VILNIUS UNIVERSITY

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The Final thesis

The Management of Bleeding in Patients Hospitalised in the Intensive Cardio Care Unit

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1. Summary

Patients treated in the intensive cardio care unit have an increased risk profile and are more susceptible to further morbidity due to comorbidities and existing long-term medications. In cardiology, risk stratification scores based on risk factors are used to select the most appropriate management. Anticoagulants and antiplatelet agents are cornerstones of cardiology and comprehensively used. However, in the case of bleeding events, they are also non-modifiable risk factors. Evidence suggests that bleeding increases all-cause mortality in the same way as recurrent myocardial infarction. As a result, they have equivalent prognostic significance. In particular, the first 30 days are decisive for the subsequent treatment outcome. As a result, bleeding and the associated risk characteristics of the patient population need to be given the same attention as the risk of other life-threatening cardiac events when determining further management.

2. Keywords and abbreviations

Abbreviation	Meaning
ACI	Angiotensin-converting inhibitors
ACRB	Angiotensin-converting receptor blockers
ACS	Acute coronary syndrome
AHF	Acute heart failure
ANMCO	The Italian Association of Hospital Cardiologists
AMI	Acute myocardial infarction
aPTT	Activated partial thromboplastin time
BARC	Bleeding academic research consortium
CAD	Coronary artery disease
CABG	Coronary artery bypass graft
CBC	Complete blood count
CHF	Chronic heart failure
CK-MB	Creatin-kinase-myoglobin-binding
CVP	Central venous pressure
CVDs	Cardiovascular diseases
DAPT	Dual antiplatelet therapy
DM	Diabetes mellitus
ECG	Electrocardiogram
FFP	Fresh frozen plasma
GI	Gastrointestinal
GPI	Glycoprotein Inhibitor
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
Hb	Hemoglobin
Hct	Hematocrit
HR	Heart rate
ICCU	Intensive cardio care unit
ICH	Intracranial hemorrhage
INR	International normalized ratio
JVA	Jugular venous pressure
LBBB	Left bundle branch block
NICE	National institute for health and care excellence
NSTE-ACS	Non-ST-elevation ACS
PAR-1	Protease-activated-receptor 1
PCI	Percutaneous coronary intervention
PPR	Percent platelet recovery
RCC	Reticulocyte cell count
RR	Respiratory rate
STE-ACS	ST-Elevation ACS
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TT	(plasma) Thrombin time
VKAs	Vitamin K antagonists
vWF	Von Willebrand factor
WBC	White blood cell
4-PCC	4-factors prothrombin complex concentrate

3. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally today(1). Patients in critical state are treated in the intensive cardiac care unit (ICCU), typically presenting with Acute coronary syndrome (ACS), acute and exacerbated chronic heart failure (AHF, CHF), cardiogenic shock, sudden cardiac arrest, electrical storm or indications for immediate or urgent cardiac surgery(2). One of the most important determinants of mortality in hospitalized patients in cardio-intensive care is bleeding as a complication(3). By appropriately treating the underlying pathology on an evidence-based basis, the risk of a bleeding event can be influenced in anticipation. What makes this task so demanding? Patients with underlying cardiac disease often have a wide range of comorbidities and are often treated with medications that can lead to an increased risk of bleeding. Balancing the risks and benefits of the chosen therapy against the occurrence of potential complications is therefore a major challenge in determining further investigations and management strategies. This literature review illustrates and discusses the management of bleeding in patients hospitalized in the ICCU and how to minimize their risks of bleeding events.

4. Literature selection strategy

The literature review is based on the management of bleeding in patients hospitalized in the ICCU and provides data on outcomes in terms of short- and long-term bleeding events. Databases were searched for most frequent pathologies in the ICCU and their association with bleeding and associated outcomes in terms of mortality and morbidity. Inclusion criteria were patients aged ≥ 18 years admitted to the ICCU, studies in humans, studies on bleeding management including bleeding duration and transfusion requirements, studies on anticoagulants and their reversal agents, studies on antiplatelet therapy, studies reporting major and minor bleeding events in trials, studies published in English, publication Dates were from November 2006 till April 2023. Exclusion criteria were studies in patients <18 years of age, studies in patients with conditions not related to cardiac or critical care, studies that did not include management outcomes. The female-to-male ratio and the average of the patients age are similar in all three presented studies. All included a hypothesis related to anticoagulant therapy. All documented concomitant medications. They all highlighted ACS as an occurring pathology. The endpoints that were defined were either related to bleeding or to death due to a CV event. The bleeding endpoints can be compared as similar bleeding classifications are applied in those studies. They differ in the length of their observational period (6 months, 12 months, 31 months). This allows the comparison of endpoints related to management strategies

from the perspective of short-and long-term-mortality and morbidity. Furthermore, the influence of modifiable and non-modifiable risk factors has a greater explanatory value. As these studies were published between 2006 and 2012, the expert opinion published in 2019 by the Association of Intensive cardiac care and section of cardiovascular Pharmacotherapy of the polish cardiac society in cooperation with specialist in other fields of medicine, is incorporated into the discussion of management strategies. Additionally, for an overview and clarification of bleeding Classifications the special report of the standardized Bleeding definitions for cardiovascular trial has been considered.

Databases used: Cochrane Library, Web of Science, MED LINE via PubMed, Scopus, Embase.

Search terms: ICCU, Bleeding, TWILIGHT-Study, DAPT, Hemorrhage, Thrombosis, Unstable Angina, anticoagulant treatment, antiplatelet treatment, intensive cardio care unit, BARC, TIMI, GUSTO, Bleeding scale, risk stratification scores, Aspirin, clopidogrel, mortality, vorapaxar, PCI, MI, MB,

5. Clinical description of bleeding and ischemic events

Major Bleeding is defined as clinically significant hemorrhage that may be a life-threatening event. It is objectively defined as symptomatic bleeding in a critical area (e.g., intracranial) or bleeding in any area leading to a decrease in hemoglobin ≥ 2g/dL, transfusion of ≥ 2 units of pRBCs or death. In studies observing bleeding endpoints a variety of bleeding classification scores are used with different subcategorizations. The BARC, TIMI and GUSTO classifications are the main classifications used in the material of this review.

Type 0		no bleeding
Type 1		bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare profession
Type 2		any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3	a	Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
		Any transfusion with overt bleeding
	b	Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
		Cardiac tamponade
		Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
		Bleeding requiring intravenous vasoactive agents
	c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
		Subcategories confirmed by autopsy or imaging or lumbar puncture
		Intraocular bleed compromising vision
Type 4 CABG-related bleeding		Perioperative intracranial bleeding within 48 h
		Reoperation after closure of sternotomy for the purpose of controlling bleeding
		Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
		Chest tube output ≥ 2 L within a 24-h period
Type 5	a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
	b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event. *Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).
†Cell saver products are not counted.

Figure 1 Bleeding Academic Research Consortium (BARC) scale (23)

Acute myocardial infarction (AMI) is a medical emergency caused by a sudden blockage of blood flow to the heart muscle. This can damage or kill the heart muscle and lead to a range of symptoms, including chest pain, shortness of breath and nausea. Patients with AMI may need to be treated in the ICCU, where they receive specialized care and monitoring. One of the risks

associated with treatment in the ICCU is bleeding, which can occur as a result of invasive procedures used to treat AMI, such as angioplasty or cardiac catheterization. (4)

Acute coronary Syndrome is the clinical manifestation of a myocardial infarction, related to the suspicion or confirmation of acute myocardial ischemia and can be further classified into non-ST-elevation ACS (NSTE-ACS) and ST-Elevation ACS (STE-ACS). NSTE-ACS can be subdivided into NSTEMI and Unstable angina.

Cardiogenic shock is a life-threatening condition where the heart suddenly fails to meet the body's blood demand. The most frequent cause is MI. However, it can result from several underlying cardiac pathologies as HF or arrhythmia. Current studies are inconsistent about whether antiplatelet therapy or anticoagulants increase the risk of cardiogenic shock but do suggest that they worsen the outcome.(5)

Acute Heart Failure. Patients hospitalized with AHF often have rapid onset or worsening of heart failure symptoms, which include symptoms of congestion and hypoperfusion, e.g., a patient presenting with jugular venous distention, S3 gallop and lung crackles/rales with matching laboratory values (e.g., elevated BNP) is highly likely to have AHF. These patients have a significant association with hospital morbidity, as major bleeding is one of the causes. They often have multiple comorbidities, such as atrial fibrillation, anemia and renal dysfunction. Each of these is associated with an increased risk of bleeding. In addition, they are often treated with medications that carry a high risk of bleeding, such as anticoagulants and antiplatelet agents.(6)

Atrial fibrillation (Afib) represents as the most frequent persistent cardiac arrhythmia and occurs either without any underlying pathology (primary Afib) or in the context of various underlying cardiac or extracardiac pathologies (secondary Afib). Due to a lack of synchronicity between the atrium and the ventricle, symptoms of heart failure can be caused or aggravated. Turbulent flow conditions in the left atrium during ineffective contraction also favor thrombus formation, leading to a significantly increased risk of thromboembolism. Therefore, long-term oral anticoagulation is often indicated in these patients, who also have an elevated risk profile, increasing the risk of bleeding

Table 1. TIMI and GUSTO bleeding definitions.

TIMI bleeding definitions [12]	
Major	Intracranial hemorrhage ≥5 g/dl decrease in the hemoglobin concentration ≥15% absolute decrease in hematocrit
Minor	Observed blood loss: ≥3 g/dl decrease in the hemoglobin concentration ≥10% decrease in the hematocrit No observed blood loss: ≥4 g/dl decrease in the hemoglobin concentration ≥12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage associated with a <3 g/dl decrease in the hemoglobin concentration or <9% decrease in the hematocrit
GUSTO bleeding definitions [13]	
Severe or life-threatening	Intracranial hemorrhage Bleeding that causes hemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not lead to hemodynamic instability
Mild	Bleeding that does not meet criteria for severe or moderate bleeding

GUSTO: Global Use of Strategies to Open Occluded Arteries; TIMI: Thrombolysis In Myocardial Infarction.

Figure 2 TIMI and GUSTO bleeding definitions (24)

events in general. The team around P. Kirchhof evaluated the modifiable and non-modifiable risk factors associated with major bleeding events in patients with Afib treated with Rivaroxaban. They investigated that at least 1 modifiable risk factor was present in 39% of patients who experienced major bleeding events, however most of them had also additional nonmodifiable risk factors present as well. Nevertheless, the presence of 1 or more of the 3 independent modifiable risk factors was associated with a 2-fold increase in the risk of major bleeding event. This suggests that eliminating or reducing modifiable risk factors may be an effective strategy to reduce the risk of bleeding in anticoagulated patients with atrial fibrillation. (7,8)

Valvular diseases. Patients with valvular disease of one or more heart valves often present with stenosis or insufficiency of the valves, resulting in problems with blood flow. The treatment strategy depends on the underlying cause and includes surgical procedures to repair, reconstruct or replace the valves. Patients receiving mechanical or bioprosthetic valve replacement as an interventional treatment need to be assessed for their ability to take anticoagulants. In the case of mechanical valve replacement, they require lifelong anticoagulation with a vitamin K antagonist to achieve the target INR (target for aortic valve replacement INR = 2, target for mitral valve replacement and additional risk of thromboembolism INR = 3). Patients undergoing biological valve replacement should be anticoagulated with VKAs for 3-6 months after the procedure. Continuation of 75-100 mg aspirin P.O. after discontinuation of VKAs is recommended in certain cases. Furthermore, peri-interventional anticoagulation with NOACs starting >3 months prior to valve replacement should be considered in patients also suffering from atrial fibrillation based on their CHA2DS2-VASc score.(9)

Aortic dissection occurs when there is a tear in the inner lining of the aorta, which can lead to a progressively growing hematoma in the intima-media space. The typical pain described by patients is a severe tearing or ripping pain. The location of the pain depends on the part of the aorta affected. Pain in the front of the chest is associated with the ascending aorta, whereas pain in the back, interscapular or retrosternal region is associated with the descending aorta (thoracic dissection). Pain is typically felt in the neck and jaw when the aortic arch is involved. It has been observed that the pain often radiates caudally. In addition, they often present with hypertension or hypotension and often have asymmetric blood pressure and pulse readings between the limbs. Anticoagulants can increase the risk of aortic dissection in patients with a

pre-existing aneurysm. Patients with a history of aortic dissection are at increased risk of bleeding complications. (10)

6. Discussion

6.1. Management of bleeding related to ischemic events

The following paragraph describes the treatment options evaluated based on the presented data and the referenced publications, with the purpose to outline structured management approaches. One of the main reasons for the lack of clear data on the association and management of bleeding and cardiac events is that for a long time there was no standardized classification for defining bleeding endpoints and reporting cardiovascular risk in trials. The Bleeding Academic Research Consortium proposed the BARC classification in 2011 to serve as a standardized definition and grading of bleeding for cardiovascular clinical trials. A retrospective analysis of the TRACER trial compared the endpoint of all-cause death regarding the prognostic value of the BARC scale with the prognostic value of TIMI and GUSTO. Prediction with BARC classification grades 2,3, and 4 in the 1-year mortality model with baseline characteristics improved the model's significance in comparison to that of TIMI and GUSTO. In patients with NSTE-ACS, bleeding according to the BARC scale was significantly associated with the risk of subsequent death up to 1 year after the event, with the risk of death increasing progressively with higher BARC grades. Non-CABG related bleeding occurred in 15.4% according to BARC scale 2,3 and 5, 3.7% according to TIMI-minor or major and 4.0% according to GUSTO. In 1.2% of patients, CABG-related BARC 4 bleeding occurred. Patients with BARC 2, 3, and 4 had a significant increased risk of death compared to no bleeding BARC 0 or 1.

Table 1 Comparison of the three main studies under review

Study	**Management of patients with acute coronary syndromes in real-world practice in Italy: an outcome research study focused on the use of Antithrombotic Agents: MANTRA registry**(11)	**Acute Catheterization and urgent intervention triage strategy trial – ACUITY** (12)	**Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes - TRACER** (13)
Objective	Evaluate in-hospital management and outcomes of unselected patients with ACS focusing on antithrombotic therapies and bleeding	Evaluate treatment with heparin plus glycoprotein (GP) IIb/IIIa inhibition compared with bivalirudin with or without GP IIb/IIIa inhibition among patients with acute coronary syndromes.	Vorapaxar would be superior as compared with placebo for secondary prevention in patients with recent ACS.
Method	Observational study	Randomized controlled trial	Randomized trial (Parallel, stratified, blinded, placebo controlled)
Date of publication	24/11/2012	23/11/2006	13/11/2011
Journal of publication	European Heart Journal	The NEW ENLAND JOURNAL of MEDICINE	The NEW ENLAND JOURNAL of MEDICINE
Author	Casella G, di Pasquale G, Oltrona Visconti L et al.	Stone G, Mclaurin Cox D et al.	Triococi P, Huang Z, Held C et al.

Total number of enrollees	6,394	13,819	12,944
Duration of follow-up	6 months	30 days	31 months
Mean patient age	71years	63 years	64 years
Male:female ratio	37% female	30% female	28%
Patient population	NSTE-ACS: 55,3% STE-ACS or new LBBB: 54,7% Mechanical reperfusion: 79,8%	Unstable angina or NSTE-ACS with 10 minutes of cardiac chest pain within 24 hours, plus A or B: A) one or more out of: Troponin or CK-MB elevation, dynamic ECG changes, documented prior CAD B) all the following: Age ≥65 years, aspirin taken in prior 7 days, ≥2 episodes of angina in the prior 24 hours, ≥ 3 Risk factors present: hypertension, hypercholesterolemia, family history or coronary artery disease, diabetes, current smoker	Onset of symptoms in the past 24 hours, elevated biomarkers or ECG changes, plus ≥1 out of: Age ≥55 years, prior MI, PCI/CABG, DM, peripheral arterial disease
Primary endpoints	No bleeding 3.1% Minor TIMI 1.2% Major TIMI	Composite of death, MI, unplanned revascularization for ischemia, and major bleeding at 30 days; Composite of death, MI and unplanned revascularization for ischemia at 30 days; Major bleeding at 30 days	In terms of: A) Efficacy: Composite of CV death: MI, stroke, recurrent ischemia with hospitalisation, urgent coronary revascularization B) Safety: Moderate or severe GUSTO bleeding, clinically significant TIMI bleeding CV death defined in secondary endpoints: MI, stroke
Concomitant medications	Aspirin, clopidogrel, DAPT, UFH, thrombolytic agents, anticoagulant drugs	Aspirin, clopidogrel was recommended but not mandated	GP IIb/IIIa inhibitor use (21%), DTI (17%), aspirin (96.7%), and thienopyridine (91.8%)
Results	Bleeding: Older, women, lower body weight, more non-cardiac morbidities; On admission bleeding: lower systolic BP, more HF, higher GRACE risk score, worse renal function, higher proportion of low ejection fraction;	Cardiac enzymes elevated (troponin CKMB) at baseline in 59%, Diabetes in 28%management strategy: PIC56%, medical therapy 33%, CABG 11%, Median time from start of study drug to angiography was circa 4 hours	17% ≥75 years old, 86% white, 31% had DM, 29% had prior history of MI, Median-BW 80 kg, Majority were Troponin/Creatinine kinase-myocardial band positive (94%), high TIMI risk score 5-7 in 48%, 88% underwent cardiac angiography during index hospitalization, 57,8% underwent PCI, 10,1% CABG

The Tracer trial initially aims to evaluate the safety and efficacy of vorapaxar, a new oral protease-activated-receptor 1 (PAR-1) antagonist that inhibits thrombin-induced platelet activation in patients with recent ACS. They included patients who had acute symptoms of coronary ischemia within 24 hours before hospital presentation and at least one of the following findings: Increased cardiac troponin (I or T) levels > 0,4 µg/l, CK-MB >25 U/l, or new ST-segment depression of more than 0.1 mV or transient ST-segment elevation (< 30 minutes) of more than 0.1 mV in at least two contiguous leads. All required ≥ 1 out of the following criteria: age ≥ 55 years, previous MI, PCI or CABG, DM or peripheral artery disease. The primary endpoint was defined as death from CV causes including MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. The primary endpoint occurred in 1031 out of 6473 patients in the vorapaxar group and in 1102 out of 6471 patients in the placebo

group, corresponding to a 2-year rate of 18.5% in the vorapaxar group and 19.9% in the placebo group (Vorapaxar group HR 0.92; 95% CI, 0.85 to 1.01; P = 0.07). The secondary endpoint included death from CV causes consisting of MI and stroke occurred in 822 patients in the vorapaxar group and 910 patients in the placebo group for 2-year Kaplan–Meier estimates of 14.7% and 16.4%, respectively (HR 0.89; 95% CI, 0.81 to 0.98; P = 0.02). With respect to the individual components of the efficacy endpoints, the reduction in the rate of myocardial infarction was the main effect observed in the vorapaxar group compared to placebo (11.1% vs. 12.5% at 2 years; HR 0.88; 95% CI, 0.79 to 0.98; P = 0.02). In terms of bleeding outcomes, vorapaxar increased the rate of moderate or major GUSTO bleeding compared to placebo (7.2% vs. 5.2%; HR 1.35; 95% CI, 1.16 to 1.58; P < 0.001). The rate of clinically significant TIMI bleeding was increased in patients treated with vorapaxar (20.2% vs. 14.6%; hazard ratio, 1.43; 95% CI, 1.31 to 1.57; P < 0.001). The higher number of bleeding events also occurred during the follow-up period of 31 months. The vorapaxar group also had higher rates of major bleeding according to GUSTO (2.9% vs. 1.6%; HR 1.66; 95% CI, 1.27 to 2.16; P < 0.001), major bleeding according to TIMI (4.0% vs. 2. 5%; HR 1.53; 95% CI, 1.24 to 1.90; P < 0.001) and ICB (1.1% versus 0.2%; HR 3.39; 95% CI, 1.78 to 6.45; P < 0.001), with the risk increasing over time. The rate of in-hospital CABG-related bleeding was not significantly different between the two groups, and the rates of reoperation for hemorrhage and major hemorrhage were similar. The average treatment duration was 386 days. **The risk was highest in the 30 days after bleeding**: HR: 7.35; 95% CI 5.59 to 9.68; p < 0.0001 and remained significant up to 1 year. The risk of death increased progressively within 30 days (HR: 10.05; 95% confidence interval: 5.41 to 18.69; p<0. 001), but not thereafter. The study was stopped early following a safety review. At that time, a total of 12,944 patients had been enrolled in 818 centers in 37 countries. 6,471 patients received vorapaxar and 6,473 received placebo. (13,14)

The purpose of the large-scale **ACUITY trial** was to determine the predictors and outcomes of major bleeding on 30-day mortality in patients with ACS. Outcomes of independent predictors for major bleeding were advanced age, female gender, diabetes, hypertension, renal insufficiency, anemia, no prior PCI, cardiac biomarkers elevation (Troponin I/T, CK-MB), ST-Segment deviation ≥1 mm, and treatment with heparin plus GPI IIb/IIIa versus bivalirudin monotherapy. Patients suffering from major bleeding had a higher 30-day rate of mortality (7.3% vs 1.2%; P < 0.0001), composite ischemia (23.1% vs. 6.8%, P < 0.0001), and stent thrombosis (3.4% vs 0.6%, P < 0.0001) compared to those without major bleeding. Major bleeding was an independent predictor of 30-day mortality (OR 7.55, 95% CI, 4.68 to 12.18, P

< 0.0001). In terms of anticoagulation therapy, major bleeding was higher in patients treated with heparin plus GPI IIb/IIIa compared to bivalirudin monotherapy (5.7% vs 3.0%, P < 0.0001)(12)

The Italian Association of Hospital Cardiologists (ANMCO) designed the **MANTRA registry** as a nationwide, multicenter, prospective, observational study to evaluate the in-hospital management and outcomes of unselected patients with ACS, focusing on antithrombotic therapies and bleeding. All patients age ≥18 admitted to 52 participating hospitals in Italy with a suspected diagnosis of ACS during a 12-month period were included. Eligibility required a clinical history of ACS and at least one of the following: ECG changes consistent with ACS, serial elevation of cardiac biomarkers (troponin, CK- MB) or prior documented CAD. TIMI definitions was used for bleeding classification. Major bleeding was defined as an ICH, or overt bleeding Hb ≥5 g/dl or decrease in Hct ≥15%. Minor bleeding was defined as spontaneous gross hematuria (blood can be see with the naked eye), spontaneous hematemesis, or observed bleeding with a decrease in Hb ≥3 g/dl but Hct ≤15%. The analysis was divided into two predefined patient groups: STE-ACS or new onset LBBB and NSTE-ACS. Patients were further categorized according to bleeding into (1) no bleeding, (2) minor TIMI bleeding and (3) major TIMI bleeding. Of the total patient group, 1.2% had a major TIMI bleeding during hospitalisation, of which 8.9% were intracranial, 35.4% gastrointestinal and 38% access site related. The rate of major bleeding was 1.4% for STE-ACS and 1.1% for NSTE-ACS. The risk of bleeding was not influenced by the previous intervention, either the choice of reperfusion therapy in STE-ACS (primary PCI, thrombolysis, no reperfusion) or early invasive management in NSTE-ACS (in-hospital coronary angiography or no in-hospital coronary angiography). Patients with bleeding were more likely to be older, female, have a lower body weight, and have more non-cardiac comorbidities. Compared to those without bleeding, they had lower systolic blood pressure, more heart failure, higher GRACE risk scores, worse renal function and a higher proportion of low ejection fraction on admission. During their hospital stay patients with major bleeding received aspirin, clopidogrel and dual antiplatelet therapy (DAPT) less often than those without bleeding, while they were more likely to receive UFH, thrombolytics or a change of anticoagulants. Medication doses at the time of bleeding were not recorded. All patients with ICH and 76.5% of patients without major ICH discontinued at least one antithrombotic medication at the time of bleeding. Patients with major bleeding received fewer angiotensin-converting enzyme inhibitors (ACIs) or angiotensin II receptor blockers (ACRBs) at discharge. They also received fewer statins but more diuretics. They were less

likely to receive PCI but more likely to receive an intra-aortic balloon pump (IABP) or CABG than patients without bleeding. The outcome of patients with ACS who experienced major bleeding was significantly worse compared to minor- or no bleeding. Unadjusted in-hospital and 6-month all-cause mortality was 6.7% in patients without bleeding, 8.6% in patients with TIMI minor, and 26.6% in patients with TIMI major bleeding ($P < 0.0001$ in-hospital and 6-month). Patients with major bleeding had a higher rate of in-hospital cardiac death, reinfarction, heart failure or stroke. This difference persisted at 6 months. Kaplan-Meier-Curve regressed all-cause mortality and the composite endpoint and showed a worse outcome in patients with major bleeding. Furthermore, the time interval between major bleeding and adverse outcome was relatively short (median 6 days, IQR 1 - 28 for death; 11 days, IQR 5 - 48 for reinfarction). Predictors of 6-month composite endpoints or major bleeding in both syndromes (STE and NSTE-ACS) were older age, low blood pressure, heart failure on admission major in-hospital TIMI bleeding. TIMI major bleeding was one of the strongest predictors, while predictors of in-hospital TIMI major bleeding included low body weight, female sex, history of peripheral vasculopathy, change in anticoagulant therapy, intra-aortic balloon pump implantation, and creatinine ≥2 mg/dl.(11)

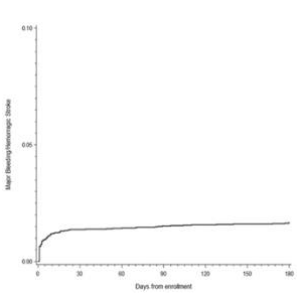

Figure 3 unadjusted Kaplan-Meier curve of major TIMI bleeding and 6 months(22)

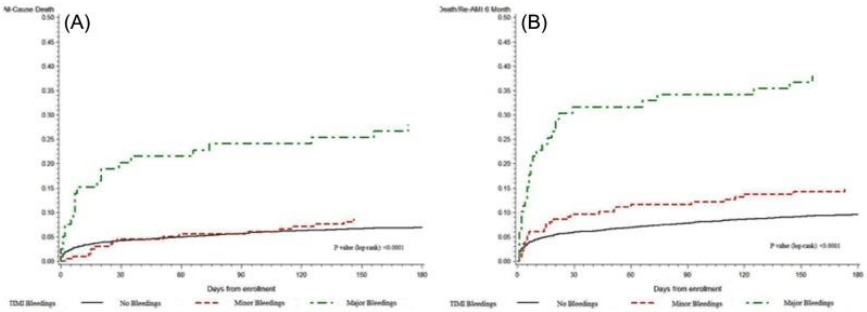

Figure 4 unadjusted Kaplan-Meier curves at 6 months among patients with major and minor TIMI bleeding or no bleeding for total mortality (A) and composite endpoints (B)(22)

Overview of management in patients hospitalised in the ICCU based on the presented data

Steps	Examples of relevance to this review		
1. Risk stratification	- Non-modifiable risk factors e.g., age, gender, Family history, comorbidities (controlled) - Modifiable risk factors: e.g., medications, uncontrolled hypertension - Common scores used for Risk stratification: GRACE, TIMI, GUSTO, BARC		
2. Monitoring	- oximeter, ECG, blood pressure, clinical data		
3. **Laboratory values**	- Hematological parameters: CBC (e.g., including blood smear, BMP, liver chemistries, urea creatinine. Electrolytes) - Coagulation parameters: PT, aPTT, INR, Reptilase time, vVF and vWF activity - VHA - Parameters for Blood transfusion: PPR formula, corrected count increment, inadequate blood volume, tissue oxygenation or hemostasis.		
4. Drugs	Antiplatelet agents		- Irreversible cyclooxygenase inhibitors - P2Y12 receptor antagonists (ADPRI) - Glycoprotein IIb/IIIa inhibitors
	Oral Anticoagulants		- Vitamin K antagonists/coumarins (Phenprocoumon, Warfarin) - Direct oral thrombin inhibitors (Dabigatran) - Direct oral factor Xa inhibitors (Apixaban, Rivaroxaban, Edoxaban)
	Parenteral anticoagulation		- UFH - LMWH - Synthetic heparin - Heparinoid (glycosaminoglycan) - Direct thrombin inhibitors
	Reversal agents of Anti-coagulants		- Vitamin K - Protamine - Recombinant activated factor VII - Idarucizumab - Andexanet alfa
5. Blood Transfusion-products	pRBC	- RBCs preservative, typically citrate-based (200-350 mL)	
	Platelets	- SDAP unit: derived from 1 unit of whole blood from a single donor and contains 310 X 10^9 platelets in 300 mL - RDP pack: derived from 4-6 units of whole blood from various donors and contains 280 X 10^9 platlets in 200 mL	
	FFP	- Plasma including all coagulation factors & plasma proteins, cellular components are removed (Unit volume: 200-300 mL)	
	Cryo-precipitate	- Clotting factors (fibrinogen, factor VIII, factor XIII), vWF, and fibronectin	
	Plasma derivatives	- 3-factor PCC (II, IX, X) - 4-Factor PCC (II, VII, IX, X) - aPCC: Clotting factors & ≥1 activated added anticoagulant (Protein C, protein S, antithrombin, heparin)	
		- Single-factor concentrate (clotting factors pooled from multiple donors)	
		- Antithrombin III	
		- Albumin	
6. **Nutrition** Parenteral feeding, specialized diet	Parenteral fluid therapy	Crystalloids	- Hypotonic: D5W, D10W, ½ NS, ¼ NS - Hypertonic: 3% NaCl, 5% NaCl - Isotonic: 0.9% NaCl, LR
		Colloids	- Artificial: gelatins, dextrans, HES - Natural: Albumin, FFP
7. Procedures	- PCI, angioplasty, stenting, surgery		
8. Rehabilitation	- speech therapy, occupational therapy, psychological counseling		

6.2. **Fluid resuscitation and blood and blood product transfusion**

Patients with significant **blood loss should** be connected to the monitor and have adjusted blood pressure ranges and intervals for supervision. Attention should be paid on signs of hypoperfusion, HR and RR. Every patient should get a CBC, coagulation system, creatinine values and blood group. Crystalloids should be administered at a volume 3- to 4-fold higher

than the blood volume loss, because only one-third of the volume remains in the intravascular space. Therefore 500 ml of blood should be compensated with 2000 ml of crystalloids.

First steps in case of minor (BARC 2) and major bleeding (BARC 3) include the identification of the bleeding source followed by assessment of possible treatment options. Medication anamnesis and analysis is needed for possible steps related to modification (BARC 2) or discontinuation (BARC 3) of antiplatelet and anticoagulation therapy. Depending on the hemodynamic status, assessed due BP, central venous pressure (CVP) and diuresis, patients with minor bleeding (BARC 2) should receive 500-1000 ml IV of crystalloid infusion for 15-30 minutes.(15) In case of discontinuing antiplatelet and anticoagulation treatment in patients with **major bleeding (BARC 3)** close monitoring should be performed and reassessment of coagulation parameters due to increased risk of thromboembolic events. Constant reassessment of hemodynamic status and mental status should be performed. Important is to locate the bleeding source for evaluation and selection of bleeding control possibilities like surgery or an antidote. For hemodynamic stability it is recommended to administer either 500 ml of IV crystalloid Infusion for ≤ 15 minutes, 200-500 ml of colloids or 200 ml of albumin 5% for 30 minutes. If the mean BP is > 65 mmHg, the CVP increases by 3 cm H_2O from baseline, and Diuresis is 1ml/h/kg body weight, intensive fluid therapy can be stopped. Otherwise, the therapy should be continued. Additionally, RBC, FFP and platelet transfusion can be started. Posttransfusion reassessment of the patient's hemodynamic status based on HR, RR, BP, SpO_2, diuresis, arterial blood gases, CVP and lactate levels should be performed. Pulmonary congestion and elevated jugular venous pressure (JVP) are clinical signs of fluid overload, which can occur as adverse effect of fluid therapy. In case of gaining hemodynamic stability, the intensive fluid therapy can be stopped. In case the reassessment shows lack of hemodynamic stability infusion doses of 200-500 ml for 30 minutes will be added on top of the 2000ml. In case of **persistent hypotension** add noradrenalin (Levonor) 1-20 mcg/kg/min (max. 1-2 ug/kg/min), adrenaline 0.05 ug/kg/min, or dopamine 3-30 mcg/kg/min (max. 50mcg/kg/min). Moreover, packed RBC and FFP transfusion is continued. After assessing fibrinogen and platelet levels, IV tranexamic acid (loading dose of 1g for 10 min, then 1 g for 8h) or VIIa can be administered due current ineffective or insufficient coagulation levels. Hyperchloremic acidosis, hypernatremia, and hyperosmolarity are risk factors of 0.9% NaCl large-volume fluid resuscitation, therefore daily control of serum chloride is recommended. Furthermore, an excess intake of chloride ions might increase the risk of kidney damage. Patients suffering from heart failure and LVSD have a higher risk for hypervolemia and need

adjusted administration of colloids or crystalloids at a lower dose and longer timer period, accompanied by continuous supervision of intra-arterial BP, CVP and diuresis. In those patients ECG should be included in the hemodynamic assessment for supervision of left and right ventricular filling pressures, IVC pressure collapsibility and LVSD.

Patients with cardiogenic shock and respiratory disorders should be intubated and started on mechanical ventilation.

In case of **posthemorrhagic anemia** laboratory values (Hb, Hct, CBC) are combined with clinical data for therapy indication of Platelet transfusion. In major bleeding with large volume loss the Hb and Hct levels may be insignificant to ongoing hemorrhage. In case of blood product transfusion, fluid resuscitation is started for shock prevention until blood transfusion products are available, which may lead to falsified coagulation parameters. Therefore, decision for blood transfusion will be made based on clinics and diagnostic values. It takes 24 to 48 hours until the diagnosis of posthemorrhagic anemia can be made, classified as normocytic and normochromic anemia. For bone marrow response supervision, the reticulocyte count (RCC) and the erythroblastic reaction is assessed. Increased RCC is observed, along with an increase of White blood cell count (WBC), most seen in neutrophils. Even tough in the beginning patients may show thrombocytopenia, an increase of platelets is observed 48 to 72 hours post-bleeding-onset. Further assessments that should be done before transfusion include iron studies, serum vitamin B12 and folate levels, noting that the serum iron levels will decrease few days post-hemorrhage. Indications for blood transfusion are the loss of 30% to 40% of circulating blood volume, usually corresponding with Hb $\leq$7g/dl and Hct <30%. In patients with preexisting CVD or if the patient is planned for cardiac or orthopedic surgery the cut-off value is Hb $\leq$8g/dl. The Transfusion of 1 unit of packed RBCs should result in an increase in Hb levels by about 1g/dl and Hct by 3% to 4%. In Patients with ischemic heart disease the target Hb is set around 1 to 2 g/dl higher. Platelet transfusion needs strong indications and even may be contraindicated in thrombocytopenia due to HIT, TTP ITP or HUS due to associated higher rates of arterial thrombosis and mortality in comparison to no transfusion.

Thrombocytopenia as complication occurs when there is a loss of more than 1.5 of the circulating blood volume. The cut-off is $50x10^9$/l, and $\geq 50x10^9$ may be considered in cases of hemostatic disturbance. A therapeutic dose of platelets is equivalent to 3×10^{11} units of platelets from apheresis or 4 to 6 units of pooled platelets. Indicated for surgical and percutaneous procedures such as angiography, the platelet count threshold is 20×19^9 to minimize the risk

of bleeding complications at the injection site. If the platelet count is lower, the indication for transfusion is the planned procedure itself. On the other hand, in the case of emergency angiography for acute arterial thrombosis, platelet transfusion would increase the risk of thrombotic complications. The absence of new petechiae or subcutaneous and mucosal bleeding is considered a successful platelet transfusion.

In case of bleeding with underlying **coagulation disorders** FFP should immediately administered along the recommendation of 1-unit FFP per each 2 units of packed RBCs followed by 15 to 20 ml/kg. Bleeding coagulopathy is caused by dilution of clotting factors and platelets due to fluid therapy or packed cell transfusion, as well as by excessive consumption of clotting factors during activation of coagulation and fibrinolysis, and by platelet dysfunction. Significant values used for diagnostics are aPTT and PT by showing an increase in time of ≥ 1,5-fold. Therapy choice is made by adding clinical data to existing coagulation parameters. FFP is preferred in patients, where the bleeding is not related to NOACs and should be avoided in patients with VKA, except there is emergency indication. In case of **Hypofibrinogenemia** clotting factors (fibrinogen, factor VIII, factor XIII), vWF and fibronectin need to be administered via cryoprecipitate transfusion. Recommended is 1 unit of cryoprecipitate per 7-10 kg BW, which leads to an increase of serum fibrinogen by 50-75 mg/dL. In case of vWD, hemophilia A or factor XIII deficiency it is recommended to administer **plasma derivatives** as single factor concentrates or recombinant synthetic factors, with preference on the second one because they aren't associated with increased infection risk.

In massive blood loss **Prothrombin complex concentrate** (PCC) is used at a dose of 15 to 25 IU/kg bw with the aim to increase thrombin generation. PCC is indicated for reversing the effect of NOACs in significant bleedings when an antidote is unavailable.

Human **Antithrombin III,** which is synthesized in the liver and inhibits coagulation factors IXa, Xa, XIa, XIIa and thrombin is indicated for patients with hereditary antithrombin III deficiency to optimize thrombosis prophylaxis with heparin (increases effect), patients on cardiopulmonary bypass who are experiencing heparin resistance and in selected DIC cases.

Albumin increases the intravascular volume, maintains colloid osmotic pressure and functions as transport protein is considered in case of therapeutic plasmapheresis.

6.3. **Management of drug-related bleeding and modification treatment**

Bleeding during **antiplatelet treatment** has limited range of choices due to lack of reversal agents. Corresponding units of platelet transfusion may restore platelet aggregation, depending

on the agent. Indicated for ASS (acetylsalicylic acid) are 2-5 units of platelet concentrate. In Adenosine diphosphate-induced (ADP/P2Y12 receptor Antagonists) thrombocytopenia as with clopidogrel or prasugrel, management is more challenging, however their risk of hemorrhage is decreased compared to ASS. Platelet transfusion can restore platelet activity in clopidogrel and Prasugrel within 4-6 hours after the last dose. In patients treated with ticagrelor, hemostasis can be restored at least after 24 hours.

Anticoagulant reversal is a critical step in management of patients with major bleeding. The most reversal agents increase the risk of thromboembolic events. Therefore, the patient should undergo close supervision via monitoring. The anticoagulant effect of VKAs requires reduction in the level of prothrombin (factor II). In case of active hemorrhage in a patient taking warfarin, stop the therapy and administer IV vitamin K 10 mg PLUS 4-factor PCC. PCC can be given either as fixed dose of 1500 units or based on INR and BW. In case PCC is unavailable FFP can be given instead with a dosage of 10 - 15 ml/kg IV once. INR should be monitored every 6 hours until warfarin has been fully reserved (INR ≤ 1.1). PCC and FFP act immediately, however IV Vitamin K takes 8 – 12 hours to have an impact. In general warfarin should be discontinued for 2.5 days to achieve an INR of 4, whereas in acenocoumarol INR reduction that is effective can be achieved within less than 1 day in most patients. The higher the INR, the higher is the risk of bleeding, it increases significantly if the INR exceed 4.5. Vitamin K1 (phytomenadione) may be considered in patients without symptoms but with a high bleeding risk INR > 10. Major bleeding cases may require a treatment combination of Vitamin K1 with PCC, FFP or recombinant factor VIIa.

Table 2 PCC regimen based on INR and BW for warfarin reversal in active bleeding (16)

INR*	Treatment Dose
2 - 4	25 units/kg once (max. 2500 units)
4 - 6	35 units/kg once (max. 3500 units)
> 6	50 units/kg (max. 5000 units)

**pretreatment*

FFP is typically used to reverse the effect of coumarin derivatives. However, PCC has a higher efficacy and may be associated with lower thrombosis risk than recombinant factor VIIa. For reduction of anaphylactic reaction, the vitamin k1 should be diluted in 100 ml 0,9% NaCl and administered in a 20-to-30-minute infusion. The PT should be evaluated 3 hours after the start of the infusion. If it's prolonged the infusion will continue, but should not exceed 40 mg/d. The blood coagulation parameters should be measured, based on patients condition until the target values are reached.

Because of their short duration of action, elimination of **NOACs** by normal metabolic pathways may be more beneficial than aggressive treatment in patients with minor bleeding. Haemostasias is usually restored within 12 to 24 hours (half-life of 12 hours) after discontinuation of NOACs. Especially with dabigatran, which is mainly excreted by the kidneys, prolonged drug elimination may occur with deterioration in renal function. Dabigatran causes a prolonged TT. However, no change in PTT or PT is observed. Therefore, APTT and TT are used to monitor the elimination of dabigatran. In the event of bleeding, discontinue dabigatran and give a single intravenous infusion of 5 mg of idarucizumab (a monoclonal antibody). Transfuse aPCC when idarucizumab is not available. Depending on the patient's condition and renal function, hemodialysis may be considered. Ecarin Clotting time (expressed in seconds; it is 2 to 4 times longer in patients on long-term dabigatran, 150 mg/12 h)(17) or diluted thrombin time (expressed in seconds or ng/ml)(18) are used to quantitively measure of the anticoagulant effect of dabigatran.

The PT is used in case of bleeding in patients with direct **oral factor Xa inhibitors** like Apixaban, Rivaroxaban and Edoxaban. Management starts with stopping the the factor Xa inhibitor. As antidote Andexanat alfa with high-dose regimen of 800 mg IV infusion over 30 min, followed by 8 mg/min IV infusion up to 120 minutes if the Rivaroxaban dose is ≥ 10 mg and Apixaban dose ≥ 5 mg. If the dose of Rivaroxaban is < 10 mg and Apixaban < 5 mg the or the dose is unknown taken > 8 hours ago low-dosing regimen is recommended with 400 mg IV Infusion over 30 minutes, continued with 4 mg IV transfusion over 120 minutes. In inactive recombinant factor Xa Chromogenic anti-factor Xa assays are recommended for monitoring their concentrations. The Evaluation of hemostasis parameters should always be evaluated with respect to the time of the last dose administration due to fast changing plasma concentrations and short half-life of NOACs. Other management options are the administration of 3-factor or 4-factor PCC 25-50 units/kg IV once or aPCC 25 units/kg once, secondly can be repeated after 6 hours depending on the hemostasis, both increasing the risk of thrombosis.

In case of **bleeding Heparin** administration needs to be stopped. As antidote **Protamine** sulphate is given, a cationic peptide that forms a stable ion pair with LWMH or UFH, thus no anticoagulant function is provided. It reverses completely UFH and partially LWMH (~60%)(16). Dose antidote selection is based on the time elapsed from the last heparin dosage. In **UFH** 1 mg Protamine to neutralize 100 IU UFH. Dose calculation in case of IV infusion of UFH includes dosage of the previous 3 hours. Controls of aPTT values serve as monitoring function.

In patients receiving **LMWH** the dosage depends on the specific drug and as in UFH on the time elapsed since the last dose. In Enoxaparin, if 8 hours or less have elapsed: 1 mg protamine per 1 mg of enoxaparin, or if more than 8 hours have elapsed: 0.5 mg per 100 IU, if its more than 12 hours no protamine is required. In case of Tinzaparin or dalteparin: 1mg IV per 100 UI of LWMH once, if PTT remains elevated after 2-4 hours or bleeding persists, a lower second dose can be given: 0.5 mg IV per 100 UI of LWMH. The total dose should never exceed 50 mg. Anaphylactic reactions can occur as adverse effects, these include cardiovascular complications like bradycardia, fall in BP, cardiovascular arrest and shock. Crucial for risk minimalization is a slow infusion rate. Prophylactic administration of H1 and H2 antihistamines (clemastine or ranitidine) can be given prior to infusion, especially in patients with an increased risk profile (e.g., previous protamine infusion or protamine insulin, allergy to fish protein, or vasectomy) (19)For fondaparinux, a Factor Xa inhibitor, no antidote is currently available. Treatment options for reversal in case of bleeding include administration of aPCC (50 units/kg IV once) or recombinant activated factor VII (90 mcg/kg IV once). Due to the increased risk of thrombosis associated with therapy, prior hematological consultation is recommended. Determining whether and when to discontinue treatment with anticoagulant treatment is resumed after a severe bleeding will depend on the identification of the bleeding site and the type of therapy used to control bleeding site and the type of therapy used to control bleeding. Aspects to consider include changing the medication, a dose reduction or a change in concomitant therapy.

6.1. **Management of acute bleeding**

Steps in case of acute bleeding due to hemostasis and bleeding disorders ABCDE approach and stabilization of the patient. In best case scenario the patient has two appropriate IV accesses present. Diagnostic set-up should include CBC with blood smear, BMP, liver chemistries and type and cross. Coagulation parameters performed are PT, aPTT, INR, Reptilase time and measurement of vVF and vWF activity. VHAs can be performed as POCT but are primary used in cases of cardiac and liver transplant surgery, trauma, DIC, peripartum hemorrhage because they quantify the speed of formation, strength and resolution time of a clot within minutes. Furthermore, in complex hemostasis disorders as liver disease. In case of anticoagulation medications, consider anticoagulant reversal and discontinue ongoing anticoagulants and platelet inhibitors. Contraindicated if risk of thromboembolic events are overwhelming. Evaluation if procedural intervention is needed for bleeding control. Start blood product transfusion and replacement of coagulation factors, if needed. In case of hemophilia factors

VII, IX or XI. In case of known vWD administer concentrates containing vWF and factor VIII. Reassessment of adjuvant drug therapy after including diagnostic results and suspected etiology.(20)

7. Conclusions and suggestions

Treatment of cardiovascular diseases experienced a major advance in the recent years, leading to significant improvements in outcome. However, bleeding is still an issue. Ultimately, the management strategy in patients at the cardiac intensive cardio care Unit should be carefully considered on a case-by-case basis, considering the patient's individual risk factors and medical history. Patients on anticoagulant or antiplatelet therapy either have an increased risk of thromboembolism or a significantly increased risk of bleeding depending on the medication dose, highlighting the difficulty in choosing the right dose and therapy. The team led by Marquis-Gravel analysed data from 4 multicentre randomized trials in 2020, involving a total of 45,000 patients and concluded that there was no difference in mortality prediction whether the previous event was a repeat Myocardial infarction or a major bleeding episode(21), correlating and emphasizing the importance with the presented results. Therefore, the risk-benefit-balance of both outcomes must be considered equally and individually in every case when choosing the treatment plan. Especially the first 30 days after hospitalisation are crucial in determining the outcome in terms of mortality and morbidity. Consequently, continuous monitoring for surveillance should be done in patients hospitalized at the intensive cardio care unit and should include at least following three parameters: Pulse oximeter, electrocardiogram, and blood pressure, with the alarm and frequency of the measurement adjusted to individual acceptable limits. If the patient's condition deteriorates, a rapid re-assessment can be made by re-evaluating the clinical data and adding additional diagnostics required until the high-risk period of 30 days has overcome. The population parameters of all three presented studies showed strong predictive value for hospitalization and related outcome. Despite, the high incidence and importance of bleeding in cardiovascular diseases it is still difficult to compare research results relating management outcomes, because there is still a lack of standardized classification parameters used in the current presented studies. These should be clearly stated, thus the increasing incidence of cardiovascular diseases and the accompanied use of anticoagulants and antiplatelets can be applied with the best possible benefit-risk-balance. Given the high impact of risk factors and the associated burden on global society, which will increase in the forthcoming years, greater emphasis needs to be given to preventive measures in order to move away from "Reparative-Medicine".

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