EJA

Eur J Anaesthesiol 2017; **34:**332–395

GUIDELINES

Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology

First update 2016

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The management of perioperative bleeding involves multiple assessments and strategies to ensure appropriate patient care. Initially, it is important to identify those patients with an increased risk of perioperative bleeding. Next, strategies should be employed to correct preoperative anaemia and to stabilise macrocirculation and microcirculation to optimise the patient's tolerance to bleeding. Finally, targeted interventions should be used to reduce intraoperative and postoperative bleeding, and so prevent subsequent morbidity and mortality. The objective of these updated guidelines is to provide healthcare professionals with an overview of the most recent evidence to help ensure improved clinical management of patients. For this update, electronic databases were searched without language restrictions from 2011 or 2012 (depending on the search) until 2015. These searches produced 18 334 articles. All articles were assessed and the existing 2013 guidelines were revised to take account of new evidence. This update includes revisions to existing recommendations with respect to the wording, or changes in the grade of recommendation, and also the addition of new recommendations. The final draft guideline was posted on the European Society of Anaesthesiology website for four weeks for review. All comments were collated and the guidelines were amended as appropriate. This publication reflects the output of this work.

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DOI:10.1097/EJA.0000000000000630

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1. Summary: recommendations, suggestions and statements

Grade of recommendation shown in bold type (Table 1)

1.1. Evaluation of coagulation status

Before surgery or invasive procedures, we recommend the use of a structured patient interview or standardised questionnaire which considers clinical and family bleeding history and detailed information on the patient's medication. **1C**

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as activated partial thromboplastin time (aPTT), international normalised ratio (INR) and platelet count in elective surgery. **1C**

We recommend the application of intervention algorithms incorporating pre-defined triggers and targets based on viscoelastic haemostatic assay (VHA) coagulation monitoring to guide individualised haemostatic intervention in the case of perioperative bleeding. **1C**

If VHA is not available we recommend the application of intervention algorithms incorporating pre-defined triggers based on conventional coagulation tests. **1C**

1.1.1. Evaluation of platelet function

We suggest preoperative platelet function testing only in association with a positive bleeding history. **2B**

We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions or antiplatelet medication. **2B**

Bleeding time is influenced by many variables and is not useful for stratifying bleeding risk. **C**

1.2. Preoperative and postoperative correction of anaemia

Preoperative anaemia in adults and children appears to be a strong predictor for perioperative blood transfusion across various types of conditions and surgeries and may be associated with adverse events. **B**

We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. **1C**

If anaemia is present, we recommend identifying the cause (iron deficiency, renal insufficiency or inflammation). **1C**

We recommend treating iron deficiency with iron supplementation. **1B**

We recommend the use of intravenous iron in preference to oral iron. **1C**

Table 1 Grades of recommendation – Grading of Recommendations Assessment, Development and Evaluation system

	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation. High-quality evidence.	Benefits clearly outweigh risk and burdens, or vice versa.	Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Strong recommendation, can apply to most patients in most circumstances without reservation.
1B Strong recommendation. Moderate-quality evidence.	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation, likely to apply to most patients.
1C Strong recommendation. Low-quality evidence.	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.	Relatively strong recommendation; might change when higher quality evidence becomes available.
2A Weak recommendation. High-quality evidence.	Benefits closely balanced with risks and burdens.	Consistent evidence from well performed, randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values.
2B Weak recommendation. Moderate-quality evidence.	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.
2C Weak recommendation. Low-quality evidence.	Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.

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If other causes of anaemia have been excluded or treated, we suggest erythropoietin-stimulating agents. **2B**

If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. **2C**

In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. **1C**

In non-cancer patients with preoperative anaemia scheduled for elective major surgery, we recommend postponing surgery until anaemia has been corrected. **1C**

In patients who are anaemic following surgery, we suggest the use of intravenous iron. **2C**

1.3. Optimising circulation

We recommend aggressive and timely stabilisation of cardiac pre-load throughout the surgical procedure, as this appears beneficial to the patient. **1B**

In cases of uncontrolled bleeding we suggest lower thresholds for cardiac pre-load and/or permissive hypotension may be considered. **2C**

We recommend the avoidance of hypervolaemia secondary to crystalloids or colloids to a level exceeding the interstitial space in steady state, and beyond an optimal cardiac pre-load. **1B**

We recommend against the use of central venous pressure (CVP) and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimisation of pre-load during severe bleeding. Dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead. **1B**

We suggest the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol-based manner. **2C**

Compared with crystalloids, haemodynamic stabilisation with iso-oncotic colloids, such as human albumin and hydroxyethyl starch, causes less tissue oedema. **C**

Infusion of colloids in patients with severe bleeding can aggravate dilutional coagulopathy by additional effects on fibrin polymerisation and platelet aggregation. **C**

We suggest the use of balanced solutions for crystalloids and as a basic solute for iso-oncotic preparations. **2C**

1.3.1. Transfusion triggers

We recommend a target haemoglobin concentration of 7 to 9 g dl^{-1} during active bleeding. **1C**

Continuous haemoglobin monitoring can be used as a trend monitor. **C**

1.4. Oxygen fraction

We recommend that the inspiratory oxygen fraction should be high enough to prevent arterial hypoxaemia in bleeding patients, while avoiding excessive hyperoxia [PaO_2 >26.7 kPa (200 mmHg)]. **1C**

1.5. Monitoring tissue perfusion

We recommend repeated measurements of a combination of haematocrit (Hct)/haemoglobin, serum lactate, and base deficit to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. These parameters can be extended by measurement of cardiac output, dynamic parameters of volume status [e.g. stroke volume variation (SVV), pulse pressure variation (PPV)], CO_2 gap and central venous oxygen saturation. **1C**

1.5.1. Normovolaemic haemodilution

We suggest the use of acute normovolaemic haemodilution (ANH) in selected settings. **2C**

We recommend against ANH in combination with controlled hypotension. **1B**

In patients with pre-existing or acquired coagulopathy we suggest that the use of ANH is considered carefully. **2C**

1.6. Transfusion of labile blood products

We recommend that all countries implement national haemovigilance quality systems. **1B**

We recommend a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products. **1A**

We recommend pathogen inactivation for fresh frozen plasma (FFP) and platelets. **1C**

We recommend that labile blood components used for transfusion are leukodepleted. **1B**

We recommend that blood services implement standard operating procedures for patient identification and that staff be trained in early recognition of, and prompt response to, transfusion reactions. **1C**

We recommend a male-only donor policy for plasma-containing blood products to prevent the onset of transfusion-related acute lung injury (TRALI). **1C**

We recommend that all red blood cell (RBC), platelet and leukocyte donations from first-degree or second-degree relatives be irradiated even if the recipient is immunocompetent, and all RBC, platelet and leukocyte products be irradiated before transfusing to at-risk patients. **1C**

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections. **B**

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1.6.1. Storage lesions

We recommend that RBCs should be transfused according to the first-in, first-out method in the blood services to minimise wastage of erythrocytes. **1A**

1.6.2. Cell salvage

We recommend the use of red cell salvage which is helpful for blood conservation in major cardiac and orthopaedic surgery. **1B**

We recommend against the routine use of intraoperative platelet-rich plasmapheresis for blood conservation during cardiac operations using cardiopulmonary bypass (CPB). **1B**

We recommend that cell salvage is not contraindicated in bowel surgery, provided that the initial evacuation of soiled abdominal contents is undertaken, additional cell washing is performed and broad-spectrum antibiotics are used. **1C**

We suggest that cell salvage is not contraindicated in cancer surgery, provided that blood aspiration close to the tumour site is avoided and leukodepletion filters are used. **2C**

1.6.3. Plasma and platelet transfusion

We recommend against the use of plasma transfusion for pre-procedural correction of mild-to-moderately elevated INR. **1C**

We recommend early and targeted treatment of coagulation factor deficiencies in the plasma. Sources of coagulation factors are coagulation factor concentrates, cryoprecipitate or high volumes of plasma, depending on the clinical situation, type of bleeding, type of deficiency and resources provided. **1B**

In the treatment of acquired coagulation factor deficiency, we suggest the consideration of a ratio-driven protocol (RBC : plasma : platelet concentrates) early in uncontrolled massive bleeding outside the trauma setting followed by a goal-directed approach as soon as possible. **2C**

We suggest coagulation factor concentrates for the primary treatment of acquired coagulation factor deficiency due to their high efficacy and their minimal infectiousness. **2C**

We recommend against indiscriminate use of plasma transfusion in perioperative bleeding management. **1C**

We suggest platelet concentrate transfusion in bleeding situations clearly related to antiplatelet drugs or thrombocytopaenia less than $50 \times 10^9\ l^{-1}$. **2C**

1.7. General coagulation management

Fibrinogen concentration of less than 1.5 to $2\ g\ l^{-1}$ is considered as hypofibrinogenaemia in acquired coagulopathy and is associated with increased bleeding risk. **C**

We recommend treatment of hypofibrinogenaemia in bleeding patients. **1C**

We suggest an initial fibrinogen concentrate dose of 25 to $50\ mg\ kg^{-1}$. **2C**

In cases wherein fibrinogen concentrate is not available we suggest cryoprecipitate at an initial dose of 4 to 6 ml kg^{-1}. **2C**

Plasma transfusion alone is not sufficient to correct hypofibrinogenaemia. **C**

In cases of bleeding and low factor XIII activity (e.g. <30%) we suggest administration of factor XIII concentrate (30 IU kg^{-1}). **2C**

In severe perioperative bleeding we recommend that patients on vitamin K antagonists (VKAs) should be given prothrombin complex concentrate (PCC) and intravenous vitamin K before any other coagulation management steps. **1B**

Prolonged INR/prothrombin time (PT) or VHA clotting times alone are not an indication for PCC in bleeding patients not on oral anticoagulant therapy. **C**

We recommend against the prophylactic use of recombinant activated factor VII (rFVIIa) due to increased risk of fatal thrombosis. **1B**

We suggest that off-label administration of rFVIIa can be considered for life-threatening bleeding which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails. **2C**

We recommend tranexamic acid to prevent bleeding during major surgery and/or treat bleeding due to (or at least suspected) hyperfibrinolysis (e.g. a dose of 20 to $25\ mg\ kg^{-1}$). **1B**

We suggest the use of desmopressin (DDAVP) under specific conditions [acquired von Willebrand syndrome (VWS)]. **2C**

Based on the current literature there is no evidence to recommend antithrombin supplementation in elective surgical patients while they are bleeding.

We recommend structured staff education and training. **1C**

1.7.1. Correction of confounding factors

We recommend maintaining perioperative normothermia because it reduces blood loss and transfusion requirements. **1B**

We recommend that pH correction should be pursued during treatment of acidotic coagulopathy, although pH correction alone cannot immediately correct acidosis-induced coagulopathy. **1C**

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We recommend that rFVIIa should only be considered alongside pH correction. **1C**

We recommend that calcium should be administered during massive transfusion if calcium concentration is low, to preserve normocalcaemia (>0.9 mmol l^{-1}). **1B**

We suggest that endovascular embolisation is a well tolerated alternative to open surgical intervention after failed endoscopic treatment for non-variceal upper gastrointestinal bleeding (UGIB). **2C**

We suggest super-selective embolisation as primary therapy for treatment of angiogram positive lower gastrointestinal tract bleeding. **2C**

We suggest embolisation as first-line therapy for arterial complications in pancreatitis. **2C**

1.7.2. Cost implications

Both bleeding and transfusion of allogeneic blood products independently increase morbidity, mortality, length of stay in ICU and hospital and costs. **B**

Tranexamic acid can reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several major surgical and trauma settings. **B**

We recommend restricting the use of rFVIIa to its licensed indication as, outside these indications, the effectiveness of rFVIIa to reduce transfusion requirements and mortality remains unproven and the risk of arterial thromboembolic events, as well as costs, are high. **1A**

Cell salvage can be cost-effective in selected patients. **A**

The cost-effectiveness of a ratio-driven transfusion protocol has not been investigated.

Goal-directed therapy with coagulation factor concentrates (fibrinogen and/or PCC) may reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. **C**

1.8. Algorithms in specific clinical fields

1.8.1. Cardiovascular surgery

Withdrawal of aspirin therapy increases the risk of coronary thrombosis; continuation of aspirin therapy increases the risk of bleeding. **B**

Withdrawal of clopidogrel therapy increases the risk of coronary thrombosis; continuation of clopidogrel therapy increases the risk of bleeding. **A**

We recommend prophylactic administration of tranexamic acid before CPB in patients undergoing coronary artery bypass grafting (CABG) surgery. **1A**

We suggest tranexamic acid can be applied topically to the chest cavity to reduce postoperative blood loss following cardiac surgery. **2C**

In complex cardiovascular surgery we recommend fibrinogen concentrate infusion guided by VHA monitoring to reduce perioperative blood loss. **1B**

We suggest that rFVIIa may be considered for patients with intractable bleeding during and after cardiovascular surgery once conventional haemostatic options have been exhausted. **2B**

We suggest that antiplatelet therapy with aspirin or clopidogrel may be administered in the early postoperative period without increasing the risk of postoperative bleeding. **2C**

We recommend the use of standardised VHA-guided haemostatic algorithms with pre-defined intervention triggers. **1B**

1.8.2. Gynaecological (non-pregnant) surgery

We suggest that normovolaemic haemodilution should not be used as it does not reduce allogeneic transfusion. **2B**

Cell salvage may reduce allogeneic transfusion in gynaecological (including oncological) surgery. **B**

We suggest using preoperative intravenous iron to reduce allogeneic transfusion requirements in anaemic gynaecological cancer patients receiving chemotherapy. **2B**

We suggest using intravenous iron to correct preoperative anaemia in women with menorrhagia. **2B**

Tranexamic acid may reduce perioperative bleeding in gynaecological cancer surgery. **C**

1.8.3. Obstetric bleeding

We recommend that peripartum haemorrhage (PPH) should be managed by a multidisciplinary team. **1C**

We recommended the use of an escalating PPH management protocol including uterotonic drugs, surgical and/or endovascular interventions and procoagulant drugs. **1B**

Risk awareness and early recognition of severe PPH are essential. **C**

We suggest that patients with known placenta accreta be treated by multidisciplinary care teams. **2C**

Cell salvage is well tolerated in obstetric settings, provided that precautions are taken against rhesus isoimmunisation. **C**

We suggest that using perioperative cell salvage during caesarean section may decrease postoperative homologous transfusion and reduce hospital stay. **2B**

Intravenous iron supplementation improves fatigue at 4, 8 and 12 weeks postpartum. **B**

We suggest assessing fibrinogen levels in parturients with bleeding, as levels less than 2 g l^{-1} may identify those at risk of severe PPH. **2B**

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Dynamic platelet count decrease or a level less than 100×10^9 l^{-1} at the onset of labour, particularly if combined with plasma fibrinogen level less than 2.9 g l^{-1}, may indicate an increased risk of PPH. **C**

At the beginning of labour aPTT and PT are of little predictive value for PPH. **C**

VHA can identify obstetric coagulopathy. **B**

We recommend against pre-emptive fibrinogen replacement; however, in ongoing PPH with hypofibrinogenaemia we recommend fibrinogen replacement. **1C**

In severe PPH we suggest a VHA-guided intervention protocol. **2C**

We suggest that tranexamic acid be considered before caesarean section and in cases of antepartum bleeding. **2B**

We recommend the administration of tranexamic acid in PPH at a dose of 1 g intravenously (IV) as soon as possible, which can be repeated if bleeding continues. **1B**

1.8.4. Orthopaedic surgery and neurosurgery

Reduced platelet activity is associated with early haematoma growth, more intraventricular haemorrhage and worse 3-month outcomes following intracranial haemorrhage (ICH). **C**

Low platelet count, low plasma fibrinogen concentration and factor XIII deficiency are predictive of bleeding complications in ICH, intracranial surgery and major spine surgery, particularly when they occur in combination. **C**

1.8.5. Paediatric surgery

We suggest low-volume sampling for standard coagulation tests and VHA-guided interventions. **2C**

We recommend the use of isotonic and balanced resuscitation fluids in bleeding children. **1C**

Except for premature babies and cyanotic newborns, haemoglobin targets in bleeding children are 7 to 9 g dl^{-1}. **C**

1.8.6. Visceral and transplant surgery

Despite PT, aPTT and INR indicating coagulopathy in chronic liver disease (CLD), global coagulation tests (thrombin generation and VHA) suggest that haemostasis is balanced in stable CLD. **C**

Mild-to-moderate prolongation of the preoperative PT and INR do not predict bleeding in patients with CLD. **C**

We recommend that, in acute liver failure, moderately elevated INR should not be corrected before invasive procedures, with the exception of intracranial pressure monitor insertion. **1C**

Fluid restriction, phlebotomy, vasopressors and transfusion protocols may be associated with low transfusion rates during orthotopic liver transplant (OLT). **C**

We recommend a low CVP and restrictive fluid administration during liver surgery to reduce bleeding. **1B**

We recommend tranexamic acid for treatment of fibrinolysis (evident from microvascular oozing or VHA clot lysis measurement) but not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis postreperfusion. **1C**

We suggest that tranexamic acid should be considered in cirrhotic patients undergoing liver resection. **2C**

1.8.7. Acute upper gastrointestinal bleeding

We recommend that acute variceal bleeding should be managed by a multidisciplinary team. A specific multimodal protocol for upper gastrointestinal haemorrhage should be available. **1C**

Transjugular intrahepatic portosystemic stent-shunt (TIPSS) can be suggested as an option for rescue therapy after initial medical and endoscopic therapy fail. **2B**

We recommend early interventional endoscopy and the immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding. **1B**

Tranexamic acid reduces mortality but not re-bleeding. **B**

1.8.8. Coagulopathy and renal disease

Point-of-care tests of platelet function and bleeding time provide no reliable platelet function assessment in uraemia and no prediction of bleeding in this setting. **C**

We suggest that conjugated oestrogen therapy should be used in uraemia. **2C**

We suggest that DDAVP should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. **2C**

1.9. Antithrombotic drugs

1.9.1. Antiplatelet agents

We recommend that aspirin therapy should continue perioperatively in most surgical settings, especially cardiac surgery. **1C**

Where aspirin withdrawal before surgery is considered, we recommend a time interval of 3 days. **1C**

In patients with risk factors for vascular complications naïve of any antiplatelet treatment, it is not recommended that treatment with aspirin be initiated preoperatively. **1B**

In patients treated chronically with aspirin for the secondary prevention of cardiovascular events, except those patients with coronary stents, we recommend aspirin interruption for procedures where there is a very high bleeding risk. **1B**

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In patients chronically treated with aspirin for secondary prevention of cardiovascular events, we recommend aspirin be maintained during and after low and medium bleeding risk procedures. **1B**

We suggest careful consideration of postoperative bleeding complications when timing the first postoperative administration and dose of anticoagulants along with resumption of aspirin. **2C**

For intraoperative or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7×10^{11} per 10 kg body weight in adults). **2C**

We recommend that aspirin be continued for at least 4 weeks after bare metal stent (BMS) implantation and 3 to 12 months after drug-eluting stent (DES) implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high. **1A**

We suggest that P2Y12 inhibitor treatment be considered for at least 4 weeks after BMS implantation and 3 to 12 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high. **2A**

If clinically feasible, we suggest postponing (semi-urgent) surgery for at least 5 days after cessation of ticagrelor and clopidogrel, and for 7 days in the case of prasugrel, unless the patient is at high risk of an ischaemic event. **2B**

We recommend that antiplatelet agent (APA) therapy should resume as soon as possible postoperatively to prevent platelet activation. **1C**

We suggest that the first postoperative dose of clopidogrel or prasugrel should be given no later than 24 h after skin closure. We also suggest that this first dose should not be a loading dose. **2C**

We recommend that a multidisciplinary team meeting should decide on the perioperative use of APAs in urgent and semi-urgent surgery. **1C**

We suggest that urgent or semi-urgent surgery should be performed under aspirin/clopidogrel or aspirin/prasugrel combination therapy if possible, or at least under aspirin alone. **2C**

We suggest that platelet transfusion be considered (dose: 0.7×10^{11} per 10 kg body weight in adults) in cases of intraoperative or postoperative bleeding clearly related to clopidogrel or prasugrel. **2C**

According to pharmacological characteristics, we suggest that the management of ticagrelor may be comparable to clopidogrel (i.e. withdrawal interval of 5 days). **2C**

Platelet transfusions may be ineffective for treating bleeding related to ticagrelor if given within 12 h of the drug's administration. **C**

1.9.2. Heparin

We recommend that severe bleeding associated with intravenous unfractionated heparin (UFH) should be treated with intravenous protamine at a dose of 1 mg per 100 IU UFH given in the preceding 2 to 3 h. **1A**

We suggest that severe bleeding associated with subcutaneous (SC) UFH unresponsive to intravenous protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of intravenous protamine, with the dose guided by aPTT. **2C**

We suggest that severe bleeding related to SC low molecular weight heparin (LMWH) should be treated with intravenous protamine at a dose of 1 mg per 100 antifactor Xa units of LMWH administered and, if unresponsive, with a further 0.5 mg protamine per 100 antifactor Xa units. **2C**

1.9.3. Fondaparinux

We suggest that the administration of rFVIIa could be considered to treat severe bleeding associated with SC administration of fondaparinux (off-label treatment). **2C**

1.9.4. Vitamin K antagonists

We recommend that VKAs should not be interrupted in patients undergoing low bleeding risk procedures: skin surgery, dental and oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomies), nor for most ophthalmologic surgery [i.e. mainly anterior chamber (cataract)]. **1C**

We recommend that for low or moderate thrombotic risk patients [e.g. atrial fibrillation patients with $CHADS_2$ score ≤ 4; patients treated for >3 months for a non-recurrent venous thromboembolism (VTE)] undergoing procedures requiring INR less than 1.5, VKA should be stopped 3 to 5 days before surgery (acenocoumarol, warfarin). No bridging therapy is needed. Measure INR on the day before surgery and give 5 mg oral vitamin K if INR exceeds 1.5. **1C**

We recommend bridging therapy for high thrombotic risk patients (e.g. atrial fibrillation patients with a $CHADS_2$ score >4; patients with recurrent VTE treated for less than 3 months; patients with a prosthetic cardiac valve). Warfarin: last dose 5 days before surgery; 4 days before surgery, no heparin; 3, 2 and 1 day before surgery, LMWH (last dose 24 h before surgery) or SC UFH twice or thrice daily; day 0, surgery. Acenocoumarol: 3 days before surgery, last dose; 2 and 1 day before surgery, same protocol as for warfarin. **1C**

We suggest that the therapeutic dose of LMWH or UFH should be tailored for each patient, depending on the respective thrombotic and bleeding risks. **2C**

We recommend that for low bleeding risk patients, VKAs should be restarted during the evening or the day after the procedure (at least 6 h after). Therapeutic doses of

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LMWH should be given postoperatively until the target INR is observed in two following measurements. **1C**

We recommend that for moderate to high thrombotic risk patients, prophylactic doses of heparin (UFH or LMWH) should be started during the evening or the day after the procedure (at least 6 h after) and given for up to 48 to 72 h, and then therapeutic anticoagulation should be resumed. VKA can restart at that time or later, only when surgical haemostasis is achieved. **1C**

In VKA-treated patients undergoing an emergency procedure, we recommend that INR must be measured on the patient's admission to the hospital, with the administration of four-factor PCC to reverse VKA anticoagulant effects (e.g. at an initial dose of 25 IU factor IX kg^{-1} at an INR of 4) rather than the transfusion of plasma. **1B**

In bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the administration of four-factor PCC 25 to 50 IU factor IX kg^{-1} plus 5 to 10 mg IV vitamin K. **1B**

If PCC is not available, then in bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the transfusion of plasma (15 to 20 ml kg^{-1} plus 5 to 10 mg IV vitamin K). **1C**

1.9.5. Direct oral anticoagulants

We recommend assessment of creatinine clearance in patients receiving direct oral anticoagulants (DOACs) who are scheduled for surgery. **1B**

We suggest that DOACs should only be withheld the day before surgery for patients undergoing low bleeding risk procedures such as skin surgery, dental and oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but no polypectomies) and most ophthalmological surgery. **2C**

For intermediate and high bleeding risk procedures

(1) we recommend that rivaroxaban, apixaban and edoxaban should not be given for 2 days before the procedure (i.e. last oral intake 3 days before), pending a creatinine clearance (Cockcroft–Gault formula) above 30 ml min^{-1}. No bridging therapy is needed. **1C**
(2) we recommend that dabigatran should not be given for 3 days before the procedure (i.e. last oral intake 4 days before), if the creatinine clearance is above 50 ml min^{-1} and 4 days before the procedure (i.e. last oral intake 5 days before), if the creatinine clearance is between 30 and 50 ml min^{-1}. No bridging therapy is needed. **1C**

We suggest that in severe bleeding patients treated with dabigatran, a specific antidote (idarucizumab) should be considered. **2C**

We suggest that for low bleeding risk procedures, when haemostasis is achieved, DOACs should be recommenced during the evening after the procedure (at least 6 h after). **2C**

We suggest that for intermediate and high bleeding risk procedures, prophylactic doses of LMWH or DOACs (according to specific indications) should be given postoperatively whenever VTE prophylaxis is requested and then the full therapeutic dose of DOAC should be resumed up to 72 h postoperatively, when surgical haemostasis is achieved. **2C**

1.10. Comorbidities involving haemostatic derangement

1.10.1. Systemic, metabolic and endocrine diseases

We suggest that patients with haemostatic derangements associated with systemic, metabolic and endocrine diseases should be managed perioperatively in collaboration with a haematologist. **2C**

We suggest individualised preoperative discontinuation of selective serotonin reuptake inhibitor (SSRI) treatment. **2B**

We suggest individualised preoperative discontinuation of antiepileptic agents, such as valproic acid, which may increase bleeding. **2C**

We do not recommend preoperative discontinuation of gingko biloba extracts. **1B**

1.11. Patients with congenital bleeding disorders

1.11.1. Preoperative assessment

We suggest referring the patient to a haematologist for assessment and planning of the intervention if inherited bleeding disorders (IBDs) are suspected preoperatively. **2C**

We recommend the use of bleeding assessment tools (BATs) for detecting and predicting the perioperative risk of bleeding before surgery and invasive procedures. **1C**

1.11.2. General perioperative management

Surgery can be safely performed in patients with IBDs when there is appropriate careful preoperative planning, appropriate replacement/substitution therapy, and multidisciplinary team management. **C**

We recommend that patients with IBDs be managed perioperatively in collaboration with a haematologist, preferably in dedicated centres with expertise in coagulation disorders. **1C**

We suggest preoperative haemostatic correction in patients with IBDs depending on the type of surgery. **2C**

1.11.3. Von Willebrand disease

We recommend DDAVP as a first-line treatment for minor bleeding/surgery in patients with von Willebrand disease (VWD), after a trial testing. The standard

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regimen is 0.3 $\mu g\,kg^{-1}$ dissolved in 50 ml saline and infused IV over 20 to 30 min, repeated every 12 to 24 h usually for no more than 3 days. **1C**

We recommend replacement of von Willebrand factor (VWF) with plasma-derived products for major bleeding/surgery. Treatment regimens are specified by published guidelines. **1C**

We suggest that antifibrinolytic drugs be used as haemostatic adjuncts. Treatment regimens are specified by published guidelines. **2C**

1.11.4. Platelet defects

We suggest that DDAVP be used to prevent/control perioperative bleeding in patients with mild inherited platelet defects. **2C**

We suggest that antifibrinolytic drugs be used as haemostatic adjuncts in procedures involving patients with inherited platelet defects. **2C**

We recommend that rFVIIa treatment should be considered in patients with Glanzmann thrombasthenia undergoing surgery. **1C**

We recommend against routine platelet transfusion in patients with inherited platelet disorders. **1C**

1.11.5. Haemophilia A and B

We recommend adequate perioperative replacement therapy to ensure well tolerated surgery in haemophilia patients. **1C**

We suggest that perioperative replacement therapy (target factor level and duration) in haemophilia patients follows published guidelines. **2C**

We recommend either recombinant products or plasma-derived concentrates for perioperative replacement therapy in haemophilia patients. **1C**

We suggest that coagulation factors be given perioperatively by continuous infusion. **2C**

We suggest either rFVIIa or activated PCCs for haemophilia patients with inhibitors. **2C**

We suggest antifibrinolytic drugs as perioperative adjunct therapy in haemophilia patients. **2C**

We suggest DDAVP as first-line perioperative therapy in patients with mild haemophilia A as long as factor VIII can be raised to an appropriate therapeutic level. **2C**

1.11.6. Rare bleeding disorders

There are insufficient data to recommend routine perioperative supplementation of deficient factors in patients with rare bleeding disorders (RBDs).

We suggest that rFVIIa be used in perioperative bleeding due to inherited factor VII deficiency. **2C**

If rFVIIa is given to control perioperative bleeding in inherited factor VII deficiency, we suggest lower doses (e.g. 20 to 25 $\mu g\,kg^{-1}$ every 4 to 6 h) than in haemophilia patients with inhibitors. **2C**

There are insufficient data to recommend rFVIIa in perioperative bleeding for patients with other RBDs.

There are insufficient data to recommend periprocedural DDAVP or antifibrinolytic drugs in patients with mild RBDs.

2. Introduction

Perioperative bleeding management is a complex and changing field requiring multiple assessments and appropriate strategies to optimise patient care. There is an ongoing drive to find new alternatives to transfusion, a desire to reduce unnecessary use of blood products and a focus towards more evidence-based perioperative practice. In this dynamic area of medicine it is imperative to provide healthcare professionals with clinically useful and up-to-date data concerning the diagnosis and treatment of patients with perioperative bleeding. As such, the European Society of Anaesthesiology (ESA) strongly supports the development of high-quality, evidence-based clinical practice guidelines to help standardise the approach to patient care and to improve overall clinical practice.[1]

In 2013, the ESA developed an extensive set of evidence-based guidelines[2] for the management of severe perioperative bleeding with the overall aim of providing an up-to-date review and synthesis of the evidence and recommendations to help guide clinicians towards safer and more cost-effective strategies for minimising severe perioperative bleeding and thus maximising blood conservation. The current guidelines update provides additional information to assist the clinician to PREPARE, PLAN and take ACTION. PREPARE for any potential bleeding risks by performing preoperative assessments, particularly to detect anaemia and allow time for its correction. PLAN for any intraoperative bleeding that may occur by utilising transfusion algorithms that incorporate pre-defined transfusion triggers to help guide haemostatic intervention, by being aware of the limitations of standard coagulation tests and by modifying the approach accordingly to use point-of-care testing and others. If potential bleeding risks are known in advance and a plan of treatment is in place, the necessary ACTION can be set in motion as required. Because of the increasing evidence in this field, an update of the guidelines was planned every 2 years.

This document not only details the retained recommendations, suggestions and statements from the original guidelines published in 2013[2] but also includes new recommendations as well as revisions to the wording and grades of some of the original recommendations. Additional clinical questions have been included in the update.

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3. Methods

3.1. Task force selection

In the planned process of revising the guideline, 'Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology' published in 2013,[2] the ESA Guideline Committee (Chairman, EDR) re-nominated the ESA Task Force previously selected, chaired by SAKL, and composed of AA, PWo, CA, and EDR. The ESA Guideline Committee and the task force defined the scope of the guideline revision, which prompted the core group to invite scientific societies involved in the field to suggest experts to join the task force as affiliate co-authors (advisory group). The first meeting of the extended panel was held during the Euroanaesthesia meeting in Berlin in May 2015.

3.2. Search for evidence

For this update we searched Medline (Ovid), Embase (Embase.com), the Cochrane Library (Wiley), BIOSIS (Web of Science), Science Citation Index Expanded (Web of Science), Conference Proceedings Citation Index – Science (Web of Science), and PubMed (for non-Medline contents). The searches were conducted between March and July 2015 and limited to publication dates since 2011 or 2012 (depending on the search). Guidelines, case reports, editorials and commentaries were excluded from the search result. No other limitations were used. As with the original guidelines, we conducted 12 separate searches, using both free text terms and subject headings: one general search on the topic of perioperative bleeding, one search for systematic reviews, and one search for each topic within these guidelines. A total of 18 334 references were retrieved. The exact search strategies and numbers of references for each search are reported in Appendix 1 (Supplemental Digital File: ESA POB guidelines update search Nov2016.docx, http://links.lww.com/EJA/A118). Both task force members and the extended panel members reviewed the selected articles relevant to their sections and evaluated these according to the ESA policy on guidelines development.[1] A total of 733 references were included for the guideline update.

3.3. Guideline preparation

To revise the guidelines, the task force referred to the same series of key clinical questions about the management of severe perioperative bleeding as used for the previous guideline. These questions formed the basis for reviewing the evidence published after 2012 and, when the new evidence was strong enough, for developing new recommendations or modifying the existing recommendations. Downgrading of the quality of evidence occurred for some existing recommendations; this was due to methodological issues in the studies and not because of new contradictory evidence. All downgraded recommendations are still valid and should be considered as clinically relevant.

Guidance in the clinical fields of anaemia management, optimisation of haemostasis, and blood conservation modalities makes these ESA guidelines the first European guidelines on patient blood management (PBM). The World Health Organization encouraged all member states to implement PBM programmes employing such multiple combined strategies to increase and preserve autologous erythrocyte volume to minimise the transfusion of blood components such as RBCs, platelets, FFP.[3] Anaemia is associated with increased morbidity and mortality and may also be a condition that prompts medical professionals to initiate RBC transfusion.[4] The latter itself may be associated with increased morbidity due to infectious, immunological or pulmonary complications.[5–8] These complications are also recorded following the administration of platelets and/or FFP.[8]

General guidance on the management of severe perioperative bleeding is applicable across all clinical settings. Therefore, to reduce redundancy, the section on general coagulation management is relevant to all patient categories whereas guidelines that are specific to a particular setting are detailed in separate sections. Any guidance for therapeutic interventions is always based on the prerequisite of severe bleeding manifestations: in the absence of bleeding the correction of a laboratory result indicating a pathological coagulation parameter is not recommended.

The final draft of the guideline was reviewed by external reviewers and posted on the ESA website for four weeks, and all individual and national ESA members were invited to comment. The final manuscript was approved by the Guidelines Committee and the ESA Board before submission for publication.

The overall aim of these updated guidelines is to provide healthcare professionals with the most recent evidence to help ensure improved clinical management of patients with perioperative bleeding. The search strategy was based on pre-defined criteria, and supplementary searches were performed to make this process as robust as possible. The authors assessed all publications relevant to their sections and the existing 2013 recommendations were revised with respect to wording or changes to the grading of the quality of evidence, as appropriate. New recommendations were also prepared to reflect additional clinical questions.

The guideline uses the same grading system as in the previous guidelines – the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[2] (Table 1). Therefore, recommendations and suggestions are assigned a number (relating to the strength of the recommendation) and a letter (relating to the quality of the supporting evidence). Statements are

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accompanied only by a letter, to indicate the quality of the evidence supporting the statement.

It is important to emphasise that these recommendations can be adopted, modified, or not implemented, depending on the requirements of different institutions or countries.

4. Evaluation of coagulation status

4.1. Perioperative coagulation testing

New evidence supports the existing recommendations and this is detailed below for the relevant sections.

4.1.1. Standard laboratory tests for coagulation monitoring

4.1.1.1. Fibrinogen concentration

Fibrinogen concentration is often determined indirectly using the Clauss method.[9] In a recent paper, considerable differences were found between Clauss-based plasma fibrinogen measured using different detection methods.[10] However, the similarity between measurements, shortly before weaning from CPB and after CPB within the same centres, indicated that on-pump measurements could provide an early estimation of fibrinogen deficit after CPB.

Fibrinogen levels may be linked with postoperative blood loss and a recent systematic review reports a significant but weak-to-moderate correlation between preoperative and postoperative fibrinogen levels and postoperative blood loss in cardiac surgery.[11]

4.1.2. Viscoelastic haemostatic assay coagulation monitoring

VHA coagulation monitoring uses whole blood and is performed in the emergency room, operating theatre, or the central laboratory. In a recent systematic review, VHA coagulation monitoring was found to be cost-saving and more effective than standard laboratory tests (SLTs), in both patients undergoing cardiac surgery and trauma patients.[12]

4.1.2.1. Commonly used blood modification agents for viscoelastic haemostatic assay coagulation monitoring

VHA coagulation monitoring can be performed using recalcified, citrated blood alone [native thromboelastometry (NATEM) assay with no activation enhancement or additional modifications, and clotting is initiated intrinsically by the surface of the cup and pin]. More usually, activators are added to accelerate coagulation, and modifying agents can suggest the cause of the observed coagulopathy. The most commonly used VHAs to measure fibrin clot quality include the functional fibrinogen and FIBTEM (Fibrinogen thromboelastometry) assays. These assays measure the strength of the fibrin-based clot and a low functional fibrinogen/FIBTEM clot strength usually indicates fibrinogen deficiency. In a study by Erdoes *et al.* [13] the authors concluded that, when measured on CPB prior to weaning, a FIBTEM A10 (clot amplitude at 10 min) 10 mm or less may be an early alert for post-CPB fibrinogen levels below, or within, the range for supplementation (1.5 to 2.0 g l^{-1}) recommended in case of post-CPB coagulopathic bleeding.

There are indications that EXTEM (extrinsic thromboelastometry), INTEM (intrinsic thromboelastometry) and APTEM (aprotinin thromboelastometry) are associated with fibrinogen and platelet levels: INTEM clotting time (CT) correlated significantly with aPTT and FIBTEM correlated significantly with fibrinogen, whereas factor VIII (FVIII) correlated significantly with all ROTEM (rotational thromboelastometry) parameters except EXTEM CT, INTEM CT, FIBTEM CT and APTEM clot formation time (CFT) and maximum clot firmness (MCF).[14] However, other publications have found it difficult to find a clear correlation between findings from VHA [TEG (thromboelastography) and ROTEM] monitoring to SLTs such as PT and aPTT perioperatively and overall haemostatic measurement.[15–17]

4.1.3. Which approaches can be used for preoperative evaluation of coagulation status?

4.1.3.1. Standardised bleeding history and clinical evaluation

Recommendations

Before surgery or invasive procedures, we recommend the use of a structured patient interview or standardised questionnaire which considers clinical and family bleeding history and detailed information on the patient's medication. **1C**

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, INR and platelet count in elective surgery. **1C**

Structured patient interviews are a primary tool for preoperative assessment of bleeding risk, and physical examination should focus on signs of bleeding or diseases which may cause haemostatic failure. Comorbidities, including renal dysfunction, are independent risk factors for bleeding and transfusion; for example, a recent systematic review found that chronic kidney disease is associated with perioperative bleeding but not bleeding that required reoperation.[18] Among cardiac surgery patients, patient-related predictors of excessive bleeding after surgery were reported to be male gender, higher preoperative haemoglobin levels, lower BMI, diabetes mellitus, impaired left ventricular function, lower amount of pre-bypass thrombin generation, lower preoperative platelet counts, decreased preoperative platelet aggregation, preoperative platelet inhibition level more than 20%, preoperative thrombocytopaenia, and lower preoperative fibrinogen concentration.[19]

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4.1.3.2. Preoperative use of standard laboratory tests

Preoperative use of SLTs is not recommended by current ESA guidelines. Furthermore, in patients without a previous history of bleeding or bleeding disorders, SLTs are not generally recommended.[20] In the neurosurgical setting, the value of preoperative PT testing is limited in patients awaiting elective procedures in whom a normal bleeding history can be established.[21]

A recent meta-analysis reported a significant but weak-to-moderate correlation between preoperative and postoperative fibrinogen levels and postoperative blood loss in cardiac surgery.[11] Preoperative measurement of fibrinogen may be useful to identify those patients at risk of postoperative bleeding.

Recent evidence indicates that patients with end-stage liver disease and an elevated INR can safely undergo invasive cardiac procedures as elevated INR does not predict catheterisation-related bleeding complications.[22] However, in paediatric living donor liver transplantation, preoperative INR was the only predictive risk factor for massive blood transfusion.[23] In adult OLT recipients, a higher preoperative INR was also found to be associated with increased RBC administration (both autologous and cell salvage). Each INR increase of 1 unit resulted in a 36% increase in the predicted number of units of RBCs required.[24] However, there is currently little evidence to support additional, routine application of point-of-care INR testing in the preoperative setting to predict bleeding tendency. For example, point-of-care INR measurements for trauma patients during various stages of admission and resuscitation could not be used to identify or exclude patients with acute traumatic coagulopathy.[25]

4.1.3.3. Preoperative use of viscoelastic haemostatic assay coagulation monitoring

VHA is used for rapid diagnosis of bleeding causes and is of most value intraoperatively. Indiscriminate preoperative coagulation monitoring using VHAs is unlikely to be cost-effective, but it may be warranted in combination with SLTs in patients with bleeding disorders such as VWD, factor XIII (FXIII) deficiency, and haemophilia A with dysfibrinogenaemia, or in patients with preoperative anticoagulant treatment.[26,27]

4.1.4. Which coagulation monitoring tests can be used to guide intraoperative haemostatic therapy?

4.1.4.1. Intraoperative use of standard laboratory tests

For laboratory measurement of fibrinogen to be useful in cardiovascular surgery, analysis would need to begin before the patient is taken off CPB. Such measurement is prevented by the sensitivity of the Clauss assay to heparin. However, a study by Solomon *et al.*[10] demonstrated that there were no significant differences in fibrinogen concentration before and after weaning from CPB, for most centres and methods used. The similarity between measurements shortly before weaning from CPB and after weaning suggests that on-pump measurements could provide an early estimation of a likely deficit in fibrinogen post-CPB, and therefore guidance for any haemostatic therapy. In paediatric non-cardiac surgery patients, SLTs correlate poorly with intraoperative activated clotting time (ACT).[28]

4.1.4.2. Intraoperative use of viscoelastic haemostatic assay coagulation monitoring

A recent health technology assessment reports findings from a meta-analysis showing that perioperative VHA monitoring is associated with a reduced need for transfusion of RBCs, platelets and FFP compared with monitoring by SLTs.[12] If using VHA coagulation monitoring, appropriate transfusion triggers should be considered carefully.[29]

4.1.4.2.1. Intraoperative viscoelastic haemostatic assay monitoring in trauma

In paediatric patients with traumatic brain injury, hypocoagulation measured by TEG is associated with mortality and hypercoagulation is associated with survival.[30] The timing of sampling and pre-hospital haemostatic assessment was investigated in a prospective study of 50 trauma patients and no additional information was gained by pre-hospital assessment.[31] A small randomised controlled trial (RCT) of 30 patients with surgical excision of burn wounds performed on the third day after burn trauma showed a reduced need for allogeneic blood transfusions when a bleeding management algorithm based on thromboelastometry was used.[32] A recent Cochrane systematic review investigating the diagnostic test accuracy of TEG and ROTEM in patients with clinically suspected trauma-induced coagulopathy found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM: this was due to the small number of included studies and concerns about the risk of bias.[33] These results are supported by other studies.[34,35]

4.1.4.2.2. Intraoperative viscoelastic haemostatic assay monitoring in cardiovascular surgery

The value of VHA monitoring to guide haemostatic therapy following CPB has been demonstrated in several RCTs.[36–46] The majority of published randomised trials investigating VHA-guided transfusion have been performed in cardiac surgery and several reviews have reported a reduced need for allogeneic blood transfusion.[12,47,48] Thus, 11 randomised trials have been published investigating different algorithms and triggers, different devices, and different subgroups of cardiac surgery patients.[47] Special attention has been given to the study by Weber *et al.*[45] which was terminated prematurely after an interim analysis showed a significantly improved survival using VHA-guided therapy. The study specifically investigated the use of a VHA-guided

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algorithm in patients with coagulopathy or severe postoperative bleeding. Meta-analysis of pooled data from 1089 patients suggests a benefit in terms of reduced blood requirements, even if insufficient data were available on mortality.[12] However, most trials have a high risk of bias.[47,48] Finally, in cardiac surgery with CPB, it might be an advantage to combine VHA with platelet function assays.[37,45,46,49]

4.1.5. Postoperative evaluation of coagulation status

Potential complications following surgery include thromboembolic events and, conversely, recurrent or excessive bleeding. Postoperative coagulation monitoring in the ICU can provide information regarding appropriate haemostatic interventions or further procedures which may be required.

Currently, it remains uncertain whether low postoperative fibrinogen levels are causally associated with postoperative bleeding.[50] In paediatric cardiac surgery, post-CPB plasma fibrinogen concentration appears to influence blood loss, with a fibrinogen concentration of at least 1.5 g l^{-1} or an MCF of at least 3 mm accurately predicting excessive blood loss.[51] Prediction of postoperative bleeding volume using haemostatic assessment, including VHAs, is not convincing.[52,53] However, haemostatic deficiencies are not the sole cause of postoperative bleeding and attempts to predict bleeding are often thwarted by the presence of more obvious surgical causes. The ability to rapidly exclude haemostatic impairment is of great value as normal haemostasis in a patient with postoperative bleeding would indicate a surgical cause of bleeding and this differentiation might speed up the decision to re-operate. Two RCTs, with a total of 192 patients, investigated the use of VHAs in the treatment of excessive postoperative bleeding or suspected coagulopathy in cardiac surgery patients.[42,45] Both studies suggest a reduced need for allogeneic transfusion and the study by Weber *et al.*[45] showed reduced mortality. Six other RCTs investigating intraoperative use of VHA-monitored haemostatic treatment also applied the interventional algorithm to the beginning of the postoperative period from 2 h postoperatively up until the entire ICU stay.[32,36,37,39,40,46]

4.1.6. Are patient outcomes improved by algorithms that incorporate monitoring for perioperative haemostatic management?

Recommendations

We recommend the application of intervention algorithms incorporating pre-defined triggers and targets based on VHA coagulation monitoring to guide individualised haemostatic intervention in the case of perioperative bleeding. **1C**

If VHA is not available we recommend the application of intervention algorithms incorporating pre-defined triggers based on conventional coagulation tests. **1C**

Long turnaround times may preclude the use of some tests in emergency situations. However, implementation of VHA monitoring appears rational if the alternative is haemostatic management guided by clinical judgement alone. In a recent analysis, the use of VHAs was found to be effective in reducing RBC transfusion, platelet transfusion and FFP transfusion.[12] VHAs were also cost-saving and more effective than SLTs in patients undergoing cardiac surgery and in trauma patients.

Antithrombin III (AT III), a potent anticoagulant with independent anti-inflammatory properties, irreversibly inhibits serine proteases (e.g. activated factor X and thrombin). There have often been arguments to increase the antithrombin concentration to supranormal values because the activity of pro-inflammatory and pro-coagulant molecules are increased in critically ill patients.[54] However, in a recent Cochrane systematic review, the effect of supplementation with AT III in critically ill patients was found to be of questionable value based on the available evidence, and there was an increased risk of bleeding in those receiving AT III to attain supranormal values.[55]

Nevertheless, supplementation with AT III in a cardiac surgical setting to avoid FFP transfusion may be considered as an option, although one has to consider the extensive cost and the risk of heparin rebound in the early postoperative period.[56]

In the paediatric liver transplantation population, the AT III levels are often found to be reduced postoperatively but there is still controversy as regards management of this deficit.[57]

4.2. Evaluation of platelet function

Identification of platelet function is important for informing perioperative haemostatic management. There are several methods for assessing platelet function, each with its own limitations. The number of existing devices and their clinical validation is constantly evolving, as is their utility in various settings.

Recommendations

We suggest preoperative platelet function testing only in association with a positive bleeding history. **2B**

We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions or antiplatelet medication. **2B**

Bleeding time is influenced by many variables and is not useful for stratifying bleeding risk. **C**

4.2.1. Which platelet function tests can be used preoperatively for identifying disturbances of primary haemostasis?

In thrombocytopaenic patients, several tests such as platelet indices, Multiplate, Cone and Plate(let) Analyser

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(CPA, Impact-R), viscoelastic methods and PFA-100 (Platelet function analyser-100) are rapid and easy to perform.[58] However, PFA-100 lacks sensitivity for known platelet secretion defects and, while others appear superior in this regard, the evidence remains sparse in thrombocytopaenic patients. Current evidence indicates that the flow cytometric marker for activation of P-selectin and surface coverage by the Cone and Plate(let) analyser may predict bleeding in selected thrombocytopaenic populations.

4.2.2. Preoperative platelet function testing in different clinical settings

4.2.2.1. Trauma

In the setting of traumatic brain injury with trauma-induced coagulopathy, multi-modality monitoring of platelet function appears to detect patients at risk of bleeding and may, together with TEG/ROTEM, guide transfusion management.[26,59]

4.2.2.2. Cardiac surgery

Preoperative platelet function testing may increase the predictive value of postoperative bleeding in patients undergoing CABG surgery.[60] Platelet dysfunction measured during re-warming and postprotamine has been shown to be independently associated with high blood loss in cardiac surgery.[61]

In a recent large observational study in adult cardiac surgery examining the predictive value of multiple electrode platelet aggregometry (Multiplate), the ADP test (adenosine diphosphate test) and the TRAPtest (thrombin receptor activator peptide test) were found to predict the requirement for perioperative blood transfusion.[62]

A recent systematic review on the role of point-of-care platelet function testing in predicting postoperative bleeding concluded that incorporation of point-of-care platelet function tests into transfusion management algorithms was associated with a reduction in blood loss and transfusion requirements following cardiac surgery.[63] However, this has been disputed by others due to the lack of high-quality studies.[64]

In a recent European guideline on the role of platelet function testing in patients undergoing percutaneous coronary intervention, the authors advocate the use of VerifyNow and Multiplate as point-of-care tests to prevent methodological errors during testing and to allow for easier generalisation of test results.[65] Nevertheless, the authors recommend that platelet function results should only be interpreted in the clinical and angiographic context of each individual as platelet reactivity to ADP should not be the only criterion on which to base the clinical decision.

In an observational study of patients undergoing off-pump CABG surgery the authors sought to compare the role of preoperative platelet function testing by comparing VerifyNow, TEG, AggreGuide, Plateletworks, vasodilator-stimulated phosphoprotein (VASP) phosphorylation and light transmission aggregometry (LTA).[66] However, they observed little correlation among the platelet function tests and little correlation between those assays and perioperative bleeding.

4.2.2.3. Neurointerventional procedures

Despite the increasing use of point-of-care platelet function assays, in a recent guideline, the authors state that most of the current evidence is extrapolated from other settings and there is insufficient data to recommend routine platelet function testing prior to neuroinvasive procedures.[67]

4.2.3. Genetic testing of patients with suspected platelet function disorders

Inherited platelet function disorders (PFDs) may be associated with normal or reduced platelet counts. PFDs account for a significant proportion of bleeding diatheses and the identification of the underlying genetic defects remains challenging.[68,69] The majority of patients with PFDs have normal platelet counts and mild bleeding symptoms but are at increased risk of bleeding in the context of trauma, surgery or childbirth.[70] In these patients, a significant number of mutations are heterozygous and, in isolation, are unlikely to cause extensive bleeding. The genetic complexity of PFDs highlights plausible candidate genes for targeted analysis.[71]

5. Anaemia management

5.1. Preoperative correction of anaemia

5.1.1. Introduction

Perioperative anaemia increases the risk of numerous complications, such as acute kidney injury.[72] Preoperative anaemia has been shown to be predictive for perioperative transfusion of allogeneic blood products such as RBCs, which itself carries a significant risk of adverse events and mortality.[73] A large study estimated the prevalence of preoperative anaemia to be 31.1% in women and 26.5% in men.[74] High rates have been reported in some orthopaedic procedures such as total knee arthroplasty (TKA), whereas lower rates have been observed in other orthopaedic procedures such as treatment of hip fracture.[75]

5.1.2. Preoperative assessment of anaemia

Recommendation

Preoperative anaemia in adults and children appears to be a strong predictor for perioperative blood transfusion across various types of conditions and surgeries and may be associated with adverse events. **B**

We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. **1C**

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