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ABSTRACT

Major bleeding complications are common after acute coronary syndromes (ACS) and are associated with increased mortality. Thus, identification of high bleeding risk (HBR) patients during clinical decision making can be lifesaving. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria are recommended for bleeding risk assessment in ACS. This thesis investigated the prevalence of HBR and its association with major bleeding complications and major adverse cardiovascular or cerebrovascular events (MACCE) in ACS patients, with a focus on ST-elevation myocardial infarction (STEMI). Furthermore, bleeding and ischemic risk factors not included in the ARC-HBR criteria were identified. The study population was identified by a database search and data was collected by patient record review.

Study I included 212 suspected non-ST-segment elevation myocardial infarction patients and 209 of these were in study II. Study III included 1564 STEMI patients and the 1367 treated with primary percutaneous coronary intervention (PPCI) were in study IV. The prevalence of HBR among ACS was over 40%. Among STEMI, the 1-year major bleeding incidence in HBR patients was over 10% (3-fold increased risk vs. non-HBR). However, only few individual criteria were independent bleeding predictors. Current smoking was identified as a major bleeding risk factor, and the prevalence was 40.4% among patients classified as non-HBR according to the ARC-HBR. This finding suggests that guideline recommended bleeding risk assessment failed to identify a large proportion of patients who were at HBR, demonstrating the need to consider risk factors not included in the ARC-HBR framework. The 1-year incidence of MACCE after PPCI for STEMI among HBR patients was 19.5%, corresponding to a 3.3-fold risk compared to non-HBR. After accounting for comorbidities such as diabetes and reduced left ventricular ejection fraction, it seems that the higher incidence of MACCE among HBR patients could be explained by underlying conditions and not only bleeding risk status itself. Careful evaluation of ischemic risk factors is warranted, particularly among HBR patients to adequately assess the balance of these opposing risks.

KEYWORDS: Acute coronary syndrome, ARC-HBR, bleeding, smoking

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TIIVISTELMÄ

Suuret verenvuotokomplikaatiot ovat yleisiä sepelvaltimotautikohtauksen (ACS) jälkeen ja ne lisäävät kuolleisuutta merkittävästi. Korkean verenvuotoriskin (HBR) potilaiden tunnistaminen voi olla elintärkeää. Kansainvälisissä hoitosuosituksissa määritellään joukko kliinisiä kriteereitä korkean vuotoriskin tunnistamiseksi (ARC-HBR-kriteerit). Väitöskirjassa selvitettiin HBR:n esiintyvyyttä ja sen yhteyttä merkittäviin vuotokomplikaatioihin sekä suuriin kardiovaskulaari- tai aivoverenkiertotapahtumiin (MACCE) ACS-potilailla. Tutkimuksessa keskityttiin erityisesti ST-nousuinfarktipotilaisiin. Lisäksi tunnistettiin riskikriteeristöön kuulumattomia merkittäviä vuotoriskitekijöitä sekä iskeemisiä riskitekijöitä. Tutkimusaineisto tunnistettiin datahaulla ja data kerättiin suoraan potilastiedoista.

Osatyö I sisälsi 212 ei-ST-nousuinfarktipotilasta ja 209 näistä sisältyi osatyö II:een. Osatyö III sisälsi 1564 ST-nousuinfarktipotilasta ja osatyöhön IV otettiin näistä 1367 pallolaajennuksella hoidettua potilasta. Korkean vuotoriskin esiintyvyys ACS-potilailla oli yli 40 %. ST-nousuinfarktipotilailla verenvuotojen ilmentyvyys vuoden seurannassa HBR-ryhmässä oli yli 10 % (kolminkertainen riski). Kuitenkin vain harvat yksittäiset kriteerit olivat itsenäisiä verenvuotoriskin ennustajia. Aktiivinen tupakointi tunnistettiin vuotoriskitekijäksi ja sen esiintyvyys oli 40.4 % potilailla, jotka kuuluivat ei-korkean vuotoriskin ryhmään. Näin ollen hoitosuositusten mukaisella vuotoriskiarviolla ei tunnistettu suurta potilasjoukkoa, joka oli korkeassa vuotoriskissä. Löydökset osoittavat tarpeen huomioida riskitekijöitä, jotka eivät sisälly vuotoriskikriteeristöön. Pallolaajennuksella hoidetun ST-nousuinfarktin jälkeen MACCE:n esiintyvyys vuoden seurannassa HBR-potilailla oli 19,5 %, vastaten 3,3-kertaista riskiä verrattuna ei-korkean vuotoriskin potilaisiin. Kun huomioitiin liitännäissairaudet, kuten diabetes ja heikentynyt vasemman kammion ejektiofraktio, näyttää siltä, että korkeampi MACCE:n esiintyvyys HBR-potilailla voi selittyä myös perussairauksilla eikä vain kuulumisella HBR-ryhmään. Iskeemisten riskitekijöiden huolellinen arviointi on tarpeen erityisesti HBR-potilailla, jotta näiden vastakkaisten riskien tasapainoa voidaan arvioida asianmukaisesti ja hoitostrategiaa muuttaa tarvittaessa.

AVAINSANAT: sepelvaltimotautikohtaus, riski, verenvuoto, tupakointi

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Abbreviations

ACS	acute coronary syndrome
ADP	adenosine diphosphate
ARC-HBR	Academic Research Consortium for High Bleeding Risk
ASA	acetylsalicylic acid
AUC	area under the receiver-operating characteristic curve
BARC	Bleeding Academic Research Consortium
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	chronic coronary syndrome
CI	confidence interval
CIF	cumulative incidence function
CKD	chronic kidney disease
COX	cyclooxygenase
cTn	cardiac troponin
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DAT	dual antithrombotic therapy
DOAC	direct oral anticoagulants
ECG	electrocardiogram
ESC	European Society of Cardiology
GI	gastrointestinal
GP	glycoprotein
GUSTO	The Global Use of Strategies to Open Occluded Arteries
HBR	high bleeding risk
HR	hazard ratio
ICH	intracranial haemorrhage
IQR	interquartile range
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiac or cerebrovascular event
MACE	major adverse cardiac event
MI	myocardial infarction

NSAID	non-steroidal anti-inflammatory drugs
NSTE-ACS	non-ST-elevation acute coronary syndrome
NSTEMI	non-ST-elevation myocardial infarction
OAC	oral anticoagulant
PCI	percutaneous coronary intervention
PPCI	primary percutaneous coronary intervention
RCT	randomized clinical trial
SAPT	single antiplatelet therapy
STEMI	ST-elevation myocardial infarction
TAT	triple antithrombotic therapy
TIMI	Thrombolysis in Myocardial Infarction
TXA2	thromboxane A2
UAP	unstable angina pectoris
VKA	vitamin K antagonist
VSSHP	The Hospital District of Southwest Finland

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kesti H, Mäkinen H, Mattila K, Jaakkola S, Lintu M, Porela P. Prevalence of High Bleeding Risk among Hospitalized Suspected NSTEMI Patients. *Journal of Clinical Medicine*, 2022; 5: 1324.

II Kesti H, Mäkinen H, Mattila K, Jaakkola S, Lintu M, Porela P. High Bleeding Incidence in Unselected Hospitalized Suspected Non-ST-Segment Elevation Myocardial Infarction Patients Aged Under 65 Years. *The American Journal of Cardiology*, 2023; 206: 101-104.

III Kesti H, Mattila K, Jaakkola S, Lehto J, Söderblom N, Kalliovalkama K, Porela P. Performance of the ARC-HBR Criteria in ST-Elevation Myocardial Infarction. Significance of Smoking as an Additional Bleeding Risk Factor. *European Heart Journal – Quality of Care and Clinical Outcomes*, 2024 Nov 30:qcae104. Epub ahead of print.

IV Kesti H, Mattila K, Jaakkola S, Lehto J, Söderblom N, Kalliovalkama K, Porela P. Impact of high bleeding risk and associated risk factors on major adverse cardiovascular or cerebrovascular events in primary percutaneous coronary intervention treated ST-elevation myocardial infarction. *International Journal of Cardiology,* 2025 Jan 11:132986. Epub ahead of print.

1 Introduction

The identification of high bleeding risk (HBR) patients is essential in the management of acute coronary syndromes (ACS) as major bleeding complications increase mortality to a similar extent as recurrent myocardial infarction (MI) [1]. HBR patients seem to benefit from shortened dual antiplatelet therapy (DAPT) durations due to reduction in bleeding and therefore this strategy is considered favourable especially in the absence of factors associated with increased ischemic risk [2].

The Academic Research Consortium for High Bleeding Risk (ARC-HBR) defined a set of clinical criteria to identify HBR patients and the European Society of Cardiology (ESC) guideline recommends using these criteria for bleeding risk assessment in ACS [2,3]. The criteria were based on a literature review and expert opinion. According to the ARC-HBR consensus, HBR was defined as 1-year Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding risk ≥ 4% or 1-year intracranial haemorrhage (ICH) risk ≥ 1%. BARC 3 corresponds to bleeding resulting in haemoglobin drop of 30 g/L or more severe bleeding and BARC 5 is fatal bleeding [4]. HBR is commonly encountered among ACS and the criteria have successfully predicted bleeding risk exceeding the aforementioned thresholds [5]. However, possible alternative bleeding risk factors not included in the ARC-HBR criteria have rarely been considered in previous studies. When this has been done, only a small number of individual ARC-HBR criteria remain independent bleeding predictors and new variables of interest have been identified [6]. Studies have demonstrated that HBR patients are also at increased risk of ischemic complications [7]. Therefore, it is essential to establish which individual components of the ARC-HBR criteria are ischemic risk factors. Furthermore, HBR patients are older and have an excess burden of comorbidities, which could explain the higher observed incidence of ischemic complications. Studies investigating the association of individual ARC-HBR criteria and other comorbidities to ischemic events are lacking.

The ARC-HBR criteria requires a comprehensive review of medical history. Many previous studies used modified or incomplete criteria due to restrictions in registry data, increasing the risk of misclassification bias. Additionally, ST-elevation

myocardial infarction (STEMI) patients are underrepresented in bleeding risk studies. This thesis sought to establish the prevalence of HBR in real-world ACS populations and evaluate the association of HBR to bleeding and ischemic complications, while identifying independent risk factors for these events.

2 Review of the Literature

2.1 Acute coronary syndromes

2.1.1 Definition and pathophysiology

ACS is a group of acute manifestations of coronary artery disease (CAD). ACS is divided into subgroups based on clinical findings and cardiac biomarkers: STEMI and non-ST-elevation ACS (NSTE-ACS), comprising of non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). MI is defined as acute myocardial injury in the setting of evidence of acute myocardial ischemia [8]. Myocardial injury is defined as detection of an elevated cardiac troponin (cTn) value above the 99th percentile of upper reference limit and is considered acute, if a rise and/or fall of cTn is detected. STEMI is a MI with persistent ST-segment elevation in at least two contiguous leads or other equivalent findings in the electrocardiogram (ECG) as defined by the fourth universal definition of MI [8]. In coronary angiography, a completely occluded coronary artery is often detected. A MI without such ECG findings is considered NSTEMI. MI can further be classified according to the underlying etiological mechanism of acute myocardial injury as described in detail in the fourth universal definition of MI [8]. Briefly, type 1 MI is caused by atherothrombotic CAD and often an atherosclerotic plaque disruption such as erosion or rupture is present. Erosion and rupture of the plaque can lead to intraluminal thrombus formation, which restricts or completely occludes the blood flow of the affected coronary artery. In type 2 MI, myocardial ischemia is caused by oxygen supply and demand mismatch without acute coronary atherothrombosis. Other types of MI include those related to invasive coronary procedures (type 4 and type 5) and cardiac death before collection of cardiac biomarkers with signs suggestive of myocardial ischemia (type 3). UAP is defined as myocardial ischemia at rest or minimal exertion without acute myocardial injury [2].

2.1.2 Epidemiology

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide [9]. In a recent report from the 57 ESC member countries, CVD caused

nearly 2 million deaths in males and 2.2 million deaths in females in the most recent year for which data was available (median year 2016) [10]. Therefore, CVD accounted for 45% and 39% of all deaths in females and males, respectively. The most common cause of CVD death was ischemic heart disease (38% of CVD deaths in females and 44% in males). According to the report, approximately 5.8 million new cases of ischemic heart disease were observed in 2019 with median age-standardized incidence per 100 000 people at 293.3 (interquartile range [IQR] 195.8–529.5). ACS is often the first manifestation of ischemic heart disease [2]. In Europe during 2020 (or the latest year of available data), the age-standardized median mortality rate for ACS per 100 000 people was 26.3 (IQR 19.9–38.0) in males and 10.2 (IQR 8.1–14.9) in females [11].

2.1.3 Trends in prognosis and complications

In recent years the complication rates of ACS-patients have changed markedly. According to a large study investigating patients with MI in the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry between 1995 and 2018, the incidence of 1-year bleeding complications has doubled (from 2.9% to 6.3%) [12]. This was parallel to increased use of invasive management and more potent antiplatelet therapy. Although these changes came with increased bleeding risk, at the same time there was a decrease in ischemic complications. After the index-MI, the incidence of in-hospital MI decreased from 2.8% to 0.6% while post discharge MI decreased from 12.6% to 7.1%. The composite of post-discharge cardiovascular death, MI and stroke decreased from 22.5% to 13.7%. Additionally, all-cause mortality was reduced by 40%, from 24.4% to 14.6%.

2.2 Overview of acute coronary syndrome management

2.2.1 Reperfusion

Prolonged myocardial ischemia results in myocardial cell necrosis, i.e. myocardial infarction. The necrosis develops starting from the centre of the affected ischemic myocardium from the subendocardial layers and progresses transmurally into subepicardial layers and to the borders of the affected area during ongoing ischemia [13,14]. In 1970's researchers first demonstrated that reperfusion salvages myocardium from necrosis [15,16]. Shortly after, coronary reperfusion by fibrinolysis in humans was introduced [17]. The ISIS-2 (The second international study of infarct survival) randomized clinical trial (RCT) demonstrated a significant reduction in all-

cause mortality after MI in patients managed with fibrinolysis, acetylsalicylic acid (ASA) or both [18].

Currently, percutaneous coronary intervention (PCI) is the cornerstone of ACS management and is usually recommended as the primary reperfusion therapy for all subcategories of ACS [2]. PCI includes placement of a coronary stent via vascular access and adjunctive as well as post-procedural antithrombotic therapy for prevention of stent thrombosis and myocardial infarction [19]. A large meta-analysis of RCTs comparing fibrinolysis with PCI showed that PCI was associated with reduced overall mortality, non-fatal reinfarction and stroke compared with fibrinolysis, demonstrating the superiority of the more contemporary approach for reperfusion [20]. Among STEMI, primary PCI (PPCI) is the preferred reperfusion strategy if it can be performed within 120 minutes of the diagnosis [2]. In NSTE-ACS, the urgency of reperfusion by PCI should be decided based on the presence or absence of high-risk features such as haemodynamic instability or ongoing chest pain.

2.2.2 Antiplatelet therapy

2.2.2.1 Arterial thrombus formation

Arterial thrombus formation is a complex process involving multiple factors. In the context of ACS, it is initiated with atherosclerotic plaque rupture or erosion. After 1 minute of the rupture, platelets are activated and their adhesion and aggregation on the collagenous components of the plaque (such as collagen and von Willebrand factor) occurs and is mediated by glycoprotein (GP) VI and GP-receptor-Ia/IIa (integrin $\alpha_2\beta_1$) [21]. The formation of thrombin and fibrin follows within 3 minutes and the coagulation cascade is activated triggered by tissue factor [21]. Additionally, activated platelets produce several factors that further increase platelet activation and aggregation [22]. Thromboxane A2 (TXA_2), a strong platelet activator, is produced by activated platelets from prostaglandin H_2, which is produced by the enzymes cyclooxygenase (COX) 1 and 2. Adenosine diphosphate (ADP) released from damaged endothelium and activated platelets binds to the receptors P2Y1 and P2Y12, which are expressed in platelets. Identification of platelet activation pathways has provided therapeutic targets for thrombus prevention.

2.2.2.2 ASA and P2Y12 receptor inhibitors

ASA is an irreversible inhibitor of COX 1 and 2 and thus reduces platelet activity by inhibiting TXA_2 [23]. The benefit of ASA in MI was demonstrated in the ISIS-2 trial [18]. The trial investigated the effect of reperfusion by fibrinolysis and the use of ASA in

patients presenting with a MI. ASA alone was associated with 23% reduction in the risk of 5-week vascular mortality. Furthermore, the addition of ASA to fibrinolysis reduced the risk even further to a 42% lower risk compared to those who received neither ASA nor fibrinolysis. This indicated that the addition of ASA to reperfusion therapy is beneficial. The Antithrombotic Trialists' Collaboration meta-analysis of over 280 studies showed that antiplatelet therapy, mainly with ASA, reduced the incidence of vascular death, MI or stroke by approximately 22% in patients with vascular disease [24]. Among patients with acute MI, the reduction was 30%. Due to these findings, ASA has been the cornerstone of antiplatelet therapy in ACS for decades.

Another key part of antiplatelet medication are ADP receptor inhibitors, which inhibit the P2Y12 receptor expressed in platelets, supressing platelet activation [25]. Routinely used P2Y12 receptor inhibitors are clopidogrel, ticagrelor and prasugrel. Of these, clopidogrel was discovered first and it was compared with ASA in the CAPRIE (A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events) trial [26]. This RCT compared the efficacy of ASA and clopidogrel in patients with atherosclerotic vascular disease consisting of stroke, MI or peripheral arterial disease. Clopidogrel was more effective in reducing the composite endpoint of stroke, MI and vascular death in the overall study population. However, no significant difference in efficacy was observed among the MI subgroup.

2.2.2.3 Dual antiplatelet therapy

The benefit of single antiplatelet therapy (SAPT) with aspirin or a P2Y12 receptor inhibitor in patients with vascular disease has been firmly established [24]. Since ASA and P2Y12 receptor inhibitors inhibit different pathways in platelet activation, they can be used in conjunction to attenuate the antithrombotic effect. This combination of ASA and a P2Y12 receptor inhibitor is DAPT. DAPT with ASA and clopidogrel was compared to SAPT with ASA in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial involving over 12 000 NSTE-ACS patients [27]. Compared to SAPT, DAPT was associated with significantly lower risk of 1-year composite ischemic endpoint comprised of cardiovascular death, nonfatal MI or stroke (relative risk 0.80, 95% confidence interval [CI] 0.72-0.90, incidences 9.3% vs 11.4%). However, DAPT came with increased risk of major bleeding (relative risk 1.38, CI 1.13-1.67, incidences 3.7% vs 2.7%). The excessive bleeding risk of DAPT was observed both within 30 days after randomization (relative risk 1.31, CI 1.01-1.70) and more than 30 days after randomization (relative risk 1.48, CI 1.10-1.99), with higher bleeding incidences in the former (2.0% in DAPT vs 1.5% in SAPT within 30 days and 1.7% vs 1.1% after 30 days). Since this trial, DAPT has

been the recommended antiplatelet strategy in ACS. DAPT is also recommended in ACS patients managed without revascularisation [2,28]. Although this represents only a minority of ACS-patients in countries with advanced health care systems, there is variation in revascularisation rates [29,30].

2.2.2.4 Anticoagulation and triple therapy

Many patients with ACS have an indication for long term use of oral anticoagulants (OAC), mainly due to atrial fibrillation, which is encountered in up to about 20% of ACS patients [31,32]. In addition, ACS can cause new onset atrial fibrillation, which has been a topic of interest for researchers recently [33]. Antiplatelets without OAC are not sufficient for stroke prevention in atrial fibrillation, even if DAPT is used as demonstrated by the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial [34]. In this patient group, OAC is indicated, and antiplatelet regimens need adjustment. Possible strategies are triple antithrombotic therapy (TAT) with OAC in addition to DAPT and dual antithrombotic therapy (DAT) with OAC in addition to SAPT. The combination of OACs and antiplatelet medications comes with increased bleeding risk. The risk is higher in TAT compared to DAT and the use of vitamin K antagonist (VKA) OACs seems to be associated with greater bleeding risk than the use of direct oral anticoagulants (DOAC) [35]. Compared to monotherapy with VKA, hazard ratios (HRs) were 0.84 (CI 0.79-0.90) for DOAC monotherapy, 1.82 (CI 1.76-1.89) for a combination of VKA and an antiplatelet agent, 1.28 (CI 1.13-1.44) for DOAC with an antiplatelet agent, 3.13 (CI 2.84-3.45) for TAT with VKA and 2.28 (CI 1.67-3.12) for TAT with DOAC. A meta-analysis of 5 RCTs investigating antithrombotic strategies in patients using OACs undergoing PCI showed that long term use of TAT should be avoided because it may lead to increased bleeding without difference in antithrombotic effectiveness and that DOACs should be preferred over VKA [36]. For ACS-patients undergoing PCI and with an indication for long term OAC, the recommended antiplatelet management strategy is to use TAT with DOAC, P2Y12 inhibitor (preferably clopidogrel) and ASA for up to 1 week, and then stop ASA and continue with dual therapy with DOAC and P2Y12 inhibitor for up to 12 months. The recommendation to stop ASA after 1 week is based on the interventional arm of the AUGUSTUS (A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis [Blood Clots] Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart) trial [37]. The choice of clopidogrel over other P2Y12 receptor inhibitors is due to clopidogrel being used in > 90% of patients in the pivotal RCTs [37–40]. Furthermore, clopidogrel seems to be associated with decreased bleeding compared to the more

potent inhibitors ticagrelor and prasugrel as demonstrated by the PLATO (Platelet Inhibition and Patient Outcomes) and the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) trials [41,42].

It should be noted that peri-procedural anticoagulation is recommended during the management of ACS in the setting of PCI even if long term anticoagulation is not indicated [2]. The primary recommendations are parenteral unfractionated heparin and bivalirudin. However, prolonged use of these therapeutic agents post-PCI is not recommended, since it increases bleeding risk without benefits in cardiovascular event reduction [43]. The choice between unfractionated heparin and bivalirudin is under debate. A recent meta-analysis including 10 RCTs demonstrated that among ACS patients, compared to bivalirudin heparin increased bleeding risk and the risk of cardiovascular death without benefits in reduction of MI, stent thrombosis or stroke [44].

2.3 Bleeding complications

2.3.1 Definition of major bleeding

Post PCI bleeding complications have been defined in numerous different ways in RCTs and observational studies. Heterogeneity in bleeding endpoints is problematic as it complicates the comparison of study results. To solve this issue, the Bleeding Academic Research Consortium (BARC) published a consensus document for the purpose of standardising bleeding definitions [4]. The BARC definition has generally been accepted as the primarily used bleeding endpoint in clinical trials. According to BARC, bleeding events are classified based on the severity of the bleeding events into 5 categories (BARC types 1-5). Briefly, BARC type 1 is non-actionable bleeding, type 2 is minor bleeding requiring evaluation or intervention by healthcare professionals and not meeting the following criteria for major bleeding. Types 3-5 are regarded as major bleeding events. At minimum, BARC 3a is bleeding with haemoglobin drop of 30 g/L or bleeding requiring transfusion. BARC 3b is bleeding resulting in haemoglobin drop of 50 g/L or requiring surgical intervention or intravenous vasoactive agents. BARC 3c is ICH, which is always considered major bleeding, excluding microbleeds or haemorrhagic transformations (in stroke). Type 4 is coronary artery bypass grafting (CABG) -related major bleeding, and this is often excluded from clinical trial bleeding endpoints. BARC type 5 is definite or probable fatal bleeding. Thus, the most prevalent bleeding endpoint definitions in contemporary trials and observational studies investigating bleeding events are BARC type 3 or 5 (major bleeding) or BARC types 2, 3 or 5 (actionable bleeding).

Other common definitions that were used for decades prior to BARC are The Thrombolysis in Myocardial Infarction (TIMI) and The Global Use of Strategies to Open Occluded Arteries (GUSTO) definitions [45,46]. Both were intended for bleeding classification in trials investigating fibrinolysis and come with limitations that were addressed by BARC. The TIMI definition relies on decreases in haemoglobin and haematocrit values while GUSTO excludes these completely and bleeding events are classified based on the clinical impact of bleeding. The BARC definition combines elements from both and is designed for the current era of ACS management, where PCI is the predominant management strategy.

2.3.2 Clinical significance of bleeding complications

The impact of post ACS bleeding and recurrent MI on mortality has been compared to evaluate which complication is associated with less favourable prognosis. Mehran and colleagues investigated the impact of early (within approximately 30 days after ACS) major bleeding events and recurrent MI on 1-year mortality in NSTE-ACS patients [47]. Occurring after the index-ACS, MI was associated with 3.1 times increased risk of mortality and bleeding with 3.5 times increased risk. The risk associated with MI was highly time dependent. The risk of death was 17-fold during the first day after MI and declined rapidly thereafter being 1.4-fold from 30 days onwards. On the other hand, the impact of bleeding was more constant, about 5.6-fold increased risk for 30 days and 2.4-fold thereafter. However, for overall 1-year mortality the risks were comparable. The definition of major bleeding did not perfectly match the BARC definition but is fairly comparable. More recently, > 30 days post-NSTE-ACS bleeding events according to the BARC definition were compared with MI [1]. MI was associated with greater risk of mortality compared to BARC 2 (relative risk 3.5, CI 2.08-4.77) and 3a bleeding events (relative risk 2.23, CI 1.36-3.64). The impact on mortality was similar compared to BARC 3b bleeding. BARC 3c bleeding was associated with far greater risk of mortality compared to MI (relative risk of death from MI vs BARC 3c bleeding 0.22, CI 0.13-0.36). The impact on mortality increased when moving up the BARC scale. BARC type 1 was not associated with mortality, type 2 had 1.7-fold increased risk (incidence of death among those with bleeding vs no bleeding 6.32% and 3.79%), type 3 collectively 5.7-fold (incidences 22.83% and 3.41%). In further inspection of BARC 3a, 3b and 3c bleeding, the HRs and incidences of death among those with bleeding vs without bleeding were 2.77 (18.29% and 3.75%), 4.51 (20.00% and 3.78%) and 28.2 (42.11% and 3.76%) respectively, highlighting the significance of ICH. Contrary to the previously discussed results by Mehran et al., MI and bleeding had a similar temporal association with mortality. The risk being highest for the first week and declining rapidly afterwards. Another study demonstrated that after PCI, post-

discharge bleeding events occurring within 2 years after discharge increased the risk of all-cause 2-year mortality 5-fold [48]. Compared to post-discharge MI, bleeding was a stronger predictor of mortality (HR 1.92, CI 1.18-3.12). Unfortunately, the bleeding endpoint in the study was a mixture of several bleeding definitions and no sensitivity analysis investigating the impact of each was performed. However, given the 5-times increased risk of mortality associated with bleeding, it is reasonable to assume that the average bleeding event in the study would be considered major bleeding if converted to the BARC definition. A recent meta-analysis involving > 140 000 patients confirmed the comparable prognostic impact of bleeding and MI [49]. Both complications increased all-cause mortality over 4-fold. Collectively, existing literature has firmly established the detrimental prognostic impact of major bleeding events.

Based on a registry of over 3 million PCI treated patients, in-hospital bleeding events were associated with increased in-hospital mortality after propensity-matching [50]. According to the results, approximately 12% of all in-hospital deaths were attributable to bleeding complications. Kikkert et al. showed that in PCI treated STEMI patients, in-hospital bleeding events had different impacts on mortality based on bleeding definitions [51]. BARC type 3b and 3c bleeding as well as major bleeding based on TIMI classification increased the risk of 1-year mortality 2-fold. GUSTO bleeding had no association with mortality. Bleeding complications seem to be equally prognostically significant compared to MI even in ACS patients managed without revascularisation [52]. Even though the impact of minor bleeding events on prognosis has been minor to none, they are still associated with impaired quality of life and could be considered as secondary endpoints in clinical trials and observational studies [53].

To determine whether the prognostic significance of PCI access site bleeding differs from non-access site, a meta-analysis of nearly 2.4 million patients undergoing PCI was conducted [54]. The investigators reported that access-site bleeding was associated with 1.7-fold increased risk of mortality. The impact of non-access site related bleeding was far greater, with over 4-fold increased risk. It should be noted that due to the heterogeneity of bleeding definitions in the individual studies used in the analysis, it is unclear whether the higher prognostic significance of non-access site bleeding events is driven by the severity of the bleeding events or the site itself. However, some studies have reported that non-access site bleeding is more prognostically significant than access site bleeding even after standardising the severity of these bleeding events [55,56]. It should be noted that femoral access was used in almost all subjects in these studies, while in contemporary practice radial access is generally preferred due to reduced bleeding risk and mortality compared to femoral access [57]. Compared with femoral access, possibly severe retroperitoneal bleeding events are not an issue with radial access. Therefore, the prognostic

significance of access site bleeding in contemporary practice could be lesser than what has been previously reported.

The mechanism linking bleeding complications with mortality is multifactorial. It is apparent that acute bleeding could be fatal, such as ICH or massive gastrointestinal bleeding. However, elevated risk of mortality associated with non-fatal bleeding is prolonged beyond the acute phase. Bleeding could lead to cessation of antithrombotic medication, which increases the risk of stent thrombosis [58]. However, it seems that after PCI the occurrence of both bleeding and an ischemic complication is rare [1,59,60]. Excessive bleeding could require blood transfusions in order to manage the condition. Blood transfusions after PCI have been shown to independently predict mortality, with those receiving transfusion having a 3-fold increased risk of death and major adverse cardiac events [61,62]. The risk is elevated even in the absence of bleeding events and when adjusted for baseline haematocrit and anaemia. The risk could be mediated by increased platelet reactivity via the P2Y12 receptor pathway among other mechanisms such as impaired oxygen delivery and reduced capillary vasodilation associated with transfused red blood cells [63,64].

Major bleeding complications can be life threatening. In these situations, cessation of DAPT may be necessary in order to control bleeding. However, DAPT discontinuation after PCI is a predictor of mortality and ischemic complications such as stent thrombosis and recurrent MI as demonstrated by the patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) study [58]. PARIS was a prospective observational international registry enrolling a real-world PCI population. The investigated ischemic endpoint was major adverse cardiac events (MACE) comprising of cardiac death, MI, stent thrombosis and target lesion revascularisation. The underlying reason of cessation played an important role in observed risk of MACE. Physician-recommended withdrawal of antiplatelet treatment for patients thought to no longer need DAPT did not increase the risk of MACE and neither did a temporary cessation of DAPT for up to 14 days due to surgery. However, cessation of antiplatelet treatment due to bleeding or non-compliance was associated with increased MACE risk, which was greatest early after cessation. Bleeding events can therefore predict ischemic complications and have been shown to increase the risk of MACE by 3-fold in a large meta-analysis [65].

2.3.3 Bleeding sites

Since PCI involves puncturing either the femoral or radial artery, the punctured access-site is prone to bleeding. In contemporary practice, the use of radial access is recommended since it reduces access-site bleeding complications and increases

prognosis compared to femoral access [66]. This changed practice and subsequent lowering in access-site bleeding has shifted the focus on non-access site events. In a European cohort of ACS patients (managed between 2009 and 2018), the 1-year incidence of BARC 3 or 5 access site bleeding was 0.62% whereas the incidence of non-access site major bleeding events was 4.40% [67]. Non-access site bleeding complications occur most often in the gastrointestinal (GI) tract with about half of all events originating from this source, while other less common sites include urinary, central nervous system and pulmonary bleeding [48,68–70].

Since GI bleeding encompasses majority of all bleeding complications, they are of special interest. Antiplatelet medication and OACs increased GI bleeding risk from 1.8-fold with low dose aspirin up to 7.4-fold with DAPT [71]. Interestingly, DAT (OAC + ASA) was associated with a lower risk than DAPT, although still 5-times elevated. The gastric mucosal injury caused by antiplatelets was recently demonstrated in a RCT [72]. The injury progressed with higher intensity of antiplatelets and when the duration of treatment lengthened. GI bleeding is associated with 3-fold increased mortality [73,74]. Risk factors for GI bleeding include advanced age, prior GI bleeding, anaemia, malignancy, smoking, use of non-steroidal anti-inflammatory drugs (NSAIDs) and liver disease [73–77].

2.4 Definitions of high bleeding risk

2.4.1 The Academic Research Consortium for High Bleeding Risk Criteria

In an effort to standardise trial design and to aid in clinical decision-making, The ARC-HBR defined a set of clinical criteria to identify those patients who are at HBR after PCI [3]. HBR was defined as 1-year BARC 3 or 5 bleeding risk of ≥ 4% or ICH risk of ≥ 1% at 1-year. The criteria are divided into major and minor criteria. A major ARC-HBR criterion should confer a BARC 3 or 5 bleeding risk of ≥ 4% or ICH risk of ≥ 1% at 1-year when encountered in isolation. That is, when no other ARC-HBR criteria are met. A minor ARC-HBR criterion in isolation, is associated with bleeding but confers BARC 3 or 5 bleeding risk < 4% at 1-year. A patient is considered to be at HBR if at least 1 major criterion or 2 minor criteria are met. ARC-HBR was based on literature review and expert opinion.

The cutoff of 4% for major bleeding as HBR definition was based on bleeding rates in previous DAPT trials and trials investigating drug eluting stents. DAPT trials such as the GLOBAL LEADERS (Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent) and the DAPT (The Dual Antiplatelet Therapy) trial excluded HBR

patients and 1-year major bleeding incidences were < 3% [78,79]. On the other hand, in drug eluting stent trials enrolling HBR patients, such as the LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) and the ZEUS-HBR (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates trial sub-analysis), 1-year major bleeding rates were 7.2% and 4.2% respectively [80,81]. Individual ARC-HBR criteria were chosen based on previous evidence. The criteria are summarised in **Table 1**. Since ACS management strategies such as deciding between invasive or conservative management could be dependent on individual patients bleeding risk, the criteria should be assessed before PCI. However, this could be problematic in some clinical settings such as STEMI requiring urgent revascularisation, due to the need to assess such wide range of clinical characteristics with specific definitions. While majority of the criteria are well defined, the definition for long-term use of oral NSAIDs or corticosteroids is quite vague. ARC-HBR recognises that bleeding risk associated with both NSAIDs and corticosteroids is dose-dependent [82,83], but does not define dosages of these drugs, other than the intake should be at least 4 days a week. Of note, ASA is a NSAID, but ASA use does not count as a minor ARC-HBR criterion. This is not directly stated in the source document but can be reasonably assumed due to the discussion of very low prevalences of NSAIDs/steroid use and underreporting in randomized stent trials (generally majority of patients in sinus rhythm should be on ASA after PCI and the usage is well documented in trials). This seems to be the consensus among the research field as well.

Table 1. Major and minor ARC-HBR criteria.

MAJOR CRITERIA	MINOR CRITERIA
Anticipated use of long-term oral anticoagulation*	Age ≥75 y
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/ min)
Haemoglobin <11 g/dL	Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100×10^9/L)	Long-term use of oral NSAIDs or steroids
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo	
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 mo Presence of a bAVM Moderate or severe ischemic stroke§ within the past 6 mo	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

Reproduced from Urban et al. 2019 [3], Table 3. (Under Creative Commons CC BY-NC-ND license, https://creativecommons.org/licenses/)

bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and PCI, percutaneous coronary intervention.

*This excludes vascular protection doses[84]

†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

‡Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

§National Institutes of Health Stroke Scale score ≥5.

2.4.1.1 Prevalence of high bleeding risk according to the Academic Research Consortium criteria

Several studies including PCI-treated patients from PCI registries or institutional databases have reported the prevalence of HBR according to the ARC-HBR (**Table 2**.) [5–7,67,85–98]. While some geographical variation exists, in general HBR is commonly encountered in clinical practice with a prevalence of about 45% in USA, 35% in Europe and 20-50% in Asia. In these studies, the prevalence is slightly lower among ACS as compared to chronic coronary syndrome (CCS). For example, in a European

cohort the prevalences among ACS and CCS were 31% and 39% respectively [67], while in Japan and Korea they were 45.3% vs 50.5% and 19.6% vs 22.2% [7,93]. However, studies including datasets from USA have reported different results, with slightly higher prevalence among ACS as compared to CCS (about 46% in ACS and 43% in CCS) [85,86]. Altogether the differences are small. The exceptionally high prevalence reported by Marquis-Gravel and colleagues is explained due to the source population being the LEADERS FREE trial, which enrolled specifically patients at HBR (with a previous definition) [96]. Interestingly, over 20% of these patients were not considered HBR based on the more recent ARC-HBR definition, introducing uncertainty to the applicability of the results of LEADERS FREE into managing HBR patients in real-life practice where the ARC-HBR criteria are recommended for bleeding risk assessment.

The prevalence of each individual ARC-HBR criteria varies significantly. This is demonstrated by a meta-analysis including 10 studies investigating the ARC-HBR criteria with over 67 000 patients in total [99]. The most prevalent major criteria were long-term use of OAC (11.7%) severe or end-stage chronic kidney disease (CKD) (8.2%), haemoglobin < 110 g/L (12%) and active malignancy (5.5%). The rest of the major criteria were exceedingly rare with prevalences ≤ 1.6%. Among the minor criteria, the highest prevalences were in age ≥ 75 years (35.9%), moderate CKD (32.2%), anaemia (19.7%) and previous stroke (8.5%). It should be noted that due to restrictions in variables recorded in the datasets used in this meta-analysis, some of the criteria were modified, which is common in many of the studies on ARC-HBR criteria. Notably, the prevalence of chronic bleeding diathesis was reported to be 0%, which is likely explained by the lack of required data in PCI registries. For comparison, in a study that used the exact definitions of the ARC-HBR criteria, the results regarding most prevalent criteria were comparable to the meta-analysis [88]. Notably, the reported prevalence of chronic bleeding diathesis was still close to zero, even though the fulfilment of this criterion was evaluated by reviewing patient records. This could be due to ARC-HBR mentioning only a few chronic conditions in relation to this criterion, while acknowledging that others may be sufficient. Researchers might not have realised that certain diseases fit the criterion.

Table 2. Prevalence of HBR according to the ARC-HBR criteria in patients with ACS and CCS.

Reference	HBR Prevalence	Clinical presentation	Cohort size, n (Demographics)	Data source
Cao et al., 2020[85]	44%	53% CCS 47% ACS 3% STEMI	9623 (USA)	Mount Sinai Hospital, New York, Institutional database
Nicolas et al., 2022[86]	45 %	77.1% CCS 22.9% MI 18.0% STEMI	6068 (USA)	Mount Sinai Hospital, New York, Institutional database
Breen et al., 2024[87]	46.0% type 1 MI 73.0% type 2 MI	56.4% type 1 MI 43.6% type 2 MI	2419 (USA)	Rochester Epidemiology Project (linked medical records)
Corpataux et al., 2020[88]	34,70 %	43.4% CCS 56.6% ACS 26.8% STEMI	16 580 (Switzerland)	Bern PCI registry
Ueki et al., 2020[89]	39,40 %	44.1% CCS 55.9% ACS 26.1% STEMI	12 121 (Switzerland)	Bern PCI registry
Gragnano et al., 2021[67]	39% CCS 31% ACS	43.5% CCS 56.5% ACS 26.8% STEMI	16 821 (Switzerland)	Bern PCI registry
Doomun et al., 2021[90]	32,70 %	About 32.7% CCS 57.2% ACS 22.7% STEMI	1080 (Switzerland)	Cardio-Fribourg registry
Abu-Assi et al., 2022[5]	29.5%	100% ACS 53.4 STEMI	4412 (Spain)	CardioCHUVI ACS registry
Natsuaki et al., 2019[91]	43 %	36% MI Rest unclear	13 058 (Japan)	CREDO-KYOTO registry
Nakamura et al., 2021[6]	50,80 %	67.8% CCS 32.2% ACS 14.5% STEMI	6267 (Japan)	PENDULUM registry
Watanabe et al., 2021[92]	35 %	61.8% CCS 38.2% ACS 18.6% STEMI	3009 (Japan)	STOPDAPT-2 sub-analysis (RCT)
Natsuaki et al., 2021[93]	48 %	58.4% CCS 41.6% ACS 30.8% STEMI	13 258 (Japan)	CREDO-KYOTO registry
Miura et al., 2020[94]	55 %	62% UAP 21% NSTEMI 17% STEMI	1193 (Japan)	Unlcear (retrospective single-center study)
Fujii & Ikari 2021[95]	42.9%	100% STEMI	939 (Japan)	Tokai University School of Medicine database
Kang et al., 2024[7]	20,40%	33.1% CCS 66.9% ACS 34.6% MI	325 417 (Korea)	Korean National Health Insurance Review and Assessment Service database
Marquis-Gravel et al., 2021[96]	79.7%	73.0% CCS 27.0% ACS 9.6% MI	3635 (International)	LEADERS FREE and LEADERS FREE II
Sorrentino et al., 2020[97]	22,80 %	17.0% MI Rest unclear	10 502 (USA/Asia)	Several PCI registries
Inan et al., 2024[98]	25%	100% STEMI	1441 (Unclear)	Unclear (retrospective single-centre study)

Values are either directly retrieved from the source publications or calculated from the presented data. Silent ischemia is considered CCS in the present table.
HBR, high bleeding risk; ARC-HBR, academic research consortium for high bleeding risk; CCS, chronic coronary syndrome; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomised controlled trial.

2.4.1.2 Performance of the Academic Research Consortium for High Bleeding Risk criteria

The ARC-HBR criteria have been validated in numerous studies and patient groups. A few different methods have been used. Most commonly researchers report incidences of bleeding events comparing the HBR group and the non-HBR group and the criteria are evaluated to be successful, if 1-year BARC 3 or 5 bleeding incidence among HBR patients exceeds the 4% threshold set by the ARC-HBR. Secondly, the performance of individual ARC-HBR criteria is assessed by reporting 1-year major bleeding incidence among patients fulfilling a single criterion in isolation (without fulfilling any other ARC-HBR criteria). By the ARC-HBR definition, a major criterion should in isolation confer a bleeding risk exceeding the 4% threshold. Another strategy is to enter all the individual ARC-HBR criteria into a multivariable regression model and find out which individual criteria remain independent bleeding predictors. These approaches assume that the ARC-HBR criteria include all significant bleeding predictors and possible other confounding factors associated with bleeding are neglected. Only few studies have included adjustment for other factors. The additive impact of multiple ARC-HBR criteria has been evaluated by reporting bleeding incidences when the HBR definition has been fulfilled multiple times (1 x HBR, 2 x HBR etc.) or by using ARC-HBR score. In the score, each fulfilled major criterion grants 1 point and minor criterion 0,5 points. Thus, a score of ≥ 1 is considered HBR. **Table 3** summarises the excess bleeding risk observed in HBR patients worldwide and the predictive ability of the criteria.

Table 3. Performance of the ARC-HBR criteria for bleeding risk prediction in patients with ACS and CCS.

Reference	Bleeding risk HBR vs non-HBR, HR (95% CI)	Cumulative bleeding incidence HBR vs non-HBR	AUC (95% CI) for HBR vs non-HBR (Binary)	Bleeding definition and follow-up duration
Cao et al., 2020[85]	3.10 (2.54-3.79)	9.1% vs 3.2%	0.64 (0.61-0.66)	Comparable to ≥ BARC 3a severity 1-year
Nicolas et al., 2022[86]	3.86 (2.63-5.69) in MI 2.65 (1.92-3.68) in CCS	19.5% vs 5.5% in MI 6.8% vs 2.6% in CCS	-	Comparable to ≥ BARC 3a severity 1-year
Breen et al., 2024[87]	6.5 (3.7-11.4) type 1 MI 15.6 (3.8-63.8) type 2 MI	-	-	Based on diagnosis codes 5.5 years median
Corpataux et al., 2020[88]	3.18 (2.72-3.72)	7.9% vs 2.5%	-	BARC 3 or 5 1-year
Ueki et al., 2020[89]	3.44 (2.8-4.17)	6.4% vs 1.9%	0.67 (0.64-0.70)	BARC 3 or 5 1-year
Gragnano et al., 2021[67]	-	-	0.67 (0.64-0.69) in ACS * 0.72 (0.69-0.75) in CCS *	BARC 3 or 5 1-year
Doomun et al., 2021[90]	7.5 (3.8-14.7)	10.5% vs 1.5%	-	BARC 3 or 5 2-years
Abu-assi 2022[5]	7.3 (5.1-10.4)	9.4% vs 1.3%	0.74 (0.71-0.77)	BARC 3 or 5 1-year
Natsuaki et al., 2019[91]	2.97 (2.67-3.31)	10.4% vs 3.4%	-	GUSTO moderate/severe 1-year
Nakamura et al., 2021[6]	3.00 (2.11-4.27)	4.2% vs 1.4%	0.68 (0.64-0.72)	BARC 3 or 5 1-year
Natsuaki et al., 2021[93]	-	30.1% vs 14.0% in ACS 21.9% vs 8.8% in CCS	-	BARC 3 or 5 5-years
Miura et al., 2020[94]	2.76 (1.80-4.38)	16.2% vs 5.7%	0.60 (0.55-0.64)	BARC 3 or 5 8-years
Fujii & Ikari 2021[95]	-	13.7% vs 6.7%	0.60 (CI not reported) #	BARC 3 or 5 1-year
Kang et al., 2024[7]	3.12 (3.04-3.21)	23.9% vs 8.9%	0.64 (0.63-0.64) *	BARC 3 or 5 5-years δ
Marquis-Gravel et al., 2021[96]	2.43 (1.61-3.67)	8.2% vs 3.5%	-	BARC 3 or 5 1-year
Sorrentino et al., 2020[97]	3.36 (2.61-4.34)	5.0% vs 1.5%	-	TIMI minor or major or GUSTO moderate/severe 1-year
Inan et al., 2024[98]	-	5.1% vs 2.9% **	-	BARC 3 or 5 In-hospital

Values are directly retrieved from the source publications.
*For ARC-HBR score
#Unclear whether c-statistics is calculated for binary HBR definition
δ Median follow-up 5.2 years (interquartile range 2.8-7.5 years)
**Crude rate. Calculated based on presented data.
HBR, high bleeding risk; ARC-HBR, academic research consortium for high bleeding risk; HR, hazard ratio; CI, confidence interval; AUC, area under the receiver-operating characteristic curve; BARC, bleeding academic research consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; TIMI, Thrombolysis in Myocardial Infarction.

The ARC-HBR criteria have consistently identified patients with increased bleeding risk worldwide. The 1-year major bleeding risk among HBR patients seems to be about 3-fold compared to non HBR. The excess risk continues even further with follow-up durations up to 8 years [94]. The 1-year major bleeding incidences among HBR patients exceeds the 4% threshold and rises to 20% in certain populations, such as those presenting with a MI [86]. A meta-analysis including 10 ARC-HBR validation studies concluded that the criteria successfully identify patients at increased bleeding risk [99]. HBR patients had 2.5-fold increased risk of bleeding with area under the receiver-operating characteristic curve (AUC) value of 0.64 (CI 0.60-0.68). It is noteworthy that this meta-analysis did not include a more recently published study, which is the largest ARC-HBR evaluation study ever published with a study population almost 5-times larger than the entire meta-analysis [7]. The study included over 320 000 Korean PCI treated patients with 67% ACS. The HBR group had 3-fold increased risk of major bleeding during the 5-year follow-up (HR 3.12, CI 3.04-3.21, incidences 23.9% and 8.9%). The AUC of 0.638 (CI 0.634-0.642) was the same as in the meta-analysis. While AUC of 0.64 might not seem remarkable, the researchers reported > 80% specificity and negative predictive value for the ARC-HBR criteria in terms of predicting bleeding events. This suggests that patients not fulfilling the criteria are likely to be at low bleeding risk and supports using the criteria in bleeding risk prediction during clinical practice. Unfortunately, subgroup analyses in different categories of ACS were not performed. While the large study population provides robust observations, a notable limitation of the study is the inclusion of only Korean patients. It is known that bleeding and ischemic risk profiles differ between East Asian patients who tend to have higher risk for bleeding and lower risk for ischemic complications compared with others [100,101]. Therefore, the results might not be entirely applicable to other populations. Furthermore, many of the ARC-HBR criteria were modified due to the registry-based study protocol. Finally, due to the very large study population, endpoint adjudication by reviewing patient records was not feasible. A modified major bleeding definition was used (leading to admission and red blood cell transfusion or death), which could cause differences in results compared to other studies with adjudicated BARC bleeding endpoints.

It should be noted that elderly patients are often underrepresented in bleeding risk studies, which could cause issues since the predictive performance of some bleeding risk scores seems to decline in older populations [102]. Studies validating the ARC-HBR criteria in the elderly are lacking. The ARC-HBR criteria were not associated with increased risk of post discharge bleeding (as determined by Cox regression and Kaplan-Meier analysis) in a smaller cohort of ACS patients with mean age of 81 years [103]. However, both the HBR and non-HBR groups exceeded ≥ 4% major bleeding incidence at 1-year.

Corpataux et al., presented one of the most robust ARC-HBR validation studies to date [88]. The study population included 16 580 patients from the Bern PCI registry with over 50% presenting with ACS. Data in the registry was prospectively collected and patients were followed up to 1-year after PCI. Endpoints were adjudicated using original source documents. Unmodified form of the ARC-HBR criteria was used (with exception of planned surgery on DAPT, which was not analysed), which was possible due to implementing evaluation of some criteria based on patient record review. Major bleeding incidence among the HBR group was 7.9% and only 2.5% in the non-HBR group, corresponding to almost 3.2-fold increased risk. The 3-fold increased risk was observed within and after first 30 days from PCI. Interestingly, about half of all bleeding complications occurred during the first 30 days of follow-up both among the HBR and the non-HBR groups (bleeding incidences 4.06% and 1.18% respectively). The results remained consistent during sensitivity analyses using different bleeding definitions (GUSTO and TIMI). When assessed in isolation, all major criteria exceeded the 4% threshold. However, all but one minor criterion (prior bleeding) also exceeded this bleeding incidence. Results remained the same after excluding access-site bleeding events from the analysis. This indicates, that by the ARC-HBR definition, patients fulfilling only one of these minor criteria should be considered HBR. Furthermore, the minor criteria for age, anaemia and CKD were highly prevalent, which emphasises the importance of these minor criteria. Others have reported similar findings regarding performance of individual criteria. Commonly, minor criteria conferring in isolation > 4% major bleeding risk at 1-year are age ≥ 75 years and CKD [85,91].

Corpataux et al. also reported a stepwise increase in bleeding risk with accumulation of fulfilled criteria as calculated by the ARC-HBR score [88]. Starting from patients fulfilling no criterion with a score of 0, the bleeding incidence was 1.9% and with every increase of 0.5 points, the incidences increased to 4.01%, 5.98%, 7.42%, 8.60%, 12,21%, 12.29% and 17.64% among those with a score of > 3. Although majority of the HBR patients had a score of 1 or 1.5, a third of all HBR patients had a score ≥ 2, which means that a large proportion of patients have accumulated multiple bleeding risk factors and there is variability in bleeding risks among the HBR patients. This highlights the problematic nature of a binary approach to bleeding risk assessment. The issue was addressed in the original source document, but the lack of data prevented the recommendation of a more sophisticated definition. Several studies have replicated the stepwise increase in bleeding risk with accumulating ARC-HBR criteria [6,7,85,86,89–91]. This has been demonstrated both using the ARC-HBR score and by how many times the HBR definition is fulfilled in a patient (essentially with increments of +1 in the ARC-HBR score). It is likely that in future modifications of the ARC-HBR, the binary definition

will be replaced by a system which accounts for the incremental bleeding risk associated with additive bleeding risk factors.

Although the criteria fulfil the ARC-HBR requirement for bleeding risk factors and in the current iteration each major and minor criterion is considered to have equal weights in terms of bleeding risk, evidence suggests that all major criteria do not confer comparable bleeding risks. For example, in a meta-analysis the cumulative major bleeding incidence associated with the major criterion for prior ischemic stroke was about 4.2%, while for severe CKD it was 10% [99]. Clearly these two criteria confer bleeding risks of different magnitudes even though a patient fulfilling either criterion is considered to be at HBR. In the large dataset by Kang et al., the 1-year bleeding incidences associated with each major criterion ranged from 5.8% to 27.7% [7]. It is noteworthy, that there is heterogeneity in the bleeding incidences associated with each individual criterion between studies. This could be explained by the fact that very often studies use modified definitions of the ARC-HBR criteria. However, criteria such as age, CKD, anaemia and platelet count do not have this issue since these parameters are readily available. Still, variability exists among these criteria as well. Results are probably most consistent with age. Those with age ≥ 75 as the only fulfilled ARC-HBR criterion have a 1-year major bleeding incidence of about 5% in most studies [85,88,91].

Another possible explanation for variability in the performance of the individual criteria is unmeasured confounding. While HBR status according to the ARC-HBR definition is clearly associated with increased bleeding risk and individual criteria have been shown to fulfil the definition of bleeding risk factors, patients at HBR have more comorbidities compared to non-HBR [104]. Therefore, it is reasonable to assume, that some of these underlying comorbidities could have a confounding effect to bleeding risk. The criteria are usually assessed in isolation (without the presence of other ARC-HBR criteria). This method does not account for other possible confounding factors. Only few studies have investigated how individual ARC-HBR criteria perform when adjusted for confounding bleeding risk factors and when this has been done, only a minority of the criteria remain independent bleeding predictors. Commonly after adjustment, CKD, anaemia and use of OAC remain predictive of bleeding complications [6,86,89]. However, significant bleeding predictors seem to differ between different clinical presentations. Nicolas et al. reported that after adjustment (with all the ARC-HBR criteria), about half of the criteria were not independent bleeding predictors [86]. Among MI patients, anaemia, CKD and thrombocytopenia were significant ARC-HBR criteria. Conversely, in CCS patients OAC, anaemia, malignancy, age ≥ 75 years and prior bleeding were associated with bleeding. After adjustment for other confounding bleeding risk factors and clinical presentation, from the ARC-HBR criteria anaemia, OAC, malignancy, prior bleeding, prior stroke and planned surgery remained independent predictors of major

bleeding. In a study by Nakamura et al., anaemia, CKD and OAC were significant ARC-HBR criteria in an overall PCI population, but notably, clinical presentation was adjusted for [6]. In a European patient population consisting of half CCS and half ACS (mainly MI), Ueki et al. found out that CKD, anaemia, OAC and prior bleeding were independent bleeding predictors after accounting for confounding variables [89]. Again, clinical presentation was adjusted for. It is noteworthy, that in all of the previously mentioned three studies, the majority of the ARC-HBR criteria were either modified or missing due to restrictions in registry data. Furthermore, some of the ARC-HBR criteria such as liver cirrhosis are rare, which results in wide CIs with non-significant p-values even if they are included in analyses. With larger quantities of patients fulfilling these criteria, a significant association with bleeding risk could be observed.

2.4.1.3 The impact of clinical presentation on bleeding risk

Researchers have reported that clinical presentation plays an important role in bleeding prediction. It seems that presentation with ACS (vs CCS) is an independent bleeding predictor. After formation of the ARC-HBR criteria, Gragnano et al., published a study investigating the impact of clinical presentation on bleeding risk [67]. They enrolled over 17 000 PCI treated patients from the Bern PCI registry. After extensive adjustment for confounding factors using multivariable regression, ACS was found to be associated with increased bleeding risk compared to CCS (HR 1.21, CI 1.01-1.43, 1-year incidences 4.97% vs 3.60%). Bleeding risk increased when moving up in severity of ACS subtypes. Compared to CCS, UAP had no difference, NSTEMI had 1.26-fold (CI 1.04-1.53) increased risk and STEMI had 1.92-fold (CI 1.59-2.31) increased risk. The excess risk among ACS was driven by non-access site bleeding events occurring within 30 days after PCI (HR 2.08, CI 1.60-2.70, incidences 2.25% and 1.09%). The ARC-HBR consensus did not consider presentation with ACS to be a HBR criterion, because the previously observed higher bleeding risk in ACS was thought to be caused by more intense antiplatelet treatment in this high-risk patient group. However, the previously discussed study also adjusted for the intensity and duration (12-month DAPT vs shorter duration) of antiplatelet treatment and ACS prevailed as a bleeding risk factor. Natsuaki et al. reported similar findings regarding the elevated bleeding risk in ACS compared to CCS within the first 30 days after PCI (HR 3.35, CI 2.78-4.04, incidences 11.1% and 3.0%) [93]. Another study reported that presentation with MI compared to CCS is an independent bleeding predictor with 1.64-fold increased risk and that the performance of individual ARC-HBR criteria varies based on clinical presentation [86]. Studies prior to the ARC-HBR definition have reported similar findings regarding clinical presentation as a bleeding risk factor [76,105]. However, there are previous

bleeding risk scores where clinical presentation was not associated with increased risk, such as PARIS and PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) [106,107]. This could at least partly be explained by the time-dependency of increased risk among ACS, since these risk scores focused on long-term bleeding risk. Conversely, in prior bleeding risk scores focusing on short-term bleeding, clinical presentation prevailed as a bleeding predictor [108,109].

The mechanism of increased bleeding risk in ACS is not properly understood but it could be related to systemic inflammation. Inflammatory reactions seem to play a role in the pathogenesis of thrombus formation and atherosclerotic plaque instability leading to an ACS [110]. Inflammation and hemostasis are connected by several pathways involving cytokines, platelets and white blood cells [111]. The pro-inflammatory state encountered in ACS could therefore partially explain the elevated bleeding risk in these acute conditions by inducing a pro-hemorrhagic state [111]. This is in theory supported by the previously mentioned observation that the eleveted bleeding risk in ACS vs CCS is encountered only during the following 30 days and that STEMI seems to be associated with the highest bleeding risk [67]. Inflammatory responses tend to be more potent during the early phase and with worsening clinical presentation in ACS [110].

2.4.1.4 The impact of high bleeding risk on ischemic outcomes

In addition to increased bleeding risk, HBR patients also suffer more ischemic complications such as MI, stroke and cardiovascular death compared to non-HBR [7,85,86,88–90,94]. Usually, studies report cumulative incidences or unadjusted HRs between the HBR and non-HBR groups with only few studies investigating individual criteria or adjust for confounding factors. The risk varies based on used endpoints. The risk of MI seems to be about 1.6-2-fold higher in HBR patients [85,88,104]. On further inspection, the elevated risk in the HBR group is observed in patients presenting with a MI (HR 1.92, CI 1.12-3.28, 1-year cumulative incidences 10.2% vs 4.9%), whereas no difference in CCS patients [86]. The risk of MI or stroke in a longer 5-year follow up is higher in the HBR group (16.1%) as compared to the non-HBR group (8.9%) with a 2-fold increased risk, with 1-year incidences of 8.7% vs 5.0% [91]. Mortality is higher among HBR patients, with the risk of 1-year all-cause mortality as well as cardiovascular mortality being about a 3 to 4-fold increase compared to non-HBR [88,99,104]. Although the risk of both bleeding and ischemic complications is elevated in HBR, the risk of bleeding is greater. In a long-term follow-up Kang et al. reported 2.5-fold increased risk of cardiac death, myocardial infarction or ischemic stroke, while major bleeding risk was 3.1 times higher among HBR [7].

While HBR-patients experience more ischemic complications, it is unclear if this is caused by bleeding risk status itself, some of its components or confounding risk factors. Patients at HBR are older and have increased burden of cardiovascular risk factors, which could explain higher risk of ischemic complications [85]. Furthermore, some bleeding risk criteria such as CKD, anaemia and prior stroke are well known ischemic risk factors [112–114]. Ueki et al. investigated the ischemic risk associated with the ARC-HBR criteria in 12 000 PCI-treated patients (56% ACS) [89]. A device-oriented endpoint consisting of cardiac death, target vessel myocardial infarction, and target lesion revascularisation was reported at 1-year follow-up. The cumulative incidence was 12.5% in the HBR group and 6.1% in the non-HBR group. Additionally, multivariable regression analysis was used to determine which ARC-HBR criteria are independent predictors of the device-oriented endpoint, with all the criteria as well as several other clinically important variables entered into the model. Of the ARC-HBR criteria, age ≥ 75 years, CKD and anaemia remained statistically significant predictors after adjustment, with severe or end-stage CKD associated with highest risk (2-fold increased).

Understanding how bleeding and ischemic risks are related to prognosis when managing ACS patients with HBR is essential. Urban et al. developed a model for predicting bleeding and thrombotic complications in a pooled cohort of HBR patients from several RCTs and one registry undergoing PCI [59]. They identified risk factors for both endpoints and these were included in the prediction model. Adjusted mortality risk associated with both complications was further evaluated and implemented into the model. Thus, the model predicts mortality-weighed bleeding risk versus thrombotic risk and could help in clinical decision making when contemplating which risk is greater in an individual patient. As expected, several clinical characteristics were associated with both outcomes, such as anaemia and CKD from the ARC-HBR criteria. Interestingly smoking was associated with equal risk for both bleeding and thrombotic events.

2.4.2 Other bleeding risk scores

Before the ARC-HBR, several other bleeding risk scores existed, with their respective definitions for HBR (such as PRECISE-DAPT score ≥ 25) [106,107,115–118]. These scores omitted some important variables known to be associated with increased bleeding risk, such as liver disease, bleeding diathesis and thrombocytopenia due to their low prevalence in CAD or because they were not available in the datasets used for derivation of the scores (prior bleeding, NSAIDs, malignancy). The predictive ability of these scores (AUC values) in development and validation cohorts ranges between 0.63 to 0.73. This is in line with the performance of the ARC-HBR criteria.

2.5 Management strategies to prevent bleeding

2.5.1 Choice of P2Y12 receptor inhibitor

Clopidogrel was compared with the more potent inhibitors prasugrel and ticagrelor in two pivotal RCTs. The TRITON-TIMI 38 trial compared DAPT with clopidogrel or prasugrel in 13 000 ACS patients [42]. At 14.5 months compared with clopidogrel, prasugrel reduced MACE by 19% (HR 0.81, CI 0.73-0.90, incidences 12.1% vs 9.9%) but increased non-CABG-related TIMI major bleeding by 32% (HR 1.32, CI 1.03-1.68, incidences 1.8% vs 2.4%). This trade-off resulted in neutral effect in patients aged ≥ 75 years and those with body weight < 60kg and in net harm in patients with prior stroke. There was no statistically significant difference in overall mortality between the treatment groups (incidences 3.2% for clopidogrel and 3.0% for prasugrel). Later, a meta-analysis showed similar results. Compared to clopidogrel, prasugrel reduced ischemic events but increased major bleeding risk by 26% (HR 1.26, CI 1.01-1.56) [119]. No composite ischemic endpoint was reported but the risk of MI was reduced by 19% (HR 0.81, CI 0.67-0.98) and the risk of stent thrombosis by 50% (HR 0.50, CI 0.38-0.64) among prasugrel users.

The PLATO trial showed that DAPT with ticagrelor reduced 1-year MACE by 16% compared to DAPT with clopidogrel (HR 0.84, CI 0.77-0.92, incidences 9.8% vs 11.7%) in 18 000 ACS patients [41]. On the other hand, ticagrelor was associated with a 25% increase in non-CABG-related TIMI major bleeding (HR 1.25, CI 1.03-1.53, incidences 2.8% vs 2.2%). Ticagrelor reduced overall mortality (HR 0.78, CI 0.69-0.89, incidences 4.5% vs 5.9%). The POPular AGE (Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-risk Elderly) trial enrolled ACS patients aged ≥ 70 years and randomised them to receive DAPT with either clopidogrel or ticagrelor/prasugrel (although 95% received ticagrelor) [120]. Compared to ticagrelor/prasugrel, clopidogrel reduced major or minor bleeding by 29% (HR 0.71, CI 0.54-0.94) and was non-inferior regarding net clinical benefit consisting of major or minor bleeding, MI, stroke and all-cause mortality. The reduction in bleeding events without increased risk of ischemic events with clopidogrel compared to ticagrelor was later demonstrated in a large registry-based study [121].

Compared to prasugrel, the use of ticagrelor increased the composite endpoint of 1-year death, MI or stroke by 36% (HR 1.36, CI 1.09-1.70, incidences 6.9% vs 9.3%) without increase in BARC 3-5 bleeding complications (incidences 4.8% vs 5.4%, p = 0.46) in the ISAR-REACT 5 (The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial, which enrolled 4000 ACS patients [122]. Sub-analyses showed that the results were consistent in

NSTE-ACS but among STEMI, no difference in MACE or major bleeding was observed [123,124]. However, the ticagrelor group had an increased risk of MI. There was no difference in bleeding or ischemic events between prasugrel and ticagrelor in a meta-analysis of RCTs [119]. The meta-analysis also showed that compared to clopidogrel only ticagrelor reduced overall mortality. Altogether, it seems that clopidogrel could be the best choice for patients at HBR to reduce bleeding complications.

2.5.2 Duration of dual antiplatelet therapy treatment

DAPT for 12 months has been the primary recommended antiplatelet strategy for over a decade. The recommendation was based on the results of the CURE trial, which compared ASA monotherapy to DAPT with ASA and clopidogrel in NSTE-ACS patients [27]. However, the trial was not designed to evaluate the duration of DAPT treatment but rather DAPT vs SAPT. Moreover, patients received clopidogrel for 3-12 months with a mean duration of 9 months. Only about 38% of clopidogrel users continued the drug for 12 months. Nevertheless, guidelines adopted the 12 months DAPT duration recommendation.

In 2015, a meta-analysis of RCTs investigating DAPT durations compared the efficacy and safety of short DAPT (3–6 months) or extended DAPT (> 12 months) to standard 12-month DAPT in patients with ACS or CCS [125]. Short DAPT reduced the risk of major bleeding by 40% (odds ratio 0.58, CI 0.36-0.92) without excess risk of stent thrombosis or MI compared to standard DAPT. There was no significant difference in mortality between the groups. Extended DAPT increased bleeding risk by 60% (odds ratio 1.62, CI 1.26-2.09) compared to standard 12-month DAPT while reducing very late stent thrombosis and MI. However, extended DAPT increased overall mortality (odds ratio 1.30, CI 1.02-1.66) compared to standard DAPT. The results demonstrated the time-dependent incremental bleeding risk associated with DAPT and suggested that short DAPT could be beneficial. Another meta-analysis, which pooled either individual patient data or aggregate data from 12 DAPT-duration RCTs showed that short DAPT compared to prolonged DAPT (≤ 6 months vs ≥ 12 months) reduced bleeding related deaths (HR 0.65, 95% CI 0.43-0.99) with no difference in non-bleeding related deaths [126]. Overall mortality was 15% lower in the short-DAPT group (HR 0.85, CI 0.73-1.00). It is noteworthy that these early DAPT duration trials enrolled low-risk populations in terms of ischemic risk. On the contrary, the SMART-DATE (Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes) trial showed a benefit of prolonging DAPT ≥ 12 months versus 6-month DAPT in reducing MI but it came with increased bleeding risk [127]. There was no difference in all-cause mortality. The trial enrolled exclusively high ischemic risk ACS-patients while excluding some HBR patient

groups such as those with previous recent bleeding. Furthermore, even though the exclusion criteria did not include CKD, the prevalence was only about 1% in the entire study population. The use of OACs was not reported neither any information about baseline anaemia. These were also not listed as exclusion criteria. Assessing the bleeding risk of the enrolled population based on baseline characteristics is therefore challenging, but the 18-month BARC 3 or 5 bleeding incidence in the ≥ 12-month DAPT group (which had a median DAPT duration of 18-months) was only 0.8%, indicating a very low bleeding risk population. Therefore, the results suggest a benefit of prolonged DAPT in patients with high ischemic risk, without increased bleeding risk.

The decision of DAPT duration should be based on individual patients ischemic and bleeding risks. However, based on existing evidence, it seems that bleeding risk should be the primary consideration. The PRECISE-DAPT score was designed to predict post-discharge bleeding in patients receiving DAPT [107]. The investigators combined data from 5 DAPT-duration RCTs and developed a score based on 5 variables. Those with a score ≥ 25 are considered HBR. They also retrospectively compared the efficacy and safety of different DAPT-durations in different bleeding risk categories. According to the results, ≥ 12-month DAPT-duration increased bleeding risk only in HBR patients without providing ischemic benefit. Additionally, ≥ 12-month DAPT did not increase bleeding risk in non-HBR patients and in this group, a reduction in ischemic events was observed. Similar findings supporting the concept that bleeding risk holds a higher priority compared to ischemic risk when choosing DAPT durations have been reported in a pooled dataset from several RCTs and in a retrospective analysis of the SMART-DATE trial [128,129].

In recent years several RCTs have investigated DAPT durations of ≤ 3 months versus longer durations to determine the most favourable treatment strategy to minimise bleeding without increasing ischemic risk. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial enrolled patients with high ischemic or bleeding risk and randomised those who remained event free 3 months after PCI to continue DAPT with ASA and ticagrelor or switch to ticagrelor monotherapy (ticagrelor and placebo) [130]. At 1-year, the monotherapy group had 44% lower risk (HR 0.56, CI 0.45-0.68, incidences 4.0% vs 7.1%) of BARC 2, 3 or 5 bleeding without difference in MACE consisting of all-cause death, nonfatal MI or nonfatal stroke (incidence 3.9% in both groups). Major bleeding risk (BARC 3 or 5) was also lower among the monotherapy group (HR 0.49, CI 0.33-0.74, incidences 1.0% vs 2.0%).

The MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen) trial compared 1-month (median duration 34 days) DAPT to ≥ 3 months (median duration 193 days) DAPT after PCI in HBR patients with

minimal exclusion criteria [131]. This resulted in almost 50% presenting with ACS and high prevalence of ischemic risk factors such as over 30% diabetes and 19% prior MI. However, STEMI patients were underrepresented with only about 10% of the population. The trial definition for HBR closely resembled the ARC-HBR definition with the addition of the PRECICE-DAPT score (score ≥ 25 as inclusion criterion) and the mean number of fulfilled HBR criteria among the study population was 2, suggesting a HBR population. At 1-year, 1-month DAPT was non-inferior in terms of net adverse clinical events consisting of all-cause death, MI, stroke or BARC 3 or 5 bleeding (incidence 7.5% in 1-month DAPT group vs 7.7% in ≥ 3 months) and composite endpoint of all-cause death, MI or stroke (incidences 6.1% vs 5.9%). The shorter DAPT regimen reduced the risk of BARC 2, 3 or 5 bleeding by 32% (HR 0.68, CI 0.55-0.84, incidences 6.5% vs 9.4%). However, the difference was driven by BARC 2 bleeding (BARC 3-5 incidence among short DAPT 2.3% and 2.5% among ≥ 3-month DAPT). A sub-analysis in patients with ACS, complex PCI or both had similar results [132]. A recent meta-analysis of 9000 HBR patients managed with PCI from RCTs compared short DAPT (1-3 months) with standard DAPT of ≥ 6 months [133]. Short DAPT reduced major bleeding (risk ratio 0.80, CI 0.64-0.99), major or clinically relevant bleeding (risk ratio 0.76, CI 0.61-0.94) and cardiovascular mortality (risk ratio 0.79, CI 0.65-0.95). There was no difference in all-cause death or ischemic endpoints and the results were consistent regardless of clinical presentation. Overall, the evidence indicates that shorter DAPT could be optimal for HBR patients. However, STEMI patients seem to be underrepresented in the existing DAPT trials challenging the generalisability of these findings to this high ischemic risk population. One smaller RCT has investigated abbreviated DAPT in STEMI. The DAPT-STEMI (Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction) trial compared 6 vs 12-month DAPT in 870 STEMI patients who were event free at 6 months after PCI [134]. The enrolment took place between 2011 and 2015. The abbreviated DAPT regimen was non-inferior regarding the patient-oriented composite endpoint consisting of all-cause mortality, MI, any revascularisation, stroke and TIMI major bleeding at 18 months after randomization (HR 0.73, CI 0.41-1.27, incidences 4.8% and 6.6%). However, due to limitations in the sample size (arising from issues in enrolment and excluding subjects with early events) the trial was not able to reliably assess individual endpoints.

Regarding the choice of P2Y12 receptor inhibitor for abbreviated DAPT, ticagrelor has the strongest evidence base at the moment as demonstrated by a recent individual patient data meta-analysis of randomised DAPT trials investigating ticagrelor monotherapy after PCI [135]. The analysis compared abbreviated DAPT (from 2 weeks to 3 months) and standard 12-month DAPT. In a population consisting of 23 000 patients, abbreviated DAPT was non-inferior regarding major adverse

cardiac or cerebrovascular events (MACCE) (all-cause death, MI or stroke) and reduced major bleeding risk by almost 60% (HR 0.43, CI 0.34-0.54, cumulative incidences 0.9% vs 2.1%). The results were consistent among the ACS subgroup. Interestingly abbreviated DAPT reduced the risk for BARC 3 or 5 bleeding among ACS (HR 0.34, CI 0.26-0.45, incidences 0.8% vs 2.4%) but not among those without ACS (HR 0.86, CI 0.55-1.36). Furthermore, among ACS patients, abbreviated DAPT with ticagrelor monotherapy was associated with 60% bleeding reduction regardless of bleeding risk, suggesting that abbreviated DAPT should not be reserved only for HBR patients. About 25% of the study population had STEMI but no subgroup analysis among them was performed.

2.5.3 Dual antiplatelet therapy de-escalation

Another antiplatelet strategy to minimise bleeding is DAPT de-escalation. The idea is to start management with a potent P2Y12 inhibitor and lower the dose or switch to clopidogrel after an initial duration of potent DAPT. This strategy is based on ischemic risk being highest early after PCI, while bleeding risk continues and might increase with ongoing potent antiplatelet treatment [136]. In de-escalation strategies, clopidogrel metabolism should be considered due to polymorphism of the gene encoding CYP2C19, which is an essential enzyme in clopidogrel bioactivation [137]. Several alleles are associated with decreased enzyme function and subsequent thrombocyte inhibition, leading to increased thrombotic risk after PCI [138]. Therefore, the choice to de-escalate from potent inhibitors to clopidogrel could be guided with results from CYP2C19 genetic testing or platelet function testing. This could improve safety of de-escalation due to 30% of patients being clopidogrel non-responders [139]. The TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial showed that platelet function testing guided de-escalation at 2 weeks post ACS from prasugrel to clopidogrel was non-inferior to continuing prasugrel for 12 months in terms of net clinical benefit [140]. There was no significant difference in bleeding (BARC 3 or 5 incidences 2% and 1% for de-escalation vs control groups). The POPular Genetics (Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment) trial demonstrated genotyping guided de-escalation in STEMI from potent P2Y12 inhibitors to clopidogrel was non-inferior in thrombotic complications and reduced overall bleeding (HR 0.78, CI 0.61-0.98, incidences 9.8% among de-escalation group vs 12.5% in the standard treatment group) but not major bleeding (BARC 3-5 incidence 2.5% vs 2.3%) [141]. Unguided de-escalation from ticagrelor to clopidogrel at 1-month after an ACS was compared to continuing DAPT with ticagrelor for 12-months in the TALOS-AMI (TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction)

trial [142]. De-escalation reduced net adverse clinical events (HR 0.55, CI 0.40-0.76, incidences 4.6% vs 8.2%) and overall bleeding (HR 0.52, CI 0.35-0.77, incidences 3.0% vs 5.6%). BARC 3 or 5 bleeding risk was also lower in the de-escalation group (HR 0.53, CI 0.28-0.99, incidences 1.2% vs 2.3%) The HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial - Comparison of REDUCTION of PrasugrEl Dose & POLYmer TECHnology in ACS Patients) trial investigated de-escalating prasugrel dose from 10mg to 5mg at 1 month compared to continuing DAPT with 10mg prasugrel [143]. De-escalation was associated with reduced net adverse clinical events (HR 0.70, CI 0.52-0.92, incidences 7.2% vs 10.1%) and overall bleeding (HR 0.48, CI 0.32-0.73, incidences 2.9% vs 5.9%) Major bleeding incidences were low and there was no significant difference between the groups (0.8% among the de-escalation group and 0.7% among the standard therapy group. It should be noted that the trial enrolled low-risk ACS patients (mostly UAP, age < 75). These trials demonstrate that de-escalation could be a safe strategy to minimise bleeding complications.

3 Aims

The aims of this dissertation are to:

1. Examine the prevalence of HBR according to the ARC-HBR criteria in ACS patients. (study I and study III)
2. Evaluate 1-year actionable bleeding incidence among suspected NSTEMI patients. (study II)
3. Investigate 1-year major bleeding incidence among STEMI, evaluate performance of individual ARC-HBR criteria and identify possible other significant bleeding risk factors. (study III)
4. Determine the impact of HBR on 1-year MACCE after PPCI in STEMI and to assess the significance of comorbidities. (study IV)

4 Materials and Methods

4.1 Study design and patient populations

4.1.1 Study I and II

Study populations consisted of consecutive adult suspected NSTEMI patients admitted to the emergency department of Turku University Hospital between 1 January 2019–30 June 2019 and who were hospitalised. Admission data was collected by a database search of patient-information system Safir Spider version 2.22.101.2461 (San Sai Solutions Oy, Turku, Finland) conducted by Auria Clinical Informatics. If a patient had several visits during the study period, only the first one was registered. The patient-information system was searched for emergency department visits with admission codes for chest pain. Hospitalised patients with suspected NSTEMI or UAP were evaluated. The primary cause of hospitalisation was adjudicated by reviewing electronic patient records and NSTEMI was defined according to the fourth universal definition of MI [8]. Those hospitalised for non-cardiac causes were excluded. Additionally for study II, those who died during index-hospitalisation or were lost during follow-up were excluded.

Laboratory values were acquired from the database search. Bleeding risk was assessed according to the ARC-HBR criteria (**Table 1**.). Patients were considered to be at HBR if at least 1 major or 2 minor ARC-HBR criteria were met. Fulfilment of the criteria was adjudicated by reviewing electronic patient records. Additionally, for criteria such as liver cirrhosis and prior ICH or stroke, relevant baseline characteristics were obtained from the database search using ICD-10 diagnosis codes and these were compared to the results from patient record review. If the database search result differed from adjudicated criteria, patient records were double checked but ultimately record review results were preferred. Management strategy was evaluated from patient records. In study II, medication was adjudicated from patient records and double checked as previously mentioned by database search results using Anatomical Therapeutic Chemical codes.

4.1.2 Study III and IV

The institutional database of The Hospital District of Southwest Finland (VSSHP) was searched for hospitalisations for STEMI between 2016-2022 according to ICD-10 codes I21.0-I21.3. All consecutive adults presenting with STEMI and residing in VSSHP catchment areas at the time of index hospitalisation were included to ensure reliable follow-up data. For study IV, only STEMI patients managed with PPCI were included in the study population. PPCI was defined as PCI within < 24 hours of symptom onset. For patients admitted more than once during the study period, only the first admission was included. Index STEMI diagnosis was confirmed by the authors using electronic patient records according to the fourth universal definition of MI. Patients with adjudicated diagnosis other than STEMI were excluded. In case of uncertainty regarding diagnosis, the final decision was made by an independent interventional cardiologist (AY).

Baseline laboratory values were acquired from the database search. Medication, smoking status, alcohol consumption, left ventricular ejection fraction (LVEF), comorbidities, prior cardiac procedures, management, and prescribed duration of DAPT were gathered from patient records. LVEF was searched from echocardiography reports during the index-hospitalisation. If visual inspection and measured LVEF were used, the measured one was preferred. Smoking status was adjudicated by reviewing patient records during the index-hospitalisation and follow-up. Text searches from all existing patient records at any time were also conducted with appropriate phrases. Current smoking was defined as actively smoking at the time of the index STEMI and former smoking as history of smoking, but patient had quit before the index event. Patient was considered never smoking if it was directly mentioned in patient records or smoking was not mentioned at all in the records. As a sensitivity analysis, those who had no mention of smoking were excluded. Alcohol consumption was evaluated by reviewing patient records and text search results. Excessive alcohol consumption was defined as any of the following within 12 months of the index-hospitalisation: alcohol-related diagnosis, hospitalisation or emergency department visit due to excessive alcohol use, excessive consumption mentioned in patient records, alcohol doses per week > 22 for men and > 11 for women. If alcohol consumption was not mentioned, this was considered non-excessive consumption. In a separate sensitivity analysis, those who had no mention of alcohol were excluded.

Bleeding risk was assessed according to the ARC-HBR criteria (**Table 1**.). Patients were considered to be at HBR if at least 1 major or 2 minor ARC-HBR criteria were met. Fulfilment of the criteria was adjudicated by the authors by reviewing electronic patient records. The major ARC-HBR criterion for prior stroke was slightly modified and defined as follows: previous spontaneous ICH at any time or traumatic ICH within the past 12 months; presence of brain arteriovenous

malformation; ischemic stroke within the past 6 months defined as sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that persist for ≥ 24 hours or until death and confirmed by neuroimaging or if no imaging was performed, the diagnosis was set by treating neurologist.

4.2 Endpoint definitions and follow-up

Follow-up duration for study II was 1-year starting from the discharge date. The follow-up duration for studies III and IV was 1-year starting from the hospitalisation date until first occurrence of endpoint or 365 days. The primary endpoint for study II was post-discharge non-access site BARC 2, 3 or 5 bleeding (actionable bleeding) [4]. For study III the primary endpoint was non-access site BARC 3 or 5 bleeding (major bleeding). Bleeding endpoints were adjudicated by reviewing patient records. Additionally in study III and IV, death certificates were inspected to identify possible fatal BARC 5 bleeding events occurring outside healthcare facilities.

In study IV, the primary endpoint was 1-year MACCE consisting of cardiovascular death, MI (type 1 or type 4 [stent thrombosis]) or ischemic stroke. Cardiovascular death was defined as a matching ICD-10 diagnosis code (**Table 4.**) in death certificate as immediate or underlying cause of death. Undetermined death was considered cardiovascular based on expert consensus [144]. MI and stroke endpoints were adjudicated by reviewing patient records. MI endpoint was defined according to the fourth universal definition. If angiography was not performed, the diagnosis and classification of MI subtype was verified by an independent interventional cardiologist (AY). Ischemic stroke was defined as sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that persists for ≥ 24 hours or until death and confirmed by neuroimaging or if no imaging was performed, the diagnosis was set by a treating neurologist. If such symptoms were attributed to cerebral hypoperfusion resulting from cardiac arrest, they were not considered an endpoint. The secondary endpoint of study IV was 1-year non-access site BARC 3 or 5 bleeding.

Table 4. Diagnosis codes defining cardiovascular death endpoint.

ICD-10 Codes	Description
I00-I02	Acute rheumatic fever
I05-I09	Chronic rheumatic heart diseases
I10-I15	Hypertensive diseases
I20-I25	Ischemic heart diseases
I26-I28	Pulmonary heart disease and diseases of pulmonary circulation
I30-I52, excluding I31.2	Other forms of heart disease, excluding I31.2 (hemopericardium)
I60-I69, excluding I60-I62 and I69.0-I69.2	Cerebrovascular diseases, excluding I60-I62 and I69.0-I69.2 (ICH)
I70-I79, excluding I78 and I79	Diseases of arteries, arterioles and capillaries, excluding I78 (diseases of capillaries) and I79 (disorders of arteries, arterioles and capillaries in diseases classified elsewhere)

ICD-10, International Classification of Diseases 10th revision.
Modified from the original publication IV, Supplementary Table 1. (Reproduced under CC BY licence) Abbreviation for ICH used.

4.3 Statistical analysis

In studies I and II, Statistical analyses were performed using SPSS version 27.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are reported as mean values and standard deviations. Categorical variables are presented as frequencies (percentages). Categorical variables were compared with Pearson's chi-square or Fisher's exact test. For continuous variables, mean values were compared with independent samples t-test. Normality assumptions were verified using Kolmogorov-Smirnov test, skewness and kurtosis. Significance analyses were two-tailed and a p-value < 0.05 was considered significant. In study II, crude bleeding rates at 1-year were reported.

Statistical analyses for study III and IV were conducted with R statistics software (Version 4.3.0, R Foundation for Statistical Computing, Vienna Austria) and SPSS Statistics (Version 27.0.1.0). A p-value < 0.05 was considered significant and significance analyses were two-tailed. Normality was assessed by visual inspection of histograms, computation of Q-Q plots and using skewness and kurtosis. Categorical variables are presented as frequencies (and percentages) and were compared using Chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as mean (SD) or median (IQR) and compared using t-test or Mann-Whitney U test as appropriate.

For study III, univariable and multivariable competing risk analysis with the Fine-Gray subdistribution hazard model with non-bleeding-related death as a competing event was used to estimate the association between baseline

characteristics and bleeding. The proportional hazards assumption was assessed using Schoenfeld residuals. A prespecified multivariable model included individual ARC-HBR criteria with $p < 0.05$ in univariable analysis and variables not included in the criteria that remained significant ($p < 0.05$) in univariable analysis. If both major and minor ARC-HBR criterion of the same variable had $p < 0.05$ in univariable analysis, major criterion was chosen. If significant variables were abundant and the model faced overfitting (more than 1 variable in model per 10 events), variables to be included were chosen based on existing evidence and clinical relevance. Exact bleeding sites other than ICH of newly identified independent bleeding predictors were inspected in post-hoc analyses. The risk of bleeding was reported using subdistributional hazard ratios and cumulative incidence function (CIF) curves. To compare CIFs between groups in the presence of competing risks, Gray's test was employed.

In study IV, univariable and multivariable competing risk analysis with the Fine-Gray subdistribution hazard model with non-cardiovascular death as a competing event was used to estimate the association between baseline characteristics and MACCE. The proportional hazards assumption was assessed using Schoenfeld residuals. The multivariable model included individual ARC-HBR criteria with $p < 0.05$ in univariable analysis. If both major and minor ARC-HBR criterion of the same variable had $p < 0.05$, major criterion was chosen. To avoid overfitting, the number of variables in the model were restricted to 1 variable per 10 endpoint events. Variables not included in ARC-HBR criteria were considered if they had $p < 0.05$ in univariable analysis and were chosen based on existing evidence and clinical relevance. The risk of MACCE and individual endpoints were reported as subdistributional hazard ratios and CIF curves. CIFs between groups were compared with Gray's test. All incidences were cumulative incidences unless otherwise stated. The association of HBR status and BARC 3 or 5 bleeding was evaluated using Fine-Gray subdistribution hazard model with non-bleeding-related death as a competing event and hazard ratios were derived from univariable Fine-Gray regression analyses.

4.4 Ethical considerations

All studies were approved by the Institutional Review Board of VSSHP. A permission to access causes of death was granted by Statistics Finland. Informed consent and ethical board review were waived due to the study designs. According to the Finnish Medical Research Act (488/1999) ethical review is not required for retrospective studies. The legal basis for processing personal data in these studies is public interest and scientific research, EU General Data Protection Regulation 2016/679 (GDPR), Article 6(1)(e) and Article 9(2)(j).

Prior to publications of studies III and IV, the results were inspected for anonymity by Findata, which is the data permit authority for the social and health care sector in Finland. Its activities are based on the Finnish Act on the Secondary Use of Health and Social Data (522/2019). Based on their review, some frequencies and equivalent percentages with values < 3 had to be censored to ensure anonymity of the study subjects. These were reported as the symbol "<" followed by the smallest possible value that was considered anonymised. Censoring did not affect data gathering or the results. Statistical analyses were conducted using the original data values.

5 Results

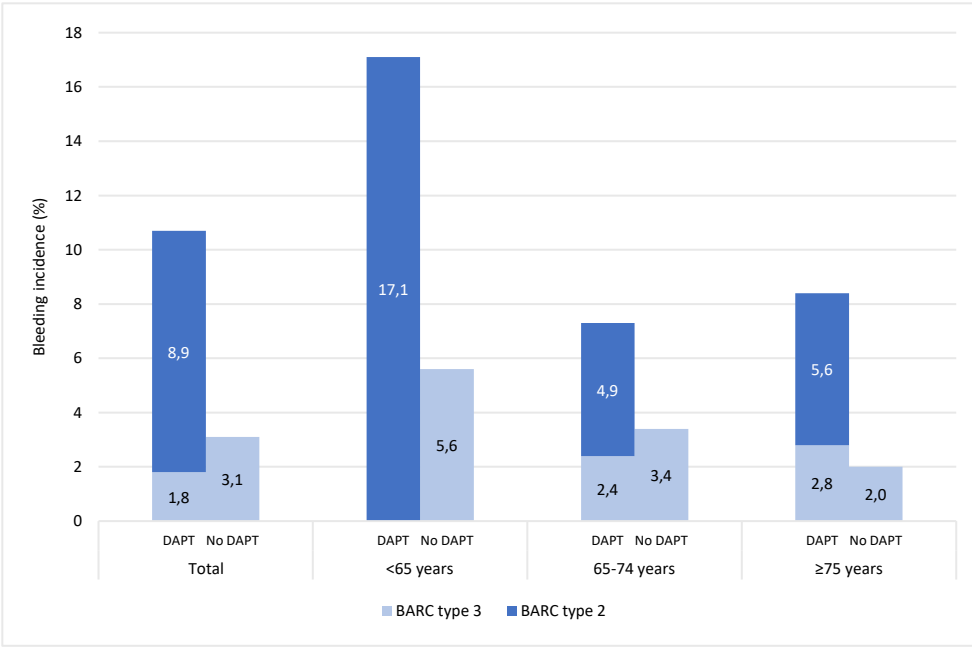
5.1 The prevalence of high bleeding risk and 1-year actionable bleeding incidence among suspected NSTEMI patients (study I and II)

The database search identified 2562 patients admitted to the emergency department of Turku University Hospital due to chest pain, of which 432 were hospitalised and 212 with suspected NSTEMI were included in study I. Adjudicated clinical presentation was type 1 NSTEMI in 68.9% (n = 146), type 2 NSTEMI in 6.1% (n = 13), UAP in 22.2% (n = 47) and takotsubo cardiomyopathy in 2.8% (n = 6). The mean age was 71.7 (11.5) years and 32.1% (n = 68) were female. Overall, 47.6% (n = 101) were at HBR. HBR patients were older (mean age 78.4 ± 8.3 years versus 65.6 ± 10.6 years in non-HBR, $p < 0.001$) and more often female. From patients allocated to non-invasive management (n = 43, 20.3%), 74.4% (n = 32) were HBR versus 25.6% (n = 11) were non-HBR ($p < 0.001$). In NSTE-ACS patients, the most prevalent major ARC-HBR criterion was use of OAC (20.2%, n = 39) including direct oral anticoagulants (n = 31) and warfarin (n = 8). The most common minor criterion was age ≥ 75 years (40.4%, n = 78), which was also overall the most prevalent criterion. Other common minor criteria include moderate CKD (28.0%, n = 54), mild anaemia (18.7%, n = 36), prior stroke (9.8%, n = 19) and long-term use of NSAIDs or corticosteroids (7.3%, n = 14), although none were using NSAIDs. Other common major criteria included haemoglobin <110 g/L (6.2% = 12) and severe or end-stage CKD (5.7% = 11).

Of the 212 patients in study I, two died during the index hospitalisation and one was lost during follow-up and were excluded from study II, which had a study population of 209 patients. Overall, DAPT was more common in the non-HBR group (66.7%, n = 74) compared to the HBR group (38.8%, n = 38). In pairwise comparisons of DAPT in age groups, a difference was found comparing < 65 years group (66.0%) and ≥ 75 years group (41.9%, $p = 0.006$) as well as 65-74 years group (58.6%) and ≥ 75 years group ($p = 0.038$). Ticagrelor was used in 11.0% (n = 16) of NSTEMI patients and was more common among the non-HBR patients (16.7%, n = 13) as compared with those at HBR (4.5%, n = 3, $p = 0.020$, calculated including only NSTEMI patients because ticagrelor was not used in other groups). Among

NSTEMI patients, 61.4% (n = 89) were on clopidogrel and there was no difference in clopidogrel use between the non-HBR group (57.7%, n = 64) and the HBR group (51.0%, n = 50, p = 0.336) in the overall population of study II.

During 1-year follow-up, 15 patients (7.2%) suffered a bleeding event, of which 66.7% (n = 10) were BARC 2 and 33.3% (n = 5) were BARC 3. Among HBR patients, 6.1% (n = 6) and in non-HBR patients, 8.1% (n = 9) suffered a bleeding event (p = 0.579). The 1-year incidences of BARC 3 bleeding among HBR and non-HBR patients were 3.1% (n = 3) and 1.8% (n = 2) respectively (p = 0.667). There were more bleeding events among DAPT users as compared with those without DAPT (**Figure 1**., p = 0.033). This difference was driven by BARC 2 bleeding (8.9%, n = 10 and 0.0% respectively, p = 0.002).



DAPT, dual antiplatelet therapy; BARC, bleeding academic research consortium.
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Figure 1. 1-year bleeding incidence by age and DAPT use.

5.2 The prevalence of high bleeding risk and 1-year major bleeding incidence among STEMI patients (study III)

5.2.1 Formation of study population and baseline characteristics

The database search identified 1935 patients and after exclusions 1564 STEMI patients were included. Due to missing laboratory values, the complete ARC-HBR criteria were not assessable in 16 patients, and these were excluded from statistical analyses involving the ARC-HBR criteria (analysed ARC-HBR population n = 1548).

Clinical characteristics are reported in **Table 5**. Medication and management are shown in **Table 6**.

Of the analysed patients, 42.7% (n = 661) were HBR and 57.3% (n = 887) were non-HBR. Majority of non-HBR patients (71.7%, n = 636) did not meet any ARC-HBR criteria. Patients at HBR were older, had more comorbidities and prior coronary procedures. Non-HBR patients were more often current smokers compared with HBR patients. Of the study population, 87.4% received primary PCI. Overall, 8.4% (n = 132) were managed without revascularisation and this was more common among the elderly and HBR-patients. Median age of those managed without revascularisation was 83.8 years (interquartile range [IQR] 76.2–88.7) versus 68.6 years (IQR 59.1–76.9) among revascularized patients ($p < 0.001$). The HBR-group was less often treated with DAPT and a potent P2Y12 inhibitor i.e. ticagrelor or prasugrel as compared with the non-HBR-group. The prescribed duration of DAPT was generally shorter among HBR-patients.

Table 5. Clinical characteristics and laboratory values.

Variable	Overall (n=1564)	HBR (n=661)	Non-HBR (n=887)	p-value
Clinical characteristics				
Sex				
Female, n (%)	478 (30.6)	262 (39.6)	209 (23.6)	<0.001
Male, n (%)	1086 (69.4)	399 (60.4)	678 (76.4)	
Age, median (Q1, Q3)	69.6 (58.7, 76.4)	76.9 (69.2, 83.7)	63.7 (55.3, 70.4)	<0.001
Smoking				
Current, n (%)	473 (30.2)	110 (16.6)	358 (40.4)	<0.001
Former, n (%)	356 (22.8)	181 (27.4)	173 (19.5)	
Never, n (%)	735 (47.0)	370 (56.0)	356 (40.1)	
Alcohol consumption				
Excessive, n (%)	118 (7.5)	46 (7.0)	72 (8.1)	0.396
Non-excessive, n (%)	1430 (91.4)	615 (93.0)	815 (91.9)	
LVEF < 35, n (%)	242 (15.5)	137 (20.7)	97 (10.9)	<0.001
Hypertension, n (%)	882 (56.4)	451 (68.2)	424 (47.8)	<0.001
Hypercholesterolemia, n (%)	914 (58.4)	346 (52.3)	564 (63.6)	<0.001
Diabetes, n (%)	350 (22.4)	172 (26.0)	174 (19.6)	0.003
Atrial fibrillation, n (%)	229 (14.6)	218 (33.0)	10 (1.1)	<0.001
Heart failure, n (%)	91 (5.8)	76 (11.5)	14 (1.6)	<0.001
Prior CAD, n (%)	657 (42.0)	317 (48.0)	331 (37.3)	<0.001
Prior MI, n (%)	215 (13.7)	124 (18.8)	88 (9.9)	<0.001
Prior PCI, n (%)	192 (12.3)	101 (15.3)	89 (10.0)	0.002
Prior CABG, n (%)	45 (2.9)	34 (5.1)	10 (1.1)	<0.001
Peripheral artery disease, n (%)	59 (3.8)	43 (6.5)	15 (1.7)	<0.001
Prior stroke, n (%)	111 (7.1)	97 (14.7)	12 (1.4)	<0.001
Prior ICH, n (%)	36 (2.3)	32 (4.8)	3 (0.3)	<0.001
Laboratory values				
Haemoglobin, g/L, mean (SD)	135.8 (18.2)	126.0 (19.4)	143 (12.9)	<0.001
Thrombocytes, $x10^9$/L, median (Q1, Q3)	237 (201, 280)	227 (184, 275)	242 (209, 283)	<0.001
White blood cell count, $x10^9$/L, median (Q1, Q3)	10.1 (8.0, 12.4)	10.1 (7.6, 12.5)	10.2 (8.3, 12.3)	0.684
Creatinine, mmol/L, median (Q1, Q3)	83.0 (69.0, 96.0)	93.0 (77.0, 116)	78.0 (67.0, 88.0)	<0.001
HbA1c, mmol/mol, median (Q1, Q3)	39.0 (35.0, 43.0)	39.0 (36.0, 43.0)	38.0 (35.0, 42.0)	<0.001

HBR, high bleeding risk; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICH, intracranial haemorrhage.

From the original publication III, Table 1. (Reproduced under CC BY licence)

Table 6. Medication and management.

Variable	Overall (n=1564)	HBR (n=661)	Non-HBR (n=887)	p-value
Medication at discharge #				
ASA, n (%)	1374 (87.9)	496 (75.0)	872 (98.3)	<0.001
Clopidogrel, n (%)	410 (26.2)	306 (46.3)	103 (11.6)	<0.001
Ticagrelor, n (%)	964 (61.6)	217 (32.8)	744 (83.9)	<0.001
Prasugrel, n (%)	13 (0.8)	5 (0.8)	8 (0.9)	0.756
DAPT, n (%)	1274 (81.5)	422 (63.8)	849 (95.7)	<0.001
DAPT duration				
< 3 months, n (%)	88 (6.9) *	79 (18.7) *	9 (1.1) *	<0.001
3-5.9 months, n (%)	39 (3.1) *	25 (5.9) *	14 (1.6) *	
6-9 months, n (%)	119 (9.3) *	57 (13.5) *	62 (7.3) *	
12 months, n (%)	1028 (80.7) *	261 (61.8) *	764 (90.0) *	
DAPT with ticagrelor or prasugrel, n (%)	959 (61.3)	210 (31.8)	746 (84.1)	<0.001
DAPT with clopidogrel, n (%)	315 (20.1)	212 (32.1)	103 (11.6)	<0.001
VKA, n (%)	53 (3.4)	53 (8.0)	0 (0.0)	<0.001
DOAC, n (%)	166 (10.6)	166 (25.1)	0 (0.0)	<0.001
TAT, n (%)	80 (5.1)	80 (12.1)	0 (0.0)	<0.001
NSAID, n (%)	< 6 (< 0.38) §	3 (0.45)	< 3 (< 0.34) §	0.319
Corticosteroid, n (%)	53 (3.4)	46 (7.0)	7 (0.8)	<0.001
PPI, n (%)	602 (38.5)	362 (54.8)	234 (26.4)	<0.001
Management				
Primary PCI, n (%)	1367 (87.4)	518 (78.4)	838 (94.5)	<0.001
Delayed PCI, n (%)	35 (2.2)	25 (3.8)	10 (1.1)	<0.001
Fibrinolysis, n (%)	< 6 (< 0.38) §	< 3 (< 0.45) §	< 3 (< 0.34) §	1.000
Rescue PCI, n (%)	< 6 (< 0.38) §	< 3 (< 0.45) §	< 3 (< 0.34) §	1.000
CABG, n (%)	26 (1.7)	11 (1.7)	15 (1.7)	0.967
Angiography without revascularization, n (%)	35 (2.2)	26 (3.9)	9 (1.0)	<0.001
Non-invasive, n (%)	97 (6.2)	79 (12.0)	13 (1.5)	<0.001

Or during endpoint if occurred before discharge.

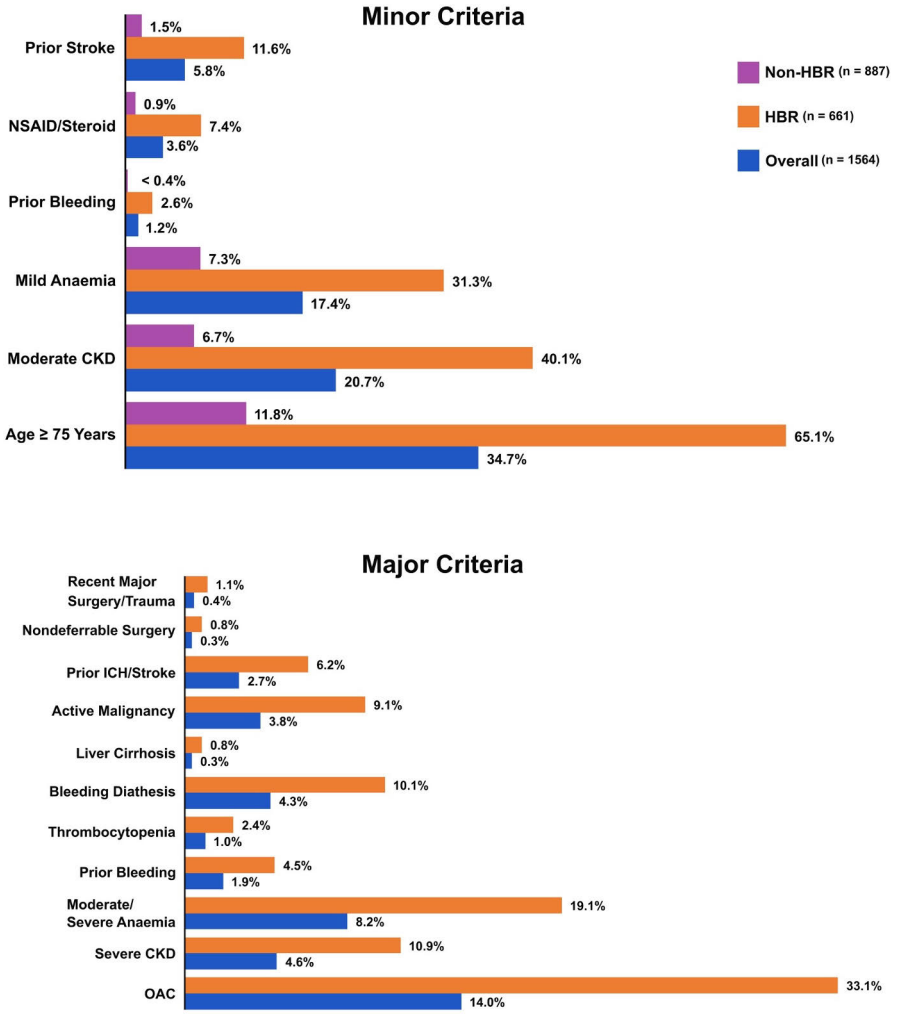
* Of those with DAPT.

§ Value < 3 censored based on the review of Findata (data permit authority for the social and health care sector in Finland) to ensure anonymity of study subjects.

ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; DAPT duration, prescribed duration of DAPT; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; TAT, triple antithrombotic therapy (ASA + P2Y12 receptor inhibitor + anticoagulant); NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PCI, percutaneous coronary intervention; Delayed PCI, performed > 24 hours after symptom onset; CABG, coronary artery bypass grafting.

Modified from the original publication III, Table 2. (Reproduced under CC BY licence) Added DAPT with clopidogrel.

The prevalence of individual ARC-HBR criteria is summarised in **Figure 2**. Most fulfilled minor criteria were age ≥ 75 years (n = 543, 34.7%), moderate CKD (n = 323, 20.7%) and mild anaemia (n = 272, 17.4%). Most frequent major criteria were oral anticoagulation (n = 219, 14.0%), moderate or severe anaemia (n = 128, 8.18%), severe or end-stage CKD (n = 72, 4.60%), bleeding diathesis (n = 67, 4.28%) and active malignancy (n = 60, 3.82%).



Percentages equivalent to frequencies < 3 were censored based on the review of Findata (data permit authority for the social and health care sector in Finland) to ensure anonymity of study subjects. They were reported as less than followed by smallest value that was considered anonymized.
ARC-HBR, Academic Research Consortium for High Bleeding Risk; HBR, high bleeding risk; NSAID, nonsteroidal anti-inflammatory drug; CKD, chronic kidney disease; ICH, intracranial haemorrhage; OAC, oral anticoagulant.
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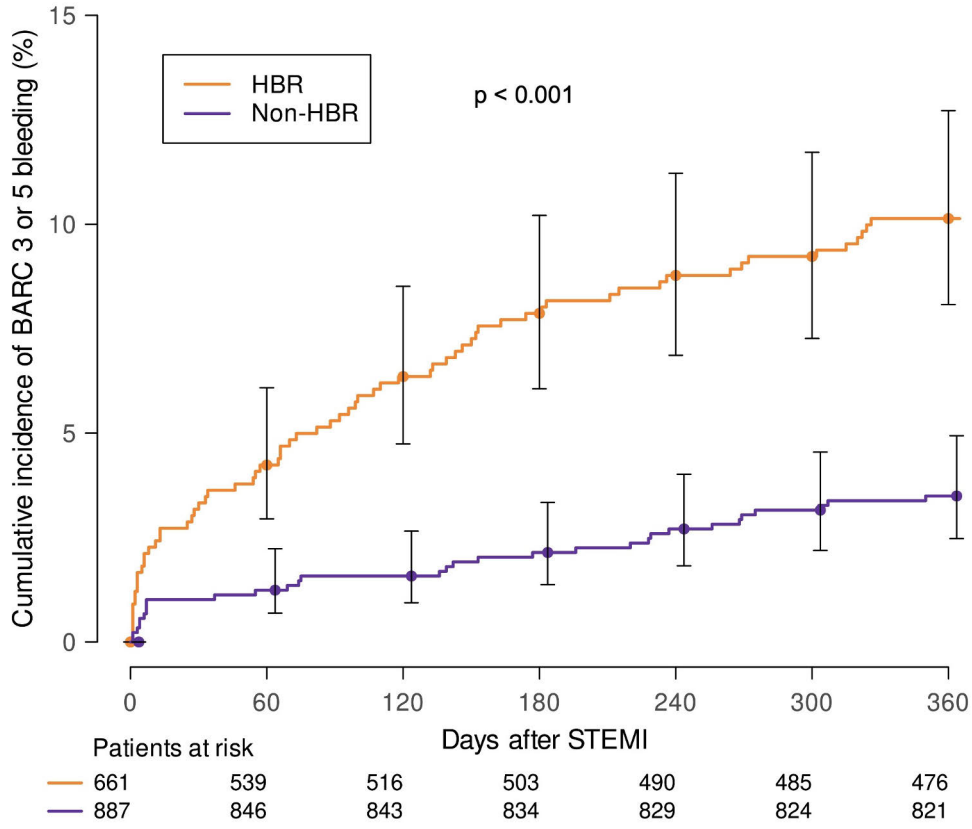
Figure 2. Prevalence of individual ARC-HBR criteria.

5.2.2 Bleeding incidence and independent predictors of bleeding

BARC 3 or 5 cumulative incidence during 1-year follow up was higher among HBR compared to non-HBR patients (10.1%, n = 67 vs 3.49%, n = 31) (**Figure 3**). The risk of 1-year BARC 3 or 5 bleeding was 3-fold higher in HBR compared to non-HBR patients (unadjusted HR 3.01, 95% CI 1.97–4.61, p < 0.001).



HBR, high bleeding risk; BARC, bleeding academic research consortium; STEMI, ST-elevation myocardial infarction.
Modified from the original publication III, Figure 1. p-value added. Reproduced under CC BY licence

Figure 3. Cumulative incidence of BARC 3 or 5 bleeding according to bleeding risk status.

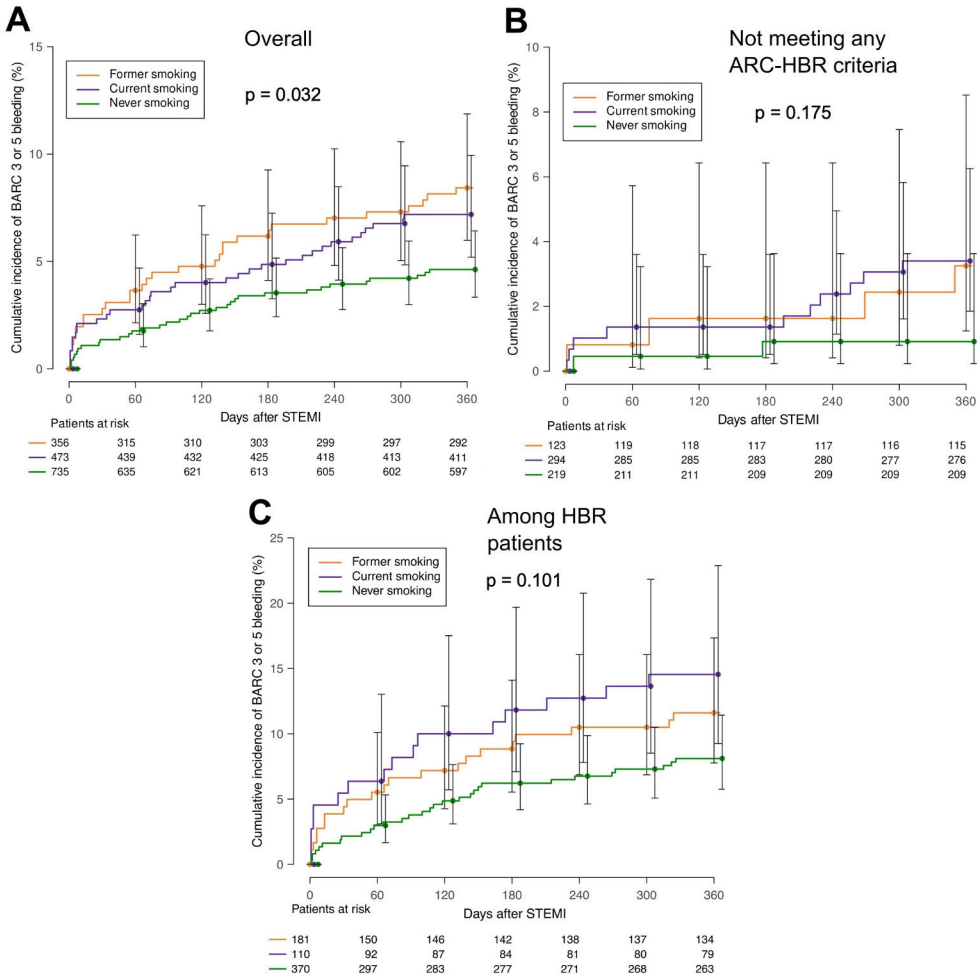
After multivariable adjustment (**Table 7**), out of the ARC-HBR criteria age, CKD, anaemia and active malignancy remained independent BARC 3 or 5 bleeding predictors. Additionally, smoking status and an increase in white blood cell count were identified as independent bleeding risk factors. Current smoking increased bleeding risk 3-fold and former smoking 2-fold compared to never smoking.

Table 7. Multivariable Fine-Gray regression model for 1-year BARC 3 or 5 bleeding.

Variable	HR	95% CI	p-value
Age ≥ 75 years*	2.36	1.38–4.03	0.002
OAC**	1.47	0.75–2.86	0.260
GFR 30-59.99 mL/min*	1.63	1.02–2.61	0.040
Haemoglobin < 110 g/L**	1.96	1.06–3.63	0.031
Prior bleeding**	1.88	0.71–4.99	0.210
Active malignancy**	3.11	1.57–6.15	0.001
Smoking	-	-	<0.001
Current§	3.01	1.62–5.61	<0.001
Former#	1.99	1.19–3.34	0.009
White blood cell count ($1x10^9$/L)	1.03	1.00–1.07	0.031
DAPT-duration$	-	-	0.280
PPI	1.50	0.98–2.29	0.060

*ARC-HBR minor criterion
**ARC-HBR major criterion
§Former smoking excluded (current vs. never)
#Current smoking excluded (former vs. never)
$Categories: no DAPT (reference), < 3 months, 3-5.9 months, 6-9 months, 12 months. HR and CI for category comparisons not provided because the variable was not significant.
In the model: Individual significant (Univariable Fine-Gray p <0.05) ARC-HBR criteria and other significant variables. If both major and minor criterion of the same variable was significant, major criterion was included.
BARC, Bleeding Academic Research Consortium; HR, hazard ratio; CI, confidence interval; OAC, oral anticoagulant; GFR, estimated glomerular filtration rate (CKD-EPI formula); Prior bleeding, Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent; Active malignancy, diagnosis within 12 months prior to index hospitalization or ongoing treatment; DAPT, dual antiplatelet therapy; PPI, proton pump inhibitor.
Modified from the original publication III, Table 3. (Reproduced under CC BY licence) Footnote text modified.

Cumulative incidences of 1-year BARC 3 or 5 bleeding among current, former and never smokers were 7.19%, 8.43% and 4.63% and the cumulative 1-year ICH incidences were 1.48%, 1.12% and 0.82% respectively. The cumulative incidences of BARC 3 or 5 and ICH were 3.40% and 1.36% respectively in current smokers who did not meet any ARC-HBR criteria, exceeding the ARC-HBR definition for a major criterion. BARC 3 or 5 cumulative incidences among former and never smokers who did not meet any ARC-HBR criteria were 3.25% and 0.91% and ICH incidences 0.81% and 0.0% respectively. **Figure 4** shows BARC 3 or 5 cumulative incidence stratified by smoking status. Bleeding sites according to smoking status were analysed post hoc. Nearly all bleeding complications originating from the respiratory tract occurred among current smokers and none among never smokers.



BARC, bleeding academic research consortium; STEMI, ST-elevation myocardial infarction; ARC-HBR, Academic Research Consortium for High Bleeding Risk; HBR, high bleeding risk. A, overall study population; B, among those not meeting any ARC-HBR criteria; C, among those classified as HBR according to ARC-HBR criteria.
Modified from the original publication III, Figure 2. p-values added. Reproduced under CC BY licence

Figure 4. Cumulative incidence of BARC 3 or 5 bleeding according to smoking status.

Among non-HBR patients, 358 (40.4%) were current smokers. If current smoking was considered a major ARC-HBR criterion, these patients would be considered as HBR. As a result, 65.8% (n = 1019) of the study population would belong in the HBR-group (compared to the original 42.7%). The incremental impact of current and former smoking in relation to fulfilment of the ARC-HBR criteria is demonstrated in **Table 8**.

Table 8. Incremental impact of smoking status on 1-year BARC 3 or 5 bleeding incidence.

Smoking status	No ARC-HBR criteria met	1 minor criterion met	HBR
Current	$\frac{10}{294}, 3.4\%$	$\frac{8}{64}, 12.5\%$	$\frac{16}{110}, 14.5\%$
Former	$\frac{4}{123}, 3.3\%$	$\frac{5}{50}, 10.0\%$	$\frac{21}{181}, 11.6\%$
Never	$\frac{< 3 *}{219}, < 1.4\%$	$\frac{< 3 *}{137}, < 2.2\%$	$\frac{30}{370}, 8.1\%$

Values are n of events divided by n of patients, bleeding incidence.
* Value < 3 censored based on the review of Findata (data permit authority for the social and health care sector in Finland) to ensure anonymity of study subjects.
BARC, Bleeding Academic Research Consortium; ARC-HBR, Academic Research Consortium for High Bleeding Risk; HBR, high bleeding risk.
From the original publication III, Table 4. (Reproduced under CC BY licence)

5.3 The incidence of 1-year major adverse cardiovascular or cerebrovascular events after primary percutaneous coronary intervention for STEMI (study IV)

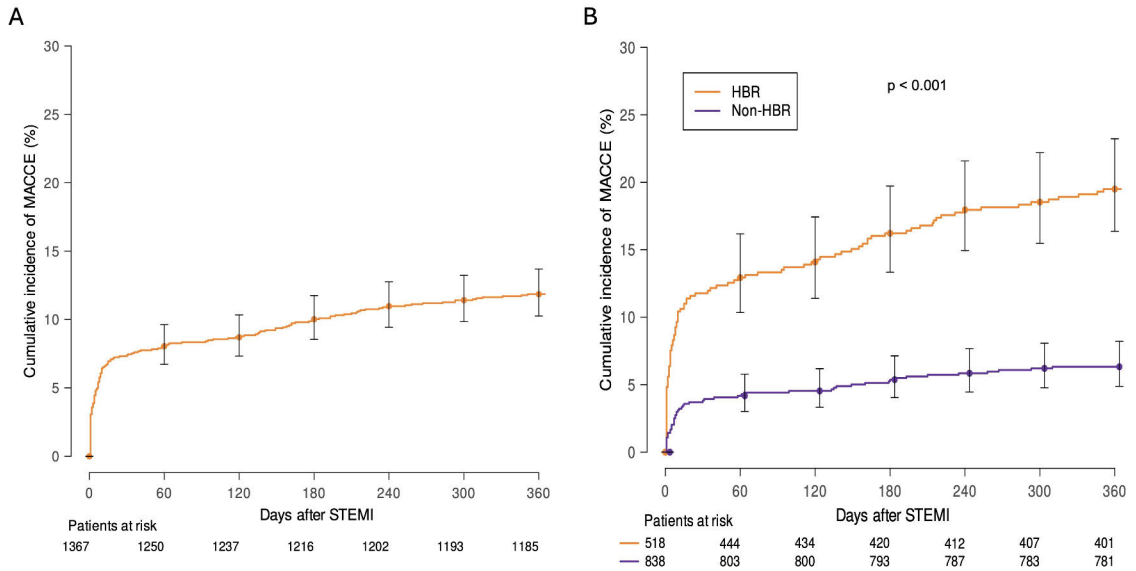
5.3.1 Baseline characteristics

Of the 1564 patients with STEMI in study III, 1367 received PPCI and were included in study IV. The median age was 68.4 (59.0, 76.9) years and 28.1% (n = 384) were female. The prevalence of HBR was 37.9% (n = 518). Most prevalent ARC-HBR criteria were age ≥ 75 years, use of OAC, anaemia and CKD. HBR patients had more comorbidities such as diabetes, heart failure and peripheral artery disease. Those at HBR more often had LVEF < 35% during hospitalisation. In the HBR group, prescribed DAPT duration was ≥ 3 months in 60.4% (n = 313) versus 97.6% (n = 818) in the non-HBR group ($p < 0.001$).

5.3.2 Incidence and predictors of major adverse cardiovascular or cerebrovascular events

In the study population, cumulative 1-year incidence of MACCE was 11.9%. HBR patients had a higher risk of MACCE during the follow-up compared to non-HBR (cumulative incidences 19.5% and 6.32%) (unadjusted HR 3.31, 95% CI 2.38–4.62, $p < 0.001$). Cumulative incidence of MACCE in the overall population and stratified by bleeding risk is shown in **Figure 5**. In the overall study population, the cumulative incidence of BARC 3 or 5 bleeding was 6.20%. The HBR-group had a higher risk of

BARC 3 or 5 bleeding compared to the non-HBR-group (cumulative incidences 10.6% and 3.58%) (unadjusted HR 3.09, 95% CI 1.98–4.82, p < 0.001).



MACCE, major adverse cardiovascular or cerebrovascular event; HBR, high bleeding risk; STEMI, ST-elevation myocardial infarction. A, overall study population; B, stratified by bleeding risk.
Modified from the original publication IV, Figure 1. p-value added. Scale of the Y-axis changed (A part). Reproduced under CC BY licence

Figure 5. 1-year cumulative incidence of MACCE in the overall study population and stratified by bleeding risk.

After multivariable adjustment, from the ARC-HBR criteria the use of NSAIDs or corticosteroids and active malignancy were independent MACCE predictors. Age and CKD showed a trend towards increased risk of MACCE without reaching statistical significance. Other significant predictors were diabetes and LVEF < 35%. DAPT duration ≥ 3 months was associated with reduced risk of MACCE. The multivariable regression model is shown in **Table 9**.

Table 9. Multivariable Fine-Gray regression model for 1-year MACCE.

Variable	HR	95% CI	p-value
Age ≥ 75 years *	1.35	0.95–1.92	0.089
Use of NSAID/steroid *	2.29	1.16–4.55	0.018
Prior stroke (minor criterion) *	1.10	0.59–2.04	0.770
Severe or end-stage CKD (eGFR < 30 ml/min) *	1.78	0.99–3.19	0.055
Moderate or severe anaemia (haemoglobin < 110 g/L) *	0.90	0.51–1.60	0.720
Prior spontaneous bleeding (within the past 6 months) *	1.01	0.32–3.23	0.980
Platelet count < $100x10^9$/L *	1.13	0.30–4.36	0.850
Active malignancy *	2.33	1.19–4.55	0.013
LVEF < 35%	5.21	3.61–7.52	<0.001
Diabetes	1.67	1.17–2.39	0.005
Prior MI	1.10	0.72–1.68	0.670
Prior peripheral arterial disease	0.91	0.39–2.16	0.840
DAPT duration ≥ 3 months	0.58	0.40–0.82	0.002
Statin	0.48	0.30–0.75	0.002
ACE-inhibitor	0.49	0.35–0.69	<0.001
Beta blocker	0.66	0.45–0.96	0.031

* Academic Research Consortium for High Bleeding Risk criterion.
MACCE, major adverse cardiovascular or cerebrovascular event; HR, hazard ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; DAPT, dual antiplatelet therapy; ACE, angiotensin-converting enzyme.
From the original publication IV, Table 3. (Reproduced under CC BY licence)

6 Discussion

The main findings of the present study are summarised as follows. The prevalence of HBR according to the ARC-HBR criteria was 47.6% among suspected NSTEMI patients and 42.7% among STEMI patients. Most prevalent ARC-HBR criteria were age ≥ 75 years, use of OACs, CKD and anaemia. No significant difference in 1-year post-discharge BARC 2, 3 or 5 bleeding was observed between the HBR and non-HBR groups among suspected NSTEMI.

The ARC-HBR criteria successfully identified patients with increased 1-year BARC 3 or 5 bleeding risk after a STEMI (HR 3.01, CI 1.97-4.61 for HBR vs non-HBR). After multivariable adjustment, from the ARC-HBR criteria only age, CKD, anaemia and active malignancy remained associated with increased bleeding risk. From variables not included in the ARC-HBR framework, smoking status and white blood cell count were identified as bleeding risk factors. Current smoking fulfilled the ARC-HBR definition for a major bleeding risk criterion and was highly prevalent among those classified as non-HBR based on the ARC-HBR criteria (40.4%).

After PPCI for STEMI, HBR patients were at increased risk of 1-year MACCE (HR 3.31, CI 2.38-4.62) and BARC 3 or 5 bleeding (HR 3.09, CI 1.98–4.82). From the ARC-HBR criteria, the use of NSAIDs or corticosteroids and active malignancy remained independent predictors of MACCE after multivariable adjustment. Other risk factors for MACCE were LVEF < 35% and diabetes, which were more prevalent in the non-HBR group compared to non-HBR.

6.1 The prevalence of high bleeding risk in suspected NSTEMI and the incidence of actionable bleeding complications during 1-year follow-up

Studies I and II examined the prevalence of HBR and 1-year actionable bleeding incidence among suspected NSTEMI patients. Over 47% were classified as HBR based on the ARC-HBR criteria, which is higher than in previous studies investigating European populations with prevalences ranging from 32-39% [88–90]. This is likely explained by patient selection. Previous studies used data from PCI registries, which tend to be selective due to the invasive nature of the procedure. In

study I, of the patients receiving non-invasive management, 74% were at HBR. In an unselected European ACS cohort, the prevalence of HBR was over 40% which similarly to our findings, exceeded the prevalences encountered in PCI registries [145].

The prevalence of individual ARC-HBR criteria is comparable to previous findings [99]. Commonly encountered criteria were use of OAC, age ≥ 75 years, CKD, anaemia and prior stroke. Previous studies have demonstrated that minor ARC-HBR criteria for age and CKD perform as major criteria (the criteria are associated with ≥ 4% 1-year BARC 3 or 5 bleeding incidence or ≥ 1% ICH incidence). This is notable, because these are commonly encountered in clinical practice and were highly prevalent among NSTE-ACS patients in study I (prevalences for age ≥ 75 years and minor CKD criterion were 40% and 28% respectively). This indicates that considering these minor criteria as major bleeding risk factors in the future could help to detect more HBR patients. On the contrary, several major criteria such as thrombocytopenia, bleeding diathesis, liver cirrhosis, recent surgery or trauma and nondeferrable major surgery were very rare in study I. This is in line with previous literature [99].

In study II, there was no significant difference in 1-year bleeding incidence between the HBR and non-HBR groups and the incidence was numerically higher among non-HBR patients. This is contradictory to previous studies demonstrating higher bleeding incidences among HBR group [85,91]. In the present study, the incidence of major bleeding events in the HBR group did not exceed the 4% threshold defined by the ARC-HBR. It is noteworthy, that the HBR group in study II was less often on DAPT compared to the non-HBR group and potent P2Y12 inhibitors were rarely chosen for them. Therefore, bleeding risk assessment probably mitigated the observed bleeding risk of HBR patients. Also, it is possible that a difference was not detected due to the small sample size.

Interestingly, the highest bleeding incidences were observed among patients under 65 years. While majority of the events were minor BARC 2 events, the incidence of major bleeding was highest among patients < 65 years and who were not on DAPT. This is surprising as advanced age is a well-known bleeding risk factor and DAPT is associated with increased bleeding risk. Furthermore, the prevalence of bleeding risk factors tends to increase with age. These findings indicate that there could be significant bleeding risk factors not included in the ARC-HBR criteria and that are particularly prevalent among younger patients. One possibility is smoking, which has been associated with bleeding in some studies [106,108], while not in others [6,86]. Indeed, it seems that smoking is more prevalent in younger age groups among MI patients [146].

6.2 The prevalence of high bleeding risk among STEMI and significant bleeding risk factors

Study III investigated bleeding risk factors in a real-world STEMI population with minimal exclusion criteria. Similarly to study I, HBR was common with over 40% fulfilling the ARC-HBR definition. Most commonly encountered ARC-HBR criteria were age ≥ 75 years, CKD, anaemia, OAC use and prior stroke. While in the present study the HBR group had 3-fold increased bleeding risk compared to non-HBR, only few individual ARC-HBR criteria remained independent bleeding predictors after adjustment, which is in line with the few previous studies that accounted for the effect of factors outside the ARC-HBR criteria [6,86,89]. Nakamura et al. showed that when adjusted, from the ARC-HBR criteria only OAC use, CKD and anaemia remained associated with bleeding among the overall PCI population and new bleeding risk factors were identified, such as heart failure, low body weight and presentation with ACS versus CCS [6]. In a European cohort of PCI-treated patients (CCS and ACS), OAC, CKD, anaemia and prior bleeding predicted increased bleeding risk [89]. Clinical presentation was adjusted for (ACS vs CCS). Nicolas et al. reported that after adjustment with individual components of the ARC-HBR criteria, only about half of the criteria were independent bleeding predictors [86]. Interestingly, the results differed between CCS and MI highlighting the importance of clinical presentation when assessing bleeding risk. Similarly to our results, anaemia and CKD were significant risk factors among MI. They also reported an increased bleeding risk associated with thrombocytopenia. Among CCS, OAC, anaemia, malignancy, age ≥ 75 years and prior bleeding were bleeding predictors. After adjustment for confounding variables outside the ARC-HBR framework, similarly to our results anaemia and malignancy were significant ARC-HBR criteria. However, CKD and age were not. Overall, it seems that anaemia and CKD are almost constantly associated with increased bleeding risk, whereas OAC could be a bleeding risk factor among CCS but have a lesser impact among ACS. It is noteworthy, that in all these three studies several individual ARC-HBR criteria were missing or modified, whereas we were able to use the original definitions (except for the slightly modified prior stroke criterion) due to patient record review.

6.2.1 Smoking as a bleeding risk factor

In our dataset, smoking status emerged as an independent bleeding predictor and current smoking fulfilled the ARC-HBR prerequisites for a major criterion by exceeding the threshold of ≥ 1% ICH incidence at 1-year. Former smoking was associated with increased bleeding risk without fulfilling the definition of a major criterion and could therefore be considered a minor criterion. Recognising smoking as a bleeding risk factor could be impactful for several reasons. Firstly, smoking is a

well-known risk factor for CAD and is associated with increased risk of ischemic complications after PCI [147]. Thus, current smokers are traditionally managed as patients with high ischemic risk which may result in longer DAPT durations. Our findings suggest that these patients also have an increased bleeding risk, a finding which could be useful when assessing the net benefit of DAPT after STEMI. Our results cannot determine the optimal DAPT duration among current smokers since the balance of ischemic and bleeding risk of smoking was not assessed. However, there is evidence suggesting that individual patients bleeding risk status rather than ischemic risk should determine the duration of DAPT treatment [107,128,129].

Secondly, the prevalence of current smoking was particularly high among patients classified as non-HBR based on the ARC-HBR criteria. Over 40% of non-HBR patients were current smokers and often those in the non-HBR group did not fulfil any ARC-HBR criteria. These HBR patients could have been identified if smoking status had been recognised as a bleeding risk factor. Current smoking seems to be more prevalent among non-HBR patients as compared to HBR patients globally, both in randomised DAPT trials and PCI registries [85,89,91,148,149]. This is likely explained by smoking being more prevalent among younger age groups compared to the elderly [146].

Thirdly, while current smoking was more prevalent among non-HBR, it was not rare in HBR patients. This is noteworthy because accumulating bleeding risk factors additively increases bleeding risk as demonstrated by multiple studies [88,90]. Although to our knowledge, the additive impact of smoking status and the ARC-HBR criteria has never been previously evaluated. Thus, our data provides novel findings and notably, the additive impact of current and former smoking was high among patients who fulfilled a single minor ARC-HBR criterion.

Smoking has been adjusted with the ARC-HBR criteria and other possible bleeding risk factors in recent studies but has not been associated with 1-year major bleeding risk [6,86]. The study populations consisted of ACS and CCS patients. On the contrary, Urban et al. showed that current smoking predicted 1-year major bleeding events in HBR patients [59]. Again, the study population was a mixture of ACS and CCS. Interestingly, the impact of smoking was lost in a subgroup analysis of MI patients. Contradictory evidence regarding smoking and bleeding risk exists before the ARC-HBR era. Current smoking was a bleeding risk factor for 2-year BARC 3 or 5 bleeding in the PARIS bleeding risk score with 2-fold increased risk [106]. Some limitations should be noted when evaluating applicability of these results to contemporary practice. Half of the study population consisted of CCS patients and enrolment was conducted in 2010, resulting in an almost exclusive use of clopidogrel as P2Y12 inhibitor. Furthermore, data of malignancy, a potent bleeding risk factor was not available and could confound the results. Abu-Assi et al. validated the PARIS score in a cohort of ACS patients and surprisingly in multivariable

adjustment, current smoking was not a significant bleeding risk factor [70]. The patients were managed in 2015 and with higher prevalence of potent P2Y12 inhibitors and although differences in antiplatelet medication could explain the different results, an interesting possibility is differences in clinical presentation. That is, current smoking predicting bleeding when CCS patients are in the investigated populations but not in ACS cohorts, as discussed earlier with Urban et al. Similar pattern is observed with another two bleeding risk scores by Mehran and colleagues published in 2010 and 2011 [108,150]. The first score was developed for ACS patients and current smoking was not associated with 30-day major bleeding [150]. However, in another study population, which also included CCS patients, current smoking was associated with 1.7-fold increased risk [108]. It should be noted that, there were differences in management strategies between the studies (former included also medically managed patients while latter only PCI), which could partly explain the different outcomes. Similarly to the PARIS score, malignancy was not accounted for in these two studies. Matteau et al. reported that current smoking is a predictor of 4-year GUSTO moderate to severe bleeding in a cohort of ACS and CCS [151], while Ismail et al. investigated ACS patients and after adjustment, current smoking was not associated with 1-year post-discharge bleeding [152]. Although the latter study did not define the severity of the bleeding endpoints and the most common type of bleeding was bruising, suggesting minor bleeding events, and thus, the results might not be comparable to the other discussed studies.

All the previously discussed studies only evaluated current smoking without considering former smoking (with exception of Ismail et al.). Therefore, current smokers were not compared to never smokers, but with a mixture of never and former smokers. This could mitigate the observed bleeding risk associated with current smoking due to unmeasured confounding since our results show that former smoking was associated with 2-fold increased bleeding risk. Recently, Sarajlic et al. published similar results [73]. Current and former smoking were independent predictors of specifically upper-GI bleeding in a large registry of 150 000 MI patients (odds ratios 1.8 and 1.3 respectively). The bleeding endpoint was defined as any rehospitalisation with upper GI bleeding related ICD-10 diagnosis code as primary or secondary diagnosis. Thus, the true severity of these events remains unclear. Compared to the study by Sarajlic and colleagues, our results extend the evidence of smoking as a bleeding risk factor among MI by introducing more careful endpoint adjudication and thus, adding robustness to the observation. Additionally, we did not restrict the bleeding endpoint to a specific site but rather focused on the severity of bleeding events. This enabled the capture of all major events, which are the most prognostically significant and are the primary targets for prevention through bleeding risk assessment. Another study reported that smoking history (current or former smoking) was associated with 1.9-fold increased risk of major bleeding

compared to never smoking in ACS patients during 240d follow-up [153]. However, the data originated from the APPRAISE-2 (The Apixaban for Prevention of Acute Ischemic Events 2) trial, which investigated the addition of DOAC to standard antiplatelet therapy in ACS patients without indication for OAC. Thus, half of the enrolled subjects were on OAC and a large proportion on TAT for a prolonged time without indication, representing a patient population that should not exist in real world practice. Moreover, several HBR patient groups were excluded from the trial, and thus, the results presented by Khan et al. are not generalisable to real world practice.

Contradictory evidence regarding smoking as a bleeding risk factor exists in general populations. A study including almost 100 000 subjects from The Copenhagen General Population Study showed that smoking predicts any major bleeding and bleeding in specific sites such as GI, intracranial, airways and urinary tract [154]. Former smoking was associated with any major bleeding and GI bleeding. Dose-dependent increase in bleeding risk was observed when pack-years increased as well as cigarettes smoked per day among current smokers. Data on smoking was collected by self-administered questionnaires. Bleeding endpoints were defined based on ICD-10 codes and no endpoint adjudication was used introducing uncertainty to whether the bleeding events were actually major. Furthermore, the results are not applicable to ACS patients due to the investigated population and unmeasured confounding. In another study including a general population of 48 000 healthcare workers with comprehensive endpoint adjudication, smoking was not a risk factor for major GI bleeding in men [155].

Possible mechanisms of how smoking can cause bleeding are speculative. Overall, smoking could damage blood vessels through toxins or impaired nitric oxide production in the endothelium [156]. This can lead to improper endothelium-dependent relaxation of arteries [157], resulting in increased shear stress and potential endothelial damage. Obtained cerebral aneurysms could explain increased bleeding since smoking seems to be strongly associated with increased risk of fatal subarachnoid haemorrhage [158]. In our data almost all bleeding events originating from the respiratory tract occurred among current smokers and none among never smokers. Smoking has been shown to impair wound healing in the respiratory epithelium [159]. Smoking is a well-known risk factor for cancer and impact on bleeding could be mediated by this mechanism. However, this does not explain our results since active malignancy was adjusted for. Finally, clopidogrel is metabolically activated by several cytochrome P450 isoenzymes and smoking has been shown to induce their activity, leading to increased platelet inhibition, which could increase bleeding risk [160,161]. Clopidogrel was used in minority of patients in our study, but this could be an important factor in previous studies with more clopidogrel users.

6.2.2 White blood cell count and bleeding risk

Another noteworthy finding in the present study is that increased white blood cell count was associated with increased bleeding risk. This corroborates findings from previous STEMI and NSTE-ACS cohorts, although the risk increase was only modest in our dataset [162,163]. There was no difference in white blood cell count between the HBR and non-HBR groups but incorporating the variable into bleeding prediction models could be beneficial as demonstrated by the PRECISE-DAPT score [107]. Interestingly, very recently Gragnano et al. developed a novel bleeding risk score (the PRECISE-HBR score) that combined the significant bleeding predictors from the ARC-HBR criteria and the PRECISE-DAPT score [164]. Significant bleeding risk factors were identified by adjusting with all the components of the former scores and white blood cell count remained a bleeding predictor. The discriminatory ability of the PRECISE-HBR score was superior to existing scores in terms of bleeding risk prediction.

The mechanism linking elevated white blood cell count to increased bleeding risk is poorly understood. White blood cell count reflects the level of systemic inflammation, and this is hypothesized to be the underlying mechanism since inflammation and haemostasis are connected by several pathways, including white blood cells [111].

6.3 Impact of high bleeding risk on major adverse cardiovascular or cerebrovascular events in STEMI patients undergoing primary percutaneous coronary intervention

In study IV, after PPCI for STEMI those at HBR had 3.3-fold increased risk of MACCE at 1-year compared to non-HBR. This is in line with previous literature, although previous studies have reported about 2-fold increased risk of ischemic complications, depending on the endpoint definition [88–90,94,97]. This could be explained by these previous studies including more stable NSTE-ACS and CCS patients as opposed to exclusively STEMI. Our results reflect the complexity of managing STEMI when HBR is present. This is noteworthy, since STEMI patients are generally underrepresented in studies investigating bleeding risk and in DAPT trials. Furthermore, the HBR group had over 3-fold increased risk of major bleeding and notably, the risk increase is of the same magnitude as increased ischemic risk. ACS management requires balancing between these two risks. Our results demonstrate the need for careful evaluation of ischemic risk factors in addition to the ARC-HBR status.

Although MACCE incidence was higher among the HBR group, only two individual ARC-HBR criteria remained independent MACCE predictors after

adjustment. Those being active malignancy and use of NSAIDs or corticosteroids. Apart from shared risk factor between malignancy and CVD (such as hyperntension, hyperlipidemia and smoking), the impact of malignancy on MACCE could be mediated by cardiotoxic cancer therapies and common disease mechanisms such as systemic inflammation and oxidative stress [165]. It should be noted that the use of NSAIDs was miniscule and therefore our results mainly reflect the impact of corticosteroids. The impact of NSAIDs and corticosteroids could be mediated by underlying rheumatoid disease or pulmonary conditions, which seem to increase ischemic risk after PCI [166,167]. In our data CKD and age ≥ 75 years were not significant predictors, but a trend towards increased risk was observed. It is likely that statistical significance would have been reached with a larger sample size. Ueki et al. reported adjusted associations of individual ARC-HBR criteria for 1-year device-oriented composite endpoint consisting of cardiac death, target vessel MI and target lesion revascularisation [89]. Age ≥ 75 years, CKD and anaemia were risk factors for the endpoint in a cohort with about half presenting with ACS and only 26% STEMI. Differences in study population could explain different results and additionally the study has limitations that should be taken into consideration. Particularly, the lack of adjustment for diabetes which is a well-known ischemic risk factor and was an independent predictor in our data as well. Secondly, most of the original ARC-HBR criteria were either not available or modified due to limitations in available data. For example, the minor criterion for NSAID or corticosteroid use excluded corticosteroids because the data was not available. In our study almost all patients fulfilling the criterion were on corticosteroids and only a small number used NSAIDs. It is possible that increased ischemic risk observed with the criterion is driven by corticosteroid use rather than NSAIDs.

In our study, diabetes and LVEF < 35% during the index-hospitalisation were predictors of MACCE and both were more common among the HBR group. Furthermore, DAPT-duration ≥ 3 months reduced the risk by more than 40% (as opposed to shorter DAPT) and was less prevalent in the HBR group. Our results indicate that the higher observed ischemic risk among HBR patients could be explained by underlying comorbidities, management strategies and the few individual bleeding risk criteria associated with increased risk, rather than bleeding risk status itself. HBR patients represent a heterogenous group, with significant variability not only in bleeding risk but also in their ischemic risk profiles. These findings may be useful when evaluating the balance between bleeding and ischemic risks based on patient specific risk factors.

Although our data indicates that ≥ 3-month DAPT is beneficial in reducing ischemic complications, results from RCTs show less consistent results. In the MASTER DAPT trial no difference in MACCE was observed between ≥ 3-month DAPT versus shorter durations in PCI treated patients [131]. Notably, only about 10%

of the trial population had STEMI. The STOPDAPT-2 ACS (Short and Optimal Duration of Dual AntiPlatelet Therapy-2 Study for the Patients With ACS) trial enrolled exclusively ACS patients with 56% STEMI and compared 12-month DAPT with 1-2 months [168]. The abbreviated DAPT group exhibited a trend towards increased ischemic complications (HR 1.50, CI 0.99-2.26). It should be noted that nearly half of the trial population received low dose prasugrel (3,75mg daily) which is less than half of the standard dose commonly used for example in Europe and USA and therefore the applicability of the results to real-world practice outside Asia can be questioned. The ULTIMATE DAPT (Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes) trial demonstrated that compared with 12-month DAPT, 1-month DAPT followed by ticagrelor monotherapy reduced risk of bleeding without excess ischemic complications in ACS [169]. However, less than 30% were STEMI and both low event rates and exclusion criteria indicate a low-risk population. In our real-life data, MACCE incidence was over 3-times higher compared to ULTIMATE DAPT trial. To overcome the issue of selection bias in RCTs, Håkansson et al. compared the safety of abbreviated versus standard DAPT treatment durations following PCI for ACS in a real-world setting, finding no difference in MACCE [170]. About 30% presented with STEMI. Altogether the safety of short DAPT durations in STEMI needs more evidence from RCTs focusing on STEMI specifically.

6.4 Strengths and limitations

The methodological approach of data gathering by patient record review allowed us to evaluate the ARC-HBR criteria as originally proposed, which is rarely possible in studies due to limitations in PCI registry data, resulting in increased risk of misclassification bias. In the present study the major ARC-HBR criterion for prior stroke had to be slightly modified. Additionally, we were able to use adjudicated endpoints. This is particularly important when investigating bleeding, since the important factor to consider is the severity of these bleeding events. Utilisation of competing risk analysis as opposed to more commonly used survival analysis techniques adds robustness to our results especially when analysing bleeding outcomes, since non-bleeding related deaths are a major competing factor in a real-world high-risk patient population. Studies III and IV focused solely on STEMI patients, which are underrepresented in previous literature investigating bleeding risk factors. As discussed earlier, CAD comes with a range of different clinical presentations, each of which seems to be associated with heterogenous risk of complications and variability in significance of bleeding risk factors. Focusing on

STEMI supports the applicability of the results in this under researched patient group compared to results derived from study populations with mixture of ACS and CCS.

Studies I-IV come with the limitations of retrospective study design. The data was recorded in patient records by treating personnel and gathered retrospectively. Thus, we were reliant on previous data documentation. Unmeasured confounding cannot be ruled out even though multivariable regression was used in studies III and IV to mitigate the risk. The small sample size in study II resulted in limited number of endpoint events and multivariable regression was not feasible. Moreover, Studies I-IV were single centre studies, which limits the generalisability of the results to other demographics.

Furthermore, in Studies III and IV, a large proportion of subjects had no mention of alcohol use and were assumed to not have excessive consumption. Underreporting of alcohol use is possible and introduces potential bias to the results. However, mitigating underreporting of alcohol abuse would be challenging even in a prospective study, let alone in a retrospective setting. Elevated blood pressure has been associated with bleeding and ischemic risk but was available in VSSHP institutional database from 2021 onwards and was excluded from Studies III and IV. Adherence to medication could not be ascertained and possible cessations could impact the results. The length and intensity of smoking history might influence how smoking impacts bleeding risk, but we did not have them recorded in the data for study III.

7 Conclusions

The following conclusions can be drawn from the present study:

This investigation represents the first report of HBR according to the ARC-HBR criteria in Finnish ACS patients. HBR is commonly encountered in routine clinical practice among ACS and comes with an increased risk of major bleeding complications after a STEMI. No difference in actionalble bleeding was detected between the HBR and non-HBR groups in suspected NSTEMI patients.

The bleeding risk associated with significant ARC-HBR criteria varied. Therefore, the criteria could be improved by accounting for the weight of the individual components. Furthermore, many of the criteria were not associated with increased bleeding risk in our data after accounting for confounding factors. This suggests that there might be a need to develop a separate set of criteria for a Finnish demographic.

In PPCI-treated STEMI patients HBR is asscociated with increased risk of MACCE. Contrary to previous studies where bleeding risk has outweighed ischemic risk among HBR patients, in the present investigation these were of the same magnitude. This suggests that careful consideration of ischemic risk factors is particularly important among HBR patients. Additionally, the present study revealed that the higher ischemic risk of HBR patients could be explained by underlying comorbidities and not bleeding risk status itself. HBR patients represent a heterogenous group, with significant variability in both their bleeding and ischemic risk profiles.

Smoking and white blood cell count are significant bleeding risk factors among STEMI and are not included in the ARC-HBR criteria. Current smoking is highly prevalent among those classified as non-HBR based on the ARC-HBR framework. These findings suggest that guideline recommended bleeding risk assessment failed to identify a large proportion of patients who were at HBR. Recognising smoking as a bleeding risk factor could help to identify more high-risk patients in clinical decision making.

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