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MEDIZINISCHE UNIVERSITÄT INNSBRUCK

Prophylactic Use of Topical Haemostatic Agents in Cardiac Surgery: A Systematic Review

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Master's thesis

Submitted to the Leopold-Franzens University of Innsbruck and the Medical University of Innsbruck in fulfilment for the acquisition of the academic degree

Master of Science

Master's programme Pharmaceutical Sciences – Drug Development and Regulatory Affairs (UC 066 607)

Innsbruck, November 2025

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Abbreviations

AE	Adverse event(s)
AGREE II	Appraisal of Guidelines for Research and Evaluation II
AIHTA	Austrian Institute of Health Technology Assessments
ATC	Anatomical Therapeutic Chemical
BASG	Bundesamt für Sicherheit im Gesundheitswesen
CABG	Coronary artery bypass grafting
CI	Confidence interval
CPB	Cardiopulmonary bypass
CT.gov	ClinicalTrials.gov
CTIS	Clinical Trials Information System (EU)
CTR.eu	ClinicalTrialsRegister.eu
EACTA	European Association of Cardiothoracic Anaesthesiology
EACTAIC	European Association of Cardiothoracic Anaesthesiology and Intensive Care
EACTS	European Association for Cardio-Thoracic Surgery
EBCP	European Board of Cardiovascular Perfusion
EU	European Union
FDA	Food and Drug Administration (US)
HAS	Haute Autorité de santé or French National Authority for Health
HTA	Health technology assessment
ICTRP	International Clinical Trials Registry Platform
ITT	Intention to treat
LVAD	Left ventricular assist device
MeSH	Medical Subject Heading
mITT	Modified intention to treat
N/A	Not applying
NCT	National Clinical Trial (identifier number)
NHS	National Health Service (United Kingdom)
NIH	National Institutes of Health (US)
N/R	Not reported
pa	Protamine administration
PICOS	Population, intervention, comparison, outcome and study design; widely used scheme to structure a research question into search components.
PICOT	Population, intervention, comparison, outcome and time; widely used scheme to structure a research question into search components.
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses

PT	Prothrombin time
PTHA	Prophylactic topical haemostatic agent application
PTT	Partial thromboplastin time
R	Correlation coefficient
RBC	Red blood cell(s)
RCT	Randomised controlled trial(s)
ris	Random index site
RoB2	Risk of Bias 2
ROBIS	Risk of Bias in Systematic Reviews
SD	Standard deviation
SR	Systematic review(s) or German: systematischer Review, systematische Reviews
Study ID	Study identification number
TBT	Topical bovine thrombin
TH	Topisches Hämostatikum, topische Hämostatika
THA	Topical haemostatic agent(s)
ULB Tirol	University and State Library of Tyrol
US	United States (of America)

Abstract

Background: Topical haemostatic agents (THA) are used to control bleeding during surgical procedures. Cardiac surgery comes with a high bleeding risk, it is therefore relevant to control but also to prevent and reduce perioperative bleeding and blood loss. THA, especially sealants and glues, are used to prevent bleeding by applying them prophylactically to suture lines and anastomoses before de-clamping and restoring pressure. This review aims to assess the efficacy and safety of the prophylactic application of topical haemostatic agents in cardiac surgery.

Methods: For this systematic review, PubMed, Cochrane Library, Embase, Web of Science, Epistemonikos and clinical trial registries were searched. Eligibility criteria were based on a predefined PICOS: patients undergoing cardiac surgery (Population), prophylactic application of THA (Intervention), no prophylactic application or comparison between agents (Comparison), efficacy and safety (Outcome), best available evidence comprising randomised controlled trials (RCT), systematic reviews (SR), guidelines and health technology assessment (HTA) reports (Study Design). Language was restricted to English and German and only studies published from 2000 until June 2025 were included. The identified evidence was narratively synthesised, and quality was assessed with the Risk of Bias 2 (RoB2), ROBIS and AGREE II tools.

Findings: Of 10,327 identified records, seven RCT, two SR, two guidelines and one HTA report were eligible. Only one RCT had low risk of bias, the quality of evidence was overall not high. Five trials reported data on haemostatic success, the prophylactic use of fibrin sealants or glues increased the achievement of haemostasis. Intra- and postoperative time-related endpoints, transfusion requirements and blood loss were not significantly influenced by the application in most RCT. The guidelines and HTA report did not recommend the application of THA in the absence of bleeding.

Interpretation: Application of THA, specifically sealants and glues, seems to have an effect in preventing suture line bleeding when applied to anastomoses before de-clamping and restoring pressure. However, the identified studies investigated different THA and cannot be compared with each other. The results do not allow to draw firm conclusions on postoperative, patient-relevant endpoints. Further studies are needed to assess if the application has a clinically relevant effect. Thus, in current clinical practice, the prophylactic application of topical haemostatic agents appears to be guided more by the surgeon’s experience and preference than by consistent evidence from controlled studies.

Kurzfassung

Hintergrund: Topische Hämostatika (TH) werden zur Blutungskontrolle bei operativen Eingriffen eingesetzt. Kardiochirurgische Operationen haben ein hohes Blutungsrisiko, weshalb sowohl die Kontrolle als auch die Vorbeugung und Verminderung von Blutungen relevant ist. TH, besonders *sealants* und Kleber, werden zur Blutungsprophylaxe eingesetzt, indem sie präventiv vor De-Clamping und Wiederherstellung des Blutflusses auf Nahtlinien und Anastomosen aufgetragen werden. Dieser Review hat zum Ziel, die Effektivität und Sicherheit der prophylaktischen Anwendung von topischen Hämostatika in der Herzchirurgie zu untersuchen.

Methoden: Im Rahmen dieses systematischen Reviews wurden PubMed, Cochrane Library, Embase, Web of Science, Epistemonikos und Klinische Studienregister durchsucht. Die Ein- und Ausschlusskriterien basierten auf einem vordefinierten PICOS: kardiochirurgische Patienten (Population), prophylaktische Applikation von TH (Intervention), Vergleich mit anderen TH oder keine prophylaktische Applikation (Comparison), Effektivität und Sicherheit (Outcome), die beste verfügbare Evidenz (Studiendesign: randomisierte kontrollierte Studien (RCT), systematische Reviews (SR), Leitlinien und Health Technology Assessment (HTA) Berichte). Die Textsprache wurde auf Englisch und Deutsch und der Publikationszeitraum auf 2000 bis Juni 2025 eingegrenzt. Die gefundene Evidenz wurde narrativ zusammengefasst, die Qualität mittels Risk of Bias 2 (RoB2), ROBIS und AGREE II beurteilt.

Ergebnisse: Von 10.327 Suchergebnissen entsprachen sieben RCT, zwei SR, zwei Leitlinien und ein HTA-Bericht den Ein- und Ausschlusskriterien. Nur ein RCT hatte ein niedriges Bias-Risiko, die Qualität der Evidenz war insgesamt nicht hoch. Fünf Studien berichteten Daten zur erfolgreichen Hämostase, die prophylaktische Anwendung von *sealants* und Klebern führte zu deren Erhöhung. Intra- und postoperative zeitbezogene Endpunkte, Transfusionen und Blutverlust wurden in den meisten RCT nicht signifikant von der Applikation beeinflusst. Die Leitlinien und der HTA-Bericht empfahlen die Anwendung von TH vor Auftreten einer Blutung nicht.

Interpretation: Die Anwendung von TH vor De-Clamping und Wiederherstellung des Blutflusses, vor allem *sealants* und Kleber, scheint effektiv zu sein, um Nahtlinienblutungen zu vermeiden. Die identifizierten Studien untersuchten jedoch unterschiedliche TH und können nicht direkt verglichen werden. Die Ergebnisse erlauben keine sicheren Aussagen zu postoperativen, patientenrelevanten Endpunkten. Weitere Studien sind notwendig, um festzustellen, ob die Anwendung klinisch relevante Effekte hat. Die derzeitige prophylaktische Anwendung scheint mehr von Erfahrung und Präferenz des chirurgischen Personals und weniger von Evidenz aus klinischen Studien geleitet zu sein.

1 Introduction and Background

Cardiac surgery is associated with bleeding complications and high risk of allogeneic blood transfusion; therefore (patient) blood management is highly important to control, reduce and prevent perioperative bleeding and blood loss. Haemostatic agents are used in surgical blood management to control bleeding and promote haemostasis during surgery. Besides systemically acting haemostatic agents topically applied haemostatic agents have substantial clinical potential and are effective in promoting haemostasis. They comprise various products that can be categorised as active or adhesive agents, mechanical haemostats or synthetic/semisynthetic sealants for clinical use. Their use is increasing with the expansion of minimally invasive approaches in cardiac surgery where conventional methods to achieve haemostasis are often not feasible or impractical. Blood transfusions are costly, and their availability is not always guaranteed. Alternative strategies for bleeding management are required for patients who refuse blood transfusion for instance due to religious beliefs like Jehovah's Witnesses. Topical haemostatic agents may be effective not only in treating but also in preventing perioperative bleeding and blood loss when used prophylactically, thereby reducing the need for blood transfusions, shortening hospital stays, and decreasing healthcare costs.

This master thesis provides a systematic review of the efficacy and safety of topical haemostatic agents when applied prophylactically. The results of this review may support health care decision makers and manufacturers in planning clinical trials to further investigate the prophylactic use of topical haemostatic agents and inform cardiac surgeons on the safe and efficacious use of topical haemostatic agents for prophylactic purposes. In the first section of this thesis, a short introduction to cardiac surgery and patient blood management will be presented. Different types of topical haemostatic agents, their use in cardiac surgery and recommendations for their use generally in surgery as available in literature will be outlined. These introductory and background chapters will be followed by a summarised outline of the research objectives and the research question. In the second part, the methods of conducting and reporting the review will be presented, including the specifications of the scope. The research question is structured by a scheme into the components population, intervention, comparison, outcome and study design (PICOS). The eligibility criteria will also be outlined. In the third part the results of the review will be reported and discussed, introducing also additional context from publications not eligible in the review but relevant for the research question. The review report will be concluded by proposals for potential future research.

The report is prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement by Page, McKenzie, et al. (2021).

1.1 Cardiac Surgery

Senst et al. (2024) define cardiac surgery as “a medical specialty focused on the surgical treatment of heart and thoracic aorta pathologies” (Introduction, para. 1). Cardiac surgery is a routine practice with which various congenital and acquired heart diseases like advanced coronary artery disease may be treated. Explained in lay language, “[h]eart surgery can help to maintain and prolong life by: • restoring blood supply to the heart by opening – or replacing – blocked coronary arteries • stretching, repairing or replacing a damaged heart valve • correcting or regulating an abnormal heart rhythm” (NHS inform, 2025, Heart surgery, para. 2). The field of cardiac surgery comprises multiple different surgical approaches, from open-heart surgery to minimally invasive techniques or transcatheter procedures. The Austrian register for quality in cardiac surgery for example captures data on heart transplantations, valve repair and replacement, coronary artery bypass grafting, surgical operations of the thoracic aorta and operations of congenital heart diseases (Santner et al., 2024). As the prevalence of cardiovascular diseases increases, so does the need for cardiac surgical procedures (Rieß et al., 2021; Senst et al., 2024). About 6000 cardiac surgical interventions are performed annually in Austria (Gesundheit Österreich, 2025). This systematic review focuses on patients undergoing cardiac surgery, elective or emergency, however excluding any vascular surgery.

1.2 Patient Blood Management

Cardiac surgery is associated with a high risk of perioperative bleeding and blood loss. This is a major complication and contributes to adverse clinical outcomes, mortality and morbidity, but also requires blood transfusion which increases the costs together with the potentially prolonged hospital stay (Casselman et al., 2025; Klein et al., 2021; Klein et al., 2022; Pagano et al., 2018; Salenger et al., 2025; Senst et al., 2024). The 2017 guidelines on patient blood management in adult cardiac surgery by the European Association for Cardio-thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA) (Pagano et al., 2018) as well as Klein et al. (2022) list the invasiveness of the surgical procedures, the cardiopulmonary bypass and the anticoagulation and antiplatelet treatment as major risk factors for the intra- and postoperative bleeding. Patient blood management guidelines for all kinds of surgical procedures and specifically for cardiac surgery have been developed and should be implemented to maintain haemostasis, to reduce bleeding and blood loss, and to decrease the demand for blood products and transfusion. All these aspects may have an influence on health care costs and patient outcomes (Klein et al., 2022; Pagano et al., 2018). The main steps in the patient blood management approach as presented in the updated 2024 guidelines by the EACTS, the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC) and the European Board of Cardiovascular Perfusion (EBCP)

(Casselman et al., 2025) are: pre-, intra- and postoperative identification of anaemia, preoperative identification of high risk patients, preoperative management of antithrombotic medication, intraoperative maintenance of haemostasis, minimisation of blood loss and haemodilution, management of heparin and prothrombin and postoperative algorithms for and treatment of bleeding patients. Intraoperative haemostasis should be achieved by systemic (e.g. systemic administration of blood products or antifibrinolytics) and local methods (including suture application, electrical tissue cauterisation or the topical administration of haemostatic agents). With the increasing use of minimally invasive techniques, the use of topical haemostatic agents has also increased as it is more difficult to achieve haemostasis with classical local methods (Al-Attar et al., 2023; Moldovan et al., 2022).

1.3 Topical Haemostatic Agents - Types

Haemostatic agents are adjuncts in surgical blood management, used to control bleeding and maintain haemostasis during surgical procedures. Besides systemically acting haemostatic agents topically applied haemostatic agents have enormous clinical potential and are effective in achieving intraoperative haemostasis in cardiac surgery. Topical haemostatic agents comprise various products that can be categorised as active, mechanical (passive, non-active) haemostatic agents or sealants, combination products are also available. Conventional local techniques to achieve haemostasis include simple pressure, placement of sutures ligature or vascular clips, electrocautery or warm saline irrigation (Achneck et al., 2010; Al-Attar et al., 2023; Besser et al., 2015; Moldovan et al., 2022).

A classical topical haemostatic agent with a physical mechanism of action in form of occlusion and tamponade effect would be bone wax (bee's wax with paraffin or Vaseline) which is used to treat bleeding from the bone like the sternum in a sternotomy. Other conventional topical haemostatic agents are passive or non-active haemostatic agents, also called absorbable agents, which have a physical or mechanical mechanism of action by providing a structure, matrix or framework where cells and platelets can adhere to. Thereby (contact activation) these agents support, initiate and promote aggregation and clot formation but they are dependent on the patient's own coagulation cascade which can be limited due to coagulation disorders or an anticoagulant or antiplatelet treatment. Examples for passive agents are oxidised regenerated cellulose, microfibrillar collagen, gelatine sponges or foams or microporous polysaccharide spheres. They can be used for mild to moderate bleeding (Achneck et al., 2010; Al-Attar et al., 2023; Besser et al., 2015; Moldovan et al., 2022).

Active or biological haemostatic agents are extrinsic clotting factors, mostly thrombin, and therefore independent of the patient's coagulation mechanism and any limitation of the cascade. They mimic the last steps of the coagulation cascade and accelerate the natural clot

formation; they may be used in a wide range of bleeding. Thrombin may also be combined with mechanical agents (e.g. gelatine). These so-called flowables directly promote the coagulation, have in addition a tamponade effect and can fill deep lesions or conform to wound contours. They are used on active bleeding sites. Topical haemostatic agents based on thrombin are called sealants, however this term is more often used for agents combining thrombin with fibrinogen or for synthetic or semisynthetic agents, also referred to as tissue sealants. Some sealants are called glues as they glue surfaces together, all being independent of the patient's own clotting cascade. The mechanism of action of sealants is the formation of a physical barrier and blocking the bleeding site. The combination of thrombin and fibrinogen is called fibrin sealants as a fibrin clot is created, mimicking the end of the coagulation cascade. By adding antifibrinolytics, the fibrinolysis can be inhibited. Tissue sealants contain no intrinsic haemostatic factors, semisynthetic sealants contain albumin, synthetic sealants contain no other plasma derivatives. Examples for tissue sealants are absorbable cyanoacrylate, polyethylene glycol polymers, chitin- or chitosan-based agents or glutaraldehyde-albumin (Achneck et al., 2010; Al-Attar et al., 2023; Besser et al., 2015; Moldovan et al., 2022).

Topical haemostatic agents are categorised as medicinal products and not as medical devices and require a marketing authorisation on either national or European level. In the Austrian National Medicines Register five products can be identified with the Anatomical Therapeutic Chemical (ATC) code B02BC for local haemostatics: ARTISS (solutions for sealant), Tisseel (solutions for a tissue glue) and Tisseel Lyo (powder and solvent for a tissue glue) by Baxter Medical Products GmbH, Vienna, Austria; TachoSil (sealant matrix) by Corza Medical GmbH, Düsseldorf, Germany; and VeraSeal (solutions for fibrin glue) by Instituto Grifols SA, Parets de Vallés, Spain (BASG, 2025). TachoSil and VeraSeal are authorised on European level. All products are combination products of fibrinogen and thrombin and can therefore be classified as sealants. However, ARTISS is contraindicated for sealing anastomoses in cardiovascular surgery (Baxter Medical Products GmbH, 2025). Tisseel, TachoSil and VeraSeal are indicated for improvement of haemostasis in surgery and suture support in vascular surgery, but a prophylactic application in cardiac surgery is not specifically mentioned in the public assessment reports (BASG, 2016; European Medicines Agency, 2017, 2018).

From literature, it cannot be inferred if topically applied antifibrinolytics should be included in the group of topical haemostatic agents or not. Topical antifibrinolytics are primarily applied to avoid postoperative bleeding and bleeding complications and are applied in a late stage of surgery. In this review, the topical application of antifibrinolytics, also in a prophylactic context, has been excluded to put the focus on pre- and intraoperative applications of agents before bleeding occurs. Therefore, these agents are not further described in this chapter. However, their use is outlined in guidelines and reviews and is thus shortly discussed in chapter 1.5.

1.4 Topical Haemostatic Agents – Applications

Topical haemostatic agents are applied locally during cardiac surgery to improve haemostasis. They are used when conventional surgical techniques are insufficient to control bleeding as supportive treatment options. Rychlik (2006) presents a comprehensive list of applications in different surgical areas for TachoSil. In cardiovascular surgery these include: “securing of anastomoses, glueing of bypass harvest areas, sealing of perforations of the cardiac wall, sealing of adhesiolyses in reoperations, securing of aortotomies, sealing of accidental lung leakages and sealing of needle hole bleedings” (Rychlik, 2006, p. 200 [Translation]). Some narrative reviews on topical haemostatic agents also include schematic depictions of the algorithm of applying topical haemostatic agents for bleeding management (Bracey et al., 2017; Burks & Spotnitz, 2014; Forcillo & Perrault, 2014; Moldovan et al., 2022; Spotnitz, 2012). While most focus on the application when bleeding has already occurred, displaying treatment pathways based on surface area and severity of bleeding, Bracey et al. (2017) and Forcillo and Perrault (2014) also include a pathway for anticipated bleeding. The selection flowchart displayed by Bracey et al. (2017) recommends the use of albumin and glutaraldehyde or polyethylene glycol polymers in cases of a high anticipated bleeding risk in patients with an unimpaired coagulation mechanism. The algorithm presented by Forcillo and Perrault (2014) leads to the use of CoSeal for anticipated anastomosis bleeding and to the application of CoSeal, Tisseel or Evicel for anticipated diffuse bleeding.

1.5 Topical Haemostatic Agents – Recommendations for Use

While some guidelines and advices for patient blood management focus on transfusion needs and pre-, intra- and postoperative testing to control bleeding and do not mention topical administration of haemostatic agents (Faraoni et al., 2019; Raphael et al., 2019), the 2017 EACTS/EACTA (Pagano et al., 2018) and updated 2024 EACTS/EACTAIC/EBCP (Casselman et al., 2025) guidelines on patient blood management in adult cardiac surgery mention the use of topical haemostatic agents as a surgical technique in intraoperative management in cardiac surgery. They describe topical haemostatic agents as a supplement for conventional approaches and classify them into active, non-active and flowable (combination) agents which include haemostatic sealants and topical antifibrinolytic agents (like aprotinin, tranexamic acid and epsilon-aminocaproic acid). They discourage the application of topical sealants to prevent blood loss and transfusion requirement and recommend their use only at localised bleeding sites when conventional haemostatic methods are insufficient (Casselman et al., 2025).

In their guideline for management of severe perioperative bleeding, Kietaibl et al. (2023) recommend the topical application of tranexamic acid in case of contraindications for the systemic administration in patients undergoing cardiovascular surgery. Ferraris et al. (2011)

and Tibi et al. (2021) suggest the use of topical antifibrinolytic agents in cardiac surgery which was performed on cardiopulmonary bypass to reduce blood loss and the demand for blood products and transfusion. Ferraris et al. (2011) also recommend the use of other topical haemostatic agents to achieve haemostasis at anastomoses, referring to agents which act through sealing or compression. Apfelbaum et al. (2015) suggest fibrin glue and thrombin gel as topical haemostatics for treating excessive bleeding. In their review of scientific evidence informing their guideline recommendations they found that these two agents may decrease blood loss, transfusion requirements and time to haemostasis (Apfelbaum et al., 2015). Kietaibl et al. (2023) advise to apply topical haemostatic agents in hepatic surgical procedures to reduce blood loss and the demand for blood products.

While the American College of Obstetricians and Gynecologists' Committee (2020) advise specifically against the use for bleeding prophylaxis in the context of obstetric and gynaecologic surgery, Barnard and Millner (2009), Besser et al. (2015) and Moldovan et al. (2022) recommend a prophylactic application of topical haemostatic agents in cardiac surgery. The agents, especially those accelerating clot formation, should be applied to the target site while blood flow is low and haemorrhage is minimal. A more detailed description of the pre-emptive application of sealants in cardiac surgery on potential bleeding sites before the blood flow is restored, is outlined by Al-Attar et al. (2023). Their prophylactic strategy, which they recommend especially if bleeding risk is high, is comprised of two steps to achieve high efficacy and minimise waste: the application of the sealant is complemented by the application of a passive haemostatic agent which forms a structure for clot formation. Al-Attar et al. (2023) further explain that, "[t]he choice of a haemostat depends on the anticipated bleeding risk, ability to achieve haemostasis with conventional surgical techniques, the need for a bolstering effect at the site of bleeding, and the degree of derangement of the coagulation system" (p. 6). Moreover, the choice and effectiveness of the application of topical haemostatic agents is often dependent on availability of the agent as well as personal preference and experience of the surgeon (Barnard & Millner, 2009; Forcillo & Perrault, 2014; Moldovan et al., 2022).

Even though there are recommendations available, literature also states that topical haemostatic agents have not yet been studied sufficiently and mostly with the primary goal of controlling, not preventing bleeding. Furthermore, it seems to be difficult to establish reliable endpoints and therefore to assess topical haemostatic agents in randomised controlled trials (Levy et al., 2022; Moldovan et al., 2022; Tibi et al., 2021). This systematic review focuses on the prophylactic application of topical haemostatic agents, since the application of topical haemostatic agents for suture line sealing and to prevent bleeding is current clinical practice.

2 Aims and Review Question

The objective of this master's thesis is to systematically review the current evidence on the prophylactic use of topical haemostatic agents in cardiac surgery. Specifically, the study seeks to assess the efficacy and safety of these agents when applied preoperatively or intraoperatively before bleeding occurs, such as for suture line sealing, rather than for the treatment of active perioperative bleeding. To achieve this aim, a systematic review of clinical trials and other relevant literature is conducted, focusing on the highest-quality evidence available.

The review question is as follows: Is the prophylactic use of topical haemostatic agents in cardiac surgery effective and safe compared to no prophylactic use or to the use of other topical haemostatic agents?

3 Methods

Systematic reviews have a high level of evidence and allow to combine publications and knowledge from various researchers to support a clinical or healthcare decision. They are based on a methodical process with pre-specified research objectives and eligibility criteria, ensuring transparency, minimal bias, and high replicability in the identification and analysis of literature. The main steps of a systematic review are first to specify and structure a research question using for example a PICO scheme; second to develop eligibility criteria and to conduct a search and screening process in order to identify relevant publications; third to evaluate the quality of included studies e.g. by assessing risk of bias; fourth to compile the evidence either qualitatively in a narrative synthesis or quantitatively in a meta-analysis; and fifth to discuss and interpret the available data and results (Calderon Martinez et al., 2023; Lasserson et al., 2024; Randles & Finnegan, 2023; Tawfik et al., 2019).

This systematic review has been conducted according to the strategies and guidelines presented by Calderon Martinez et al. (2023), Fröschl et al. (2012), Higgins et al. (2024), Nordhausen and Hirt (2022), Page, McKenzie, et al. (2021), Page, Moher, et al. (2021), Randles and Finnegan (2023) and Tawfik et al. (2019).

3.1 Protocol and Registration

The protocol for this systematic review has been developed according to the PRISMA 2020 statement (Page, McKenzie, et al., 2021) but has not been registered. The protocol is provided in Appendix A.

3.2 PICOS and Eligibility Criteria

The PICOS scheme depicted in Table 1 was predefined to formulate the research question.

The following research question was formulated based on the developed PICOS scheme: Is the prophylactic use of topical haemostatic agents in cardiac surgery effective and safe compared to no prophylactic use or to the use of other topical haemostatic agents?

Table 1: PICOS Scheme for the current review

Population	Patients undergoing cardiac or cardiovascular surgery, including surgical procedures of the ascending aorta, the valves, the chambers, coronary arteries as well as combinatory operations of heart and vessels. NOT patients undergoing vascular surgery only (including surgical procedures of carotids, the descending aorta, peripheral arteries and veins). Adult and paediatric, no age limitation.
Intervention	Prophylactic application of topical haemostatic agents to prevent bleeding. Including mechanically acting haemostatic agents (collagen-based products, polymer-based sealants etc.) OR active (pharmacologically enhanced) haemostatic agents (thrombin-containing products, fibrin sealants, tranexamic acid-coated materials etc.) OR combination products. NOT systemic application of haemostatics. Prophylactic application can be pre- or max. intraoperative before bleeding occurs, before clamps are opened and blood flow restored, for example for suture line sealing NOT postoperative.
Comparison	No prophylactic treatment with topical haemostatic agents or comparison between topical haemostatic agents applied for prophylactic treatment.
Outcome	Efficacy: Anastomotic sealing or haemostasis: proportional or time measurement; amount of perioperative bleeding, transfusion requirements; additional haemostatic procedures; reoperation incidence; operational time, length of hospital stay. Safety: (Serious) adverse events; mortality.
Study Design	Best available evidence: randomised controlled trials, systematic reviews and guidelines and health technology assessments.

PICOS is an abbreviation for population, intervention, comparison, outcome and study design and is a widely used scheme to structure a research question into search components.

Title, abstract and full text of publications were analysed according to the following, predetermined eligibility criteria, which were based mainly on the population and intervention components of the PICOS scheme. Inclusion criteria 5 and 6 were determined after establishing that studies of the highest evidence were available for the topic and that these were published from 2000 until June 2025 and thus were contemporary evidence. Exclusion criterion 7 was included because sternotomy involves bleeding and the application directly after the procedure therefore has a therapeutic effect to stop this active bleeding.

Inclusion Criteria

1. Studies in patients of all age undergoing cardiac OR cardiovascular surgery (including surgical procedures of the ascending aorta, the valves, chambers, coronary arteries as well as combinatory operations of heart and vessels).

2. Topical haemostatic agents (including mechanically acting haemostatic agents (collagen-based products, polymer-based sealants etc.) OR active (pharmacologically enhanced) haemostatic agents (thrombin-containing products, fibrin sealants, tranexamic acid-coated materials etc.) OR combination products have been applied prophylactically (pre- or intraoperatively before bleeding occurs) to prevent and reduce perioperative bleeding.
3. Publication in English or German language.
4. Outcome describes efficacy and/or safety of the intervention. Efficacy outcomes may include, but are not limited to, proportion of or time to anastomotic sealing or haemostasis, the amount of perioperative bleeding, transfusion requirements, incidence of reoperation, operational times or length of hospital stay. Safety outcomes may include, but are not limited to, (serious) adverse events or mortality.
5. Study Design: Best available evidence. Randomised controlled trials (RCT), systematic reviews and guidelines and health technology assessment (HTA).
6. Publication from 2000 until June 2025.

Exclusion Criteria

1. Studies in patients undergoing vascular surgery only (including surgical procedures of carotids, the descending aorta, peripheral arteries and veins).
2. Studies in animals or in-vitro.
3. Postoperative application of topical haemostatic agents.
4. Systemic administration of haemostatic agents.
5. Application of topical haemostatic agents to treat active perioperative bleeding.
6. Application of topical haemostatic agents after other techniques have shown to be insufficient to control bleeding.
7. Application of topical haemostatic agents directly after sternotomy to the sternum.
8. Topical application of antifibrinolytic drugs if not in combination with another haemostatic agent.
9. Publication as non-peer reviewed literature, for example conference reports.

PICOS and eligibility criteria were defined with the input of a medical expert.

3.3 Search Strategy

The systematic literature search was conducted on 17 June 2025 and 27 June 2025 in the online literature databases PubMed/MEDLINE, the Cochrane Library via Ovid, Embase via CAS ST Next (performed by a librarian of the University and State Library of Tyrol (ULB Tirol)), Web of Science and Epistemonikos. Furthermore, four clinical trial registries (https://trialsearch.who.int/, International Clinical Trials Registry Platform, ICTRP; https://www.clinicaltrials.gov, CT.gov; https://euclinicaltrials.eu/, CTIS; and

https://www.clinicaltrialsregister.eu/, CTR.eu) were consulted for ongoing studies on 18 June 2025. Reference list checking was performed as a supplementary method to database and registry searching. The reference lists of all included records were reviewed by removal of duplicates and title and abstract screening. The number of records identified for full text screening was added to the PRISMA flow chart.

The search string was constructed around the main search terms “cardiac surgery” and “topical haemostatic agents” including synonyms, variations in writing and controlled vocabulary. Terms were combined with Boolean operators and truncation. For the full search string, see Appendix B. The search strategy was developed using the research protocol for systematic literature research provided by Hirt and Nordhausen (2022), see Appendix C. A ULB Tirol librarian was consulted for support in the optimisation of the search string.

3.4 Study Selection

The systematic review was conducted according to the PRISMA statement and the method manual by the Austrian Institute of Health Technology Assessments (AIHTA) as a best practice guidance (Fröschl et al., 2012; Page, McKenzie, et al., 2021). The review was not conducted in a team but by a single person. In case of uncertainty about eligibility, the supervisor was consulted for input and discussion. The selection of studies was performed in the following steps: Title, abstract and full text screening based on inclusion and exclusion criteria. From Embase only title and keywords were provided in a first step and due to financial reasons only 50 abstracts could be retrieved. Inclusion criteria 5 and 6 were implemented after establishing the level and topicality of available evidence. Reasons for exclusion were noted for every publication during the full text screening. The prophylactic application as defined before was a criterion in title and abstract screening, but non-appearance led only to exclusion in the full text screening. The selection process is displayed in Figure 1.

3.5 Quality Assessment

Included studies were assessed for quality and risk of bias by the author. The tools and protocols for quality assessment were not defined at protocol development as it was unclear which level of evidence would be retrieved. However, protocols as provided and recommended by Cochrane and the PRISMA statement were planned to be used. As RCT were retrieved as the best available evidence, the risk of bias was assessed using the Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019), as recommended by Cochrane. Risk of bias in systematic reviews was assessed with the Risk Of Bias In Systematic reviews (ROBIS) tool (Whiting et al., 2016). The quality of guidelines was evaluated with the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool (Brouwers et al., 2010).

3.6 Data Extraction, Analysis and Presentation

Relevant data was extracted from the included studies by the reviewer. A table of evidence including Study ID, first author, publication date, study type and design, study population, in- and exclusion criteria, study arms including number of patients, intervention characteristics (experimental and comparator), study duration and location, primary and secondary study endpoints, baseline characteristics, primary and secondary outcome, safety outcome and adverse events, limitations, and conclusion of the study authors was created.

Due to heterogeneity among the included RCT, data were synthesised qualitatively, with a narrative summary and accompanying tables provided. No further analysis for comparison or any statistical analysis was conducted. Results of RCT are presented in tables, displaying: Study identification number (Study ID) and reference; the numerical results of study endpoints for the investigational arm and the (active) comparator or control (no prophylactic application of topical haemostatic agents) arm; and p-value and significance, if and as reported. Adverse events were categorised by broader Medical Subject Heading (MeSH) terms if they were reported by only one or two studies and not mentioned in a specific subsection. RCT with an active comparator and RCT with a control arm without the prophylactic application of topical haemostatic agents are included in this review, their study results are not presented separately but in joint tables for each outcome parameter. However, studies with active comparators are colour-coded in blue in the study results tables to allow a visual distinction.

The report of the systematic review was created according to the PRISMA 2020 statement (Page, McKenzie, et al., 2021).

3.7 Software

Microsoft 365 Excel, Lumivero Citavi 6.20 Windows Reference Management Software and Clarivate Endnote Web (https://www.myendnoteweb.com/EndNoteWeb.html) were used within the review process. The online dictionary and translation tools by Cambridge University Press & Assessment, Cambridge, United Kingdom (https://dictionary.cambridge.org/), Merriam-Webster Inc., Springfield, Massachusetts (https://www.merriam-webster.com/), and PONS Langenscheidt GmbH, Stuttgart, Germany (https://de.pons.com/übersetzung) were consulted for language refinement.

4 Results

4.1 Literature Screening

A total of 9,496 records were identified through database searches, and 828 possibly relevant records were identified through clinical trial registries. Reviewing the reference lists of included full-text articles, three additional records were identified. The selection process is displayed in the following flow chart (Figure 1) according to PRISMA guidelines.

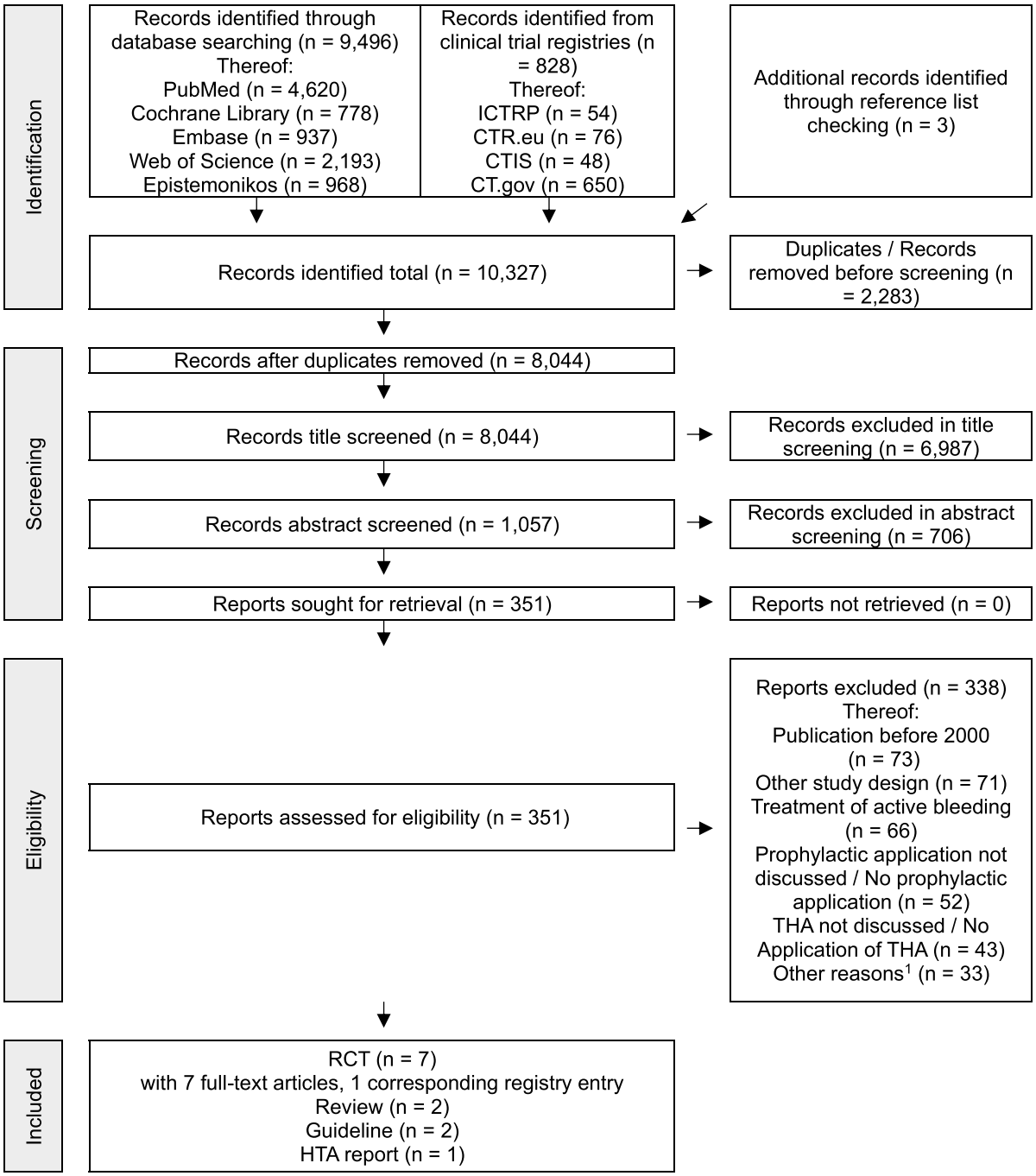


Figure 1: Flow chart of study selection. *PRISMA 2020 Flow Diagram as proposed by Page, McKenzie, et al. (2021). [1]Other reasons include not bleeding-related indications (n = 13), no relevant outcome data for assessment (n = 13), non-cardiac surgery patient population (n = 4), antifibrinolytics only (n = 2) and ongoing study without published results (n = 1). Abbreviations: RCT … Randomised controlled trial; THA … Topical haemostatic agent; HTA … Health technology assessment. Clinical trial registries abbreviated as listed in chapter 3.3.*

4.2 Included Studies

A total of twelve clinical trials and other relevant literature were included in the review for the assessment of efficacy and safety. Seven RCT with full-text articles and one corresponding accessible registry entry, two guidelines, one health technology assessment (HTA) report and two systematic reviews (SR) were deemed eligible for inclusion.

Table 2 lists the studies identified to be eligible for the assessment.

Table 2: List of included studies

Study ID[1]	Study Type	Available documentation
PTHA.01-BC-2003	Interventional, randomised controlled, single-blinded (participant)	Registry entry: N/A Publication: Coselli et al., 2003
PTHA.02-CG-2004	Interventional, randomised controlled, single-blinded (participant)	Registry entry: N/A Publication: Hagberg et al., 2004
PTHA.03-TG-2018	Interventional, randomised controlled, parallel assignment, single blinded (participant)	Registry entry: NCT01959503 (NIH ClinicalTrials.gov, 2017) Publication: Khoynezhad et al., 2018
PTHA.04-GC-2009	Interventional, randomised, controlled, open-label	Registry entry: N/A Publication: Minato et al., 2009
PTHA.05-SC-2019	Interventional, randomised, controlled, open-label	Registry entry: UMIN000023683 Publication: Morita et al., 2020
PTHA.06-TC-2018	Interventional, randomised, controlled, open-label	Registry entry: RNN/229/13/KE Publication: Ostrowski et al., 2021
PTHA.07-CS-2003	Interventional, comparative, randomised, controlled, open-label	Registry entry: N/A Publication: Sirlak et al., 2003

[1]In the following tables and text, the study will be referred to by this study ID. The review specific study ID is composed of the abbreviation PTHA (prophylactic topical haemostatic agent application), a serial number, the first letters of the investigated interventions and the publication year. Abbreviation: N/A … not applying.

Table 3 lists all other publications identified to be eligible for the review.

Table 3: List of all other included publications

Short Title[1]	Title	Publication Type	Reference
HAS HTA Report	Surgical hemostatic agents: Assessment of drugs and medical devices	Health technology assessment report	Aubourg et al., 2011
2024 Guidelines	2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP	Guideline	Casselman et al., 2025
Thrombin SR	Topical bovine thrombin and adverse events: a review of the literature	Systematic review	Clark et al., 2008
Surgicel SR	A contemporary systematic review of the complications associated with SURGICEL	Systematic review	Masoudi et al., 2023
2017 Guidelines	2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery	Guideline	Pagano et al., 2018

[1]In the following tables and text, the publication may be referred to by this review specific short title.

Studies of a lower evidence level (e.g. non-controlled trials, retrospective studies, observational studies, case series) and narrative reviews were deemed ineligible.

4.3 Study Characteristics of Randomised Controlled Trials

4.3.1 Description of Study Interventions

Table 4 presents the interventions and details of administration procedure. Three studies included an active comparator, while four studies used a control group in which the experimental intervention was not administered.

Table 4: Characterisation of the interventions of included studies

Study ID (Reference)	**Experimental Intervention** Details	**Comparator/ Control** Details
PTHA.01-BC-2003 (Coselli et al., 2003)	Standard repair plus **BioGlue Surgical Adhesive** After drying the completed anastomosis and protecting the surrounding area with moist sterile gauze paste, application of thin, even coating of BioGlue to anastomosis. After 2 min, trimming of excess glue and pressure restoring.	Standard repair alone (**control**) Completion of anastomosis using standard surgical techniques.
PTHA.02-CG-2004 (Hagberg et al., 2004)	**CoSeal surgical sealant** After confirmation of anastomotic leakage, re-clamping of graft and application of CoSeal to the suture line.	**Gelfoam/thrombin** After confirmation of anastomotic leakage, re-clamping of graft and application of Gelfoam/thrombin to the suture line.
PTHA.03-TG-2018 (Khoynezhad et al., 2018; NIH ClinicalTrials.gov, 2017)	**Tridyne vascular sealant** After confirmation of anastomotic leakage, Tridyne applied to the proximal/distal aortic anastomotic suture line/both under positive intravascular pressure. Target area blotted with a sponge/gauze before application. Bypass cross-clamp released after application.	**Gelfoam Plus** After confirmation of anastomotic leakage, Gelfoam Plus applied to anastomotic suture lines according to manufacturer's instructions for use. Bypass cross-clamp released after application.
PTHA.04-GC-2009 (Minato et al., 2009)	**Fibrin glue rub-and-spray method** Application to proximal and distal anastomoses. Dripping fibrinogen solution over needle holes and rubbing it on with fingers, then spraying fibrinogen and thrombin solutions on anastomosis simultaneously. Perfusion restarted 3 min after application.	No fibrin glue (**control**)
PTHA.05-SC-2019 (Morita et al., 2020)	**Elastomeric sealant** Application of the elastomeric sealant to anastomosis when anastomosis was made. No other haemostatic agent allowed.	Without sealant (**control**) Application of any haemostatic method/material except for elastomeric sealant.
PTHA.06-TC-2018 (Ostrowski et al., 2021)	**Tachosil** (local haemostatic, composed of a double collagen layer coated with human thrombin and fibrinogen) Application on the aortotomy suture line and aortic cannulation site.	Without application of Tachosil (**control**)
PTHA.07-CS-2003 (Sirlak et al., 2003)	**Colgel powder** (microfibrillar collagen) Application on anastomoses and atriotomies. Remaining content of Colgel box was poured into the pericardial cavity / over mediastinal tissues before closure.	**Surgicel** (oxidised cellulose) Application on anastomoses and atriotomies.

Ten different topical haemostatic agents (BioGlue, CoSeal, Gelfoam/thrombin, Tridyne, Gelfoam Plus, Tachosil, Colgel, Surgicel, fibrin glue and an elastomeric sealant) were investigated. In five studies, the topical haemostatic agents were described to be applied for sealing of anastomoses to prevent suture line bleeding. The products were applied when or after the anastomosis was prepared, before clamp release or before pressure was restored, thereby fulfilling the inclusion criteria of this review of a prophylactic and not therapeutic administration. In two studies, the anastomosis was assessed for leakages before application of the topical haemostatic agent. In PTHA.02-CG-2004, the implanted graft “was unclamped and primed with blood to verify bleeding along the suture lines.” (Hagberg et al., 2004, p. 308). In PTHA.03-TG-2018, an antegrade cardioplegia injection was performed to evaluate leakages. For PTHA.06-TC-2018 and PTHA.07-CS-2003, only the location of application (aortotomy suture line or anastomoses and atriotomies) was described but neither a more detailed procedure nor a time of application. These studies were included with the limitation that the actual indication (prophylactic or therapeutic) remains unclear. Six of the seven identified studies investigated at least one interventional product which was referred to and can be categorised as a sealant or glue; in PTHA.07-CS-2003 both applied agents were passive haemostatic agents (Coselli et al., 2003, Hagberg et al., 2004, Khoynezhad et al., 2018, Minato et al., 2009, Morita et al., 2020, Ostrowski et al., 2021, Sirlak et al., 2003).

In PTHA.01-BC-2003, BioGlue Surgical Adhesive, manufactured by CryoLife Inc., Atlanta, Georgia (now Artivion Inc.) was investigated. This agent is a tissue adhesive composed of bovine serum albumin and glutaraldehyde and is independent of the patient’s coagulation mechanism. It creates a mechanical seal by cross-linking human tissue proteins at the site of application to bovine serum albumin. Glutaraldehyde forms the covalent bond between molecules, glueing the proteins together. BioGlue is applied with a delivery system (Barnard & Millner, 2009; Coselli et al., 2003).

The application of CoSeal, manufactured by Cohesion Technologies, Inc., Palo Alto, California (today manufactured by Baxter International Inc., Deerfield, Illinois) was compared with the application of Gelfoam/thrombin in PTHA.02-CG-2004. CoSeal is a surgical, mechanical sealant described as forming a hydrogel or cohesive matrix, composed of two polyethylene glycol polymers. The sealant is FDA-approved with an indication in vascular reconstructions to support haemostasis. Gelfoam, manufactured by Upjohn, Kalamazoo, Michigan (now Pfizer Inc., New York), is a gelatine foam. For the purpose of this study, the agent was soaked in a bovine thrombin solution (Hagberg et al., 2004; Winkworth, 2025).

PTHA.03-TG-2018 compared the efficacy of Tridyne, manufactured by Neomend, Inc., Irvine, California (now part of BD, Franklin Lakes, New Jersey), with Gelfoam Plus, manufactured by Baxter Healthcare Corp., Hayward, California, when applied to aortic suture lines. Tridyne is a

FDA-approved vascular sealant composed of human serum albumin and polyethylene glycol for cross-linking. It forms a transparent hydrogel as a mechanical seal at the application site (BD, 2025; Khoynezhad et al., 2018). Gelfoam Plus is a combination product of Gelfoam (Pfizer Inc., New York), an absorbable sponge composed of gelatine, and human thrombin (FDA, 2007).

The application of fibrin glue by the rub-and-spray method was investigated in PTHA.04-GC-2009. The authors mention the name Bolheal and the Chemo-Sero Therapeutic Institute, Kumamoto, Japan, for the sealant which was used for this purpose. Fibrin glue is composed of human fibrinogen and human thrombin, each being applied as a separate solution, containing also adjunctive components. After application, the components react with each other, forming a fibrin clot (Minato et al., 2009). Bolheal is the brand name of a fibrin sealant manufactured by KM Biologics Co., Ltd., part of Meiji Holdings Co., Ltd., Tokyo, Japan.

The sealing efficacy of a newly developed elastomeric sealant called Matsudaito, manufactured by Sanyo Kasei Co., Ltd., Kyoto, Japan (Sanyo Chemical Industries, Ltd.), was assessed in PTHA.05-SC-2019. This agent contains a diisocyanate-endcapped copolymer of polyethylene glycol and polypropylene glycol. The cross-linking and polymerisation reaction of the sealant is started in contact with water at the tissue surface and a seal with elastomeric properties is formed (Morita et al., 2020). The agent can be linked to the brand name AQUABRID, which is a surgical sealant distributed also in Europe by Terumo Corporation, Tokyo, Japan (Terumo Corporation, 2020).

PTHA.06-TC-2018 investigated the efficacy of a combination product containing human thrombin and fibrinogen in form of a local haemostatic patch. The name Tachosil is mentioned for the product, however without a manufacturer (Ostrowski et al., 2021). TachoSil, manufactured by Corza Medical GmbH, Dusseldorf, Germany is an authorised fibrin sealant patch.

The efficacy of Colgel was compared in PTHA.07-CS-2003. Sirlak et al. (2003) mention Laboratorie Interphar, Aubervilliers, France as manufacturer of Colgel and Ethicon Inc., Somerville, New Jersey as manufacturer of Surgicel. Bracey et al. (2017) refer to Laboratoire Interpharm, Aubervilliers, France as the manufacturer of Colgel in the supplementary document of their review. Colgel is a microfibrillar collagen haemostat which adheres to the bleeding site, and initiates platelet aggregation and clot formation through contact activation. Surgicel consists of oxidised regenerated cellulose and has a similar mechanism as Colgel by providing a structure for platelets to adhere to, initiating their activation and aggregation. Both products are passive haemostatic agents (Barnard & Millner, 2009; Sirlak et al., 2003).

4.3.2 Description of Study Design and Study Population

Table 5 characterises the studies included in further detail. All included studies were randomised, controlled, open-label or single (participant)-blinded. The investigators and endpoint assessors (in case of different persons) were not blinded due to the perceptible and visible differences of intervention and comparator. However, in PTHA.01-BC-2003 and PTHA.02-CG-2004 the investigators only received information about the allocated treatment on the day of surgery in the operating room. PTHA.02-CG-2004 also states that the sponsor was blinded until day of surgery. The study populations consisted of patients undergoing cardiovascular surgical procedures, differing in the specific type of surgery, and in the elective or emergent nature of surgery. A total of 628 patients were included, the size of studies was in a range of 20 to 158 patients, the distribution between study arms was either 1:1 or 2:1. All studies reported on the age of participants and the mean age was 65 years. The primary endpoints of five studies were assessed intraoperatively either by measuring haemostasis, bleeding or time to haemostasis. For two studies, only postoperative outcome data like the volume of chest tube drainage was measured. Secondary endpoints included the use of other products, volume of blood loss and transfusion, procedure times, adverse events etc. One study also calculated treatment costs. Two studies were conducted in Japan, three in the United States, one in Poland and one in Turkey. The duration of study was between six months and three years and there were three single-centre studies and four multicentre studies with six, ten or 19 study sites (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003).

Table 5 Part I: Characteristics of included studies

Study ID (Reference)	**Study Type and Design**	**Study Population**	**Study Arms** (included patients)	**Study Duration and Location**	**Study Endpoints**
PTHA.01-BC-2003 (Coselli et al., 2003)	Interventional, multicentre, prospective, randomised, controlled, single-blinded (participant; investigator blinded until day of surgery)	Patients undergoing cardiovascular surgery procedure requiring cardiac and vascular anastomotic repair	BioGlue Group (n = 76) Control Group (n = 75)	Enrolment period: 04/2000 – 09/2000; Location: 6 sites (United States of America)	*Primary study endpoint:* Anastomotic haemostasis at repaired anastomotic sites (no additional intervention for bleeding control from vessel pressurisation until wound closure) *Secondary study endpoints:* Use of blood replacement products; Use of haemostatic agents; Reoperation incidence; Adverse events and mortality; Cardiopulmonary bypass time; Aortic cross-clamp time; Total procedure time; Time in intensive care unit; Hospital length of stay
PTHA.02-CG-2004 (Hagberg et al., 2004)	Interventional, multicentre, prospective, randomised, controlled, single-blinded (participant; investigator blinded until day of surgery)	Patients scheduled for aortic reconstruction with surgical placement of a Dacron vascular graft	CoSeal group (n = 37) Control (Gelfoam/thrombin) group (n = 17)	Duration not reported; Location: 10 sites (United States of America)	*Primary study endpoints:* 1. Proportion of sites achieving immediate anastomotic sealing 2. Proportion of sites achieving complete anastomotic sealing within 5 minutes *Other study endpoints:* Transfusion requirements Deaths and adverse events
PTHA.03-TG-2018 (Khoynezhad et al., 2018; NIH ClinicalTrials.gov, 2017)	Interventional, multicentre, prospective, randomised, controlled, parallel assignment, single-blinded (participant)	Patients undergoing non-emergent, primary cardiac operations involving aortic valve, ascending aorta, aortic arch, while on cardiopulmonary bypass	Tridyne Group (n = 107) Gelfoam Plus Group (n = 51)	Duration: 1 year; Completion date: 12/2014; Location: 19 sites (United States of America)	*Primary study endpoint:* Time to achieve haemostasis (start: release of surgical clamps; end: cessation of bleeding at anastomotic site) *Secondary study endpoints:* 1. Proportion of patients with successful haemostasis (within 5 minutes) at all suture lines 2. Proportion of patients with immediate haemostasis (0 seconds) 3. Chest tube drainage volume 4. Transfusion volume 5. Time from cross-clamp removal to sternal closure 6. Reoperation incidence 7. Device-related serious adverse event/patient

Table 5 Part II: Characteristics of included studies

Study ID (Reference)	**Study Type and Design**	**Study Population**	**Study Arms** (included patients)	**Study Duration and Location**	**Study Endpoints**
PTHA.04-GC-2009 (Minato et al., 2009)	Interventional, single-centre, prospective, randomised, controlled, open-label	Patients undergoing emergency replacement of ascending aorta or ascending hemiarch	Fibrin Glue Group (n = 10) Control Group (n = 10)	Enrolment period: 04/2004 – 08/2006; Location: 1 site (Japan)	*Primary study endpoint:* Bleeding from needle holes at anastomoses (bleeding proportion of needle holes per patient and total bleeding rate indicating bleeding risk per needle hole) *Secondary study endpoint:* Haemostatic period (time from protamine administration until closure); Amount of blood losses during haemostatic period and postoperative; Amount of blood transfusions; Operation time and duration of hospital stay
PTHA.05-SC-2019 (Morita et al., 2020)	Interventional, multicentre, randomised, controlled, open-label	Patients undergoing replacement surgery of a thoracic aortic aneurysm using cardiopulmonary bypass	Sealant Group (n = 54) Control Group (n = 27)	Enrolment period: 12/2006 – 09/2009; Location: 6 sites (Japan)	*Primary study endpoint:* Complete haemostasis before protamine administration; complete haemostasis 15 min after protamine administration start *Secondary study endpoints:* 1. Time from start protamine administration to end of surgery 2. Intraoperative bleeding amount 3. Transfusion amount 4. Additional haemostatic procedures Follow-up for adverse events
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Interventional, single-centre, prospective, randomised controlled, open-label	Patients undergoing elective aortic valve replacement	Tachosil Group (n = 41) Control Group (n = 52)	Duration not reported; Location: 1 site (Poland)	Drainage volume 24h and 48h and relationship between drainage volume (48 h) and explanatory variables (red blood cell concentrate volume, haemoglobin level, erythrocytes level (day 4)) Number of re-thoracotomies; Postoperative pleural and pericardial effusions; Total number of blood product transfusions; Additional usage of protamine and tranexamic acid; Postoperative period (including mechanical ventilation time, stay in intensive care unit and hospitalisation time); Postoperative renal injury prevalence; Mortality in the early postoperative period *No primary or secondary endpoint defined*
PTHA.07-CS-2003 (Sirlak et al., 2003)	Interventional, single-centre, prospective, comparative, randomised controlled, open-label	Patients undergoing elective, high risk of bleeding operations	Colgel Group (n = 35) Surgicel group (n = 36)	Enrolment period: 08/1999 – 11/2001; Location: 1 site (Turkey)	Chest tube drainage volume (24 h, total) Blood loss (first 3h, 3h-6h postoperatively) Total treatment expenditure (sum of the costs of topical haemostatic treatment and allogeneic products transfused) *No primary or secondary endpoint defined*

In Table 6, the inclusion and exclusion criteria of the studies are presented. Only two studies had an age range in their inclusion criteria, only one study specified intraoperative inclusion criteria. PTHA.02-CG-2004 assessed anastomotic leakage but did not report intraoperative eligibility criteria based on this evaluation. For PTHA.06-TC-2018 no eligibility criteria could be retrieved. All studies specified the type of surgery the patients had to undergo. Only for PTHA.03-TG-2018 a complete list of in- and exclusion criteria could be retrieved from the study registry entry, for all other studies only information provided in the report is displayed (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003).

Table 6 Part I: Inclusion and exclusion criteria of included studies

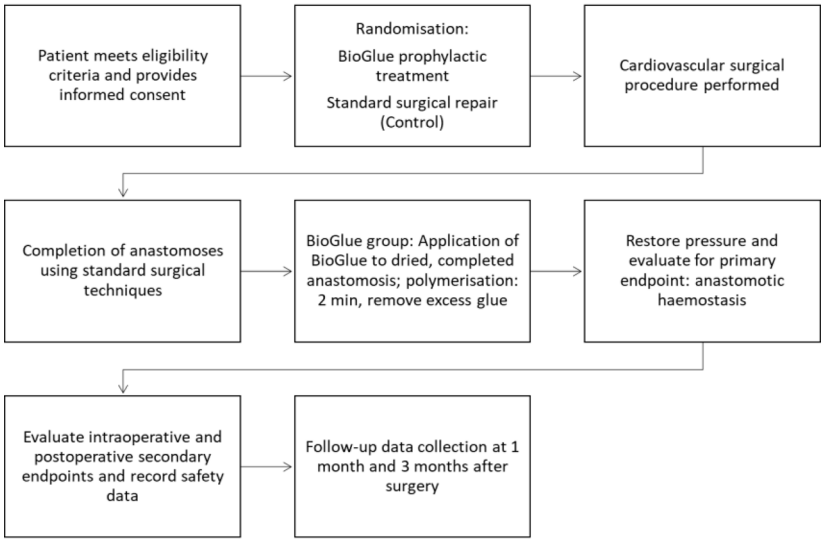
Study ID (Reference)	**Inclusion criteria**	**Exclusion criteria**
PTHA.01-BC-2003 (Coselli et al., 2003)	1. Patients undergoing a cardiovascular surgical procedure requiring anastomotic repairs. 2. Patients willing and able to give written informed consent.	1. Patients with a known hypersensitivity to albumin, bovine products, or glutaraldehyde. 2. Patients currently being treated with an investigational product. 3.Patients scheduled to undergo any repairs involving the intracerebral circulation. 4. Patients undergoing repair of acute thoracic aortic dissection.
PTHA.02-CG-2004 (Hagberg et al., 2004)	1. Male or non-pregnant female adult patients. 2. Patients scheduled for aortic reconstruction with surgical placement of a Dacron vascular graft. 3. Patients provide informed consent. 4.Patients supplying a medical history.	1. Patients requiring direct repair of aortic dissections.
PTHA.03-TG-2018 (Khoynezhad et al., 2018; NIH ClinicalTrials.gov, 2017)	1. Subject must be ≥ 18 years of age. 2. Subject is scheduled for elective, primary thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass. 3. Subject has an expected life expectancy > 6 months. 4. Subject is willing and able to comply with all aspects of the study including follow-up schedule. 5. Subject or authorised representative has the ability to provide voluntary written informed consent. *Intra-operative inclusion criteria:* 1. Subject is able to undergo an antegrade cardioplegia injection for evaluation of a leak at the aortic anastomotic site(s) during the procedure. 2. Following this injection, subject has a leaking site where a topical sealant/haemostatic agent may be used to control bleeding.	1. Subject has Type A or other acute thoracic aortic dissection. 2. Subject has undergone prior thoracic surgery (open thoracotomy not including interventional cardiology procedures). 3. Subject is undergoing a planned concomitant procedure other than coronary artery bypass graft (CABG). 4. Subject has a previous organ transplant. 5. Subject has known or suspected preoperative coagulation disorder. 6. Subject is allergic to human thrombin or has a history of allergic reactions after application of human thrombin. 7. Subject is allergic to protamine. 8. Subject has a Left Ventricular Assist Device (LVAD) or planned to receive a LVAD. 9. Subject is undergoing emergency surgery. 10. Subject is in chronic renal failure. 11. Subject has a haematocrit < 21% pre-operatively. 12. Subject has a serum creatinine ≥ 2.5 mg/dl at baseline or is currently on dialysis. 13. Subject has a cardiac ejection fraction < 25%. 14. Subject is scheduled for another cardiac surgery within 30 days of enrolment. 15. Subject has an active or latent infection which is systemic or at the intended surgery site.

Table 6 Part II: Inclusion and exclusion criteria of included studies

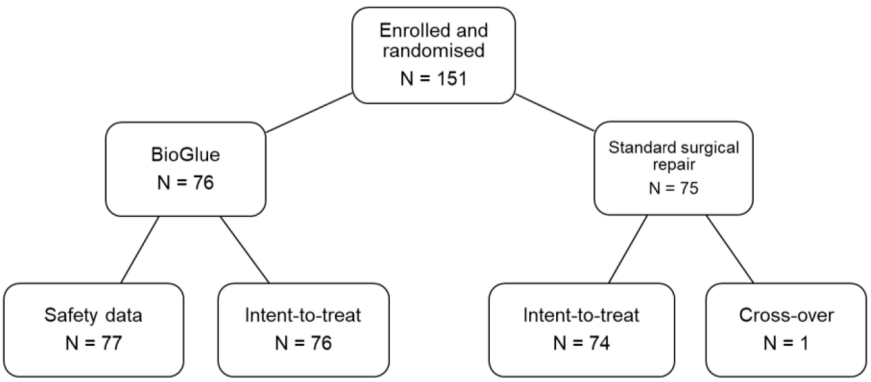
Study ID (Reference)	**Inclusion criteria**	**Exclusion criteria**
Continued: PTHA.03-TG-2018 (Khoynezhad et al., 2018; NIH ClinicalTrials.gov, 2017)		16. Subject is immuno-compromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders. 17. Subject is pregnant [confirmed] by a positive pregnancy test or has plans to become pregnant during the study period or is currently breast-feeding. 18. Subject is unwilling to receive blood products. 19. Subject has participated in another investigational research study within 30 days of enrolment. 20. In the opinion of the investigator, the subject has a clinical condition that would preclude the use of the study device, preclude the subject from completing the follow-up requirements, or would complicate the evaluation of this study.
PTHA.04-GC-2009 (Minato et al., 2009)	1. Emergency replacement of the ascending aorta or the ascending-hemiarch.	1. Patients with cardiac collapse requiring preoperative cardiac massage. 2. Those with cardiac tamponade and shock requiring open pericardial drainage at the emergency room. 3. Those with acute myocardial infarction. 4. Those with the Bentall procedure. 5. Those with the total arch replacement. 6. Those with Bentall and total arch replacement.
PTHA.05-SC-2019 (Morita et al., 2020)	1. Patients scheduled for thoracic aneurysm repair with replacement of the aorta. 2. Patients between 20 and 79 years of age. 3. Patients able to give their written informed consent.	1. Patients undergoing emergency surgery. 2. Patients with a ruptured aneurysm. 3. Patients undergoing reoperation through the same incision. 4. Patients have a severe infection. 5. Patients have anaemia (haemoglobin level < 9.0 g/100 ml). 6. Patients have liver dysfunction (total bilirubin level > 3.0 mg/100 ml). 7. Patients have renal dysfunction (creatinine level > 2.0 mg/100 ml). 8. Patients have coagulopathy (fibrin degradation product > 30 μg/ml, or platelet count < 100,000/mm^2). 9. Patients have diabetes (HbA1c > 8.0%). 10. Patients are receiving steroids. 11. Patients scheduled for aortic root surgery, such as Bentall operation or valve-sparing root replacement.
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Not reported	Not reported
PTHA.07-CS-2003 (Sirlak et al., 2003)	1. Subjects undergoing repeat cardiac operations (aorta-coronary bypass operations or valvular operations), ascending aortic aneurysm repair necessitating deep hypothermic circulatory arrest, and ascending aortic grafting without deep hypothermic circulatory arrest	1. Subjects with recent (< 5 days) acetylsalicylic acid ingestion. 2. Subjects with recent thrombolytic therapy (streptokinase, urokinase, or tissue plasminogen activator < 1 day). 3. Subjects with recent anticoagulant therapy (heparin < 4 hours preoperative or warfarin < 3 days preoperatively). 4. Subjects with preexisting coagulation defects (including abnormal preoperative coagulogram [prothrombin time (PT) > 18 s or partial thromboplastin time (PTT) > 50 s] or platelet count < 10^9/L, preexisting renal dysfunction (serum creatinine > 200 mmol/L). 5. Subjects had autologous donation of blood.

All studies report that groups were comparable at baseline and that there were no relevant differences except for a difference in weight in PTHA.03-TG-2018 and in the frequency of diabetes in PTHA.02-CG-2004. Baseline data reported by the trials are not displayed here. Only PTHA.03-TG-2018, PTHA.04-GC-2009 and PTHA.05-SC-2019 provide diagrams informing about patient allocation and PTHA.03-TG-2018 additionally for the study flow (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003). To display available information in a comparable manner, the following diagrams were created based on the data extracted from the text or, where possible, recreated from the diagrams extracted from the publication.

Figure 2 depicts the study flow and patient allocation for PTHA.01-BC-2003, as described in the study report. Of the 151 patients enrolled in the study, 76 were randomised to receive BioGlue, 75 were randomised to the control group. One patient of the control group crossed over to the BioGlue group, a possibility which had been prespecified in the protocol in case of uncontrollable bleeding and which was to be treated as a separate cross-over population to avoid investigator-induced bias. This patient was considered for the safety analysis and not for the efficacy analysis, which was based on the intention-to-treat population (Coselli et al., 2003).



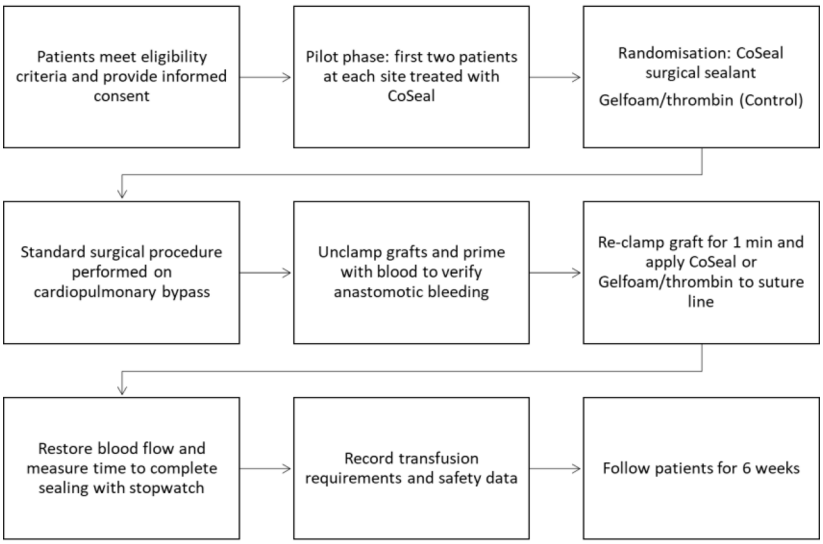
A: Flow of the study



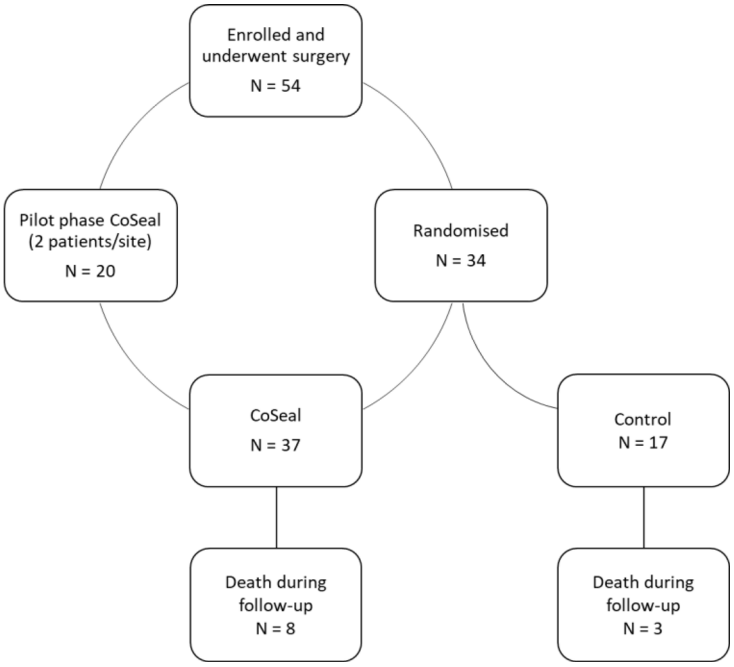
B: Patient allocation

Figure 2: Diagrams of study flow and disposition of patients in the study (PTHA.01-BC-2003). *Created from data in Coselli et al. (2003).*

The diagrams in Figure 3 present the study flow and patient allocation of PTHA.02-CG-2004. Fifty-four patients were enrolled in this study, of which the first two at each site were treated with CoSeal in a pilot phase. The remaining 34 patients were randomised 1:1 to receive either CoSeal or the control haemostatic agent (comparator) and all patients were included in the analysis of the primary endpoint. The CoSeal group therefore included 37 patients, the control group 17 patients. The procedure included a step for assessing the anastomotic suture lines for leakages. It was however not reported if patients were excluded if there was no leakage observed. Patients were followed for six weeks after the surgery, eight patients in the CoSeal group and three patients in the control group died during this period (Hagberg et al., 2004).



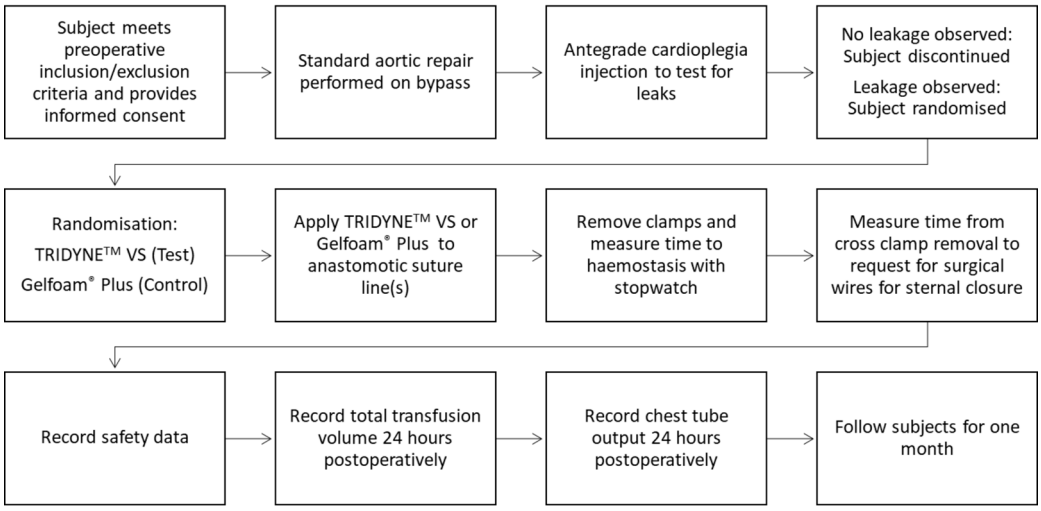
A: Flow of the study



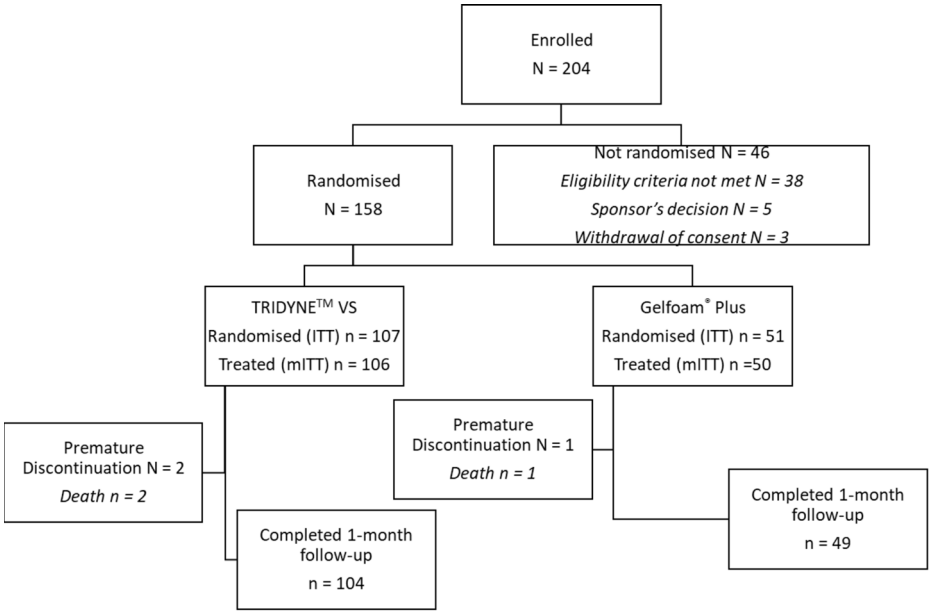
B: Patient allocation

Figure 3: Diagrams of study flow and disposition of patients in the study (PTHA.02-CG-2004). *Created from data in Hagberg et al. (2004).*

In Figure 4, the diagrams for the study flow and patient allocation from PTHA.03-TG-2018 are displayed. In this study, an intraoperative eligibility criterium was included and patients were only randomised if leakage of suture lines was observed. Of 204 enrolled patients, 158 were randomised in a 2:1 ratio; 107 patients to be included in the Tridyne group, and 51 patients in the comparator group. One patient in each group was not treated with the allocated intervention and was excluded as prespecified from the modified intention to treat population which was the basis for all outcome data. One patient in the Gelfoam Plus Group and two patients in the Tridyne group prematurely discontinued the study because of death (Khoynezhad et al., 2018).



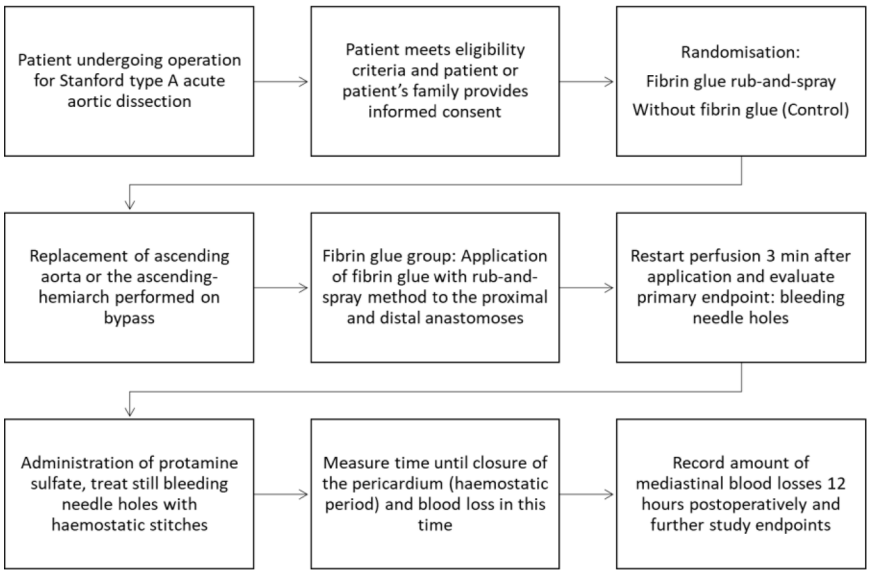
A: Flow of the study



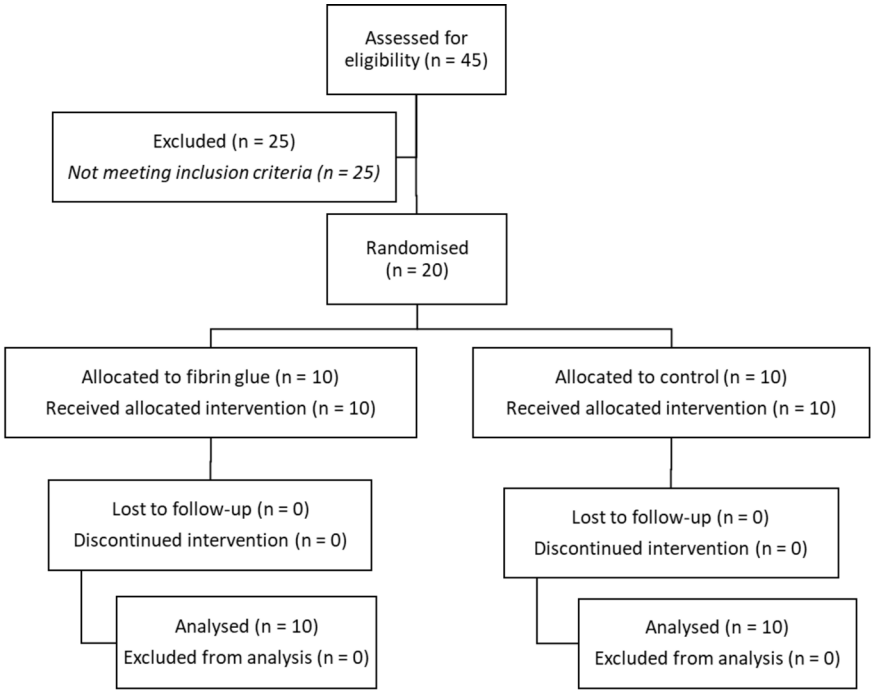
B: Patient allocation *(Abbreviations: ITT = intention to treat, mITT = modified intention to treat)*
Figure 4: Diagrams of study flow and disposition of patients in the study (PTHA.03-TG-2018). *Recreated and adapted for improved readability from diagrams extracted from Khoynezhad et al. (2018, pp. 1359–1360).*

The study flow and patient allocation diagrams for PTHA.04-GC-2009 are presented in Figure 5. In this study, 20 patients were selected from 45 consecutively in the hospital operated patients by applying exclusion criteria (see Table 5 Part II). Ten patients were each randomised

to receive fibrin glue or not. All patients were included in the analysis. Due to the emergent nature of the operation, informed consent was obtained from patients if they were conscious or from family members if the patient was unconscious or unstable (Minato et al., 2009).



A: Flow of the study

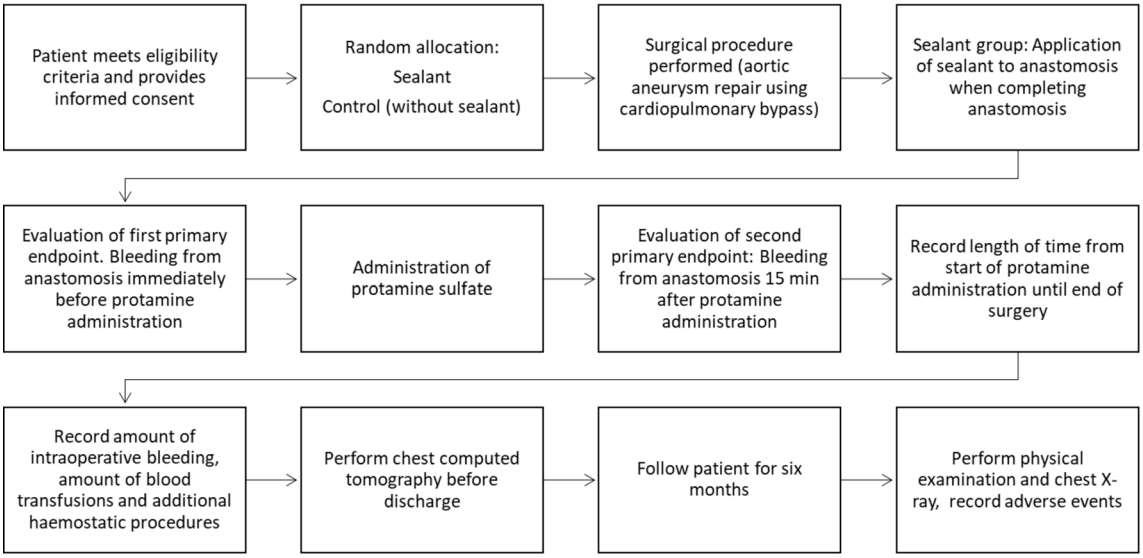


B: Patient allocation

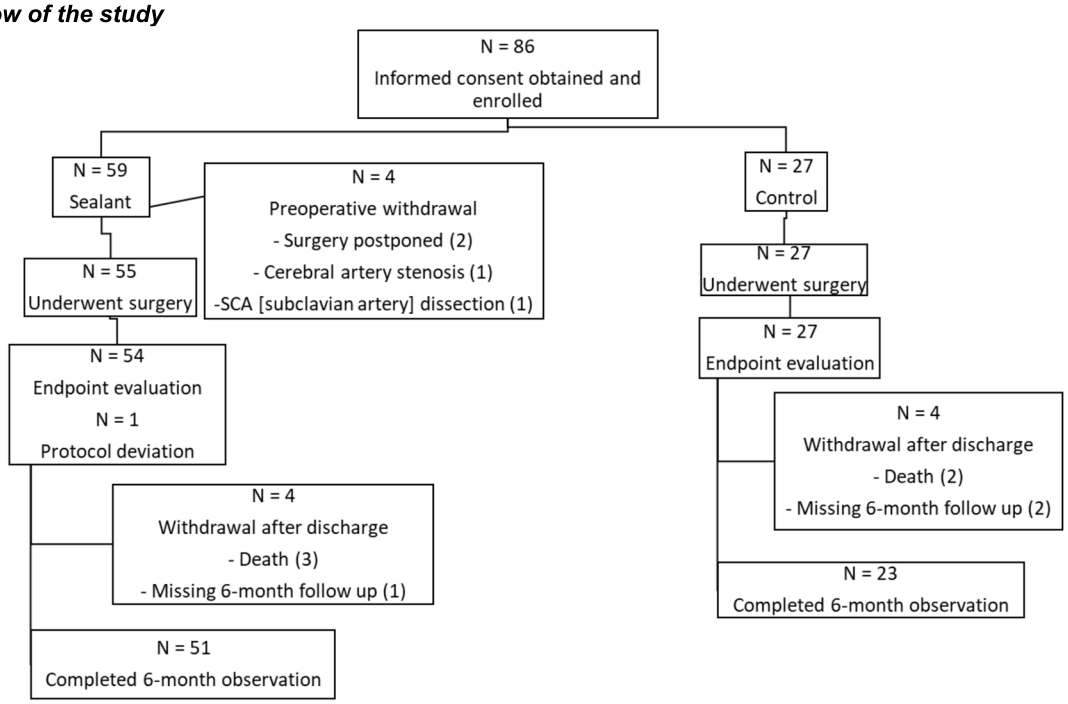
Figure 5: Diagrams of study flow and disposition of patients in the study (PTHA.04-GC-2009). *A created from data from Minato et al. (2009) and B recreated and adapted for improved readability from diagram extracted from Minato et al. (2009, p. 266).*

The diagrams in Figure 6 show the study flow and patient allocation in PTHA.05-SC-2019. In this study, 86 patients were randomly allocated in a 2:1 ratio to be treated with or without the interventional sealant. Fifty-nine patients were assigned to the sealant group, 55 underwent surgery and 54 were included in the endpoint evaluation because one case was treated as a protocol deviation due to the sealant being removed from the anastomosis. This patient was

excluded from the primary endpoint analysis but completed the 6-month follow-up. Another patient was excluded from the analysis of secondary endpoints and adverse events because of bleeding which was however considered unrelated to bleeding from the anastomosis of interest for the primary endpoint analysis. Therefore, 53 patients in the sealant group were included in the secondary endpoints and adverse events analysis. The control group included 27 patients; all were included in the endpoint evaluation. In each group four patients did not complete follow-up (Morita et al., 2020).



A: Flow of the study

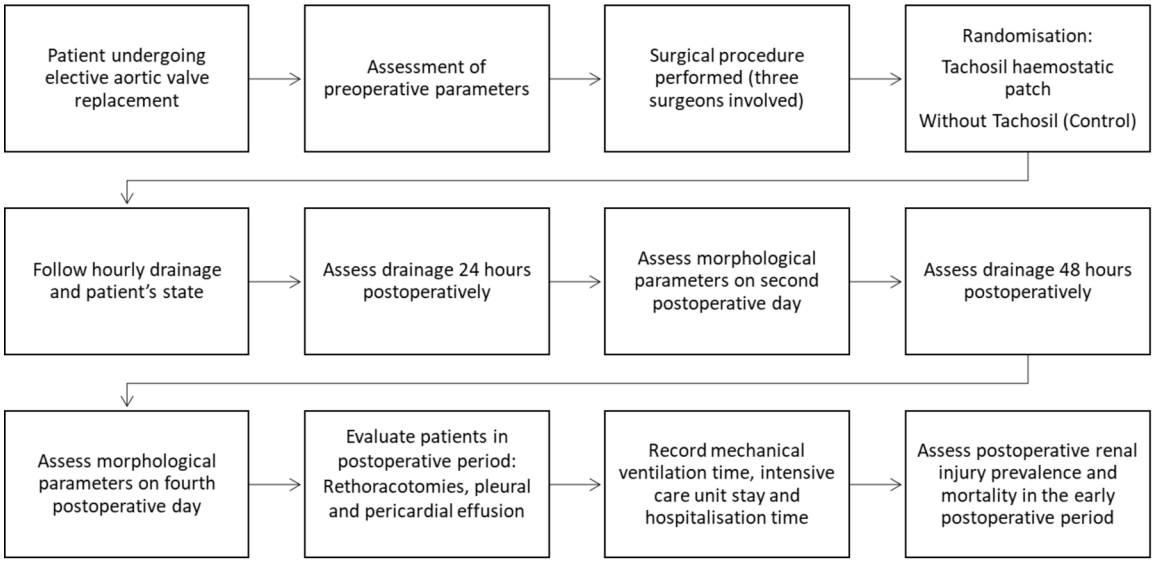


B: Patient allocation

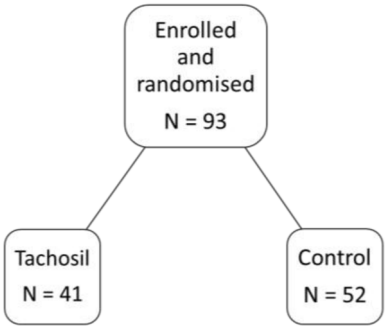
Figure 6: Diagrams of study flow and disposition of patients in the study (PTHA.05-SC-2019). *A created from data from Morita et al. (2020) and B recreated and adapted for improved readability from diagram extracted from Morita et al. (2020, p. 115).*

Figure 7 presents the diagrams for study flow and patient allocation in PTHA.06-TC-2018, as described in the study publication. Ninety-three patients were enrolled in this study, 41 patients

were randomised to be treated with the haemostatic patch Tachosil, and 52 patients were not to be treated with the intervention. The report does not describe the flow of the study but only lists which assessments were performed. There was no information if an intention-to-treat analysis was planned or if there was missing data for patients. No follow-up period was mentioned in the report (Ostrowski et al., 2021).



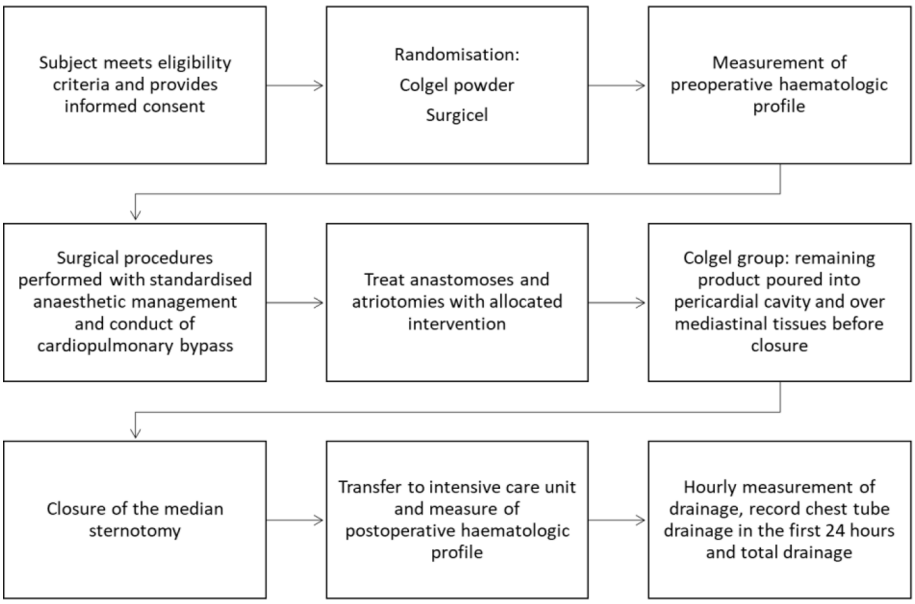
A: Flow of the study



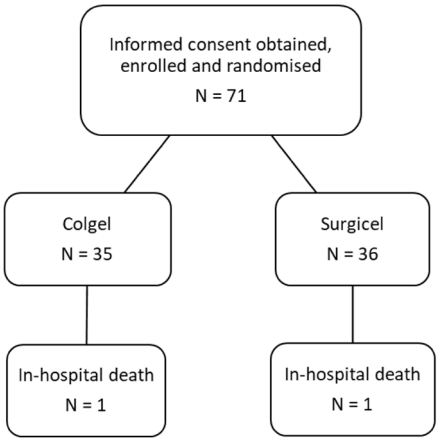
B: Patient allocation

Figure 7: Diagrams of study flow and disposition of patients in the study (PTHA.06-TC-2018). *Created from data in Ostrowski et al. (2021).*

In Figure 8, the study flow and patient allocation diagrams, as described in the publication, are displayed for PTHA.07-CS-2003. This study included 71 patients, 35 being randomised to receive Colgel and 36 to be treated with Surgicel. In each group, one death in hospital occurred. No missing data and no follow-up period were reported (Sirlak et al., 2003).



A: Flow of the study



B: Patient allocation

Figure 8: Diagrams of study flow and disposition of patients in the study (PTHA.07-CS-2003). *Created from data in Sirlak et al. (2003).*

4.3.3 Description of Study Limitations

Three of the included studies outlined some limitations to be considered. PTHA.03-TG-2018 described risk of treatment bias because it was not double-blinded and the applications could be clearly differentiated. Furthermore, the topical haemostatic agents were only applied to the aorta and therefore the results might not be applicable to other vessels. It is also mentioned that no cost comparison was performed (Khoynezhad et al., 2018). In PTHA.04-GC-2009, additional haemostatic procedures, especially when haemostasis had not been achieved, might have had influence on the result. Moreover, the tested application method was not compared to other methods of application (Minato et al., 2009). PTHA.05-SC-2019 reported limitations of the sealant as well as the study: the sealant adheres to materials like gloves or gauze pads and needs to be pressed over a silicon strip to ensure it is not removed. The study was open-label and the assessors of the endpoints were not blinded as endpoints were judged by the surgeons, which could introduce bias (Morita et al., 2020). PTHA.01-BC-2003 did not report limitations but included information on how they prepared to avoid bias: for the assessment of the primary endpoint, definitions were chosen which were supposed to minimise the subjectivity of the evaluation, the use of a patient screening log at each site was described and the potential of overriding the study randomisation was decreased by a predefined separated study analysis of the cross-over and the intention-to-treat population (Coselli et al., 2003). PTHA.02-CG-2004 did not report limitations neither but mentioned that the analysis of their results included the randomised sample and the endpoints assessed in patients in the pilot phase. The authors acknowledged that these results may distort the overall effects because they expected that the application during the pilot phase would be less successful (Hagberg et al., 2004). PTHA.06-TC-2018 and PTHA-07-CS-2003 did not inform on limitations.

4.4 Study Results of Randomised Controlled Trials

4.4.1 Intraoperative Study Endpoints

Six trials reported data for intraoperative study endpoints including the number of anastomoses, achievement of haemostasis, time to haemostasis, bleeding risk and operative time-related end points. These trials included a total of 535 patients, of which 319 were randomised to the investigational arm and 216 were assigned to the respective comparator or control arm (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Sirlak et al., 2003).

Number of Suture Line Sites

Four trials reported the number of suture line sites including anastomoses which were checked for bleeding, the number of suture lines treated or the number of needle holes and bleeding needle holes, respectively. These trials included a total of 306 patients, of which 177 were randomised to the investigational arm. In Table 7, the respective reported numbers are displayed (Coselli et al., 2003; Hagberg et al., 2004; Minato et al., 2009; Morita et al., 2020).

Table 7: Suture line sites

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**
Number of anastomoses		
PTHA.01-BC-2003 (Coselli et al., 2003)	Total: 202 Bleeding: 38	Total: 184 Bleeding: 79
PTHA.05-SC-2019 (Morita et al., 2020)	196	117
Number of treated suture line sites		
PTHA.02-CG-2004 (Hagberg et al., 2004)	59	27
Number of needle holes[2]		
PTHA.04-GC-2009 (Minato et al., 2009)	Proximal: 268 Distal: 287 Proximal, bleeding: 2 Distal, bleeding: 13	Proximal: 264 Distal: 278 Proximal, bleeding: 193 Distal, bleeding: 199

[1]Studies with active comparators are colour-coded in blue. [2]Values were reported separately for the proximal and distal anastomoses.

Achievement of Haemostasis

Four trials reported data concerning the achievement of haemostasis. These trials included a total of 444 patients, of which 274 were randomised to the investigational and 170 to the comparator or control arm. Three trials reported the achievement of haemostasis per anastomosis. All trials reported the achievement of haemostasis per patient, one by defining one random index site per patient. Two trials reported on the immediate haemostatic success and the haemostasis success at or within five minutes. One trial reported the proportion of complete haemostasis before and 15 minutes after protamine administration. One trial reported the number of failed haemostasis after ten minutes. All trials reported a significantly

higher achievement of haemostasis in the investigational arm in their respective endpoint. The respective reported numbers are displayed in Table 8 (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Morita et al., 2020). PTHA.05-SC-2019 also reported haemostasis per anastomosis for each anastomotic site; these data are not presented.

Table 8: Achievement of haemostasis

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Haemostasis per anastomosis			
PTHA.01-BC-2003 (Coselli et al., 2003)	164 of 202 anastomoses, 81.1%	105 of 184 anastomoses, 57.1%	P < 0.001, significant
PTHA.02-CG-2004 (Hagberg et al., 2004)	Immediate: 48 of 59 sites, 81.4% At 5 minutes: 50 of 59 sites, 84.7%	Immediate: 10 of 27 sites, 37.0% At 5 minutes: 14 of 27 sites, 51.9%	Immediate: P = 0.002, significant At 5 minutes: P = 0.01, significant
PTHA.05-SC-2019 (Morita et al., 2020)	Before pa: 155 of 196 anastomoses (79.1%) After pa: 173 of 196 anastomoses (88.3%)	Before pa: 45 of 117 anastomoses (38.5%) After pa: 71 of 117 anastomoses (60.7%)	Before pa: P < 0.001, significant After pa: P < 0.001, significant
Haemostasis per patient			
PTHA.01-BC-2003 (Coselli et al., 2003)	46 of 76 patients, 60.5%	29 of 74 patients, 39.2%	P = 0.014, significant
PTHA.02-CG-2004 (Hagberg et al., 2004)	Immediate: 29 of 37 ris, 78.4% At 5 minutes: 30 of 37 ris, 81.1 %	Immediate: 7 of 17 ris, 41.2% At 5 minutes: 8 of 17 ris, 47.1%	Immediate: P < 0.05, significant At 5 minutes: P < 0.05, significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Immediate: 63 of 106 patients Within 5 minutes: 90 of 105 patients[3] Failed haemostasis: 13 of 105, 12.4%	Immediate: 8 of 50 patients Within 5 minutes: 20 of 50 patients Failed haemostasis: 24 of 50, 48.0%	Immediate: P < 0.0001[3], significant Within 5 minutes: P < 0.0001[3], significant
PTHA.05-SC-2019 (Morita et al., 2020)	Before pa: 79% After pa: 88%	Before pa: 38% After pa: 61%	Before pa: P < 0.001, significant After pa: P < 0.001, significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]As reported in the text by the study authors (see Khoynezhad et al., 2018, p. 1361). Abbreviations: ris … random index sites; pa … protamine administration.

Time to Haemostasis

One trial reported additionally to the achievement of haemostasis the time to haemostasis. This time was measured from the cross-clamp removal until each treated anastomosis was haemostatic or until the cut-off at ten minutes. The haemostatic anastomotic sites were observed additionally for one minute in case of re-bleeding. The authors reported the mean as well as the median time to haemostasis, the numbers are displayed in Table 9. The time to haemostasis was significantly shortened in the investigational arm (Khoynezhad et al., 2018).

Table 9: Time to haemostasis

Study ID (Reference)	**Investigational Arm**	**Comparator Arm**[1]	**Significance**[2]
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	**Mean +/- SD**		
	2.07 +/- 3.37 minutes	6.3 +/- 4.21 minutes	P < 0.0001[3], significant
	Median		
	0.0 minutes	9.98 minutes	N/A

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]As reported in the text by the study authors (see Khoynezhad et al., 2018, p. 1361). Abbreviations: SD … standard deviation; N/A … not applying.

Bleeding Risk

One trial reported bleeding risks per patient and per needle hole as a method of evaluating the haemostatic effectiveness of their intervention. In both study arms the bleeding risk per patient was calculated as the bleeding proportion of needle holes per patient and the bleeding risk per needle hole was calculated as total bleeding rate. The total bleeding rates of both groups were further used to calculate the bleeding risk ratio to evaluate the difference of the bleeding risk between arms. The reported numbers are displayed in Table 10. The bleeding proportion and the bleeding risk ratio were significantly reduced in the investigational arm (Minato et al., 2009).

Table 10: Bleeding risk

Study ID (Reference)	**Investigational Arm**	**Control Arm**	**Significance**[1]
PTHA.04-GC-2009 (Minato et al., 2009)	**Bleeding proportion** (Mean +/- SD)		
	Proximal: 0.7 +/- 1.6% Distal: 4.4% +/- 3.7%	Proximal: 73.8% +/- 16.0% Distal: 71.9% +/- 15.7%	P < 0.001, significant
	Total bleeding rate		
	Proximal: 0.008 (2/268) Distal: 0.045 (13/287)	Proximal: 0.731 (193/264) Distal: 0.716 (199/278)	N/R
	Bleeding risk ratio		
	Proximal: 0.010 [95% CI, 0.003-0.041] Distal: 0.063 [95% CI, 0.036-0.111]		N/R; significant reduction

Values were reported separately for proximal and distal anastomoses. [1]P-value and/or significance presented if and as reported. Abbreviations: SD … standard deviation; N/R … not reported; 95% CI … 95% confidence interval.

Intraoperative Time-Related Endpoints

Five trials reported intraoperative time-related endpoints. These trials included a total of 481 patients, 282 were randomised to the investigational arm. The trials reported one or multiple of the following endpoints: All five trials reported the time on cardiopulmonary bypass; two trials reported total operative time. Three trials reported average cross-clamp time. One trial reported the time between the removal of the cross-clamp and sternal closure, the so-called surgical time; one trial reported the 50% haemostatic period (time from protamine administration until pericardial closure) estimated by a Kaplan Meier's survival curve; one trial reported the operation time after protamine administration. The reported numbers are displayed in Table 11 (Coselli et al., 2003; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Sirlak et al., 2003). PTHA.04-GC-2009 and PTHA.05-SC-2019 further reported brain circulatory and

cardiac arrest time, respectively, these data are not presented. Only the 50% haemostatic period reported by PTHA.04-GC-2009 was significantly reduced in the investigational arm. All other intraoperative time-related endpoints were not associated with a significant difference between arms.

Table 11: Intraoperative time-related endpoints

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Total operative time (Mean +/- SD)			
PTHA.01-BC-2003 (Coselli et al., 2003)	237.7 +/- 125.1 minutes	228.7 +/- 100.8 minutes	N/R; considered equivalent
PTHA.04-GC-2009 (Minato et al., 2009)	292 +/- 51 minutes	320 +/- 44 minutes	N/R; no statistical difference
Cardiopulmonary bypass time (Mean +/- SD)			
PTHA.01-BC-2003 (Coselli et al., 2003)	168.0 +/- 67.4 minutes	144.2 +/- 60.6 minutes	N/R; considered equivalent
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	139.9 +/- 57.6 minutes	134.5 +/- 77.7 minutes	N/R; not significant
PTHA.04-GC-2009 (Minato et al., 2009)	159 +/- 31 minutes	170 +/- 20 minutes	P = 0.769, not significant
PTHA.05-SC-2019 (Morita et al., 2020)	216.3 +/- 62.5 minutes	216.1 +/- 74.4 minutes	P = 0.715, not significant
PTHA.07-CS-2003 (Sirlak et al., 2003)	105 +/- 11 minutes	111 +/- 17 minutes	P = 0.07, not significant
Cross-clamp time (Mean +/- SD)			
PTHA.01-BC-2003 (Coselli et al., 2003)	74.0 +/- 46.1 minutes	69.1 +/- 41.3 minutes	N/R; considered equivalent
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	105.1 +/- 45.7 minutes	104.0 +/- 46.3 minutes	N/R; not significant
PTHA.07-CS-2003 (Sirlak et al., 2003)	88 +/- 14 minutes	95 +/- 13 minutes	P = 0.10, not significant
Surgical time[3] (Mean +/- SD)			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	59.4 +/- 30.96 minutes	58.5 +/- 24.74 minutes	P = 0.8553[4], not significant
50% haemostatic period[4]			
PTHA.04-GC-2009 (Minato et al., 2009)	41.5 minutes	51 minutes	P = 0.036, significant
Operation time after protamine administration (Mean +/- SD)			
PTHA.05-SC-2019 (Morita et al., 2020)	137 +/- 46 minutes	141 +/- 64 minutes	P = 0.815, not significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]Surgical time: time between removal of cross-clamp and sternal closure. [4]As reported in the text by the study authors (see Khoynezhad et al., 2018, p. 1362). [5]50% haemostatic period: estimated by a Kaplan Meier's survival function, the cumulative haemostasis rate curve is displayed in the study report (Minato et al., 2009 p.269). Abbreviations: SD … standard deviation; N/R … not reported.

4.4.2 Perioperative Study Endpoints

Perioperative study endpoints are endpoints which have been assessed intra- and/or postoperatively, including chest tube drainage and blood loss, transfusion requirements and the use of additional haemostatic agents or measures. All seven trials reported on one or more perioperative study endpoints.

Blood Loss Outcomes

Five trials reported data on blood loss. These trials included a total of 423 patients, 247 were randomised to the respective investigational arm. The trials reported one or more of the following endpoints: Two trials reported the amount of intraoperative blood loss. Four trials reported the amount of postoperative blood loss in different time frames: one trial assessed blood loss every three hours postoperatively; one trial reported blood loss until twelve hours after surgery. Three trials reported chest tube drainage at 24 hours; one trial reported chest tube drainage at 48 hours; one trial reported the total amount of postoperative chest tube drainage. One trial reported the relationship of drainage volume at 48 hours and three explanatory variables (haemoglobin level on day 4, level of erythrocytes on day 4, red blood cell concentrate volume). The reported numbers are displayed in Table 12 (Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003). The intraoperative blood loss during the haemostatic period was significantly reduced in the investigational arm in PTHA.04-GC-2009. PTHA.07-CS-2003 found that the total amount of postoperative blood loss, the chest tube drainage at 24 hours and the blood loss in the first six hours postoperatively were significantly lower in the investigational arm. The chest tube drainage at 48 hours was significantly lower in the investigational arm in PTHA.06-TC-2018. The study also found a significant relationship between the chest tube drainage at 48 hours and the level of haemoglobin and erythrocytes at day 4 in the control arm. All other blood loss endpoints were not associated with statistically significant differences between study arms.

Table 12 Part I: Blood loss outcomes

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Intraoperative: Blood loss during surgery (Mean +/- SD)			
PTHA.05-SC-2019 (Morita et al., 2020)	On gauze pads		
	749 +/- 531 g	675 +/- 341 g	P = 0.453, not significant
	Collected for autotransfusion		
	220 +/- 822 mL	378 +/- 845 mL	P = 0.423, not significant
	Chest tube drainage		
	473 +/- 314 mL	391 +/- 270 mL	P = 0.252, not significant
Intraoperative: Blood loss during the haemostatic period[3] (Mean +/- SD)			
PTHA.04-GC-2009 (Minato et al., 2009)	99 +/- 76 mL	257 +/- 163 mL	P = 0.016, significant
Blood loss assessed every 3 hours postoperatively (Mean +/- SD)			
PTHA.07-CS-2003 (Sirlak et al., 2003)	First 3 postoperative hours		
	132 +/- 41 mL	228 +/- 57 mL	P < 0.001, significant
	3 to 6 hours postoperatively		
	67 +/- 24 mL	121 +/- 49 mL	P < 0.001, significant
	Remaining 3-hours intervals: graphic presentation only, blood loss lower in intervention group than in the control group, not significant		
Blood loss during postoperative 12 hours (Mean +/- SD)			
PTHA.04-GC-2009 (Minato et al., 2009)	268 +/- 93 mL	526 +/- 363 mL	P = 0.054, not significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]Haemostatic period: time from administration of protamine until pericardial closure. Abbreviations: SD … standard deviation.

Table 12 Part II: Blood loss outcomes

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Chest tube drainage at 24 hours (Mean +/- SD)			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	701.6 +/- 499.83 mL Median: 572.5 mL	589.6 +/- 359.41 mL Median: 530.0 mL	P = 0.1612[4], not significant
PTHA.06-TC-2018 (Ostrowski et al., 2021)	506.75 mL	687.13 mL	N/R; not significant
PTHA.07-CS-2003 (Sirlak et al., 2003)	373 +/- 143 mL	571 +/- 144 mL	P = 0.01, significant
Chest tube drainage at 48 hours			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	483.98 mL	740.00 mL	P = 0.0335[4], significant
Total amount of postoperative blood loss (Mean +/- SD)			
PTHA.07-CS-2003 (Sirlak et al., 2003)	423 +/- 154 mL	677 +/- 128 mL	P = 0.01, significant
Relationship of drainage volume at 48 hours with explanatory variables[5]			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Explanatory variable: red blood cell concentrate volume		
	P = 0.0613[4] R = 0.365 (N = 27) Not significant	P = 0.1262[4] R = 0.268 (N = N/R) Not significant	N/A
	Explanatory variable: haemoglobin level on day 4		
	Numbers not reported; not significant	P = 0.0109[4] R = -0.380 (N = 44) significant	N/A
	Explanatory variable: level of erythrocytes on day 4		
	Numbers not reported; not significant	P = 0.0048[4] R = -0.418 (N = 44) significant	N/A

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [4]As reported in the text by the study authors (see Khoynezhad et al., 2018, p. 1362 and Ostrowski et al., 2021, pp. 1615–1616). [5]For values of explanatory variables see Tables 13 and 17. Abbreviations: SD … standard deviation; N/R … not reported; N/A … not applying; R … correlation coefficient.

Transfusion Requirements

All trials reported on transfusion requirements or the use of blood replacement products. PTHA.02-CG-2004 stated that there was no statistical difference in transfusion requirements between groups but reported no numbers to support this statement (Hagberg et al., 2004). Six trials reported on the transfusion volume, five of these detailed which blood replacement products were required in which quantities. Two of these trials reported on administered products in specified time frames: PTHA.01-BC-2003 reported specifically data on intraoperatively used products; PTHA.03-TG-2018 reported type of blood products administered for transfusions within 24 hours and from cardiopulmonary bypass until discharge. Two trials reported the incidence or number of patients who required transfusion. One trial reported the number of patients who required no transfusion of blood products. In Table 13, the reported numbers are displayed (Coselli et al., 2003; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003). PTHA.01-BC-2003 additionally reported data on donor exposure, these numbers are not presented.

Table 13 Part I: Transfusion requirements

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Transfusion volume (Mean +/- SD)			
PTHA.04-GC-2009 (Minato et al., 2009)	Blood transfusion		
	7.2 +/- 4.6 units	5.2 +/- 3.8 units	N/R; no statistical difference
PTHA.05-SC-2019 (Morita et al., 2020)	Packed red cells		
	5.7 +/- 4.4 units	6.4 +/- 5.0 units	P = 0.535, not significant
	Platelets		
	7.4 +/- 7.9 units	9.3 +/- 10.4 units	P = 0.407, not significant
	Fresh frozen plasma		
	6.0 +/- 4.9 units	8.4 +/- 6.2 units	P = 0.057, not significant
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Packed red blood cells		
	493.05 mL	523.18 mL	N/R
	Platelet transfusion		
	5.80 mL	15.20 mL	N/R
	Fresh frozen plasma		
	456 mL	298.48 mL	N/R
Transfusion volume (Total)			
PTHA.07-CS-2003 (Sirlak et al., 2003)	Packed red blood cells		Packed red blood cells & total number of blood products: 2-tailed test: P < 0.07, not significant; 1-tailed test: P < 0.03, significant
	28 units	120 units	
	Fresh frozen plasma		
	8 units	46 units	
Transfusion volume: Intraoperative use of blood replacement products (Mean +/- SD)			
PTHA.01-BC-2003 (Coselli et al., 2003)	Red blood cells		
	2.3 +/- 3.6 units	1.9 +/- 2.4 units	N/R; not significant
	Platelets		
	5.1 +/- 10.1 units	5.2 +/- 10.0 units	N/R; not significant
	Fresh frozen plasma		
	3.8 +/- 6.6 units	3.3 +/- 5.0 units	N/R; not significant
	Cryoprecipitate		
	4.3 +/- 11.9 units	2.0 +/- 8.3 units	N/R; not significant
Transfusion volume: Within 24 hours (Mean +/- SD)			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Red blood cells (RBC)		
	0.6 +/- 1.50 units	0.3 +/- 0.75 units	N/R
	Fresh frozen plasma		
	0.5 +/- 1.30 units	0.3 +/- 0.99 units	N/R
	Platelets		
	0.3 +/- 0.66 units	0.2 +/- 0.59 units	N/R
	Cryoprecipitate		
	0.1 +/- 0.42 units	0.1 +/- 0.44 units	N/R
	Non-RBC		
	0.9 +/- 1.96 units	0.7 +/- 1.65 units	N/R
Transfusion volume: From cardiopulmonary bypass to discharge (Mean +/- SD)			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Red blood cells (RBC)		
	1.0 +/- 1.88 units	0.7 +/- 1.36 units	N/R
	Fresh frozen plasma		
	0.6 +/- 1.41 units	0.4 +/- 1.02 units	N/R
	Platelets		
	0.4 +/- 0.98 units	0.3 +/- 0.72 units	N/R
	Cryoprecipitate		
	0.2 +/- 1.05 units	0.2 +/- 0.53 units	N/R
	Non-RBC		
	1.2 +/- 2.61 units	0.9 +/- 1.79 units	N/R

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: SD … standard deviation; N/R … not reported; RBC … red blood cell.

Table 13 Part II: Transfusion requirements

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Transfusion incidence			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	39 of 106 patients, 36.8%	16 of 49 patients, 32.7%	P = 0.6174[3], not significant
PTHA.07-CS-2003 (Sirlak et al., 2003)	Packed red blood cells		
	6 of 35 patients	20 of 36 patients	N/R
	Fresh frozen plasma		
	2 of 35 patients	8 of 36 patients	N/R
Transfusion incidence: Patients requiring no blood products			
PTHA.01-BC-2003 (Coselli et al., 2003)	Red blood cells		
	37 of 76 patients	33 of 74 patients	N/R
	Platelets		
	47 of 76 patients	42 of 74 patients	N/R
	Fresh frozen plasma		
	43 of 76 patients	41 of 74 patients	N/R
	Cryoprecipitate		
	63 of 76 patients	67 of 74 patients	N/R

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]As reported in the text by the study authors (see Khoynezhad et al., 2018, p. 1362). Abbreviations: SD … standard deviation; N/R … not reported.

Additional Use of Haemostatic Agents and Measures

Three trials reported numbers for the additional use of haemostatic agents and measures. These trials included a total of 325 patients, of which 171 were randomised to the investigational arm. One trial reported the need for reinforcing pledgets; two trials reported the incidence of additional haemostatic procedures and detailed the methods used, one evaluated the incidence specifically for the bleeding anastomoses, the other for all anastomotic sites. One trial reported the additional usage of tranexamic acid and protamine. The reported numbers are displayed in Table 14 (Coselli et al., 2003; Morita et al., 2020; Ostrowski et al., 2021). In PTHA.01-BC-2003, the investigational arm was associated with a significantly lower need for reinforcing pledgets, in PTHA.05-SC-2019 the use of the interventional product was associated with a significantly lower use of additional haemostatic procedures. PTHA.05-SC-2019 detailed the incidence of the additional use of other haemostatic agents additionally for different types of products, these numbers are not presented.

PTHA.07-CS-2003 stated that there were no significant differences in the perioperative usage of heparin or protamine but provided no further data to support this statement (Sirlak et al., 2003).

Table 14: Additional use of haemostatic agents and measures

Study ID (Reference)	Investigational Arm	Control Arm	Significance[1]
Reinforcing pledgets			
PTHA.01-BC-2003 (Coselli et al., 2003)	53 of 202 anastomoses, 26%	66 of 184 anastomoses, 36%	P = 0.047, significant
Incidence of additional haemostatic procedures			
PTHA.01-BC-2003 (Coselli et al., 2003)	Make-up stitches		
	31 of 38 bleeding anastomoses, 82%	64 of 79 bleeding anastomoses, 81%	P = 1.00, not significant
	Haemostatic device (use of other haemostatic agents)		
	3 of 38 bleeding anastomoses, 8%	8 of 79 bleeding anastomoses, 10%	P = 1.00, not significant
	Additional BioGlue (intervention)		
	21 of 38 bleeding anastomoses, 55%	N/A	N/A
	Other (additional pledgets, Teflon felt ring, FloSeal)		
	3 of 38 bleeding anastomoses, 8%	15 of 79 bleeding anastomoses, 19%	P = 0.17, not significant
PTHA.05-SC-2019 (Morita et al., 2020)	Any additional haemostatic procedure		
	38 of 196 anastomoses, 19.4%	65 of 117 anastomoses, 55.6%	P < 0.001, significant
	Additional stitches		
	20 of 196 anastomoses, 10.2%	25 of 117 anastomoses, 21.4%	P = 0.008, significant
	Reapplication of the interventional sealant		
	1 of 196 anastomoses, 0.5%	N/A	N/A
	Use of other haemostatic agents		
	26 of 196 anastomoses, 13.3%	58 of 117 anastomoses, 49.6%	P < 0.001, significant
Additional usage of tranexamic acid and protamine			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Additional Tranexamic acid usage		
	70%	68%	N/R; no difference
	Additional Protamine Usage		
	75%	70%	N/R; no difference

[1]P-value and/or significance presented if and as reported. Abbreviations: N/A … not applying; N/R … not reported.

4.4.3 Postoperative Study Endpoints

Five trials reported postoperative study endpoints, excluding any safety endpoints besides the reoperation incidence. These trials included a total of 503 patients, 288 of which were randomised to the respective investigational arm (Coselli et al., 2003; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021).

Reoperation Incidence

Four trials reported on the incidence of reoperations. These trials included a total of 483 patients, 278 of which were randomised to the investigational arm. Two trials reported the numbers of reoperation for anastomotic site or aortic bleeding; one trial the number of resternotomies due to bleeding; one trial the prevalence of rethoracotomies. The reported

numbers are displayed in Table 15 (Coselli et al., 2003; Khoynezhad et al., 2018; Morita et al., 2020; Ostrowski et al., 2021).

Table 15: Reoperation incidence

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Reoperation for bleeding			
PTHA.01-BC-2003 (Coselli et al., 2003)	0 patients	1 patient	N/R; no difference
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	0 patients	1 patient	N/R
Resternotomy for bleeding			
PTHA.05-SC-2019 (Morita et al., 2020)	1 of 53 patients, 1.9%	0 of 27 patients, 0%	P = 1.000, not significant
Prevalence of rethoracotomies			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	5%	10%	N/R; no significant difference

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: N/R … not reported.

Time-related Endpoints

Four trials reported data on postoperative time-related endpoints. These trials included a total of 422 patients, of which 234 were randomised to the investigational arm. All four trials reported the length of hospital stay; two trials reported the time in the intensive care unit. The reported numbers are displayed in Table 16. The use of the interventional product was not associated with a significant reduction of length of hospital stay or time spent in the intensive care unit (Coselli et al., 2003; Khoynezhad et al., 2018; Minato et al., 2009; Ostrowski et al., 2021).

Table 16: Postoperative time-related endpoints

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Length of hospital stay (Mean +/- SD)			
PTHA.01-BC-2003 (Coselli et al., 2003)	10 days	11 days	N/R; considered equivalent
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	7.5 +/- 5.85 days	6.9 +/- 4.53 days	N/R
PTHA.04-GC-2009 (Minato et al., 2009)	21 +/- 6 days (for 6 of 10 patients)	20 +/- 8 days (for 8 of 10 patients)	N/R; no statistical difference
PTHA.06-TC-2018 (Ostrowski et al., 2021)	15.10 days	13.98 days	N/R
Stay in intensive care unit			
PTHA.01-BC-2003 (Coselli et al., 2003)	4 days	5 days	N/R; considered equivalent
PTHA.06-TC-2018 (Ostrowski et al., 2021)	4.6 days	3.25 days	N/R

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: SD … standard deviation; N/R … not reported.

Other measured postoperative parameters

Two trials reported numbers for the postoperative haematologic profile, these are displayed in Table 17 (Ostrowski et al., 2021; Sirlak et al., 2003). The corresponding preoperative values as well as any other preoperative background characteristics, which were reported by all trials, are not displayed.

Table 17: Other measured postoperative parameters

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Haematocrit (Mean +/- SD)			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	2nd postoperative day		
	27.025%	27.13%	N/R
	4th postoperative day		
	26.53%	25.14%	N/R
PTHA.07-CS-2003 (Sirlak et al., 2003)	25.8 +/- 3.5%	24.5 +/- 2%	p = 0.1, not significant
Haemoglobin (Mean +/- SD)			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	2nd postoperative day		
	9.02 g/L	9.00 g/L	p < 0.001, significant[3]
	4th postoperative day		
	8.73 g/L	8.39 g/L	p = 0.0002, significant[3]
PTHA.07-CS-2003 (Sirlak et al., 2003)	8.9 +/- 1.2 g/dL	8.6 +/- 1.1 g/dL	p = 0.4, not significant
Level of erythrocytes / Red blood cell count			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	2nd postoperative day		
	3.71 million/L	2.93 million/L	N/R; significant
	4th postoperative day		
	2.88 million/L	2.72 million/L	N/R; significant
Platelets (Mean +/- SD)			
PTHA.06-TC-2018 (Ostrowski et al., 2021)	141.58 x 10^3/L	121.75 x 10^3/L	N/R
PTHA.07-CS-2003 (Sirlak et al., 2003)	109 +/- 31 x 10^3	109 +/- 28 x 10^3	p = 0.9, not significant
Other parameters in the postoperative haematologic profile.			
PTHA.07-CS-2003 (Sirlak et al., 2003)	Prothrombin time (Mean +/- SD)		
	16 +/- 2.5 s	15.7 +/- 1.4 s	p = 0.8, not significant
	Partial thromboplastin time (Mean +/- SD)		
	39.7 +/- 16 s	42.1 +/- 34 s	p = 0.9, not significant
	Fibrinogen (Mean +/- SD)		
	208 +/- 61 mg/dL	178 +/- 28 mg/dL	p = 0.1, not significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]As reported in the text by the study authors (see Ostrowski et al., 2021, p. 1616). Abbreviations: SD … standard deviation; N/R … not reported.

4.4.4 Safety Endpoints

Six trials reported one or more safety endpoints including mortality, serious adverse events and other adverse events. These trials included a total of 608 patients; 350 patients were randomised to the respective investigational arm. PTHA.04-GC-2009 did not report any safety data (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003).

Mortality

All six trials reported mortality and/or the number of deaths in hospital and/or during follow-up. Five trials reported the number of deaths; one trial reported early and late mortality; one trial reported the hospital mortality rate; one trial reported the perioperative mortality. The reported numbers are displayed in Table 18 (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003).

Table 18: Mortality

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Mortality			
PTHA.01-BC-2003 (Coselli et al., 2003)	Early mortality (before hospital discharge)		
	3 of 77 patients, 3.8%	2 of 74 patients, 2.7%	N/R; considered equivalent
	Late mortality		
	1 of 77 patients, 1.3%	3 of 74 patients, 4.1%	N/R; considered equivalent
PTHA.05-SC-2019 (Morita et al., 2020)	Hospital mortality rate		
	5.7%	7.4%	P = 1.000, not significant
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Perioperative mortality (deceased up to the 10th day)		
	3%	5%	N/R; not significant
Number of deaths			
PTHA.01-BC-2003 (Coselli et al., 2003)	5 of 77 patients, 6.5%	5 of 74 patients, 6.8%	P = 0.999, not significant
PTHA.02-CG-2004 (Hagberg et al., 2004)	8 of 37 patients, 22%	3 of 17 patients, 18%	N/R
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	2 of 106 patients, 1.9%	1 of 50 patients, 2.0%	N/R
PTHA.05-SC-2019 (Morita et al., 2020)	3 of 53 patients, 5.7%	2 of 27 patients, 7.4%	P = 1.000, not significant
PTHA.07-CS-2003 (Sirlak et al., 2003)	1 of 35 patients	1 of 36 patients	P = 0.90, not significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: N/R … not reported.

Adverse Events

Five trials reported on adverse events which occurred during the study; however, the events were reported very differently by the trials. PTHA.02-CG-2004 did not report any numbers or a detailed list of adverse events but only stated that there were no complications related to the sealant. Six adverse events were reported by three or four trials: pericardial and pleural effusion, infection, renal and respiratory insufficiency and stroke or cerebral infarction. The numbers reported for these adverse events are displayed in Table 19 (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Morita et al., 2020; Ostrowski et al., 2021).

Table 19: Adverse events

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Pericardial effusion			
PTHA.05-SC-2019 (Morita et al., 2020)	8 of 53 patients, 15.1%	1 of 27 patients; 3.7%	P = 0.260, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	1 patient	0 patients	N/R
PTHA.06-TC-2018 (Ostrowski et al., 2021)	93%	70%	N/R; described as considerably higher
Pleural effusion			
PTHA.01-BC-2003 (Coselli et al., 2003)	20 of 77 patients, 26.0%; 25 events	21 of 74 patients, 28.4%; 22 events	P = 0.855, not significant
PTHA.05-SC-2019 (Morita et al., 2020)	19 of 53 patients, 35.8%	6 of 27 patients, 22.2%	P = 0.308, not significant
PTHA.06-TC-2018 (Ostrowski et al., 2021)	53%	25%	N/R; described as considerably higher
Infection			
PTHA.01-BC-2003 (Coselli et al., 2003)	13 of 77 patients, 16.9%; 15 events	10 of 74 patients, 13.5%; 13 events	P = 0.653, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	1 of 106 patients, 0.9%	0 of 50 patients, 0%	N/R
PTHA.06-TC-2018 (Ostrowski et al., 2021)	23%	18%	N/R; described as comparable
PTHA.05-SC-2019 (Morita et al., 2020)	Pneumonia		
	4 of 53 patients, 7.5%	1 of 27 patients, 3.7%	P = 0.658, not significant
Renal insufficiency			
PTHA.01-BC-2003 (Coselli et al., 2003)	13 of 77 patients, 16.9%; 13 events	9 of 74 patients, 12.2%; 10 events	P = 0.492, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	1 of 106 patients, 0.9%	0 of 50 patients, 0%	N/R
PTHA.05-SC-2019 (Morita et al., 2020)	2 of 53 patients, 3.8%	0 of 27 patients, 0%	P = 0.547, not significant
PTHA.06-TC-2018 (Ostrowski et al., 2021)	3%	15%	N/R; not significant
Respiratory insufficiency			
PTHA.01-BC-2003 (Coselli et al., 2003)	13 of 77 patients, 16.9%; 18 events	12 of 74 patients, 16.2%; 15 events	P = 1.000, not significant
PTHA.05-SC-2019 (Morita et al., 2020)	1 of 53 patients, 1.9%	0 of 27 patients, 0%	P = 1.000, not significant
PTHA.06-TC-2018 (Ostrowski et al., 2021)	15%	8%	N/R; described as similar
Stroke or cerebral infarction			
PTHA.01-BC-2003 (Coselli et al., 2003)	1 of 77 patients, 1.3%; 1 event	3 of 74 patients, 4.1%; 5 events	P = 0.360, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	2 patients	2 patients	N/R
PTHA.05-SC-2019 (Morita et al., 2020)	4 of 53 patients, 7.5%	3 of 27 patients, 11.1%	P = 0.683, not significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: N/R … not reported.

While most adverse events were judged to be non-significant, PTHA.01-BC-2003 reported the incidence of neurologic deficits as statistically significant, see Table 20 (Coselli et al., 2003). PTHA.06-TC-2018 described the incidence of pericardial and pleural effusion (see Table 19) as considerably higher in the investigational arm but did not report the corresponding p-value to support this description (Ostrowski et al., 2021).

Table 20: Adverse events with statistical significance

Study ID (Reference)	**Investigational Arm**	**Control Arm**	**Significance[1]**
Neurologic deficits			
PTHA.01-BC-2003 (Coselli et al., 2003)	5 of 77 patients, 6.5%; 6 events	16 of 74 patients, 21.6%; 18 events	P = 0.009, significant

[1]P-value and significance presented as reported.

PTHA.01-BC-2003 also reported two complications related to the investigational haemostatic agent, one application to a non-targeted intravascular tissue and one failure of the investigational product to adhere to the tissue. Both complications were resolved, the first by removing the misapplied product, the second by reclamping and reapplying the agent (Coselli et al., 2003).

PTHA.03-TG-2018 reported the number of possible device-related serious adverse events as determined by the clinical events committee, see Table 21 (Khoynezhad et al., 2018).

Table 21: Possible device-related serious adverse events

Study ID (Reference)	**Investigational Arm**	**Comparator Arm[1]**	**Significance[2]**
Possible device-related serious adverse events: Total			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	3 of 105 patients[3], 2.9%	4 of 49 patients, 8.2%	P = 0.2097[3], not significant
Possible device-related serious adverse events: Types			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Haematoma		
	0 patients	1 patient	N/R
	Hypotension		
	0 patients	1 patient	N/R
	Stroke and pericardial effusion: see Table 19		

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. [3]As reported in the text by the study authors (see Khoynezhad et al., 2018, p. 1362). Abbreviations: N/R … not reported.

PTHA.03-TG-2018 also reported a total number of adverse events and serious adverse events, see Table 22. These numbers are listed as procedure-related by the study authors (Khoynezhad et al., 2018).

Table 22: Adverse events and serious adverse evens

Study ID (Reference)	**Investigational Arm**	**Comparator Arm[1]**	**Significance[2]**
Adverse events			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	79 of 106 patients, 74.5%	43 of 50 patients, 86.0%	N/R
Serious adverse events			
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	50 of 106 patients, 47.2%	29 of 50 patients, 58.0%	N/R

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: N/R … not reported.

Three trials reported further adverse events in detail, these are displayed in Table 23, categorised into nervous system diseases, heart diseases, vascular diseases, haemorrhage, and other adverse events (Coselli et al., 2003; Khoynezhad et al., 2018; Morita et al., 2020). PTHA.03-TG-2018 reported the adverse events separated according to relation to the device or the procedure, however listed only one device-related event, namely one patient with azotaemia.

Table 23 Part I: Other adverse events

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Nervous system diseases			
PTHA.01-BC-2003 (Coselli et al., 2003)	Paraplegia		
	1 of 77 patients, 1.3%; 3 events	2 of 74 patients, 2.7%; 3 events	P = 0.615, not significant
PTHA.05-SC-2019 (Morita et al., 2020)	Paraparesis		
	1 of 53 patients, 1.9%	0 of 27 patients, 0%	P = 1.000, not significant
Heart diseases			
PTHA.01-BC-2003 (Coselli et al., 2003)	Myocardial infarction		
	3 of 77 patients, 3.9%; 3 events	1 of 74 patients, 1.4%; 1 event	P = 0.620, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Cardiac arrest		
	1 of 106 patients, 0.9%	2 of 50 patients, 4.0%	N/R
	Cardiac failure		
	0 of 106 patients, 0%	1 of 50 patients, 2.0%	N/R
	Aortic valve incompetence		
	1 of 106 patients, 0.9%	0 of 50 patients, 0%	N/R
PTHA.05-SC-2019 (Morita et al., 2020)	Atrial fibrillation		
	6 of 53 patients, 11.3%	4 of 27 patients, 14.8%	P = 0.726, not significant
Vascular diseases			
PTHA.01-BC-2003 (Coselli et al., 2003)	Thromboembolism		
	1 of 77 patients, 1.3%; 1 event	1 of 74 patients, 1.4%; 4 events	P = 1.000, not significant
	Thrombosis		
	0 of 77 patients, 0%; 0 events	1 of 74 patients, 1.4%; 1 event	P = 0.490, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Thrombosis		
	1 of 106 patients, 0.9%	1 of 50 patients, 2.0%	N/R
Haemorrhage			
PTHA.01-BC-2003 (Coselli et al., 2003)	3 of 77 patients, 3.9%; 3 events	3 of 74 patients, 4.1%; 3 events	P = 1.000, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	0 of 106 patients, 0%	1 of 50 patients, 2.0%	N/R

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: N/R … not reported.

Table 23 Part II: Other adverse events

Study ID (Reference)	**Investigational Arm**	**Comparator[1]/ Control Arm**	**Significance[2]**
Other adverse events			
PTHA.01-BC-2003 (Coselli et al., 2003)	Ischemia		
	3 of 77 patients, 3.9%; 3 events	2 of 74 patients, 2.7%; 2 events	P = 1.000, not significant
	Inflammatory, immune systemic allergic reaction		
	2 of 77 patients, 2.6%; 2 events	0 of 74 patients, 0%; 0 events	P = 0.497, not significant
	Organic system dysfunction/failure		
	3 of 77 patients, 3.9%; 4 events	2 of 74 patients, 2.7%; 2 events	P = 1.000, not significant
	Irreversible morbidity		
	0 of 77 patients, 0%; 0 events	1 of 74 patients, 1.4%; 1 event	P = 0.490, not significant
	Other adverse events		
	46 of 77 patients, 59.7%; 108 events	40 of 74 patients, 54.1%; 100 events	P = 0.514, not significant
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Azotaemia		
	2 of 106 patients, 1.8%, thereof 1 device-related	0 of 50 patients, 0%	N/R
	Wound necrosis		
	1 of 106 patients, 0.9%	0 of 50 patients, 0%	N/R
PTHA.05-SC-2019 (Morita et al., 2020)	Mediastinitis		
	3 of 53 patients, 5.7%	1 of 27 patients, 3.7%	P = 1.000, not significant

[1]Studies with active comparators are colour-coded in blue. [2]P-value and/or significance presented if and as reported. Abbreviations: N/R … not reported.

4.5 Characteristics and Results of Systematic Reviews

Masoudi et al. (2023) and Clark et al. (2008) prepared systematic reviews specifically on safety and adverse events of Surgicel and topical bovine thrombin, which can be a component in fibrin glue products, respectively. The characteristics of the systematic reviews are displayed in Table 24. The systematic reviews are not specific for the prophylactic use of topical haemostatic agents, but report safety aspects of products which may be used with this indication and which were used in RCT included in this review. Masoudi et al. (2023) highlighted that the formation of Surgicel-induced masses is a possible complication of the product, as well as the appearance in imaging diagnostics where it might be confused with a potential tumour or foreign body. For nine studies identified in their review, the type of surgery was cardiovascular surgery; seven studies identified in their review reported cardiovascular complications. Clark et al. (2008) identified for topical bovine thrombin an increased risk of immunogenicity and antibody development. However, they concluded that this is no risk factor for clinically relevant adverse events. Thirteen studies identified in their review were associated with cardiovascular surgery.

Table 24: Characteristics of included systematic reviews

Short Title (Reference)	**Aim or Purpose**	**Search Databases**	**Number of Included Studies**	**Study Design of Included Studies**	**Study Eligibility Criteria**	**Key Findings/Summary of Results**
Thrombin SR (Clark et al., 2008)	Review of published evidence to evaluate the relation between TBT and important AE or immunogenicity.	MEDLINE via PubMed; Reference searching	Mentioned in text: 37, listed in tables: 33 (No total number of studies or patients reported) / min. 9 case reports and 4 longitudinal studies in cardiovascular surgery (no exact numbers disclosed)	Case reports; Case series; Review articles; Retrospective, prospective or observational studies; Quantitative studies of antibodies or AE.	*Inclusion criteria:* 1. English language. 2. Studies of surgical patients treated with TBT, reporting AE. 3. Case reports of surgical patients treated with TBT reporting AE. 4. Longitudinal studies of surgical patients treated with TBT reporting incidence of antibodies and/or AE. *Exclusion criteria:* 1. Editorials, news, commentaries, reviews. 2. Animal or in vitro studies. 3. Language not English. 3. Study participants not undergoing surgery. 4. Studies not reporting AE in patients treated with TBT. 5. Case reports/case series only reporting information regarding blood coagulation antibody level change without information on clinical AE. 6. Longitudinal studies of surgical patients treated with TBT not reporting on incidence of post-surgical antibodies or AE.	Increased risk for post-TBT antibodies based on immunogenicity studies. No evidence that TBT or anti-bovine antibody elevation are risk factors to increase clinically important AE risk or severity.
Surgicel SR (Masoudi et al., 2023)	Review of recent literature reporting on complications that resulted from surgical use of Surgicel for intraoperative haemostasis.	MEDLINE via Ovid; Embase; Cochrane Central Register of Controlled Trials via Ovid	70 studies / 8 case reports and 1 prospective randomised clinical trial in cardiovascular surgery	Case studies; Retrospective cohort studies; Prospective cohort studies; Randomised control studies; Case series studies.	*Inclusion criteria:* 1. English language. 2. Studies published until 30 April 2022. *No further inclusion criteria reported.* *Exclusion criteria:* 1. Studies which outline specific techniques for using Surgicel. 2. Studies that evaluated experimental animal models. 3. Studies which were reported as abstracts only. 4. Studies which examined the use of Surgicel external to the human body. 5. Articles not written in English.	Reported complications included: Surgicel induced masses (granulomas, abscesses, haematomas, cysts); Haemorrhagic complications; Masses misdiagnosed as tumours; Cardiovascular, nervous system and hepatobiliary complications; Pain and infections and others.

Abbreviations: AE … adverse event(s); TBT … topical bovine thrombin

4.6 Recommendations from Guidelines and HTA Report

The two guidelines identified during the literature search are the 2017 EACTS/EACTA guidelines on patient blood management in adult cardiac surgery and the updated 2024 EACTS/EACTAIC/EBCP guidelines on patient blood management (Casselman et al., 2025; Pagano et al., 2018). Both advise on the use of topical haemostatic agents, more specifically on the use of topical sealants. The wording of the recommendations has slightly changed, therefore both versions are presented in Table 25.

Table 25: Guideline recommendations

Short Title (Reference)	**Recommendation**
2024 Guidelines (Casselman et al., 2025)	Routine use of topical sealants in cardiac surgery is not recommended to reduce blood loss and the need for transfusions. (p.19) Topical sealants may be considered in clinical situations where conventional approaches to surgical and medical improvement of haemostasis are insufficient and where bleeding problems are more local than generalized. (p.19)
2017 Guidelines (Pagano et al., 2018)	Routine use of topical sealants in cardiac surgery is not recommended. (p.89) Topical sealants may be considered in clinical situations where conventional approaches to surgical and medical improvement of haemostasis and where bleeding problems are more local than generalized. (p.89)

In the text of each guideline, the two recommendations are also summarised:

> Based on the available evidence, the routine use of topical sealants in cardiac surgery is not recommended and may only be considered in cases of persistent bleeding where haemostasis cannot be achieved with mechanical haemostatic agents in the absence of coagulopathy. (Casselman et al., 2025, p. 18)

> Based on the available evidence, the routine use of topical sealants in cardiac surgery is not recommended and may only be considered in cases of persistent bleeding where the bleeding is localized. (Pagano et al., 2018, p. 90)

The guidelines do not specifically mention the terms prophylactic or preventive or any synonyms, neither literally nor descriptively, in the context of application of topical haemostatic agents.

The French National Authority for Health (HAS) performed a health technology assessment of surgical haemostatic agents in 2011. Nine different classes of haemostatic agents were assessed, including products containing human fibrinogen and thrombin and devices based on gelatine, collagen and other components. The assessment was not specific for cardiac surgery, but 19 of 52 studies identified in the systematic review involved cardiovascular surgery. The authors conclude that there is a lack of high quality studies and relevant results (Aubourg et al., 2011). The following recommendation is formulated:

> Given the current knowledge and the absence of satisfactory evaluation of the risk/benefit ratio in these situations, the HAS considers that these surgical hemostatic agents are not recommended:
> · in the absence of identified bleeding;
> · or as an alternative to conventional methods in the presence of identified bleeding.
> Surgical hemostatic agents should be considered as a complement to conventional methods of hemostasis. The HAS recommends the use of these agents only as a last resort in rescue situations. (Aubourg et al., 2011, e407)

4.7 Quality of the Evidence

To evaluate the quality of the identified evidence, risk of bias was assessed. Only study PTHA.01-BC-2003 was judged to have a low risk of bias, the risk of bias assessment for studies PTHA.03-TG-2018, PTHA.04-GC-2009 and PTHA.05-SC-2019 resulted in some concerns. PTHA.02-CG-2004, PTHA.06-TC-2018 and PTHA.07-CS-2003 were judged to have a high risk of bias. For PTHA.03-TG-2018, PTHA.06-TC-2018 and PTHA.07-CS-2003 no information on the randomisation process was provided, only PTHA.01-BC-2003 and PTHA.02-CG-2004 provided information on concealment of the allocation. All studies were open-label or only single (participant)-blinded due to the perceptible and visible differences of experimental intervention and control. PTHA.01-BC-2003 and PTHA.02-CG-2004 mention that the investigators only received information about the allocated treatment on the day of surgery in the operating room. Only PTHA.01-BC-2003 and PTHA.03-TG-2018 state to use a (modified) intention-to-treat-analysis, no information about the analysis used was found for PTHA.02-CG-2004, PTHA.04-GC-2009, PTHA.05-SC-2019, PTHA.06-TC-2018 and PTHA.07-CS-2003. PTHA.02-CG-2004 included both patients from the pilot phase which had not been randomised and a randomised sample of patients. The risk of bias due to missing outcome data and in measurement of the outcome was assessed to be low for all studies except for PTHA.06-TC-2018 and PTHA.07-CS-2003, where no information was provided on this domain leading to judgement of high risk. No information was provided on neither the measurement of the outcome nor on the choice of study endpoints for PTHA.06-TC-2018. There was no information about availability of a protocol or a pre-specified analysis plan for PTHA.02-CG-2004, PTHA.04-GC-2009, PTHA.06-TC-2018 and PTHA.07-CS-2003. The study record, which allowed to confirm some pre-specifications, was only retrieved for PTHA.03-TG-2018 (Coselli et al., 2003; Hagberg et al., 2004; Khoynezhad et al., 2018; Minato et al., 2009; Morita et al., 2020; Ostrowski et al., 2021; Sirlak et al., 2003). Table 26 presents the summary of the risk of bias evaluation for the identified randomised controlled trials, see the complete RoB 2 assessment table in Appendix D1. Apart from the risk of bias assessment, the poor linguistic quality in some parts of the full-text article needs to be mentioned for PTHA.06-TC-2018.

Table 26: Risk of bias assessment for randomised controlled trials (RoB2)

	Risk of bias assessment					
Study ID (Reference)	**Randomisation process**	**Intervention assignment**	**Missing outcome data**	**Outcome measurement**	**Reported result selection**	**Overall**
PTHA.01-BC-2003 (Coselli et al., 2003)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PTHA.02-CG-2004 (Hagberg et al., 2004)	Low risk	High risk	Low risk	Low risk	Some concerns	High risk
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
PTHA.04-GC-2009 (Minato et al., 2009)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	Some concerns
PTHA.05-SC-2019 (Morita et al., 2020)	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Some concerns	High risk	High risk	Some concerns	Some concerns	High risk
PTHA.07-CS-2003 (Sirlak et al., 2003)	Some concerns	High risk	High risk	Low risk	Some concerns	High risk

The risk of bias of the two included systematic reviews was judged to be unclear, as no sufficient information was provided in either review. The objectives of both reviews were clearly outlined, however no protocol was available to check for pre-specification or for predefined analyses. While Clark et al. (2008) provided a list of eligibility criteria, Masoudi et al. (2023) only described that the review followed the PRISMA protocols and listed exclusion criteria but disclosed no comprehensive list of eligibility criteria in the review report. Clark et al. (2008) only searched MEDLINE via PubMed but performed an additional manual search; Masoudi et al. (2023) searched MEDLINE and the Cochrane Central Register of Controlled Trials via Ovid as well as Embase but performed no additional manual search. Masoudi et al. (2023) provided their search strategy in a supplementary file and consulted a librarian for support, no sufficient information to judge the search strategy was disclosed by Clark et al. (2008). Both reviews were restricted to publications in English, which might lead to a potential publication bias. Masoudi et al. (2023) stated in their introduction that their review aimed to summarise recent literature from 2010 to 2022, however disclosed no corresponding eligibility criteria except to include studies published until 30 April 2022. The studies included were published between 1993 and 2021. Clark et al. (2008) set no date limit and included studies published between 1989 and 2007. Masoudi et al. (2023) described that the selection process of the review was conducted by two independent reviewers, Clark et al. (2008) did not state this except for using the plural form in the methods section. Neither review assessed risk of bias or quality of studies. In their synthesis, Masoudi et al. (2023) presented 67 of their 70 included studies,

three did not report complications, which was the focus of the review. Clark et al. (2008) did not provide information about the total number of studies included in their review; they presented 33 studies in synthesis tables, the number of studies mentioned in the text sums up to 37. Both reviews presented a narrative synthesis. Clark et al. (2008) did not describe limitations of their review; Masoudi et al. (2023) described limitations but mostly in relation to the identified studies and not regarding the review conduct. The reviews did not explain how the relevance of included studies was assessed and did not highlight which results were statistically significant. This lack of information makes it difficult to judge the reliability and overall quality of these reviews. In Table 27, a summary of the risk of bias assessment is presented, a complete ROBIS assessment table is provided in Appendix D2.

Table 27: Risk of bias assessment for systematic reviews (ROBIS)

	Risk of bias assessment				
Short Title (Reference)	**Study Eligibility Criteria**	**Identification and Selection of Studies**	**Data Collection and Study Appraisal**	**Synthesis and Findings**	**Overall**
Thrombin SR (Clark et al., 2008)	Unclear	Unclear	High concern	High concern	Unclear
Surgicel SR (Masoudi et al., 2023)	Unclear	Unclear	High concern	High concern	Unclear

The health technology assessment by the French National Authority for Health (Aubourg et al., 2011) was not assessed for quality or risk of bias because the complete evaluation and synthesis are only available in French.

The two guidelines were both judged to be of high quality and to be recommendable, the 2024 Guidelines show an increase in quality compared to the 2017 Guidelines. Scope and purpose were clearly defined in both guidelines; the 2024 Guidelines provided more information on the professionals involved but the target users were less clearly defined. Neither version reported involvement of the target population, but the 2024 Guidelines included a section for specific patient populations like Jehovah's Witnesses. The 2024 Guidelines provided more information on the systematic methods used and included the PICOT scheme (population, intervention, comparison, outcome and time) and search strings in a complementary document. No complementary document was retrieved for the 2017 Guidelines. Both described the method of formulating recommendations and clearly linked recommendation with evidence. Both guidelines were externally reviewed, the 2024 Guidelines provided more information concerning this process. No procedure for updating or information on monitoring and audit is provided in neither document. In the 2024 Guidelines a chapter on implementation of the guidelines is included and information on funding and influence of funding body is provided, in both guidelines conflicts of interest are disclosed (Casselman et al., 2025; Pagano et al., 2018). The AGREE II assessment table is provided in Appendix D3.

5 Discussion

The current review was performed to answer the question if the prophylactic use of topical haemostatic agents in cardiac surgery is effective and safe compared to no prophylactic use or to the use of other topical haemostatic agents. All the identified randomised controlled trials inform on efficacy of the prophylactic use of topical haemostatic agents. Six of the seven studies reported safety data, the two identified systematic reviews informed additionally on safety of topical haemostatic agents. The 2017 and 2024 Guidelines and HAS HTA report were included as reliable sources of advice on the use of topical haemostatic agents.

Before conducting the review, the definition of prophylactic use was established using both literature sources and input from a cardiac surgery specialist. For example, Al-Attar et al. (2023) describe the pre-emptive application of sealants for anticipated bleeding in cardiothoracic surgery with a high risk of bleeding. Other types of topical haemostatic agents are mostly used to treat active bleeding. This is also reflected in the studies identified in the current review, as six of seven studies investigated an intervention which was referred to either as sealant or glue and only in one study passive haemostatic agents were applied. While also the preoperative application was considered in the definition of a prophylactic application for this review, no study investigating such an administration was found. A preoperative administration would need to be performed on the outer body surface, and the inner surfaces and possible bleeding sites cannot be reached before the surgical procedure.

In the current review, seven eligible studies were identified. These can be classified into two groups: the first group includes five of the seven studies (PTHA.01-BC-2003, PTHA.02-CG-2004, PTHA.03-TG-2018, PTHA.04-GC-2009, PTHA.05-SC-2019), their description of application aligns well with the definition of prophylactic application. The investigated topical haemostatic agents are applied to suture lines before pressure is restored, or cross-clamps are removed and are not applied to treat an active bleeding. These studies also report intraoperative outcomes concerning the haemostasis of the suture lines where the agent was applied to. The second group includes the remaining two studies (PTHA.06-TC-2018 and PTHA.07-CS-2003), these described only that the topical haemostatic agent under investigation was applied to anastomosis or aortotomy suture lines, but not at which time or under which circumstances. Therefore, it is not certain if these studies investigated the prophylactic or the therapeutic application of topical haemostatic agents, which needs to be kept in mind as a limitation. Furthermore, these studies only report peri- and postoperative outcomes, for example blood loss, transfusion requirements or length of hospital stay, which are highly clinically relevant. However, intraoperative endpoints, i.e. haemostatic success, allow to determine the direct effect of the haemostatic agent in preventing bleeding from the

suture line. The current review also revealed a few studies including two randomised controlled trials investigating sternal intramedullary bleeding prevention. These studies were not eligible for the review, because a sternotomy involves bleeding and an application directly after this procedure does not only have a prophylactic but also a therapeutic effect to stop bleeding.

The identified randomised controlled trials can also be classified according to their applied interventions: three studies included an active comparator, while four studies used a control group in which the experimental intervention was not administered. Six studies used different products of fibrin sealants or glue as the interventional agent, two of these studies included Gelfoam in combination with thrombin as the active comparator. One study compared the prophylactic application of two passive haemostatic agents with each other. These differences in the study design need to be considered in the interpretation of the results.

Furthermore, only one of the identified randomised controlled trials has been performed in Europe and with a product possibly available in the European Union. This cannot be stated with certainty as the authors of the study did not disclose the manufacturer of their investigated product. All other products investigated in the study are neither authorised in the European Union nor in Austria, therefore their singular performances are of a lacking geographical context from a European perspective.

A total of 628 patients were included, the size of studies was in a range of 20 to 158 patients, thus only a small number of patients were assessed in these studies and overall, again limiting the informative value of the retrieved studies. Limitations of interpretation and transferability of the results also need to be considered concerning the risk of bias of published studies and reviews, as the identified evidence was overall judged not to be of high quality. Thus, it is not possible to assess safety and efficacy of the prophylactic use of topical haemostatic agents in cardiac surgery with high certainty or to draw any firm conclusions.

While this systematic review only investigated efficacy and safety of the prophylactic use of topical haemostatic agents and no systematic search for pharmacoeconomic studies was performed, two of the identified studies also reported on cost-benefit outcomes. Coselli et al. (2003) defined all reported time-related outcomes as cost-benefit outcome measurements and concluded that the study arms were equivalent in these measures. Sirlak et al. (2003) calculated the cost of the treatment, considering the cost of the topical haemostatic agent and of the required transfusion products. They concluded that the treatment cost was significantly lower in their investigational arm than in their comparator arm.

5.1 Efficacy

All randomised controlled trials assessed in the review investigated different topical haemostatic agents and used different endpoint measurements. Due to this heterogeneity of interventions and outcome parameters no direct comparison could be performed.

As mentioned above, a subgroup including five studies reported intraoperative efficacy endpoints informing about the haemostatic success of the intervention and allowing to determine its direct effect on the site of treatment. This parameter was measured as the proportional achievement of haemostasis at the treated anastomoses, time to haemostasis and bleeding risk. The results indicate that the prophylactic application of topical haemostatic agents is increasing the haemostatic success and is therefore effective in sealing suture lines and needle holes compared to no prophylactic application. The application of a fibrin sealant seems to achieve a better haemostatic success than the application of Gelfoam with thrombin.

The intraoperative haemostasis success is of relevance for the surgical procedure itself, especially as cardiac surgery is often at high risk of bleeding. However, postoperative outcome data like blood loss, transfusion requirements or hospital length of stay may be more patient-relevant. Glickman et al. (2002) also point out this questionableness of clinical relevance of endpoints related to sealing success. They argue, however, that immediate sealing and a decreased need of additional haemostatic interventions might shorten the operative time (Glickman et al., 2002).

Intraoperative time-related endpoints, for example cardiopulmonary bypass time or the total operative time, were reported by five studies included in this systematic review. Only one study reported a significant decrease of the time from protamine administration until pericardial closure in the investigational arm. Thus, this argumentation by Glickman et al. (2002) is not supported by the studies identified in this review and the results do not indicate that the prophylactic application of topical haemostatic agents shortens the intraoperative time. Furthermore, the prophylactic application of topical haemostatic agents was not associated with a decrease of postoperative time-related endpoints, including length of hospital stay and stay in intensive care unit.

All trials reported on transfusion requirements; however, they considered different time ranges for this endpoint. P-values were only reported by a limited number of studies for their respective transfusion-related outcomes. The results do not indicate that the prophylactic application of a topical haemostatic agent reduces or elevates the transfusion requirements in cardiac surgery. The results concerning blood loss are again very heterogeneous, three studies reported a significant difference in their respective blood loss parameters, including both intra- and postoperative blood loss. Specifically, the trial comparing two passive haemostatic agents

reported significant differences in the blood loss parameters, suggesting that the application of Colgel reduces the postoperative blood loss compared to the application of Surgicel. No conclusion can be drawn with certainty about the influence of the prophylactic application of topical haemostatic agents on perioperative blood loss based on the available evidence.

Carless et al. (2003) performed a systematic review to assess the application of fibrin sealants to reduce perioperative blood transfusion. The authors concluded that this use was associated with decreased blood transfusion requirements and reduced postoperative blood loss. However, they included multiple surgical settings and did not report a more specific definition of their application of interest. Only one included trial concerned cardiac surgery, in which the sealant was applied to sites of active bleeding but not in a prophylactic capability (Carless et al., 2003).

In 2006, Rychlik prepared a benefit assessment of TachoSil according to the German Social Law and concluded that there was evidence that the application of TachoSil in surgery has a therapeutic benefit. However, his assessment includes only a few publications concerning cardiovascular surgery (four in vascular surgery, one in cardiac surgery, one thoracic surgery on the mediastinum) and even though the application for securing anastomoses and aortotomies is mentioned, neither outcome data for the prophylactic application nor general safety data for TachoSil could be retrieved from the report (Rychlik, 2006).

Lewis et al. (2018) prepared a multidisciplinary systematic review on the use of HEMOPATCH and mention that “[i]n cardiac applications, HEMOPATCH has prevented suture-line bleeding without the need for surgical revision […]” (p.369) citing a review article of case studies (Fingerhut et al., 2014). However, in this case study review a single case of prophylactic application in cardiac surgery is described, providing only very limited information concerning this case. This review by Lewis et al. was excluded in the current review because of the design of the study included for prophylactic application and the lack of relevant outcome data. In general, several case reports and technical descriptions were identified but excluded because of their study design and/or publication dates before 2000.

Three narrative reviews on topical haemostatic agents in cardiovascular and cardiothoracic surgery were prepared by Barnard and Millner (2009), Forcillo and Perrault (2014) and Bracey et al. (2017), but excluded because of their non-systematic methodology. All three reference the randomised controlled trials by Coselli et al. (2003) and Sirlak et al. (2003), Bracey et al. (2017) additionally refer to Minato et al. (2009) and both Barnard and Millner and Forcillo and Perrault include the study by Hagberg et al. (2004). Another randomised control trial in patients undergoing vascular surgery, specific for CoSeal in comparison with Gelfoam and thrombin by Glickman et al. (2002) is discussed by all three narrative reviews. This study investigated the application of CoSeal for sealing anastomosis leakage sites after identifying bleeding of the

anastomosis. More immediate sealing in the CoSeal group was demonstrated in this trial (Glickman et al., 2002). This study shows that the prophylactic application of topical haemostatic agents in the context of sealing suture lines and anastomoses to prevent bleeding might not only be relevant in cardiac, cardiovascular and cardiothoracic but also in vascular surgery.

Overall, the results suggest that the prophylactic use of topical haemostatic agents is effective in achieving haemostasis at the suture lines but without or with limited effect on postoperative parameters. Further trials are required with focus on patient-relevant endpoints to assess the efficacy of the prophylactic application of topical haemostatic agents.

5.2 Safety

The assessed studies report no statistical differences in mortality and the incidence of adverse events. Only one study reported a higher number of neurological deficits in the control arm, and another study reported a considerably higher incidence of effusion in the investigational arm. Not all studies reported safety data. Overall, all studies concluded that their investigated interventions were safe. It is not possible to draw firm conclusions regarding the safety of the prophylactic use of topical haemostatic agents as only a small number of patients were included in the studies reviewed here, both individually and in aggregate.

Apart from the randomised controlled trials included in the review concerning the safety of topical haemostatic agents used on anastomoses in cardiac surgery, two retrospective studies were identified, which were not eligible for assessment because of their study design. These report specifically BioGlue related complications, which are mainly pseudoaneurysm formations at anastomoses (Luk et al., 2012; Ma et al., 2017). Achneck et al. (2010) mention in their narrative review CoSeal and BioGlue as effective haemostatic agents in cardiac surgery. They advise against the use of BioGlue in paediatric patients as it may interfere with developing structures, possibly also impairing remodelling and repair of tissues.

The use of proteins of bovine origin (e.g. topical bovine thrombin) is associated with immunogenicity and antibody development, which may also be directed to the human equivalent of these proteins. The manufacturer of Thrombin-JMI (Pfizer), for example, warns about severe bleeding and thrombosis complications because of antibody development. Patients should not be re-exposed to the product (Pfizer Laboratories Div Pfizer Inc., 2024). The immunogenicity and antibody formation after administration of topical bovine thrombin in cardiac surgery has for example been investigated by Ortel et al. (2001) and Su et al. (2002). The latter study was also included in the Thrombin SR by Clark et al. (2008), which discusses immunogenicity and antibody development as adverse events of bovine thrombin, however

not specifically for prophylactic application. Clark et al. (2008) concluded that the immunogenicity of bovine thrombin is not a risk factor for clinically relevant adverse events.

The Surgicel SR by Masoudi et al. (2023) reports complications of Surgicel applications, however again not specifically for prophylactic application. The authors highlight the formation of Surgicel-induced masses as a possible complication and its possible interference in imaging diagnostics, similar to the pseudoaneurysm formation after BioGlue application reported by Luk et al. (2012) and Ma et al. (2017). Neither of the systematic reviews included in this review was specific for the prophylactic application of topical haemostatic agents but reported safety issues of topical haemostatics which can be applied and were investigated in the identified randomised controlled trials to prevent bleeding in cardiac surgery.

Apart from the presented publications, several case reports ineligible in the review because of their study design were identified in the screening process which reported among others pseudoaneurysms, mass formation and antibody development. To gather further information on the safety of the prophylactic application of topical haemostatic agents, larger studies and real-world data are needed. Information retrieved from any use of topical haemostatic agents can also be informative for the safety.

5.3 Recommendations from Guidelines and HTA Report

The French National Authority for Health concluded in their health technology assessment report published in 2011 that there is not sufficient evidence to support the application of topical haemostatic agents in absence of bleeding (Aubourg et al., 2011). The 2017 EACTS/EACTA guidelines on patient blood management in adult cardiac surgery advised against the routine use of sealants and in the updated 2024 EACTS/EACTAIC/EBCP guidelines on patient blood management this recommendation is specified to not use sealants to reduce blood loss and transfusion requirements. They recommend the use of sealants only in cases of persistent bleeding (Casselman et al., 2025; Pagano et al., 2018). Thus, these guidelines as well as the published health technology assessment advise against the prophylactic use of topical haemostatic agents, specifically sealants in cardiac surgery.

Contrary to these guidelines and the health technology assessment report which were included in this review, there are also recommendations for an application of topical haemostatic agents to prevent bleeding found in non-systematically conducted, narrative reviews (Al-Attar et al., 2023; Besser et al., 2015; Moldovan et al., 2022). Bracey et al. (2017) present in their review recommendations offered by the International Hemostatic Expert Panel. They refer to the rub-and-spray method to apply fibrin glue presented by Minato et al. (2009) to reduce needle hole bleeding and suggest the use of sealants at suture lines and anastomoses when the bleeding risk is high. Barnard and Millner (2009) and Forcillo and Perrault (2014) further conclude in

their narrative reviews that the choice and application of topical haemostatic agents is based on the surgeon's personal preferences and experience and the haemostatic's availability and is not evidence-based.

5.4 Supportive Evidence

Concerning geographical context from a European perspective, one additional study performed in Europe was identified in the review, which was not eligible for assessment due to its uncontrolled design. However, this prospective, open-label, single-arm study investigated the use of the surgical sealant PreveLeak specifically to prevent bleeding at suture lines in cardiac surgery (Skorpil et al., 2015). PreveLeak is described as a sealant like BioGlue consisting of bovine serum albumin and polyaldehyde which forms a mechanical seal and is independent of the patient's coagulation mechanism. The agent is manufactured by Tenaxis Medical, Inc., a subsidiary of The Medicines Company, Mountain View, California, who also funded the study, and is available in the European Union and the United States (Skorpil et al., 2015). PreveLeak is neither listed in the Austrian National Medicines Register nor on the European Medicines Agency webpage.

Forty-four patients at three sites in the European Union undergoing cardiovascular surgical procedures who had an elevated risk for poor haemostasis were included in the study. PreveLeak sealant was applied to the suture line at anastomoses or incision sites while the artery was still clamped. As primary efficacy endpoint immediate sealing and as primary safety endpoint the cumulative incidence of four specified safety events was assessed. All treated sites were immediately sealed in 42 of 44 patients, respectively 125 of 127 treatment sites were immediately sealed, meeting the prespecified 55 % threshold. Eight infections and one neurological deficit were observed within 6 weeks postoperatively, in summary a cumulative incidence of nine specified safety events in eight patients (Skorpil et al., 2015). The results of this study agree with the results reported by the identified randomised controlled trials: the prophylactic application of sealants is safe and effective in achieving haemostasis at treated suture lines.

5.5 Ongoing Studies

Studies published between 2000 and June 2025 were eligible for inclusion in this systematic review. Actual publication dates ranged from August 2003 until October 2021. The most recent reported study completion date was December 2014 (published four years later in May 2018), and the earliest reported study completion date was September 2000 (published three years later in August 2003). Two studies did neither report when they were conducted nor the duration of the study; one of these studies disclosed a trial number from 2013 and was first

published in February 2018 and republished in October 2021. No new study was published since 2020; there was no study published which was started or conducted in the last decade. The identified health technology assessment report from the National French Authority for Health was published in 2011 and no more recent health technology assessment was identified in the review. Thus, there is no recent published data available on the review topic.

As part of the screening, clinical trial registries were searched for study records supporting published randomised controlled trials and ongoing studies investigating prophylactic application of topical haemostatic agents. Only for one included randomised controlled trial the corresponding study registry entry (NCT01959503) was retrieved from clinicaltrials.gov. One study registry entry (NCT06918496) could be identified for a new, ongoing study, six study registry entries were identified with an unknown study status or no reported results.

The clinical study with the study registry identification number NCT06918496 is supposed to investigate prophylactic suture line sealing with NE'X Glue R-eco and evaluate its effectiveness and safety. Sixty patients undergoing cardiovascular surgery at two sites in the European Union are planned to be included in this prospective, open-label, single-arm study. NE'X Glue R-eco is described as a surgical adhesive or glue like BioGlue, consisting of recombinant human serum albumin and glutaraldehyde and is manufactured by Grena BioMed Ltd., London, United Kingdom. The agent is supposed to be applied to suture lines, followed by releasing the clamp and restoring the blood flow two minutes after the application. As primary endpoint the immediate sealing at anastomoses is to be assessed. Secondary endpoints include haemostasis at defined points in time, time to haemostasis, additional use of haemostatic methods, product handling and performance of the intervention, device deficiencies, postoperative blood loss, intake of anticoagulant or antiplatelet medication, intra- and postoperative complication rates, reoperation rates, mortality and use of blood replacement products. The study registration was first submitted in March 2025; study start was planned for end of June 2025, and the foreseen duration is nine months with an estimated completion in March 2026. Currently (November 2025) the study status is still set as not yet recruiting. Even though the trial sites of this study are in the European Union, no equivalent clinical trial was found in the European Clinical Trials Information System (CTIS) (NIH ClinicalTrials.gov, 2025).

5.6 Future research

The current review shows limited high-quality evidence for the prophylactic use of topical haemostatic agents, although they are commonly used in practice. Thus, there is a need for further trials investigating the prophylactic application of topical haemostatic agents to inform clinicians, health care providers and guidelines and to gain relevant and valid data for this type

of application. From the findings of this review, a few basic proposals for future studies can be concluded.

First, the available evidence from the included studies does not allow to draw firm conclusions regarding the benefit of prophylactic application in cardiac surgery. While the studies identified in this review demonstrate a favourable safety profile and report positive outcomes for intraoperative efficacy endpoints, the evidence provides limited information on patient-relevant benefits. Therefore, additional studies are required to establish whether the prophylactic application has a benefit for the patient. For this purpose, relevant and sufficiently powered primary endpoints, concerning intraoperative haemostasis as well as postoperative and clinically relevant outcomes need to be defined and assessed. This might require a larger study size and a higher number of study sites. An additional proposal for a study plan assessing the efficacy of the prophylactic application would be to introduce a test for leakage of suture lines and compare the difference in applying the topical haemostatic agent to the whole suture line, only to sites of leakage or not at all. While cost-benefit of the prophylactic application of topical haemostatic agents was not within the scope of this review, cost-relevant outcome parameters might also be considered in future research.

Second, products either authorised and available or planning to be authorised and marketed in the European Union and/or Austria should be assessed to introduce a higher geographical relevance of study outcomes. Products should be assessed in comparison to other products as well as against control or placebo. Information on prophylactic use should be included in the authorisation documents.

Third, future trials should incorporate appropriate blinding procedures. While blinding of patients is feasible but of limited relevance, blinding of surgeons is generally not possible due to visible differences between interventions. As the use of placebo is also not feasible, the control group should receive either an active comparator or no prophylactic topical haemostatic agent. However, blinding of outcome assessors should be implemented whenever possible. For intraoperative endpoints, this may be achieved by shielding assessors from the application process, provided that no visible differences remain once the product is set. For postoperative endpoints, blinding of assessors should be readily achievable, as treatment allocation is unlikely to be apparent after surgical closure. Furthermore, individuals responsible for data analysis who are not involved in the surgical procedures or endpoint assessments should remain blinded.

In any case, future studies should adhere to high methodological standards, including rigorous randomisation procedures, adequate allocation concealment until immediately before application, and a pre-specified statistical analysis plan.

5.7 Limitations of the systematic review

This review has certain limitations: First, the review was performed by a single person. This comes with a risk of bias in study selection and exclusion, as well as data extraction and quality assessment. However, all decisions were based on the predefined eligibility criteria, documented and in cases of doubt, the supervisor and a medical expert were contacted for input. Second, only publications in English and German were considered eligible, possibly excluding relevant information published in other languages and therefore potentially introducing a publication bias. Third, some eligibility criteria were not strictly defined in the first protocol as it was unclear in the beginning which endpoints would be reported, what type of studies could be retrieved for the topic of the review and how recent they would be. The PICOS was defined and specified together with a medical expert. Fourth, the screening of publications identified in Embase was performed in a first step based on title and keywords only and the number of retrievable abstracts was limited to 50. Thus, this introduces a potential of missing relevant publications.

6 Conclusion

This master thesis aimed to assess efficacy and safety of the prophylactic use of topical haemostatic agents in cardiac surgery by performing a systematic literature review of the best available evidence. A total of seven randomised controlled trials investigating this mode of administration were identified, alongside two systematic reviews addressing safety aspects of topical haemostatic agents included in the review, one health technology assessment report, and two clinical guidelines providing recommendations on the use of topical haemostatic agents, including their preventive application. Overall, the studies reported favourable outcomes with respect to efficacy and safety. However, the results are not directly comparable, as different topical haemostatic agents – predominantly sealants or glues – were evaluated across studies. Furthermore, the identified studies and systematic reviews were generally of low methodological quality and most included trials were small in sample size. Regarding safety, some adverse events may only become apparent as long-term effects and may require specific diagnostic follow-up for detection. The available evidence suggests that prophylactic application of a topical haemostatic agent to suture lines before de-clamping and restoration of pressure may reduce intraoperative bleeding. This intervention might also have a potential effect on postoperative blood loss and transfusion requirements; however, the evidence remains limited and should be interpreted with caution. Further well-designed studies are required to evaluate both intraoperative and postoperative primary endpoints with adequate statistical power. Future research should also address the clinical and patient-relevant significance of outcomes and focus on topical haemostatic agents that are authorised and available within the European Union and Austria. The identified guidelines as well as the health technology assessment report do not recommend the application in the absence of bleeding. While the HTA report, which was published in 2011, advises specifically against this use, the two guidelines, which were published more recently, do not mention the preventive use in their recommendations. In current clinical practice, the prophylactic application of topical haemostatic agents appears to be guided more by the surgeon’s experience and preference than by consistent evidence from controlled studies and should therefore be applied with caution until more robust data on efficacy and patient-relevant outcomes become available.

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Appendix

A Review Protocol

SYSTEMATIC REVIEW PROTOCOL

REVIEW TITLE AND BASIC DETAILS

Review title

Prophylactic Use of Topical Haemostatic Agents in Cardiac Surgery: A Systematic Review

Review objectives

The objective of this research project is to identify and review clinical trials and literature investigating the use of topical haemostatic agents, focusing on their prophylactic application rather than their use in treating active perioperative bleeding. The aim is to review and assess the efficacy and safety of these agents in a preventive context, meaning the topical haemostatic agent has to be applied pre- or intraoperatively before bleeding occurs, for example for suture line sealing. To address these aims a systematic review of clinical trials, choosing the best available evidence, and other literature will be performed. Optionally, three expert interviews with established Austrian cardiac surgeons will complete the data gathered in the review with recent and application-oriented information.

Review question: Is the prophylactic use of topical haemostatic agents in cardiac surgery effective and safe compared to no prophylactic use or to the use of other topical haemostatic agents?

Keywords

Topical haemostatic agent (synonyms and different spellings), sealant, sealing cardiac surgery, cardiovascular surgery, heart surgery, blood management.

Medical Subject Headings

Cardiac surgical procedures, surgical blood loss/prevention & control, hemostatics, fibrin tissue adhesive, surgical hemostasis

SEARCHING AND SCREENING

Searches

The systematic review will be carried out according to the PRISMA guidelines in the following databases: MEDLINE (via PubMed), Cochrane Library (via Ovid), Web of Science and optionally in Embase and Epistemonikos.

The search will include publications in English and German language. We will use keywords and medical subject headings where available to identify clinical trials on prophylactic application of topical haemostatic agents in cardiac surgery. Boolean operators (AND / OR / NOT) will be used. We will also search clinical trial registries (WHO, EU, US) for ongoing and registered trials. Additional manual searches of related studies listed in the references, footnotes and citations will be carried out to include any relevant papers that may have not been included by the search. The search strategy is developed using a research protocol.

Study design

No limitation of the study design is chosen upfront; however, publications should be peer-reviewed. In the screening of the literature randomised controlled trials were uncovered, allowing the limitation of the study design for the efficacy analysis to the best available evidence of randomised controlled trials, guidelines and systematic reviews.

ELIGIBILITY CRITERIA

Condition or domain being studied

Prophylactic application (pre- or intraoperatively before bleeding occurs) of topical haemostatic agents in cardiac surgery to prevent and reduce perioperative bleeding.

Population

Patients undergoing cardiac or cardiovascular surgery, with no specification of the surgical operations (including surgical procedures of the ascending aorta, the valves, chambers, coronary arteries as well as combinatory operations of heart and vessels).

Inclusion: Included are all studies in patients of any age (age limitations may be included at a later point) who are undergoing cardiac surgery irrespective of the specifical surgical operations. Exclusion: Studies in patients undergoing vascular surgery only (including surgical procedures of carotids, the descending aorta, peripheral arteries and veins) or any non-cardiac surgery.

Intervention(s) or exposure(s)

Topical haemostatic agents of different product groups and types without specification/limitation (including mechanically acting haemostatic agents (collagen-based products, polymer-based sealants etc.) OR active (pharmacologically enhanced) haemostatic agents (thrombin-containing products, fibrin sealants, tranexamic acid-coated materials etc.) OR combination products). Prophylactic application means the pre- or perioperative administration before bleeding occurs, before clamps are opened and blood flow restored, for example for suture line sealing.

Exclusion: Systemic application, application of topical haemostatic agents to treat or control active perioperative bleeding, application of topical haemostatic agents only after other techniques have shown to be insufficient, postoperative application of haemostatic agents.

Comparator(s) or control(s): No prophylactic use OR application of other topical haemostatic agents.

Context: N/A

In- and Exclusion Criteria

Inclusion Criteria

Studies in patients of all age undergoing cardiac OR cardiovascular surgery (including surgical procedures of the ascending aorta, the valves, chambers, coronary arteries as well as combinatory operations of heart and vessels).

Topical haemostatic agents (including mechanically acting haemostatic agents (collagen-based products, polymer-based sealants etc.) OR active (pharmacologically enhanced) haemostatic agents (thrombin-containing products, fibrin sealants, tranexamic acid-coated materials etc.) OR combination products have been applied prophylactically (pre- or intraoperatively before bleeding occurs) to prevent and reduce perioperative bleeding.

Publication in English or German language.

Outcome describes efficacy and/or safety of the intervention. Efficacy outcomes may include, but are not limited to, proportion of or time to anastomotic sealing or haemostasis, the amount of perioperative bleeding, transfusion requirements, incidence of reoperation, operational times or length of hospital stay. Safety outcomes may include, but are not limited to, (serious) adverse events or mortality.

Study Design: Best available evidence. Randomised controlled trials (RCT), systematic reviews and guidelines and health technology assessment (HTA).

Publication from 2000 until June 2025.

Exclusion Criteria

Studies in patients undergoing vascular surgery only (including surgical procedures of carotids, the descending aorta, peripheral arteries and veins).

Studies in animals or in-vitro.

Postoperative application of topical haemostatic agents.

Systemic administration of haemostatic agents.

Application of topical haemostatic agents to treat active perioperative bleeding.

Application of topical haemostatic agents after other techniques have shown to be insufficient to control bleeding.

Application of topical haemostatic agents directly after sternotomy to the sternum.

Topical application of antifibrinolytic drugs if not in combination with another haemostatic agent.

Publication as non-peer reviewed literature, for example conference reports.

OUTCOMES TO BE ANALYSED

Main outcomes

1. Efficacy of prophylactically applied topical haemostatic agents in cardiac surgery.
2. Safety of prophylactically applied topical haemostatic agents in cardiac surgery.

Additional outcomes: N/A

DATA COLLECTION PROCESS

Data extraction (selection and coding)

The systematic review will be reported in accordance with the PRISMA statement.

Study selection

• The eligibility criteria in this protocol will be applied to screen study titles, abstracts and full texts.
• Excel® (Microsoft 365) and Citavi 6 Software will be used for this process.

Data extraction

• The identification, screening, eligibility and inclusion of papers will be performed and presented according to the PRISMA statement, checklist and flow diagram.

• Extracted data will include: title, date of publication, study ID, author, date of study, design, duration, size, methods, eligibility criteria, type of cardiac surgery, characteristics of intervention (agent used, way of administration), therapeutic outcomes on efficacy and safety (outcome and endpoints, results, adverse events), risk of bias, comments.

• Authors will not be contacted for unreported data and any missing data will be reported as missing in the data extraction form.

• No specialised data extraction software will be used. Excel and Word will be the software of choice.

Risk of bias (quality) assessment

Quality assessment will be performed dependent on the resulting publication types. Tools and protocols provided and recommended by Cochrane and/or PRISMA will be employed.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

A narrative synthesis of the data will be undertaken to answer the study aim. The strategy is dependent on the amount and type of publications resulting from the search. Expert interviews may be performed to support and to add to the search results.

Analysis of subgroups or subsets: N/A

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members: This systematic review will be performed by a single person, Victoria Hagenbuchner. The supervisor, Sabine Geiger-Gritsch will support and consult in cases of uncertainty.

Review affiliation: University of Innsbruck

Funding source: No funding provided

TIMELINE OF THE REVIEW

Review timeline: June/July/August 2025

CURRENT REVIEW STAGE

Publication of review results: The intention is to publish the review as a master's thesis once completed. The review will be published in English.

Optional Interviews: Will not be performed.

Revision Notes

Original: 16.06.2025

Update 1: Update of Eligibility Criteria after receiving additional medical input. (17.06.2025)

Update 2: Update limitation of the study design and inclusion criterium time frame. (11.08.2025)

Update 3: Format adaption for inclusion in appendix of thesis. Correction of word use intra-, post- and perioperative. (08.09.2025)

Update 4: Update of Review Question to include Comparator, update of Eligibility Criteria (Comparator, Specification of Inclusion Criterium Outcome, Exclusion Criterium Application to sternum). (27.10.2025)

B Search Strategy

DATABASE SEARCH

PubMed (17.06.2025)

#	Search	Details	Results
1	cardiac surgery[TIAB] OR heart surgery[TIAB] OR cardiovascular surgery[TIAB] OR valve repair[TIAB] OR valve replacement[TIAB] OR surgery of ascending aorta[TIAB] OR coronary artery bypass[TIAB] OR bypass surgery[TIAB] OR cardiac surgical procedures[MH]	"cardiac surgery"[Title/Abstract] OR "heart surgery"[Title/Abstract] OR "cardiovascular surgery"[Title/Abstract] OR "valve repair"[Title/Abstract] OR "valve replacement"[Title/Abstract] OR (("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields]) AND "of ascending aorta"[Title/Abstract]) OR "coronary artery bypass"[Title/Abstract] OR "bypass surgery"[Title/Abstract] OR "cardiac surgical procedures"[MeSH Terms]	337097
2	topical h*emostatic agent*[TIAB] OR topical h*emostat*[TIAB] OR topical h*emostatic*[TIAB] OR sealant[TIAB] OR sealing[TIAB] OR blood management[TIAB] OR hemostatics[MH] OR blood loss, surgical / prevention and control[MH] OR hemostasis, surgical[MH] OR fibrin tissue adhesive[MH] OR gelatin sponge, absorbable[MH] OR hemostatics [PA] OR tissue adhesives [PA]	"topical h*emostatic agent*"[Title/Abstract] OR "topical h*emostat*"[Title/Abstract] OR "topical h*emostatic*"[Title/Abstract] OR "sealant"[Title/Abstract] OR "sealing"[Title/Abstract] OR "blood management"[Title/Abstract] OR "hemostatics"[MeSH Terms] OR "blood loss, surgical/prevention and control"[MeSH Terms] OR "hemostasis, surgical"[MeSH Terms] OR "fibrin tissue adhesive"[MeSH Terms] OR "gelatin sponge, absorbable"[MeSH Terms] OR "hemostatics"[Pharmacological Action] OR "tissue adhesives"[Pharmacological Action]	225240
3	#1 AND #2	("cardiac surgery"[Title/Abstract] OR "heart surgery"[Title/Abstract] OR "cardiovascular surgery"[Title/Abstract] OR "valve repair"[Title/Abstract] OR "valve replacement"[Title/Abstract] OR (("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields]) AND "of ascending aorta"[Title/Abstract]) OR "coronary artery bypass"[Title/Abstract] OR "bypass surgery"[Title/Abstract] OR "cardiac surgical procedures"[MeSH Terms]) AND ("topical h*emostatic agent*"[Title/Abstract] OR "topical h*emostat*"[Title/Abstract] OR "topical h*emostatic*"[Title/Abstract] OR "sealant"[Title/Abstract] OR "sealing"[Title/Abstract] OR "blood management"[Title/Abstract] OR "hemostatics"[MeSH Terms] OR "blood loss, surgical/prevention and control"[MeSH Terms] OR "hemostasis, surgical"[MeSH Terms] OR "fibrin tissue adhesive"[MeSH Terms] OR "gelatin sponge, absorbable"[MeSH Terms] OR "hemostatics"[Pharmacological Action] OR "tissue adhesives"[Pharmacological Action])	4934
4	#1 AND #2, Filters: English, German	N/A	4620

Cochrane Library via Ovid (17.06.2025)

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 11, 2025>

EBM Reviews - ACP Journal Club <1991 to May 2025>

EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>

EBM Reviews - Cochrane Clinical Answers <May 2025>

EBM Reviews - Cochrane Central Register of Controlled Trials <May 2025>

EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>

EBM Reviews - Health Technology Assessment <4th Quarter 2016>

EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

#	Search	Results
1	(cardiac surgery or heart surgery or cardiovascular surgery or valve repair or valve replacement or (surgery and ascending aorta) or coronary artery bypass or bypass surgery).ab,kw,ti. or cardiac surgical procedures.ab,kw,sh,ti.	30269
2	(topical h*emostatic agent* or topical h*emostat* or topical h*emostatic* or sealant or sealing or blood management).ab,kw,ti. or (hemostatics or blood loss, surgical or hemostasis, surgical or fibrin tissue adhesive or gelatin sponge, absorbable).ab,kw,sh,ti.	9339
3	1 and 2	778

Web Of Science Core Collection (17.06.2025)

#	Search	Results
1	TS=("cardiac surgery" OR "heart surgery" OR "cardiovascular surgery" OR "valve repair" OR "valve replacement" OR (surgery AND "ascending aorta") OR "coronary artery bypass" OR "bypass surgery" OR "cardiac surgical procedures")	209823
2	TS=("topical hemostatic agent*" OR "topical haemostatic agent*" OR "topical hemostat*" OR "topical haemostat*" OR "topical hemostatic*" OR "topical haemostatic*" OR sealant OR sealing OR "blood management" OR hemostatic* OR "blood loss, surgical" OR "hemostasis, surgical" OR "fibrin tissue adhesive" OR "gelatin sponge, absorbable" OR "tissue adhesive*")	157473
3	1 and 2	2248
4	1 and 2 and English or German (Languages)	2193

Epistemonikos (17.06.2025)

#	Search	Results
1	(title:((cardi* surgery OR "cardiac surgery" OR "heart surgery" OR "cardiovascular surgery" OR "valve repair" OR "valve replacement" OR (surgery AND "ascending aorta") OR "coronary artery bypass" OR "bypass surgery" OR "cardiac surgical procedures") AND ("topical hemostatic agent*" OR "topical haemostatic agent*" OR "topical hemostat*" OR "topical haemostat*" OR "topical hemostatic*" OR "topical haemostatic*" OR sealant OR sealing OR "blood management" OR hemostatic* OR "blood loss, surgical" OR "hemostasis, surgical" OR "fibrin tissue adhesive" OR "gelatin sponge, absorbable" OR "tissue adhesive*")) OR abstract:((cardi* surgery OR "cardiac surgery" OR "heart surgery" OR "cardiovascular surgery" OR "valve repair" OR "valve replacement" OR (surgery AND "ascending aorta") OR "coronary artery bypass" OR "bypass surgery" OR "cardiac surgical procedures") AND ("topical hemostatic agent*" OR "topical haemostatic agent*" OR "topical hemostat*" OR "topical haemostat*" OR "topical hemostatic*" OR "topical haemostatic*" OR sealant OR sealing OR "blood management" OR hemostatic* OR "blood loss, surgical" OR "hemostasis, surgical" OR "fibrin tissue adhesive" OR "gelatin sponge, absorbable" OR "tissue adhesive*")))	968

Embase (27.06.2025)

#	Search	Results
L1	CARDIAC SURGERY/TI OR CARDIAC SURGERY/AB	81288
L2	HEART SURGERY/TI OR HEART SURGERY/AB	24758

L3	CARDIOVASCULAR SURGERY/TI OR CARDIOVASCULAR SURGERY/AB	9515
L4	VALVE REPAIR/TI OR VALVE REPAIR/AB	15559
L5	VALVE REPLACEMENT/TI OR VALVE REPLACEMENT/AB	67701
L6	SURGERY OF ASCENDING AORTA/TI OR SURGERY OF ASCENDING AORTA/AB	18
L7	CORONARY ARTERY BYPASS/TI OR CORONARY ARTERY BYPASS/AB	67119
L8	BYPASS SURGERY/TI OR BYPASS SURGERY/AB	35963
L9	CARDIAC SURGICAL PROCEDURES (CARDIAC(W)SURGICAL(W)PROCEDURES)	3483
L10	L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9	252958
L11	TOPICAL H!EMOSTATIC AGENT?/TI OR TOPICAL H!EMOSTATIC AGENT?/AB	109
L12	TOPICAL H!EMOSTAT?/TI OR TOPICAL H!EMOSTAT?/AB	148
L13	TOPICAL H!EMOSTATIC?/TI OR TOPICAL H!EMOSTATIC?/AB	136
L14	SEALANT/TI OR SEALANT/AB	6882
L15	SEALING/TI OR SEALING/AB	18209
L16	BLOOD MANAGEMENT/TI OR BLOOD MANAGEMENT/AB	3419
L17	HEMOSTATICS	464
L18	SURGICAL BLOOD LOSS (SURGICAL(W)BLOOD(W)LOSS)	1054
L19	SURGICAL HEMOSTASIS (SURGICAL(W)HEMOSTASIS)	1107
L20	FIBRIN TISSUE ADHESIVE (FIBRIN(W)TISSUE(W)ADHESIVE)	313
L21	ABSORBABLE GELATIN SPONGE (ABSORBABLE(W)GELATIN(W)SPONGE)	354
L22	HEMOSTATICS/TI OR HEMOSTATICS/AB	267
L23	TISSUE ADHESIVES/TI OR TISSUE ADHESIVES/AB	1126
L24	L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23	31750
L25	L10 AND L24	1015
L26	L25 NOT MEDLINE/FS	937

CLINICAL TRIAL REGISTRIES SEARCH

ICTRP (18.06.2025)

Search	**Results**
(CARDI* SURGERY OR "CARDIAC SURGERY" OR “HEART SURGERY” OR "CARDIOVASCULAR SURGERY" OR “VALVE REPAIR” OR “VALVE REPLACEMENT” OR (SURGERY AND ASCENDING AORTA) OR "CORONARY ARTERY BYPASS" OR "BYPASS SURGERY” OR "CARDIAC SURGICAL PROCEDURES") AND ("TOPICAL HAEMOSTATIC AGENT*” OR "TOPICAL HEMOSTATIC AGENT*” OR "TOPICAL HAEMOSTAT*" OR "TOPICAL HEMOSTAT*" OR "TOPICAL HAEMOSTATIC*" OR "TOPICAL HEMOSTATIC*" OR "SEALANT*" OR "BLOOD MANAGEMENT" OR "SEALING" OR "SURGICAL BLOOD LOSS" OR "ABSORBABLE GELATIN SPONGE" OR "HEMOSTATICS" OR "TISSUE ADHESIVES" OR "FIBRIN TISSUE ADHESIVE" OR "SURGICAL HEMOSTASIS")	63 records for 54 trials

CTR.eu (18.06.2025)

Search	**Results**
(CARDIAC SURGERY OR CARDIAC SURGICAL PROCEDURES OR HEART SURGERY) AND (HEMOSTATIC OR HEMOSTATICS OR HEMOSTATIC AGENTS OR TISSUE ADHESIVES OR SEALANT OR SEALING)	76

CTIS (18.06.2025)

Search	**Results**
SEARCH TERM: SURGERY, THERAPEUTIC AREA: DISEASES [C] – CARDIOVASCULAR DISEASES [C14]	48

CT.gov (18.06.2025)

Search	**Results**
(CARDIAC SURGERY OR CARDIAC SURGICAL PROCEDURES \(D006348\) OR HEART SURGERY) AND (HEMOSTATIC OR HEMOSTATICS OR HEMOSTATIC AGENTS OR TISSUE ADHESIVES OR SEALANT OR SEALING)	650

C Research Protocol

This research protocol has been created by translation, adaption and modification from (Hirt & Nordhausen, 2022).

Hirt, J., Nordhausen, T. (2022). Rechercheprotokoll für eine systematische Literaturrecherche. In: Nordhausen, T., Hirt, J. RefHunter. Systematische Literaturrecherche. https://refhunter.org/research_support/rechercheprotokoll/ [17.06.2025]

GENERAL INFORMATION ON THE DEVELOPMENT OF THE SEARCH STRATEGY

The search strategy was developed by: Victoria Hagenbuchner
The search strategy was developed in: May/June 2025

RESEARCH QUESTION

Is the prophylactic application of topical haemostatic agents in cardiac surgery effective and safe, compared to no prophylactic use or the application of different topical haemostatic agents?

PICOS

Population	Patients undergoing cardiac or cardiovascular surgery, including surgical procedures of the ascending aorta, the valves, the chambers, coronary arteries as well as combinatory operations of heart and vessels. NOT patients undergoing vascular surgery only (including surgical procedures of carotids, the descending aorta, peripheral arteries and veins). Adult and paediatric, no age limitation.
Intervention	Prophylactic application of topical haemostatic agents to prevent bleeding. Including mechanically acting haemostatic agents (collagen-based products, polymer-based sealants etc.) OR active (pharmacologically enhanced) haemostatic agents (thrombin-containing products, fibrin sealants, tranexamic acid-coated materials etc.) OR combination products. NOT systemic application of haemostatics. Prophylactic application can be pre- or max. intraoperative before bleeding occurs, before clamps are opened and blood flow restored, for example for suture line sealing NOT postoperative.
Comparison	No prophylactic treatment with topical haemostatic agents OR comparison with another agent.
Outcome	Efficacy and Safety
Study Design	Best available evidence

ELIGIBILITY CRITERIA

Domain	Inclusion Criteria	Exclusion Criteria
Domain 1: Population	Studies in patients of all age undergoing cardiac OR cardiovascular surgery (including surgical procedures of the ascending aorta, the valves, chambers, coronary arteries as well as combinatory operations of heart and vessels).	Studies in patients undergoing vascular surgery only (including surgical procedures of carotids, the descending aorta, peripheral arteries and veins).
Domain 2: Intervention	Topical haemostatic agents (including mechanically acting haemostatic agents (collagen-based products, polymer-based sealants etc.) OR active (pharmacologically enhanced) haemostatic agents	Postoperative application of topical haemostatic agents. Systemic administration of haemostatic agents.

	(thrombin-containing products, fibrin sealants, tranexamic acid-coated materials etc.) OR combination products) have been applied prophylactically (pre- or intraoperatively before bleeding occurs) to prevent and reduce intra- and postoperative bleeding.	Application of topical haemostatic agents solely to treat active perioperative bleeding. Application after other techniques have shown to be insufficient to control bleeding. Topical application of antifibrinolytic drugs if not in combination with another haemostatic agent.
Domain 3: Outcome	Outcome describes efficacy and/or safety of the intervention.	N/A
Domain 4: Study design	N/A, best available evidence	Animal studies, in-vitro studies
Domain 5: Publication Type	N/A	Non-peer reviewed publications, e.g. conference reports, meeting abstracts.
Domain 6: Publication Date	Optional: Last 20-25 years.	Optional: Before 2000.
Domain 7: Language	German, English	Other languages

Reasoning for Eligibility Criteria:

☒ Domain 1: No specification of the surgical procedure, however focus on operations of the aorta ascendens and aortic valves.
Domain 2: Prophylactic application is defined as the pre- or intraoperative application before bleeding occurs, before clamps are opened and blood flow restored. Suture line sealing is an example for a prophylactic application.
Domain 3: Efficacy and Safety of the intervention shall be established. These can be measured in different ways which cannot all be defined pre-emptively.
Domain 4: The application in human patients is to be investigated; the study design is dependent on the best available evidence.
Domain 6: The most contemporary evidence is to be used.
Domain 7: Languages known by researcher, translation of other languages would be an unreasonable effort.

☐ No reasoning necessary.

1 ESTABLISHING THE RESEARCH PRINCIPLE

☐ Sensitive Research Principle
Goal: Find possibly all relevant hits.

☐ Specific Research Principle
Goal: Find as fast as possible the most relevant and important hits.

☒ Mixed Principle (partly sensitive partly specific)
Goal: Find as many relevant hits as possible with an optimised effort ratio.
The aim is to write a systematic review and to identify possibly all relevant search results, however with an optimised effort ratio as this is a master's thesis project and the systematic review is performed by a single person.

2 DEFINITIONS OF SEARCH COMPONENTS

Definition of search components based on research question and PICO scheme.

Search component	Definition
Search component 1	Patients undergoing cardiac surgery (Population)
Search component 2	Prophylactic application of topical haemostatic agents to prevent perioperative bleeding / Blood management (Intervention)

Reasoning for defined or non-defined search components:

☒ Only population and intervention are deemed as relevant search components.
Exclusion of component comparison: would exclude studies without comparator control, it is not possible to define all possible control interventions, therefore not operational.
Exclusion of component outcome: Efficacy and safety can be measured by a multitude of endpoints, therefore not operational.
Exclusion of component study design, publication type, date, language: not relevant as search components however might be relevant as filters.

☐ No reasoning necessary.

3 CHOICE OF DATABASES TO BE SEARCHED

Choice of databases to be searched and search engines to search the databases

Database	Name
	Reasoning
Database 1	MEDLINE via PubMed
	Includes publications in broad spectrum of health care sector
Database 2	Cochrane Library via Ovid
	Includes publications in broad spectrum of health care sector in high quality
Database 3	Web of Science Core Collection
	Includes publications in broad spectrum of health care sector
Database 4	Embase via CAS STNext
	Includes publications in broad spectrum of health care sector
Database 5	International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, CTR EU, EU CTIS
	Includes recent and ongoing clinical trials
Database 6	Epistemonikos
	Epistemonikos is a collaborative, multilingual database of health evidence. It is the largest source of systematic reviews relevant for health-decision making, and a large source of other types of scientific evidence

Database Operators to be used:

Database	Operator
Database 1 (PubMed)	[TIAB] = Title/Abstract; [MH] = MeSH Term, [PA] = Pharmacological Action
Database 2 (Cochrane Library)	.ab,kw,sh,ti = Abstract, Keyword, MeSH Term, Title
Database 3 (Web of Science)	TS = Topic, includes Title, Abstract and Keywords
Database 4 (Embase)	/TI = Title; /AB = Abstract
Database 5 (Clinical Trial Registries)	N/A
Database 6 (Epistemonikos)	Title/Abstract

4 IDENTIFICATION OF KEYWORDS

Identification of keywords, their synonyms and writing variants per search component.

Search component	Keywords
Search component 1: Population	cardiac surgery Heart Surgery Cardiovascular Surgery Valve Repair Valve Replacement Surgery of Ascending Aorta Coronary Artery Bypass Bypass Surgery
Search component 2: Intervention	topical haemostatic agent(S) topical hemostatic agent(S) topical haemostat(S) topical hemostat(S) topical haemostatic(S) topical hemostatic(S) sealant Sealing blood management

Reasoning for defined and non-defined keywords:

☒ Search component 2: exclusion of adjective prophylactic, preventive, pre-emptive. Will be part of selection process however not in search process as these adjectives might not have been necessarily used but the description of the administration should align with this kind of application. Exclusion of keyword adjunct as this term refers to haemostatic but also several other agents.

Inclusion of keywords blood management and sealing as synonym for the intervention as the synonym terms for topical haemostatic agents are not necessarily in title, abstract or full text. Different types of topical haemostatic agents may be in use, not possible to list all possibilities.

☐ No reasoning necessary.

5 IDENTIFICATION OF CONTROLLED VOCABULARY

Keywords	**Search components**	**Controlled Vocabulary: PubMed**	**Controlled Vocabulary: Cochrane Library**	**Controlled Vocabulary: Web Of Science**	**Controlled Vocabulary: Embase**	**Controlled Vocabulary: Clinical Trial Registries**	**Controlled Vocabulary: Epistemonikos**
CARDIAC SURGERY HEART SURGERY CARDIOVASCULAR SURGERY VALVE REPAIR VALVE REPLACEMENT	**Search component 1: Population**	CARDIAC SURGICAL PROCEDURES	CARDIAC SURGICAL PROCEDURES	N/A	CARDIAC SURGICAL PROCEDURES	N/A	N/A

Keywords	Search components	Controlled Vocabulary: PubMed	Controlled Vocabulary: Cochrane Library	Controlled Vocabulary: Web Of Science	Controlled Vocabulary: Embase	Controlled Vocabulary: Clinical Trial Registries	Controlled Vocabulary: Epistemonikos
SURGERY OF ASCENDING AORTA CORONARY ARTERY BYPASS BYPASS SURGERY							
TOPICAL HAEMOSTATIC AGENT(S) TOPICAL HEMOSTATIC AGENT(S) TOPICAL HAEMOSTAT(S) TOPICAL HEMOSTAT(S) TOPICAL HAEMOSTATIC(S) TOPICAL HEMOSTATIC(S) SEALANT SEALING BLOOD MANAGEMENT	**Search component 2: Intervention**	HEMOSTATICS BLOOD LOSS, SURGICAL / PREVENTION & CONTROL HEMOSTASIS, SURGICAL FIBRIN TISSUE ADHESIVE GELATIN SPONGE, ABSORBABLE HEMOSTATICS [PA] TISSUE ADHESIVES [PA]	HEMOSTATICS BLOOD LOSS, SURGICAL HEMOSTASIS, SURGICAL FIBRIN TISSUE ADHESIVE GELATIN SPONGE, ABSORBABLE	N/A	HEMOSTATICS SURGICAL BLOOD LOSS SURGICAL HEMOSTASIS FIBRIN TISSUE ADHESIVE ABSORBABLE GELATIN SPONGE	N/A	N/A

Identification of controlled vocabulary for identified keywords per search component and database.

Reasoning for defined and non-defined controlled vocabulary:

☒ Search component 1: Only cardiac surgical procedures was used, not thoracic surgery, as the second term includes more operation in the thorax and the first term should sufficiently include all cardiac surgical procedures
Search component 2: Exclusion of Topical Administration as Controlled Vocabulary as this would lead to too much and irrelevant results.
Database 3, 5 and 6: No support of controlled vocabulary, use of keywords only.
Database 4: No support of Emtree terms by searching via CAS STNext. Controlled vocabulary was searched without field operators.

☐ No reasoning necessary.

6 DEVELOPMENT OF THE SEARCH STRING

Combination of identified keywords and controlled vocabulary per search component and database column wise to one search string. Definition of search techniques (e.g. wildcards like truncation, search of phrases with quotation marks) and Syntax/Operators.

Search component	Search String: PubMed	Search String: Cochrane Library	Search String: Web Of Science	Search String: Embase	Search String: Clinical Trial Registry	Search String: Epistemonikos
Search component 1: Population	cardiac surgery[TIAB] OR heart surgery[TIAB] OR cardiovascular surgery[TIAB] OR valve repair[TIAB] OR valve replacement[TIAB] OR surgery of ascending aorta[TIAB] OR coronary artery bypass[TIAB] OR bypass surgery[TIAB] OR cardiac surgical procedures[MH]	(cardiac surgery OR heart surgery OR cardiovascular surgery OR valve repair OR valve replacement OR (surgery AND ascending aorta) OR coronary artery bypass OR bypass surgery).ab,kw,ti. OR cardiac surgical procedures.ab,kw,sh,ti.	TS=("cardiac surgery" OR "heart surgery" OR "cardiovascular surgery" OR "valve repair" OR "valve replacement" OR (surgery AND "ascending aorta") OR "coronary artery bypass" OR "bypass surgery" OR "cardiac surgical procedures")	(cardiac surgery/TI OR cardiac surgery/AB) OR (heart surgery/TI OR heart surgery/AB) OR (cardiovascular surgery/TI OR cardiovascular surgery/AB) OR (valve repair/TI OR valve repair/AB) OR (valve replacement/TI OR valve replacement/AB) OR (surgery of ascending aorta/TI OR surgery of ascending aorta/AB) OR (coronary artery bypass/TI OR coronary artery bypass/AB) OR (bypass surgery/TI OR bypass surgery/AB) OR cardiac surgical procedures	(cardi* surgery OR "cardiac surgery" OR “heart surgery” OR "cardiovascular surgery" OR “valve repair” OR “valve replacement” OR (surgery AND ascending aorta) OR "coronary artery bypass" OR "bypass surgery” OR "cardiac surgical procedures")	(cardi* surgery OR "cardiac surgery" OR "heart surgery" OR "cardiovascular surgery" OR "valve repair" OR "valve replacement" OR (surgery AND "ascending aorta") OR "coronary artery bypass" OR "bypass surgery" OR "cardiac surgical procedures")
	AND	AND	AND	AND	AND	AND
Search component 2: Intervention	topical h*emostatic agent*[TIAB] OR topical h*emostat*[TIAB] OR topical h*emostatic*[TIAB] OR sealant[TIAB] OR sealing[TIAB] OR blood management[TIAB] OR hemostatics[MH] OR blood loss, surgical / prevention and control[MH] OR hemostasis, surgical[MH] OR fibrin tissue adhesive[MH] OR gelatin sponge, absorbable[MH] OR	(topical h*emostatic agent* OR topical h*emostat* OR topical h*emostatic* OR sealant OR sealing OR blood management).ab,kw,ti OR (hemostatics OR blood loss, surgical OR hemostasis, surgical OR fibrin tissue adhesive OR gelatin sponge, absorbable).ab,kw,sh,ti	TS=("topical hemostatic agent*" OR "topical haemostatic agent*" OR "topical hemostat*" OR "topical haemostat*" OR "topical hemostatic*" OR "topical haemostatic*" OR sealant OR sealing OR "blood management" OR hemostatic* OR "blood loss, surgical" OR "hemostasis, surgical" OR "fibrin tissue	(topical h!emostatic agent?/TI OR topical h!emostatic agent?/AB) OR (topical h!emostat?/TI OR topical h!emostat?/AB) OR (topical h!emostatic?/TI OR topical h!emostatic?/AB) OR (sealant/TI OR sealant/AB) OR (sealing/TI OR sealing/AB) OR (blood management/TI OR blood management/AB) OR hemostatics OR surgical blood loss OR surgical	("topical haemostatic agent*” OR "topical hemostatic agent*” OR "topical haemostat*" OR "topical hemostat*" OR "topical haemostatic*" OR "topical hemostatic*" OR "sealant*" OR "blood management" OR "sealing" OR "surgical blood loss" OR "absorbable gelatin sponge" OR "hemostatics" OR "tissue	("topical hemostatic agent*" OR "topical haemostatic agent*" OR "topical hemostat*" OR "topical haemostat*" OR "topical hemostatic*" OR "topical haemostatic*" OR sealant OR sealing OR "blood management" OR hemostatic* OR "blood loss, surgical" OR "hemostasis, surgical" OR "fibrin tissue

Search component	Search String: PubMed	Search String: Cochrane Library	Search String: Web Of Science	Search String: Embase	Search String: Clinical Trial Registry	Search String: Epistemonikos
	hemostatics [PA] OR tissue adhesives [PA]		adhesive" OR "gelatin sponge, absorbable" OR "tissue adhesive*")	hemostasis OR fibrin tissue adhesive OR absorbable gelatin sponge OR (hemostatics/TI OR hemostatics /AB) OR (tissue afhesives/TI OR tissue adhesives/AB)	adhesives" OR "fibrin tissue adhesive" OR "surgical hemostasis")	adhesive" OR "gelatin sponge, absorbable" OR "tissue adhesive*")

Reasoning for employed and non-employed search techniques, keywords and controlled vocabulary:

☒ Database 1: Quotation marks not required for phrase search – automatically provided by PubMed. Truncations in search component 2 to include British and American style of writing and singular and plural terms.
Database 2: Use of Expert Search to enter search string.
Database 3: Perplexity AI used to transform and optimise search string based on Database 1 search string.
Database 4: Prepared by ULB Tirol librarian
Database 5: The search string shown above is for the international clinical trial registry platform (ICTRP). For the Clinical Trial Registries ClinicalTrials.gov, clinicaltrialregister.eu and EUClinicalTrials.eu shortened search strings were used as not all operators are supported.
Clinical Trials.gov: (Cardiac Surgery OR Cardiac Surgical Procedures \(D006348\) OR Heart Surgery) AND (Hemostatic OR Hemostatics OR Hemostatic Agents OR Tissue adhesives OR Sealant OR Sealing)
Clinicaltrialsregster.eu: (Cardiac Surgery OR Cardiac Surgical Procedures OR Heart Surgery) AND (Hemostatic OR Hemostatics OR Hemostatic Agents OR Tissue adhesives OR Sealant OR Sealing)
Euclinicaltrials.eu: search term: surgery, therapeutic area: diseases [C] – cardiovascular diseases [C14]
Database 6: Same search query as in Database 3. Title/Abstract query is added by the database.

☐ No reasoning necessary.

7 CONDUCTING THE RESEARCH

Documentation of search filters (e.g. based on eligibility criteria for study selection), which are applied in the research and of special features that occurred in conducting the research in the databases. Reasoning for application of search filters can be written down here.

Filter for language (PubMed): German or English.

Clinical trial registries: only results from clinicaltrials.gov are downloaded as RIS file and can be added to Endnote. All entries for clinical trial records or protocol will need to be assessed in Excel.

8 RESEARCH DOCUMENTATION

Documentation of database-specific search strings. State date of search and number of results.

8.1 PubMed

Date of search: 17.06.2025

#	Search	Number of Results
1	CARDIAC SURGERY[TIAB] OR HEART SURGERY[TIAB] OR CARDIOVASCULAR SURGERY[TIAB] OR VALVE REPAIR[TIAB] OR VALVE REPLACEMENT[TIAB] OR SURGERY OF ASCENDING AORTA[TIAB] OR CORONARY ARTERY BYPASS[TIAB] OR BYPASS SURGERY[TIAB] OR CARDIAC SURGICAL PROCEDURES[MH]	337.097
2	TOPICAL H*EMOSTATIC AGENT*[TIAB] OR TOPICAL H*EMOSTAT*[TIAB] OR TOPICAL H*EMOSTATIC*[TIAB] OR SEALANT[TIAB] OR SEALING[TIAB] OR BLOOD MANAGEMENT[TIAB] OR HEMOSTATICS[MH] OR BLOOD LOSS, SURGICAL / PREVENTION AND CONTROL[MH] OR HEMOSTASIS, SURGICAL[MH] OR FIBRIN TISSUE ADHESIVE[MH] OR GELATIN SPONGE, ABSORBABLE[MH] OR HEMOSTATICS [PA] OR TISSUE ADHESIVES [PA]	225.240
3	#1 AND #2	4.934
4	#1 AND #2, FILTERS: ENGLISH, GERMAN	4.620

8.2 Cochrane Library/Ovid

Date of search: 17.06.2025

#	Search	Number of Results
1	(CARDIAC SURGERY OR HEART SURGERY OR CARDIOVASCULAR SURGERY OR VALVE REPAIR OR VALVE REPLACEMENT OR (SURGERY AND ASCENDING AORTA) OR CORONARY ARTERY BYPASS OR BYPASS SURGERY).AB,KW,TI. OR CARDIAC SURGICAL PROCEDURES.AB,KW,SH,TI.	30.269
2	(TOPICAL H*EMOSTATIC AGENT* OR TOPICAL H*EMOSTAT* OR TOPICAL H*EMOSTATIC* OR SEALANT OR SEALING OR BLOOD MANAGEMENT).AB,KW,TI. OR (HEMOSTATICS OR BLOOD LOSS, SURGICAL OR HEMOSTASIS, SURGICAL OR FIBRIN TISSUE ADHESIVE OR GELATIN SPONGE, ABSORBABLE).AB,KW,SH,TI.	9.339
3	#1 AND #2	778

8.3 Web of Science Core Collection

Date of search: 17.06.2025

#	Search	Number of Results
1	TS=("CARDIAC SURGERY" OR "HEART SURGERY" OR "CARDIOVASCULAR SURGERY" OR "VALVE REPAIR" OR "VALVE REPLACEMENT" OR (SURGERY AND "ASCENDING AORTA") OR "CORONARY ARTERY BYPASS" OR "BYPASS SURGERY" OR "CARDIAC SURGICAL PROCEDURES")	209.823
2	TS=("TOPICAL HEMOSTATIC AGENT*" OR "TOPICAL HAEMOSTATIC AGENT*" OR "TOPICAL HEMOSTAT*" OR "TOPICAL HAEMOSTAT*" OR "TOPICAL HEMOSTATIC*" OR "TOPICAL HAEMOSTATIC*" OR SEALANT OR SEALING OR "BLOOD MANAGEMENT" OR HEMOSTATIC* OR "BLOOD LOSS, SURGICAL" OR "HEMOSTASIS, SURGICAL" OR "FIBRIN TISSUE ADHESIVE" OR "GELATIN SPONGE, ABSORBABLE" OR "TISSUE ADHESIVE*")	157.473
3	#1 AND #2	2.248
4	#1 AND #2 AND ENGLISH OR GERMAN (LANGUAGES)	2.193

8.4 Embase

Date of search: 27.06.2025

#	Search	Number of Results
1	(CARDIAC SURGERY/TI OR CARDIAC SURGERY/AB) OR (HEART SURGERY/TI OR HEART SURGERY/AB) OR (CARDIOVASCULAR SURGERY/TI OR CARDIOVASCULAR SURGERY/AB) OR (VALVE REPAIR/TI OR VALVE REPAIR/AB) OR (VALVE REPLACEMENT/TI OR VALVE REPLACEMENT/AB) OR (SURGERY OF ASCENDING AORTA/TI OR SURGERY OF ASCENDING AORTA/AB) OR (CORONARY ARTERY BYPASS/TI OR CORONARY ARTERY BYPASS/AB) OR (BYPASS SURGERY/TI OR BYPASS SURGERY/AB) OR CARDIAC SURGICAL PROCEDURES	252.958
2	(TOPICAL H!EMOSTATIC AGENT?/TI OR TOPICAL H!EMOSTATIC AGENT?/AB) OR (TOPICAL H!EMOSTAT?/TI OR TOPICAL H!EMOSTAT?/AB) OR (TOPICAL H!EMOSTATIC?/TI OR TOPICAL H!EMOSTATIC?/AB) OR (SEALANT/TI OR SEALANT/AB) OR (SEALING/TI OR SEALING/AB) OR (BLOOD MANAGEMENT/TI OR BLOOD MANAGEMENT/AB) OR HEMOSTATICS OR SURGICAL BLOOD LOSS OR SURGICAL HEMOSTASIS OR FIBRIN TISSUE ADHESIVE OR ABSORBABLE GELATIN SPONGE OR (HEMOSTATICS/TI OR HEMOSTATICS /AB) OR (TISSUE AFHESIVES/TI OR TISSUE ADHESIVES/AB)	31.750
3	#1 AND #2	1015
4	#3 NOT MEDLINE/FS	937

Search performed by an ULB Tirol librarian. Results received as .rtf files including information on title and descriptor terms. Removal of duplicates with other databases not directly possible, only based on available information. Title screening to choose abstracts to screen. Maximum of 50 abstracts were possible to be retrieved.

8.5 Clinical Trial Registries

Date of search: 18.06.2025

#	Search	Number of Results
1 (ICTRP)	(CARDI* SURGERY OR "CARDIAC SURGERY" OR "HEART SURGERY" OR "CARDIOVASCULAR SURGERY" OR "VALVE REPAIR" OR "VALVE REPLACEMENT" OR (SURGERY AND ASCENDING AORTA) OR "CORONARY ARTERY BYPASS" OR "BYPASS SURGERY" OR "CARDIAC SURGICAL PROCEDURES") AND ("TOPICAL HAEMOSTATIC AGENT*" OR "TOPICAL HEMOSTATIC AGENT*" OR "TOPICAL HAEMOSTAT*" OR "TOPICAL HEMOSTAT*" OR "TOPICAL HAEMOSTATIC*" OR "TOPICAL HEMOSTATIC*" OR "SEALANT*" OR "BLOOD MANAGEMENT" OR "SEALING" OR "SURGICAL BLOOD LOSS" OR "ABSORBABLE GELATIN SPONGE" OR "HEMOSTATICS" OR "TISSUE ADHESIVES" OR "FIBRIN TISSUE ADHESIVE" OR "SURGICAL HEMOSTASIS")	63 records for 54 trials
2 (CTR.eu)	(CARDIAC SURGERY OR CARDIAC SURGICAL PROCEDURES OR HEART SURGERY) AND (HEMOSTATIC OR HEMOSTATICS OR HEMOSTATIC AGENTS OR TISSUE ADHESIVES OR SEALANT OR SEALING)	76
3 (CTIS)	SEARCH TERM: SURGERY, THERAPEUTIC AREA: DISEASES [C] – CARDIOVASCULAR DISEASES [C14]	48
4 (CT.gov)	(CARDIAC SURGERY OR CARDIAC SURGICAL PROCEDURES \(D006348\) OR HEART SURGERY) AND (HEMOSTATIC OR HEMOSTATICS OR HEMOSTATIC AGENTS OR TISSUE ADHESIVES OR SEALANT OR SEALING)	650

8.6 Epistemonikos

Date of search: 17.06.2025

#	Search	Number of Results
1	(TITLE:((CARDI* SURGERY OR "CARDIAC SURGERY" OR "HEART SURGERY" OR "CARDIOVASCULAR SURGERY" OR "VALVE REPAIR" OR "VALVE REPLACEMENT" OR (SURGERY AND "ASCENDING AORTA") OR "CORONARY ARTERY BYPASS" OR "BYPASS SURGERY" OR "CARDIAC SURGICAL PROCEDURES") AND ("TOPICAL HEMOSTATIC AGENT*" OR "TOPICAL HAEMOSTATIC AGENT*" OR "TOPICAL HEMOSTAT*" OR "TOPICAL HAEMOSTAT*" OR "TOPICAL HEMOSTATIC*" OR "TOPICAL HAEMOSTATIC*" OR SEALANT OR SEALING OR "BLOOD MANAGEMENT" OR HEMOSTATIC* OR "BLOOD LOSS, SURGICAL" OR "HEMOSTASIS, SURGICAL" OR "FIBRIN TISSUE ADHESIVE" OR "GELATIN SPONGE, ABSORBABLE" OR "TISSUE ADHESIVE*")) OR ABSTRACT:((CARDI* SURGERY OR "CARDIAC SURGERY" OR "HEART SURGERY" OR "CARDIOVASCULAR SURGERY" OR "VALVE REPAIR" OR "VALVE REPLACEMENT" OR (SURGERY AND "ASCENDING AORTA") OR "CORONARY ARTERY BYPASS" OR "BYPASS SURGERY" OR "CARDIAC SURGICAL PROCEDURES") AND ("TOPICAL HEMOSTATIC AGENT*" OR "TOPICAL HAEMOSTATIC AGENT*" OR "TOPICAL HEMOSTAT*" OR "TOPICAL HAEMOSTAT*" OR "TOPICAL HEMOSTATIC*" OR "TOPICAL HAEMOSTATIC*" OR SEALANT OR SEALING OR "BLOOD MANAGEMENT" OR HEMOSTATIC* OR "BLOOD LOSS, SURGICAL" OR "HEMOSTASIS, SURGICAL" OR "FIBRIN TISSUE ADHESIVE" OR "GELATIN SPONGE, ABSORBABLE" OR "TISSUE ADHESIVE*")))	968

9 ADDITIONAL RESEARCH POSSIBILITIES

☐ Forward Citation Searching

☒ Backward Citation Searching

Date of search: 04.09.2025

☒ Reference list checking: manually reviewing reference lists

Reference lists of reports included after screening primary database search

☐ Using a database

Number of rounds: 2

Number of results: 1

☐ Hand search

D Risk of Bias Assessment Tables

D1 RoB2

Questions scheme

The risk of bias of randomised controlled trials was assessed with the risk of bias 2 (RoB2) tool (Sterne et al., 2019).

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Domain 1: Risk of bias arising from the randomisation process					
Random allocation sequence	*Concealed allocation sequence*		*Baseline Differences*		*Risk of bias*
Was the allocation sequence random?	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Did baseline differences between intervention groups suggest a problem with the randomisation process?		
Domain 2: Risk of bias due to deviations from the intended interventions					
Participant aware	*Carers aware*	*Deviations*	*Analysis*		*Risk of bias*
Were participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Were there deviations from the intended intervention that arose because of the trial context?	Was an appropriate analysis used to estimate the effect of assignment to intervention?		
Domain 3: Risk of bias due to missing outcome data					
Data availability	*No bias by missing data (Optional)*	*True value (Optional)*	*Likely (Optional)*		*Risk of bias*
Were data for this outcome available for all, or nearly all, participants randomised?	Is there evidence that the result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Could missingness in the outcome depend on its true value?		
Domain 4: Risk of bias in measurement of the outcome					
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*		*Risk of bias*
Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		
Domain 5: Risk of bias in selection of the reported result					
Pre-specified analysis plan	*Multiple outcome measurements*		*Multiple analyses*		*Risk of bias*
Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?		
Overall risk of bias					

Detailed risk of bias evaluations

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.01-BC-2003 (Coselli et al., 2003)	Prospective Randomized Study of a Protein-Based Tissue Adhesive Used as a Hemostatic and Structural Adjunct in Cardiac and Vascular Anastomotic Repair Procedures				Journal article
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	Standard repair plus BioGlue	Standard repair alone	Immediate complete haemostasis at each individual anastomotic repair site	60.5% vs 39.2% (p=0.014)	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
Yes	Yes	Probably no	Low risk

Domain 2: Risk of bias due to deviations from the intended interventions				
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Risk of bias*
No	Yes	No	Probably Yes	Low risk

Domain 3: Risk of bias due to missing outcome data	
Data availability	*Risk of bias*
Yes	Low risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
No	Probably no	Yes	Probably no	Low risk

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
Yes	Probably no	Probably no	Low risk

Overall risk of bias
Low risk

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.02-CG-2004 (Hagberg et al., 2004)	Improved Intraoperative Management of Anastomotic Bleeding During Aortic Reconstruction: Results of a Randomized Controlled Trial				Journal article
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	CoSeal	Gelfoam/thrombin	Immediate anastomotic sealing	81.4% vs 37.0%	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
Yes	Yes	Probably no	Low risk

Domain 2: Risk of bias due to deviations from the intended interventions					
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Impact of failure*	*Risk of bias*
No	Yes	No information	No information	No information	High risk

Domain 3: Risk of bias due to missing outcome data	
Data availability	*Risk of bias*
Probably yes	Low risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
Probably no	Probably no	Yes	Probably no	Low risk

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
No information	Probably no	Probably no	Some concerns

Overall risk of bias
High risk

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.03-TG-2018 (Khoynezhad et al., 2018)	A Prospective, Randomized Study to Compare Progel Vascular Sealant to Gelfoam Plus as an Adjunct for the Control of Bleeding in Subjects Undergoing Thoracic Aortic Surgery (PROTECT Trial)				Journal article, trial registry record
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	Tridyne (Progel Vascular Sealant)	Gelfoam Plus	Time to achieve haemostasis at aortic anastomotic suture line from time surgical clamps were released to cessation of bleeding	2.07 min vs 6.3 min (p < 0.0001)	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
No information	No information	No	Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions				
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Risk of bias*
No	Yes	No	Yes	Low risk

Domain 3: Risk of bias due to missing outcome data	
Data availability	*Risk of bias*
Yes	Low risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
No	Probably no	Yes	Probably no	Low risk

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
Probably Yes	Probably no	Probably no	Low risk

Overall risk of bias
Some concerns

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.04-GC-2009 (Minato et al., 2009)	Hemostatic Effectiveness of a New Application Method for Fibrin Glue, the "Rub-and-Spray Method" in Emergency Aortic Surgery for Acute Aortic Dissection				Journal article
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	Rub-and-spray method, fibrin glue	No fibrin glue	Bleeding proportion of needle holes at anastomoses	Proximal: 0.7% vs 73.8%; distal: 4.4% vs 71.9%	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
Yes	No information	No	Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions					
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Impact of failure*	*Risk of bias*
No	Yes	No	No information	No	Some concerns

Domain 3: Risk of bias due to missing outcome data	
Data availability	*Risk of bias*
Probably yes	Low risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
No	Probably no	Yes	Probably no	Low risk

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
No information	Probably no	Probably no	Some concerns

Overall risk of bias
Some concerns

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.05-SC-2019 (Morita et al., 2020)	Randomized clinical trial of an elastomeric sealant for hemostasis in thoracic aortic surgery				Journal article
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	Sealant	No sealant	Bleeding from the anastomosis immediately before protamine administration	79% vs 38%	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
Yes	No information	No	Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions					
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Impact of failure*	*Risk of bias*
Probably No	Yes	Probably No	Probably No	No	Some concerns

Domain 3: Risk of bias due to missing outcome data	
Data availability	*Risk of bias*
Probably yes	Low risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
No	Probably no	Yes	Probably no	Low risk

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
Probably Yes	Probably no	Probably no	Low risk

Overall risk of bias
Some concerns

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.06-TC-2018 (Ostrowski et al., 2021)	Does the additional usage of a local hemostatic patch reduce bleeding after aortic reimplantation?				Journal article
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	Tachosil	No Tachosil	Postoperative drainage	p = 0.0335	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
No information	No information	Probably no	Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions					
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Impact of failure*	*Risk of bias*
No information	Yes	No information	No information	No information	High risk

Domain 3: Risk of bias due to missing outcome data				
Data availability	*No bias by missing data*	*True value*	*Likely*	*Risk of bias*
No information	Probably no	No information	No information	High risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
No information	No information	Yes	Probably no	Some concerns

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
No information	No information	No information	Some concerns

Overall risk of bias
High risk

Preliminary Considerations					
Study ID (Reference)	*Title*				*Sources*
PTHA.07-CS-2003 (Sirlak et al., 2003)	Comparative study of microfibrillar collagen hemostat (Colgel) and oxidized cellulose (Surgicel) in high transfusion-risk cardiac surgery				Journal article
Study Design	*Experimental Intervention*	*Comparator Intervention*	*Outcome assessed*	*Numerical result assessed*	*Aim for this result*
Individually-randomised parallel-group trial	Colgel	Surgicel	Chest tube drainage	373 mL vs 571 mL	Intention to treat

Domain 1: Risk of bias arising from the randomisation process			
Random allocation sequence	*Concealed allocation sequence*	*Baseline Differences*	*Risk of bias*
No information	No information	Probably no	Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions					
Participant aware	*Carers aware*	*Deviations*	*Analysis*	*Impact of failure*	*Risk of bias*
No information	Yes	No information	No information	No information	High risk

Domain 3: Risk of bias due to missing outcome data				
Data availability	*No bias by missing data*	*True value*	*Likely*	*Risk of bias*
No information	Probably no	No information	No information	High risk

Domain 4: Risk of bias in measurement of the outcome				
Method inappropriate	*Difference in groups*	*Outcome assessors blinded*	*Assessment influence*	*Risk of bias*
Probably no	Probably no	Yes	Probably no	Low risk

Domain 5: Risk of bias in selection of the reported result			
Pre-specified analysis plan	*Multiple outcome measurements*	*Multiple analyses*	*Risk of bias*
No information	Probably no	Probably no	Some concerns

Overall risk of bias
High risk

D2 ROBIS

Questions scheme

The risk of bias of systematic reviews was assessed with the ROBIS tool (Whiting et al., 2016).

Preliminary Considerations					
Reference	*Title*				
Domain 1: Study Eligibility Criteria					
Pre-defined	*Appropriate*	*Unambiguous*	*Study Characteristics*	*Information Sources*	*Concerns*
Did the review adhere to pre-defined objectives and eligibility criteria?	Were the eligibility criteria appropriate for the review question?	Were eligibility criteria unambiguous?	Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	
Domain 2: Identification and Selection of Studies					
Range of Databases	*Additional methods*	*Search Strategy*	*Restrictions*	*Error minimisation*	*Concerns*
Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Were methods additional to database searching used to identify relevant reports?	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Were restrictions based on date, publication format, or language appropriate?	Were efforts made to minimise error in selection of studies?	
Domain 3: Data Collection and Study Appraisal					
Error minimisation	*Sufficient study characteristics*	*All relevant study results*	*Risk of bias*	*Error minimisation*	*Concerns*
Were efforts made to minimise error in data collection?	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Were all relevant study results collected for use in the synthesis?	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Were efforts made to minimise error in risk of bias assessment?	
Domain 4: Synthesis and Findings						
All studies	*Pre-defined analyses or departures*	*Appropriate*	*Heterogeneity*	*Robust findings*	*Biases*	*Concerns*
Did the synthesis include all studies that it should?	Were all pre-defined analyses reported or	Was the synthesis appropriate given the	Was between-study variation (heterogeneity) minimal or	Were the findings robust, e.g. as	Were biases in primary studies	

	departures explained?	nature and similarity in the research questions, study designs and outcomes across included studies?	addressed in the synthesis?	demonstrated through funnel plot or sensitivity analyses?	minimal or addressed in the synthesis?	
Judging risk of bias						
Interpretation		*Relevance*		*Emphasis*		
Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?		Was the relevance of identified studies to the review's research question appropriately considered?		Did the reviewers avoid emphasizing results on the basis of their statistical significance?		
Risk of bias in the review						

Detailed risk of bias evaluation

Reference	*Title*				
Clark et al., 2008	Topical bovine thrombin and adverse events: a review of the literature				
Domain 1: Study Eligibility Criteria					
Pre-defined	*Appropriate*	*Unambiguous*	*Study Characteristics*	*Information Sources*	*Concerns*
No information	Probably Yes	Probably yes	Yes	Probably yes	Unclear
Domain 2: Identification and Selection of Studies					
Range of Databases	*Additional methods*	*Search Strategy*	*Restrictions*	*Error minimisation*	*Concerns*
No	Yes	No information	Probably no	Probably yes	Unclear
Domain 3: Data Collection and Study Appraisal					
Error minimisation	*Sufficient study characteristics*	*All relevant study results*	*Risk of bias*	*Error minimisation*	*Concerns*
Probably yes	Probably yes	Probably yes	No	No information	High
Domain 4: Synthesis and Findings						
All studies	*Pre-defined analyses or departures*	*Appropriate*	*Heterogeneity*	*Robust findings*	*Biases*	*Concerns*
No information	No information	Probably yes	Probably yes	Probably yes	No	High
Judging risk of bias						
Interpretation		*Relevance*		*Emphasis*		
Probably no		No information		Probably yes		
Risk of bias in the review						
Unclear						

Reference	*Title*				
Masoudi et al., 2023	A contemporary systematic review of the complications associated with SURGICEL				
Domain 1: Study Eligibility Criteria					
Pre-defined	*Appropriate*	*Unambiguous*	*Study Characteristics*	*Information Sources*	*Concerns*
Probably yes	No information	No information	Probably yes	Probably yes	Unclear
Domain 2: Identification and Selection of Studies					
Range of Databases	*Additional methods*	*Search Strategy*	*Restrictions*	*Error minimisation*	*Concerns*
Yes	No	Yes	Probably no	Yes	Unclear
Domain 3: Data Collection and Study Appraisal					
Error minimisation	*Sufficient study characteristics*	*All relevant study results*	*Risk of bias*	*Error minimisation*	*Concerns*
Probably yes	Probably yes	Probably yes	No	No information	High
Domain 4: Synthesis and Findings					
All studies	*Pre-defined analyses or departures*	*Appropriate*	*Heterogeneity*	*Robust findings*	*Biases*	*Concerns*
Probably yes	No information	Probably yes	Probably yes	Probably yes	No	High
Judging risk of bias					
Interpretation		*Relevance*		*Emphasis*	
Probably no		Probably yes		Probably yes	
Risk of bias in the review					
Unclear					

D3 AGREE II

Items scheme

The quality of guidelines was assessed with the AGREE II tool (Brouwers et al., 2010). The items were rated on a scale from 1 (strongly disagree) to 7 (strongly agree).

Reference	*Title*

Domain 1: Scope and Purpose		
Overall Objectives	*Health Questions*	*Population*
The overall objective(s) of the guideline is (are) specifically described.	The health question(s) covered by the guideline is (are) specifically described.	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Domain 2: Stakeholder Involvement		
Professionals	*Target population*	*Target users*
The guideline development group includes individuals from all relevant professional groups.	The views and preferences of the target population (patients, public, etc.) have been sought.	The target users of the guideline are clearly defined.

Domain 3: Rigour of Development							
Systematic methods	*Eligibility criteria*	*Strengths and Limitations*	*Formulating Methods*	*Benefits and Risks*	*Link*	*External review*	*Update*
Systematic methods were used to search for evidence.	The criteria for selecting the evidence are clearly described.	The strengths and limitations of the body of evidence are clearly described.	The methods for formulating the recommendations are clearly described.	The health benefits, side effects, and risks have been considered in formulating the recommendations.	There is an explicit link between the recommendations and the supporting evidence.	The guideline has been externally reviewed by experts prior to its publication.	A procedure for updating the guideline is provided.

Domain 4: Clarity of Presentation		
Recommendations	*Options*	*Identify*
The recommendations are specific and unambiguous.	The different options for management of the condition or health issue are clearly presented.	Key recommendations are easily identifiable.

Domain 5: Applicability			
Facilitators and Barriers	*Advice/Tools*	*Resource implications*	*Monitoring/Audit*
The guideline describes facilitators and barriers to its application.	The guideline provides advice and/or tools on how the recommendations can be put into practice.	The potential resource implications of applying the recommendations have been considered.	The guideline presents monitoring and/or auditing criteria.

Domain 6: Editorial Independence	
Influence	*Competing interest*
The views of the funding body have not influenced the content of the guideline.	Competing interests of guideline development group members have been recorded and addressed.

Overall	
Quality	*Recommend*
Rate the overall quality of this guideline.	I would recommend this guideline for use.

Detailed risk of bias evaluation

Reference	*Title*
Casselman et al., 2025	2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP

Domain 1: Scope and Purpose		
Overall Objectives	*Health Questions*	*Population*
7	7	7

Domain 2: Stakeholder Involvement		
Professionals	*Target population*	*Target users*
7	1	5

Domain 3: Rigour of Development							
Systematic methods	*Eligibility criteria*	*Strengths and Limitations*	*Formulating Methods*	*Benefits and Risks*	*Link*	*External review*	*Update*
7	5	5	7	5	7	7	1

Domain 4: Clarity of Presentation		
Recommendations	*Options*	*Identify*
7	7	7

Domain 5: Applicability			
Facilitators and Barriers	*Advice/Tools*	*Resource implications*	*Monitoring/Audit*
7	7	6	1

Domain 6: Editorial Independence	
Influence	*Competing interest*
7	7

Overall	
Quality	*Recommend*
6	Yes

Reference	*Title*
Pagano et al., 2018	2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery

Domain 1: Scope and Purpose		
Overall Objectives	*Health Questions*	*Population*
7	7	7

Domain 2: Stakeholder Involvement		
Professionals	*Target population*	*Target users*
5	1	7

Domain 3: Rigour of Development							
Systematic methods	*Eligibility criteria*	*Strengths and Limitations*	*Formulating Methods*	*Benefits and Risks*	*Link*	*External review*	*Update*
4	1	5	7	5	7	5	1

Domain 4: Clarity of Presentation		
Recommendations	*Options*	*Identify*
6	7	7

Domain 5: Applicability			
Facilitators and Barriers	*Advice/Tools*	*Resource implications*	*Monitoring/Audit*
1	1	1	1

Domain 6: Editorial Independence	
Influence	*Competing interest*
1	6

Overall	
Quality	*Recommend*
5	Yes, with modifications

Acknowledgement

I would like to express my gratitude to all people who supported me. Special thanks to the ULB Tirol librarian team for their support in developing a search string and in searching the database Embase, to Univ. Ass. Dr. Christian Mayer (Medical University of Graz) for his medical input and for being available to answer my questions and to my supervisor Dr. Sabine Geiger-Gritsch (AIHTA) for providing me with the topic for this master's thesis and for her continuous guidance, feedback and support throughout the development process of this thesis.

Last but not least I want to thank everyone else who accompanied and supported me throughout my university journey – mentors, friends and family alike.