Management of bleeding in vascular surgery

Y. E. Chee*, S. E. Liu and M. G. Irwin

Department of Anesthesia, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong

*Corresponding author. E-mail: yeeeot@gmail.com

Abstract

Management of acute coagulopathy and blood loss during major vascular procedures poses a significant haemostatic challenge to anaesthetists. The acute coagulopathy is multifactorial in origin with tissue injury and hypotension as the precipitating factors, followed by dilution, hypothermia, acidemia, hyperfibrinolysis and systemic inflammatory response, all acting as a self-perpetuating spiral of events. The problem is confounded by the high prevalence of antithrombotic agent use in these patients and intraoperative heparin administration. Trials specifically examining bleeding management in vascular surgery are lacking, and much of the literature and guidelines are derived from studies on patients with trauma. In general, it is recommended to adopt permissive hypotension with a restrictive fluid strategy, using a combination of crystalloid and colloid solutions up to one litre during the initial resuscitation, after which blood products should be administered. A restrictive transfusion trigger for red cells remains the mainstay of treatment except for the high-risk patients, where the trigger should be individualized. Transfusion of blood components should be initiated by clinical evidence of coagulopathy such as diffuse microvascular bleeding, and then guided by either laboratory or point-of-care coagulation testing. Prophylactic antifibrinolytic use is recommended for all surgery where excessive bleeding is anticipated. Fibrinogen and prothrombin complex concentrates administration are recommended during massive transfusion, whereas rFVIIa should be reserved until all means have failed. While debates over the ideal resuscitative strategy continue, the approach to vascular haemostasis should be scientific, rational, and structured. As far as possible, therapy should be monitored and goal directed.

Key words: acute coagulopathy; bleeding management; vascular surgery

Editor’s key points

• Much of the evidence on the management of major bleeding comes from studies conducted in trauma patients.
• Blood and FFP and platelets should be administered early in major bleeding.
• The use of fibrinogen concentrate is recommended in major bleeding where low circulating concentrations of fibrinogen have been demonstrated or are suspected.
• Data from the IMPROVE trial suggest that aggressive permissive hypotension (SAP<70 mm Hg) may be associated with worse outcome.

Acute coagulopathy with significant blood loss is frequent in major vascular procedures. The problem is confounded by the high prevalence of antithrombotic agent use among patients undergoing vascular surgical procedures and intraoperative heparin administration. The management of perioperative bleeding is constantly evolving with ongoing debate over several contentious issues such as optimal transfusion and fluid management strategies. Much of the existing evidence and guidelines are derived from studies on patients with trauma. This article aims to review the management of bleeding in vascular surgery. The approach to vascular haemostasis should be scientific, rational, and...
structured. As far as possible, therapy should be monitored and goal directed.

**Pre-existing and acquired coagulopathy**

Patients with vascular disease often pose complex haemostatic challenges. They are usually elderly with cardiovascular comorbidities, are frequently taking antiplatelet or antithrombotic agents including oral anticoagulants (NOACs), may have platelet dysfunction secondary to renal impairment, and often receive intraoperative heparin. Many, therefore, have pre-existing coagulopathy.

Acute coagulopathy acquired in vascular procedures has not been well studied. In a pooled analysis of seven studies of patients with ruptured abdominal aortic aneurysms the prevalence of coagulopathy at presentation was 12.5%, but serum fibrinogen was normal in most (97%) of them. This contrasts with acute trauma coagulopathy (ATC) where one in four patients after major trauma had coagulopathy before resuscitation and this was associated with a four-fold increase in mortality. ATC is usually multifactorial in origin with tissue injury and hypothermia as the initial triggering factors, followed by dilutional coagulopathy, hypothermia, acidemia, hyperfibrinolysis and systemic inflammatory response syndrome (SIRS), producing a spiral of events that are self-perpetuating. Recognition of ATC as an intrinsic phenomenon has prompted the concept of early haemostatic treatment. Acute coagulopathy in vascular surgery may share similar pathophysiology. The severity of shock or tissue hypoperfusion correlates with coagulopathy. In the absence of shock, patients often have a normal coagulation profile. How shock leads to coagulopathy remains unclear. Tissue injury activates both cellular and humoral elements of the immune system. Activation of coagulation proteases triggers complement release, platelet degranulation releases phospholipid mediators, widespread endothelial disruption, increased thrombomodulin activity, and Protein C activation, and these have all been implicated.

The dilution of coagulation factors is now recognized as a major cause of acute coagulopathy. Reduced intravascular hydrostatic pressure during shock causes fluid shift into the intravascular space and dilution. This is exacerbated by crystalloidal use during resuscitation and more red cell (RBC) transfusion. Hypothermia inhibits coagulation protease activity and platelet function. Platelet activation is mediated through glycoprotein Ib/IX. At low temperature, effect of von Willebrand factor (vWF) on the glycoprotein is depressed. The activity of FVIIa and platelets are all retarded. A decrease in pH from 7.4 to 7.0 reduces the production of thrombin and the activity of clotting factors and coagulation factor complexes and cell surface interactions.

Acidosis occurs as a result of tissue hypoperfusion and excess chloride administration. It impairs plasma protease activities and coagulation factor complexes and cell surface interactions. The production of thrombin and the activity of clotting factors are all retarded. A decrease in pH from 7.4 to 7.0 reduces the activity of factor VIIa by 90%, factor VIIa/tissue factor complex formation by 55% and factor Xa/Va complex formation by 70%. Administration of buffer solution does not seem to correct this coagulopathy. Other key changes in acute coagulopathy are reduction in thrombin generation, fibrinogen depletion and impaired fibrin formation. A reduced serum fibrinogen concentration to unstable clots is associated with increased transfusion requirement and mortality in patients with trauma. Rapid restoration of serum fibrinogen has been shown to reduce transfusion and mortality. Certain synthetic colloids with high molecular weight such as older generation hydroxyethyl starches, are large molecules that are difficult to be broken down. These high molecular weight colloids, although seldom used nowadays, can interfere with clot formation. Hyperfibrinolysis is common after endothelial injury and release of tissue plasminogen activator, has also been shown to play an important role in acquired coagulopathy.

**Perioperative management of antiplatelet and anticoagulant drugs**

Drugs used for thromboembolic prophylaxis increase patients’ risk of bleeding. The decision to discontinue such therapy before vascular surgery is a dilemma between the risk of bleeding and that of ischaemic events.

**Anti-platelet agents**

Current guidelines recommend that for elective procedures with high-to-very-high bleeding risk, non-aspirin antiplatelet agents should be discontinued five days before surgery, to minimize the risk of bleeding and need for allogeneic blood transfusion, while aspirin be continued throughout the perioperative period. Aspirin is indicated for secondary prevention in cardiovascular disease, hence, should be stopped when it is taken for primary prevention (http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm390574.htm#primary). Surgery results in an inflammatory and pro-thrombotic state with increased platelet aggregation. It is thought that the anti-inflammatory and antiplatelet effects of aspirin confer cardio-protection during the perioperative period. In the placebo-controlled trial POISE-2 that enrolled patients undergoing noncardiac elective surgery, the use of aspirin did indeed reduce cardiovascular mortality, but this advantage was offset by an increase in postoperatively bleeding, which itself can contribute to myocardial events. Worth noting from the POISE 2 trial is the fact that only 23% of the patients enrolled had underlying ischaemic heart disease, and patients that had less than six weeks of bare metal stent (BMS) placement or within a year of drug eluting stent (DES) placement were excluded from the study. Furthermore, patients requiring aspirin for secondary prevention made up less than 36.3% of those assigned to the aspirin group. Therefore, one can argue that the high-risk group in the POISE 2 trial may have been diluted with lower risk patients. The increase in bleeding with perioperative aspirin use demonstrated in the POISE 2 trial, has been demonstrated in several other studies. In a recent randomized placebo controlled trial involving 5784 patients who underwent coronary artery bypass surgery, it was shown that the composite of death, thrombotic events, and rate of major bleeding were similar between the two groups. Based on a review of studies, continuation of aspirin in patients with ischaemic heart disease, cerebrovascular disease or peripheral artery disease is still the current recommendation for vascular surgery.

In the event of emergency surgery with significant intraoperative bleeding, platelet concentrates with or without desmopressin can be administered to reverse the anti-platelet effect. Based on limited evidence, it is recommended to maintain the platelet count above 50×10⁹ cells litre⁻¹ in mild to moderate bleeding, and above 100×10⁹ cells litre⁻¹ in severe or ongoing bleeding.

**Vitamin-K antagonists**

Vitamin-K antagonists (e.g. warfarin), are still commonly prescribed but are progressively being superseded by more titratable drugs. They work by inhibiting the enzyme vitamin K epoxide reductase and, hence, the recycling of the inactive vitamin K.
epoxide back to the active reduced form, resulting in depletion of the active form of vitamin K. They are structurally similar to vitamin K and act as competitive inhibitors of the enzyme. Perioperative management of vitamin-K antagonists depends on the urgency of surgery and bleeding severity as cessation of effect requires synthesis of more vitamin K. Options include dose omission, administration of vitamin K and administration of coagulation factor concentrates. Current guidelines recommend warfarin to be stopped five days before all elective operations. In patients that are at high-risk of thromboembolic events, bridging with low molecular weight heparin (LMWH) or unfractionated heparin is recommended. In the event of serious bleeding or emergency surgery, guidelines recommend 4-factor prothrombin complex concentrate (4F PCC) to be administered to provide rapid and complete reversal of the anticoagulant effects, in addition to Vitamin K 10 mg intravenously if a sustained effect is desirable.

New oral anticoagulants (NOAC)
The NOACs offer efficacy and safety profiles comparable with those of warfarin. These agents have a rapid onset of action, shorter half-life and more predictable pharmacokinetics than warfarin, that renders regular coagulation monitoring unnecessary. The major downside of all NOACs is the lack of specific antidotes. Recent European guidelines thus recommend the use of PCC in the event of life-threatening bleeding perioperatively. Specific antidotes are being evaluated. In a cohort of 90 patients with life-threatening bleeding, the use of idarucizumab, a monoclonal antibody that binds dabigatran, has been shown to reverse its anticoagulation effect within min. In a randomized controlled trial (RCT) on volunteers given factor Xa inhibitor, its anticoagulation effect was reversed with a factor Xa binding protein, Andexanet alfa. In another RCT, arispazine, a synthetic molecule (D-arginine compound) that has activity against unregulated thrombin has been shown to reverse its anticoagulation effect within min. All these agents will soon be commercially available.

Intraoperative measures
In the context of major perioperative bleeding, nothing replaces early and meticulous surgical haemostasis. Nonetheless, there are important measures that help to control nonsurgical bleeding. These include permissive hypotension, avoidance of the ‘lethal triad’ (dilutional coagulopathy, hypothermia, acidosis), and ‘early haemostatic resuscitation’.

Early haemorrhage control
Rapid control of the source of bleeding is, of course, a prerequisite for haemostasis. This usually means proximal and distal control of a major artery, followed either by restoration of continuity with a conduit or its ligation. A damage control approach is indicated in patients with severe coagulopathy, hypothermia (T<34°C) and acidosis (pH<7.2). This involves packing of inaccessible venous bleeding or generalized bleeding, or temporary shunts in extremity vascular injuries, before definitive repair. In ruptured abdominal aortic aneurysms, endovascular repair (EVAR), if technically feasible, is now preferred to open surgery. In the IMPROVE trial, EVAR under local anaesthesia was associated with the lowest mortality. Rapid control of bleeding with the use a large occlusion balloon catheter allows time for resuscitation before definitive repair.

Topical agents are useful adjuncts in achieving haemostasis. They are used in suture hole and anastomotic bleeding, difficult microvascular bleeding and in areas that are difficult to access. Haemostats are generally collagen or collagen based. Tissue adhesives are mostly fibrin derivatives or made from a mixture of albumin and glutaraldehyde (e.g. Bioglue®). There are a number of trials attesting to the haemostatic efficacy in vascular surgery.

Permissive hypotension
Restoration of adequate tissue oxygenation is the ultimate goal of resuscitation. Conventionally, a normotensive resuscitation strategy with early and aggressive fluid therapy, targeting a systolic blood pressure (SBP) above 100 mm Hg was adopted. This, however, often resulted in reversal of vasoconstriction, dislodgement of blood clots, dilution of coagulation factors and hypothermia. Hence, permissive (controlled) hypotension resuscitation, as part of a ‘damage control’ strategy, targeting a SBP of 50–100 mm Hg, emerged. Despite endorsement of the practice of permissive hypotension in the management of rAAA by various guidelines, no RCT has compared permissive hypotension with normotensive resuscitation, in patients with vascular surgical bleeding. Much of the evidence is derived from animal models and cohort studies in such patients. Crawford and colleagues published a series of 180 patients, that showed a survival benefit with the adoption of a permissive hypotension strategy targeting a SBP of 50–70 mm Hg and fluid restriction. A survival benefit was also demonstrated in two subsequent studies on patients with trauma but could not be confirmed by two others. In a post doc analysis of the IMPROVE trial, SBP, but not the volume of fluid administered, predicted mortality. Patients with a SBP <70 mm Hg had a mortality of 51% compared with a mortality of 34% among those with SBP ≥70 mm Hg. Every 10 mm Hg increase in SBP was associated with a 13% improvement in odds of survival. It was concluded that SBP <70 mm Hg may be too low a target, especially in elderly patients with significant cardiovascular co-morbidities. It is likely that an approach using blood pressure as the sole resuscitation endpoint oversimplifies the physiology of tissue oxygenation, lacks context sensitivity and commits an ‘argumentum ad fallacy’ that led to the conflicting evidence regarding its outcome benefits. The European Society for Vascular Surgery has recommended a restrictive fluid replacement and permissive hypotension resuscitation strategy aiming at a SBP between 50 and 100 mm Hg in patients with rAAA, tailored to the patient’s underlying condition (Level 4, Recommendation C). The recent European guidelines on management of major bleeding and coagulopathy after trauma has recommended a similar restrictive fluid and controlled hypotensive strategy, but aiming at a higher SBP of 80–90 mm Hg.

Restrictive fluid replacement
The revised Advanced Trauma Life Support (ATLS) guidelines have now restricted the initial resuscitation volume to one litre, after which blood products should be given. Retrospective analyses demonstrated detrimental effects of aggressive pre-hospital resuscitation in patients with bleeding secondary to trauma. In the German Trauma Registry database of 17 200 patients, the incidence of coagulopathy increased with the volume of pre-hospital fluid administration; 40% in those who received >two litres and 70% after four litres. In a matched pairs analysis from the same registry (n=1896, injury severity score ≥16, prehospital SBP≥20 mm Hg), a survival benefit was seen in those given a low volume (0–1.5 litre). In a cohort study of 248 patients with rAAA,
it was shown that the rate of fluid infused correlated with 30-day mortality independent of blood pressure. Each extra litre of fluid infused per hour increased the odds of death by 1.57 fold (95% CI 1.06–2.33). Two meta-analyses, however, suggest no benefit with a restrictive fluid strategy. Despite much effort spent in search of the optimal fluid for resuscitation, none of the crystalloid or colloid solutions commonly in use have been shown to be superior to others in terms of important outcomes such as the need for allogeneic blood transfusion, incidence of organ failure and length of hospital stay. Recent prospective studies on healthy volunteers (n=12), critically ill (n=1533) and trauma (n=46) patients respectively, have demonstrated a reduced incidence of acute renal injury, acidosis and cost with physiologically normal electrolyte solutions over 0.9% saline. A Cochrane meta-analysis that compared the efficacy and safety of different colloid solutions in 5484 patients needing volume resuscitation, was unable to demonstrate a benefit of any one colloid over the others. However, the wide confidence intervals have precluded authors from excluding the existence of clinically significant differences between them. The most recent Cochrane meta-analysis that included 24 trials with a total of 9920 critically ill patients in ICU, comparing resuscitation using colloid or crystalloids, did not show a difference in survival, and suggested that HES may even be harmful. A meta-analysis of the safety profile of HES has suggested that HES use increases the incidence of acute renal impairment and mortality in critically ill patients. This may, however, be difficult to extrapolate to the perioperative setting and there has also been some recent controversy with data related to the CHEST trial that included the biggest cohort for these analyses.

Amidst the controversies, the European Society for Vascular Surgery has recommended a combination of crystalloid and colloid solutions to be used during initial resuscitation (Level 1a, Recommendation B) and early institution of haemostatic resuscitation in abdominal aortic surgery. However, as per European guidelines on major bleeding and coagulopathy after trauma, the recommended fluid of choice is balanced electrolyte solution (Grade 1A), and restricted colloid use is recommended because of their adverse effects on haemostasis (Grade 2C).

Transfusion triggers

For patients with acute major bleeding, transfusion should be guided by rate and magnitude of blood loss, intravascular volume status, signs of organ ischaemia, and adequacy of cardiopulmonary reserve, rather than an empiric transfusion threshold. In haemodynamically stable patients, the lower threshold for transfusion varies from 6 to 8 g dl⁻¹. Transfusion is generally not indicated when the Hb is >10 g dl⁻¹. A Cochrane review of 19 trials (n=6264) showed that a restrictive transfusion strategy reduced the risk of receiving RBC transfusion by 39%, transfusion by an average of 1.19 units of blood, in hospital mortality (RR 0.77) but not 30-day mortality (RR=0.85). Fominskiy and colleagues conducted a similar systematic review (17 RCTs, n=7552) that assessed the effects of transfusion strategies on mortality in surgical and critically ill adult patients. The review concluded that patients in the perioperative period receiving a liberal transfusion strategy had lower all-cause mortality compared with those who received a restrictive transfusion strategy (OR 0.81; 95% CI 0.66–1.00; P=0.05; I²=25%; NNT=97). In adult patients undergoing cardiac surgery, the TITRe2 trial (n=2003) compared restrictive (7.5 g dl⁻¹) vs liberal (9 g dl⁻¹) red cell transfusion triggers. The primary outcome was a serious infection or an ischaemic event within 30 days after randomization. The study showed no difference with respect to morbidity or health care costs. Evidence remains conflicting. A restrictive transfusion strategy seems to be best for most patients but in higher risk patients, such as those in the TITRe2 trial, transfusion should be individualized.

Intuitively, autologous transfusion has a role to play in the management of patients with anticipated massive bleeding, although much of the blood may not be salvaged during rapid massive bleeding. In a Cochrane review, the requirement for red blood cells was reduced by 19% among 12 comparative studies in cardiac surgery, but no difference was demonstrated in the three trials on vascular surgery. As an overall group, a modest volume of 0.67 units per patient was saved using cell salvage techniques. On the other hand, Markovic and colleagues found that intraoperative cell salvage reduced the need for allogeneic blood transfusion in abdominal aortic surgery and recommended the use of cell salvage if suction of at least 400 ml is anticipated. Currently, the European Society of Anaesthesiology recommends the use of cell salvage in cardiac surgery involving cardiopulmonary bypass and major orthopaedic surgery (1A), but not specifically for vascular surgery. Should a cell salvage technique be used, suction pressure must be kept low to avoid haemolysis.

Optimal fresh frozen plasma (FFP) and platelets to red blood cell ratios

Transfusion with higher FFP to RBC (FFP: RBC) ratio has been shown to confer a survival benefit in both military and civilian trauma patients who needed massive transfusion. Duchesne and colleagues compared the mortality of 626 patients who received low FFP: RBC ratio (ratio=1:4) to that of patients receiving a high FFP: RBC ratio (ratio=1:1) and demonstrated significant differences in mortality (87.5% vs 26%, respectively) (relative risk, 18.88; 95% CI, 6.32–56.36; P=0.001). A multicentre, retrospective review of the effect of high FFP and platelets to RBC ratios on survival in the first 6 h after trauma showed an FFP: RBC of 1:1 led to an improved 6 h mortality (from 37.3% for ratio of 1:4 to 2% for ratio of 1:1) and platelets: RBC (from 22.8% for ratio of 1:4 to 3.2% for ratio of 1:1). The overall number of RBC units transfused was also decreased when high FFP: RBC and platelets: RBC ratios were used during early haemostatic resuscitation. However, because of the retrospective nature of the study, it is difficult to differentiate between true survival benefit and survival bias. The PROPR trial compared the effectiveness and safety in patients with severe trauma and major bleeding of using FFP, platelets and RBC in a 1:1:1 ratio compared with a 1:1:2 ratio. Although there was no significant difference in mortality at 30 days, exsanguination was significantly decreased in the 1:1:1 group within the first 24 h (9.2% vs 14.6%; P=0.03). Although the 1:1:1 group received more plasma and platelets over the first 24 h, no differences in transfusion related complications were found.

In the absence of high quality evidence for vascular surgery specifically, the existing guidelines advocate a restrictive fluid regime and permissive hypotensive strategy targeting a SBP of 50 to 100 mm Hg, tailored to the patient’s underlying co-morbidities (Level 4, Recommendation C). Based on the results from the IMPROVE Trial, however, the authors caution that a SBP lower than 70 mm Hg for a prolonged period of time may not be desirable, especially in elderly patients with significant cardiovascular...
co-morbidities. The fluid of choice can be a combination of crys-
talloid and colloids (Level 1a, Recommendation B). To avoid ex-
cessive haemodilution and potential adverse effects on haemostasis, indiscriminate use of colloids is not advisable (Grade 2C). The initial resuscitation volume should be limited to one litre, after which blood products should be given. During massive transfusion, a high FFP: platelets: RBC ratio of 1:1:1 is re-
commended as this has been demonstrated to confer a survival benefit.

Component therapy

FFP vs fibrinogen concentrate

Fibrinogen is a substrate in the cell-based model of haemostasis where its conversion to a covalently linked fibrin network is the final step in clot formation. In addition, it induces platelet activa-
tion and aggregation by binding to the platelet fibrinogen recep-
tor glycoprotein GPIIb/IIIa. Fibrinogen deficiencies can develop rapidly during massive transfusions in the context of loss and di-
lution coagulopathy, and is usually the first procoagulant factor to
decline below the critical level of 1.5 to 2.0 g litre–1 for normal haemostasis. Fibrinogen concentrate is prepared from pooled human plasma using the Cohn procedure into lyophilized pow-
der at room temperature, that can be reconstituted quickly with
50 mls of sterile water, allowing rapid administration of known concentration of fibrinogen at low volume without delays for thawing or cross-matching. In contrast to FFP and cryoprecipi-
tate, viral inactivation steps by solvent/detergent exposure or pasteurization are routinely included in the manufacturing pro-
cess such that risk of viral transmission is minimized.

Several prospective studies have shown fibrinogen concen-
trate to reduce perioperative bleeding and transfusion require-
ment in patients without a congenital deficiency. When fibrinogen was compared with placebo in bleeding surgical pa-
tients who developed a coagulopathy after resuscitation with hy-
droxymethyl starch, maximum clot firmness (MCF) measured by
thromboelastography (TEG) continued to reduce in the placebo
arm, but increased when fibrinogen concentrate was adminis-
tered. Only 20% of patients given fibrinogen required RBC transfu-
sion compared with 80% in the placebo group (P=0.023).

A systematic review of 91 studies reported the outcome (blood loss, transfusion requirement, length of stay, survival and plas-
ma fibrinogen concentration) of FFP or fibrinogen concentrate ad-
ministration, to patients in a perioperative or massive trauma set-
ing and concluded that the use of fibrinogen concentrate was associated with improved outcomes whereas the evidence for FFP was inconclusive.74 In another retrospective analysis of trauma patients comparing FFP only administration to the ad-
ministration of fibrinogen concentrate and/or PCC as guided by
ROTEM, found that allogeneic RBC transfusion was avoided in
29% of patients in the fibrinogen-PCC group (n=80) compared with only 3% in the FFP group (n=601).75

A meta-analysis of 6 RCTs involving 248 patients undergoing elective surgery found that the use of fibrinogen concentrate led to reduced allogeneic blood transfusion (RR, 0.47; 95% CI, 0.31–0.72) without an increase in thrombotic events or mortal-
ity. Fibrinogen concentrate appears to be a more effective and
safe alternative to FFP in reducing the need for allogeneic blood transfusion in bleeding patients. Despite the lack of clinical trials in emergency surgery, the recent European guidelines recom-
mand administration of fibrinogen concentrate in the event of
significant bleeding where low concentrations of fibrinogen have been demonstrated or suspected.85

Activated recombinant factor VII (rFVIIa)

Factor VII (FVII) reacts with tissue factor on the surface of endo-
thelial cells in response to vascular injury, which triggers the for-
formation of fibrin polymers and the activation of platelets. Several clinical trials have shown that rFVIIa can reduce red blood cell transfusion in surgical bleeding and in the trauma setting.83 84 In abdominal aortic aneurysm surgery, an observational study reported a reduced mortality in critical bleeding when bleeding was stopped or attenuated by the use of rFVIIa, compared with patients where rFVIIa was not administered.85 The CONTROL trial investigated the effect of rFVIIa on mortality in major trauma pa-
tients, who were continuing to bleed despite damage con-
rol resuscitation and operative management. As a result of an
unexpected low mortality, the study was terminated at 573 pa-
tients (of 1502 planned). Administration of rFVIIa was associated
with reduced blood product use compared with placebo.85

Thromboembolic risk is a concern with the use of rFVIIa and
was evaluated in a randomized, placebo-controlled trial of off-
label use of rFVIIa. Arterial thromboembolic events were higher
among those who received rFVIIa (5.5% vs 3.2%, P=0.003), and
the rates were especially high among patients >75 yr of age
(10.8% vs 4.1%, P=0.02). Interestingly there was no difference in
the rates of venous thromboembolic events.87 88

A Cochrane review on the use of rFVIIa in patients without
thrombophilia or coagulation factor deficiency found that,
when given as a prophylaxis, compared with placebo, there was
no mortality benefit (RR 1.04; 95% CI 0.55–1.97) but a trend in fa-
vour of rFVIIa in reducing the number of patients receiving RBC
transfusion (RR 0.85; 95% CI 0.72–1.01).89 A trend against rFVIIa
use with respect to adverse thromboembolic events (RR 1.35;
95% CI 0.82–2.25) was seen. The use of rFVIIa should, therefore,
be considered only for bleeding that cannot be stopped by

Prothrombin complex concentrates (PCCs)

PCCs are produced from the cryoprecipitate supernatant of large
plasma pools after removal of antithrombin and factor XI. Either
die three-factor (factors II, IX and X) or four-factor (factors II, VII, IX
and X) concentrates are produced, with a final overall clotting fac-
tor concentration approximately 25 times higher than that of
normal plasma. PCC is licensed for urgent reversal of vitamin K
antagonist therapy.77 In patients on concurrent warfarin therapy
with major bleeding, either PCC or FFP can be used to rapidly re-
verse the anticoagulation. PCC has been shown to be, at least,
non-inferior to plasma when used for warfarin reversal.89 Leis-
singer and colleagues reviewed 14 studies and found 4F PCC to
be more effective in correcting international normalized ratio
(INR) compared with FFP when urgent warfarin reversal is
needed.89 Several retrospective studies also demonstrated the ef-
effectiveness of 4F PCC in attenuating bleeding that was not in-
duced by warfarin therapy.80 81 Holland and colleagues82 studied the effectiveness of 3F PCC in correcting supratherapeu-
ptic INR in patients receiving warfarin and found that supplemen-
tal FFP was needed in order to fully correct the anti-coagulation
effect of warfarin, likely because of the lack of FVII in the prep-
eration.83 Furthermore, transfusion-related acute lung injury has
been a concern with FFP use. Therefore, the much smaller vol-
ume of PCC needed to achieve the desirable clinical effect has
made it a good alternative to FFP. PCC is currently the first line
treatment for rapid reversal of anticoagulant therapy in life
threatening bleeding, whereas its efficacy and, particularly,
safety in patients not on vitamin K antagonists remain to be
confirmed.
conventional, surgical or interventional radiological means and when comprehensive coagulation therapy has failed.

**Antifibrinolytics**

Fibrinolysis is a process in which plasminogen removes excess fibrin deposition at the site of vascular injury, which acts to improve localization of the fibrin clot and promote wound healing. Hyperfibrinolysis can be significant in acute coagulopathy. Fibrinolytic agents include tranexamic acid, aprotinin and ε-aminocaproic acid.

Aprotinin is a non-specific serine protease inhibitor. In an observational study and a RCT, aprotinin was shown to be associated with a higher risk of renal, cardio- and cerebrovascular events when compared with tranexamic acid and ε-aminocaproic acid in patients undergoing myocardial revascularization. The BART trial (Blood Conservation Using Antifibrinolytics in a Randomised Trial) randomized high-risk cardiac patients to receive prophylactic aprotinin, ε-aminocaproic acid or tranexamic acid. The mortality was increased in patients who received aprotinin compared with the combined rate for the two other antifibrinolytics (RR 1.53, 95% CI 1.06–2.22). Aprotinin was withdrawn from the market in 2008.

Tranexamic acid and ε-aminocaproic acid are synthetic lysine-analogues and act by reversibly blocking the lysine binding sites of plasminogen, thus preventing its activation to plasmin. The use of high doses of tranexamic acid, however, is associated with an increased risk of postoperative seizures. It is proposed that this is as a result of its competitive antagonistic action on the inhibitory glycine receptor. In the Clinical Randomization of Antifibrinolitics in Significant Haemorrhage 2 (CRASH-2) trial, early use of tranexamic acid, compared with placebo, reduced all-cause mortality at 28 days (14.5% vs 16%; RR 0.91 (95% CI 0.85–0.99; P=0.0035) and bleeding related deaths (4.9% vs 5.7%; RR 0.85% (95% CI 0.76–0.96; P=0.008). Vascular occlusive events did not differ significantly between the two groups. In a Cochrane review largely based on CRASH 2 trial data and trauma patients, the use of tranexamic acid reduced the chance of receiving a blood transfusion by 30%. Tranexamic acid reduces mortality from bleeding and transfusion requirement with little evidence of adverse effects. It should be administered in a dose of 20–25 mg kg⁻¹ in the management of major perioperative bleeding.

**Role of point of care coagulation testing**

Traditional coagulation tests such as PT, INR and aPTT provide a quantitative measure of plasma clotting factors, monitor the first 4% of thrombin production and the initiation phase of the coagulation cascade. These tests do not reflect the complex interplay of haemostatic components in vivo and are poor predictors of bleeding. In addition, laboratory testing results, on average, take 30–60 min to be available, which is too slow to support clinical decision making during vascular surgery in acute and profuse bleeding. The activation of coagulation factors and platelet function are temperature-sensitive yet most laboratory assays are performed in an artificial milieu of 37°C instead of the patient’s actual body temperature. These limitations render conventional coagulation tests time-insensitive, with low predictive values for bleeding, and restrict their usefulness in the intraoperative management of bleeding. As such, point-of-care diagnostic tools (POCT) have gained growing interest as more promising alternatives.

Viscoelastic methods are among the many POCTs that have been developed to provide rapid assessment of coagulation status. Johansson and collagues reported a before-and-after study design (n=832) that implemented a TEG-guided early haemostatic resuscitation regime, and showed improved outcomes. A retrospective study on 3865 patients who underwent cardiovascular surgery, demonstrated that using combined thromboelastometry and portable coagulometry to guide intraoperative transfusion resulted in a reduction in blood product use and thromboembolic events, but not mortality. Furthermore, parameters measured by viscoelastic testing have been shown to be good predictors for the need for massive transfusion, incidence of thromboembolic events and mortality in surgical and trauma patients.

Two commercially available viscoelastic-based products dominate the market, TEG 5000 (Haemonetics Corporation, Braintree, MA) and ROTEM (TEM International GmbH, Munich, Germany). Both devices consist of a pin suspended in a cup of native whole blood. As the pin and cup rotate relative to each other in controlled, repetitive, low shear movements, the formation and eventual dissolution of clot are captured as changes in torque that are transduced and displayed graphically. Both devices provide whole blood clotting tests that evaluate different aspects of haemostatic status including platelet function, fibrinogen and fibrinolysis. Although the mechanical principles underlying the two devices are similar, the different hardware and activators used have resulted in different output values and reference ranges that are not interchangeable. The principles and reference ranges of both devices have been extensively reviewed. A large body of literature has demonstrated the effectiveness of TEG® 5000 and ROTEM in guiding transfusion therapy, leading to a reduction in the need for and the volumes of blood and plasma transfusion.

Despite the popularity of viscoelastic-based POCTs, their usefulness has been questioned. A recent systematic review found insufficient evidence to support the diagnostic accuracy of thromboelastometry, and hence, was unable to offer advice on its use as a global measure of haemostatic function in trauma patients. Another systematic review concluded that viscoelastic POCT predicts the need for blood product transfusion but does not alter mortality or other important outcomes in trauma patients. Several other limitations have also been described, including the inability of TEG to discriminate between dilutional coagulopathy and coagulopathy secondary to thrombocytopenia, the lack of sensitivity to detect and monitor platelet dysfunction as a result of antplatelet drugs, and the need for trained personnel to guarantee quality of test performance.

Evidence on POCT-guided transfusion is largely derived from trauma or cardiac surgery. The latest edition of the ‘European Guidelines on Management of Major Bleeding and Coagulopathy Following Trauma’ has recommended institution of early and repeated coagulation monitoring in managing trauma induced coagulopathy (TIC), using conventional laboratory assays (Grade 1A) and/or viscoelastic methods (Grade 1C). On the contrary, the consensus statement on viscoelastic POCT-based guided transfusion that was published in 2015 prompted clinicians to take ‘practical advantages’ into consideration when deciding the mode of coagulation testing during bleeding management. The practical advantages include rapid results to guide clinical decisions, a logistic advantage with less laboratory travel, treatment efficiency by obtaining crucial information on fibrinogen and fibrinolysis, and cost saving from avoidance of transfusion.
Conclusion
Although there has been improved understanding on the management of perioperative bleeding through laboratory and clinical research, it remains the single most important adverse prognostic factor for mortality and continues to pose a major challenge. The optimal management of perioperative bleeding is likely to evolve into real-time monitoring and goal directed transfusion protocols, especially in regards to component therapy.

Authors' contributions
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