

Perioperative management of the bleeding patient

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Abstract

Perioperative bleeding remains a major complication during and after surgery, resulting in increased morbidity and mortality. The principal causes of non-vascular sources of haemostatic perioperative bleeding are a preexisting undetected bleeding disorder, the nature of the operation itself, or acquired coagulation abnormalities secondary to haemorrhage, haemodilution, or haemostatic factor consumption. In the bleeding patient, standard therapeutic approaches include allogeneic blood product administration, concomitant pharmacologic agents, and increasing application of purified and recombinant haemostatic factors. Multiple haemostatic changes occur perioperatively after trauma and complex surgical procedures including cardiac surgery and liver transplantation. Novel strategies for both prophylaxis and therapy of perioperative bleeding include tranexamic acid, desmopressin, fibrinogen and prothrombin complex concentrates. Point-of-care patient testing using thromboelastography, rotational thromboelastometry, and platelet function assays has allowed for more detailed assessment of specific targeted therapy for haemostasis. Strategic multimodal management is needed to improve management, reduce allogeneic blood product administration, and minimize associated risks related to transfusion.

Key words: coagulopathy; direct oral anticoagulants (DOACs); hemostasis & thrombosis; point-of-care testing; thromboembolism; transfusion algorithm

Multiple factors contribute to the complex causes of bleeding in surgical patients that include blood loss, haemodilution, acquired platelet dysfunction, coagulation factor consumption in extracorporeal circuits, activation of fibrinolytic, fibrinogenolytic and inflammatory pathways, and hypothermia.^{1,2} Acquired haemostatic defects often present in surgical patients as a result of prescribed oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) and platelet inhibitors (P₂Y₁₂ receptor inhibitors-clopidogrel, prasugrel, or ticagrelor). Thus, bleeding after surgery includes both preexisting and/or acquired defects in haemostasis. Congenital bleeding disorders are less common and, hopefully already addressed if a patient presents for surgery. From a preoperative evaluation standpoint, the ISTH bleeding questionnaire is as effective as multiple, laboratory tests for identifying perioperative bleeding risk.³

Surgical bleeding is usually characterized by a site of bleeding and confined exclusively to the operative site. Meticulous surgical technique, patience, and good patient selection all contribute significantly to minimizing surgical bleeding in the high-risk patient. The spectrum of available topical haemostatic agents and devices are beyond the scope of this review.⁴ **The focus of this review is** microvascular or coagulopathic bleeding as a consequence of abnormal haemostatic mechanisms. While typically manifested as generalizing bleeding within the operative site, this can extend to percutaneous cannulation sites, nasogastric tubes, and urinary catheters.

Management of perioperative bleeding consists of identifying patients at risk, understanding the impact of the operation on haemostasis, institution of allogeneic blood and factor concentrate based therapies, utilizing point-of-care laboratory

Editor's key points

- Perioperative bleeding can involve acquired coagulation abnormalities secondary to haemorrhage, haemodilution, or haemostatic factor consumption.
- Novel approaches for prophylaxis and therapy of perioperative bleeding include use of tranexamic acid, desmopressin, fibrinogen and prothrombin complex concentrate.
- Point-of-care testing of haemostatic function using thromboelastography, thromboelastometry, and platelet function assays allows specific targeted therapy of coagulopathy.

testing, and understanding the limitations of monitoring techniques.⁵ Clinically important bleeding can paradoxically evolve into pathologic thrombosis, with the transition of perioperative coagulopathy to hypercoagulability related to the acute phase response. This can be exacerbated by overzealous replacement of deficient procoagulant factors, inattention to deficient anticoagulant factors, and reluctance to initiate needed anticoagulant agents for venous thromboembolic prophylaxis after a recent bleed. Navigating this complex, rapidly changing haemostatic balance exemplifies the value of the perioperative physician with detailed knowledge of haemostasis, anticoagulation, and transfusion medicine. In this review, we address specific and general considerations for various pathophysiological states or circumstances and haemostatic agents and provide algorithmic approaches to bleeding management, in order to place the administration of agents in clinical context.

The following section represents general considerations of haemostasis related to hypothermia and fibrinolysis, which can occur in all patient populations undergoing invasive procedures and require review before approaching the coagulation defects particular to specific patient populations.

General considerations: hypothermia and fibrinolysis

Temperature regulation and the coagulopathy of hypothermia

In controlled circumstances, such as during cardiopulmonary bypass or hypothermic circulatory arrest, hypothermia is used as a neuroprotective mechanism.⁶ Inadvertent hypothermia seen with severe trauma, or poorly maintained intraoperative temperature regulation can be associated with worse outcomes. For example, isolated hypothermia of 32.2 °C is associated with a 23% mortality rate, while trauma-induced hypothermia below 32 °C is associated with 100% mortality.^{7–8,9} The coagulopathy of hypothermic patients includes dysregulation of coagulation enzyme processes, platelet function, activation of fibrinolysis, and endothelial injury.¹⁰ Bleeding observed at reduced temperatures (33 – 37 °C) often occurs because of defects in platelet adhesion, while at temperatures below 33 °C, both reduced platelet function and coagulation enzyme activity contribute.¹¹ Active warming should be applied perioperatively if exposed surface area allows. Additionally, hypothermia and acidosis frequently occur together requiring correction of metabolic abnormalities.^{11–14}

Fibrinolysis

Activation of the fibrinolytic system is an important mechanism of vascular homeostasis (Figure 1). Mechanistically, plasmin generation is the enzymatic serine protease responsible for fibrinolysis and is formed after the action of t-PA on plasminogen. Plasmin cleaves key coagulation proteins such as fibrin and fibrinogen, but also causes proteolysis of other critical proteins, including fibronectin and von Willebrand factor.¹⁵ In the urogenital tract, hyperfibrinolysis occurs as a result of liberation of the urokinase plasminogen activator system.¹⁶ After cardiopulmonary bypass and/or tissue injury that occurs with surgery or trauma, fibrinolysis is activated and represents an important cause of coagulopathy.¹⁷ In trauma, orthopaedic surgery, and cardiac surgery, multiple studies support the role of antifibrinolytic agent administration in order to decrease bleeding and the need for allogeneic transfusions.¹⁷ These agents can also be used as an adjunct to treating congenital bleeding disorders.¹⁸

Since CRASH-2 was published in 2010,¹⁹ meta-analyses recommend antifibrinolytic use (mostly tranexamic acid) in abdominal bleeding²⁰ and trauma, while on-going major studies are being conducted for gastrointestinal bleeding (HALT-IT trial)²¹ and postpartum haemorrhage (WOMAN trial).²² The use of tranexamic acid (TXA) is increasing and additional data are forthcoming. Despite initial concerns about aprotinin, this agent is now being reintroduced in many European markets.²³

While we will not discuss postpartum haemorrhage in detail, three major considerations are emerging for managing bleeding parturients: routine use uterotonics, aggressive fibrinogen replacement, and prevention of excessive fibrinolysis, as recently reviewed.^{24,25}

Antifibrinolytic agents: lysine analogues

The two antifibrinolytic agents administered clinically include epsilon aminocaproic acid (EACA) and TXA.²⁶ While both medications competitively inhibit plasminogen conversion to the active protease plasmin,²⁷ only TXA has been shown to inhibit higher plasma concentrations of plasmin.^{28,29} Although most of the data for the antifibrinolytic lysine analogues are with TXA, EACA continues to be extensively utilized in the USA.³⁰ Although multiple studies (primarily meta-analyses of randomized-controlled trials) have shown that lysine analogues decrease bleeding in cardiac surgical patients, there are limited prospective safety data regarding the use of antifibrinolytic agents. Most dosing studies include total EACA doses of 20 to 30 g per patient, or total TXA doses from 2 to 25 g, mainly from 2 to 8 g.²⁶

An increase in the incidence of seizures after cardiac surgery from 1.3% to 3.8% has been temporally associated with higher-dose TXA use.³¹ The mean age of patients in this report was ~70 yr, and open chamber surgery, with possible air entrainment, was a risk factor.³¹ Mechanistically, TXA enhances neuronal excitation by antagonizing inhibitory gamma-aminobutyric acid (GABA)³² and glycine³³ neurotransmission at the receptor level, an established cause of seizures. This side-effect was not noted in prospective trials, which were notably underpowered for this outcome. Seizure activity has not been described in patients receiving EACA. For other indications such as orthopaedic, trauma and obstetric indications, the data are mostly for patients receiving a total of 2 g of TXA, where seizures have rarely been reported.

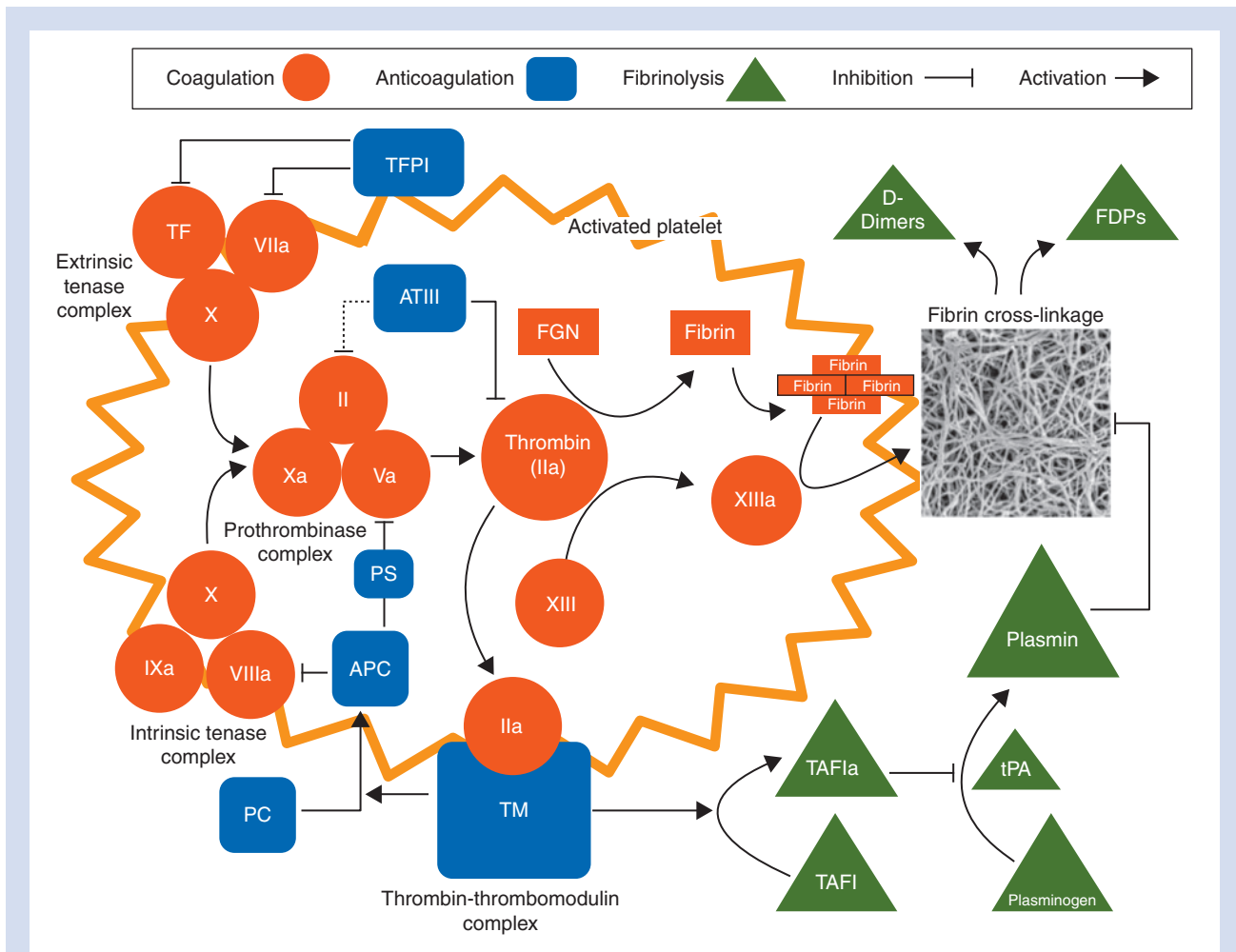


Fig 1 Interplay between coagulation, anticoagulation, and the fibrinolytic systems. In a simplified model, coagulation factors are illustrated upon the activated platelet surface. Through the activation of factor X (Xa) via intrinsic (Factor IXa, VIIIa) and extrinsic tenase (Xase) complexes, factors Xa and Va convert factor II (prothrombin) to factor IIa (thrombin). Thrombin then cleaves fibrinogen into fibrin. Fibrin polymerization is facilitated by the activation of factor XIII that forms cross links leading to clot stabilization. Factor II, VII (not pictured), IX (not pictured) and X are targeted for repletion with prothrombin complex concentrate (PCC) administration. Factor VIIa is targeted for repletion with administration of recombinant factor VIIa (rFVIIa). Simultaneously, anticoagulants negatively modulate clot formation. Antithrombin III (ATIII) modulates factor IIa (primarily) and factor Xa (secondarily), but ATIII-dependent inhibition of factor IXa, XIa, and VIIa-TF complex occurs to a lesser extent (not pictured). Other important anticoagulants include TFPI-modulation of Tissue Factor and factor VIIa, and Activated Protein C (APC) which, through activation of protein S, inhibits factor Va, weakening the prothrombinase complex and impairing thrombin generation. Upstream, APC inhibits factor VIIIa of the intrinsic Xase complex. Factor IIa complexes with Thrombomodulin (TM) to activate PC. Of note, the thrombin-TM/PC/PS system is primarily localized to the endothelium but can be expressed on platelets and monocytes. This complex initiates thrombin-activatable fibrinolysis inhibitor (TAFI), which prevents plasmin production by inhibiting tissue-plasminogen activator and through direct inhibition of plasminogen (not pictured). Plasmin is a serine protease and, as the primary driver of fibrinolysis, results in clot destabilization, degradation of fibrin cross linkage, and production of fibrin degradation products, which include D-dimers. Plasmin triggers platelet activation (not pictured) thereby competing with TAFI at the local level. TF, Tissue Factor; PC, Protein C; PS, Protein S; TFPI(a), Tissue-Factor Pathway Inhibitor (activated); ATIII, Antithrombin III; FGN, Fibrinogen; TM, Thrombomodulin; FDPs, Fibrin Degradation Products; tPA, tissue-Plasminogen Activator.

Coagulation abnormalities in different patient populations

Trauma

The coagulopathy of trauma is a complex pathophysiologic state that results in diffuse, microvascular bleeding.^{34,35} Approximately 40% of trauma-related mortality is associated with profound coagulopathy.³⁶ Management of major bleeding requires repair of the underlying cause after surgery or trauma, volume resuscitation with blood products, and diagnosis and management of the

ongoing coagulation defects.³⁷ Initial retrospective analyses from military trauma reported repletion of intravascular volume using predetermined ratios of fresh frozen plasma (FFP), platelet concentrate (PC), and red blood cells (RBCs) at 1:1:1 reduced mortality in patients with major bleeding.³⁸⁻⁴² To prospectively evaluate this strategy, Holcomb and colleagues⁴³ reported that with severe trauma and major bleeding, early administration of FFP, PC, and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio, did not significantly decrease mortality at 24 h or 30 days. They also reported more patients in the 1:1:1 group achieved haemostasis and with less mortality from exsanguination at 24 h (9.2% vs 14.6%;

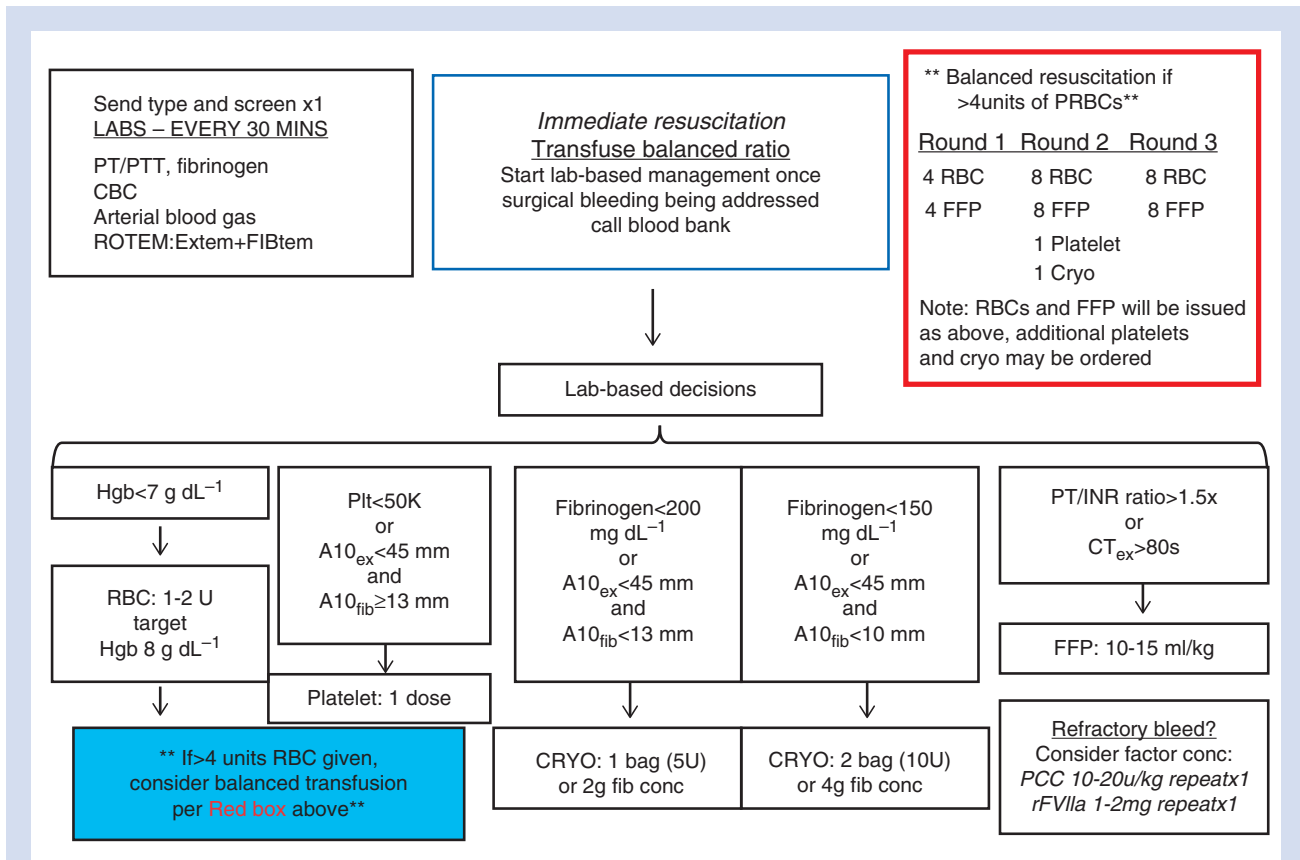


Fig 2 Transfusion algorithm for intraoperative bleeding during noncardiac surgery. Focus on a laboratory-based, viscoelastic testing paradigm, with opportunities for intervention based on clinical decision-making. Our protocol advocates antifibrinolytic therapy, correction of acidosis, and correction of acute hypocalcaemia. Inside the redbox, our balanced ratio recommendations are presented if the patient has been transfused four units of blood and intraoperative haemorrhage is ongoing. Consideration is given to low-dose factor concentrate usage (PCCs, rFVIIa) if bleeding is refractory to balanced resuscitation and algorithmic options. Figure modified from a draft version of our local massive transfusion protocol. CBC, complete blood count; Cryo, cryoprecipitate; FFP, fresh frozen plasma; Hgb, haemoglobin; RBC, red blood cell; PLT, platelet count; T & S, type and screen; PCC, prothrombin complex concentrates.

P=0.03). Although use of FFP and PC in the 1:1:1 group was higher, transfusion related complications including multiorgan failure were similar.⁴³ While evidence supports the 1:1:1 approach, it is not conclusive, and the optimal ratio of FFP:PC:RBCs is still not clear.⁴⁴⁻⁵⁰ Extension of this principle into the arenas of civilian trauma and massive surgical blood loss has been guided by local massive transfusion protocols, as illustrated in Figure 2, but high-volume transfusions are associated with complications. Without massive bleeding criteria, defined as <10 Units of packed RBCs within 12 h of admission, FFP transfusion is associated with acute lung injury (ALI).^{46,51-54} FFP is associated with a dose-dependent relationship with both transfusion associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI).^{53,55} While 1:1:1 transfusion might be appropriate for out-of-hospital resuscitation, such complications support refining these protocols when gross exsanguination has been surgically or manually controlled. Use of viscoelastic coagulation tests (e.g. ROTEM® and TEG®) offers guided coagulopathy treatment that also includes antifibrinolytic agents, cryoprecipitate and factor concentrates.^{5,56,57} In our transfusion algorithm for adult noncardiac surgery (Figure 2), initial steps include utilization of laboratory data in parallel with packed RBCs. Discussion of specific components within this algorithm is described in

separate sections in this review. Briefly, although haemoglobin targets vary depending upon patient injuries and comorbidities, a value of >8 g dl⁻¹ is targeted. Platelet concentrate, cryoprecipitate (generally for hypofibrinogenaemia but occasionally administered in patients with known von Willebrand factor or Factor XIII deficiency), and FFP are also administered. Once 4 units of packed RBCs have been transfused, attention is turned to the red box insert within the algorithm, and balanced resuscitation is performed according to blood and blood products given (i.e., Round 1, 2, 3, etc.). Of note, PC and fibrinogen are administered early in this algorithm based on laboratory data, as they are crucial to haemostasis. Fibrinogen remains the first component to reach critically low values during haemorrhage.⁵⁸ If refractory bleeding is noted in our algorithm, consideration is given to administration of factor concentrates. Viscoelastic testing has been recently advocated in severely-injured trauma patients, in order to help guide antifibrinolytic therapy in the setting of systemic, post injury hyperfibrinolysis, physiologic/normal fibrinolysis, or hypofibrinolysis/fibrinolytic shutdown.⁵⁹ The European Task Force for Advanced Bleeding in Trauma has provided a guideline document in order to manoeuvre through the expansive possibilities related to coagulopathic management in the trauma patient.⁶⁰

Chronic liver disease and orthotopic liver transplantation

Haemostatic changes seen with end-stage liver disease are complex, resulting from reduced concentrations of pro- and anti-coagulant proteins, plasmin-related qualitative platelet dysfunction from defective thromboxane A₂ synthesis, storage pool deficiency, platelet glycoprotein Ib abnormalities,^{61–63} and platelet sequestration.⁶⁴ Platelet function defects, however, are attenuated by the exaggerated concentrations of von Willebrand Factor (vWF), resulting from deficiency of the hepatically synthesized protease ADAMTS 13.⁶⁵ Relative plasminogen activator inhibitor (PAI-1 and 2) deficiency reduces t-PA clearance increasing fibrinolytic potential. Reduced thrombin activatable fibrinolysis inhibitor (TAFI) and alpha-2 antiplasmin further exacerbate this.

During surgery, with reperfusion of the donor liver, hyperfibrinolysis can occur as a result of extensive release of t-PA into the circulation. As a result, these patients can benefit from treatment with antifibrinolytic agents, while taking care to avoid hypercoagulation.^{66–69} As previously discussed, viscoelastic testing has been utilized in severely-injured trauma patients in order to help guide antifibrinolytic therapy.⁵⁹ With that said, the rationale for utilizing viscoelastic testing might not be the best approach guide to antifibrinolytic use in hepatic failure patients undergoing orthotopic liver transplantation.⁷⁰ The balance between bleeding and clotting varies, with the potential for hepatic artery or portal vein thrombosis upon reperfusion and postoperatively coexisting with severe coagulopathic bleeding, especially in the dissection phase of liver transplantation.

Cirrhosis impairs synthesis of all procoagulant factors (except factor VIII produced by endothelium) and often co-exists with vitamin K deficiency,⁷¹ as reflected by prolongation of the prothrombin time (PT), which is highly sensitive to concentrations of factor VII. Although PT and activated partial thromboplastin time (aPTT) are widely used as a monitor in cirrhotic patients, they do not reflect the overall status of pro- and anti-coagulant deficiency or excessive fibrinolysis. More current efforts to identify relevant biomarkers, focus on pro-inflammatory cytokines such as monocyte chemoattractant protein-1.⁷² Neither PT or aPTT correlate well with bleeding after surgery, liver biopsy or other potentially haemorrhagic procedures in patients with cirrhosis,^{73–76} which are better evaluated by more global tests, such as viscoelastic testing or the endogenous thrombin potential (ETP).^{77,78} Decreased concentrations of protein C, antithrombin and factor II result in only a 25% reduction in thrombin generation in cirrhotics, reflecting a steady state, with almost “matching” anticoagulant and procoagulant deficiencies.⁷⁸ This precarious balance is lost after major stress responses such as infection or blood loss, with haemodilution resulting in profound deficiencies and extreme coagulopathy. Of note, viscoelastic testing commonly demonstrates normal coagulation profiles in these settings.⁷⁹

These findings question the usefulness and safety of targeting PT correction with procoagulants such as plasma, rFVIIa or prothrombin complex concentrate (PCC).^{80–82} An ongoing multicentre, randomized, controlled trial is studying the utility of PCCs with respect to reducing allogeneic RBC transfusion, during orthotopic liver transplantation in cirrhotic patients with INR ≥ 1.5 (PROTON Trial; Netherlands Trial Register: 3174).⁸³ In our opinion, focusing on fibrinogen and platelet supplementation makes more sense in this setting.

Cirrhotics are twice as likely to suffer venous thromboembolism than the general population,⁸⁴ presumably when

anticoagulant concentrations are further depleted and procoagulant constituents predominate. Portal vein thrombosis can occur in cirrhotics with specific prothrombotic coagulation factor mutations that include factor V Leiden and prothrombin G20210A,⁸⁵ especially with commonly elevated concentrations of vWF and factor VIII.⁸⁶ Antithrombin concentrate can restore the balance between pro- and anti-coagulants through direct modulation of clot formation (Figure 1).⁸⁷ In a retrospective, observational study of laparoscopic splenectomy, 4% of cirrhotics receiving antithrombin III (ATIII) suffered portal vein thrombosis compared with 36% who did not.⁸⁸ ATIII supplementation is also considered after liver transplant, to minimize allograft thrombosis, but high quality data are limited.

Cardiopulmonary bypass and cardiac surgery

Coagulation abnormalities encountered during cardiac surgery are multifactorial and include preoperative antiplatelet agents, heparin reversal with protamine, acquired platelet dysfunction after cardiopulmonary bypass (CPB), haemodilution, and loss of clotting factors and platelets. Although off-pump cardiac surgery avoids the effects of CPB discussed below, other causes of coagulopathy still apply. CPB induces a complex pathophysiologic state, with pathophysiologic changes that are potentially similar to sepsis and a systemic inflammatory response.^{89,90} In a more severe form, coagulopathy after prolonged CPB can produce a consumptive coagulopathy, leading to clinically significant bleeding and/or thrombosis with factor consumption.⁹¹ Excessive thrombin generation and activation of tissue factor causes endothelial dysfunction (predisposing to microvascular thrombosis), with concomitant coagulopathy developing as a result of consumption of both pro- and anti-coagulant proteins (especially fibrinogen and antithrombin), deposition and loss of platelets, and potent activation of fibrinolysis.^{92,93} Laboratory findings pathognomonic for diffuse intravascular coagulation (DIC), characterized by decreased platelet counts, low fibrinogen, increased PT, PTT, and D-dimer concentrations, also commonly occur in patients after CPB.^{92,93} One important difference is that D-dimer concentrations might not be elevated after cardiac surgery because of routine administration of antifibrinolytics.⁹⁴ Acquired ATIII deficiency can occur in cardiac surgical patients as a result of multiple causes that include preoperative heparin administration, haemodilution, and consumption. Low concentrations of ATIII that range from 20% to 50% commonly occur in cardiac surgical patients associated with CPB.^{95,96} Ongoing studies are evaluating the role of ATIII supplementation during support with extracorporeal membrane oxygenation (ECMO) and in cardiac surgery.^{97,98}

Our group has developed a transfusion algorithm for cardiac surgery (Figure 3), adopted from similar concepts related to trauma-induced coagulopathy (Figure 2), while incorporating the concepts highlighted above. In our algorithmic approach, laboratory data, including viscoelastic testing with ROTEM® (assays for determination of extrinsic pathway coagulation deficiencies – EXTEM®, and determination of fibrinogen-platelet interaction - FIBTEM®), platelet count, and fibrinogen values, are obtained once rewarming is initiated on CPB. If hypofibrinogenaemia is noted and the EXTEM® Clotting Time is > 80 s, consideration is given to administration of four units of FFP during CPB, followed by administration of cryoprecipitate upon separation from CPB. Other management modalities are illustrated, and clinically important bleeding is determined along the way, in order to determine further laboratory investigation and focus administration of deficient coagulation components.

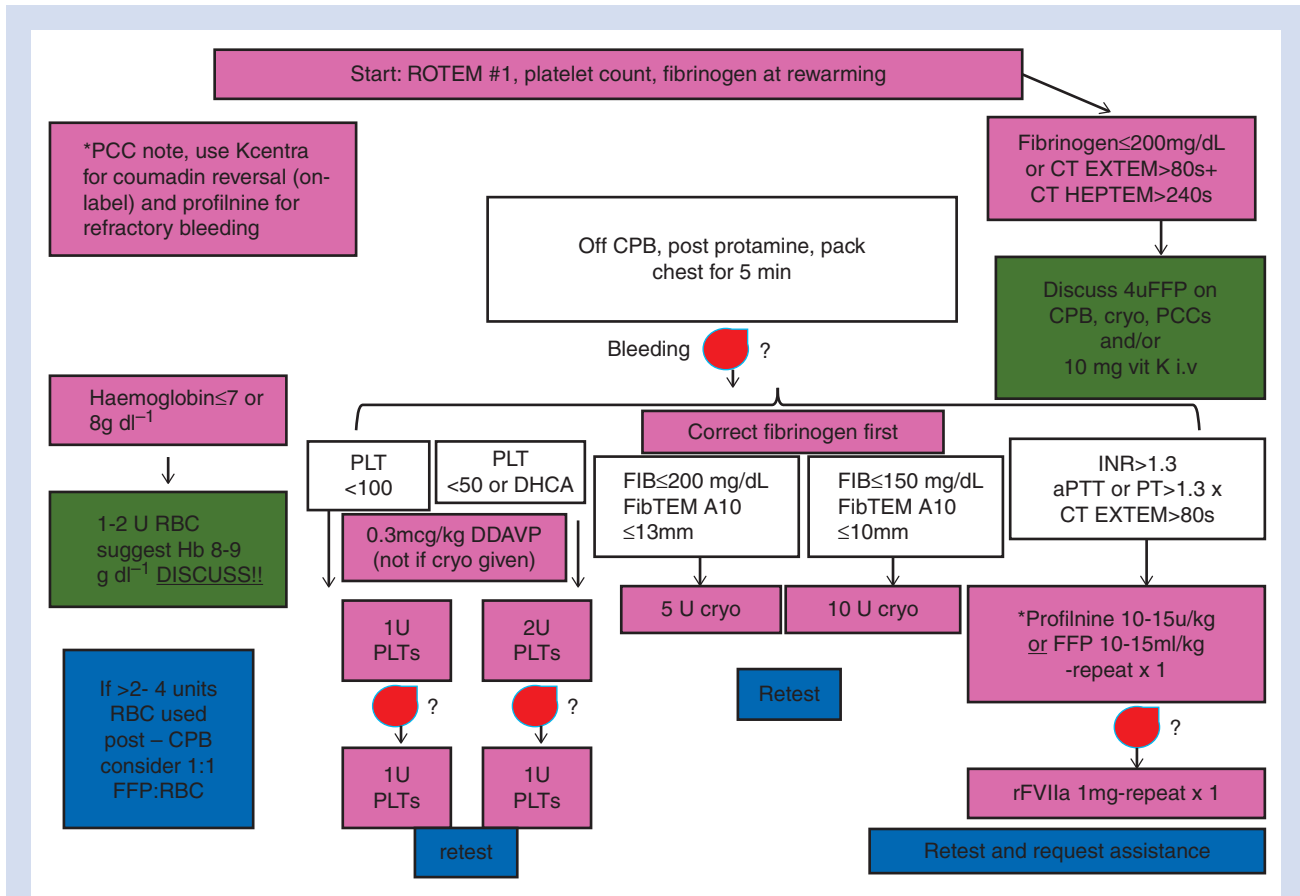


Fig 3 Transfusion Algorithm for intraoperative bleeding during cardiac surgery. In this laboratory, viscoelastic testing (ROTEM®) paradigm, samples are sent upon body temperature rewarming during CPB. Our algorithm directs the correction of hypofibrinogenemia (using the Klaus Fibrinogen assay or FibTEM® A10 values and thrombocytopenia. Patients who have undergone hypothermic circulatory arrest and the ensuing platelet dysfunction of hypothermia, receive platelet concentrate transfusion depending on platelet value during on-CPB rewarming values, when temperatures are >33 °C. Notably, because of established institutional practices, a first set of haemostasis blood samples are sent to the laboratory on CPB, and in order to account for heparin effect, HEPTEM® is sent in addition to EXTEM®. Thus, if HEPTEM® is >240 s, then it is presumed the added prolonged clotting time is as a result of additional factor deficiencies and requires FFP administration. A HEPTEM® CT <240 s indicates manufacture-established values after heparin antagonism. This value aids the practitioner in deciding on FFP administration while on CPB, in order to avoid delayed initiation of coagulation management after separation from CPB. Consideration is also made to post-CPB PCC administration, as PCC usage on CPB might be less useful owing to the larger volume of distribution and potential deposition of PCC factors onto CPB filters. With opportunities for clinical observation and laboratory values for deciding further clinical intervention, various deficiencies are managed through such blood, plasma, and factor concentrate administration. Antifibrinolytic therapy is standard practice for our cardiac surgical patients that require CPB. Notably, we have internally tested our 5U-pack of cryoprecipitate and have found fibrinogen concentration to range between 1.5-2.5 grams. We recommend a similar assessment locally within each hospital to help with best practice. *Figure modified from a draft version of our local cardiac surgery transfusion protocol.* AT III = Antithrombin III; CT = Clotting time; CPB = cardiopulmonary bypass; Cryo = Cryoprecipitate; FFP = fresh frozen plasma; FIB = Fibrinogen concentration; Hb = Haemoglobin; PCCs = Prothrombin complex concentrate; PLT = platelet count; RBC = Red blood cell; rFVIIa = Recombinant activated factor VIIa; U = unit.

Pharmacological haemostatic agents

A review of allogeneic blood products and dosing is beyond the scope of this article. Outside of the massive trauma setting, their use is guided by laboratory testing. In average adults, one unit of RBCs increases haemoglobin concentrations by ~1g dl⁻¹, one adult dose of platelets increases platelet count by ~25-35x10⁹ l⁻¹, and a typical dose of 10-20 ml kg⁻¹ plasma raises factor levels by ~10%. Cryoprecipitate is discussed separately below.

Desmopressin

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that releases vWF multimers from endothelial stores.⁹⁹ vWF is a critical protein that facilitates platelet adherence, by acting as a protein bridge between platelet glycoprotein 1b receptors and

damaged vascular subendothelium. DDAVP decreases bleeding times in mild haemophilia A or von Willebrand disease, but beyond these indications, and despite widespread perioperative use, efficacy is limited.¹⁰⁰ DDAVP is administered intravenously at doses of 0.3mcg kg⁻¹, and should be infused over 15-30min to avoid changes in bp or cardiac chronotropy.¹⁰¹ Despite 18 trials of desmopressin in 1295 patients undergoing cardiac surgery, only minimal reduction of perioperative blood loss (~115 ml) was reported.^{102,103} The benefit of administering DDAVP in these patients is unclear, especially with concomitant use of vasopressin.

Coagulation factor concentrates

Although allogeneic blood products are the basis of coagulopathy management, they require cross matching, have well

documented transfusion reactions and other risks, require blood bank management, and can be limited by availability and need for transport from the blood bank. Factor concentrates, including fibrinogen concentrates and PCCs, are evolving as a way to replace or reduce allogeneic blood product administration.^{104–106} Several factor concentrate based algorithms have been described favourably.^{107,108}

Fibrinogen

Fibrinogen is a critical haemostatic factor for the development of effective local clot in surgical patients, and for managing perioperative bleeding in cardiac surgical patients.^{106,109–111} Normal fibrinogen concentrations are 200–400 mg dl⁻¹ in the non-parturient, but can be > 400 mg dl⁻¹ during the third trimester of pregnancy. While the target fibrinogen concentration in a bleeding patient is not known, bleeding increases for each 100 mg dl⁻¹ decrease in fibrinogen concentration in parturients,¹¹² and fibrinogen concentrations decrease in proportion to increased blood loss after cardiac surgery.^{113,114} Many society guidelines suggest a transfusion trigger of 100 mg dl⁻¹ of fibrinogen, based on the threshold of 80–100 mg dl⁻¹ that begins to affect the PT or aPTT, despite the absence of *in vivo* clinical evidence for this recommendation. European guidelines have recommended targeting low normal concentrations (~200 mg dl⁻¹) since at least 2010.^{60,115} To achieve this, 3–4 g fibrinogen concentrate or 15–20 single donor units of cryoprecipitate have been recommended in the bleeding patient, ideally targeted by laboratory data.

While the exact fibrinogen content of each unit of cryoprecipitate is unknown, in a 70 kg adult, a 5-unit bag of cryoprecipitate increases fibrinogen by approximately 25–35 mg dl⁻¹.¹¹⁶ This approximate incremental increase might be reduced in the event of ongoing haemorrhage. In mainland Europe, fibrinogen concentrates are used for fibrinogen repletion as cryoprecipitate is not readily available. Fibrinogen concentrates lack other components of cryoprecipitate such as vWF and factors VIII and XIII.¹⁰⁶ In a prospective study, patients randomized to fibrinogen concentrate as a first line therapy had a significantly lower rate of any allogeneic blood product transfusions, including packed RBCs and FFP.¹¹⁷ Conversely, fibrinogen concentrate was not effective after aortic reconstruction surgery, possibly attesting to the multifactorial nature of this coagulopathy and a complexity that confounds a single agent panacea.¹¹⁸

Prothrombin complex concentrates. Prothrombin complex concentrates (PCCs) are purified coagulation factors that include procoagulant factors II, VII, IX and X and anticoagulant proteins C, S and Z in variable concentrations; minimal antithrombin and heparin are present in some preparations, as recently reviewed.⁵ The use of PCCs for the emergent or urgent vitamin K antagonist anticoagulants reversal is extensively reported in guidelines.^{105,119} Currently, there is extensive and increased use for off-label applications, include reversing direct oral anticoagulants (DOACs) such as apixiban, dabigatran, rivaroxaban, and edoxaban, and for treating refractory bleeding in surgical patients.^{108,120–122} Initially developed as a source of factor IX in haemophilia B,⁵ PCCs were used in activated form as a bypassing agent for haemophiliacs, with alloantibodies or inhibitors to purified or recombinant factor VIII (haemophilia A) or factor IX (haemophilia B). Factors VIII and IX are bypassed with activated PCCs, which enhance factor Xa production through the extrinsic tenase complex, which feeds into the prothrombinase complex and restores downstream thrombin generation (Figure 1). Of note factor VIIa was developed from activated PCCs.⁵

Recombinant activated factor VIIa. Recombinant FVIIa (rFVIIa, Novoseven®, Novo Nordisk, Denmark) is approved in most countries for treating bleeding episodes in patients with haemophilia A or B with inhibitors, congenital Factor VII deficiency, and Glanzmann's thrombasthenia who are refractory to platelet transfusions, with or without antibodies to platelets; and for treating bleeding for perioperative management in adults with acquired haemophilia. In these examples, rFVIIa is effectively used as a bypassing agent at doses of 90–120 mcg kg⁻¹ and infusions. Conversely, off-label dosing is unknown, with lower doses (~20 mcg kg⁻¹) increasingly favored,^{123,124} and rFVIIa is still included in guidelines for refractory bleeding.^{125,126* 127,128} It is important to have other coagulation substrates present for optimal efficacy of generated FXa; predictors of rFVIIa-treatment failure include evidence of coagulation substrate deficiency, haemodilution, or consumption, leading to altered laboratory measurements (INR > 2.0, platelet count < 80 × 10⁹ L⁻¹, fibrinogen < 100 mg dl⁻¹).¹²⁸ High thromboembolism rate (> 20%),¹²⁹ a complication rate of 44%,¹²⁸ and a mortality of 32%¹²⁸ are also described in retrospective evaluations of registries for refractory bleeding patients. Prospective trials report a lower incidence of thrombosis, but high rFVIIa doses increase the risk of arterial, but not venous, thromboembolic events, especially among the elderly.¹³⁰ Recent large reviews of nonsurgical, noncardiac and cardiac surgical patients, demonstrated effectiveness.¹³¹ A modest increase in thromboembolic risk was seen with both therapeutic (RR 1.21; 95% C.I. 0.93 – 1.58) and prophylactic use (RR 1.32; 95% CI 0.84 – 2.06).¹³²

The overenthusiastic initial adoption of rFVIIa was subsequently tempered by thromboembolism complications.^{130,132,133} We can apply this knowledge to PCC use in refractory bleeding by addressing substrate repletion and minimizing dosage (10–15 IU kg⁻¹; Figures 2 and 3). Failure to address platelet, fibrinogen, Factors II, VIII, IX or X deficiencies in patients with severe haemorrhage can limit the effectiveness of rFVIIa or PCC to restore thrombin generation and fibrin clot formation.⁵

Protamine

Protamine, isolated from salmon sperm, is a highly basic nuclear histone, that binds DNA to provide structural integrity. Its molecular weight is ~5000 Da with ~70% arginine residues that result in its highly basic nature. Protamine binds to the acidic heparin molecule via a simple acid-base interaction,¹³⁴ but only partially antagonizes low-molecular-weight heparin (LMWH) activity. Excess protamine should be avoided when antagonizing heparin as it can contribute to coagulopathy¹³⁵ by inhibiting factor V activation and platelet activity.¹³⁶ To better match the pharmacokinetic profile of heparin slowly released from poorly perfused tissues, such as adipose tissue after CPB (heparin rebound), a protamine infusion of 25–50 mg h⁻¹ can significantly reduce blood loss after cardiac surgery.¹³⁷ Heparin concentrations during rebound usually range from 0.1 to 0.3 IU mL⁻¹, which is at the low end of the therapeutic range. The activated clotting time (ACT) is poorly sensitive as a measure of heparin at such low concentrations.

Direct oral anticoagulants

Direct oral anticoagulants (DOACs) represent a class of orally administered factor inhibitors approved for anticoagulation in patients with venous thromboembolic disease and stroke prevention in patients with nonvalvular atrial fibrillation. As the prevalence of patients taking DOACs continues to increase, so

does the importance of understanding how to best antagonize the anticoagulant effect of these agents. Although the reader is directed elsewhere for review of approaches to management of bleeding in these patients,¹³⁸ general efforts using PCCs or aPCCs remain unproved with unknown dosing regimens. Additionally, specific antidotes are currently available or under development, as follows.

Specific antidotes for direct oral anticoagulants

Recently, idarucizumab (Praxbind™, Boehringer Ingelheim, Germany) was approved for antagonism of dabigatran, a direct thrombin inhibitor (DTI) within the class of the direct oral anticoagulants (DOACs). Concentrations of unbound dabigatran remained low at 24 h in 79% of the patients, and for most operative normal haemostasis was restored. One thrombotic event occurred within 72 h after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.¹³⁹

Factor Xa inhibitors are another subclass of DOACs without an approved antagonism agent. Andexanet alfa (Portola Pharmaceuticals, South San Francisco, California, USA) is a modified, recombinant derivative of Factor Xa with the serine on the FXa-active site mutated to alanine, inactivating the serine protease activity and thus removing its ability to cleave prothrombin to thrombin.^{140,141} The membrane-binding domain of plasma-derived Factor X has also been deleted, precluding inclusion of andexanet into the prothrombinase complex. This “decoy molecule” sequesters FXa inhibitors, rapidly reducing free plasma concentration and neutralization anticoagulant effect. Andexanet alfa binds to antithrombin complexed with LMWH, fondaparinux, rivaroxaban, apixaban and edoxaban. The short half-life of andexanet alfa relative to FXa inhibitors can be insufficient to correct coagulopathy, particularly in the setting of renal dysfunction or older age,¹⁴² although interim reports from a clinical trial are encouraging.¹⁴³ Other antagonism agents in development include PER977.¹⁴⁴ But antagonism of anticoagulation incurs a thrombosis risk that will have to be balanced with bleeding and will likely need to be addressed once haemostasis is achieved.¹⁴¹ Despite the potential for these specific antagonism agents, a multimodal approach to coagulation management is needed during management of bleeding related to DOACs, which might necessitate coagulation factor concentrate administration.

Antiplatelet agents: aspirin and thienopyridine derivatives

Aspirin is used extensively for the secondary prevention of atherothrombotic disease that includes occlusive coronary artery and peripheral arterial disease, and cerebrovascular thromboembolism.¹⁴⁵ Although aspirin has the potential to increase blood loss after major surgery, this probably does not result in increased needs for transfusions and should always be considered for risk vs benefit effects.¹⁴⁶ As such aspirin should not be discontinued preoperatively except before neurosurgery procedures. Antagonism of aspirin is rarely necessary 48 h after the last dose and can be achieved by DDAVP¹⁴⁷ or platelet transfusion.

Clopidogrel (Plavix), prasugrel (Efient, Effient), ticagrelor (Brilinta), and cangrelor (Kengreal) belong to the class of thienopyridine derivatives that act by blocking the adenosine diphosphate (ADP) P₂Y₁₂ receptor on platelets. Dual antiplatelet therapy with aspirin and clopidogrel is a current standard of care after percutaneous coronary intervention (PCI), however

this combination is associated with an increased bleeding risk.¹⁴⁸ Prasugrel and ticagrelor have stronger antiplatelet effect than clopidogrel because of more effective metabolism and less dependence on cytochrome P450 enzymes subject to genetic polymorphisms.¹⁴⁹

The decision whether or not to interrupt or even antagonize antithrombotic therapy with dual platelet inhibition requires careful thrombotic risk and haemostatic benefit evaluation, especially in patients with recent drug-eluting stent rather than bare-metal stent implantation. Administration of platelet concentrates (~2 units) can correct the haemostatic defect after antiplatelet drugs have been stopped for 12–24 h (free drug can inhibit transfused platelets).^{150,151} Ideally, aspirin is restarted 6 h and P₂Y₁₂ receptor blockade is restarted 12–48 h after surgery. When continued P₂Y₁₂ receptor blockade is desirable, cangrelor infusion can serve as a bridge to surgery.¹⁵² In the actively bleeding patient, testing for platelet dysfunction has been thought to be unreliable as most tests require a relatively normal platelet count and most of the platelet function testing might not work well after the dilutional changes and activation after CPB.¹² However, a recent prospective observational study, illustrated that preoperative ADP-induced platelet aggregability predicted the risk for severe bleeding in cardiac surgical patients treated with preoperative ticagrelor.¹⁵³

Transfusion algorithms and bleeding

Transfusion algorithms represent one of the most important strategies to reduce excess transfusion, and all components of coagulation management outlined in our review have been included in the algorithms presented. Developing a specific therapeutic plan through use of transfusion algorithms has been shown to consistently reduce allogeneic blood administration.¹⁰⁷ It is important to realize that any laboratory testing that discourages empirical blood product administration, is important as part of a multimodal approach to blood conservation and reduction of allogeneic blood product use, while realizing that laboratory values can lag behind the clinical scenario, if blood loss remains rapid.^{37,154} Transfusion algorithms generally recommend administration of plasma when bleeding is accompanied by PT or aPTT > 1.5 times normal, platelet transfusions for thrombocytopenia with a platelet count < 50,000–100,000, or cryoprecipitate or fibrinogen concentrate when fibrinogen concentrations are < 200 mg dl⁻¹ (2 g l⁻¹).¹⁵⁵ The critical role of fibrinogen continues to evolve with most data suggesting the importance of normalizing fibrinogen in bleeding patients. With critical bleeds, and turn over time in standard laboratory testing, point-of-care testing, including rotational thromboelastometry (ROTEM®), thromboelastography (TEG®) and/or platelet function testing, are important.¹⁵⁵ In the actively bleeding patient, testing for platelet dysfunction is unreliable, as most tests need a relatively normal platelet count.¹² With these capabilities and limitations in mind, we have developed transfusion algorithms for both noncardiac (Figure 2) and cardiac (Figure 3) surgical patients in order to guide perioperative management of coagulopathy.

Conclusions

The potential for haemorrhage in trauma and surgical patients represents an ongoing concern for management. Anticoagulation monitoring using point-of-care testing, optimal use of transfusion therapies, adjunct administration of antifibrinolytics and purified and recombinant concentrates, provide

clinicians with the ability to administer vital coagulation therapies to treat haemorrhage. Other key considerations include management of hypofibrinogenaemia, thrombocytopenia and platelet disorders, topical haemostasis, excluding surgical sources of bleeding, and temperature regulation. The integration of the optimal use of pharmacologic agents, allogeneic transfusion, and factor concentrates into a comprehensive perioperative coagulation treatment algorithm for bleeding, is an important therapeutic approach for the management of bleeding in surgical patients.

Authors' contributions

Study conduct: K.G., I.J.W.

Data analysis: K.G., J.H.L., I.J.W.

Writing paper: K.G., J.H.L., I.J.W.

Revising paper: all authors

Declaration of interest

K.G. is a co-investigator in a prospective, open-label study of Andexanet-Alfa in patients receiving Factor Xa inhibitors with acute major bleeding, sponsored by Portola Pharmaceuticals.

J.H.L. serves on steering committees for Boehringer-Ingelheim, CSL Behring, Grifols, and Janssen; consultant to Instrumentation Laboratories and Pfizer.

I.J.W. is the Principal Investigator in a prospective, open-label study of Andexanet Alfa in patients receiving Factor Xa inhibitors with acute major bleeding, sponsored by Portola Pharmaceuticals and has recently received grant support from CSL Behring and Terumo BCT.

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References

1. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. *Anesth Analg* 2011; **113**: 1319–33
2. Despotis GJ, Avidan MS, Hogue CW. Jr., Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. *Ann Thorac Surg* 2001; **72**: S1821–31
3. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost* 2010; **8**: 2063–5
4. Achneck HE, Sileshi B, Jamiolkowski RM, Albala DM, Shapiro ML, Lawson JH. A comprehensive review of topical hemostatic agents: efficacy and recommendations for use. *Ann Surg* 2010; **251**: 217–28
5. Ghadimi K, Levy JH, Welsby IJ. Prothrombin Complex Concentrates for Bleeding in the Perioperative Setting. *Anesth Analg* 2016; **122**: 1287–300
6. Gutsche JT, Ghadimi K, Patel PA, et al. New frontiers in aortic therapy: focus on deep hypothermic circulatory arrest. *J Cardiothorac Vasc Anesth* 2014; **28**: 1159–63
7. Danzl DF, Pozos RS, Auerbach PS, et al. Multicenter hypothermia survey. *Ann Emerg Med* 1987; **16**: 1042–55
8. Jurkovich GJ, Greiser WB, Luterman A, Curreri PW. Hypothermia in trauma victims: an ominous predictor of survival. *J Trauma* 1987; **27**: 1019–24
9. Peng RY, Bongard FS. Hypothermia in trauma patients. *J Am Coll Surg* 1999; **188**: 685–96
10. Martini WZ. Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. *J Trauma* 2009; **67**: 202–8. discussion 8–9
11. Wolberg AS, Meng ZH, Monroe DM, 3rd, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma* 2004; **56**: 1221–8
12. Le Quellec S, Bordet JC, Negrier C, Dargaud Y. Comparison of current platelet functional tests for the assessment of aspirin and clopidogrel response. A review of the literature. *Thromb Haemost* 2016; **116**: 638–50
13. Ghadimi K, Gutsche JT, Ramakrishna H, et al. Sodium bicarbonate use and the risk of hypernatremia in thoracic aortic surgical patients with metabolic acidosis following deep hypothermic circulatory arrest. *Ann Card Anaesth* 2016; **19**: 454–62
14. Ghadimi K, Gutsche JT, Setegne SL, et al. Severity and Duration of Metabolic Acidosis After Deep Hypothermic Circulatory Arrest for Thoracic Aortic Surgery. *J Cardiothorac Vasc Anesth* 2015; **29**: 1432–40
15. Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. *Br J Haematol* 2005; **129**: 307–21
16. Wada Y, Uchiba M, Kawano Y, et al. Severe bleeding tendency caused by a rare complication of excessive fibrinolysis with disseminated intravascular coagulation in a 51-year-old Japanese man with prostate cancer: a case report. *J Med Case Rep* 2012; **6**: 378
17. Levy JH. Antifibrinolytic therapy: new data and new concepts. *Lancet* 2010; **376**: 3–4
18. Tran HT, Sorensen B, Rea CJ, et al. Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. *Haemophilia* 2014; **20**: 369–75
19. Collaborators C-T, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32
20. Bennett C, Klingenberg SL, Langholz E, Gluud LL. Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2014; CD006640
21. Roberts I, Coats T, Edwards P, et al. HALT-IT—tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014; **15**: 450
22. Shakur H, Roberts I, Edwards P, Elbourne D, Alfirevic Z, Ronsmans C. The effect of tranexamic acid on the risk of death and hysterectomy in women with post-partum haemorrhage: statistical analysis plan for the WOMAN trial. *Trials* 2016; **17**: 249
23. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358**: 2319–31
24. Katz D, Beilin Y. Disorders of coagulation in pregnancy. *Br J Anaesth* 2015; **115** Suppl 2: ii75–88
25. Pavord S, Maybury H. How I treat postpartum hemorrhage. *Blood* 2015; **125**: 2759–70
26. Koster A, Faraoni D, Levy JH. Antifibrinolytic Therapy for Cardiac Surgery: An Update. *Anesthesiology* 2015; **123**: 214–21
27. Estcourt LJ, Desborough M, Brunskill SJ, et al. Antifibrinolytics (lysine analogues) for the prevention of bleeding in people with haematological disorders. *Cochrane Database Syst Rev* 2016; **3**: CD009733

28. Levy JH. Hemostatic agents. *Transfusion* 2004; **44**: 58S–62S
29. Levi MM, Vink R, de Jonge E. Management of bleeding disorders by prohemostatic therapy. *Int J Hematol* 2002; **76 Suppl 2**: 139–44
30. Levi M, Cromheecke ME, de Jonge E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; **354**: 1940–7
31. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth Analg* 2010; **110**: 350–3
32. Kratzer S, Irl H, Mattusch C, et al. Tranexamic acid impairs gamma-aminobutyric acid receptor type A-mediated synaptic transmission in the murine amygdala: a potential mechanism for drug-induced seizures?. *Anesthesiology* 2014; **120**: 639–49
33. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest* 2012; **122**: 4654–66
34. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. *Curr Opin Crit Care* 2007; **13**: 680–5
35. Doury P, Pattin S, Eulry F, Maurel C, Masson C, Tabaraud F. [Treatment of Horton's disease and rhizomelic pseudopolyarthritides with dapsone. Preliminary results]. *Presse Med* 1983; **12**: 104
36. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma* 1995; **38**: 185–93
37. British Committee For Standards In H, Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; **135**: 634–41
38. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 2007; **63**: 805–13
39. Holcomb JB, Zarzabal LA, Michalek JE, et al. Increased platelet:RBC ratios are associated with improved survival after massive transfusion. *J Trauma* 2011; **71**: S318–28
40. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma* 2009; **66**: 41–8. discussion 8–9
41. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg* 2008; **248**: 447–58
42. Cotton BA, Gunter OL, Isbell J, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma* 2008; **64**: 1177–82; discussion 82–3
43. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *Jama* 2015; **313**: 471–82
44. Ho AM, Dion PW, Yeung JH, et al. Prevalence of survivor bias in observational studies on fresh frozen plasma: erythrocyte ratios in trauma requiring massive transfusion. *Anesthesiology* 2012; **116**: 716–28
45. Allen SR, Kashuk JL. Unanswered questions in the use of blood component therapy in trauma. *Scand J Trauma Resusc Emerg Med* 2011; **19**: 5
46. Murad MH, Stubbs JR, Gandhi MJ, et al. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. *Transfusion* 2010; **50**: 1370–83
47. Mitra B, Mori A, Cameron PA, Fitzgerald M, Paul E, Street A. Fresh frozen plasma (FFP) use during massive blood transfusion in trauma resuscitation. *Injury* 2010; **41**: 35–9
48. Stansbury LG, Dutton RP, Stein DM, Bochicchio GV, Scalea TM, Hess JR. Controversy in trauma resuscitation: do ratios of plasma to red blood cells matter?. *Transfus Med Rev* 2009; **23**: 255–65
49. Zehtabchi S, Nishijima DK. Impact of transfusion of fresh-frozen plasma and packed red blood cells in a 1:1 ratio on survival of emergency department patients with severe trauma. *Acad Emerg Med* 2009; **16**: 371–8
50. Scalea TM, Bochicchio KM, Lumpkins K, et al. Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. *Ann Surg* 2008; **248**: 578–84
51. Inaba K, Branco BC, Rhee P, et al. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg* 2010; **210**: 957–65
52. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma* 2009; **67**: 221–7. discussion 8–30
53. Chaiwat O, Lang JD, Vavilala MS, et al. Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. *Anesthesiology* 2009; **110**: 351–60
54. Dara SI, Rana R, Afessa B, Moore SB, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. *Crit Care Med* 2005; **33**: 2667–71
55. Edens JW, Chung KK, Pamplin JC, et al. Predictors of early acute lung injury at a combat support hospital: a prospective observational study. *J Trauma* 2010; **69 Suppl 1**: S81–6
56. Woolley T, Midwinter M, Spencer P, Watts S, Doran C, Kirkman E. Utility of interim ROTEM((R)) values of clot strength, A5 and A10, in predicting final assessment of coagulation status in severely injured battle patients. *Injury* 2013; **44**: 593–9
57. Schochl H, Maegele M, Solomon C, Grolinger K, Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. *Scand J Trauma Resusc Emerg Med* 2012; **20**: 15
58. Levy JH, Szlam F, Tanaka KA, Sniecinski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg* 2012; **114**: 261–74
59. Moore EE, Moore HB, Gonzalez E, Sauaia A, Banerjee A, Silliman CC. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. *Transfusion* 2016; **56 Suppl 2**: S110–4
60. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013; **17**: R76
61. Ordinas A, Escolar G, Cirera I, et al. Existence of a platelet-adhesion defect in patients with cirrhosis independent of hematocrit: studies under flow conditions. *Hepatology* 1996; **24**: 1137–42
62. Rubin MH, Weston MJ, Langley PG, White Y, Williams R. Platelet function in chronic liver disease: relationship to disease severity. *Dig Dis Sci* 1979; **24**: 197–202
63. Thomas DP, Ream VJ, Stuart RK. Platelet aggregation in patients with Laennec's cirrhosis of the liver. *N Engl J Med* 1967; **276**: 1344–8

64. Peck-Radosavljevic M. Thrombocytopenia in liver disease. *Can J Gastroenterol* 2000; **14 Suppl D**: 60D–6D
65. Hugenholtz GC, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT, Lisman T. An unbalance between von Willebrand factor and ADAMTS13 in acute liver failure: implications for hemostasis and clinical outcome. *Hepatology* 2013; **58**: 752–61
66. Porte RJ, Bontempo FA, Knot EA, Lewis JH, Kang YG, Starzl TE. Systemic effects of tissue plasminogen activator-associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. *Transplantation* 1989; **47**: 978–84
67. Lewis JH, Bontempo FA, Awad SA, et al. Liver transplantation: intraoperative changes in coagulation factors in 100 first transplants. *Hepatology* 1989; **9**: 710–4
68. Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans: role of tissue-type plasminogen activator. *Blood* 1988; **71**: 1090–5
69. Kang Y, Lewis JH, Navalgund A, et al. Epsilon-aminocaproic acid for treatment of fibrinolysis during liver transplantation. *Anesthesiology* 1987; **66**: 766–73
70. Nicolau-Raducu R, Ku TC, Ganier DR, et al. Epsilon-Aminocaproic Acid Has No Association With Thromboembolic Complications, Renal Failure, or Mortality After Liver Transplantation. *J Cardiothorac Vasc Anesth* 2016; **30**: 917–23
71. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011; **365**: 147–56
72. Graupera I, Sola E, Fabrellas N, et al. Urine Monocyte Chemoattractant Protein-1 Is an Independent Predictive Factor of Hospital Readmission and Survival in Cirrhosis. *PLoS One* 2016; **11**: e0157371
73. Segal JB, Dzik WH. Transfusion Medicine/Hemostasis Clinical Trials N. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005; **45**: 1413–25
74. Grabau CM, Crago SF, Hoff LK, et al. Performance standards for therapeutic abdominal paracentesis. *Hepatology* 2004; **40**: 484–8
75. Terjung B, Lemnitzer I, Dumoulin FL, et al. Bleeding complications after percutaneous liver biopsy. An analysis of risk factors. *Digestion* 2003; **67**: 138–45
76. Diaz LK, Teruya J. Liver biopsy. *N Engl J Med* 2001; **344**: 2030
77. Hemker HC, Giesen P, Al Dieri R, et al. Calibrated automated thrombin generation measurement in clotting plasma. *Pathophysiol Haemost Thromb* 2003; **33**: 4–15
78. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 2005; **41**: 553–8
79. Stravitz RT, Lisman T, Luketic VA, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *J Hepatol* 2012; **56**: 129–36
80. Lodge JP, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005; **11**: 973–9
81. Planinsic RM, van der Meer J, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl* 2005; **11**: 895–900
82. Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004; **127**: 1123–30
83. Arshad F, Ickx B, van Beem RT, et al. Prothrombin complex concentrate in the reduction of blood loss during orthotopic liver transplantation: PROTON-trial. *BMC Surg* 2013; **13**: 22
84. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol* 2009; **104**: 96–101
85. Sobhonslidsuk A, Reddy KR. Portal vein thrombosis: a concise review. *Am J Gastroenterol* 2002; **97**: 535–41
86. Hollestelle MJ, Geertzen HG, Straatsburg IH, van Gulik TM, van Mourik JA. Factor VIII expression in liver disease. *Thromb Haemost* 2004; **91**: 267–75
87. Liumbruno G, Bennardello F, Lattanzio A, et al. Recommendations for the use of antithrombin concentrates and prothrombin complex concentrates. *Blood Transfus* 2009; **7**: 325–34
88. Kawanaka H, Akahoshi T, Kinjo N, et al. Impact of antithrombin III concentrates on portal vein thrombosis after splenectomy in patients with liver cirrhosis and hypersplenism. *Ann Surg* 2010; **251**: 76–83
89. Kinet JP. The high-affinity receptor for IgE. *Curr Opin Immunol* 1989; **2**: 499–505
90. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest* 1997; **112**: 676–92
91. Thachil J. Disseminated intravascular coagulation - new pathophysiological concepts and impact on management. *Expert Rev Hematol* 2016; **9**: 803–14
92. Edmunds LH, Jr., Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg* 1998; **66**: S12–6. discussion S25–8
93. Vincent JL, Sun Q, Dubois MJ. Clinical trials of immunomodulatory therapies in severe sepsis and septic shock. *Clin Infect Dis* 2002; **34**: 1084–93
94. Faraoni D, Willems A, Melot C, De Hert S, Van der Linden P. Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2012; **42**: 781–6
95. Kalter RD, Saul CM, Wetstein L, Soriano C, Reiss RF. Cardiopulmonary bypass. Associated hemostatic abnormalities. *J Thorac Cardiovasc Surg* 1979; **77**: 427–35
96. Zaidan JR, Johnson S, Brynes R, Monroe S, Guffin AV. Rate of protamine administration: its effect on heparin reversal and antithrombin recovery after coronary artery surgery. *Anesth Analg* 1986; **65**: 377–80
97. Levy JH, Sniecinski RM, Welsby IJ, Levi M. Antithrombin: anti-inflammatory properties and clinical applications. *Thromb Haemost* 2016; **115**: 712–28
98. Niebler RA, Christensen M, Berens R, Wellner H, Mikhailov T, Tweddell JS. Antithrombin replacement during extracorporeal membrane oxygenation. *Artif Organs* 2011; **35**: 1024–8
99. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90**: 2515–21
100. Mannucci PM. Treatment of von Willebrand's Disease. *N Engl J Med* 2004; **351**: 683–94
101. de Prost D, Barbier-Boehm G, Hazebroucq J, et al. Desmopressin has no beneficial effect on excessive postoperative bleeding or blood product requirements associated with cardiopulmonary bypass. *Thromb Haemost* 1992; **68**: 106–10
102. Mannucci PM, Levi M. Prevention and treatment of major blood loss. *N Engl J Med* 2007; **356**: 2301–11

103. Cattaneo M, Harris AS, Stromberg U, Mannucci PM. The effect of desmopressin on reducing blood loss in cardiac surgery—a meta-analysis of double-blind, placebo-controlled trials. *Thromb Haemost* 1995; **74**: 1064–70
104. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. *Transfusion* 2014; **54**: 1389–405; quiz 8
105. Grottke O, Levy JH. Prothrombin complex concentrates in trauma and perioperative bleeding. *Anesthesiology* 2015; **122**: 923–31
106. Levy JH, Goodnough LT. How I use fibrinogen replacement therapy in acquired bleeding. *Blood* 2015; **125**: 1387–93
107. Gorlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology* 2011; **115**: 1179–91
108. Weber CF, Gorlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology* 2012; **117**: 531–47
109. Nielsen VG, Levy JH. Fibrinogen and bleeding: old molecule-new ideas. *Anesth Analg* 2007; **105**: 902–3
110. Levy JH. Massive transfusion coagulopathy. *Semin Hematol* 2006; **43**: S59–63
111. Blome M, Isgro F, Kiessling AH, et al. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. *Thromb Haemost* 2005; **93**: 1101–7
112. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 2007; **5**: 266–73
113. Karlsson M, Ternstrom L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost* 2009; **102**: 137–44
114. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. *Transfusion* 2008; **48**: 2152–8
115. Rossaint R, Bouillon B, Cerny V, et al. Management of bleeding following major trauma: an updated European guideline. *Crit Care* 2010; **14**: R52
116. Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. *Br J Anaesth* 2014; **113**: 922–34
117. Ranucci M, Baryshnikova E, Crapelli GB, et al. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. *J Am Heart Assoc* 2015; **4**: e002066
118. Rahe-Meyer N, Levy JH, Mazer CD, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. *Br J Anaesth* 2016; **117**: 41–51
119. Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. *Anesthesiology* 2008; **109**: 918–26
120. Levy JH, Spyropoulos AC, Samama CM, Douketis J. Direct oral anticoagulants: new drugs and new concepts. *JACC Cardiovasc Interv* 2014; **7**: 1333–51
121. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation* 2015; **131**: 82–90
122. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost* 2014; **12**: 1428–36
123. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009; **120**: 21–7
124. Andersen ND, Bhattacharya SD, Williams JB, et al. Intraoperative use of low-dose recombinant activated factor VII during thoracic aortic operations. *Ann Thorac Surg* 2012; **93**: 1921–8. discussion 8-9
125. Despotis G, Avidan M, Lublin DM. Off-label use of recombinant factor VIIa concentrates after cardiac surgery. *Ann Thorac Surg* 2005; **80**: 3–5
126. Goodnough LT, Lublin DM, Zhang L, Despotis G, Eby C. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; **44**: 1325–31
127. Hacquard M, Durand M, Lecompte T, Boini S, Briancon S, Carteaux JP. Off-label use of recombinant activated factor VII in intractable haemorrhage after cardiovascular surgery: an observational study of practices in 23 French cardiac centres (2005-7). *Eur J Cardiothorac Surg* 2011; **40**: 1320–7
128. Karkouti K, Beattie WS, Arellano R, et al. Comprehensive Canadian review of the off-label use of recombinant activated factor VII in cardiac surgery. *Circulation* 2008; **118**: 331–8
129. Lee AI, Campigotto F, Rawn JD, Neuberger D, Kaufman RM, Berliner N. Clinical significance of coagulation studies in predicting response to activated recombinant Factor VII in cardiac surgery patients. *Br J Haematol* 2012; **157**: 397–400
130. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010; **363**: 1791–800
131. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev* 2012; CD005011
132. Sultan A, Abidi S, Hellman Y, Hadi A, Wang I, Malik A. Higher incidence of thromboembolic events with the use of recombinant activated factor VII during placement of left ventricular assist device. *J Am Coll Cardiol* 2014; **63**(12_S): doi:10.1016/S0735-1097(14)60864-0
133. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; **295**: 293–8
134. Levy JH, Adkinson NF. Jr., Anaphylaxis during cardiac surgery: implications for clinicians. *Anesth Analg* 2008; **106**: 392–403
135. Mochizuki T, Olson PJ, Szlam F, Ramsay JG, Levy JH. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. *Anesth Analg* 1998; **87**: 781–5
136. Ni Ainle F, Preston RJ, Jenkins PV, et al. Protamine sulfate down-regulates thrombin generation by inhibiting factor V activation. *Blood* 2009; **114**: 1658–65
137. Teoh KH, Young E, Blackall MH, Roberts RS, Hirsh J. Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery?. *J Thorac Cardiovasc Surg* 2004; **128**: 211–9

138. Levy JH, Faraoni D, Spring JL, Douketis JD, Samama CM. Managing new oral anticoagulants in the perioperative and intensive care unit setting. *Anesthesiology* 2013; **118**: 1466–74
139. Pollack CV, Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med* 2015; **373**: 511–20
140. Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013; **19**: 446–51
141. Ghadimi K, Dombrowski KE, Levy JH, Welsby IJ. Andexanet alfa for the reversal of Factor Xa inhibitor related anticoagulation. *Expert Rev Hematol* 2016; **9**: 115–22
142. Lohrmann GM, Atwal D, Augoustides JG, et al. Reversal Agents for the New Generation of Oral Anticoagulants: Implications for the Perioperative Physician. *J Cardiothorac Vasc Anesth* 2016; **30**: 823–30
143. Connolly SJ, Milling TJ, Jr., Eikelboom JW, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med* 2016; **375**: 1131–41
144. Ansell JE, Bakhrui SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014; **371**: 2141–2
145. Patrono C, Baigent C, Hirsh J, Roth G. American College of Chest P. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 199S–233S
146. Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. *J Thromb Thrombolysis* 2004; **17**: 21–7
147. Reiter RA, Mayr F, Blazicek H, et al. Desmopressin antagonizes the in vitro platelet dysfunction induced by GPIIb/IIIa inhibitors and aspirin. *Blood* 2003; **102**: 4594–9
148. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502
149. Bhatt DL. Prasugrel in clinical practice. *N Engl J Med* 2009; **361**: 940–2
150. Vilahur G, Choi BG, Zafar MU, et al. Normalization of platelet reactivity in clopidogrel-treated subjects. *J Thromb Haemost* 2007; **5**: 82–90
151. Thiele T, Sumnig A, Hron G, et al. Platelet transfusion for reversal of dual antiplatelet therapy in patients requiring urgent surgery: a pilot study. *J Thromb Haemost* 2012; **10**: 968–71
152. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *Jama* 2012; **307**: 265–74
153. Malm CJ, Hansson EC, Akesson J, et al. Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study. *Br J Anaesth* 2016; **117**: 309–15
154. Despotis GJ, Grishaber JE, Goodnough LT. The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. *Transfusion* 1994; **34**: 290–6
155. Steiner ME, Despotis GJ. Transfusion algorithms and how they apply to blood conservation: the high-risk cardiac surgical patient. *Hematol Oncol Clin North Am* 2007; **21**: 177–84

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