Beverly, A., Ong, G., Wilkinson, K. L., Doree, C., Welton, N. J., & Estcourt, L. J. (2019). Drugs to reduce bleeding and transfusion in adults undergoing cardiac surgery: A systematic review and network meta analysis. *Cochrane Database of Systematic Reviews*, 2019(9), [CD013427]. <https://doi.org/10.1002/14651858.CD013427>

Publisher's PDF, also known as Version of record

Link to published version (if available):
[10.1002/14651858.CD013427](https://doi.org/10.1002/14651858.CD013427)

[Link to publication record in Explore Bristol Research](#)
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Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD013427.

DOI: 10.1002/14651858.CD013427.

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Drugs to reduce bleeding and transfusion in adults undergoing cardiac surgery: a systematic review and network meta-analysis

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Editorial group: Cochrane Heart Group.

Publication status and date: New, published in Issue 9, 2019.

Citation: Beverly A, Ong G, Wilkinson KL, Doree C, Welton NJ, Estcourt LJ. Drugs to reduce bleeding and transfusion in adults undergoing cardiac surgery: a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 2019, Issue 9. Art. No.: CD013427. DOI: 10.1002/14651858.CD013427.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of haemostatic drugs (including antifibrinolytics) and topical agents for reducing bleeding, transfusion, and reoperation in adults undergoing cardiac surgery.

BACKGROUND

Description of the condition

Cardiac surgery in adults

Cardiac surgery treats disease of the coronary arteries, heart muscle, valves, surrounding membrane (pericardium), and great vessels flowing out from the heart (aorta). Such disease may be acquired, age-related (degenerative), inherited, or congenital (present at birth). Coronary heart disease (CHD) is a form of cardiovascular disease affecting the coronary arteries. Cardiovascular disease is common, causing approximately one-third of deaths in people

over the age of 35 years and is, therefore, the largest single contributor to global mortality (Abubakar 2015; WHO 2009). Depending on severity and anatomy of CHD, it is treated with medications, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) of one or more coronary arteries (Chang 2016; Windecker 2014). PCI has become more common since the late 1990s, now accounting for four in five CHD interventions (Blumenfeld 2017; Ko 2012; Yeh 2015). However, CABG remains the most frequently performed cardiac operation in adults (SCTS 2015; STS 2018). Cardiac valve repairs or replacements are the second most frequently performed cardiac operations (SCTS 2015; STS 2018). The aortic valve, followed by the mitral valve most commonly require surgery (SCTS 2015). CABG and valve surgery may be conducted in a combined operation, if coronary artery and valvular disease coexist (Bonow 2006). Some

valve procedures can be conducted percutaneously, for example a transcatheter aortic valve implant (TAVI), rather than with open surgery, which decreases the risk of bleeding and other complications (Daubert 2017; Nishimura 2017). Surgery on the cardiac outflow tract (ascending aorta and aortic arch) is less commonly performed (SCTS 2015; STS 2018), and usually involves graft replacement or repair for aneurysm (dilation), dissection (a tear in the vessel wall), or infection (Stamou 2015).

Cardiac surgery can be elective, urgent, or emergency, and can be primary or revision surgery (Chiu 2016; Goodwin 2003; Kurki 2003). Cardiac operations vary in their complexity, risk, and complication rates, and individualised mortality risk prediction models have been developed using large cardiac surgery registries, namely EuroSCORE and its update, EuroSCORE II (Nashef 1999; Nashef 2012; Nilsson 2006). Traditionally, cardiac surgery requires a sternotomy (opening of the breastbone) and artificial circulation in the form of a cardiopulmonary bypass (CPB) circuit. This remains standard practice but newer alternatives include minimally invasive incisions, miniature CPB, and off-pump (beating heart) surgery, though this is less widely used (Møller 2014).

Bleeding in cardiac surgery

Intra- or postoperative bleeding is a recognised complication of cardiac surgery, but severity of bleeding varies greatly (Bennett-Guerrero 2010). Bleeding risk prediction scores, for example, the Papworth Bleeding Risk Score, predicts higher bleeding risk using variables of: non-elective surgery, surgery other than CABG or single valve surgery, presence of aortic valve disease, low body mass index (BMI), and older age (Vuylsteke 2011). It defines severe postoperative bleeding by any of: at least 2 mL/kg/hour from chest drains for the first three hours after surgery; transfusion of fresh-frozen plasma, platelets, or cryoprecipitate; return to theatre for bleeding; or death. Several other cardiac surgery-specific scoring systems measure and classify bleeding (Bartoszek 2018). These include the Universal Definition of Perioperative Bleeding (UDPB) grades, the European Coronary Artery Bypass Graft (E-CABG) grades, and the WILL-BLEED Risk Score, which is specific for CABG (Biancari 2015; Biancari 2017; Dyke 2014). Severe bleeding severity varies according to surgery, occurring in only 3.4% of people undergoing CABG, 23% of people undergoing aortic valve replacement, and over 30% of people undergoing aortic root replacement (Genereux 2014; Kinnunen 2017; Williams 2011).

Coagulation in cardiac surgery

Severe bleeding in cardiac surgery is made worse by factors which impair normal clotting (coagulation). People may be taking anticoagulant and antiplatelet drugs for concurrent medical conditions and such drugs are often stopped prior to non-cardiac surgery to reduce the risk of bleeding (Levine 2016; Sousa-Uva 2018). However, antiplatelet drugs may be deliberately continued before elective cardiac surgery if the risk of pre-existing cardiac stent

thrombosis outweighs the risk of bleeding (Sousa-Uva 2014). Antiplatelet drugs may also not be stopped with adequate washout times prior to emergency surgery.

CPB facilitates surgery by providing a bloodless, motionless surgical field (Mulholland 2015), but can impair coagulation in several ways. First, the CPB circuit is usually primed with large volumes (approximately 1.5 L) of fluid, which dilutes the circulating blood by 10% to 20%, and this in turn dilutes clotting factors in the blood (Ranucci 2017). Second, the CPB is primed with heparin (an anticoagulant) to prevent clotting within the circuit, but heparin can enter the systemic circulation and increase bleeding (O'Carroll-Kuehn 2007). Third, contact of blood with the CPB tubing, pumps, and gas exchange membranes can alter normal coagulation pathways, causing both bleeding and blood clots (Hess 2005; Sato 2015). Finally, low body temperatures (hypothermia) using active or passive cooling are used for some cardiac operations because this reduces organ oxygen requirements, thus reducing organ damage during periods of poor or absent blood flow. However, hypothermia also negatively affects coagulation by slowing the enzyme rate of many steps in the coagulation pathway (Campos 2008).

Severe bleeding can cause low blood pressure and anaemia with inadequate oxygen supply to organs (Pittman 2011; Sabatine 2005). Postoperative bleeding can also cause a collection of blood and clots within the fibrous membrane around the heart, preventing adequate blood flow through the heart (pericardial tamponade) (Haneya 2015). This life-threatening complication requires emergency return to theatre to reopen the chest (resterernotomy) and occurs in 4% to 5% of adults undergoing cardiac surgery. It is associated with significantly worse outcomes, including cardiac arrest, and longer hospital admission and increased costs (Biancari 2011; Biancari 2018). Studies have investigated the source of bleeding identified at emergency resterernotomy. While inadequate surgical closure of arteries and veins were occasionally found, the source of bleeding was frequently diffuse, unidentified, or attributed to oozing despite adequate surgery (Biancari 2018). Clotting is activated at sites of tissue injury, but if bleeding is persistent, circulating coagulation factors (e.g. fibrinogen) and platelets are continually consumed and can eventually drop to critically low levels (Marietta 2006). This 'consumptive coagulopathy' may cause a persistent bleeding which cannot be managed surgically (Brohi 2008).

Transfusion in cardiac surgery

People with the same amounts of bleeding may be given different amounts and types of blood components, due to institutional variations in normal transfusion practice (Rogers 2009; Sandhu 2017; Snyder-Ramos 2008). Several trials and one systematic review suggested that a restrictive transfusion threshold (giving red cells only if haemoglobin was 70 g/L or below) was as safe as a liberal transfusion threshold (90 g/L or below) even in cardiac surgery, and this persisted on five-year follow-up (Carson 2016;

Hajjar 2010; Mazer 2017; Mazer 2018). This is despite concerns that people with coronary artery disease tolerate anaemia poorly (Murphy 2015). Establishing an ideal transfusion threshold is important for minimising unnecessary transfusion and, therefore, reducing harms associated with transfusion (Carson 2018).

Description of the intervention

When an injury occurs, the formation of a blood clot (normal haemostasis) stops excessive bleeding. Blood clot formation is initiated by tissue injury, endothelial and collagen exposure, and release of factors which cause blood vessel constriction (vasoconstriction) and platelet activation (Blanco 2017). Activated platelets stick to each other, forming a weak plug (Mackman 2007). At the same time, multiple enzyme pathways are activated and amplified, finally producing thrombin, an enzyme that converts fibrinogen to fibrin. Fibrin forms long chains and crosslinks with platelets to form an insoluble, stable blood clot. The clot is further strengthened by cross-linking of the fibrin strands by factor XIII (Chapin 2015).

To prevent harmful, unregulated clot extension beyond the injury, blood clots are contained and broken down by fibrinolysis (clot dissolution) (Blanco 2017). The protease enzyme, plasmin, cuts through fibrin, releasing soluble fragments that are metabolised in the liver and kidneys (Hudson 2017). Plasmin formation and fibrinolysis occur more slowly than clot formation, so clot breakdown is delayed until after clot formation and tissue remodelling (Chapin 2015). To prevent digestion of tissues other than clot, plasminogen is mainly converted to plasmin only within the blood clot, as bound, rather than free plasmin. Free plasmin will indiscriminately digest plasma proteins and clotting factors and is normally neutralised by circulating alpha-2-plasmin inhibitor (Madurska 2018).

Antifibrinolytic drugs

Antifibrinolytic drugs inhibit plasmin and thus reduce blood clot breakdown, resulting in greater early and persistent clot strength (Okamoto 1997). Antifibrinolytic drugs are usually administered intravenously (IV) after induction of anaesthesia. A loading dose is usually given, sometimes followed by an infusion. Dose regimens vary but high doses appear to be more effective in reducing bleeding than low doses (Henry 2011).

Tranexamic acid

Tranexamic acid (TXA) is a synthetic analogue of the amino acid, lysine. It binds reversibly to lysine receptor sites on plasminogen, prevents activation of plasminogen into plasmin, and reduces fibrin breakdown. This improves clot formation, stability, and duration. TXA has been well validated for use in perioperative, obstetric, and trauma care, as well as in cardiac surgery (Henry 2011; Ker

2015; Shakur 2018). One systematic review and network meta-analysis of antifibrinolytic adverse drugs effects in the setting of cardiac surgery suggested TXA use reduced mortality compared to placebo or aprotinin. In addition, it does not increase myocardial infarction (MI), cerebrovascular attack (CVA), or renal failure or dysfunction (Hutton 2012). However, TXA in high doses has been associated with seizures in the cardiac surgery setting (Murkin 2010).

Epsilon-aminocaproic acid

Epsilon-aminocaproic acid (EACA) is another synthetic lysine analogue, with a similar mechanism of action to TXA. EACA is about seven to 10 times less potent than TXA (Thomsen 2006). There is no known association with seizures. Antifibrinolytic drugs such as EACA and TXA are usually administered IV after induction of anaesthesia. Usually a loading dose is given followed by continuous infusion. High doses appear to be more effective than low doses (Henry 2011).

Aprotinin

Aprotinin is a competitive inhibitor of several serine proteases, including plasmin and kallikrein (McCarthy 1994). Plasmin inhibition reduces fibrinolysis. However, aprotinin particularly inhibits free plasmin, more than bound plasmin. This improves the problems caused by unregulated free plasmin activity, such as destruction of clotting factors. This particularly reduces abnormal pathological, rather than normal physiological fibrinolysis (Royston 2015). Additionally, kallikrein inhibition reduces factor XIIa activity, which inhibits the formation of thrombin and fibrin. Overall, aprotinin is classed as antifibrinolytic, as its net clot-stabilising effect outweighs its kallikrein-mediated anticoagulant effects.

Aprotinin has been associated with a higher rate of adverse effects than the lysine analogues (Henry 2009). Evidence from three observational studies and from one randomised study in adults undergoing cardiac surgery showed an increased risk of renal dysfunction, cardiovascular events, pulmonary embolism (PE), and death with aprotinin (Bremerich 2006; Cooper 2006; Mangano 2007; Royston 2015). This led to its withdrawal from many national markets in 2007 (FDA 2007). However, these data have been revisited and reanalysed, questioning the validity of the conclusions of the four studies (Howell 2013). Despite this, aprotinin remains unavailable or on a restricted license, for example, for myocardial revascularisation only, in some countries (Henry 2011).

Other haemostatic drugs

Haemostatic drugs are a broad class of drugs which act on various parts of the coagulation cascade to replace or enhance missing or poorly functioning procoagulant enzymes, substrates, or factors. These could be deficient due to inherited conditions, such as

haemophilia or von Willebrand's disease, or acquired conditions, such as prolonged bleeding with consumption of clotting factors, liver failure, autoimmune disease, or drug therapy.

Desmopressin

Desmopressin is a synthetic analogue of the human antidiuretic hormone, vasopressin. Desmopressin increases the plasma levels of von Willebrand factor (vWF) two- to three-fold by stimulating vWF release from endothelial cells. vWF plays an important role in platelets sticking to damaged tissue and early clot formation, so vWF deficiency prolongs bleeding. vWF also increases the availability of factor VIII, because factor VIII degrades rapidly unless it is bound to vWF. Activated factor VIII is a precursor in the enzyme cascade producing thrombin and fibrin. Desmopressin is usually administered at a dose of 0.3 µg/kg subcutaneously or IV with peak effect within 30 minutes and effect duration of six to eight hours (Franchini 2007).

Increases in vWF and factor VIII can potentially increase the risk of arterial or venous clots, and this is an important safety consideration (Franchini 2007). Desmopressin also causes nitric oxide release from endothelial cells, causing facial flushing, fast heart-beat, and low blood pressure from blood vessel dilation (Kaufmann 2003). In rare cases, desmopressin administration may be associated with low sodium levels and seizures, especially in young children (Smith 1989).

Prothrombin complex concentrate

There are two main types of prothrombin complex concentrate (PCC). Three-factor PCC contains factors II, IX, and X, whereas four-factor PCC also contains factor VII, protein C, and protein S. PCC is a powder concentrate, extracted from human plasma and reconstituted prior to use, dosed at 25 units/kg to 50 units/kg. It is used for perioperative prophylaxis or treatment of severe bleeding in people treated with vitamin K antagonists, such as warfarin, or with clotting factor deficiencies, whether inherited, for example, haemophilia, or acquired, such as in severe liver disease (BNF 2019). Adverse effects include fever, hypertension, and thromboembolism (migrating blood clots). In the setting of cardiac surgery, observational studies and systematic reviews showed that compared to fresh frozen plasma, PCC reduced both bleeding and transfusion, without increased thromboembolic events (Cappabianca 2016; Roman 2019). Randomised controlled trials (RCTs) comparing PCC to placebo or other drugs are less common, though there are observational studies showing benefits of PCC used both as a rescue therapy in the setting of coagulopathy and excess bleeding after cardiac surgery, and compared to recombinant factor VIIa (rFVIIa) (Harper 2018; Song 2014).

Recombinant factor VIIa

rFVIIa is a serine protease which catalyses conversion of factors IX and thrombin (X) into active forms. This increases the conversion of fibrinogen to fibrin by thrombin and promotes clot formation and propagation. It is currently licensed only for bleeding in people with a diagnosis of haemophilia, or severe uncontrolled haemorrhage (Simpson 2012). Studies have suggested an association with rFVIIa and arterial thromboembolic events (Levi 2010; Simpson 2012).

Recombinant factor XIII

Recombinant factor XIII (rFXIII) is a transglutaminase enzyme which crosslinks fibrin monomers between adjacent fibrin polymer strands to stabilise and strengthen the clot. It also acts to contract the clot into a more dense and insoluble unit (Ariëns 2002). rFXIII treatment is currently indicated for congenital or acquired factor XIII deficiencies, identified with quantitative methods but has been studied as an agent that can reduce bleeding in cardiac surgery (Muszbek 2008).

Fibrinogen concentrate

Fibrinogen is isolated from human plasma. Fibrinogen is a plasma glycoprotein synthesised by the liver. Fibrinogen is the precursor to fibrin, but also helps platelets activate and aggregate by binding to the platelet's GPIIb/IIIa receptor. Fibrinogen substitution may normalise and improve clot formation by providing more substrate and by enhancing the strength and speed of clot generation in people with depleted or dysfunctional fibrinogen (Nielsen 2005). Within the context of cardiac surgery, systemic fibrinogen replacement is currently indicated for prophylaxis or treatment of bleeding in congenital and acquired deficiencies of fibrinogen that have been identified with quantitative methods (Bracey 2017). In people with bleeding in elective and cardiac surgery, fibrinogen concentrate was associated with a small reduction in transfusions but no survival benefit (Wikkelsø 2013).

Internal topical agents (excluding surface dressings)

Internal topical application of drugs or biomaterials can be used as an adjunct to surgical control of bleeding, particularly where there are many microscopic bleeding vessels or raw tissue which cannot be surgically closed (Gabay 2013). A biomaterial is any substance that has been engineered to physically interact with biological tissue for a specific purpose (Park 2007). Topical agents include active drugs or clotting factors applied directly as a liquid, paste, foam, or gel, or impregnated into biomaterials, or application of passive biomaterials which promote clotting through physical means only with no drug activity (Vyas 2013). There are many agents available, and these have been classified as active, passive, and combined haemostatic agents (Bracey 2017). They can also be classified as flowable, or non-flowable, or fibrin and non-fibrin sealants.

Active agents enhance enzyme pathways in clotting and include antifibrinolytic drugs, fibrin sealants, or topical thrombin. Passive biomaterials include: collagens, porcine gelatins, regenerated oxidised cellulose, and polysaccharide spheres. Passive synthetic sealants include: cyanoacrylate, polyethylene glycol, and bovine serum albumin with glutaraldehyde. Combination agents include liquid gelatins with thrombin, and fibrin sealants with equine collagens. These diverse groups have the advantage of acting locally at the site of bleeding, potentially avoiding systemic adverse effects (Seyednejad 2008). The passive biomaterial and sealants may have the advantage of promoting clotting even in hypothermia or with deficits in normal clotting factors, as they operate independently from enzymatic biological clotting processes.

How the intervention might work

Bleeding can occur in any surgical speciality, often in proportion to the degree of tissue trauma and the vascularity of the tissues in the operating field. Trauma to tissues causes release of tissue plasminogen activator (tPA), stimulating some fibrinolytic activity (Hartmann 2006). However, in cardiac surgery there are specific factors to consider, which make drug therapies particularly important for reducing intra- and postoperative bleeding.

Antifibrinolytics in cardiac surgery

Most cardiac surgery still uses CPB, typically for one to two hours, but often up to four hours and occasionally much longer for more complex surgeries. CPB itself causes an acquired, duration-dependent hyperfibrinolysis, which has been well characterised and detected with point-of-care testing such as thromboelastography (Sharp 2018; Vanek 2007). Massive activation of coagulation then fibrinolysis pathways occurs in response to contact of the blood with foreign, non-endothelial surfaces (Lazarus 2014). Returning suctioned blood from the surgical field to the systemic circulation enhances this pathological process further, as cytokines, tissue factor, and tPA from the damaged tissue enter the systemic circulation. Biomaterial coatings within CPB circuits and pump design modifications (centrifugal versus roller) have helped reduce circuit-related hyperfibrinolysis and pump-related haemolysis but it remains a major issue (Passaroni 2018). Hyperfibrinolysis also contributes to severe bleeding by preventing new clots forming, because fibrin degradation products interfere with platelet activation, adhesion, and normal fibrin polymerisation, inhibiting normal coagulation. Additionally, the high levels of free plasmin associated with hyperfibrinolysis also cause degradation of the fibrin precursor, fibrinogen reducing the substrate available for fibrin polymerisation. By inhibiting these pathways, antifibrinolytics have an important role in cardiac surgery, to an even greater extent than in non-cardiac surgery. Aprotinin may have additional effect in the context of cardiac surgery from its greater action on free rather than bound plasmin.

Other haemostatic drugs in cardiac surgery

PCC or desmopressin may be of particular benefit in people undergoing cardiac surgery with bleeding compounded by warfarin or glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors and other antiplatelet medications respectively (Raja 2006). rFVIIa is used off-label for a variety of major surgeries, occasionally as prophylaxis, or more frequently in catastrophic haemorrhage after other options have failed to arrest bleeding. Its usefulness in reducing bleeding in cardiac surgery remains unproven (Simpson 2012). Analysis of rFVIIa usage in intractable bleeding in cardiothoracic surgery demonstrated a reduction in transfusion requirement, at the expense of a higher thrombotic event rate, but it has not been determined whether this translates into more favourable patient outcomes (Omar 2015). Factor XIII levels appear to drop after exposure to CPB; however, replenishing levels by giving FXIII has no effect on transfusion or reoperation rates and factor XIII administration only appears useful if there is pre-existing deficiency (Godje 2006; Karkouti 2013).

Internal topical agents in cardiac surgery

Several trials in cardiac surgery showed improved local haemostasis and reductions in overall blood use with topical agents, and there are theoretical advantages of local versus systemic treatments in terms of unwanted adverse effects (Bracey 2017). However in people with coagulopathy, local active treatments which work via coagulation pathways may also have limited effect due to systemic coagulation derangement. Thus, any outcome differences, both for active drugs and passive biomaterial agents, are of interest. Trials are complicated by the potential lack of surgeon blinding when handling materials, and the diverse range of agents used.

Why it is important to do this review

Bleeding and reoperation for bleeding are serious adverse patient outcomes, which are associated with increased mortality, complications, and risk of transfusion (Shaw 2013). Bleeding requiring a red blood cell transfusion has also been shown to increase the duration of hospital stay and the costs associated with surgery, after taking into consideration confounding factors (Stokes 2011; Zbrozek 2015). The negative impact on outcomes associated with allogenic transfusion is observed even when a patient only receives a transfusion of one or two units of red blood cells (Paone 2014; Paone 2018). Infection rates are reported to be higher in people who receive a transfusion, which may be due to impaired immune function (Rohde 2014). Other transfusion-related adverse effects include incompatibility reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO) (Harvey 2015; Maxwell 2006). In addition, transmission of infectious diseases (e.g. HIV, hepatitis C) remains a concern (Kiely 2017; Rerambiah 2014). This is particularly a concern in countries with higher prevalence of these diseases, or less-robust

screening capabilities (Seo 2015). Blood components, particularly platelets, can also have bacterial contamination that may cause sepsis in the recipient (Benjamin 2016; Makuni 2015; Morel 2013). One ampoule of TXA or desmopressin is significantly less expensive than procuring, storing, and delivering blood products, and does not carry risks such as transmission of blood-borne diseases. Some drugs which reduce bleeding may have a favourable cost-benefit analysis in comparison to transfusion-related costs (Davies 2006; Guerriero 2011).

Patient blood management (PBM) focuses on improving patient care by reducing unnecessary transfusions, one of the main strategies is reducing intraoperative blood loss (Butcher 2018). Several guidelines have recommended the use of antifibrinolytic drugs to reduce blood loss (Boer 2018; Ferraris 2011). TXA is now probably the most widely used, though aprotinin was routinely used prior to its withdrawal in the late 2000s. While there are many RCTs and systematic reviews evaluating various aspects of drug efficacy and adverse effects, not all drugs, doses, or routes of administration have been directly compared (Henry 2009; Henry 2011; Hutton 2012).

Drugs may be given as a single dose, multiple doses, or infusion, before, during, or after surgery, and various different routes (e.g. topically into the sternal wound or IV. Optimal dosing is important for establishing minimum effective dose and appropriate duration of exposure, so that other drug adverse effects are minimised. However, quantitative comparisons between such a diverse groups of treatments, which may be used in combination, are challenging. RCTs making direct comparisons between treatments are not always available, therefore, systematic review with network meta-analysis may be useful to provide indirect comparisons between treatments, where appropriate. Finally, this review will investigate the effect of antiplatelet/anticoagulant drug use, type or surgery and use of CPB as treatment effect modifiers, to establish different performances of different drugs in these different circumstances (Berger 2012). Analysis of different subgroup responses to study drugs may be useful for risk versus benefit considerations or justify use of a drug or dose which reduces bleeding more in specific circumstances, despite higher adverse effects and risks.

OBJECTIVES

To assess the efficacy and safety of haemostatic drugs (including antifibrinolytics) and topical agents for reducing bleeding, transfusion, and reoperation in adults undergoing cardiac surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs in all languages. We will include cluster RCTs if the analyses have accounted for clustering, or if we are able to adequately adjust for clustering (McKenzie 2014). We will include RCTs published as abstracts if they contain sufficient data, or if sufficient data is provided by the authors on request. We will include unpublished RCTs identified through handsearching reference lists of articles, contacting experts in the fields, and gathering information about ongoing trials. We will exclude studies with purely experimental laboratory outcomes (e.g. blood tests for inflammatory markers).

Types of participants

We will include adults (aged 18 years or over) undergoing the following types of open cardiac surgery or any combination of these:

- CABG;
- cardiac valve(s) (aortic mitral, tricuspid, or pulmonary) repair or replacement;
- surgery of the thoracic aorta.

We will include emergency, urgent, and elective procedures. We will include participants undergoing open (sternotomy incision), modifications of open, and minimally invasive surgical approaches.

We will exclude people:

- with known inherited coagulation disorders, such as vWF deficiency, haemophilia, or hypofibrinogenaemia;
- undergoing purely percutaneous or endovascular procedures;
- undergoing surgical repair on isolated descending thoracic or thoracic-abdominal aorta, being procedures potentially conducted by vascular surgeons or interventional radiologists.

For trials consisting of mixed populations of participants (e.g. including participants who are under 18 years old, or including procedures other than CABG, valve, or specified aortic surgery), we will extract only data from desired participant subgroups. If the subgroup data required are not provided, we will contact corresponding authors of the trial to request this information. If the subgroup data are still not available, we will exclude the whole trial if less than 80% of participants fit the inclusion criteria.

Types of interventions

We will include RCTs comparing the following interventions, compared to usual care, placebo, or each other:

- tranexamic acid (TXA);
- ϵ -aminocaproic acid (EACA);
- aprotinin;
- desmopressin;
- prothrombin complex concentrate (PCC);

- recombinant activated factor VII (rFVIIa);
- factor XIII (FXIII);
- fibrinogen;
- other topical agents, categorised as:
 - fibrin-based agents;
 - thrombin-based agents;
 - synthetic sealants;
 - passive biomaterials;
 - combination agents.

The list of drugs and topical agents, by classification, generic, or tradename appear within the search strategy ([Appendix 1](#)). We will include RCTs that compare one or more of the interventions listed above. We will include studies using any combination of the above drugs. We will not exclude trials on the basis of the route, dose, or timing, or frequency of drug administration. The comparison groups will be as defined by the study, which could be a control group using placebo, standard care (i.e. no placebo but otherwise identical care, except for the study drug), or another study drug. We will combine studies which use placebo or usual care, and treat these as a single comparator for the direct comparison.

Types of outcome measures

Primary outcomes

- Red cell transfusions (units per participant*) at up to 30 days postsurgery.
- Chest drain output (total mL) at up to 24 hours postsurgery.
- All-cause mortality at up to 30 days and at 31 to 90 days postsurgery.

Secondary outcomes

- Risk of receiving any allogenic blood product at up to 30 days postsurgery.
- Risk of undergoing reoperation for bleeding at up to seven days postsurgery.
- Risk of a thrombotic/thromboembolic event at up to 30 days and at 31 to 90 days postsurgery (MI, CVA, deep vein thrombosis (DVT), PE).
 - Risk of an MI at up to 30 days postsurgery.
 - Risk of a CVA at up to 30 days postsurgery.
 - Risk of a DVT at up to 90 days postsurgery.
 - Risk of a PE at up to 90 days postsurgery.
- Risk of acute kidney injury (AKI**) at up to 30 days postsurgery.
- Risk of serious adverse events (SAEs***) at up to 30 days postsurgery.
- Risk of seizures at up to 30 days postsurgery.

- Length of hospital stay (days).
- Health-related quality of life postsurgery.

*If the red cell transfusion outcome is reported in millilitres, we will convert that into units, according to any local mean unit volume data given in the study, or as per the “Guidelines for the Blood Transfusion Services in the UK” mean stated volume per unit of red cells of 280 (standard deviation (SD) 60) mL ([Red Book 2013](#)).

**We will use the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI ([Kellum 2012](#)). Where studies report an AKI outcome using an alternative definition, we will record what definition of AKI was used and discuss suitability for inclusion in analysis with an expert panel, prior to extracting outcome data.

***We will use the International Conference on Harmonisation Good Clinical Practice definition of SAEs ([ICH GCP](#)). Where studies report an SAE outcome using an alternative definition, we will record what definition of SAE was used and discuss suitability for inclusion in analysis with an expert panel, prior to extracting outcome data.

For the composite outcome of thrombotic/thromboembolic, we will record which of the components were included in the composite. We will record whether a health-related quality of life outcome was included, the scale used, and if so the impact (positive or negative) of the study drug(s). We will comment on any cost data, if presented, in a narrative form ([Ryan 2013](#)). Cost information will provide useful additional information, but will not be a formal economic evaluation.

Reporting one or more primary or secondary outcomes will not be an inclusion criterion for the review. Where a published report does not appear to report on one or more of these primary or secondary outcomes, we will, if feasible, contact the trial authors for data in case an outcome measure was proposed in the protocol but was not reported on. Relevant trials which measured outcomes but did not report the data in a usable format will be included in the systematic review as part of the narrative.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE (Ovid, 1946 to present);
- Embase (Ovid, 1974 to present);
- Emcare (Ovid, 1995 to present);
- Transfusion Evidence Library ([Transfusion Evidence Library](#); 1950 to present).

We will search for ongoing or unpublished trials in the following clinical trial registers:

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

We will apply the Cochrane sensitivity- and precision-maximising RCT filter (Lefebvre 2008) to MEDLINE, and adaptations of it to Embase and Emcare, in combination with a systematic review filter (to include systematic reviews to allow manual screening for additional citations, see [Searching other resources](#)) based on the Scottish Intercollegiate Guidelines Network (SIGN) filter (www.sign.ac.uk/methodology/filters.html). Searches will use a combination of subject headings and free-text terms and will be carried out from database inception to the present, without restriction on language or publication status. The preliminary search strategy for MEDLINE (Ovid) is presented in [Appendix 1](#). We will not perform a separate search for adverse effects of interventions used to reduce bleeding and transfusions in adults undergoing cardiac surgery. We will consider adverse effects described in included studies only.

Searching other resources

We will check reference lists of all included studies, relevant systematic review articles, and other current evidence. We will also examine any relevant retraction statements and errata for included studies. We will contact experts in the field to help identify additional published and unpublished studies (Lefebvre 2011). In this way, we will identify additional trials potentially missed by the electronic searches.

Data collection and analysis

We will conduct and report the review in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and also in accordance with PRISMA checklist extension for network meta-analyses (Hutton 2015).

Selection of studies

Two review authors (AB, GO) will use Covidence software to screen electronically derived citations and abstracts of papers identified by the review search strategy for relevance (Covidence). We will exclude any studies that are clearly irrelevant at this stage. We will retrieve the full text of references when eligibility cannot be assessed by title and abstract alone. We will translate studies reported in non-English language journals before assessment. We will exclude studies not meeting eligibility criteria from further analysis and detail these in the 'Characteristics of excluded studies' table.

At all stages, the two review authors will resolve any disagreements and if needed, they will consult with a third review author (LE).

We will record the reasons why studies failed to meet the inclusion criteria and display the results of the search in a PRISMA flow chart (Liberati 2009).

If we include any multi-arm studies with more than two relevant arms, we will only add it once to the 'Characteristics of included studies' table, to avoid double counting the study in terms of the number of RCTs, and avoid the study appearing twice in the 'Risk of bias' figures.

Data extraction and management

Two review authors (AB, GO) will independently undertake data extraction from included studies. We will design, pilot, and modify data extraction forms. We anticipate there are many potential options for dose, route, and timing within each drug intervention, which are tabulated in [Appendix 2](#).

We will consider the following data for extraction from each study, dependent on feasibility and performance in the pilot test.

- General information: prospective trial registration, start and end date of data extraction, study ID, first author of study, author's contact address, citation of paper, type/source of publication.
- Trial details: trial design, aims of the trial, funding, location, setting, number of centres, number of treatment arms, power calculation and whether reached, treatment allocation method, randomisation, blinding, total number recruited, total number randomised, total number analysed in each study group, participant inclusion and exclusion criteria, antiplatelet and anticoagulant cessation protocol, intervention inclusion and exclusion criteria, transfusion decision strategy (physician's discretion, thromboelastometry/thromboelastography-guided, other protocol), comparability of groups according to participants characteristics, length of follow-up, stopping rules, thrombotic event definition, SAE definition, AKI definition, protocol violations, results, method of statistical analysis, conclusions.
- Characteristics of participants: age, sex, ethnicity, weight, preoperative haemoglobin, type of cardiac operation, risk stratification (EuroSCORE/EuroSCORE II), urgency of surgery (e.g. elective, non-elective, mixed, not stated), antiplatelet and anticoagulant medication (including washout period).
- Characteristics of surgery: surgical duration, CPB use, aortic cross-clamp use, aortic cross-clamp duration, use of hypothermia, mean minimum temperature, percentage in each arm dropping out (with reasons), percentage in each arm lost to follow-up.
- Characteristics of intervention: description of intervention and comparison arms, description of control arms (including placebo, usual care, etc.), intervention(s) given, 'prophylactic' or 'rescue' intention*, intervention inclusion and exclusion criteria, route of administration of intervention, timing of intervention, methods of dosing (e.g. standard, dose per kilogram, dose

categories), dose, dose delivery (single bolus, multiple bolus, infusion).

*Prophylactic indicates participants are randomised to prophylactic drug(s) or control prior to surgery. Rescue indicates that a subgroup of participants who are experiencing active bleeding during surgery are subsequently randomised intraoperatively to a rescue drug(s) or control in response to bleeding.

Prior to extracting primary and secondary outcome data, we will undertake an intervention taxonomy process to identify if any interventions are similar enough to cluster. We will do this immediately prior to extracting outcome data to avoid introducing bias. Using the extracted data will make a list of all the different regimens of each intervention (dose, route, timing, bolus, repeat bolus, infusion) encountered in the included studies. We will then consult an independent, expert panel to determine potential groupings of the interventions which can be usefully clinically compared. We will include anaesthetic, surgical, intensive care, haematologist, pharmacologist, and statistician expertise within this panel review. This will be blinded in so far as authors and panel will not have access to the results of data extraction at this point, though some may have some incidental familiarity with the literature. We will then extract primary and secondary outcome data.

This two-stage approach was suggested to us by experts in the area of complex systematic reviews. In this way, we hope to ensure that the network meta-analysis with different intervention groups, different comparison groups, various doses, routes, and timings will be meaningful, relevant, and manageable.

In stage two, two review authors (AB, GO) will independently extract data on outcomes, and resolve disagreements by discussion and consensus and, if necessary, we will consult with a third review author (LE). The review authors will not be blinded to names of authors, institutions, journals, or the outcomes of the trials.

Assessment of risk of bias in included studies

Two review authors (GO, AB) will independently assess the risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011b). We will resolve any disagreements by discussion or by consulting a third review author (LE).

For the network meta-analysis, we will use the corresponding 'Risk of bias' tool for network meta-analysis, called Confidence in Network Meta-Analysis (CINeMA 2017).

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will express measures of treatment effect using the criteria laid out by Cochrane for dichotomous outcomes and continuous outcomes. For dichotomous outcomes, we will record the number of events and total number of participants in treatment and control

groups. For continuous outcomes, we will record the mean, SD, and total number of participants in both the treatment and control groups.

For dichotomous variables, we will express the results as odds ratios (OR) with 95% confidence intervals (CI). Where the number of observed events is small (less than 5% of sample per group), and where trials are balanced treatment groups, we will report the Peto's OR with 95% CI (Deeks 2011).

For continuous variables using the same scale, we will express the results as mean difference (MD) with 95% CIs (Takeshima 2014). For continuous outcomes measured with different scales, we will present the standardised mean difference (SMD) with 95% CIs. We are aware that certain outcomes, for example, red cell transfusions, could be reported with different units (millilitres, millilitres per kilogram, units). Therefore, if unable to convert all these measures to the desired unit (e.g. units of packed red cells), we will conduct separate meta-analyses.

If available, we will extract and report hazard ratios (HRs) for time-to-event data (mortality or time in hospital). If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provide HRs, we will to use these in favour of other reported treatment effects in the meta-analysis, otherwise we will perform a separate meta-analysis for all types of reported treatment effects, for example, ORs. If the events are rare and the follow-up times are similar, we will consider the perceived similarity of OR, risk ratios (RR), and HRs.

For cluster-randomised trials, we will extract and report direct estimates of the effect measure (e.g. OR with 95% CIs) from an analysis that accounts for the clustered design. We will obtain statistical advice to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will produce narrative descriptions of skewed data, reported as medians and interquartile ranges. If we cannot synthesise the data, we will provide a narrative summary of the available information and when appropriate, present the data in tables.

Treatment effect modifiers

We will expect to investigate the following population characteristics as treatment effect modifiers:

- concurrent preoperative antiplatelet or anticoagulant use;
- CPB use;
- elective or emergency surgery;
- type of operation:
 - CABG;
 - valve(s) repair or replacement;
 - surgery of the thoracic aorta;
 - Combination.

These will be used for the evaluation of the transitivity assumption.

Relative treatment ranking

We will attempt to obtain a hierarchy of the competing interventions and to present these with probability of different rankings tables (Mbuagbaw 2017).

Unit of analysis issues

Participants will be the unit of analysis (McKenzie 2016). We will consider and report on the impact of including any cluster trials in our analysis. With cluster RCTs we will respect the appropriate unit of analysis (e.g. hospitals), and consult a statistician to ensure appropriate treatment of data from cluster RCTs.

Where trials present multiple follow-up times, we will use the longest follow-up data at 30 days or less for the 'up to 30 day' outcome, and the longest follow-up data at 31 to 90 days for the '31 to 90 day' outcome. We will document the actual time point of each outcome recorded, or whether a time point for that outcome was not reported. For trials with only single follow-up times, we will use either the 'up to 30 days' or '31 to 90 days' category as appropriate, depending on the length of the trial.

Studies with multiple treatment groups

In pair-wise meta-analyses, we will treat trials with multiple treatment group comparisons as individual, independent two-arm studies. To avoid duplicate data in pair-wise meta-analysis, multi-arm studies will either be combined if it is clinically appropriate, or we will make appropriate adjustments, for example, dividing the sample size of a group for a continuous outcome.

We will include all different interventions in the network meta-analysis, if participant populations are comparable, regardless of how many arms there are in the study. The control group will act as a node in the network meta-analysis, which will help with indirect analyses and formation of a hierarchy of interventions.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where possible, we will use the Review Manager 5 calculator to calculate missing SDs using other data from the trial, such as CIs (Review Manager 2014). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results using a sensitivity analysis (Higgins 2011a).

Assessment of heterogeneity

If we consider the clinical and methodological characteristics of individual studies to be sufficiently homogeneous, we will combine the data to perform a meta-analysis (Deeks 2018). If considerable heterogeneity is present, we will explore the data and try to understand the underlying reasons. In standard pair-wise meta-analyses, we will estimate different heterogeneity variances for each pair-wise comparison. In network meta-analysis, we will assume a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

During initial data extraction, we will assess if clinical and methodological heterogeneity are present by looking at trial and participant characteristics across all included trials.

We will use STATA to assess statistical heterogeneity within each pair-wise comparison using the I^2 statistic and its 95% CI, which measures the percentage of variability that cannot be attributed to random error (I^2 greater than 50% = moderate heterogeneity, I^2 greater than 80% = considerable heterogeneity) (Stata 2011). The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the network meta-analysis models. We will assume a random-effects model, but we will test this assumption with a likelihood ratio test comparing random-effects and fixed-effect models (Borenstein 2010). We will compare the magnitude of the heterogeneity variance with previously suggested empirical distributions (Rhodes 2015). We will also estimate a total I^2 value for heterogeneity in the network and estimate prediction intervals for all relative effects. We will explore potential causes of heterogeneity using subgroup analyses if possible (Dias 2018).

Assessment of transitivity across treatment groups

We will assess the assumption of transitivity by comparing the distribution of the potential treatment effect modifiers across the different pair-wise comparisons. We will also epidemiologically evaluate the assumption of transitivity by comparing the clinical and methodological characteristics of sets of studies grouped within the network (Chaimani 2018; Jansen 2013).

Assessment of reporting biases

If we are able to pool more than 10 trials for pair-wise meta-analyses, we will create and examine a funnel plot to explore possible small-study biases for the primary outcomes and use a formal statistical test for asymmetry (Egger 1997). For investigating small-study effects, we will use an alternative Harbord or Sterne test (Harbord 2006; Sterne 2002).

Data synthesis

Methods for direct treatment comparisons

We will perform the statistical analysis for the meta-analysis using Review Manager 5 software (Review Manager 2014). Where studies may be estimating different yet related intervention effects, we will use a random-effects model. We will use the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes. If we use random-effects analyses, we will present the results as the mean treatment effect with its 95% CI, and the estimates of the τ^2 or I^2 statistics. We will remove any studies with zero events in both arms from the forest plot and discuss such studies using a narrative method, alongside the meta-analysis results. We will present all data that cannot be included in meta-analyses in additional tables.

Methods for network meta-analysis

We will undertake meta-analyses only where this is meaningful (i.e. if the participants and the underlying clinical question are not overly heterogeneous) (Salanti 2008). We will create network diagrams for each outcomes to check if the network is connected with direct or indirect comparisons. The expert panel, together with the network diagrams, will guide us towards grouping the interventions, comparisons, routes, doses, and timings into appropriate nodes.

We will perform network meta-analysis using Stata using the method of multivariate meta-analysis that treats the different comparisons in studies as different outcomes (Stata 2011; White 2012). We will perform this analysis using a network package with the mvmeta command (White 2011), and we will present the results using the network graphs package in Stata (Chaimani 2013; Chaimani 2015). To evaluate the assumption of transitivity, we will compare the distribution of the potential effect modifiers across the available direct comparisons. A list of prespecified effect modifiers is in the Measures of treatment effect section. We will assess inconsistency between the evidence from direct comparison and indirect comparison for interventions included in the network analysis, which is an additional method to assess transitivity of treatment effect. We will consider using both loop and global approaches as appropriate (Dias 2013).

Relative treatment ranking

We will obtain a hierarchy of the competing interventions and present these with probability of different rankings tables (Mbuagbaw 2017).

'Summary of findings' tables

We will create a 'Summary of findings' table for each intervention using the following outcomes.

- Red cell transfusions (mean units per participant).
- Chest drain output (total mL) at up to 24 hours postsurgery.
- All-cause mortality at up to 30 days postsurgery.
- Risk of receiving any allogenic blood product.
- Risk of undergoing reoperation for bleeding at up to seven days postsurgery.
- Risk of a thrombotic/thromboembolic event at up to 90 days postsurgery (MI, CVA, DVT, PE).
- Risk of acute kidney injury at up to 30 days postsurgery.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes. We will use methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), using GRADEpro software (GRADEpro GDT 2015). We will justify all decisions to downgrade the certainty of studies using footnotes and we will make comments to aid reader's understanding of the review where necessary.

Two review authors (AB, GO) will independently make judgements about the certainty of the evidence, with disagreements resolved by discussion or involving a third review author (LE). We will justify, document, and incorporate judgements into reporting of results for each outcome.

We will extract study data, format our comparisons in data tables, and prepare 'Summary of findings' tables before writing the results and conclusions of our review. A template 'Summary of findings' table is included (Table 1).

Subgroup analysis and investigation of heterogeneity

We will carry out the following subgroup analyses, using all primary outcomes, and any secondary outcomes with considerable heterogeneity.

- CPB use versus no CPB use.
- Perioperative use or continuation (or both) versus absence or cessation (with adequate washout times) (or both) of medications affecting coagulation:
 - aspirin;
 - antiplatelets;
 - anticoagulants.
- Type of operation:
 - CABG;
 - valve(s) repair or replacement;
 - surgery of the thoracic aorta;
 - combination.

We will use the formal test for subgroup differences in Review Manager 5 (Review Manager 2014), and base our interpretation on this.

Sensitivity analysis

We will carry out the following sensitivity analyses, to test whether key methodological factors or decisions affect the main results.

- Only including studies at low risk of bias in the overall risk of bias domain as specified by Cochrane Heart (Cochrane Heart Group 2018).
- Broader versus narrower groupings of interventions (on the basis of similar dosing, timings, and routes as outlined for intervention categorisation in).

Our sensitivity analysis including only studies at low risk of bias will use only the following areas within the risk of bias assessment:

- sequence generation;
- allocation concealment;
- selective outcome reporting;
- incomplete outcome data;
- blinding where this is relevant to the outcome, considered separately for subjective and objective outcomes.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review.

ACKNOWLEDGEMENTS

We thank the National Institute of Health Research (NIHR), who provided external support. This review is part of a series of reviews that have been funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. This research

was also supported by the NIHR Oxford Biomedical Research Centre Programme.

We thank NHS Blood and Transplant (NHSBT) who provided internal support. The views expressed are those of the review authors and not necessarily those of NHSBT.

We thank the NIHR Complex Reviews Support Unit, particularly Professor Olivia Wu and Dr Yiqiao Xin for advice about methods for data extraction and grouping of interventions for analysis.

We thank Susan Brunskill (NHSBT) for systematic review advice, software training, and procurement.

The authors are grateful to Dr Marialena Trivella, Centre for Statistics in Medicine, University of Oxford, UK, for reviewing the protocol and advising on statistical methodology.

We thank the following members of the Cochrane Heart and peer/consumer reviewers for their editorial review and comments:

- Nicole Martin, Managing Editor, Cochrane Heart, UCL, London, UK;
- Andrea Takeda, Systematic Review Specialist, Cochrane Heart, UCL, London, UK;
- Giovanni Mariscalco, contact editor, Cochrane Heart, University of Leicester, Leicester, UK;
- Pascal Colson, peer reviewer, Montpellier University, Montpellier, France;
- Gavin Murphy, peer reviewer, BHF Chair of Cardiac Surgery, University of Leicester, Leicester, UK;
- Vivek Podder, consumer reviewer, Tairunnessa Memorial Medical College and Hospital, Bangladesh.

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. Summary of findings table - draft

Efficacy and safety of (intervention) for reducing bleeding in adults undergoing major cardiac surgery					
Patient or population: e.g. adults undergoing aortic valve surgery Setting: hospital Intervention: e.g. tranexamic acid 1-2 g, IV, at induction, not repeated Comparison: e.g. placebo					
Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments

Table 1. Summary of findings table - draft (Continued)

	Risk with <i>con-</i> <i>trol</i>	Risk with <i>treat-</i> <i>ment</i>				
Red cell trans- fusions (mean units per participant)						
Chest drain output (to- tal mL) at up to 24 hours' post- surgery						
All-cause mor- tality at up to 30 days post- surgery						
Risk of receiving any allogenic blood product						
Risk of under- going reoperation for bleeding at up to 7 days post- surgery						
Risk of throm- botic/ thromboem- bolic event at up to 90 days (MI, CVA, DVT, PE)						
Risk of acute kidney injury at up to 30 days postsurgery						
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval; CVA: cerebrovascular attack; DVT: deep vein thrombosis; IV: intravenous; MI: myocardial infarction; PE: pulmonary embolus.</p>						

Table 1. Summary of findings table - draft (Continued)

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix I. Preliminary MEDLINE (Ovid) search strategy

1. Cardiovascular Surgical Procedures/
2. Cardiac Surgical Procedures/
3. exp Cardiac Valve Annuloplasty/
4. Heart Valve Prosthesis Implantation/ or Heart Valve Prosthesis/
5. Myocardial Revascularization/
6. exp Coronary Artery Bypass/
7. Transmyocardial Laser Revascularization/
8. Cardiopulmonary Bypass/
9. Heart Bypass Left/
10. Coronary Artery Disease/su or Coronary Occlusion/su or Coronary Stenosis/su or Coronary Thrombosis/su
11. exp Heart Valve Diseases/su
12. Heart Valves/su or Aortic Valve/su or Mitral Valve/su or Pulmonary Valve/su or Tricuspid Valve/su
13. Aorta/su
14. ((cardiac or heart or cardiovascular or cardiothoracic or coronary or myocardial or aortic valv* or mitral valv* or tricuspid valv* or pulmonary valv* or off-pump or bypass or on-pump or opcab or op-cab or vineberg) adj6 (operat* or surg* or procedure*)).tw,kf.
15. (CABG or CPB or cardiac valvuloplasty or heart valvuloplasty or aortic valvuloplasty or aortic valvotomy or mitral valvuloplasty or tricuspid valvuloplasty or transluminal valvuloplasty or balloon valvotomy).tw,kf.
16. ((cardiac or heart or cardiovascular or coronary or myocardium or myocardial or transmyocardial or aortocoronary or cardiopulmonary) adj5 (bypass or anastomosis or revasculari?ation)).tw,kf.
17. ((cardiac valv* or heart valv* or aortic valv* or mitral valv* or tricuspid valv* or pulmonary valv*) adj5 (implant* or reimplant* or graft* or replac* or repair* or reconstruct* or artificial* or prosth* or valvotom* or valvulotom* or annuloplast* or valvuloplast* or commissurotom*)).tw,kf.
18. ((ascending aort* or transverse aort* or aortic root or aortic arch or aortic outflow) adj5 (operat* or surg* or procedure* or implant* or reimplant* or graft* or replac* or repair* or reconstruct* or resection* or artificial* or prosth*)).tw,kf.
19. or/1-18
20. Antifibrinolytic Agents/
21. Tranexamic Acid/
22. Aminocaproic Acid/
23. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokaprone or cyclo-F or femstural or ugurol or aminomethylcyclohexanecarbonic

acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis adj2 inhibitor*).tw,kf.

24. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espencil or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Traptic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw,kf.

25. (6-aminohexanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogl or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177 or neocaprol or nsc?26154 or resplamin or tachostyptan).tw,kf.

26. or/20-25

27. Aprotinin/

28. (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator).tw,kf.

29. (iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren).tw,kf.

30. or/27-29

31. Factor VIIa/

32. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog* or proconvertin).tw,kf.

33. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw,kf.

34. (factor seven or factor vii or factor 7).ti.

35. 31 or 32 or 33 or 34

36. Fibrinogen/ad, ae, de, sd, tu, th, to

37. *Fibrinogen/

38. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw,kf.

39. 36 or 37 or 38

40. Deamino Arginine Vasopressin/

41. (desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin).tw,kf.

42. 40 or 41

43. exp Factor XIII/

44. (factor XIII or fXIII or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw,kf.

45. 43 or 44

46. exp Tissue Adhesives/

47. *Adhesives/

48. Collagen/tu

49. Thrombin/tu

50. Gelatin/tu

51. Gelatin Sponge, Absorbable/

52. ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)).tw,kf.
53. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw,kf.
54. (surgical* adj3 (glue* or sealant* or adhesive*)).tw,kf.
55. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw,kf.
56. (8Y or Aafact or Actif-VIII or Advate or Artiss or Bioglue or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostat or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humacloot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha).tw,kf.
57. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw,kf.
58. (Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat).tw,kf.
59. (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset).tw,kf.
60. (polysaccharide adj (sphere* or hemostatic powder)).tw,kf.
61. *Chitosan/
62. *Polyethylene Glycols/
63. *Hydrogel, Polyethylene Glycol Dimethacrylate/
64. Polyurethanes/ad, ae, pd, tu, to
65. ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)).tw,kf.
66. Cellulose, Oxidized/
67. (absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose).tw,kf.
68. (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem).tw,kf.
69. (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal).tw,kf.
70. or/46-69
71. exp Waxes/
72. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw,kf.
73. 71 or 72
74. Blood Coagulation Factors/
75. (prothrombin adj5 (complex* or concentrate*)).tw,kf.
76. (PCC* or 3F-PCC* or 4F-PCC* or Beriplex* or Feiba* or Autoplex* or Ocplex* or Octaplex* or Kcentra* or Cofact or Prothrombinex* or "Proplex-T" or Prothroras* or Hemosolvex* or Prothromplex* or "HT Defix" or Facnyne* or Kaskadil* or Kedcom* or Confidex* or PPSB or Profil?ine* or Pronativ* or Proprex* or Prothar* or ProthoRAAS* or Protromplex* or "Pushu Laishi" or "Uman Complex").tw,kf.
77. or/74-76
78. (((haemosta* or hemosta* or antihemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) ((coagulat* or clotting) adj factor*)).tw,kf.

79. 26 or 30 or 35 or 39 or 42 or 45 or 70 or 73 or 77 or 78
80. Meta-Analysis.pt.
81. ((meta analy* or metaanaly*) and (trials or studies)).ab.
82. (meta analy* or metaanaly* or evidence-based).ti.
83. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kf.
84. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
85. Cochrane Database of systematic reviews.jn.
86. (additional adj (papers or articles or sources)).ab.
87. ((electronic* or online) adj (sources or resources or databases)).ab.
88. (relevant adj (journals or articles)).ab.
89. or/80-88
90. Review.pt.
91. exp Randomized Controlled Trials as Topic/
92. selection criteria.ab. or critical appraisal.tw.
93. (data adj (abstract* or extract* or analys*)).ab.
94. exp Randomized Controlled Trial/
95. or/91-94
96. 90 and 95
97. 89 or 96
98. Randomized Controlled Trial.pt.
99. Controlled Clinical Trial.pt.
100. (placebo or randomly or groups).ab.
101. (randomi* or trial).tw,kf.
102. exp Clinical Trial as Topic/
103. 97 or 98 or 99 or 100 or 101 or 102
104. exp animals/ not humans/
105. 103 not 104
106. 19 and 79 and 105

Appendix 2. Intervention range of drug delivery methods for possible categorisation

Variable		TXA	EACA	Aprotinin	PCC	Desmo- pressin	Factor VIIa	Factor XIII	Fibrinogen
Timing	Preopera- tive	✓	✓	✓	✓	✓	✓	✓	✓
	Intraoper- ative	✓	✓	✓	?	✓	✓	✓	✓
	Postoper- ative	✓	✓	✓	?	✓	✓	✓	✓
Route	IV	✓	✓	✓	✓	✓	✓	✓	✓
	Topical	✓	✓	✓	x	?	x	?	?

(Continued)

	IV and topical	✓	✓	✓	x	?	x	?	?
	Oral	?	?	?	x	x	x	x	x
	Intranasal	x	x	x	x	✓	x	x	x
Dose calculation	Standard trial dose	✓	✓	✓	x	✓	✓	✓	✓
	Cate-gorised trial doses	✓	✓	✓	x	✓	✓	✓	✓
	mg/kg or units/kg	✓	✓	✓	✓	✓	✓	✓	✓
	Dose-response titration^a	✓	✓	✓	x	✓	✓	✓	✓
Dose method	Single dose/ap-plication	✓	✓	✓	✓	✓	✓	✓	✓
	Multiple dose/ap-plications	✓	✓	✓	x	?	?	?	?
	Contin-uous infu-sion	✓	?	?	x	?	?	?	?

EACA: ε-aminocaproic acid; IV: intravenous; PCC: prothrombin complex concentrate; TXA: tranexamic acid.

^ae.g. with viscoelastic testing guiding treatment algorithms.

✓ = intervention delivery method anticipated in randomised controlled trials (RCTs); x = intervention delivery method not expected in RCTs; ? = unsure whether to expect this delivery method in RCTs.

CONTRIBUTIONS OF AUTHORS

AB: protocol development, content expert.

GO: protocol development, content expert.

KW: content expert

CD: searching and selection of studies.

NW: statistical expertise in evidence synthesis and network meta-analysis.

LE: protocol development, methodological expert, content expert.

DECLARATIONS OF INTEREST

AB: none.

GO: none.

KW: none.

CD: none.

NW: has received research grants from the NIHR and MRC. Pfizer part-funded a junior researcher working on a methodology project using historical data in a clinical area unrelated to this project. NW has received honoraria from ABPI for delivering masterclasses on evidence synthesis. NW has delivered a short-course on network meta-analysis to ICON plc, the funds from which were paid to her institution.

LE: none.

SOURCES OF SUPPORT

Internal sources

- NHS Blood & Transplant, Systematic Review Initiative, UK.

External sources

- National Institute of Healthcare Research Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol, UK.
- National Institute for Health Research, UK.

This project was funded by the National Institute for Health Research and was supported by the Complex Reviews Support Unit, also funded by the National Institute for Health Research (project number 16/114/04). Department of Health Disclaimer: the views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.