Management of bleeding in patients hospitalized in the intensive cardiac care unit

Expert opinion of the Association of Intensive Cardiac Care and Section of Cardiovascular Pharmacotherapy of the Polish Cardiac Society in cooperation with specialists in other fields of medicine

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ABSTRACT

Nowadays, the intensive cardiac care unit (ICCU) provides care for patients with acute coronary syndrome, acute and exacerbated chronic heart failure, cardiogenic shock, sudden cardiac arrest, electrical storm, as well as with indications for urgent cardiac surgical treatment. Most of these patients require the use of 1, 2, or frequently even 3 drugs that act on the blood coagulation pathway. While antithrombotic drugs prevent thromboembolic events, they are associated with a higher risk of bleeding. In this population of patients, bleeding may often have a worse impact on prognosis than the primary disease. In this expert opinion of the Association of Intensive Cardiac Care, we presented practical guidelines on the management of bleeding in patients hospitalized at the ICCU, including bleeding risk reduction and treatment recommendations. Because of multiple comorbidities and diverse organs that may be the source of bleeding, we provided also recommendations from specialists in other fields of medicine. We hope that this document will facilitate the management of one of the most challenging populations at the ICCU.

KEY WORDS
anticoagulant treatment, antiplatelet treatment, antithrombotic treatment, bleeding, intensive cardiac care unit

Introduction Nowadays, the intensive cardiac care unit (ICCU) provides care for patients with acute coronary syndrome (ACS), acute and exacerbated chronic heart failure, cardiogenic shock, sudden cardiac arrest, electrical storm, as well as with indications for urgent cardiac surgery. Other patients commonly include also those with complications after planned invasive procedures or surgical treatment. An increasing number of patients with cardiovascular diseases have indications for antiplatelet, anticoagulant, or antithrombotic therapy. However, the use of drugs that reduce blood clot formation is associated with a high risk of bleeding. Moreover, the risk is augmented by the presence of a primary disease, comorbidities, or the use of one or more coagulation modifiers.

The aim of the present document, developed by specialists in various fields of medicine, was to provide practical guidelines on prevention, diagnosis, and treatment of bleeding in patients hospitalized at the ICCU in the era of modern antithrombotic treatment.

Incidence of bleeding at the intensive cardiac care unit There are no precise data describing the population of patients with bleeding during hospitalization at the ICCU. Therefore, it is difficult to establish the exact incidence of bleeding in this setting. The estimated data can be obtained from registries on the incidence of in-hospital bleeding or bleeding that occurred within a few days since admission.[1-3] The incidence of bleeding in everyday clinical practice is higher than that reported in clinical trials on the use of antiplatelet and anticoagulant drugs. The rate of minor and major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) classification in the first 30 days after ST-segment myocardial infarction (STEMI) in unselected patients was 7.2%, as compared with 2.9% in the randomized population of the DANAMI-3 (Danish Multicenter Study of Acute Myocardial Infarction-3) trial. Bleeding was significantly correlated with mortality, with a 3-fold higher 30-day mortality rates among patients with bleeds.[4] Registry studies reported the incidence of major in-hospital bleeding (defined according to different classification systems) in patients with ACS of 3.5%,[3] 5.8%,[2] and even 7.5%.[1] The bleeding risk is particularly high in patients with loss of consciousness, anemia, or cardiogenic shock, who are generally excluded from randomized trials. In patients with ACS complicated by cardiogenic shock, the incidence rate of bleeding types 2, 3abc, and 5ab according to the Bleeding Academic Research Consortium (BARC) scale (TABLE 1) reached 19.3%.[5]

TABLE 1 Bleeding Academic Research Consortium (BARC) scale[17]

Type 0		No bleeding
Type 1		Bleeding that is not actionable and does not cause the patient to seek specialist treatment; may include episodes leading to discontinuation of antiplatelet / anticoagulant therapy.
Type 2		Any overt, actionable sign of bleeding (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging studies alone) that does not meet the criteria for type 3, 4, or 5 bleeding but does meet at least 1 of the following criteria: 1) requiring nonsurgical medical intervention; 2) leading to increased level of care, or 3) prompting evaluation.
Type 3	a	Overt bleeding plus reduction in hemoglobin levels of 3–5 g/dl (provided hemoglobin drop is related to bleeding) Any transfusion with overt bleeding
	b	Overt bleeding plus reduction in hemoglobin levels of ≥5 g/dl (provided hemoglobin drop is related to bleeding) Cardiac tamponade Bleeding requiring surgical intervention (excluding dental/nasal/skin/hemorrhoid bleeding) Bleeding requiring intravenous vasoactive agents
	c	Intracranial hemorrhage (excluding microbleeds or hemorrhagic transformation, including intraspinal) Subcategories confirmed by autopsy or imaging Intraocular bleed compromising vision
4[a]		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 48 h Chest tube output ≥2 l within 24 h
5	a	Probable fatal bleeding; based on clinical suspicion, no autopsy or imaging confirmation
	b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

a If a CABG-related bleed is not classified as at least type 3 event, it will not be considered as a bleeding event.

Abbreviations: CABG, coronary artery bypass grafting

The incidence of bleeding is associated both with primary disease and comorbidities.

In patients with STEMI included in the HORIZONS-AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction), 90.8% of all bleeding events (TIMI major and minor bleeding) occurred in the first 30 days since the index event, with the highest rate (1.3%) observed between days 2 and 3 after percutaneous coronary intervention.[6] In patients with non-STEMI (NSTEMI) included in the DIOCLES registry, the incidence of in-hospital major bleedings (fatal, intracranial, or requiring surgery or blood transfusion) was 2.77%, while the FAST-MI 2010 registry reported the incidence of TIMI minor bleeding of 2.27%.[7] Acute kidney failure, which occurs in up to 16% of patients with ACS, is associated with a 3-fold higher risk of bleeding in comparison with patients without renal failure.[8] Also patients with concomitant chronic kidney disease have a higher risk of bleeding (up to 5%) than patients without the disease.[9] Finally, patients with diabetes were shown to have a higher risk of in-hospital bleeding than nondiabetic patients (risk ratio, 1.35; 95% CI, 1.21–1.51), with major bleeding events reported in 3.8% of diabetic patients while in hospital.[10]

The above data indicate that the rate of major in-hospital bleeding ranges from 3% in patients with ACS to 19% in patients with cardiogenic shock depending on the classification used and characteristics of the study population.

Major bleedings are associated with worse prognosis. In patients with ACS, the impact of bleeding on prognosis is similar to that of ischemic events,[11] although there are data suggesting that bleeding after 30 days since ACS (BARC types 3b and 3c) may be associated with higher mortality than recurrent myocardial infarction.[12] The absolute increase in mortality due to bleeding in patients with ACS was 11% (95% CI, 8–14), corresponding to a number needed to harm of 9.1 (95% CI, 7.1–12.5).[13] Major bleeding in patients with ACS is associated with a 2- to 3-fold higher risk of mortality.[14] On the other hand, major or life-threatening bleeding after transcatheter aortic valve implantation is associated with a 5-fold higher risk of 30-day mortality. [15]

Classification of bleedings There are numerous classification systems for bleedings, which are used in randomized and registry trials. The most common include TIMI, GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries), ISTH (International Society on Thrombosis and Haemostasis), and ACUITY (Acute Catheterization and Urgent Intervention Triage). The use of various scales makes it difficult to compare results between studies. For example, the incidence of major in-hospital bleeding among patients with ACS varies from 0.2% to 11.5%, depending on the definition used.[16] The BARC scale has been proposed to standardize the existing definitions of bleeding (TABLE 1).[17]

We recommend the use of the BARC scale in daily clinical practice at the ICCU.

Risk factors for bleeding Risk factors for bleeding differ between individual patients depending on a primary disease and comorbidities. Common risk factors for patients with cardiovascular disease include age, low body mass, invasive treatment, renal failure, antiplatelet and anticoagulant treatment, and history of bleeding.[13] For some cardiovascular diseases, risk scores that include additional factors related to particular patient populations have been developed.

In patients with ACS without ST-segment elevation, the CRUSADE score is used, which includes heart rate, systolic blood pressure (BP), hematocrit, creatinine clearance, sex, signs of congestive heart failure at presentation, history of diabetes, as well as history of vascular disease. Available registries have also indicated other independent risk factors of in-hospital bleeding in these patients, including prehospital sudden cardiac arrest (odds ratio [OR], 2.99 [95% CI, 2.77–3.22]), cardiogenic shock at presentation (OR, 2.22 [95% CI, 2.05–2.40]), STEMI (OR, 1.72 [95% CI, 1.65–1.80]), heart failure at presentation (OR, 1.55 [95% CI, 1.47–1.63]), hemoglobin levels at presentation lower than 12 g/dl (OR, 1.55 [95% CI, 1.47–1.63]), heart rate (per 10-bpm increase; OR, 1.13 [95% CI, 1.12–1.14]), creatinine clearance (per 5-ml/min increase; OR, 1.07 [95% CI, 1.07–1.08]), and weight (per 10-kg decrease; OR, 1.12 [95% CI, 1.11–1.14]).[1]

In patients with atrial fibrillation, the following risk-stratification scores are used: HAS-BLED[18] (hypertension, liver and kidney function, history of stroke or thromboembolism, history of bleeding, labile international normalized ratio [INR], age, use of nonsteroidal anti-inflammatory drugs, and alcohol abuse) and ORBIT[19] (age, anemia, history of bleeding, kidney function, antiplatelet treatment). Moreover, the first results on the GARFIELD-AF risk model (Global Anticoagulant Registry in the Field-Atrial Fibrillation) are now available.[20] The GARFIELD-AF score, developed on the basis of registry data on mortality, stroke, and bleeding events, has been designed to aid decision making regarding antithrombotic treatment in patients with atrial fibrillation.

Association between bleeding and ischemic events A bleeding event is thought to increase the risk of an ischemic event. This association may have several underlying mechanisms, including a complete and rapid withdrawal of anticoagulant and antiplatelet drugs or compensatory response to bleeding. As a result, bleeding may occur before

an ischemic event.[21] In the HORIZONS-AMI study (patients with STEMI), only 7.9% of bleeding events occurred after ischemic events, while 15.9% of ischemic events occurred after a bleeding event, all within 30 days.[6]

Identification of patients at high bleeding risk Each patient admitted to the ICCU should be evaluated for the risk of thromboembolic complications and bleeding. Modifiable and nonmodifiable risk factors are listed in TABLE 2.

We recommend that each patient admitted to the ICCU is evaluated for the risk of bleeding, the modifiable risk factors are managed with the aim to reduce the bleeding risk, and that the bleeding site is closely monitored in patients with a history of bleeding.

TABLE 2 Modifiable and nonmodifiable risk factors for bleeding

Nonmodifiable risk factors	Modifiable risk factors
Common risk factors	
Age[a]	Renal failure
Previous bleeding	Anemia
	Weight[b]
Risk factors in patients with ACS	
Sex	Heart rate[c]
Signs of heart failure on admission	Systolic blood pressure[d]
Coexistent symptomatic peripheral atherosclerosis	Hematocrit
Diabetes	Creatinine clearance[e]
Cardiogenic shock	Vascular access[f]
Previous sudden cardiac arrest	
STEMI	
Risk factors in patients with AF	
Malignancy	Hypertension[g]
Previous stroke	Labile INR[h]
Dialysis or previous kidney transplant	Use of antiplatelet drugs and / or NSAIDs
Liver cirrhosis	Alcohol abuse
Genetic factors (CYP 2C9 polymorphism)	Anemia
	Kidney[i] and / or liver dysfunction[j]
	Thrombocytopenia[k]

a >65 or >75 years

b Body mass index <18.5 kg/m^2

c Per 10-bpm increase

d Lower values related to higher bleeding risk

e Per 5-ml/min increase

f Femoral access associated with higher bleeding risk

g Systolic blood pressure >160 mm Hg

h <60% of time in the therapeutic range

i Dialysis or previous kidney transplant

j Creatinine >200 µmol/l or >2.3 mg/dl; cirrhosis; bilirubin level >2× the upper limit of normal; AST, ALT, ALP >3× the upper limit of normal

k <150 000/mm^3

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; STEMI, ST-segment elevation myocardial infarction

General recommendations for bleeding risk reduction at the intensive cardiac care unit In each patient hospitalized at the ICCU, a blood group should be determined and a vascular access should be secured. Patients in severe general condition should undergo central venous catheterization. In each patient, a careful analysis of indications for treatment that may affect hemostasis is required. Any modifications in dual antiplatelet therapy (DAPT) or triple antithrombotic therapy (TAT) should be consulted with an interventional cardiologist. Potential drug-drug interactions as well as the effect of anti-inflammatory and analgesic drugs on hemostasis should be considered.

The recommendations for bleeding risk reduction are listed below:

1 Consider switching TAT to DAPT with discontinuation of acetylsalicylic acid therapy.

2 Consider switching ticagrelol to clopidogrel in patients with a history of clinically relevant gastrointestinal (GI) bleeding in the previous 6 months, intracranial hemorrhage, clinically significant anemia, thrombocytopenia, major surgeries in the previous 30 days, moderately severe or severe liver disease

3 Switch prasugrel to clopidogrel in patients with previous stroke or transient ischemic attack, severe liver disease (Child–Pugh score, class C), recent trauma, surgery, previous or recurrent GI bleeding, active peptic ulcer disease. In patients older than 75 years and/or with a body mass of less than 60 kg, the maintenance dose of prasugrel should be reduced to 5 mg/d.

4 Switch a vitamin K antagonist (VKA) to a non–vitamin K antagonist oral anticoagulants (NOAC).

5 Use reduced doses of NOACs with confirmed efficacy in patients at higher risk of bleeding.

6 Adjust NOAC dose depending on kidney and liver function.

7 Adjust low-molecular-weight heparin (LMWH) dose depending on kidney function.

8 Use fondaparinux as an anticoagulant drug in noninvasive treatment of patients with ACS.[22]

9 Carefully assess indications for treatment with any of the used drugs that affect hemostasis on daily basis.

To reduce the risk of upper GI bleeding, we recommend using proton-pump inhibitors (PPIs) in patients: 1) aged ≥60 years; 2) with a history of peptic ulcer disease or GI bleeding; 3) with chronic kidney disease; 4) with *Helicobacter pylori* infection; 5) on DAPT or TAT; and 6) using nonsteroidal anti-inflammatory drugs or corticosteroids.

In patients after percutaneous coronary interventions, the recommendations are as follows:

1 The operator should include detailed information on any difficulties with vascular access in the patient's medical records (femoral arterial puncture too low or too high, posterior vessel wall puncture, multiple vascular access failure, bending of a vascular sheath), complex interventions (a larger size of the vascular sheath, prolonged duration of intervention, prolonged activated clotting time), indication for a prolonged use of vascular sheath.

2 In the case of femoral access, measurement of the thigh circuit with monitoring over subsequent hours and days.

3 Evaluation of the compression dressing, or the site of arterial puncture or artery access closure; auscultation at the puncture site to detect arteriovenous fistulas, aneurysms, or arterial bleeding.

4 Ultrasound of the puncture site if bleeding, pseudoaneurysm, or arteriovenous fistula is suspected.

We recommend an echocardiographic examination on admission to the ICCU. For each patient, views that visualize the presence of pericardial effusion fluid should be recorded.

During the ICCU stay:

1 Measure complete blood count regularly.

2 Measure iron deficiency level in patients with anemia that was not diagnosed previously.[23]

3 In patients with a history of bleeding, identify the cause of bleeding on the basis of medical records and monitor the relevant bleeding site: GI tract (repeat complete blood count, occult blood in stool, pharmacological protection with PPI); genitourinary tract (urinalysis); central nervous system (neurologic examination; computed tomography [CT] may be considered).

4 Analyze indications for use of the central venous catheter, urinary catheter, intubation tube, and stomach probe as additional risk factors for bleeding; depending on indications, consider their removal or close monitoring (FIGURE 1).

Recommendations for bleeding risk reduction in selected groups of patients at the intensive cardiac care unit **Patients after electrophysiological interventions** The most common arrhythmias requiring ablation among patients treated at the ICCU are atrial fibrillation (ablation for arrhythmias and atrioventricular node ablation) and ventricular tachycardia. The other group includes patients undergoing cardiac device implantation during the ICCU stay. Recommendations for anticoagulant therapy in these patients are presented in TABLES 3 and 4.[24-26]

Patients with cancer The assessment of bleeding risk in patients with malignancy, particularly those undergoing vascular procedures and receiving combined antiplatelet and anticoagulant treatment, is challenging as there are no objective risk scores or results from randomized clinical trials for these populations. Some data have been obtained from meta-analyses and registry studies.[27-29]

Importantly, cancer treatment is associated with a number of risk factors for bleeding due to

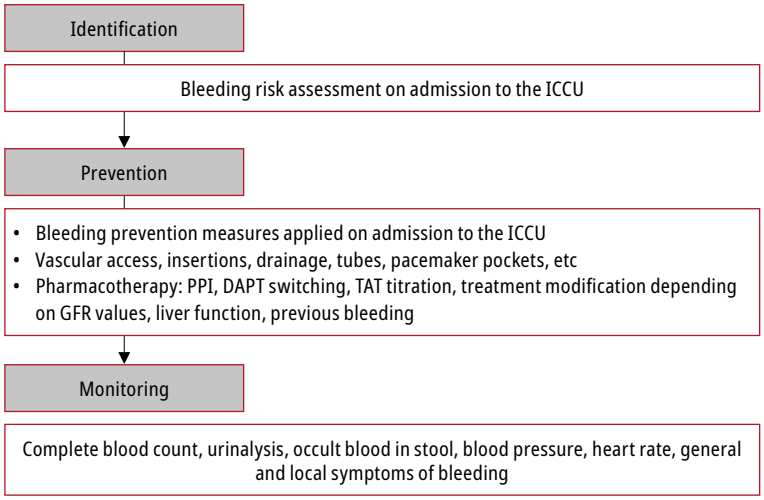


FIGURE 1 Identification, prevention, and monitoring of bleeding in the intensive cardiac care unit

Abbreviations: DAPT, dual antiplatelet therapy; GFR, glomerular filtration rate; ICCU, intensive cardiac care unit, PPI, proton-pump inhibitor; TAT, triple antithrombotic therapy

a complex and heterogeneous character of the disease itself as well as specific therapy, which should be considered when administering drugs that act on the blood coagulation pathway. General risk factors for bleeding complications in patients with cancer who receive anticoagulation include drug--drug interactions, vomiting, cachexia, hypoalbuminemia, vitamin K deficiency, fever, diarrhea, infections, age, dementia, low body mass, liver dysfunction, heart failure, and thyroid disorders.

Bleeding complications that are considered most severe and are associated with the highest mortality include bleeding and bleeding to vital organs. Bleeding risk is significantly associated with the histopathologic type of cancer. A considerable body of evidence suggests that the risk of bleeding complications is also significantly higher in patients with metastases and reduced estimated glomerular filtration rate (<30 ml/min), as well as in those with

TABLE 3 Guidelines on the management of patients undergoing percutaneous ablation of atrial fibrillation and left-sided ventricular tachycardia [24,25]

Management of patients undergoing percutaneous ablation of AF
Before the procedure
In all patients undergoing ablation of AF, anticoagulant therapy with a NOAC or VKA (INR, 2–3) at least 3 weeks before the procedure should be administered or a TEE study should be performed.
In patients treated with a VKA or dabigatran or rivaroxaban, ablation should be performed without interruption of anticoagulant therapy.
In patients treated with a NOAC other than dabigatran or rivaroxaban, consider ablation of AF without interruption of anticoagulant therapy.
TEE before the procedure may be useful in all patients with a CHA_2DS_2-VASc score ≥2.
In NOAC-treated patients with normal kidney function, the final drug dose should be administered 24 h before the procedure. In dabigatran-treated patients with impaired kidney function, this time should be longer[a]. Consider restarting NOAC treatment 24–48 h postprocedure after hemostasis assessment.
During the procedure
During ablation of AF, the use of UFH with an ACT >300 s is recommended. After the procedure, consider administration of protamine (before removing the vascular access) to reverse heparin effect.
After the procedure
In patients who did not receive anticoagulant treatment before the procedure and those who are scheduled for VKA treatment after the procedure, bridging therapy with LMWH or UFH is recommended.
Anticoagulant therapy (VKA or NOAC) should be administered for at least 2 months irrespective of thromboembolic risk.
Decision on continuation of anticoagulant treatment after 2 months since the procedure should be made on the basis of thromboembolic risk irrespective of whether the procedure was effective in terms of sinus rhythm control.
In patients who did not receive anticoagulant treatment or in whom VKA or NOAC treatment was discontinued before the procedure, consider starting a NOAC 3–5 h after achieving hemostasis.
Management of patients undergoing percutaneous ablation of left-sided VT
During the ablation, the use of UFH with an ACT >300 s is recommended. After the ablation, consider administration of protamine (before removing the vascular access) to reverse heparin effect.
In patients on anticoagulant treatment (VKA or NOAC), ablation should be performed without interruption of anticoagulant therapy.
After the procedure, consider oral anticoagulant treatment or ASA (75–150 mg) for 4–12 weeks.
Unless there are other indications, routine anticoagulant therapy before the procedure is not recommended.

a For a creatinine clearance of 50–80 ml/min, 36 hours; 30–50 ml/min, 48 hours; 15–30 ml/min, 72 hours.

Abbreviations: ACT, activated clotting time; AF, atrial fibrillation; ASA, acetylsalicylic acid; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulants; TEE, transesophageal echocardiography; UFH, unfractionated heparin; VKA, vitamin K antagonist; VT, ventricular tachycardia

thrombocytopenia, especially in the case of primary gastric or intestinal cancer.[30]

The risk of bleeding, particularly intracranial hemorrhage, is higher in patients with a primary diagnosis of malignant melanoma, renal cell carcinoma, thyroid cancer, and choriocarcinoma. A lower risk of spontaneous bleeding is observed in patients with lung and breast cancer with brain metastases. These data should be considered when making decisions on the type and duration of treatment in patients with indications for use of antiplatelet drugs, particularly in combination with anticoagulants. The higher risk of thromboembolic complications associated with various types of malignancy should also be considered in therapeutic decision making.[31] The cumulative incidence of thromboembolic events is shown in TABLE 5.[32]

For bleeding risk reduction in patients with ACS and malignancy, it is important to consider the fact that drugs used for cancer treatment often lead to hepatic and renal damage. Liver and kidney dysfunction may cause disturbances in the metabolism of antiplatelet and anticoagulant drugs. Clopidogrel, a prodrug, is metabolized in the liver; impaired liver synthesis of antithrombin II reduces heparin effects; and impaired kidney function may disturb the metabolism of LMWH. Therefore, cancer patients receiving drugs with high hepato- and nephrotoxicity, who are on antiplatelet and anticoagulant treatment, require particular attention. Nephrotoxic drugs used in oncology include cisplatin, streptozotocin, methotrexate, cyclophosphamide, ifosfamide, asparaginase, hydroxycarbamide, and etoposide. Hepatotoxic drugs include methotrexate, mercaptopurine, nitrosourea derivatives (carmustine, lomustine), dacarbazine, cytarabine, hydroxycarbamide, etoposide, and paclitaxel. [33]

Symptoms and laboratory parameters used as markers of bleeding risk Local symptoms of bleeding depend on the source of bleeding and are not always clinically overt. The clinical presentation largely depends on the circulating blood volume loss and the rate of loss. Blood pressure may not drop until the volume loss reaches 750 to 1500 ml of blood, while an orthostatic decrease in BP of at least 10 to 20 mm Hg with a simultaneous heart rate acceleration by at least 20 to 30 bpm indicates hypovolemia (TABLE 6). A reduction in hematocrit, hemoglobin levels, and red blood cell (RBC) count usually occurs at least 1 to 3 hours after blood loss.[34]

TABLE 4 Periprocedural antithrombotic management of patients undergoing implantation of cardiac implantable electronic devices[25,26]

In patients with indications for VKA treatment, implantation of cardiac implantable electronic devices should be performed without interruption of anticoagulant therapy.
On the day of the procedure, INR should be below the upper normal limit (<3–3.5).
Interruption of VKA treatment and use of bridging therapy should be avoided.
NOAC treatment should be interrupted in the periprocedural period.
Duration of NOAC interruption should depend on the characteristics of a given drug.
The first NOAC dose should be used 24–48 h after the procedure depending on individual risk assessment.

Abbreviations: INR, international normalized ratio; NOAC, non–vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonist

TABLE 5 Cumulative incidence (%) of thromboembolic events (modified from Falanga et al)[32]

Type of cancer	Regional	Metastatic
Pancreas	4.0	7.5
Stomach	4.4	6.6
Colon	2.7	3.5
Ovary	1.9	4.2
Uterus	2.1	5.3
Breast	1.2	2.8
Kidney	6.8	6.3
Bladder	3.8	5.6
Prostate	1.3	1.2
Lung	2.3	3.2
Lymphoma	3.6	2.8

TABLE 6 Clinical signs and symptoms depending on blood volume loss

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Circulating blood volume loss, ml (%)	750 (<15)	750–1500 (15–30)	1500–2000 (30–40)	>2000 (>40)
Heart rate, bpm	<100	>100	>120	>140
Respiratory rate, breaths/min	14–20	20–30	30–40	>35
SBP and DBP in the supine position	Within the reference range	Within the reference range	Reduced	Reduced
Capillary refill time	Normal (≤2 s)	Delayed (>2 s)	Delayed (>2 s)	Delayed (>2 s)
Skin	Normal	Pale	Pale	Pale and cold
Diuresis, ml/h	>30	20–30	5–15	<5
Mental state	Anxiety	Agitation	Confusion	Somnolence
Fluid therapy (crystalloid-to-colloid ratio)	3:1	3:1	3:1 + packed RBCs	3:1 + packed RBCs

Abbreviations: DBP, diastolic blood pressure; RBC, red blood cell; SBP, systolic blood pressure

TABLE 7 Crystalloids and colloids

Crystalloids

Aqueous solutions of:

- mineral salts such as sodium chloride, potassium chloride, calcium chloride, magnesium chloride;
- organic acid salts, eg, sodium acetate, sodium lactate, and trisodium citrate;
- monosaccharides.

After intravenous infusion, crystalloids rapidly escape from the intravascular to extravascular space, providing only short plasma volume replacement.

Colloids

Aqueous solutions of high-molecular-weight substances. In contrast to crystalloids, they stay longer in plasma before passing the vascular membrane to extravascular space, thus providing better plasma volume replacement. Colloids include:

- hydroxyethyl starch (HES, artificial colloid);
- gelatin solutions (artificial colloid);
- dextrans (artificial colloid);
- albumins (natural colloid).

Plasma is also a colloid, although it is not used as a typical infusion fluid.

Fluid resuscitation and blood and blood product transfusion

General management In patients with significant blood loss, prompt transfusion therapy is crucial. The patient should be constantly monitored for BP changes and signs of hypoperfusion. Fluid resuscitation until blood transfusion is used for shock prevention. In stable patients with normal BP values, BP measurement should be repeated in a standing position. Patients with cardiogenic shock and respiratory disorders should be intubated and started on mechanical ventilation.

Fluid resuscitation To replenish blood volume loss, 2 short cannulas with a large diameter (>1.8 mm) should be inserted into peripheral veins. According to the 2013 National Institute for Health and Care Excellence guidelines, fluid therapy in patients with shock should be started with intravenous (IV) infusion of crystalloids or colloids (TABLE 7). The transfusion is continued depending on BP, central venous pressure, and diuresis, while avoiding fluid overload.

The aim of fluid therapy is to achieve hemodynamic stability. 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; 2000 ml of crystalloid replaces about 500 ml of blood. In the case of minor bleeds, a 500- to 1000-ml infusion of crystalloids is sometimes sufficient to achieve hemodynamic stability.[35] The algorithm for fluid therapy in patients with bleeding is presented in FIGURE 2.

In 2013, the European Medicines Agency limited the use of the colloid hydroxyethyl starch (HES) only to patients with hypovolemia due to acute blood loss if crystalloid transfusion alone is insufficient. The benefits of using HES are questionable, with studies reporting higher mortality rates. Contraindications to the use of HES include kidney failure and coagulopathy. The colloid should be administered for a short time, no longer than 24 hours, at the lowest effective dose: maximum 30 ml/kg of body weight (bw) for 6% HES 130/0.4 and 130/0.42 solutions. Kidney function monitoring is mandatory during treatment.

It is sometimes necessary to administer more than 2000 ml of fluid. Subsequent doses (200–500 ml) should be administered to achieve a mean intra-arterial BP higher than 65 mm Hg, an increase in central venous pressure by more than 3 cm H_2O, and an increase in diuresis by at least 1 ml/kg bw per hour as compared with baseline. Arterial blood gases should be measured (pH, serum lactates), and the patient should be monitored for the signs of fluid overload. At the same time, if hypotension persists, noradrenaline (Levonor) at a dose of 1 to 20 µg/min (maximum, 1–2 µg/kg/min), adrenaline at a dose of 0.05–0.5 µg/kg/min, or dopamine at a dose of 3–30 µg/min should be administered.[36,37]

In large-volume fluid resuscitation, 0.9% NaCl alone should not be used because large amounts of this solution result in hyperchloremic acidosis,

hypernatremia, and hyperosmolarity. Excessive intake of chloride ions may also increase the risk of kidney damage.[34]

Patients with heart failure and left ventricular systolic dysfunction constitute a specific population, in which fluid therapy should be administered with caution due to a high risk of hypervolemia. Therefore, fluid infusion should start at lower volumes (250–500 ml of crystalloids or 150–200 ml of colloids or 150–200 ml of albumin 5%) and should be administered over a longer period (during 30 min) with hemodynamic monitoring including intra-arterial BP, central venous pressure, and diuresis.

Bedside echocardiography is particularly useful in hemodynamic assessment. It should be used to evaluate left and right ventricular filling pressures, inferior vena cava pressure and collapsibility, as well as left ventricular systolic function.

Blood and blood product transfusion The loss of whole blood due to bleeding usually leads to the so called posthemorrhagic anemia. Its

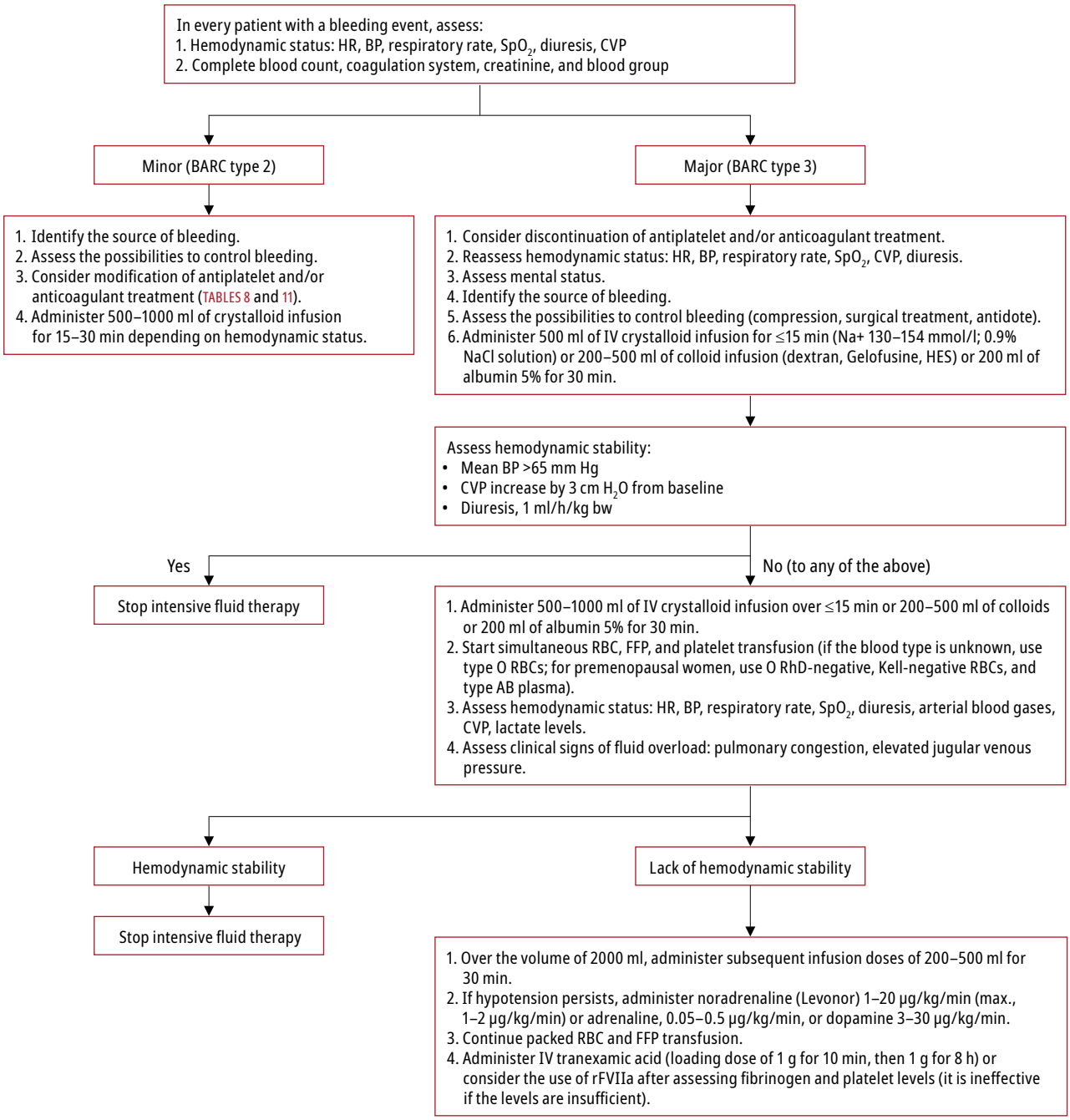


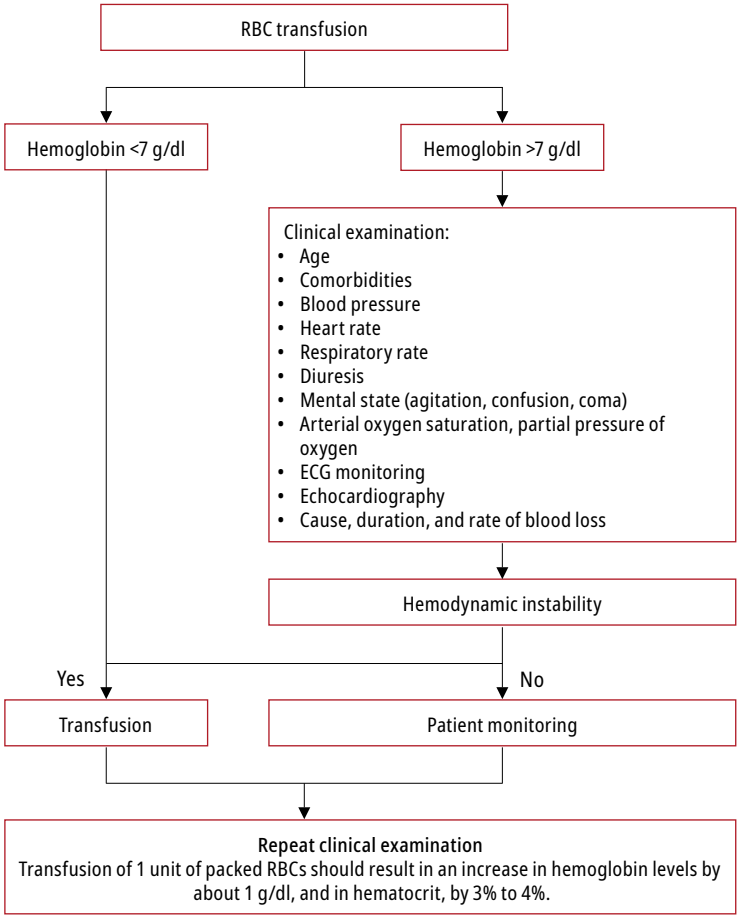
FIGURE 2 Fluid resuscitation in patients with bleeding

Abbreviations: BARC, Bleeding Academic Research Consortium; BP, blood pressure; CVP, central venous pressure; FFP, fresh frozen plasma; HES, hydroxyethyl starch; HR, heart rate; IV, intravenous; RBC, red blood cell; rFVIIa, recombinant factor VIIa

severity depends on the blood volume loss. However, the measurement of complete blood count, hemoglobin levels, and hematocrit is not a fully reliable marker of blood volume loss, and these parameters should be analyzed in combination with clinical data.[38] In large-volume bleedings, hemoglobin levels are not initially reduced. Additionally, the interpretation of laboratory workup is hampered by fluid therapy. Therefore, in the early stage of bleeding, hemoglobin levels alone cannot be used to guide decision making regarding RBC transfusion. Due to multiple compensatory mechanisms, anemia can be diagnosed only after 24 to 48 hours. Acute posthemorrhagic anemia is normocytic and normochromic anemia. During 48 hours after bleeding, an increase in reticulocyte count is also observed, along with the erythroblastic reaction in the bone marrow. A nonspecific but typical symptom is an increase in total white blood cell count, particularly neutrophils. Massive bleedings can initially present with reduced platelet count, but after the bleeding is stopped, it gradually increases over 48 to 72 hours. Reduced serum iron levels are observed only after a few or more than 10 days since bleeding.

Treatment of patients with bleeding is aimed at obtaining an adequate blood volume, maintaining an adequate level of tissue oxygenation, and ensuring hemostasis. Red blood cell transfusion is usually necessary in patients who have lost about 30% to 40% of circulating blood volume, for example, about 1500 ml of blood in a male patient with a weight of 70 kg.[39] Most guidelines recommend that restrictive criteria for RBC transfusion are followed, with the hemoglobin level of less than 7 g/dl and hematocrit levels maintained above 30%. This approach is recommended to avoid potential adverse effects of transfusion, including cardiac events, recurrent bleeds, or bacterial infections.[40] However, the optimal target hemoglobin levels in the treatment of bleeding has not been established. Usually, the target level above 7 g/dl is recommended, while in patients with ischemic heart disease, it is 8 to 9 g/dl.[41,42] Transfusion of 1 unit of packed RBCs should result in an increase in hemoglobin levels by about 1 g/dl, and in hematocrit, by 3% to 4% (FIGURE 3).

Coagulopathy in patients with bleeding is caused by dilution of coagulation factors and platelets due to fluid therapy or packed RBC transfusion, but also by excessive consumption of coagulation factors during activation of coagulation and fibrinolysis as well as by platelet function disorders. The treatment of choice in coagulation disorders in patients with bleeding as well as in significant bleedings is transfusion of fresh frozen plasma (FFP). The treatment should be started immediately without waiting for laboratory workup. Initially, transfusion of at least 1 unit of FFP per each 2 units of packed RBCs is recommended, followed by a dose of 15 to 20 ml/kg depending on whether hemostasis is achieved.[43] Decision on FFP transfusion should be made on the basis of activated partial thromboplastin time (APTT) and prothrombin time (PT) in combination with the evaluation of the patient's clinical condition. A 1.5-fold increase in APTT and PT activity are clinical signs of coagulopathy. A standard FFP dose is not always sufficient to prevent coagulation factor deficiency; therefore, the treatment of hypofibrinogenemia, which is the first manifestation of coagulation disorders in massive bleeding, should also include cryoprecipitate transfusion in addition to FFP. To maintain hemostatic levels of fibrinogen at 1 g/l, 1 unit of cryoprecipitate per 10 to 15 kg bw should be administered. In 2011, fibrinogen concentrate was approved in Poland, with indications for off-label use in quick hemostatic therapy



RBC transfusion rates:
1. Transfusion should be started within 30 min since obtaining the product from a blood bank.
2. Massive hemorrhage may require transfusion of even 10 units within 10–15 min (transfusion of FFP is also recommended at 1:2 ratio).
3. In patients with heart failure, packed RBCs should be transfused at a rate of 1 ml/kg bw per hour (1 unit of packed RBCs for 1–2 h on average).

The total transfusion duration for 1 unit should not exceed 4 h.

FIGURE 3 Recommendations for red blood cell transfusion

Abbreviations: ECG, electrocardiography; FFP, fresh frozen plasma; RBC, red blood cell

TABLE 8 **Management of bleeding in patients on new oral anticoagulants (modified from Kasprzak et al)**[62]

General principles		
Establish the time of intake of the last NOAC dose; consider administration of activated charcoal if the drug was ingested not later than in the last 3 to 4 h. Establish the time since the onset of bleeding; estimate the volume of blood loss; assess if the bleeding remains active. Establish if the patient took any of the following: ASA, $P2Y_{12}$ inhibitors, NSAIDs, P-gp inhibitors, CYP3A4 inhibitors. Assess the parameters of hemostasis (hematocrit, hemoglobin, platelet count, PT, TT, APTT) and renal function (GFR). Identify the site of bleeding. Assess comorbidities and cardiovascular status.		
Minor bleeding (BARC type 2)	**Moderate bleeding (BARC type 3a)**	**Life-threatening bleeding (BARC type 3b and 3c)**
Delay or omit the next dose of the drug Establish if the patient uses any of the following medications: • ASA • $P2Y_{12}$ inhibitors • NSAIDs • P-gp inhibitors • CYP3A4 inhibitors	Supportive treatment: • Mechanical compression • Surgical hemostasis, endoscopic hemostasis if GI bleeding • Fluid therapy (preferably colloids, if indicated), FFP (only to increase plasma volume) • RBC transfusion if indicated (consider if hemoglobin <7–8 g/dl) • Platelet transfusion (if concomitant antiplatelet treatment or platelet count ≤50 G/l) In patients on dabigatran: • Maintain appropriate diuresis • Consider hemodialysis, hemoperfusion with activated charcoal • Consider idarucizumab (Praxbind®), 5 g IV	Consider administration of: • PCC (eg, Octaplex®, Beriplex®, K-Centra®, Co-Fact®, Confidex®) at a dose of 25 U/kg bw, increase the dose 1–2-fold to 50–75 U/kg bw, if clinically indicated • aPCC (Feiba®) at a dose of 50 U/kg bw, max. 200 U/kg bw In patients on dabigatran: • idarucizumab (Praxbind®), 5 g IV

Abbreviations: aPCC, activated prothrombin complex concentrate; APTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; CYP3A4, cytochrome P450 3A4; BARC, Bleeding Academic Research Consortium; bw, body weight; FFP, fresh frozen plasma; GFR, glomerular filtration rate; GI, gastrointestinal; IV, intravenous; NOAC, new oral anticoagulant; max., maximally; NSAID, nonsteroidal anti-inflammatory drug; PCC, prothrombin complex concentrate; P-gp, P-glycoprotein; PT, prothrombin time; RBC, red blood cell; TT, thrombin time

of fibrinogen deficiency. In massive blood loss, PCC is used at a dose of 15 to 25 IU/kg bw with the aim to increase thrombin generation. Both drugs can be used before blood typing, and their volume after dilution is much lower than that of FFP containing the corresponding amount of coagulation proteins, for example, 1 vial contains 20 ml of PCC, which corresponds to about 750 ml of FFP.

Importantly, FFP is used more often in massive bleedings not related to the use of NOACs, while PCC and activated PCC (aPCC) are recommended for reversing the effect of NOACs in significant bleedings when an antidote is unavailable (TABLE 8). Recommendations for FFP transfusion are presented in FIGURE 4.

Thrombocytopenia is considered a late complication of massive bleeding and usually occurs in patients with the loss of more than 1.5 of circulating blood volume.[44] The current platelet count threshold for platelet transfusion in patients with active bleeding is 50×10^9/l. However, as concomitant platelet dysfunction is possible, including an iatrogenic disorder, associated with the use of antiplatelet drugs, the platelet count threshold of $>50 \times 10^9$/l should be considered in patients with impaired hemostasis. Platelets are administered at 1 therapeutic dose of platelet concentrate, that is, 3×10^{11} of platelets from apheresis or 4 to 6 units of pooled platelets.

Specific indications for platelet transfusion include surgical procedures, but also percutaneous interventions, including angiography. Angiography may be performed when the platelet count is at least 20×10^9 l to avoid bleeding complications at injection site. At lower platelet count, platelet transfusion is indicated for the diagnostic workup of bleeding source or vascular disorders. These indications apply to planned procedures. In the case of angiography due to acute arterial thrombosis, routine platelet transfusion increases the thrombotic risk. Therefore, the transfusion is recommended only in patients with clinically relevant postprocedural bleeding.[45]

In patients without high bleeding risk and a platelet count exceeding 10×10^9/l, central venous catheterization is possible without platelet transfusion. On the other hand, patients with high bleeding risk and a platelet count of less than 20×10^9/l require platelet transfusion as a preventive measure.[46,47] A therapeutic dose of platelet concentrate should result in an increase of platelet count by 30×10^9/l to 50×10^9/l in a patient with a body surface area of 1.8 m^2. Indications for platelet transfusion are presented in FIGURES 5 and 6.

Platelet transfusion is considered effective if the bleeding is stopped and the patient does not develop new petechiae or subcutaneous and

mucosal hemorrhage. In addition, the following parameters are assessed:

1 Absolute platelet increment = posttransfusion platelet count – pretransfusion platelet count; the normal value is 10×10^9/l or 5×10^9/l after 1 hour and 24 hours posttransfusion, respectively.

2 Percent platelet recovery (PPR), calculated using the following formula:

$$PPR = \frac{\text{Posttransfusion platelet count} - \text{pretransfusion platelet count} \times \text{body mass} \times 0.075}{\text{Number of platelets transfused}} \times 100\%,$$

where platelet count is expressed in 10^{11} and body mass in kg. In patients without hypersplenism, a normal increase in platelet count should reach about 60%, and in patients after splenectomy, even up to 100%. An increase of 40% after platelet transfusion is considered satisfactory.

3 Corrected count increment, calculated using the following formula:

$$CCI = \frac{\text{Posttransfusion platelet count} - \text{pretransfusion platelet count} \times \text{body surface area}}{\text{Number of platelets transfused}} \times 100\%,$$

where platelet count is expressed in 10^{11} and body surface area in m^2. A CCI exceeding 7.5 at 1 hour posttransfusion indicates good response to platelet transfusion. A CCI lower than 7.5 at 1 hour and lower than 5 at 24 hours posttransfusion indicates platelet transfusion refractoriness and platelet dysfunction due to immune causes.

The recommendations for patients with active bleeding are as follows:

1 The minimum hemoglobin levels should be maintained above 7 g/dl with RBC transfusion.

2 In massive, life-threatening bleeding, transfusion of type O RBCs, and for premenopausal women, O RhD-negative, Kell-negative, or compatible RBCs for patients with available blood typing results, is allowed.

3 To maintain hemostasis in massive bleeding, RBCs, FFP, and platelets should be transfused at a 1:1:1 ratio, and cryoprecipitate should be administered at a dose of 1 unit per 10 kg bw to maintain fibrinogen levels of 1 g/l.

4 In patients with PT and APTT exceeding the normal values by 1.5-fold, FFP at a dose of 15 to 20 ml/kg bw should be additionally administered, and in patients with a platelet count of less than 50×10^9/l, platelet transfusion is required.[45]

5 Transfusion should be started within 30 minutes since arrival of the product from a blood bank. If more than 1 unit is transfused, subsequent units should be successively obtained from the blood bank.

6 In patients with left ventricular heart failure, due to the risk of circulatory fluid overload, the transfusion rate should not be higher than 1 ml/kg bw per hour, which corresponds to 1 unit of RBCs for 1 to 2 hours on average. The total transfusion duration per unit should not exceed 4 hours.

Adverse events of blood transfusion and recommended management are presented in TABLES 9 and 10.

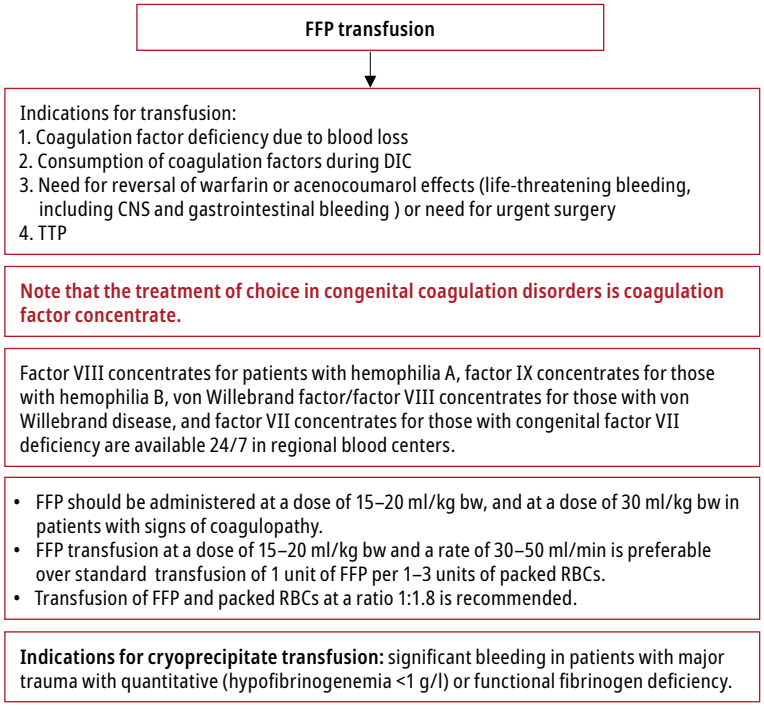


FIGURE 4 Recommendations for fresh frozen plasma transfusion

Abbreviations: CNS, central nervous system; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

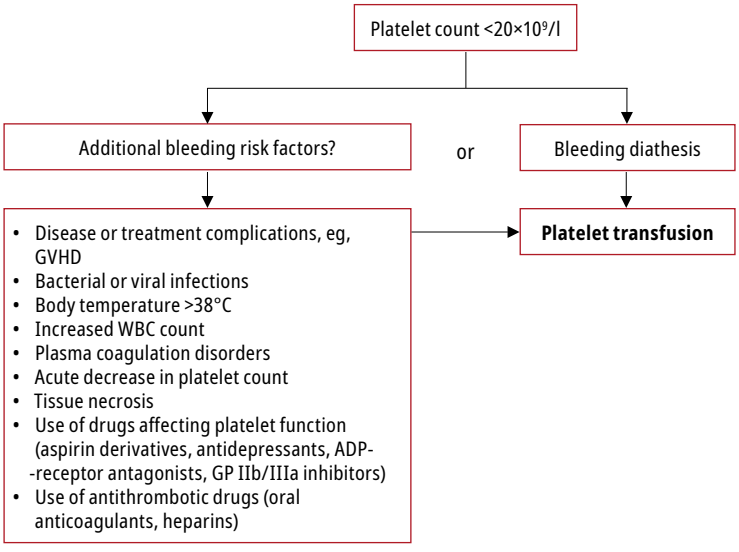


FIGURE 5 Indications for platelet transfusion

Abbreviations: ADP, adenosine diphosphate; GP, glycoprotein; GVHD, graft-versus-host disease; WBC, white blood cell

Management of drug-related bleeding and modification of treatment

Bleeding during antiplatelet treatment Lack of a reversal agent

for oral antiplatelet drugs limits the treatment of bleeding in patients on antiplatelet treatment. In clinical practice, platelet transfusion is relatively common. However, its efficacy has been investigated only in a few studies, and it depends on the mechanism of platelet inhibition.[48,49] In a patient taking acetylsalicylic acid, platelet aggregation may be restored after the administration of 2 to 5 units of platelet concentrate, while it is much more difficult to restore adenosine diphosphate–induced platelet aggregation. In patients treated with clopidogrel or prasugrel, platelet transfusion may restore platelet activity after 4 to 6 hours since the administration of the last dose, while in patients treated with ticagrelol, hemostasis is restored after at least 24 hours.[50,51]

Bleeding during treatment with vitamin K antagonists Anticoagulant effects of VKAs require a reduction in the levels of prothrombin (factor II), which has a relatively long half-life (about 60–72 hours) in comparison with the half-lives of other vitamin K–dependent coagulation factors (6–24 hours). Due to a longer half-life of warfarin, it should be discontinued for about 2.5 days to achieve an international normalized ratio (INR) target of 4 (range, 6–10), while with acenocoumarol, an effective INR reduction can be achieved within less than 1 day in most patients.[52,53] A recommended INR target range is 2 to 3.5, depending on the indication for use. Bleeding risk increases with a higher INR, and the risk is significantly elevated if the INR exceeds 4.5.

Vitamin K1 (phytomenadione) may be considered in patients without symptoms of bleeding but with a high bleeding risk (INR >10). In the case of severe or life-threatening bleeding, a combination of vitamin K1 with PCC, FFP, or recombinant factor VIIa may be considered. Fresh frozen plasma is the most common product used to reverse the effect of coumarin derivatives.[54] However, PCC has higher efficacy than FFP. Moreover, PCC may be associated with a lower thrombotic risk than the recombinant factor VIIa. The latter should be used only when PCC is unavailable.[55] Vitamin K1 can be administered as prolonged IV infusion at a dose of 10 to 20 mg due to a more rapid onset of action compared with an oral drug. To reduce the risk of an anaphylactic reaction, vitamin K1 preparation should be diluted in 100 ml of 0.9% NaCl and administered in a 20- to 30-minute infusion. After 3 hours, the PT should be assessed, and if prolonged, another dose of vitamin K1 should be administered. The dose of IV vitamin K1 should not exceed 40 mg/d. Blood coagulation parameters should be evaluated once daily until the target values are obtained.[55]

Bleeding during treatment with new oral anticoagulants Due to a short duration of action of NOACs, drug excretion by normal metabolic pathways may be more beneficial than aggressive treatment methods in patients with minor bleeding. After withdrawal of NOAC treatment, hemostasis is typically restored within 12 to 24 hours since the last dose, because these anticoagulants have a half-life of about 12 hours. Duration of drug excretion extends with worsening renal function, particularly in the case of dabigatran, which is excreted mainly by the kidneys (80% of the drug).

As there is no need for the monitoring of drug levels and anticoagulant effects in the case of NOACs, they are generally preferred over VKAs. However, this is not an advantage in the case of bleeding. A rapid measurement of hemostasis

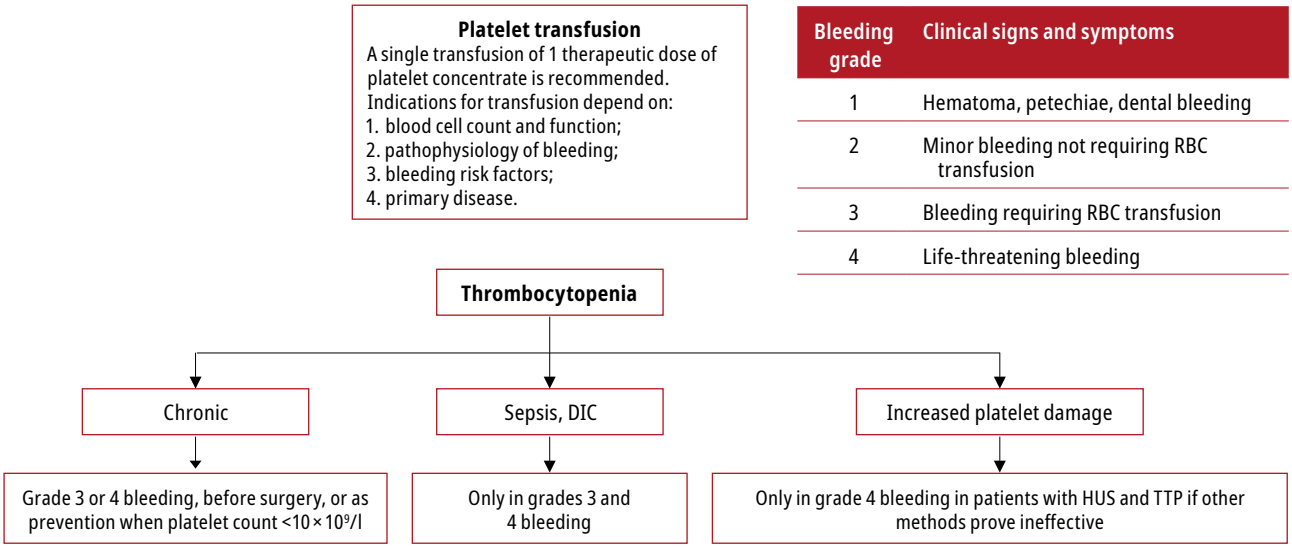


FIGURE 6 Platelet transfusion according to World Health Organization bleeding scale

Abbreviations: DIC, disseminated intravascular coagulation; HUS, hemolytic-uremic syndrome; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

TABLE 9 Transfusion reactions

Reaction	Early (<24 hours)	Late (>24 hours)
Immune	Acute hemolytic transfusion reaction Febrile nonhemolytic transfusion reaction Transfusion-related acute lung injury Allergic transfusion reaction Anaphylaxis	Delayed hemolytic transfusion reaction Alloimmunization Posttransfusion purpura Transfusion-associated graft-versus-host disease Immunomodulation Delayed hemolytic reaction
Nonimmune	Sepsis Circulatory overload Hypotension Pain during transfusion Air embolism Nonimmune hemolysis Hypothermia Hyperkalemia Hypocalcemia	Iron overload Transmission of bloodborne pathogens

TABLE 10 Management of the most common acute transfusion reactions

Type of reaction	Acute hemolytic reaction	Transfusion-related acute lung injury	Allergic reaction and anaphylaxis	Transfusion-associated sepsis
Cause and mechanism	ABO incompatibility due to so called administrative error; lack of or inappropriate identification of donor with transfused blood component; reaction of A and/or B antigen from ABO system with natural, regular ABO IgM antibodies	Reaction of donor anti-HLA or anti-HNA antibodies with recipient leukocyte and granulocyte antigens; possible after transfusion of any blood component	Reaction of recipient anti--IgE antibodies to soluble plasma components	Blood component contains bacteria, most often transferred with blood from donor, which proliferate during storage; most often in packed RBCs.
Signs and symptoms	Usually within a few minutes posttransfusion: delirium, fever, cold sweat, pain at injection site, chest or lumbar pain, nausea, vomiting, tachycardia, tachypnea, BP drop, shock, hemoglobinuria	Acute dyspnea, hypoxia, and respiratory failure usually within 6 h posttransfusion. Differential diagnosis should first exclude cardiogenic pulmonary edema.	Urticaria, bronchospasm, glottic edema, shock	Symptoms and course depend on the recipient's immune status, pretransfusion antibiotic therapy, type, number, and virulence of pathogens, among other factors; bacterial contamination is diagnosed if the same pathogen is present in the recipient's blood culture and culture of the remaining blood product.
Treatment	Stop transfusion; circulatory stabilization; prevention or treatment of acute renal failure; inform the blood transfusion laboratory and relevant blood bank.	Mainly symptomatic; passive oxygen therapy / mechanical ventilation	Antihistamine drugs; in severe cases, adrenaline administration, fluid replacement, and sometimes intubation may be required as in the management of shock.	Empiric use of broad--spectrum antibiotics until antibiogram is obtained, then targeted antibiotic therapy.
Sequelae	Acute renal failure, DIC, risk of death	Any case of respiratory failure should be reported to a relevant blood bank to perform testing; presence of anti-HLA or anti-HNA antibodies in a donor (usually female due to the risk of immunization in pregnancy) will exclude these individuals as donors.	Risk of death	Risk of death

Abbreviations: BP, blood pressure; DIC, disseminated intravascular coagulation; IgE, immunoglobulin E; IgM, immunoglobulin M; HLA, human leukocyte antigen; HNA, human neutrophil antigen; RBC, red blood cell

parameters such as APTT, thrombin time (TT), and PT makes it possible to assess if the drug is still present in a sufficient quantity to exert effects (APTT and TT for dabigatran; PT for rivaroxaban, apixaban, and edoxaban) and may indicate that the bleeding is not directly related to anticoagulant treatment. Hemostasis parameters should always be assessed relative to the period since the last dose administration because of rapid changes in plasma drug levels as well as a short half-life of NOACs. For a quantitative assessment of the anticoagulant effect of dabigatran, the following assays should be used: ecarin clotting time (expressed in seconds; it is 2- to 4-fold longer in patients on long-term dabigatran treatment, 150 mg/12 h) or diluted thrombin time (expressed in seconds or ng/ml) using HEMOCLOT®, which was approved in Europe as a test of choice for monitoring dabigatran concentrations.[56,57] For quantification of anticoagulant effects of factor Xa inhibitors, chromogenic anti-factor Xa assays are recommended. However, they are not widely available.

Of note, vitamin K, protamin, and FFP, which are used in VKA- and heparin-related bleeds, are ineffective in patients with bleeding due to NOACs.[58] The administration of antifibrinolytic drugs (eg, tranexamic acid, 1 g IV every 6 h as needed) or desmopressin (0.3 µg/kg bw IV infusion; maximal dose, 20 µg) may be considered, particularly in special situations in patients with coagulopathy or platelet disorders.[26]

Prothrombin complex concentrate, containing 4 (II, VII, IX, and X) or 3 (II, IX, and X) coagulation factors, was considered the best treatment option in major and life-threatening bleedings until a specific reversal agent for dabigatran has been approved for use in clinical practice. Administration of aPCC (Feiba®, Takeda, Tokyo, Japan) should be considered if readily available.

The recommended management of bleeding in dabigatran-treated patients changed after approval of a specific antidote for dabigatran, idarucizumab (Praxbind®, Boehringer Ingelheim, Ingelheim am Rhein, Germany), a human monoclonal antibody fragment with a rapid reversal effect on dabigatran.[59] Praxbind® is administered in 2 consecutive IV infusions (2 × 2.5 g/50 ml) lasting 5 to 10 minutes or 2 equal bolus doses. According to available studies, the drug may completely reverse anticoagulant effects of dabigatran within 5 minutes since administration.

In May 2018, the Food and Drug Administration approved andexanet alfa (Andexxa®, Portola, San Francisco, California, United States), a recombinant modified factor Xa protein with a serine to alanine mutation in the protease catalytic triad, with an indication as a reversal agent for direct factor Xa inhibitors.[60] In Europe, andexanet alfa, sold under the brand name Ondexxya, received a conditional approval by the European Medicines Agency in April 2019 for use as a reversal agent for rivaroxaban and apixaban in life-threatening bleeding. The drug is currently unavailable in Poland.

The decision on whether and when to restart anticoagulant treatment after a major bleeding event depends on the identification of the bleeding site and the type of therapy applied to control bleeding. Issues to consider include drug switching (in GI bleeding: from rivaroxaban or high--dose dabigatran to apixaban), dose reduction, or modification of concomitant therapy.[61]

Recommendations on the management of bleeding in patients treated with NOACs are summarized in TABLE 8.[62]

Bleeding during dual antiplatelet therapy with and without oral anticoagulation Patients with DAPT-related bleeding constitute a challenging population as there are no evidence-based guidelines from randomized clinical trials. The decision on interruption or continuation of DAPT depends largely on the risk of ischemia (eg, indications for DAPT use and time from the last stent implantation to a bleeding event) versus the risk of recurrent or prolonged bleeding. The practical guidelines for the management of these patients are summarized in TABLE 11. Since bleeding is an independent risk factor for recurrent bleeding, the type, dosage, and duration of DAPT should be reassessed.[63]

Bleeding during treatment with unfractionated heparin Patients with major bleeding during treatment with unfractionated heparin (UFH) should receive protamine sulphate at a dose of 1 mg IV per every 100 IU of UFH. If UFH is administered as an IV infusion, the dose of protamine sulphate should be administered to the number of IUs given in the last 3 hours. Protamine sulphate should be administered at a slow rate to avoid bradycardia or BP lowering. Its efficacy is assessed on the basis of reduction in APTT. Protamine sulphate is also used in patients treated with LMWH. The dose depends on the time elapsed since the administration of the last LMWH dose: 0.5 per 100 units of anti–factor Xa if 8 hours or less, and 1 mg per every 100 units of anti–factor Xa if more than 8 hours.[58]

Specialist consultations in patients with bleeding

Gastroenterology consultation Gastrointestinal bleeding is a life-threatening condition, with a mortality rate of 5% to 15%. In 80% of cases, the bleeding originates proximal to the ligament of Treitz (upper GI bleeding). The most common causes of this type of bleeding include peptic and duodenal ulcer disease (40%), gastroesophageal varices (10%–20%), esophagitis, Mallory–Weiss syndrome, and cancer. Lower GI bleeding is less common; it is associated with lower mortality rates (2%–4%) and its course is usually less severe. The most common causes of

lower GI bleeding are diverticulosis (up to 40% of cases), angiodysplasia, colitis of various etiologies, cancer, and anal disorders (eg, hemorrhoids, anal fissure). The annual incidence of life-threatening upper GI bleeding is 40 to 150 patients per 100 000 individuals.

The most common symptoms of upper GI bleeding include hematemesis (40%), melena, bright red blood per rectum, or blood mixed with stool. The symptoms depend on the source of bleeding and the GI transit time (fresh blood from the rectum may indicate upper GI bleeding). In acute massive bleeding with rapid blood loss, patients additionally present with a BP drop and tachycardia, followed by hypovolemic shock.

There are several scores available for the assessment of patients with upper GI bleeding. The Glasgow–Blatchford score is best for identification of patients requiring endoscopy (≥2 points) as well as those requiring hospitalization at the intensive care unit and blood product transfusion.

Pre-endoscopic management General guidelines for pre-endoscopic management are summarized below:

1 Administer IV PPI: an 80-mg bolus, then 8 mg/h.
2 Administration of tranexamic acid (Exacyl) or routine use of somatostatin or somatostatin analogues is not recommended.
3 30 to 120 minutes before endoscopy, administer erythromycin, 250 mg IV, to improve visibility during endoscopy.

Upper gastrointestinal bleeding Gastroscopy is the diagnostic test of choice in patients with symptoms of upper GI bleeding. It allows a precise identification of the bleeding source.[64] Endoscopy results should also guide the decision regarding endoscopic treatment. Patients hospitalized at the ICCU are at high risk of a severe course of GI hemorrhage. Therefore, gastroscopy within the first 24 hours since the onset of symptoms is recommended in these patients.[65] Gastroscopy within 12 hours since symptom onset should be considered in: 1) patients with hemodynamic instability despite intensive fluid resuscitation; 2) patients in whom discontinuation of anticoagulant treatment is associated with high risk of thrombotic complications; and 3) patients who develop symptoms of bleeding such as hematemesis or the presence of blood in the nasogastric tube during hospitalization.[66] Before endoscopy, appropriate fluid resuscitation and medical treatment should be applied (see above). Urgent gastroscopy, without previous patient preparation, worsens treatment outcomes. The current gold standard is combination endoscopic therapy with the use of at least 2 different endoscopic techniques to stop bleeding. In the case of GI bleeding recurrence, gastroscopy should be repeated. If permanent hemostasis cannot be obtained with endoscopic methods or if the bleeding recurs, standard angiography with embolization or surgical treatment is recommended. The decision on treatment modality in this case should be guided by the center's experience and available facilities.

The need for endoscopic therapy is determined by the proper assessment of the bleeding source. Patients with gastroesophageal reflux disease, gastritis, or duodenitis, including erosive inflammation, do not usually require endoscopic treatment. In these patients, high-dose PPIs are recommended.

In the case of gastric ulcer bleeding, the choice of endoscopic therapy depends on the severity of bleeding according to the Forrest classification (nonvariceal upper GI bleeding). Bleeding is treated with injection, mechanical, and thermal methods. If hemostasis cannot be achieved, a rescue therapy can be applied, using hemostatic spray, endoscopic clip (Ovesco), or angiography with embolization. Bleeding from angiodysplasias also requires endoscopic treatment.

For the treatment of variceal bleeding, endoscopic variceal ligation or variceal sclerotherapy is used, while for gastric variceal bleeding, endoscopic injection of tissue glue is applied. Additionally, IV vasopressin / somatostatin analogues should be administered, along with prophylactic antibiotic therapy (norfloxacin) to prevent spontaneous bacterial peritonitis.

Postendoscopic management All patients with gastric ulcer bleeding should be tested for *Helicobacter pylori* infection, and if needed, *H. pylori* eradication therapy should be applied and its efficacy confirmed. In DAPT-treated patients, chronic PPI use is recommended. Warfarin treatment should be restarted between days 7 and 15 after a bleeding event, or earlier if the thrombotic risk is high.

Lower gastrointestinal bleeding In patients with symptoms of lower GI bleeding, the diagnostic test of choice is colonoscopy.[67] Bloody stools may result from massive upper GI bleeding and a rapid passage of blood through the GI tract. Therefore, before preparation for colonoscopy, it is necessary to exclude upper GI bleeding, which may be present if there are signs of hemodynamic instability. In such a case, before colonoscopy, patients should undergo gastroscopy, while assessment of the nasogastric tube contents has a lower diagnostic value. During colonoscopy, endoscopic methods to achieve hemostasis can be applied. In patients in severe general condition, with symptoms of hemodynamic instability, the use of bowel cleansing solution for colonoscopy preparation is problematic. Therefore, in these patients, identification of the bleeding source is possible with imaging studies such as CT angiography, standard angiography, and

TABLE 11 Practical guidelines on the management of bleeding in patients on dual antiplatelet therapy with or without oral anticoagulation (modified from Valgimigli et al)[63]

Minor bleeding	Mild bleeding	Moderate bleeding	Major bleeding	Life-threatening bleeding
Any bleeding that is not actionable and does not require medical intervention or further evaluation (approx. BARC type 1)	Any bleeding that requires medical intervention but does not require hospitalization (approx. BARC type 2)	Any overt bleeding with a hemoglobin drop >3 g/dl and/or requiring hospitalization, but with hemodynamic stability and without progression to severe bleeding (approx. BARC type 3a)	Any bleeding requiring hospitalization and with large-volume blood loss (hemoglobin drop >5 g/dl) but with hemodynamic stability and without progression to severe bleeding (approx. BARC type 3b)	Any severe active bleeding that is life threatening to the patient (approx. BARC type 3c)
• Continue DAPT. • Consider continuation of OAC or omit the next single dose.	• Continue DAPT. • Consider shorter DAPT or switching to a less potent $P2Y_{12}$ inhibitor (ie, ticagrelor/prasugrel to clopidogrel), especially in recurrent bleeding. • Consider switching TAT to DAPT, preferably with clopidogrel and OAC. • Identify comorbidities related to bleeding and apply treatment if possible (eg, peptic ulcers, hemorrhoids, cancer). • Add a PPI if not administered earlier.	• Consider discontinuation of DAPT and continue SAPT, preferably with $P2Y_{12}$ inhibitor, especially in upper GI bleeding. • Restart DAPT as soon as it seems safe to do so. • Consider shorter DAPT or switching to a less potent $P2Y_{12}$ inhibitor (ie, ticagrelor/prasugrel to clopidogrel), especially in recurrent bleeding. • Consider discontinuation of OAC or even reversal of anticoagulant effect until bleeding control is achieved unless the patient is at high thrombotic risk (ie, mechanical heart valves, ventricular assist devices, CHA_2DS_2-VASc ≥4). • Restart treatment within 1 week if clinically indicated. In the case of VKA, consider target INR of 2–2.5 unless specific indications are present (ie, mechanical heart valves or ventricular assist devices). In the case of NOAC, consider the use of the lowest effective dose. • In the case of TAT, consider switching to DAPT, preferably with clopidogrel and OAC. • In the case of DAPT, consider discontinuation of antiplatelet treatment, if deemed safe for the patient. • Consider the use of IV PPI in the case of GI bleeding. • Identify comorbidities related to bleeding and apply treatment if possible (eg, peptic ulcers, hemorrhoids, cancer).	• Consider discontinuation of DAPT and continue SAPT, preferably with $P2Y_{12}$ inhibitor, especially in upper GI bleeding. • If bleeding persists despite treatment or if treatment is not possible, consider discontinuation of any antiplatelet and anticoagulant drug. • On achieving bleeding control, consider restarting DAPT or SAPT, preferably with $P2Y_{12}$ inhibitor, especially in upper GI bleeding. • In restarting DAPT, consider shorter therapy duration or switching to a less potent $P2Y_{12}$ inhibitor (ie, ticagrelor/prasugrel to clopidogrel), especially in recurrent bleeding. • Consider discontinuation of OAC and reversal of anticoagulant effect until bleeding control is achieved unless the patient is at high thrombotic risk (ie, mechanical heart valves, ventricular assist devices). • Restart treatment within 1 week if clinically indicated. In the case of VKA, consider target INR of 2–2.5 unless specific indications are present (ie, mechanical heart valves or ventricular assist devices). In the case of NOAC, consider the use of the lowest effective dose. • In the case of TAT, consider switching to DAPT, preferably with clopidogrel and OAC. In the case of DAPT, consider discontinuation of antiplatelet treatment, if deemed safe for the patient. • Consider the use of IV PPI in the case of GI bleeding. • RBC transfusion if hemoglobin <7–8 g/dl. • Consider platelet transfusion. • If possible, apply urgent surgical or endoscopic treatment of the bleeding site.	• Promptly discontinue any antiplatelet or anticoagulant drugs. • On achieving bleeding control, assess indications for restarting DAPT or SAPT, preferably with $P2Y_{12}$ inhibitor, especially in upper GI bleeding. • Discontinue OAC and use an antidote to reverse anticoagulant effects. • Apply fluid therapy in patients with hypotension. • Consider RBC transfusion irrespective of hemoglobin values. • Apply platelet transfusion. • Consider the use of IV PPI in the case of GI bleeding. • If possible, apply urgent surgical or endoscopic treatment of the bleeding site.

Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex; DAPT, dual antiplatelet therapy; GI, gastrointestinal; INR, international normalized ratio; IV, intravenous; NOAC, non–vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; PPI, proton-pump inhibitor; RBC, red blood cell; SAPT, single antiplatelet therapy; TAT, triple antithrombotic therapy; VKA, vitamin K antagonist

technetium-99m scintigraphy. During angiography, bleeding can be stopped using embolization. If the above methods are ineffective, surgical treatment should be considered.

Small-bowel bleeding Gastrointestinal bleeding in patients without an identifiable source of bleeding in the upper and lower GI tract is an indication for evaluation of the small bowel. Patients with hemodynamic instability and symptoms of massive GI bleeding should undergo urgent angiography.[68] In hemodynamically stable patients, angiography may be preceded by multidetector CT angiography. Its use may facilitate the identification of a bleeding source during standard angiography. In the remaining patients suspected for small-bowel bleeding, the diagnostic test of choice is video capsule endoscopy (VCE).[69] If the source of bleeding is confirmed on VCE, enteroscopy with endoscopic treatment should be applied. In patients in whom the bleeding source is not identified with VCE, CT enterography should be performed. This test can be used as an alternative to VCE also in patients with inflammatory bowel diseases, after radiotherapy or small bowel surgery, and in patients with suspicion of small bowel stenosis.

Intra-abdominal bleeding In patients with suspicion of intra-abdominal bleeding, dynamic CT of the abdomen is the diagnostic test of choice. However, it is contraindicated in patients with poor or rapidly worsening general condition. In these patients, bedside ultrasound of the abdomen may be used as an alternative.[70]

Surgical consultation **Local hematoma** The incidence of large hematomas (>10 cm in diameter) after femoral arterial puncture is about 2%. Noninvasive treatment is typically used. The recommended management involves regular monitoring of the puncture site, monitoring of the hemodynamic status, as well as regular assessment of hemoglobin and hematocrit levels, with potential evaluation of indications for RBC transfusion.

Retroperitoneal hematoma Retroperitoneal hematoma presents with few or minor symptoms and is known as a "silent killer." It is associated with high in-hospital mortality. In most cases, noninvasive treatment with close patient monitoring is applied. Invasive management, including stent graft implantation and surgical treatment, is indicated in patients with hemodynamic instability, reduced hematocrit despite previous blood product transfusion, or symptoms of femoral nerve compression.

Femoral artery pseudoaneurysm The treatment of femoral artery pseudoaneurysm includes procedures aiming at aneurysm closure. The most common techniques include manual compression, prolonged compression, ultrasound-guided compression repair, and ultrasound-guided percutaneous thrombin injection. Thrombin injection has immediate coagulation effects. Therefore, it should not be administered in the presence of a wide and short aneurysmal neck as well as a small aneurysmal lumen due to the risk of embolic complications.

Rare methods include administration of normal saline or collagen infusion as well as endovascular treatment (endovascular stent graft/coil implantation).

In rare cases, surgical repair of femoral artery pseudoaneurysm is required.

Arteriovenous fistula In most cases of small arteriovenous fistulas, noninvasive treatment is applied. As fistulas tend to grow, an ultrasound follow-up for at least 6 months is mandatory. About 40% of asymptomatic fistulas resolve spontaneously within 1 year.

Of note, a fistula should generally not be left untreated for a long time because it may cause venous valve dysfunction leading to venous insufficiency with painful leg edema. In rare cases, arteriovenous fistulas may cause hemodynamic disorders, and consequently, congestive heart failure.

The methods used for arteriovenous fistula closure include prolonged compression, ultrasound-guided compression, surgical repair, and percutaneous stent graft implantation.

Gynecologist consultation Abnormal uterine bleeding is present in 8% to 27% of women in the reproductive age and in about 10% of postmenopausal women. According to the classification proposed by the International Federation of Obstetricians and Gynecologists, the causes of abnormal uterine bleeding in women in the reproductive years are categorized as related or not related to anatomical abnormalities, using the PALM-COEIN acronym (Polyp, Adenomyosis, Leiomyoma, Malignacy and hyperplasia – Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not otherwise classified).

After the menopause, the most common causes of uterine bleeding are endometrial polyps, cancer, hyperplasia, and endometrial atrophy. The risk of endometrial cancer in women with postmenopausal bleeding is about 10%.[71]

In women in the reproductive age who take antiplatelet and/or anticoagulant drugs, intra-abdominal bleeding from the corpus luteum or a corpus luteum cyst may develop after ovulation. Symptoms include peritoneal irritation, hypovolemia, anemia, as well as intra-abdominal free fluid and/or ovarian tumor on ultrasound, but without uterine bleeding.[72]

Diagnostic workup In women in the reproductive age, the plasma or urinary levels of human chorionic gonadotropin β should be assessed to exclude pregnancy. The recommendations presented below apply to nonpregnant women.

The diagnostic workup of uterine bleeding includes abdominal examination to exclude symptoms of severe peritoneal irritation, followed by speculum and bimanual examinations. Uterine ultrasound is also recommended (intravaginal or, if unavailable, abdominal). The aim of the examination is to identify the source of bleeding (vulva, vagina, cervix, uterine cavity, appendages). If no signs of active or recent bleeding due to gynecologic causes are observed, other sources should be considered, such as the lower GI or urinary tract.

Management of intrauterine bleeding Medical treatment is the first-line therapeutic option in patients with intrauterine bleeding. The use of misoprostol (prostaglandin E1 analogue) at a dose of 0.2 mg per rectum 3 times a day is allowed for uterine contraction and reducing uterine blood flow. Contraindications to this treatment include, for example, asthma and glaucoma.[73]

Data on the safety of using tranexamic acid as well as estrogen and progesterone derivatives in women treated with novel anticoagulant and antiplatelet drugs are lacking. Because of thrombotic risk, they may be used only in special situations if other treatments are unavailable.

Invasive treatment includes intrauterine balloon tamponade using a Foley 26F catheter inflated with 30 ml of normal saline. Second-line treatment, particularly in patients with thickened endometrium on ultrasound, is dilation and curettage.[71]

Cases of using endometrial ablation and uterine artery embolization have also been reported. These methods have shown high efficacy in controlling intrauterine bleeding, but endometrial ablation requires access to appropriate equipment, while embolization, availability of interventional radiology services.[74]

In the case of bleeding associated with advanced malignancy, the most effective, and often the only possible, treatment is uterine artery embolization.

If bleeding persists despite treatment, including titration of antiplatelet or anticoagulant drugs, hysterectomy is required and may be performed in the absence of contraindications such as poor hemodynamic status or coagulation disorders.

Bleeding from vaginal lesions or the vaginal portion of the cervix If vaginal lesions are not due to trauma and do not require surgical management, the use of hemostatic dressing to stop the bleeding is recommended (eg, gelatin, oxidized cellulose, or collagen), followed by vaginal tamponade with sterile gauze for 24 hours.

Management after cardiovascular stabilization If abnormal uterine bleeding occurs, further gynecologic workup is needed to exclude malignancy.

For long-term prevention of abnormal uterine bleeding in patients on antiplatelet and anticoagulant treatment, the first-line treatment in reproductive-aged women is the use of levonorgestrel-releasing intrauterine system, and in women who are planning pregnancy, endometrial ablation. If intrauterine lesions are present, endoscopic resection should be performed.

Neurologic consultation Intracranial bleeding, including intracerebral hemorrhage, subdural and epidural hematomas, and subarachnoid hemorrhage, is associated with high mortality. A 30-day mortality rate is estimated at 25% to 52%, with half of cases occurring within the first 2 days after a bleeding event. Intracranial bleeds may occur in patients with vascular malformations, hypertension, cerebral small vessel disease, infective endocarditis, venous thrombosis (particularly affecting the cortical veins), and cerebral amyloid angiopathy. They may also occur in patients after trauma as well as in smokers or those with alcohol abuse, or as a complication of antiplatelet and anticoagulant treatment. The annual risk of bleeding in patients with arteriovenous malformations varies from about 2% to 4% for arteriovenous malformations to 6% to 9% for hemangiomas (which are present in about 0.5% of the population). Aneurysm rupture leads not only to subarachnoid hemorrhage, but in 25% to 33% of cases, it also causes intracerebral hemorrhage, which constitutes 15% of all intracranial bleeds in young individuals.

Signs and symptoms The diagnosis of intracranial bleeding is based primarily on physical examination, including meningeal signs and symptoms, signs of increased intracranial pressure, as well as focal neurologic damage. Brain imaging is mandatory, including CT or magnetic resonance imaging. Subarachnoid hemorrhage, subdural hematoma, or bleeding that results in increased intracranial pressure may initially present with nonspecific symptoms such as headache, nausea, vomiting, blurred vision (due to papilledema), loss of consciousness, seizures, or meningeal symptoms. Focal neurologic deficits, typical for intracerebral bleeds, depend on the site and extent of bleeding. Symptoms of cranial nerve damage are also common, including facial nerve palsy with drooping mouth corner, oculomotor nerve palsy with dilated pupil unresponsive to light, ocular motility disorders due to damage of other cranial nerves (eg, related to increased intracranial pressure or brain stem

damage), as well as speech disorders, hemiparesis, ataxia, and horizontal nystagmus due to cerebellar damage. Symptoms of nervous system irritation, such as seizures, are also seen. Intracranial hemorrhage may be associated with sudden worsening of neurologic status due to increasing volume of the hemorrhage, brain edema, or hydrocephalus, all of which lead to increased intracranial pressure.

Diagnostic workup Patients with intracranial hemorrhage should undergo routine laboratory tests, including coagulation parameters, at the ICCU. In patients with a clinical suspicion of intracranial hemorrhage, urgent diagnostic imaging should be performed. Non–contrast-enhanced CT is the standard imaging test with high sensitivity and specificity for diagnosing intracranial hemorrhage. Computed tomography scans are examined to identify the site of bleeding, assess its severity and volume, as well as detect the mass effect, blood in the ventricular system, or signs of brain displacement. As the patient's condition can worsen in the first few hours since the onset of bleeding, CT is preferred over the longer brain magnetic resonance imaging. On the other hand, brain magnetic resonance imaging is more common for further extended diagnostic workup of bleeding in the course of brain amyloid angiopathy, hemangiomas, or intratumoral hemorrhage.

Noninvasive treatment Diagnosis of intracranial hemorrhage should prompt discontinuation of anticoagulant and antiplatelet therapy. Patients treated with antithrombotic drugs and UFH should be administered an antidote to reverse their effect. Increased intracranial pressure is seen in the acute phase of intracranial hemorrhage, both in patients with and without hypertension. In patients with a history of hypertension, antihypertensive treatment is indicated if systolic and diastolic BP exceeds 180 mm Hg and 105 mm Hg, respectively, aiming at a mean arterial pressure of 125 mm Hg. In patients without a history of hypertension, the treatment should be administered at a systolic BP of more than 160 mm Hg and diastolic BP of 95 mm Hg or higher, with the target mean arterial pressure of 110 mm Hg. Blood pressure should not be reduced by more than 20% of the baseline value within the first 24 hours after the bleeding event.

Hyperglycemia in hemorrhagic stroke is associated with worse prognosis and should be managed with insulin therapy if the glucose level exceeds 185 mg/dl to achieve the target values of 140 to 180 mg/dl. Hypoglycemia should be avoided. Increased intracranial pressure due to intracranial hemorrhage can be reduced by a higher head position, hyperventilation, and the use of hypertonic solution or mannitol. Hyperventilation results in the reduction of $PaCO_2$ concentrations, which causes cerebral vasoconstriction. However, the effect is transient and lasts only several hours. Data from studies on traumatic intracranial hemorrhage suggest that hypertonic solution is more effective than mannitol.

Subarachnoid and subdural hematomas require an urgent neurosurgical evaluation. Noninvasive treatment of acute subdural hematomas may be limited to patients in stable condition and with small hematomas (<10 mm in diameter), but also to patients with coma without clinical or radiological signs of brain herniation or increased intracranial pressure. Patients should be carefully monitored, and a control CT scan should be performed about 6 to 8 hours after the initial evaluation. Hemorrhage progression or edema should prompt another neurosurgical consultation. Importantly, a decline in cognitive function and the level of consciousness in these patients may occur even a few weeks after the index event. Noninvasive treatment is aimed at reduction of intracranial pressure. The use of steroids is not recommended because it is associated with higher mortality. In patients on anticoagulant treatment, the decision to restore hemostasis should be made by carefully balancing the thromboembolic risk against further bleeding. In subarachnoid hemorrhage without indications for neurosurgical management, the triple-H therapy is applied (hypertension, hypervolemia, and hemodilution) to prevent delayed cerebral ischemia due to cerebral vasospasm. Nimodipine, administered at a dose of 60 mg every 4 hours for 3 weeks, is the only calcium channel blocker that significantly reduces the risk of mortality and disability.

Intracranial bleeding is often accompanied by seizures; they are observed in about 16% of patients with intracerebral hemorrhage. The course of seizures may be asymptomatic. They are diagnosed on the basis of electroencephalographic abnormalities with impairment of consciousness. Both clinically overt and subclinical seizures require treatment. However, there are no indications for the use of antiepileptic drugs as prevention of seizures in any type of intracranial bleeding.

Surgical treatment The decision on surgery is at the discretion of a neurosurgeon after consulting a neurologist and if approved by a cardiologist. Surgery for intracranial hemorrhage may be considered in the following cases:

1 In patients with indications for urgent surgery, including intracerebellar hemorrhage exceeding >3 cm in diameter, worsening neurologic status, signs and symptoms of brain stem compression and/or internal hydrocephalus due to blockage of cerebrospinal fluid outflow in the brain.

2 In supratentorial hemorrhage; however, there are no clear indications for surgical management and the decision should be based on the individual needs and assessment of prognosis. There are limited data indicating that surgical treatment reduces mortality in patients with life-threatening conditions, coma, a large hemorrhagic focus, herniation, and increased intracranial pressure that is unresponsive to medical treatment.

3 In acute subdural and epidural hematomas, depending on hematoma volume and thickness as well as a patient's clinical condition. The presence of anisocoria on clinical examination indicates oculomotor nerve palsy due to brain herniation.

In the presence of indications for surgical treatment, prior assessment and normalization of blood coagulation parameters is required.

In the surgical treatment of aneurysms and other arteriovenous malformations, which are a relatively rare cause of intracranial hemorrhage in the ICCU setting, the diagnostic workup should be performed in consultation with a neurologist and neurosurgeon.[75]

Predictors of poor prognosis Independent predictors of 30-day mortality in patients with intracerebral hemorrhage include the low level of consciousness according to the Glasgow Coma Scale, age older than 80 years, infratentorial hemorrhage (ie, brain stem and cerebellar), hematoma volume, and intraventricular bleeding.

Urologic consultation The prevalence of microhematuria among patients receiving anticoagulant therapy is about 2%, which is much more frequent than in patients not receiving anticoagulation (0.5%–0.7%). Microhematuria is associated with the need for medical attention, with patients presenting to the emergency department as well as undergoing hospitalization and urologic procedures.[76] It has been shown that patients taking anticoagulant drugs are more likely to develop microhematuria than those receiving antiplatelet treatment. Warfarin is associated with the highest risk of microhematuria, while dabigatran, with a higher risk of gross hematuria than clopidogrel or aspirin.[77] Of note, almost 50% of patients with hematuria during anticoagulant treatment show urinary tract disorders. About 19% to 25% of these individuals present with different types of cancer,[77,78] the most common being bladder cancer.[79]

According to a consultant urologist at the Institute of Cardiology in Warsaw, Poland, almost half of the consultations are due to hematuria.

Diagnosis of hematuria In a patient with urinary catheter, hematuria is diagnosed by visual examination of urine in the catheter bag. The color of urine indicates the presence of blood and allows an assessment of the severity of hematuria (TABLE 12).

Hematuria in patients without urinary catheter is usually reported by patients themselves. In such cases, uroscopy (visual examination) of a urinary sample should be ordered. The assessment is the same as above (TABLE 12).

Acute management Depending on the severity of hematuria, urinary catheterization is recommended to ensure the patency of the urinary tract and to monitor the patient for the presence and severity of hematuria. In patients with more severe hematuria, the use of a triple-lumen catheter is recommended to allow for continuous bladder infusion with normal saline (mean regulated rate of 1 drop/s). Administration of an IV diuretic and increased fluid intake (if possible) are recommended, along with continuous monitoring of the patient's general condition and regular laboratory tests, particularly complete blood count.

From the clinical perspective, it is important to differentiate between hematuria requiring urologic workup and urinary tract bleeding that may pose an immediate threat to the health and life of a patient and therefore requires urgent medical intervention.

Imaging diagnostic workup Acute management should be followed by a diagnostic workup of hematuria, such as physical examination (including rectal examination), abdominal ultrasonography (including full bladder ultrasound), and contrast-enhanced CT of the abdomen and small pelvis (with inclusion of the urographic phase, which is not always routinely ordered by cardiac units). The differential diagnosis should include the most common urinary tract disorders associated with hematuria, such as urinary tract infection, bladder cancer, upper urinary tract urothelial carcinoma, kidney cancer, prostate cancer, benign prostatic hyperplasia, kidney stone disease, arteriovenous fistula, and others.

Anemia that requires blood transfusion or is life threatening (or both) is an absolute indication for a urologic intervention. According to the 2018 European Association of Urology guidelines, prior to a urologic intervention, procedural bleeding risk should be assessed:

1 no bleeding risk: compression dressings, embolization, radiotherapy, and others;

2 low bleeding risk: rigid and flexible cystoscopy, urethroscopy, urinary catheterization, catheter removal, ureteroscopy, and ureterorenoscopy;

3 high bleeding risk: percutaneous nephrectomy, percutaneous cystostomy, open surgeries, laparoscopic surgeries, extracorporeal shockwave lithotripsy, percutaneous nephrolithotomy.

TABLE 12 Acute management of hematuria according to diagnosis by visual examination of urine

Urine color	Bleeding	Type of intervention	Management
Yellow	None	None	None
Tea-colored (due to hematin)	Minor	Monitoring	Complete blood count monitoring
Pink	Minor	Monitoring	Complete blood count monitoring
Dark red	Significant	Bladder irrigation	Expedited
Bright red	Severe	Bladder irrigation / advanced urologic intervention	Urgent
Red with clots	Potentially very severe	Bladder irrigation / advanced urologic intervention	Immediate
Fresh blood in the urine bag	Very severe	Advanced urologic intervention	Immediate

This approach is aimed at facilitating the decision making in difficult cases by excluding (if possible) urologic procedures that are associated with high bleeding risk and choosing lower-risk interventions. According to the National Consultant in Urology, the urologist must take active action to control life-threatening bleeding by surgical methods, even in cases when blood coagulation is significantly impaired due to iatrogenic causes. A urologic intervention usually involves endoscopic examination of the bladder under local or general anesthesia with coagulation / fulguration of bleeding sites in the bladder and prostatic urethra. In patients with renal bleeding, acute management involves renal artery embolization. In extreme cases, surgical treatment with careful local hemostatic control should be applied (eg, local hemostasis with surgical tamponade during nephrectomy). However, such an approach may save a patient's life and result in a considerable improvement of clinical condition.

Summary Bleeding is a relatively common complication in patients hospitalized at the ICCU, and it is associated with poor prognosis. In the era of novel potent antiplatelet and anticoagulant drugs, treatment of increasingly older patients with various comorbidities constitutes a considerable challenge to cardiologists and other specialists. The aim of this paper was to discuss this extensive and interdisciplinary issue, along with systematizing and presenting the most important practical guidelines. We are aware of the limitations of these recommendations, including the lack of a detailed presentation of all the relevant aspects. However, a more exhaustive discussion of this topic would require a book of its own. As there are ongoing advances in the field of cardiology and other specialties dealing with patients with bleeding, new updated editions of these guidelines will be regularly published.

SUPPLEMENTARY MATERIAL

The Polish version of the paper is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST MG received consultation fees from Astra Zeneca, Balton, Bayer and lecture fees from Balton, Bayer, Boehringer Ingelheim, Bracco Acist, and Servier. AT received lecture fees from Astra Zeneca, Bayer, Krka, Orion Pharma, and Servier. RZ received lecture and research fees from Bayer and Novartis. MB received fees from Bayer and Sanofi. KJF received fees from Adamed, Bayer, Boehringer Ingelheim, MSD, and Pfizer. AM received fees from Bayer, Boehringer Ingelheim, Pfizer. FMS received fees from Adamed, Bayer, Boehringer Ingelheim, MSD, Pfizer. BW-K received fees from Bayer, Boehringer Ingelheim, Pfizer. WB received consultation, lecture, and research fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Bayer, BMS, and Gedeon Richter. BM received consultation fees from Baxter, Shire, NovoNordisk, and Roche. WM received fees from Abott, Adamed, Astra Zeneca, Bayer, and Medtronic. AT-K received lecture fees and research grants from Boehringer Ingelheim, Bayer, Servier, Novartis, and Krka. JS received consultation and lecture fees from Astra Zeneca, Bayer, Boehringer Ingelheim, and Pfizer and research grants from Sanofi. The remaining authors declare no conflict of interest.

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