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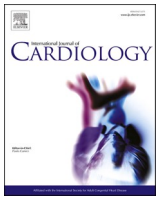

Impact of high bleeding risk and associated risk factors on major adverse cardiovascular or cerebrovascular events in primary percutaneous coronary intervention treated ST-elevation myocardial infarction

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ABSTRACT

Background: After percutaneous coronary intervention (PCI), patients at high bleeding risk (HBR) according to The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria have increased risk for ischemic complications. The underlying cause is not well documented. The aim of this study was to assess the ischemic risk among ST-elevation myocardial infarction (STEMI) patients classified as HBR according to the ARC-HBR and to identify individual risk factors.

Methods: Consecutive STEMI patients treated with primary PCI in a Finnish tertiary hospital between 2016 and 2022 were identified using a database search. Data was collected by reviewing electronic patient records. Bleeding risk was assessed according to the ARC-HBR criteria. The primary endpoint was 1-year major adverse cardiovascular or cerebrovascular event (MACCE).

Results: In total, 1367 STEMI patients were included. Cumulative incidence of MACCE was 19.5 % among HBR and 6.32 % among non-HBR. From the ARC-HBR criteria, multivariable competing risk analysis identified use of non-steroidal anti-inflammatory drugs or steroids and active malignancy as risk factors for MACCE. Diabetes and left ventricular ejection fraction <35 % were MACCE predictors and both were more prevalent among HBR patients. Dual antiplatelet therapy duration of ≥3 months significantly reduced risk of MACCE and was less prevalent among HBR.

Conclusions: The higher observed ischemic risk among HBR patients might not be explained by bleeding risk status itself but rather with some of its components and other underlying comorbidities and management strategies. These findings may be useful when evaluating the balance of ischemic and bleeding risks based on patient-specific risk factors.

1. Introduction

The management of acute coronary syndromes (ACS) requires careful balancing between ischemic and bleeding risks. While guidelines typically present broad instructions on management strategies, there has been a shift towards a more individualized approach, emphasizing the importance of understanding how various patient characteristics influence outcomes. [1] The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria are recommended for identification of high bleeding risk (HBR) patients among those undergoing percutaneous coronary intervention (PCI). [2] For patients at HBR, an abbreviated dual antiplatelet therapy (DAPT) treatment duration after PCI is considered to be optimal if high ischemic risk factors are not present. [1] However, patients at HBR have been reported to also have increased risk for ischemic complications. [3,4]

Since HBR status is accompanied by an increased ischemic risk, it is essential to establish which components of the ARC-HBR criteria predict ischemic complications. Those at HBR are older and have a higher prevalence of comorbidities, [5] which could explain the increased observed risk in this population. Only few studies have evaluated which

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ARC-HBR criteria remain associated with increased ischemic risk when accounting for comorbidities. [6] Furthermore, ST-elevation myocardial infarction (STEMI) patients were underrepresented in these studies as they generally are in randomized trials investigating bleeding risk and management strategies. Thus, further investigation in this high-risk ACS subgroup is needed.

We sought to assess the ischemic risk among STEMI patients classified as HBR according to the ARC-HBR criteria and to identify which individual ARC-HBR criteria are associated with increased ischemic risk. Additionally, the inclusion of a real-world population with minimal exclusion criteria enabled analyzing variables that are often excluded from randomized trials, such as malignancy.

2. Materials and methods

2.1. Data sources

Data used in this study was gathered from the institutional database of The Hospital District of Southwest Finland (VSSHP). VSSHP is a public municipal authority that produces specialized health care services to the 480,000 residents of the region. All STEMI patients from the region are treated in Turku University Hospital, which has round-the-clock primary percutaneous coronary intervention (PPCI) capability. VSSHP institutional database contains information stored in electronic patient information systems. Electronic patient records in VSSHP patient information system were inspected with a standardized data collection protocol. Additionally, a database search was used to gather laboratory values. Dates and causes of deaths were acquired from Statistics Finland, a governmental agency which reviews all death certificates issued in Finland.

2.2. Study population

The institutional database of VSSHP was searched for hospitalizations for STEMI between 2016 and 2022 according to International Classification of Diseases, 10th revision (ICD-10) codes I21.0-I21.3. All patients aged ≥18 years presenting with STEMI and residing in VSSHP catchment areas at the time of index hospitalization were inspected. Patients with STEMI managed with PPCI were included in this study. The index-diagnosis was ascertained by reviewing electronic patient records. STEMI was defined according to fourth universal definition of myocardial infarction (MI). [7] PPCI was defined as percutaneous coronary intervention within 24 h after symptom onset.

2.3. Baseline characteristics

Baseline laboratory values were acquired from the database search. Other patient characteristics were gathered by inspecting electronic patient records using a standardized data collection protocol. Comorbidities were defined as existing diagnosis, or a new diagnosis made by treating physician at the time of the index-hospitalization. New atrial fibrillation was included if it was not considered momentarily caused by myocardial ischemia. Left ventricular ejection fraction (LVEF) was searched from echocardiography reports during index-hospitalization and if both visual inspection and measured quantification were used, the measured one was preferred. Medication was assessed at discharge or at the time of endpoint event or death if they occurred during the index-hospitalization. Smoking status and alcohol consumption were evaluated by reviewing records during the index-hospitalization and follow-up. Smoking status was divided into current, former and never smokers and alcohol consumption into excessive and non-excessive as described in the supplementary materials.

2.4. Bleeding risk assessment

Bleeding risk was evaluated based on the ARC-HBR criteria, which have been described previously. [2] Those meeting at least 1 major or 2 minor criteria were considered HBR. The fulfilment of the criteria was adjudicated by reviewing patient records. Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration equation. The major criterion for prior stroke was slightly modified and defined as follows: previous spontaneous intracranial haemorrhage (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 h or until death and confirmed by neuroimaging or if no imaging was performed, the diagnosis was set by the treating neurologist.

2.5. Endpoints and follow-up

The primary endpoint was major adverse cardiovascular or cerebrovascular event (MACCE) during 1-year follow-up. Follow-up period was from the hospitalization date until first endpoint event or 365 days. MACCE was a composite of cardiovascular death, MI (type 1 or type 4 [stent thrombosis]) or ischemic stroke. MI and ischemic stroke were adjudicated by reviewing electronic patient records including laboratory values, electrocardiograms, angiography and echocardiography reports as well as reports from neuroimaging. All existing electronic patient records of the study subjects that were available in the VSSHP patient information system during the follow-up period were inspected for endpoints.

Cardiovascular death was defined as a matching ICD-10 diagnosis code (Supplementary Table 1) in death certificate as immediate or underlying cause of death. Undetermined death was considered cardiovascular based on expert consensus. [8] The data of death certificates is stored in the cause-of-death registry maintained by Statistics Finland, which is a governmental agency.

MI endpoint was defined according to the fourth universal definition. [7] If angiography was not performed, the diagnosis and classification of MI subtype was verified by an independent interventional cardiologist (AY). Culprit lesion locations in relation to the index-lesion were recorded and are described in the supplementary materials. Furthermore, the incidence of definite or probable stent thrombosis according to the Academic Research Consortium criteria were recorded. [9] 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 persist for ≥24 h or until death and confirmed by neuroimaging or if no imaging was performed, the diagnosis was set by the treating neurologist. If such symptoms were attributed to cerebral hypoperfusion resulting from cardiac arrest, they were not considered an endpoint.

The secondary endpoint was 1-year non-access site major bleeding according to the bleeding academic research consortium (BARC) definition (types 3 and 5). [10] Access site bleeding events were excluded due to their lesser prognostic significance compared to non-access site events. [11–13] Bleeding endpoints were adjudicated by reviewing electronic patient records. Furthermore, possible fatal BARC 5 events occurring outside healthcare facilities were identified from death certificates.

2.6. Statistical analyses

Statistical analyses 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. Categorical variables are presented as frequencies (and percentages) and were compared using Chi-square test or Fisher's exact test as appropriate. Normality was assessed by visual inspection of histograms, computation of Q-Q plots and using skewness and kurtosis. Age was presented as median

(interquartile range) and compared between groups using Mann-Whitney *U* test.

Risk of MACCE and major bleeding over time was presented using cumulative incidence function (CIF). 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 all individual ARC-HBR criteria with $p < 0.05$ in univariable analysis. If both major and minor ARC-HBR criterion of the same variable (for example chronic kidney disease) had $p < 0.05$, the 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 the 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 variable selection process is described in detail in the Supplementary Methods and Tables file.

2.7. Research permits and ethical considerations

This study was approved by the Institutional Review Board of VSSHP. A license to access causes of death was granted by Statistics Finland. Informed consent and ethical board review were waived due to the study design. 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 this study 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 publication 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 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 study subjects. These were reported as symbol "<" followed by the smallest possible value that was considered anonymized. Censoring did not affect data gathering or the results. Statistical analyses were conducted using the original data values.

3. Results

3.1. Patient population

Of 1564 patients with STEMI, 1367 were managed with PPCI and were included in the study population (Supplementary Fig. 1). Median age was 68.4 (interquartile range 59.0 to 76.9) years and 28.1 % (n = 384) were female. Overall, 518 (37.9 %) were HBR and 838 (61.3 %) were non-HBR. Fulfilment of individual ARC-HBR criteria is shown in Supplementary Table 2. Most prevalent criteria were age ≥ 75 years, chronic kidney disease (CKD), anaemia and use of oral anticoagulation (OAC). HBR patients were older and had more comorbidities (Table 1). Current smoking was more common among non-HBR patients. Those at HBR were less often on DAPT and the prescribed DAPT duration was shorter. On the other hand, 173 (33.4 %) of HBR patients used OAC and 14.1 % (n = 73) were on triple antithrombotic therapy (DAPT with OAC). Use of statins was less common among the HBR group.

3.2. Clinical outcomes

The cumulative incidences of ischemic endpoints at 1-year and 30-days are summarized in Table 2. Overall, 1-year MACCE cumulative incidence was 11.9 %. The cumulative incidences of cardiovascular death, MI and ischemic stroke were 7.1 %, 2.78 % and 1.98 % respectively. Of MI events, the culprit lesion was same as index lesion in 44.7 % (n = 17), located at the same coronary area but not index lesion in 18.4 % (n = 7), at another area in 26.3 % (n = 10), undetermined in 10.5 % (n = 4). The overall incidence of stent thrombosis was 0.9 % (n = 12). MACCE at 1-year was more common among HBR as compared with non-HBR (cumulative incidences 19.5 % and 6.32 %) (unadjusted hazard ratio 3.31, 95 % confidence interval 2.38–4.62, $p < 0.001$). The stent thrombosis incidence was 1.5 % (n = 8) among the HBR group and 0.5 % (n = 4) among the non-HBR group (p = 0.069). Over half of overall MACCE events and cardiovascular deaths and nearly half of MI events occurred within 30 days from the index STEMI. CIF curves of MACCE in the overall study population and in bleeding risk groups is demonstrated in Fig. 1. CIF curves of the individual components of MACCE according to bleeding risk are shown in Supplementary Fig. 2. The overall cumulative incidence of 1-year BARC 3 or 5 bleeding was 6.20 %, of which 89.4 % were BARC 3 and 10.6 % BARC 5 events. BARC 3 or 5 incidence was 10.6 % among the HBR group and 3.58 % in the non-HBR group (unadjusted hazard ratio 3.09, 95 % confidence interval 1.98–4.82, $p <$ 0.001). CIF curves for BARC 3 or 5 bleeding are shown in Supplementary Fig. 3.

3.3. Predictors of MACCE

Univariable regression analyses for 1-year MACCE are shown in Supplementary Table 3. Of the components of the ARC-HBR criteria, use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroids and active malignancy were associated with MACCE according to the multivariable model (Table 3). Age and CKD showed a trend towards increased risk of MACCE without reaching statistical significance. Other MACCE predictors were LVEF <35 % and diabetes. DAPT duration ≥3 months was associated with reduced risk of MACCE as were use of statins, angiotensin-converting enzyme (ACE) inhibitors and beta blockers.

4. Discussion

Among PPCI treated STEMI patients, 1-year cumulative incidence of MACCE was 11.9 %. Over half of all events occurred within 30 days after PCI. Of the 38 MI events, 44.7 % had the same culprit lesion location as the index-STEMI. MACCE was more common in HBR patients. Only two individual ARC-HBR criteria–use of NSAIDs or steroids and active malignancy–were predictors of MACCE, while CKD and age ≥ 75 years showed a trend towards increased risk. Diabetes and LVEF <35 % were independent MACCE predictors. DAPT duration ≥3 months and secondary prevention with statins, ACE-inhibitors and beta blockers significantly reduced the risk of MACCE.

In the present study, HBR patients had over 3 times higher incidence of ischemic complications compared to non-HBR, which is in line with previous literature. [6,14–17] Although in the previous studies, the incidence has been approximately 2-fold higher, which could be explained by the inclusion of more stable non-ST-segment elevation ACS and chronic coronary syndrome patients. Our results reflect the complexity of managing STEMI patients when HBR is present. In addition to increased ischemic risk, the HBR group was at an increased risk of major bleeding complications, a finding corroborated by several studies. [3,6] Recently, Kang et al. reported that HBR patients had 3-fold increased risk of major bleeding and 2.5-fold increased risk of MACCE at 5-year follow-up. [3] However, in our data the risk increases were of the same magnitude. ACS management requires balancing between bleeding and ischemic complications and HBR patients could benefit from abbreviated DAPT-regimens, especially in the absence of high ischemic risk. Our results demonstrate that careful evaluation of ischemic risk factors is particularly important among HBR patients.

Even though MACCE incidence was considerably higher among HBR patients, only two individual ARC-HBR criteria–use of NSAIDs or steroids and active malignancy–were independent MACCE predictors. It should be noted that the use of NSAIDs in our data was miniscule and therefore, the results mainly reflect the impact of corticosteroids. There are several mechanisms linking corticosteroid use to increased cardiovascular risk, such as insulin resistance, increased risk of dyslipidaemia

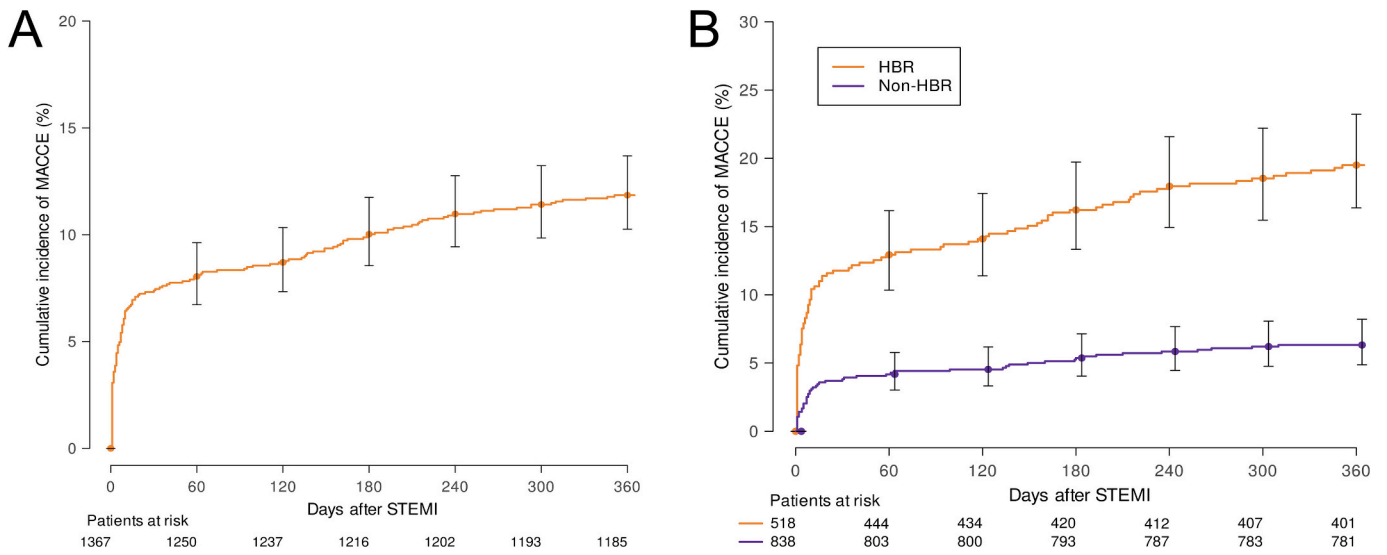

Fig. 1. 1-year cumulative incidence of MACCE in the overall study population and stratified by bleeding risk.
MACCE, major adverse cardiovascular or cerebrovascular event; HBR, high bleeding risk; STEMI, ST-elevation myocardial infarction. A, overall study population; B, stratified by bleeding risk.

and elevated blood pressure. [18] Interestingly high blood pressure is also a well-known bleeding risk factor. The impact of NSAIDs and steroids could be mediated by underlying pulmonary conditions or rheumatoid disease, which have been shown to increase ischemic risk after PCI. [19,20] The chronic systemic inflammation in these conditions accelerates atherogenesis. [21] The inflammation is then treated with anti-inflammatory medication such as corticosteroids, leading to increased bleeding risk. It should be noted that while CKD and age ≥ 75 years were not significant predictors, a clear trend towards increased risk was observed. It is likely that statistical significance would have been reached with a larger sample size. Another possibility is that the categorization of age and eGFR in the ARC-HBR framework might have reduced the granularity of the data when analyzing the impact of these variables.

A previous study assessed how individual ARC-HBR criteria predict ischemic complications when accounting for comorbidities. [6] Age ≥ 75 years, CKD and anaemia were identified as significant risk factors for ischemic events. About 56 % of the studied population were ACS and only 26 % STEMI, which could explain differences in results. The study has limitations that should be acknowledged, particularly the lack of adjustment for diabetes, which is a well-known risk factor for ischemic complications and was an independent predictor in the present study as well. Secondly, due to limitations in available data, most of the original ARC-HBR criteria were either not available or modified. In the present study, adjudication of the ARC-HBR criteria by patient record review allowed using original definitions for all except one criterion. In our data, LVEF <35 % during the index-hospitalization and diabetes were predictors of MACCE and both were more prevalent among HBR patients. Furthermore, DAPT-duration ≥3 months reduced the risk by more than 40 % (compared to shorter DAPT) and was less common in the HBR group. It seems that the higher observed ischemic risk among HBR patients might not be explained by bleeding risk status itself but rather with some of its components and other underlying comorbidities and management strategies. These findings may be useful when evaluating the balance of ischemic and bleeding risks based on patient-specific risk factors. It should be noted that cardiogenic shock and acute heart failure during the index-hospitalization could increase the risk of MACCE. Although these conditions are likely included in the LVEF <35 % group, the individual impacts cannot be determined in the present study because the variables were not recorded in the data.

In the present study, ≥ 3-month DAPT reduced the risk of MACCE in STEMI patients. However, randomized trials investigating DAPT durations have yielded less consistent results. The MASTER DAPT trial compared ≥3 months DAPT with shorter durations in PCI treated patients and there was no difference in MACCE between the groups. [22] Notably, STEMI patients were underrepresented in this trial, comprising only 12 % of the study population. The STOPDAPT-2 ACS trial enrolled only ACS patients, including 56 % presenting with STEMI. [23] The trial compared 12 months DAPT with 1–2 months. The abbreviated DAPT group exhibited a trend towards increased ischemic complications (HR 1.50, CI 0.99–2.26). It is noteworthy that almost half of the participants in this trial received low dose prasugrel (3,75 mg 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 clinical practice is questionable. The ULTIMATE DAPT trial showed that compared with 12-month DAPT, 1-month DAPT followed by ticagrelor monotherapy reduced the risk of bleeding without increasing ischemic complications among ACS patients. [24] Again, less than 30 % were STEMI and both exclusion criteria and low event rates indicate a low-risk population. In our real-world cohort, the overall MACCE incidence was over three times higher than in the ULTIMATE DAPT trial. To overcome the selection bias encountered 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. [25] However, only about 30 % of the study population had STEMI. Altogether the current evidence on the safety of short DAPT duration in STEMI patients remains insufficient and more work on the topic is needed. Randomized trials enrolling more high-risk populations are warranted to evaluate the safety and efficacy of different interventions in populations more representative of the real-world patients.

Another subcategory of high-risk patients often excluded from randomized DAPT-trials are those who suffer post-PCI complications shortly after the procedure before randomization, which in the most recent trials is conducted at 1–3 months. Therefore, evidence regarding the optimal management in these situations is lacking. In the present real-world cohort over 50 % of all MACCE complications occurred within 30 days after PCI. Similarly, nearly half of MI complications occurred within the first month. These findings highlight the importance of careful monitoring during the early phase post-PCI and possibly customizing interventions based on the clinical situation. Hospitalizations for ACS can be just a couple of days and the follow-up after discharge is left for outpatient care due to limited resources in

Table 1
Baseline characteristics and medication according to bleeding risk status.

Variable	Overall (n = 1367)	HBR (n = 518)	Non-HBR (n = 838)	p-value
Clinical characteristics				
Female sex, n (%)	384 (28.1)	190 (36.7)	189 (22.6)	<0.001
Age, median (Q1, Q3)	68.4 (59.0, 76.9)	77.3 (69.3, 83.9)	64.0 (55.6, 70.6)	<0.001
Smoking				
Current, n (%)	436 (31.9)	94 (18.1)	337 (40.2)	
Former, n (%)	312 (22.8)	142 (27.4)	168 (20.0)	<0.001
Never, n (%)	619 (45.3)	282 (54.4)	333 (39.7)	
Excessive alcohol consumption, n (%)	103 (7.5)	36 (6.9)	67 (8.0)	0.480
LVEF <35, n (%)	197 (14.4)	102 (19.7)	88 (10.5)	<0.001
Hypertension, n (%)	748 (54.7)	348 (67.2)	397 (47.4)	<0.001
Hypercholesterolemia, n (%)	820 (60.0)	279 (53.9)	539 (64.3)	<0.001
Diabetes, n (%)	293 (21.4)	129 (24.9)	162 (19.3)	0.015
Atrial fibrillation, n (%)	181 (13.2)	172 (33.2)	9 (1.1)	<0.001
Heart failure, n (%)	61 (4.50)	48 (9.3)	13 (1.6)	<0.001
Prior CAD, n (%)	576 (42.1)	251 (48.5)	320 (38.2)	<0.001
Prior MI, n (%)	178 (13.0)	90 (17.4)	86 (10.3)	<0.001
Prior PCI, n (%)	165 (12.1)	78 (15.1)	86 (10.3)	0.009
Prior CABG, n (%)	37 (2.70)	26 (5.0)	10 (1.2)	<0.001
Peripheral artery disease, n (%)	41 (3.0)	27 (5.2)	13 (1.6)	<0.001
Prior stroke, n (%)	81 (5.90)	72 (13.9)	9 (1.1)	<0.001
Prior ICH, n (%)	27 (2.0)	23–26 (4.4–5.0) *	< 3 (< 0.36) *	<0.001
Medication at discharge #				
ASA, n (%)	1233 (90.2)	400 (77.2)	829 (98.9)	<0.001
Clopidogrel, n (%)	357 (26.1)	267 (51.5)	89 (10.6)	<0.001
Ticagrelor, n (%)	943 (69.0)	207 (40.0)	733 (87.5)	<0.001
Prasugrel, n (%)	13 (1.0)	5 (1.0)	8 (1.0)	1.000
DAPT, n (%)	1209 (88.4)	382 (73.7)	824 (98.3)	<0.001
DAPT duration ≥3 months, n (%)	1134 (83.0)	313 (60.4)	818 (97.6)	<0.001
DAPT with ticagrelor or prasugrel, n (%)	938 (68.6)	200 (38.6)	735 (87.7)	<0.001
VKA, n (%)	34 (2.5)	34 (6.6)	0 (0)	<0.001
DOAC, n (%)	139 (10.2)	139 (26.8)	0 (0)	<0.001
TAT, n (%)	73 (5.3)	73 (14.1)	0 (0)	<0.001
NSAID, n (%)	< 6 (< 0.44) *	< 3 (< 0.58) *	< 3 (< 0.36) *	0.562
Corticosteroid, n (%)	43 (3.1)	37 (7.1)	6 (0.7)	<0.001
PPI, n (%)	521 (38.1)	298 (57.5)	220 (26.3)	<0.001
ACE inhibitor, n (%)	842 (61.6)	275 (53.1)	563 (67.2)	<0.001
ARB, n (%)	301 (22.0)	142 (27.4)	159 (19.0)	<0.001
Calcium blocker, n (%)	224 (16.4)	110 (21.2)	112 (13.4)	<0.001
Beta blocker, n (%)	1092 (79.9)	409 (79.0)	678 (80.9)	0.382
MRA, n (%)	180 (13.2)	78 (15.1)	100 (11.9)	0.098
SGLT2 inhibitor, n (%)	85 (6.2)	22 (4.2)	62 (7.4)	0.019
Statin, n (%)	1269 (92.8)	457 (88.2)	807 (96.3)	<0.001
Ezetimibe, n (%)	48 (3.5)	13 (2.5)	35 (4.2)	0.107

Values are n (%).
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; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; TAT, triple antithrombotic therapy (DAPT + oral anticoagulant); NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose co-transporter-2.
* Value <3 in one of the columns for this variable censored (and other columns censored as necessary) based on the review of Findata (data permit authority for the social and health care sector in Finland) to ensure anonymity of study subjects.
# or during endpoint or death if they occurred during index hospitalization.

Table 2
Cumulative incidence of endpoints in the overall study population and stratified by bleeding risk status.

	MACCE	CV death	MI	Stroke
1-year cumulative incidences				
HBR	19.5 %	12.6 %	3.86 %	3.09 %
Non-HBR	6.32 %	2.86 %	2.15 %	1.31 %
Overall	11.9 %	7.10 %	2.78 %	1.98 %
30-day cumulative incidences				
	MACCE	CV death	MI	Stroke
HBR	11.8 %	9.07 %	1.93 %	0.77 %
Non-HBR	3.82 %	2.27 %	0.96 %	0.60 %
Overall	7.39 %	5.41 %	1.32 %	0.66 %

Values are cumulative incidence estimates from Fine-Gray analysis.
MACCE, major adverse cardiovascular or cerebrovascular event; CV, cardiovascular; MI, myocardial infarction: HBR, high bleeding risk.

Table 3
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 $<100 \times 10^9$/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

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.
Correlation coefficient between variables DAPT duration ≥3 months and DAPT with ticagrelor/prasugrel was 0.600 and therefore only one was included in the model. DAPT duration was chosen based on higher significance in univariable analyses.
* Academic Research Consortium for High Bleeding Risk criterion.

specialized healthcare. Identification of risk factors could help to allocate more resources to high-risk patients.

5. Limitations

As a single centre study, the generalizability of the results requires confirmation in larger datasets preferably including patients from multiple geographical areas. While adjudicating the ARC-HBR criteria by reviewing patient records minimized misclassification bias, it led to

sample size limitations. It is possible that with a larger sample size, additional risk factors would have reached statistical significance. Particularly age ≥ 75 years and CKD. Cardiogenic shock and acute heart failure were not separately recorded in the data. Although these conditions are likely encountered in the LVEF <35 % group and thus accounted for, the individual effects cannot be determined in the present study. Unmeasured confounding cannot be ruled out despite multivariable regression because randomization was not used. We investigated exclusively STEMI patients and thus, the results might not be applicable to other subtypes of ACS and chronic coronary syndrome undergoing PCI. Adherence to prescribed medication could not be ascertained.

6. Conclusions

In real-world STEMI patients, 1-year MACCE incidence after PPCI was 11.9 % and over half of the events occurred within 30 days after the procedure. The risk of MACCE was 3 times higher among those classified as HBR according to the ARC-HBR criteria compared to non-HBR. Only few individual ARC-HBR criteria were independently associated with increased risk of MACCE. The higher MACCE incidence among HBR patients could be explained by underlying comorbidities such as lower LVEF and higher prevalence of diabetes as well as the few individual ARC-HBR criteria associated with increased risk. These findings may be useful when evaluating the balance of ischemic and bleeding risks based on patient-specific risk factors.

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Ethical statements

Informed consent and ethical board review were waived due to the study design.

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CRediT authorship contribution statement

Henri Kesti: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kalle Mattila:** Writing – review & editing, Validation, Supervision, Resources, Data curation, Conceptualization. **Samuli Jaakkola:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Joonas Lehto:** Writing – review & editing, Software, Methodology, Formal analysis. **Nea Söderblom:** Writing – review & editing, Investigation, Data curation. **Kalle Kalliovalkama:** Writing – review & editing, Investigation, Data curation. **Pekka Porela:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

Henri Kesti received research grants for the present study (listed in Funding section). Pekka Porela is the current Secretary in The Finnish Cardiac Society. Other authors have no conflicts of interest to declare.

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Data availability

Patient level data cannot be shared publicly due to legal reasons. This study uses routinely collected health and social data for a secondary purpose (research). Finnish Act on the Secondary Use of Health and Social Data (522/2019) dictates that such data can only be released into audited secure data environments.

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