Brief Report

High Bleeding Incidence in Unselected Hospitalized Suspected Non−ST-Segment Elevation Myocardial Infarction Patients Aged Under 65 Years

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High bleeding risk (HBR) is commonly encountered among patients with acute coronary syndrome (ACS), and bleeding complications are associated with worse prognosis. Data on bleeding events of patients with ACS are based almost exclusively on percutaneous coronary intervention registries. Enrolling only patients suitable for invasive procedures might have skewed the observed bleeding incidence. We sought to investigate bleeding incidence in unselected patients with ACS. Patients were retrospectively enrolled between January and June 2019 from the emergency department of a tertiary hospital. All consecutive hospitalized adults with suspected non−ST-segment elevation myocardial infarction were included. Data was gathered by a database search and verified using electronic patient records. Bleeding risk was assessed according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) definition. The primary end point was a composite of post- discharge Bleeding Academic Research Consortium type 2, 3, and 5 bleeding during 1-year follow-up. Of the 209 included patients, 15 (7.2%) suffered a bleeding event. There were more bleeding events among dual antiplatelet therapy (DAPT) users as compared with those without DAPT (10.7% vs 3.1%, p = 0.033). Among HBR patients, 6.1% and in non-HBR patients 8.1% suffered a bleeding event (p = 0.579). Notably, major bleeding (Bleeding Academic Research Consortium type 3) incidence was highest in patients <65 years and without DAPT use. In conclusion, unselected suspected non−ST-segment elevation myocardial infarction patients aged <65 years had surprisingly high bleeding incidence, regardless of ARC-HBR status or DAPT use. **(Am J Cardiol 2023;206:101−104)**

Keywords: acute coronary syndrome, dual anti-platelet therapy, hemorrhage, non−ST-elevated myocardial infarction

High bleeding risk (HBR) is common among patients with acute coronary syndrome (ACS), and major bleeding complications are associated with worse prognosis.[1,2] After percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) is essential for preventing further ischemic complications and subsequent mortality.[3] However, DAPT increases bleeding risk, especially with prolonged treatment durations.[4] The Academic Research Consortium for High Bleeding Risk (ARC-HBR) specified a list of clinical criteria to identify patients at HBR.[5] In HBR patients, the reported 1-year bleeding incidence has ranged from 4% to 30%.[6,7] Data on ARC-HBR criteria are based almost exclusively on PCI registries. Enrolling only patients suitable for invasive procedures might have skewed the observed bleeding incidence. This study aimed to investigate bleeding incidence in unselected patients with non−ST-segment elevation ACS during 1-year follow-up.

The study population and data collection have been described in detail previously.[8] This study was approved by the appropriate institutional review board. Ethical review was waived because of the retrospective nature of this study. In short, the study population consisted of patients who were admitted to emergency department in Turku University Hospital between January 1, 2019 and June 30, 2019 because of "chest pain." All consecutive hospitalized adults with suspected non−ST-segment elevation myocardial infarction (NSTEMI) were included. Patient identification and data gathering were conducted by a database search and verified by the authors using electronic patient records. Of the 212 hospitalized patients,[8] 2 died before discharge and were excluded. Six patients died during the follow-up but were included and finally, 1 patient was lost during the follow-up. Thus, 209 patients were included in

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this study. Patients were defined as being at HBR if at least 1 major or 2 minor ARC-HBR criteria were met. Bleeding events within 1 year after the primary hospitalization date were recorded. The primary end point was a composite of non-access site Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 bleeding. Furthermore, major bleeding was defined as BARC type 3 or 5 bleeding. Categorical variables are presented as frequencies (%) and compared with Pearson's chi-square or Fisher's exact test, as appropriate. The p values were two-tailed, and significance was set at $p < 0.05$. Statistical analyses were performed using SPSS, version 28.0.1.0 (SPSS Inc., Chicago, Illinois).

Clinical patient characteristics, medication, and management are shown in Table 1. Common management strategies were PCI (53.6%), non-invasive management (20.1%), and angiography without revascularization (18.2%). Non-invasive strategy was more often chosen among HBR patients as compared with non-HBR patients. DAPT was prescribed to 53.6% of all patients. DAPT prescription was more common in non-HBR patients (66.7%) as compared with HBR patients (38.8%). 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) and 65 to 74 years group (58.6%) and ≥75 years group (p = 0.038). Ticagrelor was used in 11.0% of NSTEMI patients and was more common among non-HBR patients (16.7%, n = 13) as compared with those at HBR (4.5%, n = 3, p = 0.020). During the follow-up, 15 patients (7.2%) suffered a bleeding event, of which 66.7% (n = 10) were BARC type 2 and 33.3% (n = 5) were BARC type 3. There were more bleeding events among DAPT users as compared with those without DAPT (p = 0.033; Figure 1). This difference was driven by BARC type 2 bleeding (8.9%, n = 10 and 0.0% respectively, p = 0.002). Among HBR patients, 6.1% (n = 6) and in non-HBR patients, 8.1% (n = 9) suffered a bleeding event (p = 0.579). One (8.3%) BARC type 3 bleeding event was observed among type 2 myocardial infarction.

The ARC-HBR criteria have been shown to predict major bleeding incidence ≥4% at 1 year,[1] which is defined as the threshold for HBR by the Academic Research Consortium.[5] Importantly, our results show a high bleeding incidence regardless of ARC-HBR status or DAPT use in hospitalized suspected NSTEMI patients <65 years. It is noteworthy, that we included BARC type 2 events, which were excluded from the original definition. However, even BARC type 3 incidence alone exceeded the 4% threshold, specifically in patients <65 years and without DAPT use. Therefore, this group seems to have the highest major bleeding risk. Our findings suggest that there could be predictors of bleeding not included in ARC-HBR criteria—particularly prevalent in younger age groups—such as smoking, heavy alcohol usage, and drug abuse for example. Overall, major bleeding incidence among HBR patients was only 3.1%, which is lower than expected based on previous studies enrolling European patients.[9] Even though the

Table 1
Baseline characteristics, medication, management and bleeding risk

	Total (n=209)	NSTEMI (n=145)	UAP (n=46)	Other* (n=18)	HBR (n=98)	Non-HBR (n=111)	p-value†
Age (years)							
<65	53 (25.4%)	40 (27.6%)	9 (19.6%)	4 (22.2%)	6 (6.1%)	47 (42.3%)	<0.001
65-74	70 (33.5%)	49 (33.8%)	16 (34.8%)	5 (27.8%)	22 (22.4%)	48 (43.2%)	0.001
≥75	86 (41.1%)	56 (38.6%)	21 (45.7%)	9 (50.0%)	70 (71.4%)	16 (14.4%)	<0.001
Sex							
Female	68 (32.5%)	40 (27.6%)	17 (37.0%)	11 (61.1%)	40 (40.8%)	28 (25.2%)	0.016
Male	141 (67.5%)	105 (72.4%)	29 (63.0%)	7 (38.9%)	58 (59.2%)	83 (74.8%)	
Medication							
ASA	159 (76.1%)	123 (84.8%)	28 (60.9%)	8 (44.4%)	58 (59.2%)	101 (91.0%)	<0.001
Clopidogrel	114 (54.5%)	89 (61.4%)	23 (50.0%)	2 (11.1%)	50 (51.0%)	64 (57.7%)	0.336
Ticagrelor	16 (7.7%)	16 (11.0%)	0 (0.0%)	0 (0.0%)	3 (3.1%)	13 (11.7%)	0.019
DOAC	33 (15.8%)	21 (14.5%)	10 (21.7%)	2 (11.1%)	33 (33.7%)	0 (0.0%)	<0.001
VKA	9 (4.3%)	5 (3.4%)	3 (6.5%)	1 (5.6%)	9 (9.2%)	0 (0.0%)	<0.001
DAPT	112 (53.6%)	91 (62.8%)	19 (41.3%)	2 (11.1%)	38 (38.8%)	74 (66.7%)	<0.001
Prescribed duration of DAPT (months)							
≤ 3 (≠ 0)	14 (12.5%‡)	10 (11.0%‡)	4 (21.1%‡)	0 (0.0%‡)	9 (23.7%‡)	5 (6.8%‡)	0.015‡
> 3 and ≤ 6	31 (27.7%‡)	21 (23.1%‡)	8 (42.1%‡)	2 (100%‡)	12 (31.6%‡)	19 (25.7%‡)	0.509‡
> 6	67 (59.8%‡)	60 (65.9%‡)	7 (36.8%‡)	0 (0.0%‡)	17 (44.7%‡)	50 (67.6%‡)	0.020‡
Management							
Non-invasive	42 (20.1%)	16 (11.0%)	17 (37.0%)	9 (50.0%)	31 (31.6%)	11 (9.9%)	<0.001
Angiography without revascularization	38 (18.2%)	17 (11.7%)	12 (26.1%)	9 (50.0%)	16 (16.3%)	22 (19.8%)	0.513
PCI	112 (53.6%)	95 (65.5%)	17 (37.0%)	0 (0.0%)	47 (48.0%)	65 (58.6%)	0.125
CABG	17 (8.1%)	17 (11.7%)	0 (0.0%)	0 (0.0%)	4 (4.1%)	13 (11.7%)	0.044

Values are n (%).

* Type 2 myocardial infarction or Takotsubo cardiomyopathy.

† HBR vs non-HBR.

‡ Of those with DAPT.

ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; HBR = high bleeding risk; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; UAP = unstable angina pectoris; VKA = vitamin K antagonist.

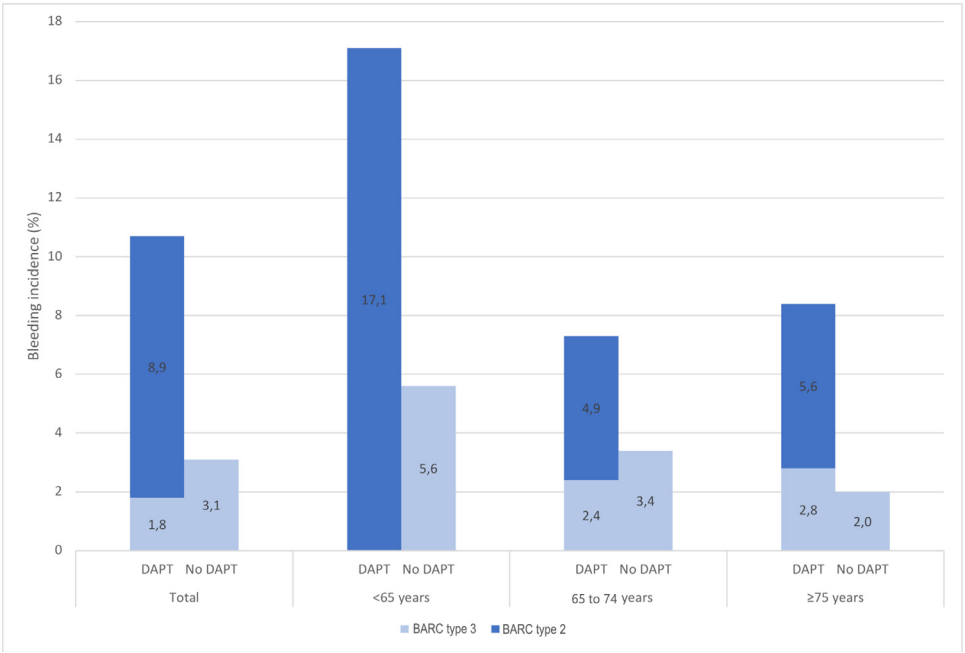

Figure 1. Bleeding incidence during 1-year follow-up according to DAPT use and age.

prevalence of HBR in the present study was nearly 50%,[8] bleeding incidence implies a low-risk population, which indicates that ARC-HBR criteria might not work in all demographics. It should be noted that DAPT use was considerably lower in HBR patients and ticagrelor was rarely the preferred choice among them. Therefore, bleeding risk assessment before initiating PCI and subsequent DAPT treatment probably helped to mitigate the bleeding risk of HBR patients.

As with all retrospective studies, our findings are mostly hypothesis-generating. Small sample size and single-center enrollment are major limiting factors, resulting in limited generalizability and low event numbers. Subsequently, regression analysis was not feasible, and we could not adjust for confounding. Therefore, these findings should be confirmed in larger-scale, multi-center studies with multivariable regression models.

In conclusion, unselected suspected NSTEMI patients aged <65 years had surprisingly high bleeding incidence, regardless of ARC-HBR status or DAPT use. This indicates that there could be significant predictors of bleeding not included in the ARC-HBR criteria.

Declaration of Competing Interest

The authors have no competing interests to declare.

Authors' Contributions

Henri Kesti: conceptualization, methodology, formal analysis, investigation, data curation, writing - original draft, writing - review & editing, visualization. Henna Mäkinen: methodology, investigation. Kalle Mattila: methodology, writing - review & editing. Samuli Jaakkola: conceptualization, writing - review & editing, visualization. Mikko Lintu: methodology, investigation. Pekka Porela: conceptualization, methodology, writing - review & Editing, Visualization, Supervision, Project Administration.

1. Cao D, Mehran R, Dangas G, Baber U, Sartori S, Chandiramani R, Stefanini GG, Angiolillo DJ, Capodanno D, Urban P, Morice MC, Krucoff M, Goel R, Roumeliotis A, Sweeny J, Sharma SK, Kini A. Validation of the Academic Research Consortium high bleeding risk definition in contemporary PCI patients. *J Am Coll Cardiol* 2020;75:2711–2722.
2. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, van de Werf F, Harrington RA, Mahaffey KW, Tricoci P. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;38:804–810.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
4. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2015;65:1298–1310.
5. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV v, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation* 2019;140:240–261.
6. Nakamura M, Kadota K, Nakao K, Nakagawa Y, Shite J, Yokoi H, Kozuma K, Tanabe K, Iijima R, Harada A, Kuroda T, Murakami Y. High bleeding risk and clinical outcomes in East Asian patients undergoing percutaneous coronary intervention: the PENDULUM registry. *EuroIntervention* 2021;16:1154–1162.
7. Choi SY, Kim MH, Lee KM, Ko YG, Yoon CH, Jo MK, Yun SC. Comparison of performance between ARC-HBR criteria and PRECISE-DAPT score in patients undergoing percutaneous coronary intervention. *J Clin Med* 2021;10:2566.

8. Kesti H, Mäkinen H, Mattila K, Jaakkola S, Lintu M, Porela P. Prevalence of high bleeding risk among hospitalized suspected NSTEMI patients. *J Clin Med* 2022;11:1324.
9. Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *EuroIntervention* 2020;16:371–379.