EJA

Eur J Anaesthesiol 2023; **40:**226–304

GUIDELINES

Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care

Second update 2022

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BACKGROUND Management of peri-operative bleeding is complex and involves multiple assessment tools and strategies to ensure optimal patient care with the goal of reducing morbidity and mortality. These updated guidelines from the European Society of Anaesthesiology and Intensive Care (ESAIC) aim to provide an evidence-based set of recommendations for healthcare professionals to help ensure improved clinical management.

DESIGN A systematic literature search from 2015 to 2021 of several electronic databases was performed without language restrictions. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to assess the methodological quality of the included studies and to formulate recommendations. A Delphi methodology was used to prepare a clinical practice guideline.

RESULTS These searches identified 137 999 articles. All articles were assessed, and the existing 2017 guidelines were revised to incorporate new evidence. Sixteen recommendations derived from the systematic literature search, and four clinical guidances retained from previous ESAIC guidelines were formulated. Using the Delphi process on 253 sentences of guidance, strong consensus (>90% agreement) was achieved in 97% and consensus (75 to 90% agreement) in 3%.

DISCUSSION Peri-operative bleeding management encompasses the patient's journey from the pre-operative state through the postoperative period. Along this journey, many features of the patient's pre-operative coagulation status, underlying comorbidities, general health and the procedures that they are undergoing need to be taken into account. Due to the many important aspects in peri-operative nontrauma bleeding management, guidance as to how best approach and treat each individual patient are key. Understanding which therapeutic approaches are most valuable at each timepoint can only enhance patient care, ensuring the best outcomes by reducing blood loss and, therefore, overall morbidity and mortality.

CONCLUSION All healthcare professionals involved in the management of patients at risk for surgical bleeding should be aware of the current therapeutic options and approaches that are available to them. These guidelines aim to provide specific guidance for bleeding management in a variety of clinical situations.

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DOI:10.1097/EJA.0000000000001803

Introduction

The management of bleeding during the peri-operative period requires a multimodal and multidisciplinary approach. Interventions begin during the pre-operative phase to identify patients who may be at higher risk of bleeding. This could be detection of any underlying coagulation abnormalities (inherited or acquired), withdrawing certain antithrombotic medications or detection and treatment of anaemia prior to any major surgical procedures. Attention to the appropriate use of blood products is increasing, with recommendations moving towards a more evidence-based peri-operative approach. In this active area of medicine, where there are multiple therapeutic options available, alongside surgical procedures of variable complexity, it is essential to remain informed by the latest evidence. As such, the European Society of Anaesthesiology and Intensive Care (ESAIC) is revisiting and updating the guidelines at least every five years to ensure that they remain relevant and incorporate the latest evidence. To address the full spectrum of care, this document includes updated recommendations, suggestions and statements from a systematic literature search, as well as retained clinical practice guidance from the guidelines published in 2017.[1]

Materials and methods

Task force assignment

In the planned process of revising the guideline, 'Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology' published in 2017,[1] in June 2020 the ESAIC Guideline Committee re-nominated the ESAIC task force previously selected, chaired by SK and composed of AA, CA and EDR. The ESAIC Guideline Committee and the task force defined the scope of the guideline revision, which prompted the four core group members to invite 20 experts to join the task force as affiliate co-authors (advisory group). During the COVID pandemic, communication with the extended panel was performed via e-mail and virtual and hybrid meetings were held.

Types of populations

The qualitative and quantitative analysis was confined to paediatric and adult surgical patients requiring major surgery with a relevant risk of bleeding and obstetric patients with (risk of) peri-partum haemorrhage. The guidelines deal with strategies for elective and (semi) urgent patients scheduled for various current surgical interventions, and for parturients but excludes trauma patients. Severe bleeding was defined in the ESAIC guidelines published in 2017 as a peri-interventional blood loss of more than 20% of the blood volume.[1]

Types of clinical queries

We identified clinical questions applicable to the broad group of patients regarding the timing of diagnostic, therapeutic and/or logistic interventions before, during and after severe peri-operative and postpartum bleeding management:

(1) Which patients should be optimised before the intervention and how?
(2) How should intra-operative and postoperative bleeding be treated and anaemia be corrected?

Types of clinical fields

Each clinical question was expanded further into 13 elements for the search strategy according to the surgical field and patient comorbidities (with delegated task force members' initials in brackets):

(1) orthopaedic surgery (LM, CS)
(2) neurosurgery (ML)
(3) visceral and transplant surgery (GB, ES)
(4) paediatric surgery (DFa, TH)
(5) cardiovascular surgery (AAh, AG, NRM)
(6) gynaecological surgery (AAf, AW)
(7) obstetric surgery (AW)
(8) patients with antithrombotic drugs (PA, JVL, CMS)
(9) patients with anaemia (SK, KZ)
(10) patients with congenital bleeding disorders (DF)
(11) patients with comorbidities and cofactors leading to haemostatic dysfunction (GB, EDR, ES)
(12) patients with uncontrolled bleeding requiring (ratio-based) allogeneic blood transfusion (SK)
(13) patients with COVID disease (AAh, DFr).

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Types of interventions

For each clinical question, the members of the task force searched the literature for indications, contraindications and complications of prophylactic and therapeutic interventions to correct anaemia and/or coagulopathy:

(1) iron, erythropoietin-stimulating agents (ESAs)
(2) antifibrinolytic agents [tranexamic acid (TXA), others]
(3) autologous cell salvage
(4) normothermia, buffers, electrolytes
(5) coagulation factor concentrates [fibrinogen, prothrombin complex concentrates (PCCs), recombinant activated factor VII (rFVIIa), factor XIII (FXIII), others]
(6) desmopressin (DDAVP)
(7) anticoagulant withdrawal, reversal agents
(8) topical haemostatic wound dressings.

The panel of task force members decided not to include surgical techniques, obstetric techniques and cost analyses.

Types of outcomes

Descriptive information was gathered for blood loss and transfusion of allogeneic blood products, including red blood cells (RBC), fresh frozen plasma (FFP), platelet concentrates, defined as the clinical outcome of interest.

Search methods for identification of studies

On the basis of the above elements, PICOs (Population/Intervention/Comparison/Outcome) were developed. However, following a decision of the ESAIC Guidelines Committee, the systematic literature search was not based on the developed series of PICO questions but, for reasons of cost-effectiveness and feasibility during the COVID pandemic, on a refined and updated bundle search strategy as applied for the ESAIC guidelines published in 2017,[1] including recent keynote publications. The search strategy was based on predefined criteria, and supplementary searches were performed to make this process as robust as possible with sufficient sensitivity to cover all of the defined PICOs. For the literature search in collaboration with the methodologist (AA) and the trial search specialist we searched Medline (Ovid), Embase (Embase.com), the Cochrane Library (Wiley) and BIOSIS (Web of Science). The searches were conducted in July 2021 and limited to publication dates between August 2015 and June 2021. Guidelines, case reports, editorials and commentaries were excluded from the search result. No other limitations were used. The exact search strategies and numbers of references for each search are reported in Appendix 1, http://links.lww.com/EJA/A802. The bibliography of all retrieved references was saved on an online platform hosted by ESAIC (SharePoint) and was accessible by all task force members.

Development of recommendations and clinical practice guidance

The following procedure for updating the previous guidelines[1] content was used: the guideline update uses the same grading system as in the previous guidelines – the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1).[2] 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 accompanied only by a letter, to indicate the quality of the evidence supporting the statement.

Subgroups of experts developed recommendations and an evidence summary relevant to their clinical question using GRADE. The strength of guidance (strong recommendations GRADE 1, weak suggestions GRADE 2) was discussed amongst the entire expert panel taking into account data synthesis, the risk of bias and the quality of evidence. All recommendations and suggestions were merged into a shared summary document by the co-ordinating author (SK). After a first round of internal review by all task force members, a revised summary document of recommendations was developed ahead of the hybrid task force meeting at Euroanaesthesia 2022. Thereafter, a second round of internal review was performed to formulate the final document for developing the consensus.

The systematic literature search did not retrieve information on all types of intervention and types of outcomes as published in the previous guidelines update in 2017.[1] To address the full spectrum of care, details from the previous guidelines[1] not retrieved from the current systematic literature search were merged into a clinical practice guidance document[2] and subjected to internal review to prepare the final document for developing the consensus. This method of updating the guidelines permits transparent and comprehensive guidance for clinicians managing severe peri-operative bleeding by implementing only this most recent publication.

During the COVID pandemic, discussions were performed via email, hybrid meetings and telephone calls without the opportunity of face-to-face meetings. All documents and files were saved on SharePoint for transparent visibility and accessibility for all task force members.

Development of consensus

A first Delphi process with the entire panel of task force members was performed on the gradings in the final version of the summary document of updated recommendations. The following definitions of the strength of the consensus were used:

(1) strong consensus: more than 90% agreement
(2) consensus: 75 to 90% agreement
(3) majority: 50 to 74% agreement
(4) no consensus: less than 50% agreement.

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 social 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

Similarly, a first Delphi process with the entire panel of task force members was performed on retaining information from the previous 2017 guidelines publication[1] in the clinical practice guidance document (without the GRADE system).

During the COVID pandemic, voting was via an online survey platform ('limesurvey') accessible to all task force members via a link sent to their email. Access to limesurvey was active for 2 weeks for voting.

A second Delphi round was conducted only on those recommendations, suggestions, statements and retained guidance with a consensus but not strong enough to reach a strong consensus threshold of 90%. This procedure permits checking if statements with consensus can achieve a strong consensus after a second reconsideration and revoting.[3–5]

Guidelines update manuscript preparation

Each manuscript draft and its revisions were reviewed by the entire panel. The final version of the document was endorsed by all members of the expert panel. This guideline update manuscript was reviewed by external reviewers and posted on the ESAIC website for 4 weeks and all individual and national ESAIC members were invited to comment. The revised manuscript was approved by the Guidelines Committee and the ESAIC Board of Directors before submission for publication.

These guidelines will be reviewed for a potential update within five years of publication.

Results

The systematic search retrieved 137 999 references; 85 519 references remained following removal of duplicates. Task force members reviewed the selected articles relevant to their sections and evaluated these according to the ESAIC policy on guidelines development.[6] Following critical appraisal of the literature, removal of duplicates and irrelevant studies and after inclusion of additional references recommended by the authors, 5131 references were selected as the systematic search result with which to formulate our recommendations, suggestions and statements.

A summary of guidance derived from the systematic literature search is listed in Table 2, listing the strength of guidance and certainty of evidence using GRADE. Reconfirmed guidance from the 2017 ESAIC guidelines version[1] is summarised in Table 3 without gradings. Using the Delphi process on 253 sentences of guidance, strong consensus was achieved in 97% and consensus in 3%; there was no lower degree of agreement (majority or no consensus). For the nine sentences subjected to a second vote, one reached a strong consensus; the remaining eight sentences were reconsidered for clarification. Results of the Delphi rounds are summarised in Table 4.

Table 2 Summary of guidance derived from the systematic literature search

Which patients should be optimised before surgery and how?
R1 Patients with pre-operative anaemia
Pre-operative anaemia in adults and children appears to be a strong predictor for peri-operative blood transfusion across various types of conditions and procedures and is associated with adverse events. A
We recommend that patients at risk of bleeding are assessed for anaemia well before surgery in order to permit time for anaemia correction if needed. 1B
We suggest a time interval of 1 to 2 weeks following parenteral stimulation of erythropoiesis and uncomplicated cause of anaemia, whereas 3 to 8 weeks may be required for oral correction of IDA and complex cause of anaemia. 2C
In noncancer patients with pre-operative anaemia scheduled for elective major surgery, we recommend postponing surgery until anaemia has been corrected. 1A
If pre-operative anaemia is present, we recommend identifying the cause (iron deficiency, renal insufficiency or inflammation). 1C
We recommend defining an internal hospital algorithm for a comprehensive differential diagnosis of pre-operative anaemia. 1C
We recommend treating IDA with iron supplementation at weight-based dosing after considering contraindications. 1A
We recommend the use of intravenous iron in preference to oral iron. 1C
We suggest erythropoietin-stimulating agents if pre-operative anaemia is present and other causes (e.g. autoimmune, bone marrow dysfunction, nutritional deficiencies) have been excluded or treated. 2A
We recommend against pre-operative RBC transfusion to mask pre-operative mild-to-moderate anaemia. 1C
We suggest that RBC transfusion can be considered in pre-operative anaemia that could not be corrected by comprehensive haematological therapy. 2C
Use of noninvasive haemoglobin monitoring early at indication for surgery/in the pre-anaesthesia clinic may speed up detection of pre-operative anaemia and correction. C
If autologous blood donation is performed, we suggest concomitant treatment with iron and/or erythropoietin-stimulating agents to avoid pre-operative anaemia and increased overall transfusion rates. 2C
R2 Patients with antithrombotic drugs
Antiplatelet agents
We recommend that aspirin for secondary prevention should be continued peri-operatively in most surgical settings, especially cardiac surgery. 1C
We recommend that aspirin should be discontinued preoperatively when prescribed for primary prevention. 1B
Where aspirin withdrawal before surgery is considered, we recommend a time from last drug intake to intervention of 3 days, although for invasive procedures at high risk of bleeding, a longer interruption (5 days) could be considered. 1C
In patients with risk factors for vascular complications with no previous antiplatelet treatment, we do not recommend starting aspirin preoperatively (except for carotid endarterectomy). 1B
In patients chronically treated with aspirin for secondary prevention of cardiovascular events, except those patients with coronary stents, aspirin may be interrupted for procedures with a very high bleeding risk. 1B
In patients chronically treated with aspirin for secondary prevention of cardiovascular events, aspirin must be maintained during and after low and moderate bleeding risk procedures. 1B
Timing of first administration and dose of postoperative anticoagulants, along with resumption of aspirin, after the procedure must be carefully discussed to mitigate postoperative bleeding complications. 2C
For intra-operative or postoperative bleeding (e.g. in neurosurgery) supposedly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7×10^{11} 10 kg^{-1} body weight in adults). 2C
We recommend that aspirin be continued for at least 4 weeks after bare metal stent implantation and for 3 to 12 months after drug-eluting stent implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high. 1A
Continuation of $P2Y_{12}$ inhibitor treatment should be considered for at least 4 weeks after bare metal stent implantation and for 3 to 6 months after drug-eluting stent implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high. 2A
In patients treated with $P2Y_{12}$ inhibitors, who need to undergo surgery, postponing surgery for at least 5 days after cessation of ticagrelor and clopidogrel (time from last drug intake to intervention) – and for 7 days in the case of prasugrel – if clinically feasible, should be considered unless the patient is at high risk of an ischaemic event. 2B
We recommend that antiplatelet agent therapy should resume as soon as possible postoperatively to prevent platelet activation and ischaemic events. 1C
If $P2Y_{12}$ inhibitors have to be discontinued peri-operatively, they should be resumed early, if possible within 24 to 72 h after surgery, given the increased thrombotic risk. Resumption is performed with the same $P2Y_{12}$ inhibitor as preoperatively. No recommendation can be made regarding the use or not of a loading dose. 2C
We recommend against peri-operative use of nonsteroidal anti-inflammatory drugs in patients treated with dual antiplatelet therapy; peri-operative use of coxibs is possible. 1C
We recommend that a multidisciplinary team meeting should decide on the peri-operative use of antiplatelet agents in urgent and semi-urgent surgery. 1C
Noncardiac elective surgery should be postponed until completion of the full course of dual antiplatelet therapy. 1A
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 in cases of intra-operative or postoperative bleeding supposedly related to clopidogrel or prasugrel. A higher dose than that used to neutralise aspirin is proposed for $P2Y_{12}$ inhibitors. 2C
Platelet transfusion may be ineffective for treating bleeding supposedly related to ticagrelor when given 12 h before. C
In high-thrombotic-risk patients under dual antiplatelet therapy, if the interruption of $P2Y_{12}$ receptors inhibitors is considered unacceptable by a multidisciplinary team, bridging with the ultra-short acting $P2Y_{12}$ receptor inhibitor (cangrelor) or short-acting glycoprotein IIbIIIa inhibitors may be considered. 2C
Heparin, fondaparinux and vitamin K antagonists (VKA)
We recommend that severe bleeding associated with i.v. UFH should be treated with i.v. 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 UFH unresponsive to i.v. protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of i.v. protamine, with the dose guided by anti-Xa activity, and if not available by aPTT. 2C
We suggest that severe bleeding related to subcutaneous LMWH should be treated with i.v. protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered and, if unresponsive, anti-Xa activity should be measured. 2C
We suggest that the administration of rFVIIa could be considered to treat severe bleeding associated with subcutaneous administration of fondaparinux (off-label treatment). 2C
We recommend that VKAs should not be interrupted in patients undergoing low-bleeding-risk procedures: skin surgery, dental and stomatological procedures, gastric and colonic endoscopies (even if biopsy is scheduled but not polypectomies), nor for most ophthalmological surgery (mainly anterior chamber, cataract surgery). 1C
We recommend that for low, moderate and high-thrombotic-risk patients undergoing procedures requiring INR less than 1.5, the time from last VKA intake to intervention should be 3 to 5 days; if INR is more than 1.5 on the day before surgery, 5 mg oral vitamin K is recommended. 1C

Table 2 (*continued*)

Which patients should be optimised before surgery and how?
We suggest against bridging of VKA with LMWH or UFH in low, moderate and high-thrombotic-risk patients; in very specific high-risk patients, the treatment should be based on case-by-case analysis. 2C
We recommend that in patients with pre-operative VKA intake, VKA should be resumed within 24 h after the procedure, administering a LMWH in prophylactic dose until the target INR is observed in two following measurements. 1C
In specific patients (such as inability to take oral medication), postoperative bridging of VKA with a LMWH in therapeutic dose could be started within 48 to 72 h after the procedure, once the haemostasis has been secured. 1C
In VKA-treated patients undergoing an emergency moderate-to-high bleeding-risk 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 (at an initial dose of 25 IU factor IX kg^{-1} at an INR of 4) over 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 intravenous vitamin K. 1B
If PCC is not available, 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 i.v. vitamin K. 1C
Direct oral anticoagulants (DOACs)
We recommend assessing creatinine clearance in patients receiving DOACs that are scheduled for surgery. 1B
We suggest that DOACs can be given up to the day before surgery for patients undergoing low-bleeding-risk procedures such as skin surgery, dental and stomatological procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but no polypectomies) and most ophthalmological surgery. 2C
For intermediate-bleeding-risk and high-bleeding-risk procedures:
We recommend that for rivaroxaban, apixaban and edoxaban, the time from last drug intake to intervention should be 3 days, pending a creatinine clearance (Cockcroft–Gault formula) above 30 ml min^{-1}. No bridging is recommended. 1C
We recommend that for dabigatran, the time from last drug intake to intervention should be 3 days, if the creatinine clearance is above 50 ml min^{-1}, and 5 days if the creatinine clearance is between 30 and 50 ml min^{-1}. No bridging is recommended. 1C
We suggest that in severe bleeding patients treated with dabigatran, a specific antidote (idarucizumab) could be considered. 2C
We suggest the use of PCC (25 IU kg^{-1} at first) rather than andexanet alpha in bleeding patients treated with anti-Xa agents (rivaroxaban, apixaban and edoxaban). 2C
We suggest that for low-bleeding-risk procedures, when haemostasis is achieved, DOACs should be restarted about 6 h after the procedure without LMWH administration. 2C
We suggest that for intermediate-bleeding-risk and high-bleeding-risk procedures, prophylactic doses of LMWH or DOACs (according to specific indications) should be given postoperatively whenever a thromboprophylaxis is requested and then the full therapeutic dose of DOAC should be resumed up to 72 h postoperatively, when surgical haemostasis is achieved. 2C
R3 Patients with comorbidities involving haemostatic derangement
Point-of-care tests of platelet function and bleeding time are not useful to predict bleeding risk in uraemic patients undergoing invasive procedures. 2C
Desmopressin therapy is suggested in high-risk uraemic patients for reducing bleeding during invasive procedures and for managing acute bleeding. 2C
Conjugated oestrogen therapy could be considered in uraemic platelet dysfunction. 2C
Despite altered standard coagulation tests, haemostasis may be balanced in stable chronic liver disease. C
Mild-to-moderate prolongation of the preprocedural PT and INR and moderate thrombocytopenia do not predict bleeding in patients with chronic liver disease. C
Fibrinogen-level assessment is suggested in patients with advanced liver disease undergoing invasive procedures. 2C
Viscoelastic haemostatic assay (VHA) guidance is recommended for reducing allogeneic blood product transfusion in cirrhotic patients undergoing invasive procedures. 1C
In cirrhotic patients with severe thrombocytopenia scheduled to undergo high-risk invasive procedures, thrombopoietin receptor agonists (avatrombopag or lusutrombopag) may be considered. 2B
Patients with chronic liver disease are not auto-anticoagulated; we recommend an individualised thromboprophylaxis strategy. 1C
In acute liver failure, elevated INR does not predict bleeding risk. 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
R4 Patients on chronic medication associated with disturbed haemostasis
We suggest individualised peri-operative management of selective serotonin re-uptake inhibitor treatment. 2B
We suggest individualised pre-operative management of antiepileptic agents, such as valproic acid, which may increase bleeding. 2C
We do not recommend pre-operative discontinuation of *Gingko biloba* extracts. 1B
R5 Patients with inherited bleeding disorders
We suggest the use of bleeding assessment tools for detecting and predicting the peri-operative risk of bleeding before surgery and invasive procedures in patients with suspected or confirmed inherited bleeding disorders. 2B
Patients with inherited bleeding disorders are at higher risk of peri-operative bleeding and should be managed in collaboration with a haematologist, preferably in dedicated centres with expertise in coagulation disorders. 1B
We suggest individualised pre-operative haemostatic correction depending on the specific disorder, type of surgery and individual factors (bleeding phenotype). 2C
We recommend replacement/substitution therapy with factor concentrates, either plasma-derived or recombinant products, for major bleeding/surgery in patients with von Willebrand disease or haemophilia A and B. 1C
For haemophilia patients with inhibitors, we suggest either recombinant factor VIIa or activated PCCs. 2C
We recommend against routine peri-operative platelet transfusion in patients with inherited platelet disorders. 1C
We suggest desmopressin as a first-line treatment for minor bleeding/surgery in patients with von Willebrand disease or mild haemophilia A, after a test trial and in the absence of contraindications. 2C
We suggest peri-operative antifibrinolytics as adjunct therapy in patients with haemophilia or von Willebrand disease. 2B
Antifibrinolytic agents may be used as peri-operative haemostatic monotherapy in patients with haemophilia or von Willebrand disease undergoing minor mucosal or dental procedures and in patients with inherited platelet defects. 2C
We suggest that recombinant factor VIIa be considered in patients with Glanzmann thrombasthenia undergoing surgery. 2C
We suggest that recombinant factor VIIa be used in peri-operative bleeding because of inherited factor VII deficiency. 2C
R6 Patients with critical illness, COVID-19 coagulopathy or post-COVID-19 disease
We recommend against major elective surgery in patients with COVID-19 coagulopathy. 1C
In (semi)urgent surgery in patients with COVID-19 coagulopathy, we suggest avoiding prophylactic tranexamic acid administration. 2C

Table 2 (*continued*)

Which patients should be optimised before surgery and how?
We suggest VHA-guided, goal-directed procoagulant treatment of peri-operatively acquired coagulopathic bleeding avoiding overcorrection. 2C
Peri-operative drug-monitoring of LMWH used as standard anticoagulant in COVID-19 critical illness is suggested. If anti-Xa activity is more than 0.3 IU ml^{-1} in clinical bleeding, reversal with protamine may be considered. 2C
We suggest a restrictive RBC transfusion strategy as in non-COVID-19 patients. 2C
In patients recovered from COVID-19 and free of post-COVID-19 symptoms, we suggest management of severe peri-operative bleeding as in non-COVID-19 patients. 2C
Postoperative thromboprophylaxis should be administered as early as possible. 1C
We recommend a restrictive RBC, plasma and platelet transfusion strategy in critical illness. 1C
We suggest the use of a goal-directed coagulation therapy algorithm in the presence of ongoing bleeding, taking into account altered laboratory tests and VHA in critical illness. 2C
We suggest in presence of ongoing bleeding unresponsive to multimodal coagulation therapy or wound healing defects in critically ill to monitor FXIII and correct deficiency. 2C
We suggest a restrictive systemic administration of tranexamic acid in case of fibrinolytic shutdown in critical illness. 2C
We recommend initiating thrombophylaxis after bleeding as soon as bleeding risk is overbalanced by the risk of thromboembolic complications. 1C
How should intra-operative and postoperative bleeding be stopped and anaemia be managed?
R7 Patients undergoing cardiovascular surgery
Withdrawal of aspirin treatment before surgery might increase the risk of coronary thrombosis; however, continuation of aspirin treatment increases the risk of bleeding. B
Withdrawal of treatment with $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor) before surgery might increase the risk of coronary thrombosis; however, continuation of clopidogrel therapy increases the risk of bleeding. B
In patients on dual antiplatelet therapy who need to undergo nonemergent cardiac surgery, postponing surgery for at least 5 days after discontinuation of ticagrelor or clopidogrel and 7 days after prasugrel should be considered. 2B
Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors. B
Bridging oral antiplatelet therapy with LMWH is not recommended. 1A
Bridging $P2Y_{12}$ inhibitors with glycoprotein IIbIIIa inhibitors or cangrelor may be considered in high-ischaemic-risk patients. 2B
We suggest that aspirin or $P2Y_{12}$ inhibitors may be administered in the early postoperative period without increasing the risk of postoperative bleeding. 2C
We recommend prophylactic administration of tranexamic acid (or if not available ε-aminocaproic acid) before cardiopulmonary bypass to reduce postoperative blood loss and blood transfusion requirements. 1B
We recommend administering tranexamic acid or ε-aminocaproic acid intravenously at low doses. 1B
If systemic administration of tranexamic acid is contraindicated (e.g. refractory seizure), topical tranexamic acid is suggested. 2C
Upon withdrawal from cardiopulmonary bypass, we suggest the use of heparin monitoring to avoid protamine-to-heparin dosing ratios above 1. 2B
We recommend treatment with fibrinogen concentrate or cryoprecipitate if bleeding is accompanied by hypofibrinogenaemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level $\leq$1.5 g l^{-1}). 1B
We recommend treatment with PCC if available instead of fresh frozen plasma if bleeding is accompanied by signs of coagulation factor deficiency (viscoelastic signs of a functional coagulation factor deficiency or a high PT ratio). 1B
We suggest that recombinant factor VIIa may be considered for patients with bleeding that remains intractable after conventional haemostatic therapy has been applied, although the risk of thrombosis must be taken into account. 2B
We recommend the use of standardised haemostatic algorithms with predefined intervention triggers over clinicians' discretion for the management of coagulopathy in cardiac surgery. 1B
We suggest the use of point-of-care haemostatic testing over conventional coagulation assays for the management of coagulopathy in cardiac surgery. 2C
In patients on ticagrelor or rivaroxaban undergoing emergency cardiac/aortic surgery on cardiopulmonary bypass, haemoadsorption may be considered as an adjuvant therapy to reduce bleeding complications. 2C
We suggest the use of acute normovolaemic haemodilution in cardiac surgical patients with normal/high initial haemoglobin concentration. 2C
We recommend the use of red cell salvage, which is helpful for blood conservation in major cardiac surgery. 1B
We recommend against the routine use of intra-operative platelet-rich plasmapheresis for blood conservation during cardiac operations using cardiopulmonary bypass. 1B
R8 Patients undergoing orthopaedic surgery
We recommend the prophylactic use of TXA as a safe pharmacological agent to reduce blood loss and transfusion requirements in patients with a relevant risk for bleeding undergoing major orthopaedic surgery. 1A
We recommend the oral, intravenous and/or topical route to administer tranexamic acid. A combination of systemic and topical administration of tranexamic acid further reduces blood loss. 1B
We suggest ε-aminocaproic acid as an alternative to tranexamic acid if not available as an antifibrinolytic agent to reduce blood loss. 2B
The use of intra-operative tourniquet in primary knee arthroplasty may not reduce global peri-operative bleeding and transfusion rate. C
The use of drainage may not decrease blood loss in knee arthroplasty, total hip arthroplasty or spine surgery. C
The type of surgical approach in total hip arthroplasty may not reduce peri-operative blood loss. C
We recommend a hip fracture treatment within 48 h to avoid global peri-operative complications. 1B
Allogeneic blood transfusion is associated with an increased incidence of surgical site infections. B
The osteosynthesis technique of proximal endomedullary nailing may reduce blood loss in trochanteric femur fracture. 1B
We suggest the maintenance of restrictive transfusion thresholds in the management of hip fracture. 2C
We suggest in the presence of ongoing bleeding as part of a goal-directed coagulation therapy algorithm, monitoring of FXIII and correction of deficiency. 2C
We suggest the intra-operative and postoperative use of cell salvage in major orthopaedic procedures with high risk of bleeding. 2B
R9 Patients undergoing visceral and transplant surgery
Liver resection
We recommend a low central venous pressure and restrictive fluid administration during liver surgery to reduce bleeding. 1A
Intra-operative hypovolaemic phlebotomy or infrahepatic inferior vena cava clamping applied together with low central venous pressure strategy are suggested in order to decrease intra-operative blood loss and transfusion requirements in selected patients undergoing major liver resection. 2C
Maintenance of high stroke volume variation (10 to 20%) could be considered in liver resection surgery to reduce bleeding. 2B
During the liver resection phase, ventilation with low airway pressures achieved by low tidal volumes, and without positive end-expiratory pressure is suggested along with a low central venous pressure strategy in order to decrease intra-operative bleeding. 2B

Table 2 (*continued*)

How should intra-operative and postoperative bleeding be stopped and anaemia be managed?
Together with other measures, terlipressin infusion may be considered during hepatobiliary surgery to reduce bleeding. 2B
Improved surgical haemostatic devices and the use of topical haemostatic agents are suggested in order to decrease bleeding and blood product requirement during liver resections. 2C
Pre-operative continuation of aspirin monotherapy might be considered in liver resection patients. 2C
VHA could be considered for the peri-operative detection of hypercoagulability and venous thromboembolic risk in chronic liver disease and in patients undergoing liver resection for cholangiocarcinoma. 2C
We suggest that tranexamic acid should be considered in cirrhotic patients undergoing liver resection. 2C
Orthotopic liver transplantation
Higher intra-operative blood loss and transfusion requirements are associated with decreased survival after liver transplantation. C
A strategy for lowering portal pressure during the dissection and liver resection phases (using a low central venous pressure strategy by fluid restriction and/or phlebotomy, vasopressors) and VHA-guided transfusion protocols are recommended in order to decrease blood product transfusion rate during orthotopic liver transplantation. 1C
Conventional coagulation test results outside the reference range in the absence of anticoagulant therapy do not reliably predict bleeding or exclude hypercoagulability in patients with chronic liver disease. C
Pre-operative VHA may be useful in predicting blood loss and intra-operative transfusion requirements in liver transplantation. C
In patients undergoing liver transplantation, VHA monitoring with assessment of fibrinogen is recommended for guiding fibrinogen replacement. 1C
In postoperative liver transplant patients, VHA with fibrinogen assessment may be considered for postoperative monitoring of coagulation together with VHA-guided use of coagulation factors and/or blood products. 2C
We recommend tranexamic acid for treatment of fibrinolysis in orthotopic liver transplantation but not for routine prophylaxis; marginal grafts (example donation after cardiac death) increase the risk of fibrinolysis postreperfusion. 1C
Prothrombin complex concentrate administration in low doses guided by VHA (prolonged coagulation initiation or increased INR if no VHA available) is suggested in the presence of clinically significant bleeding in patients without fibrinogen deficiency. 2C
In liver transplant, fibrinogen concentrate use should be restricted only to patients with documented hypofibrinogenaemia (by standard coagulation tests or VHA). 1C
Pre-emptive fibrinogen administration before liver transplantation is not recommended. 1C
Recombinant factor VIIa is not recommended for routine use in orthotopic liver transplantation and should be used only as rescue therapy for uncontrolled bleeding. 1C
We suggest the use of cell salvage and autotransfusion with leukodepletion filters in liver transplantation including patients with hepatocellular carcinoma. 2C
Other visceral surgery
Tranexamic acid administered systemically or locally in the irrigant fluid may be considered to decrease peri-operative blood loss in percutaneous nephrolithotomy. 2B
Tranexamic acid may be considered in order to decrease peri-operative blood loss in prostate surgery. 2B
Prophylactic administration of fibrinogen concentrate is not recommended in prostate surgery. 1C
Computed tomography scan or angiography are suggested for the diagnosis of late bleeding after pancreatectomy, and endovascular interventional therapy is suggested as primary treatment. 2C
Pre-operative chronic antithrombotic therapy and peri-operative chemical thromboprophylaxis seem not to increase peri-operative haemorrhagic complications in patients undergoing hepatobiliary–pancreatic surgery. C
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
R10 Patients with acute upper gastrointestinal bleeding
Beta-blockers, variceal band ligation, sclerotherapy and beta-blockers plus nitrates are recommended as primary prophylaxis for bleeding in cirrhotic patients with high-risk oesophageal varices. 1C
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
We recommend early interventional endoscopy together with vasoactive medication producing splanchnic vasoconstriction (somatostatin, terlipressin or octreotide) in acute variceal bleeding. 1B
Transjugular intrahepatic portosystemic shunt or surgical shunts can be suggested as an option for rescue therapy after initial medical and endoscopic therapy fail. 2C
Early transjugular intrahepatic portosystemic shunt placement (within 72 h from endoscopy) can also be considered in selected high-risk cirrhotic patients with acute variceal bleeding following initial haemostasis using pharmacological management and endoscopic band ligation. 2C
For secondary prophylaxis of variceal bleeding in cirrhosis, the combination of drug treatment with beta-blockers and endoscopic therapy with band ligation is recommended. 1C
Use of FFP in cirrhotic patients with acute variceal bleeding is associated with increased mortality, failure to control bleeding and longer length of stay. C
A restrictive transfusion policy aiming for a haemoglobin level of 7 to 8 g dl^{-1} is recommended in haemodynamically stable patients with upper gastrointestinal bleeding. 1B
We recommend against the systemic administration of tranexamic acid for the treatment of gastrointestinal bleeding. 1B
In nonvariceal upper gastrointestinal bleeding due to peptic ulcer, endoscopic therapy combined with high-dose proton pump inhibitors is recommended. 1C
In failed endoscopic treatment of bleeding peptic ulcer, angiographic embolisation and/or surgery are considered. 2C
R11 Patients undergoing gynaecological (nonpregnant) surgery
We suggest that normovolaemic haemodilution could be used as an alternative approach in the gynaecological cancer population in order to reduce allogeneic transfusion. 2B
Cell salvage may reduce allogeneic transfusion in gynaecological (including oncological) surgery. B
We recommend using pre-operative intravenous iron to reduce allogeneic transfusion requirements in anaemic gynaecological cancer patients receiving chemotherapy. 1C
We suggest using intravenous iron to correct pre-operative anaemia in women with menorrhagia. 2B
We recommend the combined administration of erythropoietin and iron in gynaecological patients with IDA. 1C
We recommend tranexamic acid for reduction of peri-operative bleeding in all types of gynaecological cancer surgery. 1C
We recommend tranexamic acid for reduction of peri-operative bleeding for abdominal, laparoscopic, robotic or hysteroscopic myomectomy. 1C
We recommend tranexamic acid for reduction of peri-operative bleeding for hysterectomy. 1C
Tranexamic acid is not routinely advised for hysteroscopy and surgery for ectopic pregnancies. C
The recommended dose of tranexamic acid for gynaecological surgery is either a single dose of 1000 mg intravenously or as 10 to 15 mg kg^{-1} or topically. 1C
In patients undergoing myomectomy, pre-operative misoprostol administration is recommended in order to decrease intra-operative blood loss and blood transfusion requirements. 1C

Table 2 (*continued*)

How should intra-operative and postoperative bleeding be stopped and anaemia be managed?
R12 Obstetric surgery
We recommend that postpartum haemorrhage should be managed by a multidisciplinary team. 1C
We recommended the use of an escalating postpartum haemorrhage management protocol including uterotonic drugs, surgical and/or endovascular interventions and procoagulant drugs. 1B
Risk awareness and early recognition of severe postpartum haemorrhage are essential. C
We suggest that patients with known placenta accreta spectrum disorders (PAS) be treated by multidisciplinary care teams. 2C
We suggest implementation of Patient Blood Management Programmes in obstetric patients. 2B
We recommend one unit RBC treatment (single unit strategy) as opposed to two units in haemodynamic stable patients with anaemia. 1B
Cell salvage is well tolerated in obstetric settings, provided that precautions are taken against rhesus isoimmunisation. C
We suggest that using peri-operative cell salvage during caesarean section with high risk of haemorrhage may decrease homologous transfusion. 2B
We recommend intravenous iron supplementation as this elicits a faster recovery from anaemia with fewer gastrointestinal complaints than oral iron treatment. 1B
Intravenous iron supplementation improves fatigue and depression score 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 postpartum haemorrhage. 1C
Coagulopathy risk assessment should include the obstetric conditions associated with PPH not just an estimated blood loss. 1C
High-volume resuscitation with crystalloids and colloids is associated with coagulopathy and adverse maternal outcomes in women with postpartum haemorrhage. C
Dynamic platelet count decrease or a level less than 150×10^9 l^{-1} at the onset of labour, particularly if combined with plasma fibrinogen level less than 2.0 g l^{-1}, may indicate an increased risk of postpartum haemorrhage. C
At the beginning of labour, aPTT and PT are of little predictive value for postpartum haemorrhage. C
VHA can identify obstetric coagulopathy including hypofibrinogenaemia and reduced platelet level. B
VHA-guided haemostatic treatment reduces the need for blood products. B
We recommend against pre-emptive fibrinogen replacement; however, in ongoing postpartum haemorrhage with hypofibrinogenaemia, we recommend fibrinogen replacement. 1B
Fibrinogen substitution in women with ongoing postpartum haemorrhage and a fibrinogen level above 2 g l^{-1} or FIBTEM A5 >12 mm is not indicated. 1B
In severe postpartum haemorrhage, we suggest a VHA-guided intervention protocol. 2C
We recommend the administration of tranexamic acid in postpartum haemorrhage at a dose of 1 g intravenously as soon as possible within 3 h, which can be repeated if bleeding continues. 1B
We suggest that TXA be considered before high-risk caesarean section and vaginal deliveries or cases of antepartum bleeding. 2B
We suggest that administration of recombinant factor VIIa can be considered for life-threatening postpartum haemorrhage, which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails. 2C
We recommend against a prophylactic/general use of recombinant factor VIIa in postpartum haemorrhage because of increased risk of fatal thrombosis. 1C
R13 Patients undergoing neurosurgical bleeding
For reversal of VKA-associated nontraumatic intracranial bleeding, PCC is recommended. 1B
For reversal of VKA-associated nontraumatic intracranial bleeding, we recommend against plasma transfusion. 1B
Intracranial surgery can be safely performed in the presence of low-dose aspirin. 2C
For reversal of antiplatelet agent-associated nontraumatic intracranial bleeding, we suggest platelet transfusion or desmopressin. 2C
Tranexamic acid intravenously as bolus with or without infusion, beginning from induction of anaesthesia until end of surgery are recommended prophylactically for reducing peri-operative blood loss in elective intracranial surgery and elective spine surgery. 1B
R14 Paediatric surgery
We suggest VHA-guided interventions to help guide transfusion in neonates and children undergoing cardiac and noncardiac surgery. 2C
We recommend basing the decision for transfusion of RBCs not only on laboratory analysis but also on the clinical status of the child, and the risks and benefits of the transfusion. 1C
We recommend against a transfusion if the child is haemodynamically stable and has a haemoglobin concentration of at least 7 g dl^{-1}. 1B
We suggest administering fibrinogen concentrate to a child suffering from peri-operative bleeding and who was diagnosed with hypofibrinogenaemia. 2B
We recommend the prophylactic administration of antifibrinolytics in neonates and children undergoing noncardiac surgery associated with a high bleeding risk to decrease blood loss and the need for transfusions. 1C
R15 Intra-operative transfusion triggers and volume management
We recommend a target haemoglobin concentration of 7 to 9 g dl^{-1} during active bleeding. 1B
In patients with a superior vena cava catheter in place, we recommend central venous oxygen saturation or arterial–venous oxygen difference surrogates for the oxygen delivery to consumption ratio to provide a individualised approach to identifying patients who may benefit from transfusion. 1C
We recommend repeated measurements of a combination of haematocrit/haemoglobin, serum lactate and base deficit to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. 1C
We recommend that these assessments should be extended by measurement of cardiac output, dynamic variables of volume status (stroke volume variation and pulse pressure variation), CO_2 gap and central venous oxygen saturation or the combination of these. 1C
We recommend the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol-based manner. 1B
Compared with crystalloids, macro-haemodynamic and micro-haemodynamic stabilisation can be achieved with a smaller volume of iso-oncotic colloids and 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
R16 Intra-operative and postoperative anaemia management
In the early treatment phase of uncontrolled massive elective surgery bleeding, we suggest massive transfusion (≥6 to 10 units) with a high ratio (≥1 : 1) of plasma to RBCs. 2C

Table 2 (*continued*)

How should intra-operative and postoperative bleeding be stopped and anaemia be managed?
We recommend switching to a goal-directed transfusion strategy (based on haemoglobin and/or physiological RBC transfusion triggers, coagulation factor substitution and platelet transfusion triggers) as soon as possible. 1C
We recommend monitoring of haemoglobin concentrations for anaemia detection prior to, during and after high-bleeding-risk surgery and in situations where silent bleeding, massive blood loss and fluid shifts are at least suspected. 1A
After severe peri-operative bleeding, haemoglobin levels should be monitored during the first postoperative days. 1C
When severe bleeding and volume shifts are expected and/or occurring, continuous noninvasive haemoglobin monitoring may be considered for trend analyses and for reducing blood sampling for invasive laboratory measurement of haemoglobin concentration, especially in children. 2C
In postoperative anaemia with haemoglobin at least 10 g dl^{-1}, we suggest testing for iron deficiency and subsequent administration of intravenous iron at weight-based dosing if ferritin less than 100 $\mu g\,l^{-1}$ or ferritin less than 300 $\mu g\,l^{-1}$ and transferrin saturation less than 20%. 2C
In postoperative anaemia with haemoglobin less than 10 g dl^{-1}, we recommend timely intravenous iron administration at weight-based dosing after considering contraindications. 1B We suggest considering additional treatment with an erythropoietin-stimulating agents. 2C
In postoperative anaemia with haemoglobin less than 6 to 8 g dl^{-1} or falling below physiological RBC transfusion triggers (based on signs of organ ischaemia and adequacy of cardiopulmonary reserve), we recommend RBC transfusion at a single unit strategy. 1C
For postoperative iron administration, we recommend intravenous over oral iron administration. 1B
Intravenous iron formulations allowing higher maximal single doses (such as isomaltoside and carboxymaltose) may be more effective than those with low licensed maximum single doses (such as sucrose). B

aPTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; IDA, iron deficiency anaemia; INR, international normalised ratio; LMWH, low-molecular-weight heparin; PCC, prothrombin complex concentrate; PT, prothrombin time; RBC, red blood cells; UFH, unfractionated heparin; VHA, viscoelastic haemostatic assay; VKA, vitamin K antagonist.

Table 3 **Summary of reconfirmed guidance from previous guidelines**[1]

G1 Evaluation of the 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.
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.
We recommend the use of intervention algorithms incorporating predefined triggers and targets based on viscoelastic haemostatic assay (VHA) coagulation monitoring to guide individualised haemostatic intervention in the case of peri-operative bleeding.
If VHA is not available, we recommend the use of intervention algorithms incorporating predefined triggers based on conventional coagulation tests.
We suggest pre-operative platelet function testing only in association with a positive bleeding history.
We suggest that pre-operative platelet function testing be used to identify decreased platelet function caused by medical conditions or antiplatelet medication.
Bleeding time is influenced by many variables and is not useful for stratifying bleeding risk.
G2 General coagulation management
We recommend maintaining peri-operative normothermia because it reduces blood loss and transfusion requirements.
We recommend that pH correction should be pursued during treatment of acidotic coagulopathy, although pH correction alone cannot immediately correct acidosis-induced coagulopathy.
We recommend that recombinant factor VIIa should only be considered alongside pH correction.
We recommend that calcium should be administered during massive transfusion if calcium concentration is low, in order to preserve normocalcaemia (>0.9 mmol l^{-1}).
We recommend early and targeted treatment of coagulation factor deficiencies in the plasma.
We recommend against antithrombin supplementation in elective surgical patients, while they are bleeding.
G3 Transfusions
We recommend that all countries implement national haemovigilance quality systems.
We recommend a restrictive transfusion strategy, which is beneficial in reducing exposure to allogeneic blood products.
Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections.
We recommend that RBCs should be transfused according to the first-in, first-out method in the blood services to minimise wastage of erythrocytes.
We recommend that labile blood components used for transfusion are leukodepleted.
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.
We recommend pathogen inactivation for fresh frozen plasma and platelets.
We recommend a male-only donor policy for plasma-containing blood products to prevent the onset of transfusion-associated acute lung injury.
We recommend that all RBC, platelet and leukocyte donations from first-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.
Plasma transfusion alone is not sufficient to correct hypofibrinogenaemia.
We recommend against the use of plasma transfusion for preprocedural correction of mild-to-moderately elevated INR.
We recommend against indiscriminate use of plasma transfusion in peri-operative bleeding management.
We recommend a restrictive plasma transfusion strategy and recommend against the use of plasma for volume replacement.
G4 Education and training
We recommend structured staff education and training.

aPTT, activated partial thromboplastin time; INR, international normalised ratio; RBC, red blood cell; VHA, viscoelastic haemostatic assay.

Table 4 Summary of Delphi results

	Sentences for voting (*n*)	Agreement category in first Delphi voting[a]	Conversion to strong consensus in second Delphi voting[b]
Guidance derived from the systematic literature search (Table 2)			
R1	14	Strong consensus	
R2	40	Strong consensus in 38 sentences Consensus in two sentences[c,d]	1[c]
R3	11	Strong consensus	
R4	3	Strong consensus	
R5	11	Strong consensus	
R6	12	Strong consensus in 11 sentences Consensus in one sentence[e]	0
R7	21	Strong consensus in 20 sentences Consensus in one sentence[f]	0
R8	12	Strong consensus in 11 sentences Consensus in one sentence[g]	0
R9	27	Strong consensus	
R10	11	Strong consensus	
R11	11	Strong consensus	
R12	24	Strong consensus in 23 sentences Consensus in one sentence[h]	0
R13	5	Strong consensus in four sentences Consensus in one sentence[i]	0
R14	5	Strong consensus	
R15	8	Strong consensus	
R16	11	Strong consensus	
Guidance from the 2017 ESAIC guidelines version (Table 3)			
	27	Strong consensus to retain 25 sentences Consensus in two sentences[j,k]	0

[a] Strong consensus more than 90%, consensus 75 to 90%, majority 50 to 74%, no consensus less than 50%. [b] Second round of voting only on sentences of guidance with a consenus in first round. [c] We recommend that in patients with pre-operative VKA intake, VKA should be resumed within 24 h after the procedure, administering a LMWH in prophylactic dose until the target INR is observed in two following measurements 1C. In specific patients (such as inability to take oral medication) postoperative bridging of VKA with a LMWH in therapeutic dose could be started within 48 to 72 h after the procedure, once the haemostasis has been secured. 1C. [d] Timing of first administration and dose of postoperative anticoagulants, along with resumption of aspirin, after the procedure must be carefully discussed to mitigate postoperative bleeding complications. 2C. [e] We suggest in presence of ongoing bleeding unresponsive to multimodal coagulation therapy or wound healing defects in critical illness, monitoring FXIII and target levels >60%. 2C. Consequence: target level deleted. [f] In patients undergoing extracorporeal membrane oxygenation (ECMO), cytokine haemadsorption may be considered to reduce excessive inflammatory response to the circuit. 2C. Consequence: sentence deleted. [g] We suggest in presence of ongoing bleeding as part of a goal-directed coagulation therapy algorithm, monitoring FXIII and target levels >60%. 2C. Consequence: target level deleted. [h] Intravenous iron supplementation elicits a faster recovery from anaemia with fewer gastrointestinal complaints than oral iron treatment. 1B. Consequence: change to statement B. [i] For reversal of vitamin K-associated nontraumatic intracranial bleeding (n-ICB) prothrombin complex concentrate (PCC) is recommended. 1B. [j] We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions or antiplatelet medication. [k] We recommend early and targeted treatment of coagulation factor deficiencies in the plasma.

Discussion

It is important to emphasise that any guidance in this article can be adopted, modified or not implemented, depending on the requirements of different institutions or countries. National licensing restrictions for medications and medical law also need to be considered when applying these guidelines.

Clinical query 1

Which patients should be optimised before surgery and how?

1.1 Patients with pre-operative anaemia

Recommendation 1

Pre-operative anaemia in adults and children appears to be a strong predictor for peri-operative blood transfusion across various types of conditions, and procedures and is associated with adverse events. A

We recommend that patients at risk of bleeding are assessed for anaemia well before surgery in order to permit time for anaemia correction if needed. 1B

We suggest a time interval of 1 to 2 weeks in cases of parenteral stimulation of erythropoiesis and uncomplicated cause of anaemia, whereas 3 to 8 weeks may be required in cases of oral correction of iron deficiency anaemia (IDA) and complex causes of anaemia. 2C

In noncancer patients with pre-operative anaemia scheduled for elective major surgery, we recommend postponing surgery until anaemia has been corrected. 1A

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

We recommend defining an internal-hospital algorithm for the comprehensive differential diagnosis of pre-operative anaemia. 1C

We recommend treating IDA with weight-based doses of iron supplementation after considering contraindications. 1A

We recommend i.v. iron in preference to oral iron. 1C

We suggest erythropoietin-stimulating agents (ESA) if pre-operative anaemia is present and other causes

(autoimmune, bone marrow dysfunction, nutritional deficiencies) have been excluded or treated. 2A

We recommend against pre-operative RBC transfusion to mask pre-operative mild-to-moderate anaemia. 1C

We suggest that RBC transfusion can be considered in pre-operative anaemia, which could not be corrected by comprehensive haematological therapy. 2C

Early use of noninvasive haemoglobin (Hb) monitoring at indication for surgery/in the pre-anaesthesia clinic may speed up detection of pre-operative anaemia and correction. C

If autologous blood donation is performed, we suggest concomitant treatment with iron and/or ESAs in order to avoid pre-operative anaemia and increased overall transfusion rates. 2C

Evidence summary

Pre-operative anaemia is common in surgical patients, with a prevalence varying between 10 and 48%,[7] and has been shown to be an independent risk factor for morbidity and mortality. Several studies have repeatedly demonstrated that anaemia increases the use of allogeneic blood products and is further associated with an increased rate of complications, prolonged hospital stay and increased mortality.[8–11] Musallam *et al.*[10] analysed data of more than 200 000 patients and demonstrated that even mild pre-operative anaemia was associated with an increased risk of morbidity and mortality after 30 days in noncardiac surgical patients. For Europe, similar data were published in a 7-day observational study involving nearly 40 000 noncardiac surgical patients from 28 countries.[8] In a retrospective study of 1928 paediatric trauma patients, the initial haematocrit (Hct) values were found to correlate significantly with conventional signs of shock and were a strong independent predictor for blood transfusion with a better predictability for the latter than other clinical factors.[12] Other studies in children have also demonstrated a link between pre-operative anaemia and increased RBC transfusion and hospital length of stay[13] and that preoperative anaemia is an independent risk factor for mortality.[14,15] Similarly, among 843 women undergoing major gynaecological surgery, Browning *et al.*[16] showed that pre-operative anaemia was a common disorder and was associated with increased RBC transfusion. Also in cardiac surgery, data from 943 patients demonstrated a high prevalence of pre-operative anaemia, which significantly correlated with higher transfusion rates.[17]

Anaemia is associated with prolonged bleeding times, probably caused by the rheological effect of RBCs on the margination of platelets inside the vessel, which ultimately influences platelet interaction with the endothelium and thus primary haemostasis. The degree of anaemia and the impact of low Hct on viscoelastic haemostatic assay (VHA) values remain somewhat unclear, but this may ultimately illustrate the inability of VHA devices to reflect the haemostatic impact of the vascular endothelium.[18,19]

The implementation of a Patient Blood Management (PBM) programme, which included patient assessment 4 weeks before surgery, was shown to be effective in reducing the rate of pre-operative anaemia and lowering the rate of transfusion compared with before implementation of the programme.[20–22] Other groups have successfully used PBM programmes with testing at about 3 weeks pre-operatively.[23–25] The efficacy of iron supplementation in iron-deficient patients on postoperative outcome has been demonstrated repeatedly.[26–30]

Assessment of patients 3 to 8 weeks before elective surgery provides enough time to initiate treatment and for this to take effect. This recommendation is also in agreement with current consensus and practical recommendations.[31] Accurate diagnosis of anaemia requires investigation after it has been determined that Hb levels are low.[32]

Most (though not all) studies report that pre-operative oral iron supplementation is effective in raising Hb concentration and in decreasing peri-operative transfusion. Two recent publications, a consensus statement[32] and practical recommendations,[31] both advocate the correction of iron levels before orthopaedic surgery. Oral iron supplementation may be suitable for a high proportion of patients, and any side effects are usually mild.[33]

In a prospective study, female patients with gynaecological ailments and anaemia were treated pre-operatively with iron sucrose and Hb concentration increased by a mean average of 5.15 g dl^{-1} ($P < 0.001$) within 30 days of treatment.[34]

Also, in another prospective study of 20 patients with colorectal cancer, a single dose of i.v. ferric carboxymaltose given pre-operatively increased Hb levels by 1.8 g dl^{-1} ($P < 0.001$).[35]

Recently, Spahn *et al.* analysed the effects of ultra-short-term administration of i.v. iron/erythropoietin (EPO)/vitamin B12/folic acid one day before surgery in cardiac patients. The combination significantly reduced the number of RBC transfusions from a median [IQR] of one unit in the group without treatment [0 to 3] to zero units in the treatment group [0 to 2] during the first 7 days after surgery [odds ratio (OR) 0.7, 95% CI, 0.50 to 0.98; $P < 0.036$]. In addition, patients with treatment had higher Hb concentrations during the first 7 days after surgery compared with patients without treatment ($P < 0.001$).[29] Quintana-Diaz *et al.* implemented a fast track anaemia clinic within the emergency department and supplemented 202 patients with i.v. iron resulting in a significant increase of Hb level after 4 weeks (+2 g dl^{-1}

in 79 patients) and a reduced RBC transfusion rate.[36] Triphaus *et al.* evaluated the effect of iron supplementation in 1728 patients undergoing major elective surgery. In total, 1083 patients were nonanaemic (62.7%) and 645 were anaemic (37.3%), of which 234 were diagnosed with iron deficiency and 184 received iron supplementation. Overall, the prevalence of iron deficiency was 50, 46.3 and 52.7% in patients with Hb less than 8.8 to 8.9, and 9 to 9.9 g dl^{-1}. All iron-supplemented patients with IDA required less RBC transfusions during the postoperative period compared with anaemic patients without iron treatment (31.5 versus 42.5%). A reduced intra-operative RBC transfusion rate was observed particularly if iron was administered more than 7 days before surgery. In addition, hospital stay was significantly reduced by 2.8 days in iron-supplemented IDA patients compared with anaemic patients without iron treatment (13.9 ± 0.8 versus 16.7 ± 0.7 days; $P < 0.01$).[30]

A systematic review concluded that patients with pre-operative IDA may have an earlier and more robust recovery of Hb concentration with pre-operative i.v. iron than with oral iron supplementation.[37]

The efficacy of ESAs to reduce, for example, postoperative complications, transfusion rate and mortality has been demonstrated repeatedly.[37–43] A meta-analysis evaluated the effectiveness of ESAs in patients undergoing knee or hip arthroplasty. Pre-operative use of ESAs reduced autologous blood transfusion, relative risk 0.48 ($P < 0.0001$), and mean Hb levels were 0.71 g dl^{-1} higher than for control groups ($P < 0.00001$).[38] A systematic review also concluded that a short pre-operative regimen of EPO may significantly reduce transfusion rates.[37]

The effect of EPO on transfusion rates has been shown to be significant in two separate studies of hip replacement patients with pre-operative Hb levels of 10.0 to 13.0 g dl^{-1}.[40,44] Litton *et al.*[45] performed a meta-analysis including 21 studies and 5452 critically ill patients. In-hospital mortality was lower in the treatment (12.6%) compared with the control group (15.4%). The risk ratio (RR) for serious adverse events (SAEs) (1.11, CI 0.94 to 1.31) and thromboembolic events (1.22, CI 0.95 to 1.58) was not significantly increased. Furthermore, Wijnberge *et al.*[43] performed a meta-analysis on the effect of ESAs in 3387 ICU patients of eight randomised controlled trials (RCTs). Here, a slight reduction in the proportion of transfused patients (RR 0.88, CI 0.78 to 1.00) and a small change in Hb (−0.31 g dl^{-1}; CI −0.51 to −0.05 g dl^{-1}) was found. In parallel, an increase in neither SAEs (RR 1.02, CI 0.9 to 1.15) nor in mortality (RR 0.8, CI 0.61 to 1.05) was found.

Based on the available data, ESAs have been recommended for orthopaedic surgery patients with anaemia, in whom nutritional deficiencies are absent or have been corrected.[32]

In a simulation of 50 000 individual patients, based on data from controlled trials, pre-operative administration of EPO was predicted to be more cost-effective than either autologous blood donation or an allogeneic blood transfusion strategy.[42]

In a prospective study, patients undergoing hip or knee arthroplasty were treated, according to a blood conservation algorithm, with oral or i.v. iron and EPO if they had pre-operative Hb concentration less than 12 g dl^{-1} (women) or 13 g dl^{-1} (men).[46] Compared with a retrospective comparison group, significantly fewer patients received blood transfusions for both hip and knee procedures ($P < 0.001$ and $P = 0.001$, respectively). The length of stay in hospital and rate of readmission also decreased significantly for both procedures.

Results from a retrospective study described total hip arthroplasty in Jehovah's Witnesses following a peri-operative blood management strategy.[24] Patients with pre-operative Hb less than 12.0 g dl^{-1} were treated with EPO for 3 weeks before surgery, plus oral iron and folate. None of the 53 patients received blood transfusion and there was no mortality.

Also, a retrospective study of patients undergoing cardiac valve replacement showed that EPO and i.v. iron, given for 4 weeks pre-operatively, significantly decreased the rate of RBC transfusion ($P = 0.01$) and was associated with decreased peri-operative morbidity and in-hospital mortality.[39] A recent consensus statement also advocated the pre-operative use of EPO plus iron in patients who are anaemic and likely to refuse blood products (Jehovah's Witnesses), or who are considered likely to have postoperative anaemia.[47]

Leahy *et al.*[48] described the introduction of a peri-operative PBM programme to a tertiary hospital. The PBM programme included optimising erythropoiesis, minimising blood loss and bleeding and optimising the reversal of anaemia with i.v. iron. The mean number of RBC units transfused per patient decreased by 26% compared with before the PBM programme was introduced. In another study of patients undergoing knee, hip or spinal surgery, a PBM programme consisting of the management and treatment of pre-operative anaemia, the reduction of intra-operative blood loss by surgical, anaesthesiological and pharmacological techniques, and a lowering of the transfusion threshold to a Hb 8.0 g dl^{-1} or less was investigated retrospectively.[20] Anaemic patients were treated daily for 4 weeks before surgery with i.v. iron carboxymaltose, EPO, vitamin B12 and folic acid. Compared with before implementation of the programme, the rate of transfusion decreased significantly for all three types of surgery and the incidence of anaemia immediately before surgery decreased significantly for patients undergoing hip and knee surgery. Also of note, improved surgical technique played a significant role in reducing the intra-operative blood loss.[20]

1.2 Patients with antithrombotic drugs

Recommendation 2

1. Antiplatelet agents

We recommend that aspirin for secondary prevention should be continued peri-operatively in most surgical settings, especially cardiac surgery. 1C

We recommend that aspirin should be discontinued preoperatively when prescribed for primary prevention. 1B

Where aspirin withdrawal before surgery is considered, we recommend a time from last drug intake to intervention of 3 days, although for invasive procedures at high risk of bleeding, a longer interruption (5 days) could be considered. 1C

In patients with risk factors for vascular complications naive of any antiplatelet treatment, we do not recommend initiating aspirin pre-operatively (except for carotid endarterectomy). 1B

In patients chronically treated with aspirin for secondary prevention of cardiovascular events, except those patients with coronary stents, aspirin may be interrupted for procedures with a very high bleeding risk. 1B

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

Timing of first administration and dose of postoperative anticoagulants, along with resumption of aspirin, after the procedure must be carefully discussed to mitigate postoperative bleeding complications. 2C

For intra-operative or postoperative bleeding, for example, in neurosurgery, supposedly 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 for 3 to 12 months after drug-eluting stent (DES) implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high. 1A

Continuation of $P2Y_{12}$ inhibitor treatment should be considered for at least 4 weeks after BMS implantation and for 3 to 6 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high. 2A

In patients treated with $P2Y_{12}$ inhibitors, who need to undergo surgery, postponing surgery for at least 5 days after cessation of ticagrelor and clopidogrel (time from last drug intake to intervention) – and for 7 days in the case of prasugrel – if clinically feasible, should be considered 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 and ischaemic events. 1C

If $P2Y_{12}$ inhibitors have to be discontinued peri-operatively, they should be resumed early, if possible within 24 to 72 h after surgery, given the increased thrombotic risk. Resumption should be with the same $P2Y_{12}$ inhibitor as pre-operatively. No recommendation can be made regarding the use or not of a loading dose. 2C

We recommend against peri-operative use of nonsteroidal anti-inflammatory drugs in patients treated with dual antiplatelet therapy (DAPT); peri-operative use of coxibs is possible. 1C

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

Noncardiac elective surgery should be postponed until completion of the full course of DAPT. 1A

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 in cases of intra-operative or postoperative bleeding supposedly related to clopidogrel or prasugrel. A higher dose than that used to neutralise aspirin is proposed for $P2Y_{12}$ inhibitors. 2C

Platelet transfusion may be ineffective for treating bleeding supposedly related to ticagrelor when given 12 h before. C

In high thrombotic risk patients under DAPT, if the interruption of $P2Y_{12}$ receptor inhibitors is considered unacceptable by a multidisciplinary team, bridging with the ultra-short acting $P2Y_{12}$ receptor inhibitor (cangrelor) or short-acting glycoprotein IIbIIIa inhibitors may be considered. 2C

2. Heparin, fondaparinux, vitamin K antagonists

We recommend that severe bleeding associated with i.v. unfractionated heparin (UFH) should be treated with i.v. 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 UFH unresponsive to i.v. protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of i.v. protamine, with the dose guided by anti-Xa activity and if not available by activated partial thromboplastin time (aPTT). 2C

We suggest that severe bleeding related to subcutaneous low-molecular-weight heparin (LMWH) should be treated with i.v. protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered and, if unresponsive, anti-Xa activity should be measured. 2C

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

We recommend that vitamin K antagonists (VKAs) should not be interrupted in patients undergoing low-bleeding-risk procedures: skin surgery, dental and stomatological procedures, gastric and colonic endoscopies (even if biopsy is scheduled but not polypectomies), nor for most ophthalmological surgery, mainly anterior chamber (cataract). 1C

We recommend that for low, moderate and high thrombotic risk patients undergoing procedures requiring international normalised ratio (INR) less than 1.5, the time from last VKA intake to intervention should be 3 to 5 days; if INR is more than 1.5 on the day before surgery, 5 mg oral vitamin K are recommended. 1C

We suggest against bridging of VKA with LMWH or UFH in low, moderate and high thrombotic risk patients; in very specific high-risk patients, the treatment should be based on case-by-case analysis. 2C

We recommend that in patients with pre-operative VKA intake, VKA should be resumed within 24 h after the procedure, administering a LMWH in a prophylactic dose until the target INR is observed in two following measurements. 1C

In specific patients unable to take oral medication, postoperative bridging of VKA with a LMWH in a therapeutic dose could be started within 48 to 72 h after the procedure, once haemostasis has been secured. 1C

In VKA-treated patients undergoing an emergency moderate-to-high bleeding-risk procedure, we recommend that INR must be measured on the patient's admission to hospital, with the administration of four-factor PCC to reverse VKA anticoagulant effects (at an initial dose of 25 IU factor IX per kg at an INR of 4) over 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 i.v. vitamin K. 1B

If PCC is not available, 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 i.v. vitamin K. 1C

3. Direct oral anticoagulants

We recommend assessing creatinine clearance in patients receiving direct oral anticoagulants (DOACs) and being scheduled for surgery. 1B

We suggest that DOACs can be given up to the day before surgery for patients undergoing low-bleeding-risk procedures such as skin surgery, dental and stomatological procedures, gastric and colonic endoscopies (even if biopsy is scheduled but not polypectomies) and most ophthalmological surgery. 2C

For intermediate-bleeding-risk and high-bleeding-risk procedures:

(1) we recommend that for rivaroxaban, apixaban and edoxaban, the time from last drug intake to intervention should be 3 days, pending a creatinine clearance (Cockcroft–Gault formula) above 30 ml min^{-1}. No bridging is recommended. 1C
(2) we recommend that for dabigatran, the time from last drug intake to intervention should be 3 days, if the creatinine clearance is above 50 ml min^{-1}, and 5 days if the creatinine clearance is between 30 and 50 ml min^{-1}. No bridging is recommended. 1C

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

We suggest the use of PCC (25 IU kg^{-1} at first) rather than andexanet alpha in bleeding patients treated with anti-Xa agents (rivaroxaban, apixaban and edoxaban). 2C

We suggest that for low-bleeding-risk procedures, when haemostasis is achieved, DOACs should be restarted about 6 h after the procedure without LMWH administration. 2C

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

Evidence summary

Antiplatelet agents (APAs)

Aspirin

APAs are indicated for the prevention of arterial thrombosis, mainly in patients with a history of a cardiovascular thrombotic event. Peri-operative interruption and maintenance of APAs are associated with increased thrombotic or haemorrhagic complications, respectively. Guidelines for peri-operative APA therapy are based on one large, controlled study, small observational studies, case reports and expert opinions, so most recommendations are weak. In patients with coronary stents, interruption of APAs is a risk factor for stent thrombosis. Additionally, the optimum delay between stent implantation and surgery is controversial. However, recent guidelines from the European Society of Cardiology (ESC) have clarified

the minimal duration of DAPT in patients with acute and chronic coronary syndromes.[49]

Treatment discontinuation increases the thrombotic risk. Following aspirin withdrawal, aspirin treatment should resume as soon as possible postoperatively to prevent platelet activation. A risk of surgical bleeding is also associated with APA therapy; however, this has been poorly evaluated.

In a large RCT, POISE-2, patients undergoing noncardiac surgery were randomised to receive aspirin or placebo before and after surgery.[50] Using a two-by-two factorial trial design (exploring also the efficacy and safety of clonidine to prevent cardiovascular events), 10 010 patients at risk for vascular complications undergoing noncardiac surgery were included. The patients were stratified according to whether they had not been taking aspirin before the study (initiation stratum, with 5628 patients) or they were already on an aspirin regimen (continuation stratum, with 4382 patients). Patients started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it daily (at a dose of 100 mg) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. The primary outcome, a composite of death or nonfatal myocardial infarction at 30 days, occurred in 7% of patients in the aspirin group and in 7.1% of patients in the placebo group ($P = 0.92$). Major bleeding was more common in the aspirin group than in the placebo group, 230 patients (4.6%) versus 188 (3.8%); hazard ratio 1.23 (95% CI 1.01 to 1.49; $P = 0.04$). A majority of patients included in this study had only risk factors for peri-operative cardiovascular events including a majority of aged or hypertensive and/or diabetic patients. Less than 35% of patients had a history of vascular disease. A majority of patients were Revised Cardiac Score Index 1. As a result, a majority of patients included in the initiation stratum would not have been otherwise treated by aspirin.

Major bleeding was significantly higher in the aspirin group; however, this was significant only in the initiation stratum. An interaction between antiplatelet and postoperative anticoagulant therapy may explain a higher major bleeding rate in the aspirin group. In addition, a lack of antithrombotic efficacy of aspirin was observed, but the allowed postoperative use of nonsteroidal anti-inflammatory drugs (NSAIDs; more than 40% of the patients) may have interfered with aspirin efficacy. As a result, the POISE-2 study has been criticised and several reviews have developed different standpoints.[51,52]

In summary, aspirin should not be withdrawn peri-operatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug. The risk of bleeding for a procedure under aspirin depends on the type of procedure. The benefit/risk balance needs to be discussed with the operator, the cardiologist and the anaesthesiologist, unless local consensus documents have been already discussed.

$P2Y_{12}$ inhibitors: clopidogrel, prasugrel and ticagrelor

In a systematic review of 37 studies (31 cardiac and 6 noncardiac surgery; 3 randomised, 34 observational), postoperative outcomes in patients who were or were not exposed to thienopyridine in the 5 days before surgery were compared.[53] Exposure to thienopyridine in the 5 days preceding surgery (compared with no exposure) was not associated with any reduction in postoperative myocardial infarction, but was associated with increased risks of stroke, re-operation for bleeding and all-cause mortality. Results were identical when analyses were restricted to long-term users of thienopyridines who continued versus withheld the medication in the 5 days before surgery. Although all associations were similar for the subset of patients undergoing noncardiac surgery, 97% of the outcome data in this meta-analysis came from cardiac surgery trials.

A large phase 3 study (TRITON-TIMI 38) compared prasugrel with clopidogrel in patients with acute coronary syndrome (ACS) scheduled to undergo percutaneous coronary intervention (PCI). In a subset of patients requiring coronary artery bypass graft (CABG), platelet transfusion was administered in significantly more patients, and at a significantly higher dose in patients in the prasugrel arm than in the clopidogrel arm.[54] Platelet aggregation recovery period after prasugrel interruption was longer than after clopidogrel interruption based on platelet response to $P2Y_{12}$ inhibitors.[55] This antiplatelet effect lasts for the lifespan of the platelets ($\geq$7 days). Recommendations for clopidogrel should be applicable to prasugrel, except for the duration of withdrawal (7 days of interruption for prasugrel).

No studies on efficacy of platelet transfusion in patients treated with ticagrelor were retrieved. However, when ticagrelor is administered within the preceding 12 h, its presence in plasma may render platelet transfusion ineffective.[56]

Neutralisation of ticagrelor is challenging.[57] Unlike the thienopyridines, ticagrelor is a directly active $P2Y_{12}$ inhibitor and does not require metabolic activation. Unbound plasma concentrations of ticagrelor and its first active metabolite, which is also a platelet inhibitor, are high. Although their effects are reversible, their half-lives are long: 7 and 8.5 h for ticagrelor and its active metabolite, respectively.[58] Therefore, circulating ticagrelor and its first metabolite can inhibit platelets provided by transfusion[56] for up to 24 h after the last intake. Finally, 52 patients were transfused (about 3.5×10^{11} platelets) prior to coronary artery bypass surgery because they had been treated with aspirin and clopidogrel ($n = 45$), prasugrel ($n = 6$), or ticagrelor ($n = 3$) and presented active bleeding. Platelet function testing (PFT) revealed

significant improvement of platelet function after transfusion in patients treated with clopidogrel, while there was no effect in those treated with ticagrelor and prasugrel.[59] Hence, in situations requiring neutralisation of ticagrelor and when the time-interval since the last intake is less than 24 h, no specific treatment can be proposed because platelet transfusion at the doses used to neutralise other APAs will be ineffective. MEDI2452, a specific antidote for ticagrelor, binds to circulating ticagrelor and ticagrelor-active metabolite with an affinity 100-fold higher than the affinity of ticagrelor for the $P2Y_{12}$ receptor.[60] This antidote provided immediate and sustained reversal of the antiplatelet effects of ticagrelor in healthy volunteers, as measured by multiple assays.[61] However, this neutralisation strategy is not yet available for clinical use.

Dual antiplatelet therapy (DAPT)

The prognosis of stent thrombosis appears to be worse than for de novo coronary occlusion, and premature cessation of DAPT in patients with recent coronary stent implantation is the most powerful predictor for stent thrombosis. The management of antiplatelet therapy in patients who have undergone recent coronary stent treatment, and are scheduled for noncardiac surgery, should be discussed to balance the risk of procedural bleeding on antiplatelet therapy and the risk of major adverse cardiac events (MACE), including stent thrombosis off DAPT. Current guidelines recommend delaying elective noncardiac surgery until completion of the full course of DAPT and, whenever possible, performing surgery without discontinuation of aspirin.[62] Recent ESC guidelines recommend a shorter duration of DAPT, particularly in patients with high bleeding risks (including not deferrable surgery). In ST-segment elevation myocardial infarction, the guidelines state: 'In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered'.[63]

In non-ST-segment elevation acute coronary syndrome, the guidelines state: 'After stent implantation with high risk of bleeding discontinuation of $P2Y_{12}$ receptor inhibitor therapy after 3 months should be considered'.[49]

Regardless of the type of coronary stent, DES or BMS, the first month following stent placement is a high-risk period for noncardiac surgery, and DAPT should be maintained during 1 month. Furthermore, most recent ESC guidelines considered that: 'DES are recommended over BMS for any PCI irrespective of: clinical presentation, lesion type, planned noncardiac surgery, anticipated duration of DAPT, concomitant anticoagulant therapy'.[49] However, the focus of most guidelines on stent type, surgical timing for both DES and BMS and antiplatelet cessation should probably be re-evaluated, as other underlying factors may explain postoperative MACE in these patients. In a large national, retrospective cohort study of 41 989 operations occurring in the 24 months after a coronary stent implantation between 2000 and 2010, a nested case–control study assessed the association between peri-operative antiplatelet cessation and MACE.[64] Within 24 months, 28 029 patients underwent noncardiac operations resulting in 4.7% MACE. After adjustment, the three factors most strongly associated with MACE were nonelective surgical admission, history of myocardial infarction in the 6 months preceding surgery and revised cardiac risk index greater than 2. Of the 12 variables in the model, timing of surgery ranked fifth in explanatory importance measured by partial effects analysis and stent type ranked last.

For patients at very high risk of stent thrombosis, particularly those requiring discontinuation of both APAs in the first month, bridging with a reversible i.v. APA may be considered.[65] However, for rapidly reversible anti-GPIIb-IIIa agents such as eptifibatide and tirofiban for preoperative bridging therapy for patients undergoing surgery after coronary stent implantation, the meta-analysis of the eight studies that included 280 patients concluded that there was a possible risk of bleeding associated with a persistent risk of stent thrombosis.[66] Cangrelor, a parenteral and reversible inhibitor of the $P2Y_{12}$ receptor, is another option in the peri-operative setting, with a well established antithrombotic effect[67] and a faster reversibility than anti-GPIIb-IIIa agents.[68] However, none of these parenteral APAs have marketing authorisation for this indication. The use of concomitant parenteral anticoagulation is not recommended given the potential increase in the risk of bleeding.

In patients with atrial fibrillation undergoing PCI, ESC guidelines recommend a discontinuation of antiplatelet treatment in patients treated with oral anticoagulants after 12 months. There is no data to recommend or suggest any specific bridging with antiplatelet therapy in these patients.

Anticoagulant agents

Heparin, fondaparinux, vitamin K antagonists

Although some research is ongoing,[69] currently there is no available drug acting as an antidote to fondaparinux. rFVIIa has been proposed to control severe bleeding, but limited data support this.[70]

Pre-operative interruption of VKA therapy with substitution by a short-acting anticoagulant such as LMWH or UFH (so-called bridging therapy) is common practice. However, recent studies have indicated that it may increase peri-operative bleeding without decreasing thrombotic events.[71–73] Nevertheless, current evidence supports bridging therapy when there is a high thrombotic risk, especially in mechanical valve patients[74] or with atrial fibrillation with a high CHA_2DS_2-VASc score,[75,76] also taking into account the patient's individual bleeding risk and renal function.[77] A model simulation

coupling both thrombotic and bleeding risk, has been developed for patients on atrial fibrillation, based on CHA_2DS_2-VASc and HASBLED scores concluding that only a small group of patients should benefit from bridging anticoagulation.[78] Furthermore, a recent prospective, double-blind RCT of 1471 patients with atrial fibrillation or mechanical heart valves, who had warfarin interrupted for a procedure, found no significant benefit for postoperative dalteparin-bridging therapy to prevent major thromboembolism.[79]

For urgent control of the anticoagulant effects of VKA, the administration of PCC provides faster and more effective reversal than FFP.[80–84] The optimal dosing of PCC has not been fully elucidated, so the dose should be individualised to maximise effectiveness without compromising safety. Overcorrection should be avoided as this may increase thrombotic risk. Dose selection may be influenced by the patient's clinical status, pretreatment INR, target INR and other laboratory values.

Direct oral anticoagulants

Physicians from outside the field may be unaware of the pharmacological characteristics of many direct oral anticoagulants (DOACs). Several studies have shown that withdrawing DOACs 48 to 72 h before a scheduled procedure (time from last drug intake to intervention 72 to 96 h) is effective in decreasing the plasma concentration and, therefore, controlling the bleeding risk.[85] The Peri-operative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study enrolled 3007 patients treated for atrial fibrillation and scheduled for elective surgery or other procedure. A simple standardised perioperative DOAC therapy interruption and resumption strategy based on DOAC pharmacokinetic properties, procedure-associated bleeding risk and creatinine clearance levels was proposed.[86] The DOAC regimens were omitted for 1 day before a low-bleeding-risk procedure and 2 days before a high-bleeding-risk procedure. The DOAC regimens were resumed 1 day after a low-bleeding-risk procedure and 2 to 3 days after a high-bleeding-risk procedure. The result confirmed that a peri-operative management strategy without heparin bridging or coagulation function testing was associated with low rates of major bleeding and arterial thromboembolism. The results of the prospective RA-ACOD real-world registry supports a short-term preprocedural DOAC interruption depending on the drug, haemorrhagic risk and renal function, without bridging therapy and a reduced DOAC-free time, as the safest periprocedural practice.[87]

The ESC and several other groups, such as the Groupe d'Intérêt en Hémostase Péri-opératoire, have issued proposals for managing patients treated with DOACs.[88–90] The following patient groups are considered: with atrial fibrillation or venous thromboembolism (VTE) patients treated with DOACs and undergoing an invasive procedure.

As a first option, activated charcoal (50 g) has been shown to be very effective in healthy volunteers treated with apixaban 20 mg.[91] The mean elimination half-life for apixaban alone (13.4 h) decreased to 5 h when activated charcoal was administered at 2 or 6 h postdose. For dabigatran, charcoal has only been tested in vitro. One case report is available for rivaroxaban.[92]

Another way to decrease DOAC concentration is elimination with haemodialysis. This technique been shown to be effective in decreasing the plasma concentration of dabigatran by 50% after a 4 h procedure.[93] Of note, after the interruption of dialysis, a rebound of the dabigatran concentration has been observed. It has to be understood that this technique is only available for dabigatran where binding to the proteins is weak. Even if it is usually implemented in an intensive care environment, it may be difficult and dangerous to insert a very large catheter in an old patient overdosed with dabigatran.

Treatments proposed for the reversal of anticoagulant activity, or the control of bleeding in patients treated with DOACs include PCC and activated PCC (aPCC) or factor eight inhibitor bypassing activity (FEIBA). Preclinical studies performed in rabbits and pigs have provided very positive data regarding the use of PCC for reversal of dabigatran and rivaroxaban[94] but not for apixaban. The efficacy of PCC has been demonstrated in healthy volunteers for rivaroxaban[95] but not for dabigatran. In several registries, PCC appears to be very effective for reversing the anticoagulant effects of all DOACs, although the lack of a control group limits the strength of this evidence.[96,97] It has also been used pre-emptively in DOAC-treated patients who were scheduled for an emergency procedure.[98,99] Activated PCC has also been used in some studies.[100,101]

Idarucizumab, the antidote, which has been developed for dabigatran etexilate, is a fully humanised monoclonal antibody fragment. It completely reverses the anti-IIa activity of dabigatran.[102]

An initial series of 90 patients (either bleeding patients or patients scheduled for an invasive procedure) has been treated, and complete reversal of the anticoagulant activity was observed. However, there was a safety concern because mortality reached 20%.[103,104] The results of the phase 3 study confirm the efficacy of the compound.[97] However, some rebound of the plasma dabigatran level has been reported, leading to several re-injections of half-doses.[105] Further studies and a much larger number of patients are needed to be fully reassured.

A FXa analogue (andexanet alpha), which reverses the effects of all anti-FXa agents, is an injectable drug, appears to be effective despite having a short half-life (<90 min), and being responsible for an increase in

thrombotic risk. A clinical trial comparing this agent or usual care started in 2019 and will be reported in 2023. Andexanet was approved after the ANNEXA-4 study[106] with a boxed warning for thromboembolic risks, ischaemic risks, cardiac arrest and sudden death. Treatment with the agent has been associated with serious and life-threatening adverse events, including arterial and venous thromboembolic events,[107–109] cardiac arrest, sudden deaths and ischaemic events, such as myocardial infarction and ischaemic stroke. In addition, it is very expensive. A meta-analysis of studies on PCC, idarucizumab and andexanet has shown that the three agents had a similar effective haemostasis rate and comparable mortality but there was a much higher thrombotic rate for andexanet (10.7 compared with 4.3% for PCC and 3.8% for idarucizumab).[109]

1.3 Patients with comorbidities involving impaired haemostasis

Renal, liver, systemic, metabolic and endocrine diseases

Recommendation 3

Point-of-care tests of platelet function and bleeding time are not useful for predicting bleeding risk in uraemic patients undergoing invasive procedures. 2C

Desmopressin therapy is suggested in high-risk uraemic patients for reducing bleeding during invasive procedures and for managing acute bleeding. 2C

Conjugated oestrogen therapy could be considered in uraemic platelet dysfunction. 2C

Despite altered standard coagulation test results, haemostasis may be balanced in stable chronic liver disease (CLD). C

Mild-to-moderate prolongation of the preprocedural prothrombin time (PT) and INR and moderate thrombocytopenia do not predict bleeding in patients with CLD. C

Fibrinogen level assessment is suggested in patients with advanced liver disease undergoing invasive procedures. 2C

Viscoelastic haemostatic assay (VHA) guidance is recommended for reducing allogeneic blood product transfusion in cirrhotic patients undergoing invasive procedures. 1C

In cirrhotic patients with severe thrombocytopenia scheduled to undergo high-risk invasive procedures, thrombopoietin receptor agonists (avatrombopag or lusutrombopag) may be considered. 2B

In patients with CLD who are not auto-anticoagulated, we recommend an individualised thromboprophylaxis strategy. 1C

In acute liver failure, elevated INR does not predict bleeding risk. 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

Evidence summary

Renal dysfunction

Abnormal platelet function in uraemic patients is diagnosed using point-of-care platelet function tests; however, this did not correlate with the higher risk of bleeding complications in uraemic patients undergoing invasive procedures.[110,111]

Desmopressin (DDAVP) was useful for improving platelet function in uraemic patients and was shown to be effective in reducing bleeding in patients with severe renal dysfunction undergoing kidney biopsy.[112–115] Patients given DDAVP should be closely monitored, as it can cause significant dilutional hyponatraemia.[116] Conjugated oestrogens administered via the oral, transdermal and i.v. routes have all shown efficacy in improving haemostasis by decreased bleeding times in uraemic patients.[117,118]

Endocrine diseases

A broad variety of endocrine disorders have been associated with coagulation–fibrinolysis abnormalities. Overt hypothyroidism appears to be associated with a bleeding tendency, whereas in other endocrine diseases, including subclinical hypothyroidism, the thrombotic tendency seems predominant.[119–123] The most relevant coagulation disorder associated with overt hypothyroidism is acquired von Willebrand disease, characterised by decreased factor VIII activity (FVIII:C), von Willebrand factor antigen (VWF:Ag) and ristocetin cofactor (VWF:RCo) levels.[119,123] The bleeding episodes in overt hypothyroidism are mainly mucocutaneous and are ameliorated by DDAVP administration.[120] Other coagulation abnormalities described in overt hypothyroidism are: impaired platelet function, reduction in coagulation factors, acquired inhibitors of von Willebrand factor (VWF) and coagulation factors and increased fibrinolytic activity. The pattern of fibrinolytic abnormality seems to be dependent on the severity of hypothyroidism, with decreased fibrinolytic activity, as reflected by lower D-dimer levels, higher alpha-2 antiplasmin activities and higher levels of t-PA and PAI-1 antigen in moderate hypothyroidism and opposite changes of fibrinolytic markers reflecting increased fibrinolysis in severe hypothyroidism.[123,124] The coagulation and fibrinolysis abnormalities associated with overt hypothyroidism are corrected after replacement hormonal therapy.[119,123,124]

With increasing levels of thyroid hormone, more coagulation and less fibrinolysis are present and the risk of thromboembolic events might be increased in overt and subclinical hyperthyroidism and these haemostatic abnormalities seem reversible with antithyroid

therapy.[120,123,125,126] In a recent study, genetically increased thyroid-stimulating hormone and thyroxine may be associated with decreased and increased synthesis of VWF, respectively.[127]

In patients with active Cushing's disease, the activation of the coagulation system mainly as a result of an increase in VWF and FVIII and a reduction of plasma fibrinolytic activity was observed, increasing the risk of thrombotic complications.[119,128,129] In general, chronic glucocorticoid excess can influence all three factors of the Virchow triad: endothelial dysfunction, haemodynamic changes and hypercoagulability.[128,129] Normalisation of haemostasis is seen in patients who achieved disease remission, though the thromboembolic risk persists for a period, even after biochemical remission.[123,130] Long-term use of exogenous corticosteroids seems also to be associated with a significant increase in thromboembolic risk.[128,129]

Adrenal insufficiency is not usually complicated by clinically significant thrombotic or bleeding episodes.[128] However, a recent observational study found an increased bleeding tendency and reduced levels of FVIII in patients with subnormal secretion of cortisol and probably decreased sympatho-adrenal medullary function undergoing abdominal surgery.[131]

Growth hormone deficiency causes a prothrombotic state, mainly related to hypofibrinolysis, which seems to be at least partially reversible after replacement therapy with growth hormone.[119,123] Limited available data in acromegalic patients suggest a degree of hypofibrinolysis and increased thrombogenic potential, which appear to be at least partially reversible after biochemical disease control.[119,123] Sex hormone deficiency is associated with a hypercoagulable and hypofibrinolytic state.[123]

Systemic and metabolic diseases

The metabolic syndrome is a complex clinical disorder with multifactorial pathogenesis characterised mainly by impairment of glucose metabolism, increased arterial blood pressure, atherosclerosis and abdominal obesity associated with increased cardiovascular disease morbidity and mortality.[132,133] In patients with metabolic syndrome, the coagulation system is switched toward a prothrombotic state, caused mainly by increased plasmatic coagulation, hypofibrinolysis, endothelial activation and decreased endothelial thromboresistance and platelet hyperactivity.[119,133–135]

Patients with autoimmune and malignant disorders can develop autoantibodies affecting the activity or accelerating the clearance of clotting factors (acquired inhibitors). Such inhibitors are most frequently directed against FVIII or VWF, but acquired inhibitors against other clotting factors were also described.[136] The presence of autoantibodies against clotting factors induces a high risk of bleeding, which requires immediate treatment aimed at eradicating the inhibitor.[136] In cancer patients, acquired haemophilia A (AHA) is the most common subset of the disorder and is caused by inhibitory antibodies against coagulation FVIII activity, which can cause a significant bleeding diathesis.[136–138] Successful treatment of AHA in cancer patients implies the immediate management of haemorrhagic diathesis, eradication of the autoantibody inhibitor and concurrent treatment of the underlying malignancy.[138] Depending on the situation, bleeding can be controlled using bypassing agents (aPCC, rFVIIa), DDAVP and recombinant FVIII concentrates in patients with low-titre inhibitors.[136,138] Other therapies such as plasmapheresis and/or immunoadsorption might be considered in individual cases.[136] The most common therapy used to eradicate the inhibitor in AHA is immunosuppressive therapy, and outcome is improved with earlier detection of FVIII inhibitors and timely interventions with suppression therapy.[137,138]

Abnormal bleeding manifestations were described in patients with immunoglobulin light chain amyloidosis.[139,140] According to a recent study, the most typical findings explaining the bleeding tendency in patients with immunoglobulin light chain amyloidosis are prolonged PT, elevated plasmin-α2-antiplasmin complex and acquired FX deficiency suggesting the coexistence of a hypocoagulable and hyperfibrinolytic state.[141] Deficiency of other clotting factors were described in immunoglobulin light chain amyloidosis, albeit more rare than FX deficiency.[140] Immunoglobulin light chain amyloidosis is the only described cause for acquired isolated deficiency of FX, and it is treated similar to inherited FX deficiency.[139,142]

Chronic liver disease

In observational studies, VHA were useful in identifying cirrhotic patients with a normal coagulative assessment despite severe abnormalities of INR and/or platelet count.[143–146]

In observational studies in cirrhotic patients with thrombocytopenia and/or abnormal INR values undergoing invasive procedures, postprocedural bleeding was rare and unpredicted by platelet counts or abnormal INR values.[146–149] In retrospective studies, peri-operative bleeding was not influenced by platelet count in cirrhotic patients undergoing excision of hepatocellular carcinoma (HCC) without prophylactic platelet transfusion, even when the platelet count was less than $50 \times 10^9 l^{-1}$.[150,151] Platelet count does not predict unprovoked major or minor bleeding in cirrhotic patients, according to an observational study with a follow-up period of 4 years.[152]

According to a study in patients with acute-on-chronic liver failure, low fibrinogen level is an independent predictor of bleeding events in patients with a MELD score greater than 25 undergoing invasive procedures.[148] Recent guidelines do not recommend routine prophylactic correction of the platelet count because of the lack of evidence that elevating the platelet count reduces bleeding risk, and recommend an individualised approach to

cirrhotic patients with severe thrombocytopenia before invasive procedures.[153,154] Also, the recent guidelines advise against routine prophylactic FFP transfusion before common procedures in cirrhotic patients.[145,153,154]

In cirrhotic patients undergoing invasive procedures, VHA seems able to better identify the patients with haemostasis disorders and bleeding complications than standard laboratory tests (SLTs).[143,146,155,156] Decreased clot stability assessed by VHA predicts procedure-related bleeding, and VHA assessment allows a better selection of patients in whom to consider preprocedural prophylaxis, contributing to the decrease in allogeneic blood product transfusions.[143,156] In cirrhotic patients with acute upper gastrointestinal bleeding (UGIB) and coagulopathy, a VHA-guided strategy was associated with reduced blood product transfusion to correct coagulopathy without compromising haemostasis in cirrhotic patients compared with a SLT-guided strategy.[157,158]

In two placebo-controlled trials in patients with CLD and thrombocytopenia undergoing invasive procedures, lusutrombopag was effective in achieving and maintaining the target platelet count, superior to placebo in reducing the need for platelet transfusion and had a similar safety profile as placebo.[159,160] In two phase 3 randomised trials, avatrombopag was superior to placebo in reducing the need for platelet transfusions or rescue procedures for bleeding in patients with severe thrombocytopenia and CLD undergoing a scheduled invasive procedure.[161] A meta-analysis evaluated the risk of arterial and venous thromboembolic events associated with the use of thrombopoietin receptor agonists in thrombocytopenic patients with CLD and found a significantly increased thrombotic risk only in eltrombopag-treated patients.[162]

A systematic review and meta-analysis suggests that cirrhotic patients may exhibit an increased risk of VTE compared with noncirrhotic controls.[163] Hypercoagulable features seem to occur more frequently in patients with nonalcoholic fatty liver disease and in patients with end-stage liver disease and are explained by multiple pathophysiological mechanisms including platelet hyperreactivity, endotoxaemia, endothelial dysfunction, enhanced thrombin-generating potential and prothrombotic clot fibrin structure.[164–169]

Acute liver failure

Despite prolongation of SLTs, acute liver failure (ALF) is characterised by a generally normal haemostatic state but with hypercoagulable elements.[170] Compared with controls, patients with ALF have an imbalance of VWF/ADAMTS13 and hypofibrinolysis and correcting abnormal laboratory tests of haemostasis, such as an elevated INR in the absence of bleeding, may increase the risk of thrombotic complications.[170]

In patients with ALF, elevated INR does not correlate with the risk of bleeding complications even though it is a marker of poor prognosis in many predictive indices, whereas thrombocytopenia is associated with bleeding complications as well as with poor outcome.[171–173] In a retrospective cohort of patients with ALF, bleeding occurred in around one-fifth of the patients and thrombotic events in 10% of the patients, hypofibrinogenaemia was common at ICU admission in patients with ALF and was more severe in patients with bleeding complications.[173]

As bleeding complications are not frequent in patients with ALF, routine prophylactic correction of SLTs or of platelet levels is not necessary.[172,174] However, when correction of abnormal haemostasis is necessary, platelets appear to be the most important, followed by fibrinogen correction and by PT prolongation correction.[172] In bleeding patients with ALF, recent guidelines suggest target plasma fibrinogen levels of 1.5 to 2 $g\,l^{-1}$ and a platelet count greater than $60 \times 10^9\,l^{-1}$.[174] Hypocoagulable VHA correlate with disease severity and poor outcome in patients with ALF.[172]

Placement of an intracranial pressure monitor in patients with ALF is associated with a low haemorrhagic complication rate provided a protocol for coagulopathy correction using blood products and/or factor concentrates (to correct severe thrombocytopenia, hypofibrinogenaemia and prolonged PT) is followed.[175–177]

1.4 Patients on chronic medication associated with impaired haemostasis

Recommendation 4
We suggest individualised peri-operative management of selective serotonin reuptake inhibitor (SSRI) treatment. 2B

We suggest individualised pre-operative management of antiepileptic agents, such as valproic acid, which may increase bleeding. 2C

We do not recommend pre-operative discontinuation of *Gingko biloba* extracts. 1B

Evidence summary

SSRI increase the risk for abnormal bleeding because of a decrease in platelet function that occurs when serotonin re-uptake into platelets is inhibited.[178] Observational studies have demonstrated an increased risk of blood loss associated with SSRIs in various settings.[179–181]

A systematic review and meta-analysis demonstrated that SSRI use was associated with an almost two-fold increase in the risk of developing UGIB, especially when used in combination with NSAIDs or antiplatelet drugs.[182] This risk might be reduced significantly by concomitant use of acid-suppressing drugs.[182] The long-term use of SSRIs significantly increased the risk of UGIB and lower gastrointestinal bleeding, but the association between

serotonin–norepinephrine re-uptake inhibitors and gastrointestinal bleeding is less clear.[183,184]

In a large population-based cohort of new users of antidepressants, current use of SSRIs compared with tricyclic antidepressants was associated with an increased risk for intracranial haemorrhage (ICH), particularly during the first 30 days of use, and the risk was further increased by concomitant use of oral anticoagulants.[185] Other retrospective studies showed that combined use of antidepressants and NSAIDs was associated with an increased risk of ICH.[186,187]

In a cohort of patients from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) trial, patients using concomitant warfarin and SSRIs had a supratherapeutic INR for a longer time and had an elevated risk of major bleeding compared with warfarin users who did not use SSRIs.[188] However, patients taking SSRIs in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Embolism and Stroke Trial in Atrial Fibrillation) trial experienced no significant increase in bleeding risk when SSRIs were combined with anticoagulant therapy.[189] The concomitant use of SSRIs and aspirin increases the risk of bleeding compared with each treatment alone.[190,191]

A review of the literature found that SSRI use increases the risk of bleeding complications during and immediately after surgery.[192] However, data from two pharmacovigilance databases suggest that serotonin re-uptake inhibition is not associated with an increased risk of bleeding.[193] In a large cohort study in patients undergoing CABG, neither SSRIs nor other antidepressants were associated with elevated rates of major bleeding.[194] A meta-analysis demonstrated that SSRI use in CABG surgery increased the risk of RBC transfusion, but resulted in no difference in the rate of re-operation for bleeding nor on the mortality rate.[195] In orthopaedic surgery, the use of SSRIs was reported to be associated with an increased risk of blood loss and blood transfusions.[196] The risk of peripartum haemorrhage (PPH) was higher in women taking SSRIs during pregnancy.[197] In a systematic review, pre-operative serotonergic antidepressant use was associated with increased requirement of transfusion, but the results could not be generalised to all surgical groups, as the correlation was not observed in the subgroup of patients undergoing CABG.[198]

As the risk of peri-operative bleeding associated with SSRIs has been reported differently for various types of surgery, for patients undergoing high-bleeding risk surgery, the clinicians have to weigh the risks of possibly increasing the bleeding risk against the psychiatric benefits.[199] In collaboration with a psychiatrist, in patients considered to have a high bleeding risk and who are in a stable phase of depression, discontinuation of SSRIs should be planned 2 weeks before surgery. Changing to an antidepressant associated with less serotonin re-uptake inhibition can be considered.[199]

Drug interactions may involve antiepileptic drugs and warfarin, as the most commonly used antiepileptic drugs are either potent hepatic enzyme inducers or inhibitors and interfere with warfarin metabolism.[200,201] The risk of drug–drug interaction might be significant among patients taking antiepileptic drugs and DOACs simultaneously. Phenytoin, carbamazepine and phenobarbital might significantly reduce the efficacy of all DOACs, while oxcarbazepine and valproate seem to decrease rivaroxaban efficacy, even though an interaction with other DOACs cannot be excluded.[202]

The effect of valproic acid on haemostasis is controversial. Valproate use has been associated with alteration of the coagulation cascade and reduced levels of factors VII, VIII, XIII, VWF, fibrinogen, protein C and antithrombin, in addition to changes in the platelet numbers and function.[203–207] However, in one prospective controlled study, there were no statistically significant differences in any of the studied haemostasis measurements reflecting primary and secondary haemostasis in valproate-treated patients versus controls.[208] It is not clear from existing research if valproate treatment increases clinically relevant peri-operative haemorrhagic complications.[206,209,210]

Until more research is performed, physicians need to be aware of the potential risk of bleeding in patients receiving valproic acid. A haemostatic evaluation should be considered in patients taking valproate presenting with bleeding and in those scheduled for major surgery. Haematologists should be involved in therapeutic recommendations for symptomatic patients. The decision for peri-operative management of valproate should be made after consultation with a neurologist weighing the risks of drug discontinuation against the risks of peri-operative haemorrhage.[206]

Although herbal remedies are used to treat a large variety of diseases, the safety of many products has not been proven, nor has their effect on coagulation or interaction with antithrombotic medication been determined. A narrative review provides an exhaustive list of the potential effects on haemostasis of different herbal medicines.[211] Contradictory evidence is present on bleeding risks in patients taking herbal medicines, and many of them can interact with antiplatelet and anticoagulant drugs.[211,212] Some clinically used Chinese herbal medicines can interfere with the mechanism of action of warfarin by affecting the warfarin absorption, distribution, metabolism and plasma protein binding rate or decreasing the anticoagulant effect of warfarin mainly through the induction of cytochrome P450 enzyme activity.[213]

G. biloba is one of the most widely used herbal medicines in Europe. Although in vitro studies show inhibited

platelet activation by *G. biloba* extract and cases of spontaneous bleeding after taking Ginkgo preparations have been reported, a randomised placebo controlled, double-blind study in healthy volunteers found no effect of an extract of *G. biloba* on bleeding time and coagulation.[214–217] A meta-analysis of 18 RCTs did not indicate a higher bleeding risk associated with standardised *G. biloba* extracts provided as daily oral therapy.[218] The combination of *G. biloba* with APAs seems not to affect coagulation indices; however, other studies revealed that different traditional Chinese medications administered together with clopidogrel increased the antiplatelet activity compared with clopidogrel alone, whereas others decreased the platelet inhibition.[219–221] A recent article indicated that *G. biloba* extract combined with aspirin could enhance the antiplatelet effects, having both synergistic and additive effects in inhibiting platelet aggregation.[222]

Physician awareness and patient education are crucial in identifying potential herb–drug interactions. It is difficult to ascertain whether the concurrent use of herbal medicines may increase or reduce the pharmacological effects of anticoagulant/antiplatelet drugs with adverse reactions or may influence the peri-operative bleeding risk.[223] Clinicians should perform a comprehensive drug history in patients scheduled for surgery, actively seeking herbal medicine use and should consider the risk for possible interactions of herbal medicine with antiplatelets or anticoagulant agents.

Some diets and nutrients have been shown to affect platelet function leading sometimes to unexpected abnormal results in laboratory tests; repeat laboratory testing may be required after exclusion of nutrients and foods that could have possibly altered the initial data.[224] Omega-3 polyunsaturated fatty acids (PUFAs) reduced peak thrombin generation and fibrin generation measured by overall coagulation potential and decreased platelet activation and aggregation in healthy individuals, with a greater effect on thrombotic potential in healthy individuals compared with those with cardiovascular disease.[225,226] According to a recent review, in order to obtain a significant outcome of omega-3 PUFAs' effects on haemostasis, a high daily dose of omega-3 PUFAs ($>4\,g\,day^{-1}$) for at least six weeks is necessary in patients with a Western diet characterised by generally lower intake of omega-3 PUFAs.[227] The clinical peri-operative significance of these in vitro studies is unknown.

1.5 Patients with inherited bleeding disorders

Recommendation 5
We suggest the use of bleeding assessment tools (BATs) for detecting and predicting the peri-operative risk of bleeding before surgery and invasive procedures in patients with suspected or confirmed inherited bleeding disorders (IBDs). 2B

Patients with IBDs are at higher risk of peri-operative bleeding and should be managed in collaboration with a haematologist, preferably in dedicated centres with expertise in coagulation disorders. 1B

We suggest individualised pre-operative haemostatic correction depending on the specific disorder, type of surgery and individual factors (bleeding phenotype). 2C

We recommend replacement/substitution therapy with factor concentrates, either plasma-derived or recombinant products, for major bleeding/surgery in patients with von Willebrand disease (VWD) or haemophilia A and B. 1C

For haemophilia patients with inhibitors, we suggest either rFVIIa or aPCCs. 2C

We recommend against routine peri-operative platelet transfusion in patients with inherited platelet disorders (IPDs). 1C

We suggest DDAVP as a first-line treatment for minor bleeding/surgery in patients with VWD or mild haemophilia A, after a trial test and in the absence of contraindications. 2C

We suggest peri-operative antifibrinolytics as adjunct therapy in patients with haemophilia or VWD. 2B

Antifibrinolytic agents may be used as peri-operative haemostatic monotherapy in patients with haemophilia or VWD undergoing minor mucosal or dental procedures and in patients with inherited platelet defects. 2C

We suggest that rFVIIa be considered in patients with Glanzmann thrombasthenia undergoing surgery. 2C

We suggest that rFVIIa be used in peri-operative bleeding because of inherited factor VII deficiency. 2C

Evidence summary

Patients with IBDs, which include mainly VWD, IPDs, haemophilia A, haemophilia B and deficiencies of other coagulation factors [rare bleeding disorders (RBDs)] are at risk of peri-operative bleeding even when IBDs are mild.[228] They can be detected pre-operatively by using a BAT, which includes a structured patient interview and an interpretation grid to score for the most severe presentation of each bleeding symptom resulting in an individual bleeding score. However, no questionnaire on bleeding diathesis has yet been validated for the pre-operative period and the use of the International Society on Thrombosis and Haemostasis BAT (ISTH-BAT) in two prospective observational studies including over 1800 patients undergoing elective surgery could not differentiate between patients with and without haemostatic abnormalities.[229,230] A systematic review of nine studies indicated that the BAT has not been able to

definitely exclude a mild bleeding disorder[231] and, in further cohort studies, the use of the ISTH-BAT failed to predict the risk of future bleeding.[232] Both Vicenza and ISTH-BAT had a low ability to distinguish between patients with an established bleeding disorder from those with bleeding of an unknown cause.[233]

Conversely, there is consensus that the BAT BS should be at least 4 in adult male individuals and at least 6 in adult female individuals in order to reliably select subjects with strong clinical suspicion of VWD.[228] ISTH-BAT also proved to be a useful screening tool for patients with suspected inherited platelet function disorders (IPFDs).[234,235] Patients with a BS greater than 6 and preliminarily excluded type 1 VWD had a 99% probability of having an IPFD[235] and BS greater than 6 was associated with enhanced likelihood of suffering bleeding events in IPFD, requiring more intensive prophylactic treatment.[236]

Bleeding score was also significantly higher in haemophilia A and haemophilia B patients as compared with controls[237] and a more suitable tool than conventional and global coagulation assays for predicting the bleeding phenotypes in patients with inherited FVII deficiency.[238]

In a cohort of 263 patients with RBDs, the median ISTH-BAT was 9, and the correlation between baseline factor activity levels and ISTH-BAT scores was strong for deficiencies of factor II and FX and moderate for deficiencies of fibrinogen, factor V (FV), FVII, FXIII and alfa2-antiplasmin.[239] There was no correlation with factor XI (FXI) deficiency. The RBD-BAT identified more women (94 versus 83%) and children (100 versus 71%) with an RBD than the ISTH-BAT did. However, a BAT for RBDs has not yet been validated.[240]

A study of 10 581 621 hospitalisations for major noncardiac surgery identified VWD in 3765 cases (0.036%) and the adjusted analyses showed that patients with VWD were significantly more likely to develop postoperative haemorrhage than patients without VWD (5.5 versus 1.9%, $P < 0.001$; adjusted OR 3.49, 95% CI 3.03 to 4.03).[241] Similarly, in one worldwide multicentric retrospective study [Surgery in Platelet disorders And Therapeutic Approach (SPATA)] including 829 surgical procedures carried out in 423 patients with well defined IPDs, including 238 IPFDs and 185 inherited platelet number disorders (IPNDs), the global frequency of surgical bleeding was high (19.7%).[242]

However, data from case series and cohort studies demonstrated that good surgical results are achievable over a range of procedures when there is appropriate careful preoperative planning, appropriate replacement/substitution therapy and multidisciplinary team management that includes a haematologist.[243,244] In 1065 procedures performed on 571 patients with IBDs, including patients with haemophilia A (43.5%), haemophilia B (9.7%), VWD (45.3%) and RBDs (1.6%), bleeding complications were reported in 14 procedures, and only 19 patients received factor replacement beyond standard duration of prophylaxis.[243] Importantly, approximately 50% of all procedures were performed in a haemophilia treatment centre. In another cohort study, patients with haemophilia A, haemophilia B or VWD had similar rates of adverse outcomes when undergoing minor ($n = 129$) or major ($n = 34$, 26 orthopaedic, 8 nonorthopaedic) procedures, a finding, which underscores the importance of an interdisciplinary management and procedure-specific guidelines for patients with haemophilia and VWD prior to even minor invasive procedures.[244]

The recent World Federation of Hemophilia (WFH) guidelines recommend that patients with haemophilia requiring surgery should be managed at, or in consultation with, a comprehensive haemophilia treatment centre.[245]

Furthermore, there is a risk of thromboembolic complications in IBDs, despite the higher bleeding risk. In a large surgical database, patients with VWD were significantly more likely to develop postoperative haemorrhage than patients without VWD, but had similar frequencies of peri-operative MACE and thrombotic events.[241]

Preoperative haemostatic correction

There is insufficient evidence from RCTs to identify the most effective and well tolerated treatment to prevent bleeding in patients with IBDs.[246] However, major and minor surgery are performed in these patients following national and international recommendations based on data from observational, uncontrolled studies and case series.

In the SPATA study of patients with IPDs, the frequency of surgical bleeding was significantly higher in IPFD (24.8%) than in IPND (13.4%) and varied according to the type of IPD, with biallelic Bernard Soulier syndrome having the highest occurrence (44.4%).[242] Some types of surgery were associated with a higher bleeding incidence, like cardiovascular and urological surgery. Prophylactic pre-operative pro-haemostatic treatments were associated with a lower bleeding incidence compared with those without prophylactic treatment (21 versus 41%; $P < 0.01$), with a markedly reduced frequency of surgical bleeding in IPFDs (OR 0.38, 95% CI 0.23 to 0.63) compared with IPNDs.[242] Bleeding history, type of disorder, type of surgery and female sex were associated with higher bleeding frequency in IPFDs, supporting the concept of individualised haemostatic prophylaxis.[242]

Low VWF[247] and residual plasma levels of deficient coagulation factors[239] do not always predict the bleeding tendency, and the bleeding risk in RBD patients is largely assessed by referring to databases and expert opinion.[248]

A substudy of a Dutch nationwide cross-sectional study of patients with RBDs included 308 dental and 408 surgical procedures.[249] Bleeding occurred in 50% of dental and 53% of surgical procedures performed without haemostatic treatment and in 28% of dental and 19% of surgical procedures performed with haemostatic treatment. Not only patients with severe RBDs but also patients with mild deficiencies, experienced increased bleeding without proper haemostatic treatment. Omission of peri-operative haemostatic treatment was associated with bleeding in a considerable proportion of surgical procedures in all coagulation factor deficiencies, ranging from 29% in FV deficiency to 59% in FXI deficiency. Bleeding also occurred in patients with relatively high levels of the specific deficient factor and 48% of the RBD patients had a more severe bleeding phenotype than predicted based on proposed threshold levels to remain asymptomatic or free from bleeding.[239] There was a large variety in factor levels, ranging from severe-to-mild deficiencies, in both bleeding and nonbleeding patients. Median coagulation factor activity levels of patients with and without bleeding after surgical procedures without haemostatic treatment did not differ significantly in deficiency of fibrinogen, FV, FVII and FXI. However, a lower bleeding rate was observed when peri-operative haemostatic treatment was used in patients with fibrinogen, FVII and FXI deficiency. These findings emphasise that the effect of individual bleeding phenotype on invasive procedures not only depends on the activity level of the deficient factor but also probably on other factors.

An observational study over 25 years, which included 78 patients with IBD undergoing colonoscopy, found a low bleeding rate and suggests that patients with mild bleeding disorders and a low likelihood of requiring an intervention or who require only low-risk interventions do not need any preprocedural haemostatic treatment.[250]

On the other hand, a review of 29 articles on dental extractions in patients with IBDs showed that overall reported bleeding rate in cases of both pre-operative and postoperative factor replacement or single dose of pre-operative factor replacement is similar (11.9 and 11.4%, respectively), indicating that minimising the use of clotting factor concentrate is possible, if proper local haemostatic measures are provided.[251]

Congenital FXIII deficiency is related to bleeding according to the degree: a total lack of FXIII is associated with spontaneous major bleeding, whereas a moderate deficiency with levels less than 30% is related to spontaneous mild or trauma/surgery-related bleeding. A FXIII level greater than 30% in congenital deficiency is asymptomatic.[252,253]

Replacement therapy

The specific replacement requirements for VWD and haemophilia patients in the peri-operative period are found in international guidelines.[245,254] However, they are mainly based on observational studies and case series, and are, therefore, of low grade. A systematic review performed to inform VWD clinical practice guidelines included seven case series of major procedures. It indicated that keeping the FVIII and VWF levels above 0.50 IU ml^{-1} for at least three consecutive days ensured efficient haemostasis (considered as 'excellent' by the researchers after 74 to 100% of major procedures) and a low risk of complications, but there was a high level of uncertainty in this evidence.[255] Consequently, the VWD guidelines recommend that the duration of therapeutic intervention and specific target levels should be individualised based on the patient, type of procedure and bleeding history, as well as availability of VWF and FVIII testing.[254]

High-quality studies are also needed for haemophilia patients because there is no consensus on the optimal replacement therapy and the minimum required haemostatic levels for individual factors.[256] Limited data suggested that there has been no great difference in surgical haemostasis and outcomes using low dose compared with the standard recommended protocol,[256] in line with previous WFH guidelines, which recommended different regimens for factor replacement depending on the availability of resources.[257] However, the most recent WFH guidelines recommend individualised pharmacokinetic monitoring for optimisation of therapy.[245] In an open-label, multicentre, RCT (OPTI-CLOT), pharmacokinetic-guided factor dosing in 98 patients with moderate or severe haemophilia scheduled for elective low-risk or medium-risk surgery showed an improvement in obtaining FVIII concentrations within the desired peri-operative FVIII range, although the peri-operative mean consumption of FVIII was similar compared with standard treatment.[258] Furthermore, a large international multicentre study including 255 surgical procedures performed on 118 patients with haemophilia B confirmed that targeting FIX levels in the peri-operative setting is complex and suboptimal. Importantly, 60% of trough and steady-state FIX levels were below the target level in the first 24 h after surgery, whereas 59% of FIX levels were above target more than 6 days after surgery, supporting the need for alternative dosing strategies such as pharmacokinetic monitoring.[259]

Although the preference for plasma-derived or recombinant FVIII products has been highly debated, mainly regarding the risk of inhibitor appearance,[260–262] both proved efficacious for preventing/treating bleeding episodes in haemophilia patients and the WFH recommendations do not express a preference for either recombinant or plasma-derived products.[245,257] However, the SIPPET randomised trial showed an increase in the inhibitor rate in patients using recombinant FVIII products compared with those receiving plasma-derived products in the first exposure days.[263] Two meta-analyses

also suggested a difference between inhibitor rates observed in previously untreated patients (PUPs) treated with plasma-derived or recombinant FVIII products,[264,265] but considering the high heterogeneity of included studies, this finding has to be interpreted with caution.

Recent studies performed with the different extended half-life recombinant FVIII or FIX products have demonstrated that these products are effective and well tolerated for the prevention and treatment of bleeding during major orthopaedic and nonorthopaedic procedures, as well as for other minor invasive procedures.[266–269]

For patients with haemophilia A and high-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH recommends bypassing agent therapy (rFVIIa or aPCC) at the discretion of the clinician.[245] For patients with haemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX, which may cause or worsen an allergic reaction. The evidence from a Cochrane analysis, which included four randomised studies and 116 patients with haemophilia and inhibitors, suggests that prophylaxis with bypassing agents may be effective in reducing bleeding.[270] However, there is a lack of evidence for the superiority of one agent over the other or for the optimum dosage regimen.

Although platelet transfusion was effective in the treatment of both surgical and nonsurgical bleeding in registries for patients with Glanzmann thrombasthenia,[271,272] in the SPATA retrospective study including patients with well defined forms of IPD and different procedures, prophylactic platelet transfusions alone were associated with a higher frequency of bleeding events (31.1%) compared with nonspecific therapies.[242] In particular, platelet transfusions were not associated with lower postsurgical bleeding in patients with IPND. However, when given for emergency treatment of bleeding events in IPFD, platelet transfusions were effective in 83% of cases (49 of 59) of IPFD and 100% (12 of 12) of IPND. Importantly, platelet transfusions were used more frequently in patients at higher bleeding risk and/or undergoing major surgery, and the mode of administration of platelet transfusions was rather heterogeneous and possibly sometimes incongruous.[242] Among 58 procedures in Glanzmann thrombasthenia patients, bleeding events were reported in 12 of them (20.7%) and occurred more frequently when the quantity of transfused platelets was less than six units. Interestingly, when platelet transfusions were given as prophylaxis, the bleeding rate was similar to those with or without a history of platelet refractoriness or antiplatelet antibodies (23.3 versus 37.5%).

A systematic review of evidence-based clinical practice guidelines pertaining to platelet transfusions identified seven recent studies of variable quality.[273] Considering the inconsistencies between guidelines and the fact that none of them included recommendations for IPDs, no statement can be made regarding the indication of platelet transfusion in patients with IBDs.

Data from a cross-sectional analysis support the use of peri-operative replacement therapy in patients with RBDs, but the treatment plans were heterogenous and no recommendation could be made.[249] Treatment decisions in coagulation factor deficiencies should be based on the individual bleeding phenotype as well as individual coagulation factor activity level.

Desmopressin

A literature and current practice survey performed by the European Haemophilia Therapy Strategy Board confirms that DDAVP can be effectively used to cover minor surgery and dental procedures in most VWD patients.[274] The strategy of performing a DDAVP challenge and using the results to determine therapy for surgical prophylaxis resulted in clinicians rating the haemostatic efficacy as excellent, good or effective in 94% of 211 procedures (95% CI 81 to 98%), whereas the proportion of surgical events in which patients experienced postoperative bleeding was 6% (95% CI 0.02 to 0.14) across 199 surgical events.[254] Although there is very low certainty in the evidence for a net health benefit of performing a DDAVP challenge and using the results to determine therapy, and very low certainty in the evidence for a net health harm from treating with DDAVP in the absence of trial results, the recent guidelines on the management of VWD define a positive response to DDAVP as increases of both FVIII and VWF to more than 0.50 IU ml^{-1}.[254] Furthermore, in a cohort of 122 patients with type 1 VWD, those with the highest VWF and FVIII levels 3 h after DDAVP administration had a 5-point lower bleeding score and patients with FVIII:C in the highest quartile had approximately 10 times less chance of presenting with an abnormal bleeding score.[275]

It should be noted that if DDAVP is used to increase VWF levels, there is the potential for tachyphylaxis after several doses in addition to the potential for more significant hyponatraemia.[255] Use of DDAVP is contraindicated in patients with type 3 VWD because of a lack of efficacy and in type 2B VWD because of increased platelet binding and subsequent thrombocytopenia.[254]

As DDAVP boosts plasma levels of both VWF and FVIII, it could be the treatment of choice for patients with mild haemophilia A when FVIII can be raised to appropriate therapeutic levels and the WFH recommends the use of DDAVP for peri-operative haemostasis in these patients if there is a good therapeutic response in presurgical testing.[245] Each patient should be tested before surgery, as there are significant differences between individuals.[276,277]

Moderate haemophilia A patients may also benefit. In a study of 169 patients with moderate haemophilia A, 68 patients (40%) had an adequate response to DDAVP (>0.3%), 25 of whom (15%) showed excellent response (>0.5%).[278] Intravenous administration, age, pre-DDAVP FVIII activity and VWF antigen, peak VWF activity and DDAVP-induced rise in VWF antigen were significant predictors of peak FVIII levels and explained 65% of the inter-individual variation.

The quantitative laboratory measurement of the response to DDAVP in patients with IBDs other than VWD or haemophilia is uncertain, and the use of DDAVP remains empirical. In the SPATA study performed in patients with IPD, DDAVP, alone or with antifibrinolytic agents, was the most effective preventive treatment associated with the lowest peri-operative bleeding.[242] DDAVP was used as prophylaxis in 88 procedures (10.3% minimally invasive, 26.1% dental and 63.6% major procedures), only 6 of which were followed by bleeding events (7%), 4 after major procedures and 2 after dental procedures. Postsurgical bleeding was lowest in DDAVP-treated patients (bleeding events in 8.1% of procedures, OR 0.13; 95% CI 0.04 to 0.45, compared with no treatment), followed by DDAVP and antifibrinolytics (8.3%, OR 0.13; 95% CI 0.04 to 0.46), antifibrinolytics alone (17.6%, OR 0.31; 95% CI 0.13 to 0.71), antifibrinolytics and platelet transfusions (17.8%, OR 0.31; 95% CI 0.14 to 0.70) and rFVIIa (18.5%, OR 0.33; 95% CI 0.11 to 0.95).

Antifibrinolytics

Antifibrinolytic therapy may facilitate effective clotting. A systematic review, which included two old RCTs and 12 case series of minor procedures showed that adding tranexamic acid (TXA) to increasing VWF levels to 0.50 IU ml^{-1} resulted in less bleeding complications compared with only increasing VWF levels to 0.50 IU ml^{-1}.[255] Based on this low to very low certainty evidence, the recent guidelines on the management of VWD suggest increasing VWF activity levels to at least 0.50 IU ml^{-1} with DDAVP or VWF concentrate with the addition of TXA, in patients undergoing minor surgery or minor invasive procedures, over raising VWF levels to more than 0.50 IU ml^{-1} with DDAVP or factor concentrate alone, and giving TXA monotherapy for minor mucosal procedures in patients with type 1 VWD and baseline VWF activity levels greater than 0.30 IU l^{-1} and a mild bleeding phenotype.[254]

Antifibrinolytics are also recommended by WFH for haemophilia patients undergoing surgery if ancillary therapies are required beyond factor replacement.[245] In a prospective multicentre observational cohort study including 131 total hip or knee arthroplasties, fewer haemophilia patients exhibited major bleeding (21 vs 36%) when antifibrinolytics were given as adjuvants.[279] TXA also decreased peri-operative blood loss, transfusion rate and supplementary amount of FVIII in a retrospective study of 34 haemophilia patients undergoing major orthopaedic procedures.[280]

Although antifibrinolytic agents are recommended by WFH as an alternative to use alone or as adjuvant treatment for controlling mucocutaneous bleeding and for dental surgery,[245] the limited number of RCTs identified by a Cochrane analysis, in combination with the small sample sizes and heterogeneity regarding standard therapy and treatment regimens between the trials, do not allow us to conclude definite efficacy of antifibrinolytics alone in oral or dental procedures in people with haemophilia.[281] However, tooth extractions were successfully performed without the supplementation of clotting factors in patients with mild haemophilia and VWD after an appropriate local treatment and use of antifibrinolytics.[282]

The use of antifibrinolytic drugs in IPDs is not evidence-based. Although registries of surgical and nonsurgical bleeding in patients with Glanzmann thrombasthenia showed effectiveness of antifibrinolytics alone,[271,272] in the SPATA study, antifibrinolytics were less effective in preventing bleeding events in IPFDs, than DDAVP (17.6 versus 8.1%).[242] On the other hand, antifibrinolytics were associated with lower postsurgical bleeding frequency in IPNDs (bleeding events in 6.7% of procedures) and were very effective in emergency treatment of bleeding in IPFDs (88.2% of bleedings controlled; 15 of 17).

Although in a cross-sectional study including 308 dental and 408 surgical procedures in patients with RBDs, antifibrinolytics were used in 10 and 11% of patients, respectively,[249] their benefit is not clear, and no recommendation can be made on their use in the peri-operative period.

Recombinant activated factor VII (rFVIIa)

In previous analysis of a Glanzmann thrombasthenia database, investigators found rFVIIa used alone to be effective in a majority of surgical procedures (59 of 62; 95.2%), higher than in the group that received platelet transfusion with or without antifibrinolytic agents (67%).[271] The success rate increased when rFVIIa was used with antifibrinolytics. In the SPATA study, although only used in 32 of 182 procedures in Glanzmann thrombasthenia patients, rFVIIa appeared to be effective even in severe cases when used as a single agent.[242]

A report summarising the evidence of efficacy and safety of rFVIIa in patients with Glanzmann thrombasthenia without refractoriness or antiplatelet antibodies from three different sources, including 133 patients who received rFVIIa for the treatment of 333 bleeding episodes and prevention of bleeding in 157 surgical procedures, found overall efficacy rates of 79 and 88%, respectively.[283] Effectiveness was generally similar across refractoriness/antibody status categories. Analysis

of adverse events reported in various databases did not raise any new safety concerns.[283]

In an analysis of another Glanzmann thrombasthenia registry, which included 195 patients with 810 events (619 severe bleeding episodes, 192 procedures), most rFVIIa-treated procedures were rated as successful (159/160, 99.4%; rFVIIa only, 65/66, 98.5%; rFVIIa ± platelets ± other agents, 94/94, 100.0%).[284] Efficacy was consistent in patients with platelet refractoriness ± antibodies (69/70, 98.6%), antibodies only (24/24, 100.0%) and neither/unknown (66/66, 100.0%).

Similarly, in a paediatric registry, 27 children with Glanzmann thrombasthenia treated for 44 surgical procedures (36 minor, 8 major), regardless of platelet antibody or refractoriness status, rFVIIa, administered with or without platelets (±antifibrinolytics), provided effective haemostasis with a low frequency of adverse events.[285]

No reliable data exists concerning rFVIIa usage in bleeding because of other IPDs, and the drug is not licensed for other IPDs.

rFVIIa is the treatment of choice for FVII deficiency.[248] Data from a prospective international web-based registry [Seven Treatment Evaluation Registry (STER)], which included 95 FVII-deficient patients undergoing 110 surgical procedures (61 major, 49 minor) showed that replacement therapy with a low dose of rFVIIa ($<20\ \mu g\ kg^{-1}$) was efficient in 95% of cases, as only five peri-operative bleeding events were reported, three of which occurred in patients with less than 3% FVII:C, and only one required blood cell transfusion.[286] In high-risk clinical subsets (patients with a history of major bleeding and in those with FVII:C <3%), the same dose should be repeated up to approximately eight times. In addition, a single-dose of replacement therapy was a valuable option in patients without a previous history of bleeding episodes.

Although registry data suggests that rFVIIa treatment may control or prevent bleeding in other RBDs,[249] data is insufficient to make a recommendation for using rFVIIa in other RBDs apart from FVII deficiency.

1.6 Patients with coronavirus disease 2019 coagulopathy or postcoronavirus disease 2019

Recommendation 6

We recommend against major elective surgery in patients with COVID-19 coagulopathy. 1C

In (semi)urgent surgery in patients with COVID-19 coagulopathy, we suggest avoiding prophylactic TXA administration. 2C

We suggest VHA-guided, goal-directed procoagulant treatment of peri-operatively acquired coagulopathic bleeding avoiding overcorrection. 2C

Peri-operative drug-monitoring of LMWH used as standard anticoagulant in COVID-19 critical illness is suggested. If anti-Xa activity is greater than $0.3\ IU\ ml^{-1}$ in clinical bleeding, reversal with protamine may be considered. 2C

We suggest a restrictive RBC transfusion strategy as in non-COVID-19 patients. 2C

In patients recovered from COVID-19 and free of post-COVID-19 symptoms, we suggest management of severe peri-operative bleeding as in non-COVID-19 patients. 2C

Postoperative thromboprophylaxis should be administered as early as possible. 1C

We recommend a restrictive RBC, plasma and platelet transfusion strategy in the critically ill. 1C

We suggest the use of a goal-directed coagulation therapy algorithm in the presence of ongoing bleeding, considering altered laboratory tests and VHA in critical illness. 2C

We suggest if ongoing bleeding unresponsive to multimodal coagulation therapy or wound healing defects in the critically ill to monitor FXIII and correct deficiency. 2C

We suggest a restrictive systemic administration of TXA in case of fibrinolytic shutdown in critical illness. 2C

We recommend initiation of thromboprophylaxis after bleeding as soon as bleeding risk is overbalanced by the risk of thromboembolic complications. 1C

Evidence summary

Evidence on the management of severe peri-operative bleeding in patients with COVID-19 disease or post-COVID-19 disease is not available yet. Our guidance is based on theoretical considerations and expert opinion. COVID-19-associated coagulopathy is, in general, associated with an activation of both the plasmatic and the primary haemostatic system. In addition to enhanced platelet and complement activation and improved thrombin generation, FVIII, VWF, D-dimer, and especially, fibrinogen levels are significantly increased, whereas physiological lysis and ADAMTS13 levels are decreased.[287–294] Critically ill COVID-19 patients have a high risk, at least 80 to 100%, of developing heparin resistance over the course of the disease.[295–298] In contrast to bacterial or fungal sepsis/infection, platelet numbers remain within the normal ranges. The general risk for thromboembolic complications in COVID-19 patients is still high. Compared with other virus infections such as influenza-related pneumonia, the risk of developing micro-thrombotic complications or pulmonary embolism is significantly increased. The ACTION trial will evaluate whether in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin improves clinical outcomes in hospitalised patients with COVID-19 and elevated D-dimer levels.[299]

Anticoagulation with LMWH became a standard treatment in COVID-19 patients. However, there are conflicting results concerning the benefit of the dose of anticoagulation. As expected, the amount of anticoagulation is related to the number of bleeding complications. However, these results are not really surprising as no monitoring was performed in any of these studies.[300,301]

Hypercoagulopathy in COVID-19 patients, including the presence of heparin resistance, fibrinolytic shutdown and platelet activation, is related to the degree of acute-phase reaction and changes during the course of the disease. A so-called intermediate or therapeutic anticoagulation may be too low at the beginning of COVID-19 disease, whereas a prophylactic dose in the later course, for example, in the presence of acute renal failure and/or decreased acute-phase reaction, is maybe too high and gives rise to bleeding in some individuals. Thromboelastography (TEG) has been used to guide anticoagulation therapy in COVID-19 disease.[302] Monitoring of anti-Xa levels in COVID-19 patients has been used to prevent bleeding complications from the use of not only LMWH but also UFH. For prophylaxis, anti-Xa levels between 0.3 and 0.5 IU l^{-1} have been proposed,[303–308] with protamine reversal in the event of bleeding associated with, or in the presence of UFH or LMWH.

Clinical query 2

How should intra-operative and postoperative bleeding be stopped and anaemia be managed?

2.1 Patients undergoing cardiovascular surgery

Recommendation 7

Withdrawal of aspirin treatment before surgery might increase the risk of coronary thrombosis; however, continuation of aspirin treatment increases the risk of bleeding. B

Withdrawal of treatment with $P2Y_{12}$ inhibitors (clopidogrel, prasugrel and ticagrelor) before surgery might increase the risk of coronary thrombosis; however, continuation of clopidogrel therapy increases the risk of bleeding. B

In patients on DAPT who need to undergo nonemergency cardiac surgery, postponing surgery for at least 5 days after discontinuation of ticagrelor or clopidogrel and 7 days after prasugrel should be considered. 2B

Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors. B

Bridging oral antiplatelet therapy with LMWH is not recommended. 1A

Bridging $P2Y_{12}$ inhibitors with glycoprotein IIbIIIa inhibitors or cangrelor may be considered in high ischaemic risk patients. 2B

We suggest that aspirin or $P2Y_{12}$ inhibitors may be administered in the early postoperative period without increasing the risk of postoperative bleeding. 2C

We recommend prophylactic administration of TXA [or if not available ε-aminocaproic acid (EACA)] before cardiopulmonary bypass (CPB) to reduce postoperative blood loss and blood transfusion requirements. 1B

We recommend administering TXA or EACA intravenously at low doses. 1B

If systemic administration of TXA is contraindicated (for refractory seizure), topical TXA is suggested. 2C

Upon withdrawal from CPB, we suggest the use of heparin monitoring to avoid protamine-to-heparin dosing ratios above 1. 2B

We recommend treatment with fibrinogen concentrate or cryoprecipitate, if bleeding is accompanied by hypofibrinogenaemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤ 1.5 g l^{-1}). 1B

We recommend treatment with PCC if available instead of FFP if bleeding is accompanied by signs of coagulation factor deficiency (viscoelastic signs of a functional coagulation factor deficiency or a high PT ratio). 1B

We suggest that rFVIIa may be considered for patients with bleeding that remains intractable after conventional haemostatic therapy has been applied, although the risk of thrombosis must be taken into account. 2B

We recommend the use of standardised haemostatic algorithms with predefined intervention triggers over clinicians' discretion for the management of coagulopathy in cardiac surgery. 1B

We suggest the use of point-of-care haemostatic testing over conventional coagulation assays for the management of coagulopathy in cardiac surgery. 2C

In patients on ticagrelor or rivaroxaban undergoing emergency cardiac/aortic surgery on CPB, haemo-adsorption may be considered as an adjuvant therapy to reduce bleeding complications. 2C

We suggest the use of acute normovolaemic haemodilution (ANH) in cardiac surgical patients with normal/high initial Hb concentration. 2C

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

We recommend against the routine use of intra-operative platelet-rich plasmapheresis for blood conservation during cardiac operations using CPB. 1B

Evidence summary

Antiplatelet therapy

Aspirin

Some studies have suggested that pre-operative aspirin may be beneficial in cardiovascular surgery. In a meta-analysis of 13 RCTs involving 2399 coronary artery surgery patients published in 2015, aspirin reduced peri-operative myocardial infarction, although blood loss and RBC transfusion were increased.[309] Aspirin therapy until the time of surgery was compared with cessation more than 5 days before surgery in a propensity score-matched study of 1418 CABG patients.[310] There were no significant between-group differences in intra-operative or postoperative blood loss, or (after 4 years of follow-up) major cardiac events or cardiac readmissions, but the angina-free survival rate was significantly higher in the patients taking aspirin until the time of surgery.

More recent data have increased uncertainty as to whether pre-operative aspirin is beneficial. A meta-analysis from 2019 included 9101 CABG participants of 17 studies, 12 of which were RCTs.[311] Compared with controls who did not receive aspirin, the aspirin-treated patients did not show decreased risk of postoperative myocardial infarction or mortality. Aspirin treatment was associated with increased chest tube drainage ($P = 0.011$), although the risk of re-operation due to bleeding was not significantly increased. In one RCT, CABG patients ($n = 206$) received aspirin treatment that was either continued until the day of surgery or stopped 4 days earlier.[312] Rates of bleeding and transfusion of RBCs were significantly higher in patients receiving aspirin until the day of surgery ($P < 0.001$), and there were no significant differences in postoperative myocardial infarction or stroke. Nevertheless, the ATACAS randomised trial, conducted in 2100 patients undergoing coronary artery surgery, concluded differently as the administration of pre-operative aspirin resulted in neither a lower risk of death or thrombotic complications nor a higher risk of bleeding, including re-operation for haemorrhage, than observed with placebo.[313]

$P2Y_{12}$ inhibitors and dual antiplatelet therapy

A meta-analysis of 20 observational studies ($n = 23\,668$) concluded that clopidogrel exposure within 5 days before cardiac surgery increases the risk of RBC transfusion and bleeding-triggered re-operation, without reducing postoperative myocardial infarction.[314] The overall mortality rate in those who took clopidogrel up to the time of surgery was also higher. These findings were reflected in a retrospective analysis of CABG patients ($n = 715$): a significant association was observed between bleeding and clopidogrel exposure within 5 days before surgery.[315]

A meta-analysis of 12 studies reported that continuing antiplatelet therapy (aspirin and clopidogrel) until the time of cardiac surgery was associated with increased blood loss, but carried a low risk of surgical re-exploration for bleeding.[316] The authors concluded that in patients at a high risk of stent thrombosis, this may be acceptable. One retrospective, multicentre, observational study ($n = 666$) reported that discontinuation of antiplatelet therapies significantly increased MACE, myocardial infarction and death, and did not significantly reduce bleeding.[317] However, this study included noncardiac as well as cardiac surgery, potentially reducing the risk of blood loss.

Continuation of DAPT until cardiac surgery increases the risk of excessive peri-operative bleeding, transfusions and re-exploration for bleeding.[318,319] The bleeding risk is increased with ticagrelor or prasugrel compared with clopidogrel. Therefore, it is recommended that the $P2Y_{12}$ inhibitor be discontinued whenever possible before elective cardiac surgery.

Platelet function testing

There is a significant variability in the response to $P2Y_{12}$ inhibitors evaluated with PFT, in particular for clopidogrel and to a lesser degree for prasugrel and ticagrelor. Therefore, PFT could be a better means to predict peri-operative bleeding risk than standardised duration of APA discontinuation. A few observational studies reported on measuring the degree of platelet dysfunction to determine the optimal time interval between last medication intake and cardiac surgery, especially for unplanned surgery.[320–323]

Procoagulant prophylaxis and treatment

Heparin and protamine

An RCT in elective cardiac valve surgery patients ($n = 38$) compared heparin and protamine dosage based on either heparin monitoring using a point-of-care haemostasis management system, or the standard activated clotting time (ACT)-based approach.[324] The study found that dosing heparin and protamine based on the haemostasis management system decreased the incidence of severe blood loss compared with the ACT approach. A double-blind RCT investigated the effect of basing protamine doses on protamine–heparin titrations in valve replacement patients ($n = 60$).[325] The authors found that basing protamine measurements on two separate protamine–heparin titrations, the first at termination of CPB and the second 5 min after the first dose of protamine, can reduce postoperative blood loss by reducing protamine–heparin mismatch. One RCT was performed to compare a low protamine-to-heparin dosing ratio (0.8; $n = 49$) with a high dosing ratio (1.3; $n = 47$) in patients undergoing cardiac surgery with CPB.[326] Postoperative blood loss and the percentages of patients receiving transfusions of FFP and platelets were higher among patients in the high-ratio group.

Antifibrinolytic therapy (aprotinin, ε-aminocaproic acid [EACA], tranexamic acid and ulinastatin)

Multiple RCTs and meta-analyses assessing prophylactic TXA administration in patients undergoing cardiac

surgery consistently demonstrate a reduction in bleeding and blood transfusion requirements.[327] However, data from 45 235 adults participating in 16 studies (RCTs or nonrandomised observational studies) showed that TXA therapy was associated with a 4.1-fold increase in the risk of seizure.[328] The optimal dose needed to reduce bleeding without increasing the risk of side effects, especially seizures, remains to be studied prospectively. A meta-analysis of 49 RCTs including 10 591 patients undergoing cardiac surgery reported that i.v. infusion of low-dose TXA ($<50\,mg\,kg^{-1}$ for bolus injection or $\leq 10\,mg\,kg^{-1} + 1\,mg\,kg^{-1}\,h^{-1}$ for bolus plus continuous infusion) was the preferred regimen, with no difference in efficacy between bolus injection alone and bolus plus continuous infusion, and similar efficacy to high-dose therapy without increasing the risk of seizure. A prospective clinical trial ($n = 1182$) investigated the efficacy of small and medium 'single shots' of TXA in CPB priming volume (1 and 5 g, respectively), and a medium dose (3 g) plus $15\,mg\,kg^{-1}\,h^{-1}$ infusion in elective cardiac surgical patients.[329] The results were consistent with those of the meta-analysis, with no significant between-group differences in postoperative blood loss. Finally, a model-based meta-analysis concluded that low-dose TXA (total dose of $20\,mg\,kg^{-1}$ of actual body weight) provided the best balance between reduction in postoperative blood loss and RBC transfusion and the risk of clinical seizure in adult cardiac surgical patients.[330] The use of higher doses would only marginally improve the clinical effect at the cost of an increased risk of seizure. The safety as well as the efficacy of TXA should be considered when making treatment decisions.

While it is often administered intravenously, TXA can also be used topically but that means of administration is less effective on blood loss reduction. A meta-analysis (from 2013) of four double-blind RCTs ($n = 371$) on topical TXA use in cardiac surgery found a significant reduction in 24 h postoperative blood loss but could not prove a significant reduction in transfusion.[331] Two RCTs published after this meta-analysis, each conducted in 100 patients undergoing cardiac surgery, demonstrated that topical TXA produced a significant reduction in postoperative bleeding versus placebo or control.[332,333] A more recent RCT was performed in 97 patients undergoing on-pump cardiac surgery to compare intrapericardial versus i.v. TXA. There were tendencies towards reduced chest tube drainage and reduced RBC transfusion in the intrapericardial group, although statistical significance was not reached.[334] The above-mentioned meta-analysis performed to determine the optimal dosing and delivery method of TXA in elective heart surgery reported that topical TXA had no statistically significant impact on transfusion of allogeneic blood products.[327] On the other hand, in a 2020 meta-analysis of topical (intrapericardial) TXA in cardiac surgery, topical TXA was associated with significantly reduced 24 h blood loss and no increase in the risk of postoperative seizures.[335] Taken together, the recent data are consistent with the meta-analysis from 2013.

Evidence of the benefits of TXA is less clear-cut in paediatric versus adult cardiovascular surgery. A systematic review and meta-analysis of eight studies ($n = 848$) concluded that while there was a small reduction in blood transfusions across the patients that were administered TXA, the quality of the evidence was weak and much of it was too heterogeneous to be analysed in the meta-analysis.[336] A more recent systematic review and meta-analysis of 30 RCTs demonstrated efficacy for all three antifibrinolytic drugs that were evaluated (TXA, aprotinin and EACA).[337] An RCT with 117 paediatric cardiac surgery patients included three arms: $20\,mg\,kg^{-1}$ TXA administered via CPB followed by a post-CPB dose of $20\,mg\,kg^{-1}$, $50\,mg\,kg^{-1}$ TXA poured into the pericardium and control with no antifibrinolytic treatment.[338] Chest tube drainage did not differ between the two TXA groups and was significantly higher in the control group, and there were no significant between-group differences in neurological or thromboembolic events. However, there were also no significant between-group differences in transfusion of blood products.

A small double-blind RCT compared intra-operative topical EACA with placebo in 26 adult patients undergoing off-pump cardiac surgery.[339] There were no significant differences between the two groups in blood loss or transfusion requirements. On the other hand, a number of RCTs have suggested that EACA has effects similar to TXA in cardiac surgery.[339–342] The largest of these studies was an RCT in 114 patients undergoing surgery with CPB; standard intra-operative EACA was compared with TXA, with both drugs being administered as a bolus plus continuous infusion.[342] No significant differences were observed in chest tube drainage, but the incidence of transfusion of allogeneic blood products was significantly lower with EACA. EACA appears to have a different safety profile from TXA. In one study comparing the two treatments, EACA significantly increased the risk of renal injury and failure, and TXA increased the risk of seizures.[343] A meta-analysis of prophylactic EACA in paediatric open-heart surgery included five randomised, placebo-controlled trials with 515 patients.[344] A trend towards reduced blood loss with EACA did not reach statistical significance, but EACA was associated with significantly improved coagulation tests (shorter ACT, higher fibrinogen level) and significantly reduced transfusion of allogeneic blood products. One retrospective study compared aprotinin to EACA in a consecutive infants ($n = 227$) undergoing cardiac surgery requiring CPB.[345] Chest tube output was significantly higher in the EACA group, although this did not affect transfusion requirements. Sensitivity analysis revealed lower efficacy with EACA compared with aprotinin.

Aprotinin is a serine protease inhibitor, which has been widely used in cardiac surgery as an antifibrinolytic agent to minimise patient bleeding. It was withdrawn from the European market in 2008 for safety reasons, but was re-introduced in 2012 with narrow licencing indications, specifically isolated CABG surgery in high-risk patients. However, in clinical practice, its predominant use appears to be outside its licence, mainly being used in acute aortic dissection and infective endocarditis valve surgery.[346] A meta-analysis of 106 RCTs and 11 observational studies (totalling 43 270 patients) was performed to compare the safety of aprotinin with other antifibrinolytic treatments.[347] The analysis was largely inconclusive, although the authors did observe that there was, on average, higher mortality and renal failure or dysfunction rates in patients who had been given aprotinin compared with other drugs or no treatment. The authors concluded that concerns about the safety of aprotinin in cardiovascular surgery still remain, and clinicians should be aware of the benefits and risks of the drug. Karkouti *et al.*[348] observed a lower incidence of massive bleeding associated with a significant reduced mortality in high-risk cardiac surgery. A meta-analysis of 33 501 patients suggested that, compared with TXA or EACA, aprotinin may increase mortality in low-risk to medium-risk cases but not in high-risk cases.[349] In a post hoc analysis of the arterial revascularisation trial (ART), CABG patients who received aprotinin ($n = 536$) were compared with propensity-matched controls who did not.[350] Treatment with aprotinin was associated with significantly increased risks of early and late mortality. Sander *et al.*[351]observed that the use of TXA was associated with higher cumulative drainage losses and a higher rate of repeat thoracotomy for bleeding than in the group of patients treated with aprotinin. In the subgroup of patients with open-chamber procedures, mortality was lower in the aprotinin group than in the TXA group (7.5 versus 16.2%; $P = 0.02$). In a recent meta-analysis of 32 studies ($n = 63$ 894), the results suggested that aprotinin is effective and well tolerated in paediatric cardiac surgery.[352]

An RCT with 10-year follow-up compared ulinastatin with TXA and placebo in patients undergoing cardiac surgery with CPB ($n = 142$, $n = 143$ and $n = 141$, respectively).[353] Ulinastatin and TXA were similarly effective in reducing postoperative blood loss and transfusion of RBCs versus placebo, and there were no significant differences between the three study arms in 10-year mortality or morbidity.

Allogeneic blood products (fresh frozen plasma, platelet concentrate and cryoprecipitate)

One small, prospective study ($n = 13$) reported that cryoprecipitate increased fibrinogen levels and fibrin-based clot strength in aortic surgery patients undergoing deep hypothermic circulatory arrest.[354]

A prospective, cohort study named PLASMACARD ($n = 967$), concluded that FFP use in cardiac surgery has no beneficial impact on 30-day mortality rates.[355] Evidence from another study, a retrospective analysis of 685 patients, suggests that using autologous platelet-rich plasma may be an effective haemostatic option in thoracic aortic surgery. Compared with controls, significantly reduced allogeneic blood transfusions were reported with autologous platelet-rich plasma, together with a decrease in major adverse events.[356] However, a large RCT is needed to confirm the efficacy of autologous platelet-rich plasma as a haemostatic option.

A prospective study of 10 patients receiving an intraoperative series of four apheresis concentrates showed the changes in platelet count, viscoelastic and aggregometric variables and bleeding.[357]

Desmopressin

A double-blind RCT ($n = 102$) tested the effects of DDAVP on postoperative blood loss and platelet aggregation.[358] The intervention group was treated with 0.3 $\mu g\,kg^{-1}$ during surgery and a control group received saline. The results showed a significant decrease in postoperative blood loss and FFP transfusions in the DDAVP group during the first 6 h postsurgery (the duration of drug activity). However, by 24 h, there was no significant difference between the groups. No effects on platelet aggregation, RBC or platelet transfusion were observed. A subsequent RCT compared DDAVP with placebo in patients with bleeding following elective cardiac surgery despite pretreatment with TXA.[359] The study was stopped early because of data from 135 patients showing that DDAVP did not reduce RBC transfusion or blood loss. More positive findings were reported from a randomised, placebo-controlled trial in which DDAVP was administered 30 min before heart transplant surgery.[360] Results from 48 patients showed that chest tube drainage during the first 24 h postoperatively and transfusion of RBCs were significantly lower with DDAVP versus placebo.

Coagulation factor replacement therapy

Factor XIII concentrate

A double-blind, placebo-controlled, multicentre trial ($n = 409$) investigated FXIII supplementation in CPB patients.[361] No effect on transfusion avoidance, transfusion requirements or surgical re-exploration was observed.

Fibrinogen concentrate

Eight RCTs with 597 participants were included in a meta-analysis of prophylactic or therapeutic fibrinogen concentrate in cardiovascular surgery.[362] Compared with placebo or inactive control, fibrinogen concentrate reduced RBC transfusion ($P = 0.001$), but had no significant effect on mortality, bleeding or total units of allogeneic

blood products transfused. One randomised, placebo-controlled trial was conducted in 519 aortic surgery patients with peri-operative bleeding.[363] The median number of units of allogeneic blood product administered during the first 24 h after study medication was significantly higher in the fibrinogen concentrate group ($P = 0.026$), and there were no significant between-group differences in blood loss. Post hoc analyses showed that, when considering adherence to the study algorithm, baseline fibrinogen level and previous study centre experience, there were trends in favour of fibrinogen concentrate.[364] A previous randomised, double-blind, placebo-controlled trial in patients undergoing complex cardiac surgery ($n = 116$) reported that fibrinogen concentrate, administered after protamine, was effective in reducing transfusion of allogeneic blood products and postoperative bleeding.[365] Prophylactic fibrinogen concentrate administered at the end of CPB was investigated in a randomised, placebo-controlled trial conducted in 36 CABG patients.[366] Fibrinogen concentrate was associated with significant reductions in bleeding during surgery and the need for blood transfusion (both $P \leq 0.005$). However, another randomised, placebo-controlled study in CABG patients ($n = 48$) reported that prophylactic fibrinogen concentrate had no significant impact on postoperative bleeding or transfusion of allogeneic blood products.[367]

Safety outcomes in cardiac surgery patients who received fibrinogen concentrate ($n = 564$) were compared with propensity score-matched controls who did not receive this treatment in a single-centre, observational study.[368] No significant between-group differences were observed in thromboembolic complications or death within 1 year of surgery.

An RCT published in 2019 was performed to compare fibrinogen concentrate with FFP as treatment for hypofibrinogenaemia during thoraco-abdominal aortic aneurysm repair surgery.[369] In the fibrinogen concentrate group, mean blood loss during surgery was numerically lower than in the FFP group and allogeneic blood component administration during surgery was significantly lower ($P = 0.011$). Another RCT from 2019, involving 735 patients with clinically significant bleeding and hypofibrinogenaemia after cardiac surgery, showed that fibrinogen concentrate was noninferior to cryoprecipitate regarding transfusion of blood components.[370]

In paediatric cardiac surgery, two randomised studies have compared fibrinogen concentrate with cryoprecipitate. One of these studies reported no significant differences between the two agents in blood loss or transfusion of allogeneic blood products.[371] The other showed that the number of intra-operative allogeneic blood product transfusions was significantly lower with fibrinogen concentrate ($P = 0.003$), with no significant differences in adverse events.[372] Fibrinogen concentrate was compared with placebo in a study of 90 infants undergoing cardiac surgery with CPB who exhibited FIBTEM maximum clot firmness (MCF) 6 mm or less intra-operatively.[373] The mean 24 h mediastinal drain loss was significantly lower in the fibrinogen concentrate group than in the placebo group.

Prothrombin complex concentrate (PCC)

In a systematic review and meta-analysis, data from 861 adult participants of four studies (all nonrandomised) were analysed to evaluate PCC as first-line treatment of coagulopathic bleeding after cardiac surgery.[374] Compared with FFP, PCC reduced the rate of RBC transfusion but had no significant effect on chest drain output. Two RCTs comparing PCC with FFP have since been published. The first of these was performed in 101 adults requiring coagulation factor replacement for bleeding during cardiac surgery.[375] Median 24 h chest tube drainage and transfusion of allogeneic blood products were significantly reduced in the PCC group (both $P < 0.001$), whereas adverse events were similar in both study groups. In the second study, PCC was compared with FFP as treatment for bleeding in 50 adult cardiac surgery patients.[376] Transfusion requirements were similar in the two groups, and there was no increase in thromboembolic events with PCC.

Previously, a retrospective study ($n = 168$) compared the efficacy of FEIBA and rFVIIa.[377] No significant difference was found between the two procoagulants in terms of morbidity and mortality. Platelet transfusion was higher among patients receiving rFVIIa, but no other differences in transfusion requirements were identified.

Recombinant activated factor VII (rFVIIa)

An RCT with a control group, conducted to compare a group of CABG patients receiving rFVIIa after weaning from CPB ($n = 30$), found a significant reduction in chest drain output and transfusion requirements in the intervention group.[378] A retrospective study ($n = 69$) has compared dosing and efficacy between adults and children, for intra-operative and postoperative treatment.[379] Prophylactic therapy tended to be more effective, and adults benefited from a much smaller dose per kilogram of body mass than children, because of the shorter half-life of the factor in children.

A meta-analysis of seven double-arm studies (1117 patients) was performed to assess rFVIIa in paediatric cardiac surgery.[380] Compared with placebo or blood products, rFVIIa did not improve bleeding control, and there was also no statistically significant difference in thrombotic complications.

A limited body of research suggests that rFVIIa might increase morbidity and mortality. A single-centre, retrospective review ($n = 16$) of children who received rFVIIa intra-operatively or postoperatively found a

56% mortality rate, attributed to neurological, bleeding and septic events.[381] In an observational study of patients who received rFVIIa ($n = 144$) intra-operatively or postoperatively and matched controls ($n = 359$), the in-hospital mortality was 40% in the group receiving rFVIIa and 18% in the control group.[382] Renal morbidity was also increased in the group receiving rFVIIa (31 versus 17%, respectively). In a retrospective study of 149 children, Downey *et al.*[383] demonstrated that peri-operative administration of rFVIIa was associated with an increased incidence of postoperative thrombotic complications in neonates and children undergoing cardiac surgery, without an increase in 30-day mortality. In conclusion, rFVIIa should be used with extreme caution in children undergoing cardiac surgery.

Antithrombin

An RCT of 200 patients showed that pre-operative infusion of antithrombin to levels of 120% reduced heparin resistance with no adverse effects and prevented a postoperative reduction of antithrombin activity.[384]

A review comparing antithrombin with FFP for the treatment of patients with heparin resistance found a lower risk of transfusion-related acute lung injury (TRALI), superior efficacy and a lower volume of administration with antithrombin.[385] However, there was a paucity of good quality evidence with only three case reports, one RCT and one retrospective analysis.

Factor IX

A retrospective study of 11 patients receiving 35 $\mu g\,kg^{-1}$ versus controls showed that FIX produced a significant reduction in chest tube drainage, but it had no significant effect on blood product use.[386]

Haemostatic management algorithms

Standard coagulation testing from the clinical laboratory, including plasma Clauss fibrinogen level, is often felt to be too slow for use in critical situations with actively bleeding patients. The prolonged turnaround time may delay decisions on transfusion therapy, or care providers may simply treat in the absence of data. As a result, point-of-care tests have been developed to shorten transfusion decisions on bleeding patients, based on viscoelastic methods.

A systematic review of 12 studies ($n = 6835$) observed a reduction in transfusion requirements in patients managed by TEG-guided or rotational thromboelastometry (ROTEM)-guided therapy.[387] Transfusion of FFP, platelets and RBCs were all reduced; this may have been because of TEG-guided/ROTEM-guided therapy being more restrictive than control therapy, or control therapy being too liberal. The authors concluded that evidence for the use of TEG-guided/ROTEM-guided intervention algorithms is still lacking.

Two RCTs published in 2015 also found that pre-operative and intra-operative point-of-care testing can reduce transfusion requirements. One RCT ($n = 249$) was conducted in patients undergoing CABG surgery.[388] Pre-operative PFT was used in two intervention groups: one using multiple electrode aggregometry and the other using TEG Platelet Mapping. The results showed a significant reduction in blood product transfusions in both intervention groups compared with the control group. The authors also reported a greater effect in patients who had been treated with an adenosine diphosphate-receptor antagonist within 5 days before undergoing surgery. The other RCT, conducted in children ($n = 100$), found that intra-operative ROTEM-guided therapy [EXTEM A10 and FIBTEM A10 (amplitude at 10 min following clotting time)] post-CPB significantly reduced postoperative blood loss and RBC transfusion, both postoperatively and throughout intensive care stay.[389] In addition to these RCTs, two observational studies demonstrated significant reductions in transfusion requirements after implementation of a blood product utilisation algorithm and a point-of-care monitoring based intervention algorithm.[390,391]

Implementation of haemostatic algorithms based on conventional laboratory tests or on point-of-care haemostatic testing is associated with significant reductions in transfusion requirements.[390,392,393] In particular, a Canadian multicentre RCT including patients undergoing cardiac surgery with CPB reported that implementing point-of-care haemostatic testing within a transfusion algorithm reduced RBC transfusion, platelet transfusion and major bleeding.[393] However, only a few randomised trials compared these two kinds of algorithms. More than 20 years ago, Shore-Lesserson *et al.*[394] compared a transfusion algorithm based on TEG testing with routine laboratory testing, and found the algorithm to be effective in reducing transfusion requirements. Later, Weber *et al.*[395] compared two algorithms, one based on laboratory tests, the other based on both ROTEM and multiplate in 100 patients undergoing cardiac surgery. They concluded that haemostatic therapy based on point-of-care testing reduced patient exposure to allogeneic blood products. However, a recent meta-analysis highlighted limitations of the published studies and concluded that the predictive accuracy was not demonstrated for commonly used point-of-care devices for coagulopathic bleeding in cardiac surgery.[392] Therefore, robust confirmatory studies are still warranted.

Cytokine removal

CPB is often associated with degrees of complex inflammatory response mediated by various cytokines. This response can, in severe cases, lead to systemic hypotension and organ dysfunction. The removal of cytokines, and ticagrelor and rivaroxaban may improve outcomes by reducing bleeding following complex cardiac surgery

such as type A acute aortic dissection and infective endocarditis surgery in patients on dual anticoagulants undergoing long bypass runs.[396,397] In patients undergoing extracorporeal membrane oxygenation, cytokine haemadsorption has been shown to reduce the excessive inflammatory response caused by cytokine and interleukin activation.[398]

Acute normovolaemic haemodilution

A blood conservation technique, which has previously been used frequently is ANH, defined as removing whole blood from a patient after induction of anaesthesia, and maintaining normovolaemia using crystalloidal and/or colloidal replacement. The amount of blood removed depends on various factors such as baseline Hb concentration, expected blood loss and haemodynamic stability. The use of the technique of ANH has been shown to reduce transfusion of allogeneic blood products.[399–403] Benefits of ANH include decreasing Hb concentration during the period when most surgical blood loss is occurring, thereby minimising the effects of loss of RBCs; reinfusing the patient's own fresh whole blood containing RBCs, platelets and clotting factors when it is needed during or shortly after the surgical procedure. In cardiac surgical patients with normal to high initial Hb concentrations, a decreased blood viscosity because of ANH may have cardioprotective effects.[404,405] However, this procedure also carries potential side effects such as technical problems and loss of the patient's own blood, ANH-induced anaemia, transfusion reactions, transfusion-associated circulatory overload upon retransfusion and dilution of coagulation factors.[399–401] This latter adverse effect of ANH may actually increase blood loss, if significant surgical bleeding occurs.[406,407] Also, platelet function may be impaired in the blood collected and temporarily stored in standard bags containing citrate, phosphate, dextrose and adenine, as noted in one in vitro study.[408] Furthermore, as the patient is intentionally haemodiluted during ANH, the harvested blood could potentially be wasted if the expected blood loss does not occur, with consequent loss of valuable clotting factors and RBCs that were removed from circulation. For this reason, patient selection is critical.

Cell salvage

Although the use of red cell salvage is incorporated in PBM programmes, the cost effectiveness of cell salvage and the reduction of adverse outcomes by reducing allogeneic RBC transfusion requirements is still under debate. However, many studies suggest that cell salvage is associated with a decreased proportion of patients exposed to allogeneic RBC transfusions as an individual measure in a comprehensive PBM programme.[409–414]

Although autologous platelet-rich plasmapheresis has been proposed as a blood conservation technique in complex cardiovascular surgery, whether it can improve clinical outcomes remains unclear.[415–417] The indications for autologous platelet-rich plasmapheresis require further study, particularly whether it is beneficial to low-risk patients.

2.2 Patients undergoing orthopaedic surgery

Recommendation 8

We recommend the prophylactic use of TXA as a safe pharmacological agent to reduce blood loss and transfusion requirements in patients with a relevant risk for bleeding undergoing major orthopaedic surgery. 1A

We recommend the oral, i.v. and/or topical route to administer TXA. Combination of systemic and topical administration of TXA further reduces blood loss. 1B

We suggest EACA as an antifibrinolytic agent to reduce blood loss if TXA not available. 2B

The use of intra-operative tourniquet in primary knee arthroplasty may not reduce global peri-operative bleeding and transfusion rate. C

The use of drainage may not decrease blood loss in knee arthroplasty, total hip arthroplasty or spine surgery. C

The type of surgical approach in total hip arthroplasty may not reduce peri-operative blood loss. C

We recommend hip fracture treatment within 48 h to avoid global peri-operative complications. 1B

Allogeneic blood transfusion is associated with an increased incidence of surgical site infections. B

The osteosynthesis technique of proximal endomedullary nailing may reduce blood loss in trochanteric femur fracture. 1B

We suggest the maintenance of restrictive transfusion thresholds in the management of hip fracture. 2C

We suggest, in cases of ongoing bleeding as part of a goal-directed coagulation therapy algorithm, monitoring FXIII and correction of deficiency. 2C

We suggest the intra-operative and postoperative use of cell salvage in major orthopaedic procedures with high risk of bleeding. 2B

Evidence summary

Tranexamic acid

TXA has been shown to be more effective than placebo in reducing bleeding in orthopaedic surgery, hazard ratio 0.72 (95% CI, 0.57 to 0.92).[418] Many studies have shown that patients undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA) receiving TXA had a reduced total blood loss and reduced number of blood transfusions.[419–434] It has also been proven that i.v. TXA can reduce the total blood loss, intra-operative blood loss, postoperative drainage and the incidence of

transfusion events in spinal surgery,[435–444] and there is enough evidence for TXA reducing the proportion of patients requiring blood transfusions when undergoing hip fracture surgery.[420,445–450] In reference to safety, there is strong evidence that i.v. TXA is a safe pharmacological treatment in major orthopaedic surgery. A meta-analytic pooling showed that the risk of VTE in TXA-treated patients was not significantly different from that of controls.[419,420]

There is no consensus on the best administration regimen and the best route. The oral form of TXA can decrease blood loss, postoperative Hb reduction and also transfusion requirements in TKA.[451–453] Oral TXA is equivalent to i.v. TXA in reducing peri-operative blood loss in TKA and THA.[454–460] Topical TXA could significantly reduce total blood loss, drainage loss, transfusion rates and decrease Hb level following THA, without increasing the risk of VTE.[461–463] Furthermore, topical TXA has been shown to be equivalent or superior to i.v. administration, and exhibits comparable effectiveness and safety in terms of reducing blood loss during TKA.[421,464–473] It has been proposed that intra-articular administration of TXA is superior to i.v. in primary TKA patients regarding blood loss, drain output and Hb drop, without increased risk of peri-operative complications.[474,475] The safety and efficacy of topical TXA compared with both placebo and/or i.v. TXA was also shown in adult spinal deformity surgery.[437]

Current evidence supports that administration of TXA with epinephrine may be a good topical haemostatic agent to decrease blood loss and transfusion requirements in primary TKA.[476–478] Combined administration of TXA can reduce total blood loss and postoperative Hb drop compared with i.v., topical, or oral TXA alone and was not seen to lead to an increase in the incidence of adverse events, such as deep vein thrombosis (DVT) and pulmonary embolism.[455,479-482]

There is also no unanimity on the doses. A recent meta-analysis indicated that i.v. administration of 10 mg kg^{-1} of TXA 20 min before inflation of the tourniquet followed by 10 mg kg^{-1} of TXA 15 min before deflation of the tourniquet is effective and safe. The topical administration of 2 g of TXA mixed with 100 ml of 0.9% saline after wound closure could be an alternative option in patients at greater risk of thromboembolic complications.[469]

A pre-operative bolus of TXA, associated with a restrictive transfusion trigger strategy, resulted in low erythrocyte transfusion rates in patients undergoing THA. Supplementary peri-operative administration of TXA did not achieve any further reduction in blood loss.[483]

In TKA, compared with 1 g topical TXA, 2 g topical TXA was more effective in reducing blood transfusion rate and total blood loss.[425] The current evidence does not support any dosing regimen being superior to others.

ε-aminocaproic acid (EACA) as an alternative to tranexamic acid

Several studies demonstrated that i.v. EACA is safe and efficient for reducing blood loss and transfusion volumes in spinal deformity surgery and TKA/THA when compared with placebo.[484] Additionally, no increased risk of thromboembolic events was identified.[485–487] Some studies show that TXA is associated with a significant reduction in total blood loss and postoperative Hb drop compared with EACA. No significant differences are identified in terms of transfusion rates, length of hospital stay and the incidence of postoperative complications.[488–490]

Tourniquet use in primary total knee arthroplasty

Previous meta-analyses had reported that the use of a tourniquet significantly decreased intra-operative blood loss, calculated blood loss and the duration of operation but did not reduce postoperative and total blood loss, the rate of transfusion and the incidence of DVT of the lower extremity or pulmonary embolism.[491–493]

Recent systematic reviews showed that overall blood loss, operation time and blood transfusion rate did not differ between patients using tourniquet versus not,[494–496] but SAEs were significantly more common with the use of the tourniquet, RR 1.73.[494] The intra-operative tourniquet could also increase the intensity of postoperative pain.[496]

A comparative analysis of the selective use of the tourniquet only at the time of cementing demonstrated lower intra-operative blood loss, and higher postoperative drainage volume, more hidden blood loss and higher incidence of DVT in the group that used a tourniquet during the entire surgical procedure.[495] In a systematic review, full-time use was associated with shorter procedures, lower drops in Hb and fewer transfusion units given.[497] Tourniquet application only during cementation could not limit intra-operative and total blood loss according to another meta-analysis,[498] so we cannot conclude any general benefit.

It has been claimed that to optimise its use and reduce complications, tourniquet release after wound closure, with control of the maximum pressure (300 mmHg) and the duration of application (less than 150 min), could contribute to the reduction of bleeding and postoperative complications.[499] Tourniquet inflation pressure of 120 mmHg above the SBP seems to be an effective method.[500] In patients with severe anaemia, the tourniquet could be released after wound closure to decrease blood loss.[501]

A recent RCT has reported that peri-operative blood loss was significantly lower with the use of tourniquet compared with the nontourniquet group but there was no significant increase in blood transfusions, as this differential amount was not clinically significant.[502]

The comparative use of the combination of various blood-saving techniques in TKA indicated in a

controlled trial that patients treated with multiple doses of i.v. and topical TXA without a tourniquet had less hidden blood loss than those treated with a tourniquet.[503] However, in a systematic review, it was concluded that i.v. combined with topical TXA + tourniquet patients showed decreased total blood loss and lower blood transfusion risk, which is in favour of the synergistic effect of the techniques, with probable superiority of the use of TXA.[504]

Drainage

The use of autologous drainage had been shown to be a safe and effective method that produces lower blood transfusion requirements,[505] but the peri-operative use of drains in TKA and THA has significantly decreased. Autologous blood transfusion drainage and closed-suction drainage versus no drainage demonstrated similar clinical efficacy and safety regarding postoperative Hb in a meta-analysis about TKA.[506] A heterogeneous meta-analysis reported that compared with regular drainage, autotransfusion reduced the need for allogeneic transfusion following TKA and THA, but not when compared with autotransfusion with no drainage.[507] Postoperative closed-suction drainage was found to increase total blood loss and blood transfusion requirements in THA[508,509] and provided no benefit in revision THA, as postoperative blood loss, transfusion rate and length of hospital stay may be higher with its use.[510,511] A recent prospective controlled double-blind study demonstrated that drainage of surgical wounds following primary THA might cause an increased requirement for blood transfusion.[512] A meta-analysis in posterior spinal surgery with limited quality of evidence revealed no significant differences regarding estimated blood loss between patients using closed-suction drainages.[513] Later, a randomised open-label superiority trial informed that not using closed-suction drainage after multilevel posterior spinal surgery reduces postoperative blood loss and transfusion requirements.[514]

Surgical approach in total hip arthroplasty

Despite numerous studies, there is no consensus concerning the best approach for THA.[515] The direct anterior surgical approach, compared with posterior or anterolateral approaches, seems to have short-term functional benefit but significantly greater blood loss[516–518] and higher cumulative costs compared with the posterior approach.[516] Nevertheless, results from another meta-analysis showed that the anterolateral minimally invasive approach was superior to the posterolateral approach in intra-operative blood loss and can achieve a better effect that requires the assessment of more clinical indicators.[519] When comparing mini-posterior THA to two-incision THA, blood loss and operative times were reduced.[520] Concerning a global analysis of total estimated blood loss, no significant result has been obtained.[515]

Transfusion and surgical site infections

The restrictive transfusion thresholds in orthopaedic surgery have been shown to decrease the incidence of infections.[521] A meta-analysis reviewing nearly 22 000 patients concluded that allogeneic blood transfusion was a significant risk factor for surgical-site infection after total hip and knee arthroplasty (2.88% in transfusion group versus 1.74% in nontransfusion).[522] There is a dose-dependent association between allogeneic transfusion and surgical-site infection after TKA and THA (1 unit OR 1.97 versus >3 units OR 7.4).[523]

Hip fracture

A meta-analysis investigated the difference between a liberal (10 g dl^{-1} Hb) versus restricted (8 g dl^{-1}) threshold transfusion in mortality, at 30 or 60 days posthip fracture surgery, obtaining a RR of 0.92 (95% CI, 0.67 to 1.26), and RR of 1.08 (95% CI, 0.80 to 1.44), respectively, with very low-quality evidence. No evidence of a difference in functional recovery at 60 days was found.[524] Current available evidence does not support the use of liberal RBC transfusion thresholds in preference to more restrictive transfusion thresholds based on lower Hb levels or symptoms of anaemia.

Comparative outcome of an ideal fixation of elderly trochanteric fractures is still under discussion. In terms of blood loss, lowest bleeding and shortest hospital stay were reported with proximal femoral nail antirotation (PFNA) and suggested that fixation with percutaneous compression plating (PCCP) significantly shortens operative time and decreases the units of blood transfusion required.[525] Comparing PCCP to dynamic hip screws, the blood loss, transfusion volume and complications were statistically less in PCCP patients with no significant difference in mortality rate, transfusion rate and length of hospital stay.[526]

In several systematic reviews, clinical outcomes with THA versus PFNA in the treatment of intertrochanteric fractures in the elderly were compared, and it was shown that intra-operative blood loss was significantly less with PFNA.[527–529] Another evaluation also demonstrated that the nail techniques had shorter operative time than plate approaches, and less blood loss than the plate and arthroplasty techniques.[530] Additionally, more blood loss was observed for dynamic hip screws use than for the PFNA in another meta-analysis.[531]

It cannot be concluded that any surgical technique has more advantages in the treatment of femoral intertrochanteric fractures in the elderly. It is still controversial whether to choose THA or hemiarthroplasty for femoral neck fractures. A recent meta-analysis reported that hemiarthroplasty decreased blood loss and surgery time and THA decreased the length of stay, the incidence of pneumonia and renal failure. The systematic evaluation could not find any significant differences in terms of

complications, mortality, re-operation, infection, pulmonary embolism and myocardial infarction.[532]

Regarding outcomes for daytime versus after-hours surgery in near hip fracture patients, a meta-analysis reported no significant differences in mortality, surgical time or blood loss.[533] Delaying surgery in patients on DOACs has not been shown in observational studies to reduce peri-operative bleeding or affect their mortality.[534] In a retrospective cohort, DOAC treatment was found to cause significant delay until surgery. No increased bleeding was found; however, in patients treated with DOACs compared with those treated with warfarin.[535] One RCT has demonstrated, even with limitations, the nonsuperiority of spinal anaesthesia over general anaesthesia for hip fracture surgery.[536] A recent multicentre RCT of 2970 patients with near-hip fracture showed that accelerated surgery (within 6 h) did not significantly lower the risk of mortality or a composite of major complications compared with standard care (10 to 42 h).[537]

Acquired factor XIII deficiency

Acquired FXIII deficiency with FXIII levels less than 70% in cases of trauma or surgical-related bleeding may have an effect on blood loss and transfusion. In trauma, as part of a goal-directed coagulation therapy, administration of FXIII in cases of ongoing bleeding and FXIII levels less than 60%, resulted in a reduction in allogeneic blood transfusion.[538–540] In surgical patients, FXIII levels less than 60% have been associated with increased post-operative rebleeding and transfusion including cardiac and neurosurgical procedures.[541–549] In a double-blinded randomised trial, untargeted administration of FXIII showed no effect, neither on blood transfusion nor on re-operation in cardiac surgery patients.[361] Additionally, FXIII may have some beneficial effects in surgical wound healing and burn injury.[550–555] In cases of severe haemorrhagic complications during major orthopaedic surgery that raise suspicion of accelerated factor consumption (acquired deficiency), especially in oncological or septic procedures,[556,557] it is suggested requesting a quantitative determination of FXIII activity (or antigen)[558] to determine if the patient has sufficient levels to achieve haemostasis (50 to 60%), which will also favour proper wound healing.[559] Replacement is suggested in cases of severe deficiency and risk of bleeding despite normal thrombo-elastometric or conventional coagulation variables.[560]

Cell salvage

Generally, cell salvage is an effective strategy for reducing the need for allogeneic blood transfusion, but in major orthopaedic procedures, the clinical use of autologous re-infusion systems has decreased. The risk of contamination and the nonsignificant cost-effectiveness[561,562] have limited its use to certain nonseptic revision procedures, primarily THA[563] and peri-acetabular osteotomies.[564] There is little unbiased evidence[565] to justify the routine use of cell salvage in orthopaedic surgery to reduce bleeding and transfusion. When an attempt was made to compare with TXA, the results were superior to cell salvage[475] and no consensus has been reached on what pre-operative Hb level would be optimal for effective use of cell salvage.[566] The appropriateness of its use should be assessed on an individual basis.

To prevent bleeding in major orthopaedic surgery, there is sufficient evidence of the effectiveness and safety of TXA and no conclusive data on the best dose or route of administration. As for surgical measures, the use of tourniquet in TKA or postsurgical drainage as a blood-saving measure are not recommended. There is also no conclusive evidence on the type of surgical approach for diminishing blood loss in THA or for osteosynthesis of hip fractures in the elderly, although the anterolateral minimally invasive approach and proximal endomedullary nailing would be the most optimal procedures, respectively. Femur fractures should be operated on within 48 h, even though accelerated surgery in less than 6 h after injury has not been shown to reduce global complications. Restrictive transfusion practices have been shown to decrease the incidence of surgical site infections. In a major haemorrhagic complication where other causes are discounted, it is advisable to determine the FXIII level to rule out an acquired deficiency. In severe cases, the factor should be replaced.

2.3 Patients undergoing visceral and transplant surgery

Recommendation 9

1. Liver resection

We recommend a low central venous pressure (CVP) and restrictive fluid administration during liver surgery to reduce bleeding. 1A

Intra-operative hypovolaemic phlebotomy or infrahepatic inferior vena cava clamping used together with low CVP strategy are suggested for decreasing intra-operative blood loss and transfusion requirements in selected patients undergoing major liver resections. 2C

Maintenance of high-stroke volume variation (10 to 20%) could be considered in liver resection surgery to reduce bleeding. 2B

During the liver resection phase, ventilation with low airway pressures achieved by low tidal volumes, and without positive end-expiratory pressure is suggested along with a low CVP strategy to decrease intra-operative bleeding. 2B

Together with other measures, terlipressin infusion may be considered during hepato-pancreatico-biliary (HPB) surgery to reduce bleeding. 2B

Improved surgical haemostatic devices and the use of topical haemostatic agents are suggested for reducing

bleeding and blood products requirement during liver resections. 2C

Pre-operative continuation of aspirin monotherapy might be considered in liver resection patients. 2C

VHA could be considered for the peri-operative detection of hypercoagulability and venous thromboembolic risk in CLD and in patients undergoing liver resection for cholangiocarcinoma. 2C

We suggest that TXA should be considered in cirrhotic patients undergoing liver resection. 2C

1. Orthotopic liver transplantation

Higher intra-operative blood loss and transfusion requirements are associated with decreased survival after liver transplantation. C

A strategy for lowering portal pressure during the dissection and liver resection phases (using a low CVP strategy by fluid restriction and/or phlebotomy, vasopressors) and VHA-guided transfusion protocols are recommended to decrease blood products transfusion rates during orthotopic liver transplantation (OLT). 1C

Conventional coagulation tests with results outside the reference range in the absence of anticoagulant therapy do not reliably predict bleeding or exclude hypercoagulability in patients with CLD. C

Preoperative VHA may be useful in predicting blood loss and intra-operative transfusion requirements in liver transplantation. C

In patients undergoing liver transplantation, VHA monitoring with assessment of fibrinogen is recommended for guiding fibrinogen replacement. 1C

In postoperative liver transplant patients, VHA with fibrinogen assessment may be considered for postoperative monitoring of coagulation together with VHA-guided use of coagulation factors and/or blood products. 2C

We recommend TXA for treatment of fibrinolysis in OLT but not for routine prophylaxis; marginal grafts (donation after cardiac death) increase the risk of fibrinolysis postreperfusion. 1C

PCC administration in low doses guided by VHA (prolonged coagulation initiation or increased INR if no VHA available) is suggested in the presence of clinically significant bleeding in patients without fibrinogen deficiency. 2C

In liver transplant, fibrinogen concentrate use should be restricted only to patients with documented hypofibrinogenaemia (by standard coagulation tests or VHA). 1C

Preemptive fibrinogen administration before liver transplantation is not recommended. 1C

rFVIIa is not recommended for routine use in OLT and should be used only as rescue therapy for uncontrolled bleeding. 1C

We suggest the use of cell salvage and autotransfusion with leukodepletion filters in liver transplantation including patients with HCC. 2C

2. Other visceral surgery

TXA administered systemically or locally in the irrigant fluid may be considered in order to decrease peri-operative blood loss in percutaneous nephrolithotomy. 2B

TXA may be considered in order to decrease peri-operative blood loss in prostate surgery. 2B

Prophylactic administration of fibrinogen concentrate is not recommended in prostate surgery. 1C

Computed tomography scan or angiography are suggested for the diagnosis of late bleeding after pancreatectomy, and endovascular interventional therapy is suggested as primary treatment. 2C

Preoperative chronic antithrombotic therapy and peri-operative chemical thromboprophylaxis seem not to increase the peri-operative haemorrhagic complications in patients undergoing HPB surgery. C

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

Evidence summary

Liver surgery

Higher intra-operative bleeding is an adverse prognostic factor in patients who undergo liver resection.[567–570] Maintenance of low CVP during open or laparoscopic liver resection surgery reduces blood loss and transfusion requirements.[571–573] A meta-analysis suggests that ANH used together with a low CVP strategy results in fewer intra-operative blood transfusions compared with using only low CVP; fibrin sealant could also be associated with lower intra-operative blood transfusion compared with no use and resection using a radiofrequency dissecting sealer may be associated with more adverse events than with the clamp-crush method.[571] Intra-operative hypovolaemic phlebotomy together with low CVP strategy resulted in lower intra-operative bleeding and transfusion rate in several observational trials in patients undergoing elective hepatectomy for cancer.[574–578] A pilot feasibility RCT found similar estimated blood loss in patients undergoing major liver resections with a low CVP strategy with intra-operative hypovolaemic phlebotomy and patients receiving standard care.[579] In a retrospective study in patients undergoing open or laparoscopic liver resection, intra-operative bleeding significantly correlated with a drop in CVP after hypovolaemic phlebotomy.[580]

A systematic review with meta-analysis demonstrated an association between intra-operative hypovolaemic phlebotomy in liver surgery and decreased blood loss and RBC transfusion, though not reaching statistical significance but without associated adverse events.[581] Techniques such as infrahepatic inferior vena cava clamping (or semi-clamping) combined with anaesthesiological techniques for low CVP maintenance seem beneficial to reduce blood loss during hepatic resections.[582–589]

Fluid replacement guided by stroke volume variation with target values of 10 to 20% reduces blood loss during living liver donor hepatectomy and in HCC resection surgery.[590–593]

In a small, randomised study, the use of low tidal volumes (6 to 8 ml kg^{-1}) was associated with decreased blood loss during laparoscopic liver resection compared with conventional tidal volumes (10 to 12 ml kg^{-1}).[594] In a retrospective analysis, maintaining a low positive airway pressure without positive end-expiratory pressure together with low CVP could minimise blood loss during hepatectomy in healthy liver donors.[595]

Terlipressin infusion during major liver resection and HPB surgery was associated with decreased blood loss and blood transfusion needs compared with placebo.[596,597]

In a retrospective study, the use of a bipolar sealing device and a topical haemostatic agent significantly reduced the need for inflow occlusion compared with conventional hepatic resections.[598]

Peri-operative continuation of aspirin was not significantly associated with a higher risk of severe haemorrhagic complications in patients undergoing elective hepatectomy.[599,600]

Orthotopic liver transplantation

Several studies have demonstrated the association between intra-operative bleeding and blood product transfusion with postoperative morbidity and mortality after OLT.[601–603] Intra-operative bleeding is associated with an increased likelihood of tumour recurrence following OLT for HCC, with a more pronounced effect in patients exceeding the Milan criteria.[604,605]

Portal hypertension correlated with an increased bleeding risk in cirrhotic patients undergoing OLT, thus a restrictive transfusion policy and peri-operative interventions that decrease or prevent further aggravation of portal hypertension are useful to decrease bleeding and transfusion requirements.[606,607] The interventions associated with decreased transfusion rates (and even transfusion-free transplant) are the maintenance of a low CVP during the pre-anhepatic phase by fluid restriction, vasopressor and/or phlebotomy in selected patients, the use of low tidal volumes (6 to 8 ml kg^{-1}) and avoiding high positive end-expiratory pressure and the use of VHA-guided transfusion protocols.[607–611]

According to a meta-analysis, temporary intra-operative portacaval shunts in cava-sparing OLT reduce blood loss and hepatic injury and also enhance postoperative renal function without prolonging operative time.[612]

Coagulation monitoring

SLTs such as PT/INR or aPTT are not useful for the assessment of thrombin generation and bleeding risk in cirrhotic patients.[613–616] Patients undergoing major liver resection may have a prothrombotic status in the early postoperative period, despite conventional coagulation tests indicating hypocoagulability.[617] A recent study suggested that viscoelastic tests and fibrinogen level could predict coagulopathic bleeding in patients with decompensated liver disease and acute-on-chronic liver failure.[618] Preoperative clot firmness on VHA correlated with intra-operative RBC transfusion in liver transplantation patients.[619] In a retrospective study, several preoperative thrombo-elastometric variables were good predictors of blood product transfusion requirements in recipients of living-related OLT.[620] In a small observational study, preoperative velocity waveform variables from the thrombo-elastometry trace could distinguish between patients with low or high risk for blood loss during liver transplantation surgery.[621]

In a small, randomised study, the use of VHA-guided transfusion strategy resulted in significantly lower use of blood products compared with transfusion guided by SLTs in cirrhotic patients with coagulopathy undergoing invasive procedures without an increase in bleeding complications.[622] Several studies showed that VHA-guided coagulation management during liver transplantation resulted in decreased bleeding and lower transfusion of allogeneic blood products compared with a strategy guided by SLTs.[613,623–631] In patients undergoing OLT, the use of VHA that include fibrinogen assessment (TEG functional fibrinogen assay [FF] or FIBTEM) and cut-offs for fibrinogen administration resulted in decreased allogeneic blood product transfusion compared with VHA without fibrinogen assessment.[613,632]

In a retrospective observational study, VHA were better predictors of postoperative bleeding than SLTs in OLT; VHA variables reflecting fibrinogen concentration and polymerisation significantly correlated with postoperative bleeding compared with plasma fibrinogen, which failed to predict bleeding.[633,634] VHA with fibrinogen assessment was a better predictor for thromboembolic events than plasma fibrinogen concentration in postoperative patients after living-related OLT.[635]

In a small study, Blasi *et al.*[636] found that VHA may be useful in identifying patients with cholangiocarcinoma undergoing liver resection surgery at risk of developing postoperative VTE. Increased portal vein thrombosis risk and hypercoagulability were detected using VHA in a small observational cohort of cirrhotic patients with HCC.[637]

Pharmacological therapy

Antifibrinolytic drugs

Hyperfibrinolysis is encountered in OLT and can be associated with bleeding and oozing.[638] However, hyperfibrinolysis in the late anhepatic phase and after graft reperfusion is often transient, and no additional therapy is needed.[639]

TXA administration proved effective in reducing blood loss and transfusion requirements; however, a treatment strategy based on antifibrinolytics administration in selected patients did not result in increased bleeding compared with a prophylactic regimen.[640,641]

As the benefit of prophylactic antifibrinolytic administration during OLT is not clear, antifibrinolytic administration is suggested in OLT recipients with significant bleeding when hyperfibrinolysis is either suspected or confirmed by VHA.[642,643] SLTs and VHA lack sensitivity for the diagnosis of hyperfibrinolysis, and recent guidelines propose not waiting for the appearance of typical hyperfibrinolysis traces on VHA and to use antifibrinolytics if other clinical features are present, such as diffuse or massive bleeding.[644]

Prothrombin complex concentrate

In a retrospective observational study in patients with acute or CLD, PCC therapy was effective in improving coagulation test results (PT and INR) without an excess of thrombotic events.[645] The use of PCC guided by VHA led to decreased transfusion requirements during OLT without increasing the incidence of adverse effects.[631,646,647] In a retrospective study, 372 consecutive OLT procedures were performed safely without FFP using a VHA-guided substitution of coagulation factor concentrates.[648]

Prolonged coagulation initiation on VHA indicates impaired thrombin generation only when fibrinogen levels are normal, and in this case, low coagulation factor levels should be corrected only in bleeding OLT recipients.[643,649]

In a study using thrombin generation, Abuelkasem *et al.*[650] demonstrated that in OLT recipients, PCC doses equivalent to 10 IU kg^{-1} can restore normal thrombin generation, and higher doses of 20 IU kg^{-1} might result in supranormal thrombin generation. In order to maintain the balance between bleeding and thrombotic risk, low doses of PCC (10 to 15 IU kg^{-1}) and avoidance of severe antithrombin deficiency (10 to 30%) prior to PCC administration in OLT recipients are suggested.[642,643,651]

Fibrinogen concentrate

A pre-operative plasma fibrinogen level of 2 g l^{-1} or less increases requirements for blood products during the surgical procedure of OLT.[652] However, the results of an RCT show that preemptive administration of fibrinogen concentrate resulted in increased plasma fibrinogen levels and clot firmness on VHA, but did not influence peri-operative blood product transfusion requirements.[653]

Fibrinogen concentrate administration guided by VHA or plasma fibrinogen level is recommended in bleeding patients during OLT surgery.[642,643] Trials of factor concentrate administration guided by VHA in OLT recipients showed that fibrinogen concentrate administration was necessary more often than PCC, and this coagulation management strategy resulted in decreased blood product transfusion without increased incidence of adverse effects.[631,647]

rFVIIa

According to several recent publications, since the implementation of a VHA-based algorithm, the off-label use of rFVIIa in OLT was no longer necessary, and it is currently not recommended in OLT recipients.[624,642,643,648,651,654] The off-label use of rFVIIa can only be considered as rescue therapy in OLT recipients with severe bleeding unresponsive to other haemostatic interventions.[643]

Prostate surgery

An RCT showed that 0.1% TXA in irrigant fluid significantly reduces peri-operative blood loss and the requirement for blood transfusion during percutaneous nephrolithotomy (PCNL).[655] Another RCT showed that i.v. TXA administration minimises the need for blood transfusions during percutaneous nephrolithotomy.[656]

Several small, randomised studies found that TXA use was associated with decreased intra-operative blood loss in patients undergoing transurethral resection of the prostate.[657–660] Local administration of TXA after prostate removal significantly reduced bleeding after prostatectomy surgery.[661] According to two systematic reviews with meta-analyses, TXA reduced intra-operative blood loss, without increasing the risk of DVT and pulmonary embolism in prostate surgery.[662,663]

In an RCT, pre-operative administration of fibrinogen concentrate had no significant influence on peri-operative bleeding in patients undergoing transurethral resection of the prostate.[664]

Pre-operative prostate artery embolisation in patients undergoing simple prostatectomy may be effective in reducing peri-operative bleeding and operative time.[665,666]

Pancreatic surgery

According to a recent systematic review and meta-analysis, late postpancreatectomy bleeding has a mean incidence of 5% with high overall mortality of 21%. Computed tomography scan and diagnostic angiography are equally sensitive in detecting the postpancreatectomy bleeding source, and the endovascular approach appears

to be superior to relaparotomy and endoscopy as the primary intervention for bleeding.[667–670]

Intra-operative bleeding and peri-operative blood transfusions were associated with higher incidence of postoperative clinically relevant pancreatic fistula and with lower overall survival.[671–675] A retrospective analysis showed that the risks of haemorrhagic and thromboembolic complications after HPB surgery were not increased in patients receiving long-term anticoagulant or antiplatelet therapy.[676] According to a retrospective study, chemical thromboprophylaxis after HPB surgery was safe because it did not increase the risk of major haemorrhage and decreased the risk of pulmonary embolism.[677]

Cell salvage

Intra-operative cell salvage (ICS) can help to avoid the various pitfalls of other blood conservation management strategies, such as multiple preoperative visits for autologous blood donation or complications like intra-operative hypotension with ANH.

Several observational trials showed that ICS and autotransfusion using leukodepletion filters during OLT in patients with HCC is not associated with increased tumour recurrence.[678–682] In a retrospective study of patients undergoing OLT and having a viable HCC on histopathological examination of the explanted liver, mid-term and long-term recurrence-free survival and overall survival were similar regardless of the use of ICS and autotransfusion with leukodepletion filters during OLT surgery.[683]

The use of ICS with a leukocyte depletion filter was not associated with significant differences in short-term complications, mortality or cancer recurrence in oncological patients undergoing radical prostatectomy, cystectomy, open nephrectomy or liver resection for colorectal liver metastases.[684–688] An updated meta-analysis of 34 observational trials showed a reduced RR for cancer recurrence and metastasis when ICS is used in cancer surgery.[688]

2.4 Patients with acute upper gastrointestinal bleeding

Recommendation 10

Beta-blockers, variceal band ligation (VBL), sclerotherapy and beta-blockers plus nitrates are recommended as primary prophylaxis for bleeding in cirrhotic patients with high-risk oesophageal varices. 1C

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

We recommend early interventional endoscopy together with vasoactive medication producing splanchnic vasoconstriction (somatostatin, terlipressin or octreotide) in AVB. 1B

Transjugular intrahepatic portosystemic shunt or surgical shunts can be suggested as an option for rescue therapy after initial medical and endoscopic therapy fail. 2C

Early transjugular intrahepatic portosystemic shunt (TIPSS) placement (within 72 h from endoscopy) can also be considered in selected high-risk cirrhotic patients with AVB following initial haemostasis using pharmacological management and endoscopic band ligation. 2C

For secondary prophylaxis of variceal bleeding in cirrhosis the combination of drug treatment with beta-blockers and endoscopic therapy with band ligation is recommended. 1C

Use of FFP in cirrhotic patients with AVB is associated with increased mortality, failure to control bleeding and longer length of stay. C

A restrictive transfusion policy aiming for a Hb level of 7 to 8 g dl^{-1} is recommended in haemodynamically stable patients with upper gastrointestinal bleeding. 1B

We recommend against the systemic administration of TXA for the treatment of gastrointestinal bleeding. 1B

In nonvariceal upper gastrointestinal bleeding because of peptic ulcer, endoscopic therapy combined with high-dose proton pump inhibitors is recommended. 1C

In failed endoscopic treatment of bleeding peptic ulcer, angiographic embolisation and/or surgery should be considered. 2C

Evidence summary

Variceal bleeding

Based on low-certainty evidence, a Cochrane meta-analysis showed that beta-blockers, VBL, sclerotherapy and beta-blockers plus nitrates may decrease mortality compared with no intervention in cirrhotic patients with high-risk oesophageal varices without previous bleeding.[689] According to a systematic review with network meta-analysis, monotherapy with nonselective beta-blockers (NSBBs) may decrease all-cause mortality and the risk of first variceal bleeding in patients with cirrhosis with large oesophageal varices and carries a lower risk of serious complications compared with VBL.[690] In patients with refractory ascites or infection, data from observational studies are contradictory regarding the safety of NSBBs for primary prophylaxis of variceal bleeding, and the choice and doses of NSBBs should be individualised.[691,692]

Recent guidelines suggest that patients admitted to, or under observation in, hospital for UGIB undergo endoscopy within 24 h of presentation and in cases of cirrhotic patients with AVB, endoscopic variceal ligation together with vasoactive drugs and antibiotic therapy are recommended.[693–695] In selected cirrhotic patients with severe AVB at high risk of treatment failure (Child–Turcotte–Pugh class C <14 points or Child–Turcotte–Pugh class B with active bleeding) early TIPSS within 72 h after

oesophageal variceal bleeding, results in lower rates of failure to control bleeding and re-bleeding, and significant short-term reductions in mortality than in patients treated without early TIPSS.[696–711]

According to a small observational study, emergency TIPSS could be effective as rescue therapy for patients with liver cirrhosis and uncontrolled variceal bleeding.[712] With low certainty of evidence, a Cochrane review found that surgical portosystemic shunts may have benefit over TIPSS for the treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension.[713]

For secondary prophylaxis of variceal bleeding in cirrhosis, the combination of NSBBs with VBL seems more efficient in preventing re-bleeding compared with VBL alone.[714–716] TIPSS seems more effective than VBL in preventing re-bleeding in patients who first bleed while on beta-blockers, those with contraindications to beta-blockers or with refractory ascites, and in patients with fundal varices.[696,697,714,717,718] TIPSS seems more effective than VBL with propranolol in preventing recurrent oesophageal variceal bleeding in patients with advanced cirrhosis and portal vein thrombosis or with high hepatic venous pressure gradient.[719,720] According to recent systematic reviews and network meta-analysis, TIPSS may result in a larger decrease in symptomatic re-bleeding than VBL, or VBL combined with NSBBs, whereas VBL is associated with fewer SAEs than sclerotherapy.[721,722]

A retrospective study showed that LMWH treatment does not increase the short-term risk of bleeding in cirrhotic patients after endoscopic variceal ligation either for primary or secondary prophylaxis of oesophageal variceal bleeding.[723]

Nonvariceal upper gastrointestinal bleeding

A small, randomised trial demonstrated that high-dose omeprazole infusion was not inferior to scheduled second-look endoscopy in the prevention of ulcer re-bleeding, and routine second-look endoscopy is not recommended when high-dose proton pump inhibitor infusion is prescribed after endoscopic therapy.[724,725] For large-sized, high-risk ulcers, prophylactic angiographic embolisation after therapeutic endoscopy seems to prevent ulcer re-bleeding.[726] Recent guidelines suggest that in patients with recurrent bleeding after endoscopic therapy for a bleeding ulcer, repeat endoscopy and endoscopic therapy might be associated with fewer complications than surgery or transcatheter arterial embolisation.[693,727,728] In patients who fail endoscopic therapy, transcatheter arterial embolisation shows marked reductions in complications and hospital stay with no difference in mortality compared with surgery, but it does have a higher rate of further bleeding, whereas surgery seems to have a better overall success rate and less re-bleeding events compared with angiographic embolisation.[693,729]

Transfusion strategy and pharmacological interventions

A randomised trial in patients with UGIB because of variceal or nonvariceal causes showed that a restrictive transfusion strategy (threshold of 7 g dl^{-1}) did not increase mortality, morbidity or re-bleeding rates nor the need for interventions when compared with a liberal transfusion strategy (threshold of 8 g dl^{-1}).[730] A large multicentre, cluster randomised feasibility study showed similar outcomes (re-bleeding and 28-day mortality) when a restrictive transfusion strategy (trigger Hb 8 g dl^{-1}) was compared with a liberal transfusion strategy (trigger Hb 10 g dl^{-1}) in patients with UGIB.[731] Recently, published guidelines recommend a restrictive policy of RBC transfusion with a threshold for transfusion of Hb 7 g dl^{-1} for patients with UGIB, 8 g dl^{-1} in patients with preexisting cardiovascular disease while a threshold higher than 8 g dl^{-1} may be considered in patients with UGIB and ACS, based on very limited evidence in this patient category.[693–695,732]

A retrospective study showed that FFP transfusion in patients with cirrhosis and AVB is associated with increased mortality, failure to control bleeding and a longer length of stay.[733]

A large RCT (HALT-IT) included patients with both UGIB and lower gastrointestinal bleeding (from which almost half had variceal bleeding) randomised to receive TXA or matching placebo. The trial found no evidence that TXA decreases the risk of death from gastrointestinal bleeding, but was associated with an increased risk of venous thromboembolic events and seizures, with a similar risk of fatal or nonfatal thromboembolic events and arterial thromboembolic events (myocardial infarction or stroke) in the TXA group and the placebo group.[734]

According to a small randomised trial, intragastric TXA does not decrease re-bleeding or the need for intervention in patients with upper gastrointestinal haemorrhage.[735] However, another randomised trial found that intragastric TXA administration in patients with UGIB from benign peptic ulcers was associated with reduced transfusion requirements and re-bleeding events.[736] In another study, topical TXA spraying added to standard endoscopic treatment was associated with lower blood loss and re-bleeding rates in nonvariceal UGIB.[737]

2.5 Patients undergoing gynaecological (nonpregnant) surgery

Recommendation 11

We suggest that normovolaemic haemodilution could be used as an alternative approach in gynaecological cancer in order to reduce allogeneic transfusion. 2B

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

We recommend using pre-operative i.v. iron to reduce allogeneic transfusion requirements in anaemic gynaecological cancer patients receiving chemotherapy. 1C

We suggest using i.v. iron to correct pre-operative anaemia in women with menorrhagia. 2B

We recommend the combined administration of EPO and iron in gynaecological patients with IDA. 1C

We recommend TXA for reduction of peri-operative bleeding in all types of gynaecological cancer surgery. 1C

We recommend TXA for reduction of peri-operative bleeding for abdominal, laparoscopic, robotic or hysteroscopic myomectomy. 1C

We recommend TXA for reduction of peri-operative bleeding for hysterectomy. 1C

Tranexamic acid is not routinely advised for hysteroscopy and surgery for ectopic pregnancies. C

The recommended dose of TXA for gynaecological surgery is either a single i.v. dose of 1000 mg or 10 to 15 mg kg^{-1} or topically. 1C

In patients undergoing myomectomy, preoperative misoprostol administration is recommended in order to decrease intra-operative blood loss and blood transfusion requirements. 1C

Evidence summary

Normovolaemic haemodilution

Normovolaemic haemodilution has been proposed by some as an approach to avoid peri-operative allogeneic blood transfusion with the subsequent aim of reducing not only exposure to allogeneic RBC transfusion versus standard care (RR 0.74, 95% CI 0.63 to 0.88) but also with the potential to minimise transfusion-associated risks such as surgical site infection, cancer metastasis, tumour recurrence and altered immune system.[738] However, this approach was not recommended by the previous ESAIC guideline on management of severe peri-operative bleeding in gynaecological surgery.[1]

In a prospective trial of 393 patients undergoing primary cytoreductive surgery for advanced ovarian cancer with the goal of optimal debulking, ANH at time of surgery was assessed by intra-operative blood withdrawal performed to a target Hb of 8.0 g dl^{-1}.[739] In the 41 patients who participated, median (range) blood withdrawn during ANH was 1650 ml (700 to 3000). The median (range) estimated blood loss was 1000 ml (150 to 2700) and 14 patients (34%) received allogeneic RBC transfusion intra-operatively or postoperatively, which was lower than historical controls (50%) without increasing peri-operative complications. However, the median (range) intra-operative fluid administration was 7750 ml (3000 to 14 500), median crystalloid mixture volume 6000 ml; median colloid volume 1750 ml.

The authors recently published long-term survival outcomes of the former study and found that ANH was not independently associated with worse progression-free survival (hazard ratio 0.928; 95% CI 0.618 to 1.395; $P = 0.721$) or overall survival (hazard ratio 0.588; 95%, CI 0.317 to 1.092; $P = 0.093$).[740]

In a retrospective study, Saito *et al.*[741] examined the utility of ANH in a gynaecological cancer surgery cohort from Japan. The authors obtained data from 586 patients (74.7% in the ANH group and 25.3% in the non-ANH group). They reported a lower incidence of peri-operative acute blood transfusion in the ANH group. Multivariate logistic regression analyses showed ANH use (OR 0.274; 95% CI 0.0868 to 0.863; $P = 0.027$) to predict Hb less than 8.0 g dl^{-1} (OR 182; 95% CI 50.3 to 657; $P < 0.001$), duration of surgery at least 240 min (OR 5.93; 95% CI 1.73 to 20.4; $P = 0.005$), age at least 65 years (OR 6.24; 95% CI 1.70 to 22.9; $P = 0.006$) and ASA physical status 3 (OR 5.76; 95% CI 1.25 to 26.5; $P = 0.024$) were independently associated factors for peri-operative allogeneic blood transfusion.

Cell salvage

We found no direct high-quality evidence in gynaecological surgery supporting the routine use of cell salvage. However, in a recently published systematic review evaluating the safety of cell salvage in tumour surgery, the authors found no RCTs but 27 observational and cohort studies with more than 6300 participants across various types of surgical cancer procedures.[742] Data from these observational studies indicate that cell salvage with or without leucocyte depletion filters appear to be safe.

Iron and erythropoietin

In a systematic review, use of iron supplementation during the peri-operative period was evaluated for impact on patient outcomes in women undergoing gynaecological procedures when compared with no treatment, placebo or standard of care.[743] Seven RCTs ($n = 447$) were deemed eligible for meta-analysis despite heterogeneity in treatment and dosing. The authors found a statistically significant reduction in peri-operative RBC transfusion when iron was combined with blood optimisation compound (EPO or gonadotropin-releasing hormone) compared with iron alone (RR 0.33; 95% CI 0.16 to 0.70, $I^2 = 0\%$; $P = 0.003$). Only one RCT compared iron supplementation to placebo indicating a significant increase in postoperative Hb and decrease in RBC transfusions.[744]

In a retrospective study of 97 patients undergoing gynaecological tumour surgery, 30 patients (group A) received subcutaneous recombinant human erythropoietin (rHuEPO; 10 000 IU) with iron sucrose (100 mg i.v. drip) per day from 4 days prior to surgery and until 5 days postsurgery.[745] In group B, 35 patients received iron sucrose alone daily whereas 32 patients received neither agent (group C), with the same baseline characteristics

across the three groups. The authors reported a significant increase in Hb between the time of treatment initiation and the sixth postoperative day ($P < 0.001$) in group A. There was a similar increase for RBCs ($P < 0.001$), Hct ($P < 0.001$) and reticulocyte percentage ($P < 0.001$). Additionally, at the third ($P = 0.004$, $P = 0.006$) and sixth ($P < 0.001$, $P < 0.001$) postoperative day, Hb levels for group A were higher than for groups B and C, with no statistically significant difference between group B and group C at these time points. Group A patients received fewer blood transfusions during the peri-operative period with no complications observed secondary to rHuEPO administration combined with iron sucrose.

In a recently published Cochrane systematic review, Kaufner *et al.*[746] evaluated the efficacy of pre-operative rHuEPO therapy (subcutaneous or parenteral) with iron (enteral or parenteral) in reducing the need for allogeneic RBC transfusion in anaemic adult noncardiac surgical patients (RR 0.55; 95% CI 0.38 to 0.80; participants $n = 1880$; studies $n = 12$; $I^2 = 84\%$). Most trials were in orthopaedic, gastrointestinal and gynaecological surgery (mild-to-moderate preoperative anaemia, Hb 10 to 12 g dl^{-1}). Two RCTs referred to the gynaecological setting.[747,748]

Combined administration of rHuEPO + iron was found on average to be associated with a mean 231 fewer individuals in need of transfusion for every 1000 individuals compared with the control group.

A recently conducted RCT assessed the benefit and safety of rHuEPO in combination with i.v. iron sucrose versus i.v. iron sucrose alone for the management of IDA in gynaecological patients ($n = 334$) pre-operatively.[749] Mean Hb level at day 14 among the iron sucrose-only group was 10.59 ± 1.21 g dl^{-1} while among women in the iron sucrose with rHuEPO group, Hb was 11.9 ± 0.62 g dl^{-1} ($P < 0.05$).

Moderate-quality evidence in favour of pre-operative rHuEPO + iron therapy for anaemic adults was reported, resulting in a reduced need for RBC transfusion. Higher doses (500 to 600 IU kg^{-1} body weight) seem to increase the Hb concentration versus lower doses of 150 to 300 IU kg^{-1} body weight. No increase in the risk of adverse events were reported.

Coagulation monitoring and treatment

Antifibrinolytics

In a Cochrane systematic review, Kietpeerakool *et al.*[750] examined the effectiveness of TXA (15 mg kg^{-1}) for advanced ovarian cancer surgery. Only one study met inclusion criteria.[751] The authors found insufficient evidence to recommend the routine use of TXA with a total estimated blood loss of 668.34 versus 916.93 ml. In this double-blind RCT of 100 women with ovarian cancer, the total blood loss volume and transfusion rate were significantly lower in the intervention group (median total blood loss of 520 versus 730 ml; $P = 0.03$) with the incidence of transfusion reduced (30 versus 44%; OR 0.44; 95% CI 0.97; $P = 0.02$).

In a single-centre, double-blinded RCT, 80 women undergoing open abdominal myomectomy were randomised to either tourniquet plus i.v. TXA 10 mg kg^{-1} or tourniquet plus placebo.[752] The authors found higher mean (±standard deviation) intra-operative blood loss (998.72 ± 607.21 versus 907.25 ± 529.85 ml; $P = 0.475$), intra-operative blood transfusion rate (45 versus 30%; $P = 0.166$) and mean units of blood transfused (1.13 ± 1.64 versus 0.75 ± 1.28; $P = 0.256$) in the control group compared with tourniquet plus TXA group. Additionally, the estimated blood loss per 100 g of fibroid removed was 139.80 ± 2.28 versus 104.09 ± 1.97 ml ($P = 0.001$) in the intervention group.

In a double-blind RCT, 60 women with symptomatic fibroids received a single bolus i.v. TXA 15 mg kg^{-1} in the intervention arm versus 0.9% saline of equivalent volume 20 min before the initial surgical incision.[753] Overall, 53% of patients had laparoscopic myomectomy, 40% had robotic myomectomy, whereas 7% had laparotomy. The authors found no significant reduction in peri-operative bleeding (200 versus 240 ml; $P = 0.88$) or change in peri-operative Hb (1.00 versus 1.1 g dl^{-1}; $P = 0.64$).

The findings of this study contradict the findings of a previously published double-blinded multicentre RCT among 332 women undergoing benign abdominal, laparoscopic or vaginal hysterectomy who were randomised to either 1 g i.v. TXA or placebo at the start of the surgery.[754] In this study, the authors found a statistically significant reduction of intra-operative blood loss in the intervention group (100 versus 166 ml kg^{-1}; $P = 0.004$). There was a significant reduction in the incidence of blood loss at least 500 ml (6 versus 21; $P = 0.003$), the use of open-label TXA (7 versus 18; $P = 0.024$) and the risk of re-operation secondary to postoperative haemorrhage (2 versus 9; $P = 0.034$) in the intervention group. Although no SAEs were reported, absolute risk reduction of 4.2% and number needed to treat of 24 was reported in favour of TXA.

Further evidence in favour of TXA for reducing blood loss and transfusion requirements among women undergoing myomectomy was provided by a systematic review including four RCTs of women of reproductive age undergoing abdominal, laparoscopic, robotic or hysteroscopic myomectomy.[755] However, only 313 women were included in the analyses, only three studies were eligible for meta-analyses and overall risk of bias was moderate across the reported studies. TXA significantly reduced intra-operative blood loss (mean difference 213.1 ml; 95% CI −242 to −183.7) and postoperative blood loss (56.3 ml; 95% CI −67.8 to −44.8). However, no significant differences were detected for transfusion requirement.

The above findings are further supported by a recently published review assessing the evidence for TXA in gynaecological surgery in general.[756] The authors found that TXA reduced blood loss during hysterectomy (two RCTs, $n = 432$; mean difference −66 to 180 ml)[754,757] and myomectomy (two RCTs, mean difference −213.1 ml, 95% CI −242.4 ml to −183.7 ml).[755,758] Additionally, TXA decreased the risk of delayed haemorrhage for cervical conisation (Cochrane systematic review, four RCTs, RR 0.23; 95% CI 0.11 to 0.50).[759] However, the authors found conflicting evidence for intra-operative i.v. TXA during hysteroscopy and surgery for ectopic pregnancies.

Across the published literature, TXA in gynaecological surgery is often administered either as a single dose of 1000 mg i.v. or as 10 to 15 mg kg^{-1} i.v.

Misoprostol

According to recent RCTs and a systematic review and meta-analysis, pre-operative misoprostol administration minimises blood loss and the need for blood transfusion during open myomectomy.[760–762]

2.6 Patients undergoing obstetric surgery

Recommendation 12

We recommend that postpartum haemorrhage should be managed by a multidisciplinary team. 1C

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

Risk awareness and early recognition of severe postpartum haemorrhage are essential. C

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

We suggest implementation of PBM programmes in parturients. 2B

We recommend one unit RBC treatment (single unit strategy) as opposed to two units in haemodynamic stable patients with anaemia. 1B

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

We suggest that using peri-operative cell salvage during caesarean section with high risk of haemorrhage may decrease homologous transfusion. 2B

We recommend i.v. iron supplementation as this elicits a faster recovery from anaemia with fewer gastrointestinal complaints than oral iron treatment. 1B

Intravenous iron supplementation improves fatigue and depression score 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 postpartum haemorrhage. 1C

Coagulopathy risk assessment should include the obstetrical conditions associated with PPH not just an estimated blood loss. 1C

High-volume resuscitation with crystalloids and colloids is associated with coagulopathy and adverse maternal outcomes in women with postpartum haemorrhage. C

Dynamic platelet count decrease or a level less than 150×10^9 l^{-1} at the onset of labour, particularly if combined with plasma fibrinogen level less than 2.0 g l^{-1}, may indicate an increased risk of postpartum haemorrhage. C

At the beginning of labour, aPTT and PT are of little predictive value for postpartum haemorrhage. C

VHA can identify obstetric coagulopathy including hypofibrinogenaemia and reduced platelet level. B

VHA-guided haemostatic treatment reduces the need for blood products. B

We recommend against pre-emptive fibrinogen replacement; however, in ongoing postpartum haemorrhage with hypofibrinogenaemia, we recommend fibrinogen replacement. 1B

Fibrinogen substitution in women with ongoing postpartum haemorrhage and a fibrinogen level above 2 g l^{-1} or FIBTEM A5 greater than 12 mm is not indicated. 1B

In severe postpartum haemorrhage, we suggest a VHA-guided intervention protocol. 2C

We recommend the administration of TXA in postpartum haemorrhage at a dose of 1 g intravenously as soon as possible within 3 h, which can be repeated if bleeding continues. 1B

We suggest that TXA be considered before high-risk caesarean section and vaginal deliveries or cases of antepartum bleeding. 2B

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

We recommend against a prophylactic/general use of rFVIIa in postpartum haemorrhage because of increased risk of fatal thrombosis. 1C

Evidence summary

Treatment of postpartum anaemia

Anaemia develops in up to 29% of pregnancies in the third trimester.[763] Anaemia during pregnancy may

increase the risk of PPH[764–766] and is associated with the need for blood transfusion.[767] Peripartum bleeding is the major risk factor for severe postpartum anaemia[768] but peripartum transfusions may complicate delivery.[769–772] Here, we assess whether correction of anaemia is required as part of treating obstetric haemorrhage and the therapeutic options available.

Related topics of PPH such as diagnosis of PPH, treatment of uterine atony, retained placental tissue and arterial embolisation are beyond the scope of this guideline. We recommend other evidence-based clinical guidelines such as the WHO guidelines for the management of PPH and retained placenta.[773]

Obstetric triggers for red blood cell transfusion

PPH should be treated promptly. Delayed recognition of and response to acute bleeding is a leading cause of maternal mortality and 'near misses'.[774] Peaks and developments in shock index (heart rate divided by SBP[775–779] together with venous lactate[780–782] and ionised calcium[783]) may predict further bleeding and severity of PPH. A protocol-based intervention grants an early access to blood products.[784–786] Suboptimal Hct during the acute phase of PPH is associated with end organ dysfunction.[787,788]

Blood transfusions have increased substantially in the last decade.[789] Although no clinical studies of transfusion trigger Hb thresholds in life-threatening obstetric haemorrhage were retrieved, a general observance of an Hb threshold of 8.1 g dl^{-1}, to ensure a Hb level of 7 to 8 g dl^{-1}, has been reported.[790] However, in a study of French maternity units, it was reported that RBC transfusion for PPH was not given in a large proportion of women with very low Hb levels.[791] Haemodynamically stable patients with postpartum anaemia are safely and sufficiently treated with 1 U RBC instead of 2 U in the majority of patients (>80%).[792] PBM programmes seem to reduce the use of blood transfusions.[793–796] Preeclampsia increases the risk of transfusion reactions.[797]

Hb levels and health-related quality-of-life physical fatigue scores correlate in the first week postpartum. Postpartum anaemia is associated with postpartum depression.[764,798,799] Nevertheless, transfusion in patients with low Hb concentration without clinical signs of anaemia has little effect on physical fatigue.[800,801] RBC transfusion seems to increase the risk of VTE[802] and cause immunomodulation in women with PPH.[803] Furthermore, RBC transfusion seems to be associated with reduced breastfeeding beyond the impact of anaemia,[804,805] and possibly a development of cardiovascular disease later in life[806] or cancer.[807] In this context, a restrictive strategy (Hb threshold 7 g dl^{-1}) seems equally safe and justified. Future studies will evaluate if single RBC transfusions may be replaced by i.v. iron.[808,809]

Should cell salvage be used in obstetrics?

Peri-operative cell salvage may be used in obstetric surgery[810–812] and bleeding following vaginal delivery.[813] However, it is not widely established because of technology issues and a lack of staff training.[814] The use of cell salvage during caesarean section with increased risk of haemorrhage is not associated with reduced need for allogeneic RBC transfusion.[811,812,815] Routine use has no apparent cost–benefit in a high-income country setting.[813,816] The challenge remains to predict who will suffer severe bleeding as the potential benefit is most apparent in these cases.[813,815,817,818]

Intravenous iron or erythropoietin in the treatment of postpartum anaemia

Predelivery anaemia is a strong risk factor for postpartum anaemia.[764,819] Patients with moderate (Hb <9.5 g dl^{-1}) to severe (Hb <8.5 g dl^{-1}) postpartum anaemia may benefit from i.v. iron therapy, which elicited more rapid recovery, improved fatigue and depression symptoms compared with oral therapy.[820–823] Oral treatment has more gastrointestinal complaints.[821,824] Intravenous iron might be considered as an alternative to RBC transfusion, especially if allogeneic transfusion is contraindicated.[809,825]

Coagulation monitoring and management

Fibrinogen measurement

Coagulopathy during PPH is associated with increased risk of morbidity, massive transfusion and hysterectomy.[826] Fibrinogen levels decrease with increasing blood loss and may serve as a marker of haemostatic impairment.[827,828] Functional markers of fibrinogen such as TEG functional fibrinogen maximum amplitude (MA),[829] FIBTEM MCF and FIBTEM A5 (amplitude at 5 min following clotting time) seem to be equally associated with morbidity and the need for transfusion during PPH.[830,831] However, it is not known whether a low fibrinogen level per se, or a low fibrin-based clot firmness, causes progression of PPH or reflects the severity of the bleed and the resuscitation effort required.[830] Fibrinogen level or VHA measurements are associated with severe PPH, but remain poor stand-alone predictors.[832] Evaluation of fibrinogen at the onset of labour is of less predictive value.[833–836] During rare cases of amniotic fluid embolism with disseminated intravascular coagulation,[837] placental abruption[838] or preeclampsia with haemorrhage, fibrinogen measurements are of important value.[839] Therefore, coagulopathy risk assessment during PPH should include obstetric complications and causes not just an estimated blood loss.[838] Fibrinogen concentration correlates with estimated blood loss, kaolin–TEG MA,[840,841] TEG FF MA,[842] FIBTEM MCF and FIBTEM A5.[842,843]

Despite the hypercoagulability of pregnancy, dilutional coagulopathy may occur during resuscitation with high volumes of fluids.[844] Especially volumes greater than 4 l of

crystalloids and colloids are associated with increased adverse maternal outcomes.[845] A restrictive resuscitation with crystalloids appears to be equal to a liberal strategy in mild PPH.[846]

Platelet count

Low platelet count is associated with increased risk of severe PPH, RBC and FFP transfusion.[847–852] Mild prepartum thrombocytopenia ($<150 \times 10^9 l^{-1}$) and lower platelet counts are associated with gradually increasing risk of severe PPH following vaginal delivery and caesarean section.[848,850,851,853,854] Platelet indices have limited additional predictive value in addition to platelet count.[849] When blood loss reaches 2000 ml, platelet count is significantly reduced.[840] PPH caused by trauma is less likely to be associated with low platelets but causes such as placental abruption are associated with a large drop in platelets.[838]

Activated partial thromboplastin time and prothrombin time

aPTT and PT show significant correlation with estimated blood loss in PPH.[844,851,855–857] A critical level of PT/aPTT is not reached in most women with PPH and massive transfusion.[838]

Factor XIII activity

Factor XIII activity decreases during normal pregnancy[858,859] and remains unchanged during an uncomplicated delivery.[860] A low FXIII activity at onset of labour is associated with blood loss during pregnancy and increased risk of PPH.[836,847,860] The clinical relevance of FXIII activity measurement is not established.

Viscoelastic haemostatic assays

VHAs provide results in 5 to 15 min and are faster than SLTs.[841] FIBTEM, a bedside thrombo-elastometric fibrin-clot quality test, can indicate a reduced contribution of fibrinogen to clot strength.[861,862] FIBTEM MCF is significantly decreased during PPH.[862,863]

Kaolin-TEG maximum amplitude (MA) correlates with estimated blood loss and fibrinogen concentration.[840,841] When blood loss reaches 2000 ml, TEG shows decreased MA, decreased clot initiation (prolonged *r* time) and reduced fibrinolytic activity (LY30%).[840,841] Both TEG FF and TEG kaolin MA may predict severe PPH and correlate with fibrinogen level as measured by the Clauss method.[829]

Thrombo-elastometric measurements can identify the hypercoagulability seen in normal pregnancy,[864–867] in caesarean section[868,869] and in pre-eclampsia and HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndromes, and also cases of impaired haemostasis because of other causes.[870] These measurements can also allow rapid recognition of hyperfibrinolysis,[871] hypofibrinogenaemia and low platelets[829] and guide therapy with TXA, fibrinogen concentrate, PCC, FFP and platelets.[840] A VHA-guided transfusion may reduce the need for blood products and possibly circulatory overload.[872–875] However, direct translation of trauma-based transfusion algorithms to PPH might give rise to over-transfusion with platelets.[876]

Hyperfibrinolysis

Split products of fibrin (D-dimer) may increase during PPH,[877] together with increased EXTEM maximum lysis greater than 15% on ROTEM.[871] There seems to be little evidence of hyperfibrinolysis in severe PPH versus nonsevere PPH,[840] and data suggests that some of the clot disintegration found in PPH might be caused by platelet-mediated clot retraction instead of hyperfibrinolysis as seen in traumatology.[878]

Haemostatic treatment of obstetric haemorrhage

Massive postpartum transfusion is associated with obstetric risk factors such as placental abruption, placenta accreta spectrum, placenta praevia and pre-eclampsia.[879,880] Peripartum hysterectomy whether anticipated or not is associated with large blood loss.[881] Transfusion of FFP, platelets and cryoprecipitate may be a marker for bleeding severity and volume of RBCs required.[882] A VHA-guided massive transfusion seems to reduce the need for blood products and may reduce morbidity in PPH.[883] A high RBC : FFP ratio is associated with lower risk of advanced interventional procedures to arrest the postpartum bleeding.[884] No improved outcome or adverse events were associated with early FFP administration during persistent PPH.[885,886] Platelet transfusion is associated with placental abruption caused by consumptive coagulopathy.[887] If the woman suffers no predelivery thrombocytopenia or consumptive coagulopathy, then platelet transfusion might first be required at a blood loss exceeding 5000 ml.[887,888] Pregnancy-related hypertensive disorders seem to increase the risk of TRALI in patients in need of postpartum blood transfusions.[889,890]

What are the indications for fibrinogen replacement with fibrinogen concentrate or cryoprecipitate?

Fibrinogen levels are typically elevated (approximately $5\,g\,l^{-1}$) in pregnancy; however, evidence from RCTs suggests against higher trigger levels for parturients.[891–895] Fibrinogen functionality might be impaired by dilution, local or disseminated consumption.[896] The underlying obstetric cause of bleeding should guide the clinical suspicion of impaired haemostasis.[897] However, haemostatic impairment during PPH is uncommon.[830,873,891] One retrospective study suggests that fibrinogen concentrate is equally efficacious in treating hypofibrinogenaemia compared with cryoprecipitate but seems faster to use.[898,899] Early administration of cryoprecipitate is currently being investigated.[900,901] During massive transfusion, fibrinogen concentrate

might reduce the risk of fluid overload compared with FFP.[902–904]

Two RCTs involving patients with PPH, a mean estimated blood loss of 900 to 1500 ml and normofibrinogenaemia, found no benefit of early pre-emptive treatment with 2 or 3 g of fibrinogen concentrate compared with placebo.[891–893,895,905] An RCT of targeted FIBTEM-guided fibrinogen substitution during PPH increasing the FIBTEM A5 level above 15 mm (to the normal level of pregnancy) found no clinical benefit or side-effects.[891] No SAEs were reported with fibrinogen concentrate in the obstetric setting.[891,892,895,906,907]

Guiding therapy in obstetric bleeding

What are the indications for the use of antifibrinolytic therapies (tranexamic acid) in obstetrics?

Fibrinolysis is decreased during pregnancy;[908] however, abnormally increased fibrinolysis is associated with complications such as placental abruption with antepartum bleeding.[909] Antifibrinolytic therapy used when postpartum bleeding evolves seems to reduce mortality due to bleeding and the need for acute laparotomies.[910,911]

Treatment with TXA 1 g i.v. should be given as soon as possible within 3 h to women with significant PPH (blood loss of >500 ml after vaginal birth/1000 ml after caesarean section/any blood loss sufficient to compromise haemodynamic stability) together with additional first-line treatment.[911,912]

Antifibrinolytic therapy, used prophylactically for vaginal[913,914] or caesarean delivery[915,916] might reduce blood loss and the need for additional treatment, but the clinical impact and relevance needs to be established together with the identification of relevant high-risk groups.[917] TXA might be given before or after cord clamping or delivery, but neonatal aspects are not clarified yet.[918] Oral and intramuscular administration of TXA is being investigated as an alternative route.[919]

Treatment with TXA as treatment or prophylaxis in parturients is not associated with increased risk of thrombosis.[911,914,916] Intravenous treatment with TXA is associated with nausea and vomiting.[914,916,920] Prolonged infusion and high-dose treatment with TXA might increase the risk of postpartum cortical necrosis and renal impairment in cases of severe PPH.[921]

What are the indications for other coagulation factor concentrates?

In two cases of amniotic fluid embolism, sufficient haemostasis was achieved by thrombo-elastometric-guided coagulation therapy constituting TXA, fibrinogen concentrate, platelets and PCC, as well as RBC and FFP in a 1 : 1 ratio, and rFVIIa.[922] Use of PCC might reduce the need for FFP in PPH,[923,924] but further evaluation is needed.

What are the indications for the use of rVIIa?

rFVIIa can be considered as second-line haemostatic therapy alongside intra-uterine tamponade, uterine compression sutures, pelvic vessel ligation and interventional radiology.[925,926] Case reports[927–931] and retrospective studies[926,932–936] support off-label use of rFVIIa for severe obstetric coagulopathic bleeding. Additional observational studies report increased risk of thrombosis.[937,938]

An open-label unblinded RCT of 84 patients showed reduced need for interventional second-line therapies (mainly arterial embolisation) following early administration of 60 μg rFVIIa compared with standard treatment for severe PPH (>1500 ml/24 h after delivery and unresponsive to uterotonics). No reduction in hysterectomies or arterial ligation was found. The intervention was not successful in over half of the patients. Furthermore, the risk of thromboembolism was increased (1 in 21 patients).[939] This trial was performed before TXA, and coagulation monitoring were established as standard (trial data collection period 2007 to 2010), so only 33 to 42% of patients received an initial TXA dose before rFVIIa. An extrapolation of these results and significant risk of thrombosis to present day scenarios remains to be evaluated.

2.7 Patients undergoing neurosurgical bleeding

Recommendation 13

For reversal of VKA-associated nontraumatic intracranial bleeding, PCC is recommended. 1B

For reversal of VKA-associated nontraumatic intracranial bleeding, we recommend against plasma transfusion. 1B

Intracranial surgery can be safely performed in the presence of low-dose aspirin. 2C

For reversal of APAs-associated nontraumatic intracranial bleeding, we suggest platelet transfusion or DDAVP. 2C

TXA intravenously as bolus with or without infusion, beginning from induction of anaesthesia until end of surgery, is recommended prophylactically for reducing peri-operative blood loss in elective intracranial surgery and elective spine surgery. 1B

Evidence summary

Intracranial surgery

Ten studies reported on intracranial tumour surgery.[940–949] A retrospective observational study including 8924 patients reported an RBC transfusion rate of 7% with an increased morbidity and mortality.[950] Other studies demonstrated an incidence of peri-operative bleeding resulting in RBC transfusion between 2.4 and 7%.[950,951]

Although Dasenbrock *et al.*[941] identified different levels of thrombocytopenia in a huge, retrospective cohort study ($n = 14\,852$) as risk factors for peri-operative

bleeding, Adelmann *et al.*[951] showed prospectively in a group of 290 patients that fibrinogen levels below 200 mg dl^{-1} had an OR of 10.02 for postoperative haematoma. This was in contrast to FXIII level, which was not associated with bleeding.[941,951] In a recent article on meningioma resections, Neef *et al.*[946] demonstrated patient's ASA classification, tumour size and surgical time as major risk factors for RBC transfusion. Several studies pointed out that peri-operative management of pre-existing anticoagulant or antiplatelet drug use was not well standardised.[952,953] However, the effect of continuing antiplatelet drugs on peri-operative bleeding seems less than expected. In a retrospective study on 1291 patients undergoing elective intracranial surgery stopping of acetylsalicyclic acid was equal in terms of blood loss (186 ml stopped versus 220 ml continued).[954] Similarly, Ebel *et al.*[955] demonstrated no significant difference in the occurrence of bleeding between two groups of patients (one stopped antiplatelet medication, one did not). Likewise, the rate of thromboembolic events was not significantly different between the groups.[955]

Along with two small studies recommending mechanical obliteration of larger vessels via embolisation (Manaka *et al.*, $n = 75$) or ultrasound-guided radiofrequency ablation (He *et al.*, $n = 13$), a main part of the investigations ($n = 9$) looked at the haemostatic effects of TXA.[942,945] Among those, one recent systematic review of subarachnoid and subdural haemorrhage showed a significant reduction of bleeding risk, which resulted in a nonsignificant reduction of mortality.[956] Another recent meta-analysis including three studies and 200 patients showed a reduction of peri-operative blood loss when TXA was used (mean difference of −292.8 ml; 95% CI −431 to −153 ml; $P < 0.05$). However, the use of blood transfusion was not significantly changed in the TXA cohort.[957] This is in contrast to a recent RCT in which 30 patients underwent meningioma resection with and without TXA treatment. In this study, a clear benefit of TXA was shown in terms of less blood loss (616 ± 393 versus 1150 ± 416 ml). In addition, the use of TXA resulted in a decreased need for transfusion of RBCs.[958]

Intracranial bleeding and subarachnoid haemorrhage

In a study on ICH based on oral anticoagulants, the authors retrospectively investigated the occurrence of complications after reversal by PCC compared with FFP plus vitamin K.[959] The rate of thrombotic complications was low at 1.59%. However, all of these were seen in the PCC group (1/28) versus the FFP group (0/35). Unfortunately, the study does not mention beneficial effects of both reversal strategies.[959] A recent review article by Gulati *et al.*[960]on this topic describes PCC as the preferred agent for reversal of vitamin K-associated ICH. This approach reverses the INR faster and more reliably than FFP with fewer side effects.[960]

A retrospective study of 538 patients presenting with nontraumatic ICH showed that platelet transfusion in those on antiplatelet therapy (168/538) was not associated with a worse outcome after matching for ICH score. However, the unmatched results presented a clinical deterioration (OR 4.7), a higher need for surgical intervention (OR 7.2), a worse Rankin Scale score (OR 3.6) and increased mortality (OR 6.1) in the cohort treated with platelet transfusion.[961]

In contrast is the treatment with DDAVP, which in cases of antiplatelet-associated ICH was associated with an 88% decreased haematoma expansion at 24 h without increased thrombotic risk or major changes in plasma sodium concentration.[962] Similarly, the subgroup analysis of a prospective study on the differences in surgical or pharmacological clot reduction in patients with ICH demonstrated that the group who received TXA ($n = 57$) had improved haematoma control. In addition, more patients had low-volume haematoma after the intervention versus placebo ($n = 64$).[963] This is in agreement with an earlier meta-analysis of 1702 patients with ICH. Here, the authors demonstrated that TXA reduces the growth risk of the haematomas (RR 0.78) and unfavourable outcomes (RR 0.75). However, the chance of rebleeding was not changed nor were the neurological outcomes and mortality.[964]

Although the cause of bleeding in aneurysmal subarachnoid haemorrhage (aSAH) is anatomical, the question about transfusion strategy and optimal Hb concentration is still a matter of debate. Specifically, in this field, the literature is sparse leaving us with a few publications. Dhar *et al.*[965] presented a study on 52 patients with aSAH investigating the effect of one RBC transfusion on oxygen delivery to the brain assessed by PET. According to their results, a rise in Hb from 9.6 g dl^{-1} (±1.4 g dl^{-1}) to 10.8 g dl^{-1} (±1.4 g dl^{-1}) after transfusion showed improved oxygen delivery (5 [IQR 4.4 to 6.6] versus 5.5 [IQR 4.8 to 7.0] ml per 100 g min^{-1}).[965] In contrast, a retrospective study on peri-operative transfusion of blood products on 488 patients with aSAH showed a strong correlation between transfusion and worse neurological outcome.[966]

Spine surgery

In a recent analysis of clinical data from the National Surgical Quality Improvement Program that included 16 329 patients undergoing elective lumbar fusion spine surgery, 11.8% of patients received blood transfusion. After matching the cohorts, the transfused patients stayed in hospital longer (>5 days) with an OR of 1.66 (95% CI 1.45 to 1.91), had more minor and major complications (OR 1.60; 95% CI 1.20 to 2.21 and OR 1.51; 95% CI 1.16 to 1.98, respectively), and a higher chance for discharge to a facility (OR 1.7; 95% CI 1.48 to 1.95).[967]

A similar study on patients undergoing metastatic spine tumour surgery ($n = 1601$) reported that 38.9% of patients received a blood transfusion. The authors demonstrated preoperative anaemia as the most relevant predictor (OR 3.1; 95% CI 2.11 to 4.56). The transfused patients developed significantly more complications than the nontransfused group (15 versus 22.3%).[968] Another larger database study including analysed coagulation profiles of 61 977 patients as risk factors for peri-operative bleeding found that only platelet counts below the normal range of $150 \times 10^9\,l^{-1}$ were significantly associated with transfusion. However, in the multivariate analysis only a preoperatively known bleeding tendency showed an OR of 1.6 (95% CI 0.5 to 4.6).[969] In addition, Rajan *et al.*[970] showed that an operation time longer than 200 min was associated with increased blood transfusion.

Preoperative anaemia detection and treatment was shown to reduce the need for blood transfusion from 23 to 8% ($P = 0.0019$) in 285 patients undergoing elective spinal surgery.[971]

The implementation of a restrictive blood management protocol in a group of 3709 patients with a transfusion trigger of less than $7\,g\,dl^{-1}$ could reduce the number of transfusions from 16.2 to 9.7% without negative side effects.[972]

A recent meta-analysis included 23 studies (1621 patients) investigating the efficacy of i.v. TXA on peri-operative blood loss and transfusion in elective, multilevel spine surgery. The authors showed that TXA significantly reduced peri-operative blood loss (mean difference of −284.39 ml; 95% CI −437.66 to −131.12 ml; $P < 0.001$) and intra-operative and postoperative blood transfusion (mean difference of −333.78 ml; 95% CI −540.45 to −127.01 ml; $P = 0.002$ and −114.66; 95% CI −219.58 to −9.74; $P = 0.32$, respectively).[444] Regarding potential side effects and risks of TXA, another meta-analysis found no difference in the incidence of thromboembolic events (RR 0.92; 95% CI 0.47 to 1.82).[973]

Only one small prospective, randomised study (intervention $n = 15$ versus placebo $n = 15$) investigated the beneficial effect of prophylactic administration of 1 g fibrinogen concentrate i.v. at the time of the surgical incision. The authors showed higher peri-operative blood loss in the control group compared with the intervention group.[974]

2.8 Paediatric surgery

Recommendation 14
We suggest VHA-guided interventions to help transfusion in neonates and children undergoing cardiac and noncardiac surgery. 2C

We recommend basing the decision for transfusion of RBCs not only on laboratory values but also on the clinical status of the child and the risks and benefits of the transfusion. 1C

We recommend against a transfusion if the child is haemodynamically stable and has a Hb concentration of at least $7\,g\,dl^{-1}$. 1B

We suggest administering fibrinogen concentrate to a child suffering from peri-operative bleeding and who was diagnosed with hypofibrinogenaemia. 2B

We recommend the prophylactic administration of antifibrinolytics in neonates and children undergoing noncardiac surgery associated with a high bleeding risk to decrease blood loss and the need for transfusions. 1C

Evidence summary

Coagulation monitoring

There is a broader consensus from systematic reviews, expert groups and meta-analyses to support the use of VHA-guided bleeding management in children.[975–977] Although special statistical analyses are still hampered by marked heterogeneity of published data, VHA-guided bleeding management has proven to be a feasible approach and has been shown to improve bleeding management and blood requirement, especially in paediatric cardiac patients.

Red blood cell transfusion

In 2019, the Transfusion and Anemia Expertise Initiative consensus conference published a guideline to direct RBC transfusion for critically ill children.[978] We support those recommendations, which offer additional guidance for the haemodynamically unstable child as well as for children with underlying cardiac abnormalities.

Fibrinogen concentrate

Fibrinogen concentrate is increasingly used as an alternative to cryoprecipitate to treat hypofibrinogenaemia in bleeding children. Downey *et al.*[372] compared the use of fibrinogen concentrate to cryoprecipitate in an RCT in a paediatric cardiac surgery setting. The authors reported that fibrinogen concentrate may be considered as an alternative to cryoprecipitate for the treatment of hypofibrinogenaemia in infants with bleeding after CPB.[372] Although the authors did not find any significant differences between adverse events, further studies are needed to assess safety. In another prospective randomised trial performed in infants 2.5 to 12 kg undergoing CPB, Siemens *et al.*[373] demonstrated that intra-operative, individualised dosing of fibrinogen concentrate is feasible. The need for individualised dosing is supported by the finding that a four-fold variation in fibrinogen concentrate dose is required to achieve therapeutic fibrinogen levels. Further large RCTs are needed in cardiac surgery to compare the safety of fibrinogen concentrate versus cryoprecipitate.

The evidence in the noncardiac paediatric literature remains sparse as large RCTs are lacking.

Antifibrinolytics

Although we still want for large RCTs in children, the existing evidence regarding the use of antifibrinolytic agents is high enough to support its use for neonates and children undergoing cardiac and noncardiac surgery. In a recent systematic review and meta-analysis, the available data demonstrated efficacy for all three antifibrinolytic drugs (TXA, EACA, aprotinin).[979] Therefore, the agent with the most favourable safety profile should be used. Although the safety and efficacy of aprotinin was recently addressed in a systematic review, further studies are needed to confirm its safety and efficacy in paediatric cardiac patients before its use can be considered.[352]

In children undergoing craniofacial surgery, Fenger-Eriksen *et al.*[980] studied the effect of combined intra-operative and postoperative TXA administration. In their study, the authors compared combined intra-operative and postoperative TXA treatment to a placebo and showed that combined intra-operative and postoperative TXA treatment reduced postoperative and overall blood loss and transfusion requirements. Further studies are needed to compare intra-operative administration only to a combined intra-operative and postoperative regimen.

2.9 Intra-operative transfusion triggers and volume management

Recommendation 15

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

In patients with a superior vena cava catheter in place, we recommend central venous oxygen saturation or arterial–venous oxygen difference surrogates for the oxygen delivery to consumption ratio to provide a personalised approach to identify patients who may benefit from transfusion. 1C

We recommend repeated measurements of a combination of Hct/Hb, serum lactate and base deficit to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. 1C

We recommend that these tests should be extended by measurement of cardiac output, dynamic variables of volume status (stroke volume variation, pulse pressure variation), CO_2 gap and central venous oxygen saturation or the combination of these. 1C

We recommend the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol-based manner. 1B

Compared with crystalloids, macro-haemodynamic and micro-haemodynamic stabilisation can be achieved with less volume of iso-oncotic colloids, and 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

Evidence summary

Transfusion triggers

In a recent RCT, an individualised strategy based on a central venous oxygen saturation threshold of 70% allowed for a more restrictive RBC transfusion strategy with no incidence on postoperative morbidity or 6-month mortality.[981] Furthermore, a retrospective study in critically ill patients found that when A–V O_{2diff} is greater than 3.7 ml, it could provide a more personalised approach in identifying patients who might benefit from transfusion, as indicated by lower mortality compared with those who received transfusion when A–V O_{2diff} was lower.[982]

Monitoring tissue perfusion

A before-and-after study in 204 patients undergoing gastrointestinal surgery received treatment by an algorithm combining mean arterial pressure greater than 65 mmHg, $S\rho O_2$ greater than 95%, PCO_2 gap less than 6 mmHg, and pulse pressure variation less than 13% and compared with patients previously operated on by the same team who were receiving conventional management.[983] In the intervention group, moderate and severe postoperative complications were reduced. In another recent prospective randomised trial in patients undergoing maxillofacial free flap surgery, an even more complex, contextualised approach was used.[984] The authors combined continuous measurements of pulse pressure variation, cardiac index, mean arterial pressure, and put these in the context of central venous oxygen saturation, PCO_2 gap, lactate, Hb and urine output. They measured the perfusion of the free flap by laser-Doppler, which remained stable throughout and after surgery, regardless of the type of fluid (crystalloid versus colloid) used.

Crystalloids, colloids

The crystalloid–colloid debate in peri-operative care has not been settled. In a large ($n = 1057$) randomised trial, Doppler-guided intra-operative hydroxyethyl starch administration did not significantly reduce a composite of serious complications.[985] Patients in the crystalloid arm received a median of 3.2 l of crystalloid and patients in the colloid arm only 1 l of colloid. There was no indication of renal or other toxicity.

Similar results were reported in another prospective randomised trial in patients undergoing maxillofacial free flap surgery, guided by a complex, multimodal, personalised haemodynamic approach.[984] Patients in the crystalloid group received 1.5 times higher total fluid volume than those in the colloid arm, with no significant

difference in the microcirculatory blood flow of the free flap and no adverse events in either group.

2.10 Intra-operative and postoperative anaemia management

Recommendation 16
In the early treatment phase of uncontrolled massive elective surgery bleeding, we suggest massive transfusion (≥6 to 10 units) with a high ratio (≥1 : 1) of plasma to RBCs. 2C

We recommend switching to a goal-directed transfusion strategy (based on Hb and/or physiological RBC transfusion triggers, coagulation factor substitution and platelet transfusion triggers) as soon as possible. 1C

We recommend monitoring of Hb concentrations for anaemia detection prior to, during and after high-bleeding-risk surgery and in situations where silent bleeding, massive blood loss and fluid shifts are at least suspected. 1A

After severe peri-operative bleeding, Hb levels should be monitored during the first postoperative days. 1C

When severe bleeding and volume shifts are expected and/or occurring, continuous noninvasive Hb monitoring may be considered for trend analyses and for reducing blood sampling for invasive laboratory measurement of Hb concentration, especially in children. 2C

In postoperative anaemia with Hb at least 10 g dl^{-1}, we suggest testing for iron deficiency and subsequent administration of i.v. iron at weight-based dosing if ferritin less than 100 μg l^{-1} or ferritin less than 300 μg l^{-1} and transferrin saturation less than 20%. 2C

In postoperative anaemia with Hb less than 10 g dl^{-1}, we recommend timely i.v. iron administration at weight-based dosing after considering contraindications. 1B

We suggest considering additional treatment with an ESA. 2C

In postoperative anaemia with Hb less than 6 to 8 g dl^{-1} or falling below physiological RBC transfusion triggers (based on signs of organ ischaemia and adequacy of cardiopulmonary reserve), we recommend RBC transfusion with a single unit strategy. 1C

For postoperative iron administration, we recommend i.v. over oral iron administration. 1B

Intravenous iron formulations allowing higher maximal single doses (such as isomaltoside, carboxymaltose) may be more effective than those with low licensed maximum single doses (such as sucrose). B

Evidence summary

Blood product ratio

Appropriate and rational use of blood product transfusion can improve patient outcomes but inappropriate transfusion can increase morbidity and mortality. The goal of PBM is prevention, and hence the avoidance of massive transfusion. Studies in uncontrolled trauma bleeding have indicated that a high ratio of plasma to RBCs may reduce the mortality rate when used at an early phase of treatment. However, there are no prospective studies evaluating the efficacy or benefits of fixed ratio transfusion in uncontrolled elective surgery patients and comparing a goal-directed RBC transfusion therapy to a fixed ratio approach.

Several retrospective studies have been undertaken to assess the benefits of using a fixed ratio for transfusion in cardiac surgery patients, indicating potential reductions in mortality and improved patient outcomes in patients receiving a high transfusion ratio of plasma and/or platelets to RBCs. A retrospective, multicentre study in China investigated the optimal ratio of FFP to RBCs for 1048 severely bleeding patients (808 of whom had undergone cardiac or general surgery) who received massive transfusions (≥10 U RBCs).[986] Patients were divided into three groups according to the ratio of FFP : RBC received: low (<1 : 2.3), medium (1 : 2.3 to 0.75) and high (≥1 : 0.75). Although the 24 h mortality rate was lowest when a ratio of 1 : 2.3 to 0.75 was used, there was no significant difference between groups. However, at 72 h, the mortality rate was significantly lower in the 1 : 2.3 to 0.75 FFP : RBC group (7.25%) compared with the low and high ratio groups (13.65 and 10.39%, respectively; $P = 0.007$). These results were supported by a retrospective analysis of data from a multicentre, randomised trial designed to investigate the association between blood component ratios used in massively transfused (≥6 U RBCs) patients undergoing complex cardiac surgery.[987] In patients receiving high plasma : RBC ratio (≥1 plasma : RBC) or high platelets : RBC ratio (≥0.2 platelets : 1 RBC), there was less organ dysfunction than those who received lower ratios. Additionally, there was also a lower mortality in those patients who received high ratio plasma : RBC transfusions. A single-centre, retrospective cohort study was performed to examine the impact of FFP : RBC transfusion ratio on mortality in massively transfused (≥8 U RBCs) patients undergoing cardiac surgery.[988] Patients who received a high FFP : RBC ratio (greater than 1 : 1) had improved 30-day survival compared with those who received a low FFP : RBC ratio (<1 : 2) ($P = 0.002$). High transfusion ratios were also associated with less postoperative bleeding and less renal failure, but more prolonged ventilation and more atrial fibrillation than lower ratios. This study suggests that a high transfusion ratio may improve survival but may also increase the risk of prolonged ventilation and atrial fibrillation in those patients who receive massive transfusion. Another single-centre, retrospective cohort study in a cardiovascular centre in Japan aimed to evaluate the relationship between the FFP : RBC transfusion ratio and outcomes in 1453 patients undergoing cardiovascular

surgery.[989] High transfusion ratios (>1 : 1) were associated with a significantly lower incidence of in-hospital mortality ($P = 0.001$), stroke ($P < 0.001$) and myocardial infarction ($P = 0.047$) than lower transfusion ratios but only in patients receiving massive transfusion (≥8 U RBCs). These results indicated judicious FFP replacement with a transfusion ratio greater than 1 : 1 may play a critical role in the management of massive transfusion in cardiac surgery.

In another surgical setting, a single study has assessed the impact of a fixed transfusion ratio in patients undergoing OLT.[990] This single-centre, retrospective cohort study was conducted to determine whether an intra-operative ratio of at least 1 : 1 : 2 of FFP : platelets : RBCs improved patient outcomes. Patients were grouped into those receiving an intra-operative ratio of at least 1 : 1 : 2 of FFP : platelets : RBCs versus less than 1 : 1 : 2. Patients in the at least 1 : 1 : 2 group had improved 1-month mortality (0 versus 8%, $P = 0.002$) and improved 1-year survival ($P = 0.004$) compared with the less than 1 : 1 : 2 group, suggesting a potential survival benefit associated with balanced blood product transfusion. Additionally, a retrospective cohort study evaluated the association of FFP : RBC ratio with blood loss in patients with neuromuscular scoliosis undergoing posterior spinal fusion. Risk estimation showed that patients in the low FFP group (FFP : RBCs ≤0.5) were more likely to lose more than 120% blood volume (OR 3.87; 95% CI 2.03 to 7.38) than the high FFP group (FFP : RBCs >0.5). Additionally, each unit of increase in FFP : RBC ratio was associated with a 27.5% (95% CI 43.12 to 11.89) mean reduction in blood volume loss. As such, the FFP : RBC ratio was a significant independent predictor of blood loss, and these study results indicate that the use of higher FFP : RBC ratio may decrease blood loss.[991]

Noninvasive Hb monitoring

The gold standard laboratory method for measuring accurate Hb concentrations is the Hb-cyanide method.[992] It is a complex and rarely used method in the daily clinical setting.[992] In the peri-operative setting blood gas analysers, haematology analysers in clinical chemistry laboratories and point-of-care testing devices are often used. These methods require blood sampling[993] and cause further iatrogenic blood loss and hospital-acquired anaemia when used in excess.[994] During scenarios of rapid fluid shifts such as major blood loss and volume replacement, single measurements taken at different time points may not depict accurate values. Obtaining further measurements to more accurately observe the fluctuations causes more sampling and blood loss.[995] The use of noninvasive Hb-monitoring methods may be a practical approach to monitor the Hb concentration continuously and without accumulating additional blood losses. The underlying technology of currently available noninvasive Hb-monitoring devices is based on pulse oximetry calculating the Hb concentration.[996] However, the accuracy of the method of noninvasive Hb monitoring has been criticised[997] with overestimates of the Hb concentrations in Hb ranges from 6.5 to 8 g dl^{-1} and being most accurate in Hb ranges from 10.5 to 14.5 g dl^{-1}.[998] Other studies have reported smaller differences.[999] In two meta-analyses, the overall difference between laboratory and noninvasive measured Hb-concentrations were not statistically significant.[1000,1001] Noninvasive Hb-monitoring devices are not intended to replace laboratory-measured Hb concentrations. The value of the noninvasive method is for trend analysis and to monitor changes in Hb concentrations in addition to laboratory-measured Hb concentrations during the intervals between individual invasive blood sampling and Hb measurements. Having access to continuous measurements of Hb concentrations offers timely detection of changes in Hb concentrations and adjustment, if necessary, in the clinical setting.[995,996]

Iron and erythropoietin

Postoperative anaemia may be present in up to 80 to 90% of patients, although this varies according to the definition used, aside from the WHO definition,[1002] and anaemia has a potential impact on the patient's recovery, rehabilitation and need for re-operation or readmission.[1003–1005] Therefore, detection and treatment of postoperative anaemia should form part of PBM procedures. Indeed, an international consensus statement has been published regarding the management of postoperative anaemia after major surgical procedures, which makes recommendations regarding the diagnosis, identification of patients appropriate for treatment and the practical management of iron deficiency and anaemia.[1005]

A number of RCTs have been conducted to evaluate the efficacy of i.v. iron to treat postoperative anaemia. An RCT in Australia was conducted to determine the effects of postoperative i.v. iron in patients undergoing elective major orthopaedic, abdominal, genitourinary or other surgery with functional IDA (defined as Hb 70 to 120 g l^{-1} and ferritin ≤100 μg l^{-1} or iron saturation ≤20%) on the first postoperative day.[744] A total of 201 patients received either a single 1000 mg dose of i.v. ferric carboxymaltose within 24 h of randomisation ($n = 103$) or received routine postoperative care as part of the control group ($n = 98$). Postoperative i.v. iron infusion resulted in significant improvements in Hb, serum iron, iron saturation and serum ferritin concentrations at 4 weeks, and a significant reduction in blood transfusion.[744] Similarly, an RCT conducted in adults who had undergone radical gastrectomy and had a serum Hb level of 7 to 10 g dl^{-1} at 5 to 7 days postoperatively evaluated the efficacy of a one-time or two-time injection of 500 or 1000 mg ferric carboxymaltose (according to body weight, $n = 228$) or placebo ($n = 226$).[1006] The number of Hb responders (defined as an increase of 2 g dl^{-1} or more from baseline,

a level of 11 g dl^{-1} or more, or both at week 12) was significantly higher for the ferric carboxymaltose group (92.2%) than the placebo group (54%). Additionally, patients in the ferric carboxymaltose group showed significantly greater improvements in serum ferritin and transferrin saturation levels. Additionally, an RCT in 150 patients with postoperative functional IDA (Hb <120 g l^{-1} for women or 130 g l^{-1} for men and ferritin concentrations 30 to 100 μg l^{-1} or transferrin saturation <20%) following cardiac valvular surgery demonstrated that weight-based dosing [according to the formula: total iron deficiency (mg) = body weight (kg) × (target Hb − actual Hb g dl^{-1}) × 0.24 + iron storage (mg)] with i.v. iron sucrose beginning the day after surgery and then every other day until the target dose was achieved, significantly increased Hb levels at postoperative day 14 and ferritin concentration at postoperative days 7 and 14 when compared with placebo.[1007] However, no difference in blood transfusion requirements or postoperative adverse outcomes was observed. Similarly, a single-centre retrospective study of 139 patients undergoing colorectal cancer surgery who presented with anaemia (Hb <13 g dl^{-1}), found that, compared with patients not receiving iron, 200 mg i.v. iron sucrose infusion up to three times a week during hospitalisation, there was improved recovery of Hb levels at 30 days postsurgery without increasing postoperative complications.[1008]

In contrast to these results, some studies have not demonstrated a beneficial effect of iron administration. An RCT conducted in 120 elective cardiac surgery patients with postpump Hb of 7 to 10 g dl^{-1} compared postoperative administration of i.v. iron sucrose alone (200 mg day^{-1} to reach the total iron deficit) or i.v. iron plus a rHuEPO (single dose of 300 U kg^{-1}) with a control group.[1009] No significant difference was observed between groups for transfusion requirements or Hb increase up to day 30 postsurgery; however, a significant increase in ferritin levels was observed in the two treated groups at day 5. A similar but small RCT conducted in 38 patients who had undergone cardiac or orthopaedic surgery who did not have preoperative anaemia but presented with a Hb concentration 70 to 90 g l^{-1} on postoperative day 1 concluded that early postoperative treatment with i.v. iron sucrose (200 mg on days 1, 2 and 3 postsurgery) with or without EPO (600 U kg^{-1} on days 1 and 3 postsurgery) did not improve early recovery from postoperative anaemia, with no significant increase in Hb concentrations by days 7 or 28.[1010] Additionally, another RCT in patients undergoing CPB surgery did observe an increase in serum ferritin levels at hospital discharge and 1 month later in patients receiving i.v. iron sucrose (three doses of 100 mg day^{-1} during preoperative and postoperative hospitalisation), but found no statistical difference in Hb levels (measured up to 1 month after discharge) or blood transfusion requirements between patients receiving i.v. iron ($n = 54$) and those receiving either oral ferrous fumarate ($n = 53$) or placebo ($n = 52$).[1011] All patients in this study were randomised to the treatment groups prior to surgery and did not have preoperative anaemia.

The benefits of i.v. versus oral administration of iron have also been evaluated. An RCT conducted in 122 patients with postoperative anaemia (Hb 8.5 to 12 g dl^{-1}) following TKA found that i.v. ferric carboxymaltose administration (700 to 1000 mg on postoperative day 2) resulted in patients more frequently achieving Hb levels at least 12 g dl^{-1} and demonstrated a trend towards a higher Hb increase from day 4 to day 30 compared with patients receiving oral ferrous glycine sulphate (100 mg daily from day 7 onwards).[1012] As noted above, a study in cardiac surgery found that i.v. iron iii-hydroxide sucrose complex resulted in a greater increase in serum ferritin levels than oral ferrous fumarate supplementation; however, this study did not observe a statistical difference in Hb levels between i.v. and oral therapy.[1011] Additionally, multiple RCTs in orthopaedic surgery and cardiac surgery have indicated that oral iron supplements are not effective in treating postoperative anaemia.[1013–1018] In agreement with these results, a systematic review in major orthopaedic surgery concluded that postoperative oral iron administration did not increase Hb or reduce transfusion requirements, and was associated with adverse gastrointestinal effects.[1019] In contrast, an RCT comparing i.v. iron polymaltose infusion (500 mg single dose on day 4 postoperatively) to oral ferrous sulphate (210 mg daily, from day 5 postoperatively until Hb was ≥11 g dl^{-1}) following kidney transplantation found no significant difference in the time to resolution of anaemia.[1020] Randomisation to treatment was performed pretransplant, and the mean pretransplant Hb concentration was 12 g dl^{-1}.

In addition to studies evaluating how to treat postoperative anaemia, a recent RCT has evaluated the efficacy of intra-operative i.v. iron isomaltoside administration to prevent postoperative anaemia, with a total of 89 patients undergoing TKA receiving either i.v. iron (dose based on body weight and administered after the main procedure) or placebo during surgical wound closure.[1021] At 30 days, the incidence of anaemia was significantly lower in the treatment group than in the control group. Additionally, Hb concentration, serum ferritin concentration and transferrin saturation were significantly higher in the treatment group. Similarly, a randomised trial in 57 healthy adults undergoing bimaxillary orthognathic surgery concluded that a 1000 mg dose of i.v. ferric derisomaltose after anaesthetic induction resulted in higher Hb levels and a significant increase in reticulocyte production index at 2 weeks postoperatively compared with placebo.[1022] This supports the results of an earlier study, which demonstrated that peri-operative i.v. iron isomaltoside infusion (1000 mg) resulted in significantly increased Hb levels and a lower incidence of anaemia in cardiac surgery patients at 1 month after surgery.[1023]

As noted above, two RCTs have been conducted to evaluate the efficacy of rHuEPO with i.v. iron, neither of which observed a conclusive benefit associated with EPO administration.[1009,1010] However, an RCT in 600 cardiac surgery patients with pre-operative Hb levels 14.5 g dl^{-1} or less concluded that a single 80 000 IU dose of rHuEPO 2 days before surgery reduced the need for postoperative RBC transfusion.[1024] Similarly, a clinical trial in two series of patients undergoing unilateral total knee replacement (group A, $n = 139$; group B, $n = 173$) concluded that transfusion requirements were reduced when patients with preoperative Hb levels less than 130 g l^{-1} received peri-operative i.v. iron sucrose (2×200 mg per 48 h) plus a preoperative 40 000 IU dose of EPO.[1025] Indeed, a recent systematic review regarding the use of pre-operative EPO concluded that it improved outcomes in patients with pre-operative anaemia undergoing elective surgery.[1026] Additionally, an observational study of 723 patients undergoing elective primary hip or knee arthroplasty noted that inclusion of pre-operative EPO in the PBM programme (if pre-operative Hb <13 g dl^{-1}) reduced the rate of blood transfusion and postoperative anaemia.[1027] Based on these and similar data, the international consensus statement on management of postoperative anaemia suggests considering the use of ESAs in noncancer patients with severe postoperative anaemia and inflammation-induced blunted erythropoiesis or those declining blood transfusion.[1005]

Current guidelines for PBM recommend a restrictive transfusion strategy for RBCs without specifying explicit Hb thresholds for the postoperative phase, but generally emphasising physiological RBC transfusion triggers (taking into consideration the patient's signs of organ ischaemia and the influence of pre-existing cardiovascular disease on the adequacy of cardiopulmonary reserve and tolerance to anaemia).[1028–1030]

Conclusion

Recommendations in the clinical fields of diagnosis and treatment of anaemia, optimisation of haemostasis and blood conservation modalities in surgical patients makes these updated ESAIC guidelines the European guidelines on peri-operative PBM. The WHO encouraged all member states to implement PBM programmes employing such multimodal strategies to increase and preserve autologous erythrocyte volume in order to minimise the transfusion of blood components such as RBC, platelet concentrate and FFP.[1031] Allogeneic blood transfusions may be associated with increased morbidity because of infectious, immunological or pulmonary complications.[1032–1035] Strategies presented in these guidelines aim at increasing patient safety, which requires medical education and training, infrastructure and quality management.[1036,1037]

Summarised evidence-based guidance in these updated ESAIC guidelines may assist clinicians in making medical decisions for bleeding risk reduction and in the emergency situation of severe peri-operative bleeding. Among the points included are:

(1) Severe bleeding, beyond 20% of the patient's blood volume, is a risk factor for anaemia, allogeneic blood transfusion, coagulopathy and tissue hypoperfusion. All these factors are independent predictors for survival and drivers for resource use and costs.
(2) Peri-operative PBM is indicated for the management of severe bleeding in the high-risk surgical patient. This multimodal concept permits a restrictive transfusion approach in peri-operative care.
(3) In high-bleeding-risk surgery, pre-existing anaemia should be detected and corrected preoperatively in order to increase tolerance to peri-operative surgical and coagulopathic blood loss, and to avoid allogeneic blood transfusions.
(4) In high-bleeding-risk surgery pre-existing inherited, drug-induced and/or acquired bleeding disorders, including coagulopathy in critical illness and/or COVID disease, should be detected and corrected preoperatively in order to reduce peri-operative blood loss and allogeneic blood product requirements.
(5) In high-bleeding-risk surgery, autologous cell salvage and antifibrinolytic prophylaxis should be exploited whenever possible. Body temperature, homeostasis and tissue perfusion should be monitored and kept within normal range.
(6) Surgical bleeding events should be stopped by surgical measures. Acquired coagulopathic bleeding events should be stopped by individualised correction of the actual pathomechanism(s) of bleeding by antifibrinolytic and/or procoagulant drugs, and preferably potent virus-inactivated coagulation factor concentrates.
(7) For high-bleeding-risk surgery, infrastructural requirements include laboratory tests such as blood gas analyses, global coagulation tests and preferably also tests for anticoagulant drug measurements and also VHAs.
(8) Preparation of hospital–internal standard operating procedures is recommended, preferably implementing international ESAIC guidelines, on the peri-operative management of anaemia, allogeneic blood transfusions, antithrombotic medication, coagulopathy, as well as on tolerance to anaemia, including volume management.
(9) For high-bleeding-risk surgery, education and training in peri-operative PBM of involved medical and nonmedical staff is required.

Acknowledgements relating to this article

Assistance with the guidelines: we thank Janne Vendt, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark, for performing the systematic literature search.

Financial support and sponsorship: the systematic search was funded by the European Society of Anaesthesiology.

Conflicts of interest: AAh received advisory fees from Stago, Haemonetics, CSL Behring, consulting fees from Nordic Pharma and is stock shareholder at Hemeo. PA received consultation fees from Pfizer BMS, Sanofi, Alexion. CA received consulting fees from Becton Dickinson. EDR received consultation fees from Baxter, Fresenius Kabi, MSD. He was President of the ESAIC during the period over which this guideline update was prepared. DCF received consulting fees and grants from Werfen. DFr received honoraria for lecturing, consulting fees and grants from AstraZeneca, Baxter, B. Braun, CSL Behring, LFB, Mitsubishi Tanabe Pharma, Octapharma. AG received honoraria and travel fees from Bayer-Healthcare, Boehringer-Ingelheim, Bristol-Myers-Squibb/Pfizer, Sanofi, LFB, CSL-Behring, Octapharma, Alexion. TH received honoraria for lecturing and consultation fees from Octapharma. SK received consultation fees from Baxter, Norgine, Werfen, Roche. JVL received honoraria for lecturing, educational programs or consultancies from Octapharma, CSL-Behring, Rovi, Sanofi, Cardinal. ZM received consultation fees from Pulsion Medical, ThermoFisher Scientific, CytoSorbents Europe and is senior medical director at CytoSorbents Europe. NRM received unrestricted grants for clinical studies from Biotest. ES received honoraria for lecturing from EurAsia Heart Foundation and CSL Behring. CS received research grants from CSL Behring, TEM International. Receipt of honoraria or consultation fees from CSL Behring, Boehringer Ingelheim, Portola, Shionogi, Octapharma. KZ received educational grants for his Department, honoraria for lectures from Haemonetics, med update, Pharmacosmos, Hexal AG, Vifor Pharma and advisory fees from Boston Scientific Medizintechnik GmbH, Wolters Kluwer, GE Healthcare. KZ received research grants from EU Horizon Europe CoVend and EU H2030 Envision. KZ was President of the ESAIC during the period over which this guideline update was prepared. AAf, GB, DFa, MJ, MDL, JM, LM, CMS and AW have not declared any conflict of interest.

Presentation: none.

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