemic and bleeding events was 11.6/100 person years and 2.5/100 person years, respectively in the first time-period (1997–2000), 9.6/100 person years and 3.5/100 person years, respectively in the second time-period (2001–2011) and 5.7/100 person years and 4.8/100 person years, respectively in the last time-period (2012-2017). The adjusted HR (95%CI) for mortality after an ischemic vs bleeding event was 1.17 (1.02 to 1.35) in 1997–2000, 1.18 (1.11 to 1.27) in 2001–2011 and 1.27 (1.15 to 1.40) in 2012-2017 (Table 16) There was no significant interaction between ischemic vs bleeding event and time-period $p \geq 0.646$).

Among the 77 293 patients (89.1% of the total population included in the primary analyses) with data available on smoking status, hemoglobin and eGFR, additional adjustment for these variables did not substantially affect the results.

Table 14. Characteristics at index myocardial infarction of patients discharged in 2012-2017 (Study IV)

		By event status during 365 days after discharge		
	ALL	**Ischemic event**	**Bleeding event**	**No event**
	N = 86 736	N = 4 039	N =3 399	N =79 298
Demographics n/%				
Age median years (IQR)	71 (62-80)	79 (70–86)	76 (68–83)	70 (62–79)
Female sex	29 449 / 34.0	1 666 / 42.2	1 093 / 32.2	26 690 / 33.7
STEMI	29 291 / 33.8	879 / 21.7	1 061 / 31.2	27 351 / 34.5
Medical history n/%				
Hypertension	51 546 / 59.4	3 150 / 78.0	2 290/ 67.4	46 106 / 58.1
Diabetes mellitus	21 030/ 24.3	1 568/ 38.1	972 / 28.6	18 490 / 23.3
Smoking status* never	34 408 / 42.0	1 697/ 46.5	1 276/ 40.5	31 435 / 41.9
former	29 841 / 36.4	1 391 / 38.1	1 219/ 38.7	27 231/ 36.3
active	17 631/ 21.	559 / 15.3	657 / 20.8	16 415 / 21.8
Previous MI	18 332 21.1	1 834 / 45.4	842 / 24.8	15 656 / 19.7
Previous PCI	12 387/ 14.3	1 085 / 26.9	533 / 15.7	10 769 / 13.6
Previous CABG	6 094 / 7.0	678 / 16.8	270 // 7.9	5 146 / 6.5
Previous stroke	8 870 / 10.2	895 22.2	499 / 14.7	7 476 / 9.4
Previous bleeding	4 944/ 5.7	386 / 9.6	396 / 11.7	4 162 / 5.3
Previous HF	8 001 / 9.2	912 / 22.6	517 / 15.2	6 572 / 8.3
Previous cancer	2 963 / 3.4	238 / 5.9	244 / 7.2	2 481 / 3.1
Previous LEAD	4 788 / 5.5	490/ 12.1	315 / 9.3	3 983 / 5.0
COPD	6 575 / 7.6	419 / 10.4	395 / 11.6	5 761 / 7.3
Previous Renal failure	3 931/ 4.5	508 / 12.6	311/ 9.2	3 112 / 3.9
Invasive treatment in-hospital n/%				
Coronary Angiography	73 190 / 84.4	2 398/ 59.4	2 680/ 78.9	68 112 / 85.9
PCI	59 802/ 69.0	1 763/ 43.7	2 232/ 65.7	55 807 / 70.4
CABG	4 489 / 5.2	116 / 2.9	131/ 3.9	4 242 / 5.4
Laboratory variables*				
Hemoglobin g/L median (IQR)	139 (127–150)	131 (119–143)	133 (119–145)	140 (128–150)
Creatinine µmol/L median (IQR)	82 (69–99)	91 (73–121)	86 (71–112)	81 (68–98)
eGFR ml/min median (IQR)	78 (59–91)	62 (43–81)	69 (49–86)	79 (60–91)
Discharge medication n/%				
Antithrombotic therapy				
Aspirin **	80 772 / 93.1	3 597/ 89.1	3 111 / 91.5	74 298 / 93.4
Ticagrelor **	48 760 / 56.2	1 434 / 35.5	1 732 / 51.0	45 594 / 57.5
Clopidogrel**, a	23 682 / 27.3	1 697/ 42.0	1040 / 30.6	20 944 / 26.4
Prasugrel **	890 / 1.0	22 / 0.5	35 / 1.0	833 / 1.1
Warfarin **	7 023 / 8.1	440 / 10.9	403 / 11.9	6 180 / 7.8
NOAC **	2 912 / 3.4	161 / 4.0	122 / 3.6	2 630 / 3.3
SAPT	11 461 / 13.2	770 / 19.1	479 / 14.1	10 212 / 12.9
DAPT	69 217 / 79.8	2 847 / 70.5	2 613 / 76.9	63 757/ 80.4
Dual (SAPT+APT)	4 280 / 4.9	286 / 7.1	213 / 6.3	3 709 / 4.7
Triple (DAPT+APT)	3 877/ 4.5	179/ 4.4	217 / 6.4	3 481 / 4.4
Other medication				
Beta blocker	76 369 / 88.1	3 565 / 88.3	2 951 / 86.8	69 853 / 88.1
Calcium blocker	15 555/ 17.9	1 082 / 26.8	697 / 20.5	13 776 / 17.4
Digoxin	1 143 / 1.7	124 / 3.1	84/ 2.5	1 235/ 1.6
Diuretics	22 620/ 26.1	1 882 / 46.6	1 212 / 35.7	19 528/ 24.6
Statins	77 958 / 89.9	3 275 / 811	2 959 / 87.1	79 298 / 90.5

APT: antiplatelet therapy, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, DAPT: dual antiplatelet therapy, DM: diabetes mellitus, eGFR: estimated glomerular filtration rate, HF: heart failure, IQR: interquartile range, LEAD: lower extremity artery disease MI: myocardial infarction, NOAC: non-vitamin K antagonist oral anticoagulant, OAC: oral anticoagulant, PCI: percutaneous coronary intervention, SAPT: single antiplatelet therapy, STEMI: ST-segment elevation myocardial infarction

*Smoking status and the laboratory variables were not included in the Cox regression models in the primary analyses and used only in a sensitivity analysis.

N (% of total population) with available data was 81 880 (94.4%) for smoking status; 81 878 (94.4%) for hemoglobin and 83 575 (96.4%) for creatinine.

**Not included in the Cox regression

a: ticlopidine was included in the clopidogrel group

Table 15. Crude and adjusted HRs for death after an ischemic and bleeding event among patients discharged after an MI in 2012-2017

					Event vs no event		Ischemic event vs bleeding event	
	N events	Events per 100 person-years	N deaths	Deaths per 100 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI) **
No event	-	-	7 664	6.2	Ref.	Ref.	N/A	N/A
Ischemic event	4 039	5.7	1 292	46.2	9.01 (8.48-9.58)	4.16 (3.91- 4.43)	1.65 (1.51-1.82)	HR 1.27 (1.15 – 1.40)
Bleeding event	3 399	4.8	715	27.1	5.25 (4.86-5.68)	3.43 (3.17- 3.71)	Ref.	Ref.

* Adjusted for age, sex, year of discharge, STEMI, hypertension, diabetes, previous MI, previous PCI, previous CABG, previous stroke, previous bleeding, previous HF, previous cancer, previous LEAD, COPD, previous renal failure, coronary angiography, PCI or CABG, antithrombotic treatment strategy at discharge (SAPT, DAPT, dual, triple) and discharge medication (beta blocker, calcium blocker, digoxin, diuretics and statins).
** Adjusted for the same covariates listed above plus time from discharge to the event in days.
CI: confidence interval, HR: hazard ratio, MI: myocardial infarction

Table 16. Incidence rates of events and adjusted HRs for death after an ischemic vs bleeding event in three time periods from 1997-2017

Time period	**Ischemic events per 100 person years**	**Bleeding events per 100 person years**	**Deaths per 100 person years after ischemic event**	**Deaths per 100 person years after bleeding event**	**Adjusted HR (95% CI)* for death after ischemic vs bleeding event**
1997-2000	11.6	2.5	52.3	39.5	1.17 (1.02 -1.35)
2001-2011	9.6	3.5	49.5	31.8	1.18 (1.11-1.27)
2012-2017	5.7	4.8	46.2	27.1	1.27 (1.15-1.40)

CI: confidence interval, HR: hazard ratio
** Adjusted for the same covariates listed above under Table 15 plus time from discharge to the event in days.

5 DISCUSSION

In Study I, we described the time trends of bleeding events parallel to treatment changes and ischemic outcomes over the past two decades and the main findings were: Both in-hospital and out-of-hospital bleeding events were doubled, in parallel with increased use of invasive revascularisation and more intensive antithrombotic treatment. Meanwhile ischemic events, including mortality, were nearly halved with a substantially greater absolute decrease than the absolute increase in bleeding events.
The pattern of bleeding time trends was different for in-hospital and out-of-hospital bleeding events, perhaps reflecting the changes in treatment. While out-of-hospital bleeding increased during the whole study period in a stepwise fashion, in-hospital bleeding first increased, then declined to finally end at a higher level than in the beginning of the study period.

Comparison of our results with the bleeding incidences reported in previous studies is complicated, since the incidence of bleeding varies depending on the bleeding definition used, how bleeding was reported, the characteristics of the study population and how they were treated, and when the study was performed (also listed in the introduction section Bleeding incidence).

Although interpretation of exact incidence numbers is difficult due the reasons mentioned above, some patterns can be observed. For example, the decline of in-hospital bleeding in the second decade was seen in parallel with implementation of bleeding avoidance strategies, with increased use of radial access and decreased use of GPIIb/IIIa blockers as was also shown in the British Cardiovascular Interventional Study from 2006–2013.[125]

The stepwise increase of out-of-hospital bleeding events was seen in parallel with the transition from aspirin alone to DAPT with clopidogrel and then to DAPT with a potent $P2Y_{12}$ inhibitor, mainly ticagrelor. In the CURE study[15], there was an absolute increase of major bleeding of 1% with DAPT using aspirin and clopidogrel as compared with aspirin alone, and in the TRITON TIMI-38 study[16] and the PLATO study[17] there was an absolute increase of major bleeding of 0.6% with potent DAPT using prasugrel or ticagrelor as compared with DAPT with clopidogrel.

In Study II, we developed and validated a new prediction model for in-hospital bleeding showing that in-hospital bleeding could be predicted with good accuracy using five baseline variables. As compared with the currently recommended CRUSADE score, our new model had higher discriminative capacity and showed more stable performance across different subgroups. One of the most important findings was that the CRUSADE and ACTION scores were poorly calibrated and were therefore recalibrated. Validation of a score must always evaluate both discrimination and calibration and, if needed, the score must be recalibrated before being used outside the derivation cohort.
Many prediction models have been derived but few have been successfully implemented. Whether a score is implemented or not does not seem to be mainly dependent on the performance of the score. For example, even though the $CHA_2DS\ VAS_2c$[97] score has shown only modest discriminative capacity[97,126], it is still one of the most clinically used risk scores for assessment of stroke embolic risk. The ability to derive a simple decision rule is probably one of the most important properties of a successful score in terms of implementation.

Another theoretically complicating factor is that a score gives the risk at group level but is applied at individual level, but this is how most evidence-based medicine is practiced.
Still, evidence that use of scores is better than clinical assessment alone is lacking. Personalised DAPT duration based on the DAPT score vs standard DAPT duration is being evaluated in the ongoing the PARTHOPENE study (NCT04135989) and the ABC (Age Biomarker Clinical) bleeding and stroke risk scores[96,127] are being prospectively evaluated in patients with atrial fibrillation in the ABC-AF study (NCT03753490).

Study III focused on one of the most common sources of spontaneous bleeding, UGIB, for which potential preventive measures exists. In relation to the bleeding incidence reported in Study I, UGIB constituted approximately one third of all post-discharge bleeding events (1.5% of approximately 4–5%). As previously described for major bleeding events, UGIB was associated with increased risk of mortality. UGIB was also associated with increased risk of stroke but not significantly associated with MI. When combining the results from the logistic regression and the best performing machine-learning model, the most important predictors of UGIB were haemoglobin, age, previous UGIB, smoking status, antithrombotic treatment, gastroprotective treatment, corticosteroid treatment, systolic blood pressure and blood glucose. While many of these predictors were already known to predict bleeding events, smoking status and blood glucose were perhaps surprising. Regarding smoking status, some data have indicated that Helicobacter pylori infection is more common in smokers[128] and could thus explain the link between smoking and UGIB events. The ongoing cluster randomised study on H. pylori eradication[54] will provide more clarity on the role of H. pylori infection and bleeding outcomes. In Study III, there was no aim to derive a new prediction model but only to identify the strongest predictors of UGIB. Both the logistic regression and the ML model performed modestly with respective C-indices of 0.67 and 0.73. There are several plausible explanations for this. First and perhaps most likely, we lacked some important predictors such as alcohol intake, known or previous peptic ulcer, dyspeptic disease or gastro-oesophageal reflux disease and H. Pylori infection status. Second, UGIB (or GI) bleedings may be more difficult to predict than bleedings in general. A recent study[129] used claims data to compare machine-learning models versus a modified HAS-BLED score to predict gastrointestinal bleeding among patients on either antiplatelets, OACs or both. Despite inclusion of predictor variables for alcoholism and H. pylori infection, their best performing machine-learning model had a C-index of only 0.67 (our best performing model had a C-index of 0.73). In Study II, we used logistic regression models to create a simplified five-item score which achieved a substantially higher C-index of 0.80 for prediction of in-hospital bleeding.

In the past decade, the dominant trend in cardiovascular medicine has been to recommend individualised treatment based on each patient's risk profile. To decide on duration and intensity of antithrombotic treatment, ischemic risk should be weighed against bleeding risk. Central to this trade-off is to understand the prognostic importance of ischemic and bleeding events. In Study IV, we assessed the incidence of recurrent ischemic events and bleeding events after a recent MI and the risk of mortality associated with these events.

It is known from previous studies that, with respect to associated mortality, MI vs different BARC bleeding scales separate at intracranial bleedings (BARC 3c). MI is worse than BARC 1, 2 and 3a and equal to BARC 3b bleeding, while BARC 3c bleeding is worse[26,107] but also

rarer than MI. Our study showed that, when comparing clinically relevant bleeding events vs a composite of MI and ischemic stroke, the latter was worse regarding both associated mortality and incidence.

Studies on associated outcomes after an event are complicated and highly susceptible to confounding bias yet final conclusions depend upon the severity of the compared events. Inclusion of ischemic stroke most likely increased the mortality risk of ischemic events as compared with the mortality risk of MI alone. Our bleeding definition included all bleeding events leading to or occurring during hospitalisation and as such included both major and minor bleeding events. While it is likely that the mortality risk associated with a bleeding event would be higher in analyses restricted to only severe bleeding events, such an outcome definition would also lead to a lower incidence rate of bleeding. This is important because, despite the use of a broader bleeding outcome, we found that the incidence of recurrent ischemic events was approximately 15 % higher than that of bleeding events. Furthermore, while many previous studies were based on mixed populations of patients undergoing PCI or selected low-risk patients from RCTs or included all events after the index PCI or MI, we included non-selected MI patients and restricted our exposure definitions to only post-discharge events.

When using risk-based strategies to guide treatment decisions, it is crucial to not only consider the relative mortality risks but also account for the incidence of the events of interest. To account for both the incidence and the measure of association, i.e., adjusted HR, the population attributable fraction (PAF) was calculated. The PAF was 10.1% for ischemic events and 5.2% for bleeding events, indicating that ischemic events may have a greater influence on mortality than bleeding events.

6 LIMITATIONS

Our studies have several limitations.
First, while the Swedish registries offers a unique data source of a nationwide population covering a long time span, and while validation studies have shown high accuracy regarding cardiovascular and bleeding events, there may be misclassification and underreporting of events.

Second, the bleeding definitions used were not standardised but customised to the data available in the registries. This does not affect internal validity but makes comparison with other studies more difficult.

Third (regarding Study I and secondary analyses in Study IV), despite using the same bleeding definitions throughout the study periods, we cannot exclude that registration patterns may have changed over this long time span.

Fourth, the lack of external validation of the SWEDEHEART score in other geographical regions outside Sweden and, perhaps more important, the lack of a score derived decision rule, are both limitations of Study II.

Fifth, in Study III, despite access to data concerning prescribed drugs, NSAIDs are sold over the counter in Sweden, and we might thus have underestimated actual intake.

Sixth (regarding Study IV), because ischemic and bleeding events are not interventions, it is not possible to define their causal effect on mortality[130]; as in previous studies, the estimates from our analyses should be considered as theoretical approximations of the relative importance of ischemic vs bleeding events with respect to mortality risk.

Seventh, although we adjusted our analyses for many covariates, there may be unmeasured confounders affecting both the risk of UGIB and MACE in Study III or ischemic vs bleeding events and mortality in Study IV. Finally, in Study IV, we only assessed and compared the risk of mortality associated with ischemic and bleeding events although these events may also be differentially associated with reductions in quality of life and long-term comorbidity.

7 FUTURE PERSPECTIVES

The first three paragraphs refer to the studies in this thesis while the remaining paragraphs refer to the research field on antithrombotic treatment and bleeding in general

7.1 Will the gap between bleeding and ischemic events continue to diminish?
There are concerns that post-discharge bleeding events will continue to increase. In the last decade, combination therapy with antiplatelets and OAC has increased year over year in Sweden[52]. This increase is likely driven by an ageing population and greater awareness of stroke embolic risk resulting in more frequent prescription of OACs (mainly NOACs). On the other hand, this could be counterbalanced by implementation of some of the bleeding reducing antithrombotic strategies previously mentioned.

Whether further improved stent platforms and intravascular imaging techniques together with better secondary prevention; new lipid-reducing drugs and lower LDL goals, SLGT-2 inhibitors and GLP-1 analogues, etc., will result in a continuous decrease of ischemic events is unclear. If post-discharge bleeding events continue to increase and ischemic events continue to decrease, then the gap between these events will diminish or disappear. There will be a future need to investigate the development of bleeding and ischemic trends to evaluate and improve implementation of strategies.

7.2 Bleeding risk assessment has become compulsory
Any clinician practicing guideline-directed medicine must assess bleeding and ischemic risk to decide upon antithrombotic strategy, either using a score or clinical judgement. Smartphone apps and scores incorporated in electronic medical records might be helpful to make this judgement, but it remains unclear whether scores are better than clinical judgment alone. More advanced statistic modelling using artificial intelligence might further improve the precision of risk-stratification tools but may be more difficult to interpret clinically as these models are more of "a black box"[131]. The addition of biomarkers can improve predictions[132], but the available biomarkers are perhaps not specific enough. Finding new and more specific biomarkers for prediction of bleeding and ischemic events is of interest. Furthermore, even models with good performance are far from perfect and must never replace but only aid the clinical judgement. Perhaps paradoxically, any given model's performance does not seem to be the most important reason for a score being implemented or not. Rather, new or updated prediction models should probably also focus on how to provide easy and clinically relevant decision rules.

7.3 Further investigation of specific gastrointestinal bleeding predictors
Our study indicated the existence of several predictors of upper gastrointestinal bleeding in addition to those currently well-known predictors of bleeding in general. Still, we lacked some predictors of predisposing gastrointestinal disease specifically. In a future study, it might be interesting to include variables such as previously known ulcer, dyspeptic or gastro-oesophageal reflux disease, H. pylori status and alcohol intake. Finally, it might be relevant to include stress level as a potential predictor of upper gastrointestinal bleeding even though this exposure is difficult to capture.

7.4 Further stretching the antithrombotic strategies to reduce bleeding

Bleeding outcomes will continue to be important, not only as the limiting factor for more intensive antithrombotic treatment but also as prognostically important outcomes. Many studies have investigated different antithrombotic strategies (Figure 6) to reduce bleeding with intention to improve overall outcomes. For most patients, the highest priority in these strategies must be not to decrease bleeding at the expense of increased ischemic events. (For some patients with extremely high bleeding risk, bleeding reduction might get higher priority than ischemic protection.) While shortening DAPT, (dropping the $P2Y_{12}$ inhibitor and continuing with single-aspirin therapy) might bring increased risk of ischemic events, monotherapy with potent $P2Y_{12}$ inhibitor (dropping aspirin and continuing with single potent $P2Y_{12}$ inhibitor) seems to achieve significant reduction of bleeding without increased risk of ischemic events[86,133,134]. De-escalation, either un-guided[82,83] or guided[135] by platelet-function[84] or genotype testing[85] are other strategies to reduce bleeding. The question is: what is the minimum antiplatelet treatment needed to avoid increase in ischemic events, how short can "short DAPT" be, or how much intensity is required? There are many answers depending on patient characteristics, indication and possible procedural aspects. Another question is whether DAPT is needed at all. All bleeding reducing strategies have included a first period of 1–3 months of DAPT which is believed to be necessary in the acute phase of an ACS or following PCI. A pilot study of patients with chronic coronary syndrome undergoing PCI have tested to drop aspirin immediately after the first loading dose, continuing with only prasugrel[136]. This study was not powered for clinical outcomes and did not include ACS patients. In the ongoing ASET-JAPAN study on prasugrel monotherapy, NSTE-ACS patients are included (NCT05117866) and, in the ongoing TIMO study on ticagrelor monotherapy, acute MI including both NSTEMI and STEMI patients are included (NCT05149560). Like the first pilot study on prasugrel, both these are small single-arm studies, but future studies will most likely continue to investigate shorter (< 1 month) DAPT duration or whether DAPT is necessary.

There are several important concerns regarding the studies on bleeding reducing antithrombotic strategies. All have been underpowered for ischemic events and the majority comprised low-risk patients. Ischemic or NACE events have often been tested for non-inferiority, which should be interpreted with caution, since non-inferiority margins may be arbitrary. The primary outcome has often included both major and minor bleeding even though minor bleeding events are not as prognostically important as major bleeding events. Finally, many were conducted in East Asian populations with unknown external validity in Caucasians or other non-East-Asian populations. East Asians seem to have higher risk of bleeding and lower risk of ischemic events[137] (except for stroke) on clopidogrel treatment despite higher prevalence of CYP2C19 loss-of function alleles, the so-called 'East Asian paradox'. A similar picture with increased bleeding and lower rate of ischemic events on the potent $P2Y_{12}$ inhibitors has been shown and lower doses such as 3.75mg[138] or 5 mg prasugrel[139] have been tested. The ischemic event rates in the East Asian bleeding reducing antithrombotic studies have also been extremely low[75,80,81,133]. Finally, no study has compared the different bleeding reducing strategies head-to-head[140].

7.5 The optimal antithrombotic treatment

Another way to decrease bleeding is to find new antithrombotic drugs that could decrease bleeding but still effectively reduce ischemic events. A promising target is factor XI,

which seems more important in driving thrombosis via the contact pathway, but less important for haemostasis and has thus been described as "uncoupling thrombosis and hemostasis"[141]. Phase II trials on Factor XI inhibitors have shown promising results[142] and Phase III trials in populations with ACS (NCT04304534), atrial fibrillation (NCT04218266), stroke (NCT04304508, NCT03766581) and end-stage renal disease with haemodialysis (NCT04534114) are ongoing or imminent (not yet registered on clincaltrials.gov).

7.6 Need for new study designs

The RCT is the gold standard to evaluate treatment effect since the randomisation handles both measured and unmeasured confounders and the data provided is highly granular. However, RCTs are very expensive, time-consuming and have limited external validity since they comprise selected populations. As the number of efficacy events declines, the size of these trials must increase to reach statistical power and the RCTs will become even more expensive and difficult to conduct. Thus, pragmatic trials that include more patients, faster and more cheaply are needed. The Register-based Randomised Clinical Trial (R-RCT) has shown success in combining randomisation and registry data[143]. The perfect R-RCT has an intervention that is performed once after randomisation[144-148]—such as thrombus aspiration[144] yes/no, IFR measurement[146] yes/no or influenza vaccination[148] yes/no, etc.—and the optimal R-RCT outcome is all-cause death, for which registers in Sweden have complete coverage. Interventions like medical treatment A/B might be more complicated in an R-RCT, since follow-up is not as rigorous as in an RCT and outcomes like bleeding are not captured in registers with the same granularity as in RCTs.

Many of the unanswered questions regarding antithrombotic strategies (Table 17) concern small differences between treatments and very large study populations are needed, especially to investigate ischemic outcomes.

Thus, to conduct studies on antithrombotic strategies using already established drugs, the RCTs are most likely too expensive and cumbersome, while the R-RCTs are not sufficient. Hybrid solutions (DAPA-MI NCT04564742) are needed to provide large study populations but still capture standardised bleeding outcomes and monitor compliance or adherence.

7.7 Better registration of bleeding events in registries

How can we improve the registration of bleeding events in registries? An easy definition that captures prognostically significant events would be optimal. A standardised bleeding event definition for registers should perhaps be developed. In Sweden, we could link our registries to the blood-transfusion register. This would provide data on transfusion which is not covered adequately in the National Patient Register[149].

7.8 Inclusion of different perspectives

Not often mentioned, but nonetheless important, is the differing perspectives of clinicians and patients. For example, many clinicians (and perhaps patients) may find harm caused by a treatment (i.e., bleeding) more difficult to accept than harm caused by an event that a treatment potentially could prevent (i.e., ischemic event). Moreover, different patients may have different preferences regarding risk, some may fear a particular event and accept greater risk to avoid it, or vice versa. Whenever possible, patients should be involved in shared decision making.

Finally, it might not always be a bad thing to experience a bleeding event. What if a bleeding could unmask a malignancy at an earlier and curable stage. It has been shown in the COMPASS study[150] that bleedings, especially from the genitourinary and gastrointestinal tract, were associated with a many-fold increase in newly detected cancer. Prospective evaluation would be of interest to see if this could translate into better cancer outcomes? What is most important is that a bleeding event should always be followed by a thorough investigation of underlying cause.

Table 17. List of some of the unanswered questions regarding antithrombotic treatment

- What is the minimal duration of DAPT after stenting in CCS and ACS?
- In the presence of potent $P2Y_{12}$ inhibitor, is DAPT needed at all?
- Which is the preferred bleeding reducing antithrombotic strategy; Short DAPT, monotherapy with potent $P2Y_{12}$ inhibitor or de-escalation?
- What is the optimal single antiplatelet drug during the first year after stenting in CCS and ACS or in conservatively treated ACS?
- What is the optimal single antiplatelet drug long-term after the initial year after an event; aspirin or $P2Y_{12}$ inhibitor and which $P2Y_{12}$ inhibitor (clopidogrel, ti-cagrelor or prasugrel?)
- What is the optimal antithrombotic regimen in patients with ACS plus PCI with stent, who are treated with ECMO?
- What is the optimal anticoagulant strategy regarding choice of drug and dosing in TAVI patients with indication for oral anticoagulant?
- What is the optimal anticoagulant strategy regarding choice of drug and dosing in patients with end-stage renal disease?
- Which NOAC is the best regarding both safety and efficacy?

ACS: acute coronary syndrome, CCS: chronic coronary syndrome, DAPT: dual antiplatelet therapy, ECMO: extracorporeal membrane oxygenation, , NOAC: non-vitamin K orac anticoagulant, TAVI: transcatheter aortic valve intervention

8 CONCLUSIONS

In the past two decades, the incidence of both in-hospital and out-of-hospital bleeding events have doubled in parallel with the increased use of invasive revascularisation and more intensive antithrombotic treatment. Simultaneously, a substantially greater absolute reduction of ischemic events, including mortality, occurred.

The five item SWEDEHEART score, (haemoglobin, age, sex, creatinine and CRP) can predict in-hospital bleeding with greater accuracy than the CRUSADE and ACTION scores. Risk scores need to be validated and, if necessary, recalibrated before being used outside their derivation cohorts.

During the first year of acute MI, readmission with UGIB is common and associated with poor prognosis. Using both ML and logistic regression methods, in addition to the already known predictors of major bleeding, new potential predictors of UGIB such as smoking status and blood glucose were identified.

After a recent myocardial infarction, post-discharge ischemic events, defined as a composite of ischemic stroke and recurrent myocardial infarction, were more common and associated with higher risk of mortality than post-discharge bleeding events.

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