Incidence, Predictors, and Outcome of In-Hospital Bleeding in Patients With Cardiogenic Shock Complicating Acute Myocardial Infarction

Hanna Ratcovich, MD[a,*], Jakob Josiassen, MD[a], Ole K.L. Helgestad, MD, PhD[b,c], Louise Linde, MD[b], Golnaz Sadjadieh, MD, PhD[a], Thomas Engstrøm, MD, PhD, DMSci[a,d], Lisette O. Jensen, MD, PhD, DMSci[b], Hanne B. Ravn, MD, PhD, DMSci[d,e], Henrik Schmidt, MD, DMSci[f], Christian Hassager, MD, DMSci[a,d], Jacob E. Møller, MD, PhD, DMSci[a,b,c], and Lene Holmvang, MD, DMSci[a,d]

Bleeding after acute myocardial infarction (AMI) is associated with an increased morbidity and mortality. The frequency and consequences of bleeding events in patients with AMICS are not well described. The objective was to investigate incidence and outcome of bleeding complications among unselected patients with AMI complicated by cardiogenic shock (AMICS) and referred for immediate revascularization. Bleeding events were assessed by review of medical records in consecutive AMICS patients admitted between 2010 and 2017. Bleedings during admission were classified according to Bleeding Academic Research Consortium classification. Patients who did not survive to admission in the intensive care unit were excluded. Of the 1,716 patients admitted with AMICS, 1,532 patients (89%) survived to ICU admission. At 30 days, mortality was 48%. Severe bleedings classified as BARC 3/5 were seen in 87 non-coronary bypass grafting patients (6.1%). Co-morbidity did not differ among patients; however, patients who had a BARC 3/5 bleeding had significantly higher lactate and lower systolic blood pressure at admission, indicating a more severe state of shock. The use of mechanical assist devices was significantly associated with severe bleeding events. Univariable analysis showed that patients with a BARC 3/5 bleeding had a significantly higher 30-day mortality hazard compared with patients without severe bleedings. The association did not sustain after multivariable adjustment (hazard ratio 0.90, 95% confidence interval 0.64; 1.26, p = 0.52). In conclusion, severe bleeding events according to BARC classification in an all-comer population of patients with AMICS were not associated with higher mortality when adjusting for immediate management, hemodynamic, and metabolic state. This indicates that mortality in these patients is primarily related to other factors. **(Am J Cardiol 2021;144:13−19)**

Cardiogenic shock (CS) is a life-threatening complication occurring in approximately 5% to 10% of patients with acute myocardial infarction (AMI) and have a sustained high mortality of 50%.[1] It is well known that bleeding complications after percutaneous coronary intervention (PCI), as well as bleeding events related to acute coronary syndromes (ACS), are associated with an increase in morbidity and mortality.[2−5] Patients with AMI complicated by CS (AMICS) are often excluded from clinical trials focusing on bleeding and prognosis. In the few existing studies there are of bleeding complications in AMICS, bleeding events are often not evaluated with widely acknowledged bleeding classification systems. Thus, in-depth knowledge of bleeding complications and the consequences in AMICS is lacking. We sought to investigate incidence and outcome of severe bleeding events in a large, consecutive cohort of patients with AMICS, treated at 2 tertiary heart centers in Denmark. Our hypothesis was that patients with AMICS experiencing severe bleeding events have a worse 30-day outcome than patients without severe bleeding.

Methods

Data of bleeding events in patients with AMICS were collected from the RETROSHOCK registry. A more detailed explanation of registry design and establishment has been published.[6] In brief, the registry consists of patients with AMICS admitted to 2 tertiary University

[a]Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [b]Department of Cardiology, Odense University Hospital, Odense, Denmark; [c]Odense Patient data Explorative Network, University of Southern Denmark, Odense, Denmark; [d]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [e]Department of Cardiothoracic Anaesthesia, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; and [f]Department of Cardiothoracic Anaesthesia, Odense University Hospital, Odense, Denmark. Manuscript received October 27, 2020; revised manuscript received and accepted December 22, 2020.

Funding: Dr Hanna Ratcovich has received a research grant from the Rigshospitalet and Odense University Hospital Research Foundation.

See page 18 for disclosure information.

*Corresponding author: Tel.: +45 35454007; fax: +45 35452705.

E-mail address: hanna.louise.ratcovich.01@regionh.dk (H. Ratcovich).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.12.045

facilities in Denmark between 2010 and 2017. Patients with a possible shock diagnosis were identified retrospectively from the Danish National Patient Registry based on different ICD-10 diagnose codes. Afterward patients' records underwent discharge summary review to identify patients with AMI and CS. The following criteria for CS were used: (1) persistent hypotension with systolic blood pressure ≤90 mm Hg for >30 minutes and/or need of vasoactive drugs; (2) signs of impaired organ perfusion; (3) documented reduction in left and/or right ventricular function (in the absence of hypovolemia, sepsis, anaphylaxis, pulmonary embolism, or primary valve dysfunction).

In the registry bleeding events was initially defined as none, minor (transfusion without overt bleeding), moderate (unstable patient requiring blood transfusion) and major (intracranial, severely unstable, need for intervention) bleedings. Unstable patients were defined as those with hemodynamic instability because of bleeding. Patients with "moderate" or "major" bleedings were extracted and further classified according to the Bleeding Academic Research Consortium (BARC) bleeding assessment tool.[7] The classifications were made from careful reading in the patient's medical records. Because of the heavy instrumentation related to intensive care minor bleeding episodes are common and therefore only bleeding events classified as BARC ≥3, were registered. In brief, BARC 3 is defined as an overt bleeding with a significant drop in hemoglobin of 3 to 5 g/dl, or any overt bleeding with need of transfusion (A), an overt bleeding and a hemoglobin drop of >5 g/dl (B), or an intracranial or intraocular bleeding (C). BARC 4 are bleeding events in the setting of coronary bypass grafting (CABG) and BARC 5 are fatal bleedings.

Patients were divided into 2 groups: patients with severe bleeding events not related to CABG (defined as BARC 3/5) and patients with no bleeding/less severe bleedings. For those with more than one bleeding event, the most severe bleeding during the first 30 days of hospitalization was recorded. Potentially fatal bleeding events were validated by a second reviewer. Patients who did not survive until admission to the intensive care unit (ICU) were excluded from further analyses.[8] This study was approved by The Danish Patient Safety Authority (the Danish Health and Medicines Authority formerly handling the applications, case number 3-3013-1133/1) and the Danish Data Protection Agency (file number 16/7381 and 18/23756).

Baseline characteristics are presented by number of patients and percentage for categorical variables, compared by chi-square test. Continuous variables with normal distribution are presented by means ± standard deviation (SD) and compared by *t* test, whereas continuous variables with non-normal distribution are presented as median and interquartile range and compared by Wilcoxon rank-sum test. A p value <0.05 was considered significant.

Associations between clinical characteristics and event of interest (mortality and severe bleeding events) were assessed with Cox proportional hazard model tests. Univariate and multivariate logistic regression analyses were used to determine independent predictors. Variables were added to the multivariable analysis in a stepwise manner to ensure that overfitting did not occur. In the multivariable analysis regarding mortality, variables with a possible effect on mortality were used (age, sex, out of hospital cardiac arrest [OHCA], arterial lactate, kidney function by estimated glomerular filtration rate [eGFR] and large bore interventions). Due to a paradigm shift in the use of IABP after the publication of the IABP-SHOCK II study in 2012,[9,10] the multivariable analysis regarding factors associated with 30-day mortality was adjusted for admittance in 2010 to 2012 or 2013 to 2017.

Kaplan-Meier methodology was performed when cumulated hazard of all-cause mortality during the first 30 days of hospitalization was compared between the 2 groups. Bleeding was handled as a time-varying covariate and analyzed in a time-dependent cox regression model. All statistical analyses of current study were performed by R, version 3.6.1, R Core Team (2019), https://www.r-project.org/.

Results

Between January 1, 2010 and December 31, 2017, 1,716 patients fulfilled the criteria for AMICS. The 186 patients who did not survive to ICU admission were significantly older (75.8 [±13.9] vs 66.2 [±11.8] years, p <0.001) and had lower systolic blood pressure (76.3 [±14.6] vs 83.3 [±15.4] mm Hg, p <0.01) and a higher lactate (6.6 [4.6; 10.9] vs 5.1 [3.0; 9.3] mmol/L, p <0.001) at admission. One patient had a fatal bleeding shortly after hospitalization and one had signs of moderate bleeding but died of circulatory failure shortly after the PCI (data not shown).

Of the 1,532 patients who survived to ICU admission, 115 patients (7.5%) had at least one severe bleeding episode classified as BARC 3A or worse. After initial coronary angiography, a total of 101 patients underwent CABG within 30 days of admission. Among these, 24 patients (24%) had a BARC 4 bleeding event. A distribution of the population's most severe BARC bleeding event and all bleeding events during the first 30-day of hospitalization are summarized in **Table 1a+b**.

Among the 12 patients (0.8%) who died of bleeding (BARC 5), the most common causes of death were intracranial bleeding (n = 5) and uncontrolled bleeding after surgery (n = 3). Among the nonsurgery-related severe BARC bleedings (BARC 3A-C), the most common causes of bleedings were gastrointestinal bleeding (55 patients), bleeding from insertion sites for peripheral mechanical circulatory support (23 patients), and cardiac tamponade (14 patients) (data not shown).

Baseline characteristics for non-CABG patients (n = 1,431) with and without severe bleedings are presented in **Table 2**. Patients with severe BARC 3/5 bleeding events were significantly younger. There were no significant differences in co-morbidities.

At the time of admission, patients who later experienced a BARC 3/5 bleeding had a significantly higher arterial lactate compared with patients without subsequent severe bleeding events, as well as lower systolic blood pressure. There were significantly more patients admitted after OHCA in the group without severe bleeding events. The groups did not differ with respect to eGFR and hemoglobin at admission, or treatment with antithrombotic agents and unfractionated heparin prior to coronary angiography. Treatment with vasoactive drugs such as norepinephrine,

Table 1
The distribution of the most severe bleedings and all bleeding events in the population. For patients suffering serious bleedings according to Bleeding Academic Research Consortium classification, during the first 30 days of hospitalization. Bleeding Academic Research Consortium 4 relates to coronary artery bypass graft related bleedings

Table 1a. *The most severe* Bleeding Academic Research Consortium bleeding event for every patient		**Table 1b.** All Bleeding Academic Research Consortium bleeding events in the population	
No severe bleeding	1407	No severe bleeding	1407
Bleeding Academic Research Consortium 3A	24	Bleeding Academic Research Consortium 3A	40
Bleeding Academic Research Consortium 3B	51	Bleeding Academic Research Consortium 3B	72
Bleeding Academic Research Consortium 3C	4	Bleeding Academic Research Consortium 3C	7
Bleeding Academic Research Consortium 4	24	Bleeding Academic Research Consortium 4	29
Bleeding Academic Research Consortium 5	12	Bleeding Academic Research Consortium 5	12
Number of patients with at least one bleeding	115	Total number of bleeding events	160

epinephrine, milrinone, and levosimendan were significantly more frequent in patients in the severe bleeding group, compared with the no severe bleeding group. The use of Impella and VA-ECMO were both significantly more frequent in the severe bleeding group as well.

Of the non-CABG patients, 198 patients were treated with Impella, 19% of them had a BARC 3/5 bleeding. For VA-ECMO (46 patients) and IABP (163 patients), these numbers were 39% and 6.1%, respectively (data not shown). By multivariable analysis (Figure 1), variables significantly associated with BARC 3/5 bleedings were arterial lactate at admission, acute kidney injury (defined from RIFL criteria[11]), Impella, and VA-ECMO. Patients with OHCA had significantly lower risk of BARC 3/5 bleeding.

The distribution of the crude 30-day mortality in the different BARC bleeding groups is shown in Figure 2. The unadjusted all-cause mortality hazard at each time point during the first 30 days of hospitalization, in patients with and without severe bleeding events, is shown in Figure 3. The mortality hazard among patients in the BARC 3/5 bleeding group was significantly higher compared with patients in the no severe bleeding group (hazard ratio 1.85, 95% confidence interval 1.33; 2.58, $p < 0.001$). After multivariable analysis for 30-day all-cause mortality, adjusted for age, sex, interventions (IABP, VA-EMCO, Impella), OHCA, multivessel disease, clinical presentation at admission (lactate, eGFR, and acute kidney injury) and admission before 2013, BARC 3/5 bleedings were no longer significantly associated with 30-day mortality (hazard ratio 0.90, 95% confidence interval 0.64; 1.26, $p = 0.52$) (data not shown).

Discussion

In our unselected population of patients with AMICS, surviving at least until admission to the cardiac ICU, the incidence of severe bleeding by BARC classification (3/5) was 6.1%. The higher incidence of bleedings seen in other publications such as the IABP SHOCK II study[9] can probably be explained by the use of other bleeding classifications. In IABP SHOCK II, the GUSTO bleeding classification[12] was used that relies heavily on transfusion as a criterion. This probably generates more bleeding events due to an often-liberal use of transfusions in the ICU. There are several well-validated and recommended bleeding classifications to describe bleeding complications in relation to ACS[7,13] but not for patients with AMICS. The recently published substudy from CULPRIT SHOCK classified bleedings according to BARC and reported incidence of BARC 3/5 bleedings at 21%.[14] The discrepancy between that study and our registry may somewhat be explained by a different patient selection with a population solely consisting of patients with multivessel coronary artery disease, all undergoing coronary intervention whereas only 14% of the patients in our unselected population underwent multivessel PCI.

The use of Impella and VA-ECMO were important risk factors for bleeding events in our population. This is not surprising since both devices need large-bore percutaneous interventions, which increases the risk of bleeding.[15] In a retrospective analysis of patients with CS and VA-ECMO, the rate of access-site bleedings were 6%.[16] That lower rate of access-site bleeding complications compared with ours can probably be explained by the all-comer CS population; hence patients with AMICS are treated with more aggressive antithrombotic therapy as a part of the ACS management. Previous publications, both clinical and registry-based, have investigated the risk of bleedings in patients treated with IABP compared with Impella and presented similar results where the risk of severe bleedings is significantly higher with the use of Impella.[15,17–22]

OHCA before admission was associated with a reduced risk of severe bleedings. This finding may be explained by a less severe hemodynamic compromise in OHCA survivors after return of spontaneous circulation. Most patients with OHCA undergo targeted temperature management and cerebral ischemia are more often the cause of death,[23] indicating more stable hemodynamics with less need for mechanical circulatory assist interventions,[15] compared with multiorgan failure in patients with AMICS.[24] Advanced age is a known risk factor for severe bleeding events in ACS patients who underwent PCI.[25] Nevertheless, in our population, patients in the severe bleeding group were younger. This might be a consequence of selection since younger patients may have received more advanced treatment including mechanical circulatory support that increases the risk of bleeding. Compatibly to the recent CULPRIT-SHOCK substudy,[14] there was no significant association between age and bleeding.

Previous studies of patients with ACS without CS have shown that bleeding complications increase mortality.[2–5]

Table 2
Baseline characteristics and findings at admission for the population. Patients divided into the groups Bleeding Academic Research Consortium classification 3/5 (severe bleedings not related to surgery), and no severe Bleeding Academic Research Consortium bleeding, during first 30 days of hospitalization

Variable	Bleeding Academic Research Consortium classification 3/5 (n = 87)	No severe Bleeding Academic Research Consortium classification bleeding (n = 1,344)	Missing	p value
Age. mean (standard deviation) (years)	62±13	67±12	0	0.002
Men	65 (75%)	1016 (76%)	2	0.936
Body mass index. mean (standard deviation) (kg/m^2)	26±4.2	26.4 (4%)	423	0.123
Current smoker	26 (58%)	370 (50%)	639	0.117
Previous ischemic heart disease	23 (27%)	376 (29%)	43	0.817
Previous myocardial infarction	13 (15%)	196 (15%)	43	1.000
Hypertension	41 (49%)	661 (51%)	60	0.734
Dyslipidemia	28 (34%)	432 (34%)	78	1.000
Diabetes mellitus	19 (23%)	232 (18%)	60	0.333
Peripheral arterial disease	4 (5%)	100 (8%)	65	0.454
Chronic obstructive lung disease	9 (11%)	133 (10%)	63	1.00
Previous stroke	2 (2%)	105 (8%)	62	0.093
Platelet inhibitor prior to admission	7 (15%)	123 (17%)	640	0.980
Anticoagulation prior admission	9 (20%)	83 (11%)	632	0.127
Admission findings				
Systolic blood pressure, mean (standard deviation) (mm Hg)*	77±20	83±15	57	<0.001
Diastolic blood pressure, mean (standard deviation) (mm Hg)*	50±15)	53±12	127	0.042
Heart rate, mean (standard deviation) (beats per minute)*	87±28	86±39	181	0.778
Left ventricular ejection fraction, mean (standard deviation) (%)*	27±14	29±13	56	0.291
Arterial lactate, median [interquartile range] (mmol/L)*	7 [4-13]	5 [3-9]	43	<0.001
Hemoglobin, mean (standard deviation) (mmol/L)	9±1)	8±1	39	0.207
Estimated glomerular filtration rate, mean (standard deviation) (ml/min/1.73 m^2)	60±21	57±24	48	0.350
Aspirin administration prior to coronary angiography	62 (72%)	975 (79%)	115	0.151
Adenosine di-phosphate inhibitor prior to coronary angiography	42 (49%)	552 (45%)	108	0.517
Heparin prior to coronary angiography	69 (81%)	990 (81%)	124	1.000
Resuscitation after out of hospital cardiac arrest	24 (28%)	653 (49%)	0	<0.001
Interventions				
Use of intra-aortic balloon pump	10 (12%)	153 (11%)	4	1.000
Use of Impella	38 (44%)	160 (12%)	2	<0.001
Use of veno-arterial extracorporeal membrane oxygenation	18 (21%)	28 (2%)	4	<0.001
Coronary angiograph with multivessel disease	47 (57%)	637 (54%)	171	0.649
Revascularization with percutaneous coronary intervention†	83 (95%)	1180 (88%)	167	0.0549
Multivessel percutaneous coronary intervention treatment	19 (24%)	171 (15%)	236	0.086
Temporary pacemaker	12 (15%)	222 (17%)	15	0.711
Medical treatment				
Norepinephrine	81 (93%)	1012 (77%)	29	<0.001
Dopamine	62 (72%)	885 (67%)	30	0.423
Epinephrine	49 (57%)	337 (26%)	41	<0.001
Dobutamine	5 (6%)	67 (5%)	50	0.930
Milrinone	37 (45%)	321 (25%)	42	<0.001
Levosimendan	25 (30%)	135 (10%)	40	<0.001
Outcome				
Mechanical ventilation	85 (98%)	1119 (84%)	8	<0.001
Number of days in the intensive care unit, median [interquartile range] (days)	6 [2-14]	3 [1-6]	5	<0.001
Acute kidney injury‡	60 (70%)	530 (40%)	19	<0.001
Death during admission	53 (65%)	627 (48%)	30	0.0025

* At the time of the shock diagnosis.
† Only revascularization with percutaneous coronary intervention since patients with coronary artery bypass graft are excluded.
‡ Acute kidney injury defined by RIFLE criteria.[11]

However, since patients with AMICS have a more than 10 times higher 30-day mortality rate compared with ACS patients without CS,[25] as well as a much lower bleeding rate of 1.6%,[26] it is obvious that noncardiogenic shock ACS patients constitute of a completely different population. Other factors such as progressive cardiac failure, hypoxic brain injury, and multiorgan failure may therefore have a higher impact on outcome. To the best of our knowledge, only the CULPRIT-SHOCK substudy has specifically investigated outcome of bleeding in patients with AMICS.[14] In contrast to ours, that study showed that bleedings were significantly associated with a higher mortality,

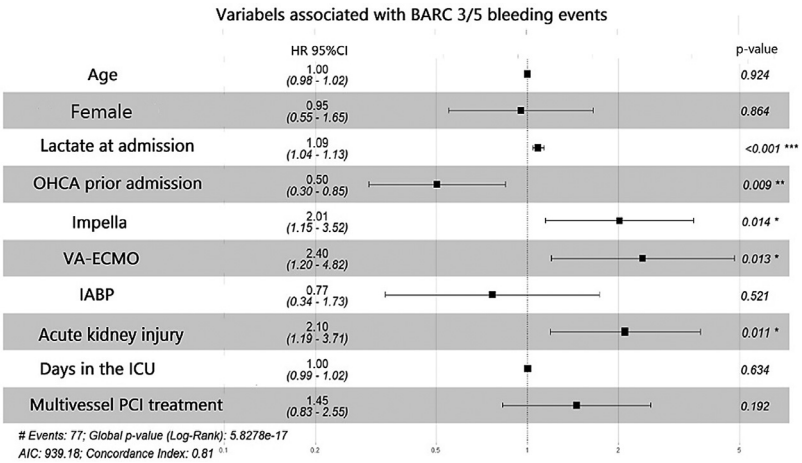

Figure 1. Variables associated with BARC 3/5 bleedings, within 30 days of hospitalization. BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; IABP = intra-aortic balloon pump; ICU = intensive care unit; OHCA = out of hospital cardiac arrest; PCI = percutaneous coronary intervention; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

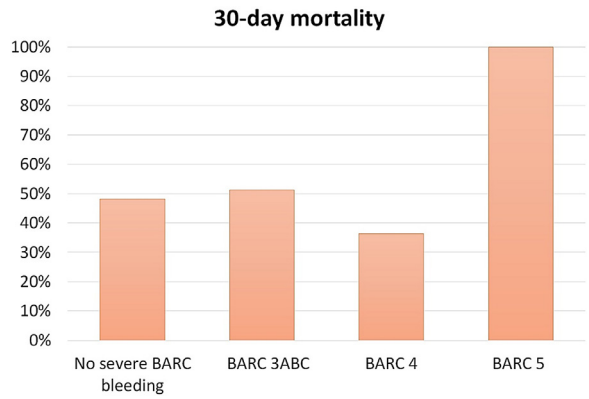

Figure 2. The distribution of all-cause 30-day mortality in patients, regarding to the BARC-bleeding classification. For all patients (n = 1,716), divided after their most severe bleeding event. BARC = Bleeding Academic Research Consortium.

even after multivariable analysis. An explanation of this inconsistency may be (1) the exclusion of BARC 3A bleedings in the survival analysis, because BARC 3A bleedings are a less severe bleeding that may have induced a weakened effect on the other bleedings' (BARC 3B, 3C and 5) fatal potential. (2) The population in the CULPRIT-SHOCK substudy only consisted of patients with multivessel coronary artery disease suitable for PCI,[14] whereas our population was an all-comer AMICS population, and thus more heterogeneous.

This study is retrospective in design which, as all registry studies, has some limitations and preclude any assumption of causality of observed associations. Bleeding events were, in contrast to many other registry studies, individually classified based on information collected from patients' records. A prospective focus on bleeding events may have influenced the level of registration. Minor bleedings are common during intensive care due to heavy instrumentation

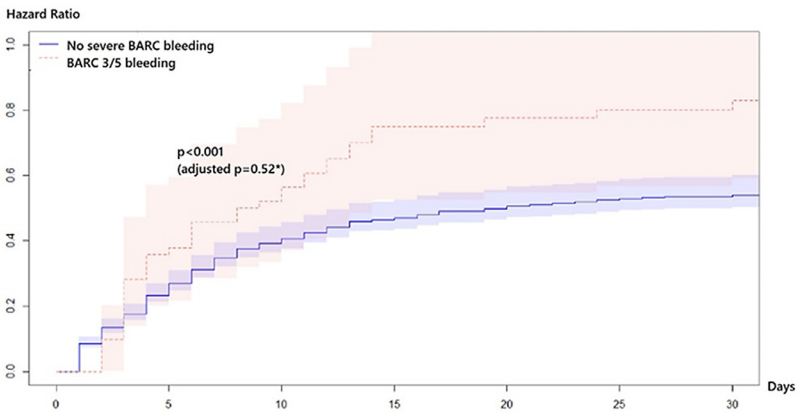

Figure 3. Unadjusted Kaplan-Meier plot showing the hazard of all-cause mortality at each time point, 30 days of hospitalization. For non-CABG patients regarding their most severe bleeding. Patients in the BARC 3/5 group compared with patients in the no severe BARC bleeding group. *Adjusted for age, sex, IABP, VA-EMCO, Impella, OHCA, multivessel disease, findings at admission (lactate, eGFR, and acute kidney injury) and admission before 2013 (HR 0.90, 95% CI 0.64 to 1.26, p = 0.52). BARC = Bleeding Academic Research Consortium; CABG = coronary artery bypass graft; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IABP = intra-aortic balloon pump; OHCA = out of hospital cardiac arrest; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

and therefore not always documented. Nevertheless, frequent observations are registered and all interventions such as blood transfusions and biochemical analyses were carefully documented, which are mandatory for the BARC 3-5 classifications. It is therefore our belief that important bleeding events affecting the patient and/or prompting transfusions are completely reported. Most patients received heparin before coronary intervention but data regarding additional use of glycoprotein IIb/IIIa inhibitors and bivalirudin during PCI was not registered and may have added valuable information regarding risk factors for bleeding. The selection of patients exclusively surviving to admittance in the ICU does create selection bias, since patients undergoing extensive but futile treatment in the catheterization lab is excluded from our analysis. Patients need to survive to have a bleeding, thus survival bias is a potential confounder. However, this applies to all studies relating bleeding to mortality in critically ill patients. Finally, our population consists of patients admitted in 2010 to 2017 were there was a paradigm shift in the use of percutaneous mechanical circulatory assist devices.[10] This can have affected the analyses regarding outcome.

In conclusion, severe bleeding events occurred in 6.1% of consecutive non-CABG AMICS patients surviving to ICU admission. Less than 1% suffered a fatal bleeding event bleeding events were highly associated with a more severe state of shock at presentation and the use of mechanical assist devices. Despite a higher crude mortality among patients with bleeding, severe bleeding events according to BARC3/5 were not associated with a higher risk of all-cause mortality when adjusting for hemodynamic compromise, comorbidities and immediate interventions.

Author Contributions

1. Conception and design: Ratcovich, Holmvang,
2. Analysis and interpretation of data: Ratcovich, Josiassen, Helgestad, Møller, Holmvang
3. Revision of the manuscript for important intellectual content: Ratcovich, Josiassen, Helgestad, Linde, Sadjadieh, Engstrøm, Jensen, Ravn, Schmidt, Hassager, Møller, Holmvang
4. Final approval of the manuscript submitted: Ratcovich, Josiassen, Helgestad, Linde, Sadjadieh, Engstrøm, Jensen, Ravn, Schmidt, Hassager, Møller, Holmvang.

Disclosures

Dr Jacob Eifer Møller has received research grant and speakers fee from Abiomed.

The remaining authors have no disclosures.

All authors declare no conflict of interest.

1. Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D, Gore JM. Decade-long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2016;9:117–125.
2. Kikkert WJ, Delewi R, Ouweneel DM, van Nes SH, Vis MM, Baan J Jr., Koch KT, Dangas GD, Mehran R, de Winter RJ, Peters RJ, Piek JJ, Tijssen JG, Henriques JP. Prognostic value of access site and non-access site bleeding after percutaneous coronary intervention: a cohort study in ST-segment elevation myocardial infarction and comprehensive meta-analysis. *JACC Cardiovasc Interv* 2014;7:622–630.
3. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB 3rd, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J Am Coll Cardiol* 2007;49:1362–1368.
4. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;24:1815–1823.
5. Sadjadieh G, Engstrom T, Helqvist S, Hofsten DE, Kober L, Pedersen F, Laursen PN, Nepper-Christensen L, Clemmensen P, Moller-Helgestad OK, Sorensen R, Ravkilde J, Terkelsen CJ, Jorgensen E, Saunamaki K, Tilsted HH, Kelbaek H, Holmvang L. Relation of bleeding events to mortality in patients with ST-segment elevation myocardial infarction treated by percutaneous coronary intervention (a DANAMI-3 substudy). *Am J Cardiol* 2018;121:781–788.
6. Helgestad OKL, Josiassen J, Hassager C, Jensen LO, Holmvang L, Sørensen A, Frydland M, Lassen AT, Udesen NLJ, Schmidt H, Ravn HB, Møller JE. Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a Danish cohort study. *Eur J Heart Fail* 2019;21:1370–1378.
7. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation* 2011;123:2736–2747.
8. Andersen LW, Grossestreuer AV, Donnino MW. Resuscitation time bias''—a unique challenge for observational cardiac arrest research. *Resuscitation* 2018;125:79–82.
9. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;367:1287–1296.
10. Helgestad OKL, Josiassen J, Hassager C, Jensen LO, Holmvang L, Udesen NLJ, Schmidt H, Berg Ravn H, Moller JE. Contemporary trends in use of mechanical circulatory support in patients with acute MI and cardiogenic shock. *Open Heart* 2020;7:e001214.
11. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204–R212.
12. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–682.
13. Capodanno D, Morice MC, Angiolillo DJ, Bhatt DL, Byrne RA, Colleran R, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock SJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhovel U, Krucoff MW, Urban P, Mehran R. Trial design principles for patients at high bleeding risk undergoing PCI: JACC scientific expert panel. *J Am Coll Cardiol* 2020;76:1468–1483.
14. Freund A, Jobs A, Lurz P, Feistritzer HJ, de Waha-Thiele S, Meyer-Saraei R, Montalescot G, Huber K, Noc M, Windecker S, Zeymer U, Ouarrak T, Schneider S, Thiele H, Desch S. Frequency and impact of bleeding on outcome in patients with cardiogenic shock. *JACC Cardiovasc Interv* 2020;13:1182–1193.
15. Redfors B, Watson BM, McAndrew T, Palisaitis E, Francese DP, Razavi M, Safirstein J, Mehran R, Kirtane AJ, Genereux P. Mortality, length of stay, and cost implications of procedural bleeding after percutaneous interventions using large-bore catheters. *JAMA Cardiol* 2017;2:798–802.
16. Koerner MM, Harper MD, Gordon CK, Horstmanshof D, Long JW, Sasevich MJ, Neel JD, El Banayosy A. Adult cardiac veno-arterial extracorporeal life support (VA-ECMO): prevention and management of acute complications. *Ann Cardiothorac Surg* 2019;8:66–75.
17. Alushi B, Douedari A, Froehlig G, Knie W, Wurster TH, Leistner DM, Stahli BE, Mochmann HC, Pieske B, Landmesser U, Krackhardt F,

Skurk C. Impella versus IABP in acute myocardial infarction complicated by cardiogenic shock. *Open Heart* 2019;6:e000987.
18. Dhruva SS, Ross JS, Mortazavi BJ, Hurley NC, Krumholz HM, Curtis JP, Berkowitz A, Masoudi FA, Messenger JC, Parzynski CS, Ngufor C, Girotra S, Amin AP, Shah ND, Desai NR. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2020;323:734–745.
19. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, Vis MM, Wykrzykowska JJ, Koch KT, Baan J, de Winter RJ, Piek JJ, Lagrand WK, de Mol BA, Tijssen JG, Henriques JP. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017;69:278–287.
20. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F, Pieri M, Skurk C, Lauten A, Landmesser U, Westenfeld R, Horn P, Pauschinger M, Eckner D, Twerenbold R, Nordbeck P, Salinger T, Abel P, Empen K, Busch MC, Felix SB, Sieweke JT, Moller JE, Pareek N, Hill J, MacCarthy P, Bergmann MW, Henriques JPS, Mobius-Winkler S, Schulze PC, Ouarrak T, Zeymer U, Schneider S, Blankenberg S, Thiele H, Schafer A, Westermann D. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation* 2019;139:1249–1258.
21. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, Eitel I, Poss J, Fuernau G, de Waha S. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J* 2017;38:3523–3531.
22. Wernly B, Seelmaier C, Leistner D, Stähli BE, Pretsch I, Lichtenauer M, Jung C, Hoppe UC, Landmesser U, Thiele H, Lauten A. Mechanical circulatory support with Impella versus intra-aortic balloon pump or medical treatment in cardiogenic shock-a critical appraisal of current data. *Clin Res Cardiol* 2019;108:1249–1257.
23. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, Carli P, Mira JP, Nolan J, Cariou A. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Med* 2013;39:1972–1980.
24. Vallabhajosyula S, Dunlay SM, Prasad A, Kashani K, Sakhuja A, Gersh BJ, Jaffe AS, Holmes DR Jr., Barsness GW. Acute noncardiac organ failure in acute myocardial infarction with cardiogenic shock. *J Am Coll Cardiol* 2019;73:1781–1791.
25. Aissaoui N, Puymirat E, Tabone X, Charbonnier B, Schiele F, Lefevre T, Durand E, Blanchard D, Simon T, Cambou JP, Danchin N. Improved outcome of cardiogenic shock at the acute stage of myocardial infarction: a report from the USIK 1995, USIC 2000, and FAST-MI French nationwide registries. *Eur Heart J* 2012;33:2535–2543.
26. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, Caixeta A, Feit F, Manoukian SV, White H, Bertrand M, Ohman EM, Parise H, Lansky AJ, Lincoff AM, Stone GW. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv* 2011;4:654–664.