Clinical Aspects of Bleeding and Transfusion in Cardiac Surgery

Lisa Ternström

Department of Molecular and Clinical Medicine
Institute of Medicine
Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Abstract

Excessive bleeding after cardiac surgery is a serious complication that is associated with increased morbidity and mortality. The bleeding is multifactorial and influenced by both surgical factors and impaired haemostasis. It is important to identify patients with increased risk of bleeding before the operation so countermeasures can be initiated. A large proportion of cardiac surgical patients receive blood transfusions during and after surgery. Transfusion therapy can save lives, but is also associated with increased risk of morbidity and mortality, so unnecessary transfusions should be avoided. There is little knowledge about when and on what indication blood transfusions are administered, and how well treating physicians follow current guidelines.

Aims: One aim was to examine the relationship between preoperative levels of fibrinogen and other coagulation factors, and their relationship to postoperative bleeding and blood transfusion. Another was to assess the effects of a structured blood conservation programme, with the objective of reducing the administration of blood transfusions in cardiac surgical patients. A third aim was to study the prevalence, volumes and indications for red blood cell transfusions in cardiac surgery patients. The final aim was to examine adherence to institutional transfusion guidelines.

Materials and methods: The first study (**Paper I**) involved 170 patients undergoing coronary artery bypass grafting (CABG). Data on each patient´s preoperative fibrinogen plasma concentration and other haemostatic tests, and postoperative bleeding and transfusion requirements, were collected. In **Paper II**, the study concerned 57 CABG patients. Plasma activity of coagulation factors involved in plasma coagulation was measured before and after surgery and related to haemodilution and postoperative blood loss. In **Paper III**, the study involved all 2162 patients who underwent cardiac surgery at our institution during a 24-month period. Transfusion requirements and transfusion-associated costs before and after introduction of a blood conservation programme were compared. In the study described in **Paper IV**, timing and indications for red blood cell transfusion in 1034 cardiac surgery patients were investigated and the adherence to institutional guidelines was assessed.

Results: **Paper I** demonstrated that preoperative plasma levels of fibrinogen correlates significantly to postoperative blood loss. Preoperative fibrinogen level was also an independent predictor of red blood cell transfusion, together with female gender and long operation time. **Paper II** demonstrated a marked disparity of clotting factor activity after cardiac surgery. Only plasma concentration of fibrinogen and coagulation factor XIII activity correlated to postoperative bleeding. **Paper III** showed that the introduction of a simple structured multifactorial blood conservation programme significantly reduces blood transfusions to cardiac surgery patients, and reduces transfusion-associated costs without compromising medical safety. The result persists for at least three years after the implementation of the programme. **Paper IV** demonstrated that red blood cells are often transfused for other reasons than anaemia. The adherence to institutional transfusion guidelines was low.

Conclusions: Pre- and postoperative fibrinogen concentration and factor XIII activity predict postoperative bleeding volume after CABG and may be used to identify patients with increased risk of bleeding. The introduction of a structured blood conservation programme is safe and reduces the use of blood products in cardiac surgery. The adherence to transfusion guidelines among treating physicians is low.

List of publications

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A.

      Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study

      Transfusion 2008;48:2152-8

II.   Ternström L, Radulovic V, Karlsson M, Baghaei F, Hyllner M, Bylock A, Hansson KM, Jeppsson A.

      Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery

      Thromb Res 2010;126:e128-33

III. Ternström L, Hyllner M, Backlund E, Scherstén H, Jeppsson A.

      A structured blood conservation programme reduces transfusions and costs in cardiac surgery

      Interact Cardiovasc Thorac Surg 2014;19:788-94

IV.   Ternström L, Hyllner M, Fröjd V, Backlund E, Jeppsson A.

      Indications and adherence to guidelines for red blood cell transfusion in cardiac surgery: a prospective observational study

      Submitted

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Sammanfattning på svenska

Bakgrund: Massiv blödning efter hjärtkirurgi är en allvarlig komplikation som är förknippad med ökad sjuklighet och dödlighet. Blödningen kan orsakas av många faktorer, bl. a av försämrad koagulationsförmåga till följd av ingreppet. Det är av stort värde att kunna identifiera patienter med ökad risk för blödning, då motåtgärder kan sättas in i samband med operationen. En stor andel hjärtkirurgiska patienter erhåller blodtransfusioner under och efter operationen. Transfusionsbehandling kan rädda liv, men kan också leda till ökad risk för sjuklighet och död efter hjärtkirurgi. Därför bör onödiga transfusioner undvikas. Det finns lite kunskap om när och på vilken indikation blodtransfusioner ges, och hur väl behandlande läkare följer rådande riktlinjer.

Frågeställning: I avhandlingen undersöktes preoperativa plasmanivåer av fibrinogen och andra koagulationsfaktorer, och deras relation till postoperativ blödning och blodtransfusion. Vidare analyserades effekten av ett aktivt åtgärdsprogram, vars syfte var att minska andelen blodtransfusioner till hjärtkirurgiska patienter. Utöver det studerades förekomst av blodtransfusioner, indikationer för transfusioner samt i vilken utsträckning klinikens transfusionsriktlinjer följdes.

Metodik: I det första delarbetet studerades 170 patienter som genomgått kranskärlskirurgi. Data rörande plasmakoncentration av fibrinogen och andra blodprover viktiga för hemostas, samt postoperativ blödning och blodtransfusionsbehov inhämtades. I **delarbete II** studerades 57 patienter som genomgått kranskärlskirurgi. Plasmaaktivitet för koagulationsfaktorer mättes före och efter kirurgi och relaterades till postoperativ blodförlust och den spädning av blodet som uppkommer i samband med användandet av hjärt- lungmaskin. I **delarbete III** studerades alla 2162 patienter som under en tvåårsperiod genomgått hjärtkirurgi på Thoraxkirurgiska kliniken, Sahlgrenska Universitetssjukhuset. Blodtransfusionsbehov och transfusionsrelaterade kostnader registrerades före och efter att ett blodbesparingsprogram infördes. I **delarbete IV** undersöktes tidpunkten och indikationerna för transfusion av röda blodkroppar hos 1034 hjärtkirurgiska patienter. Information om hur väl behandlande läkare följde klinikens riktlinjer inhämtades.

Resultat: I **delarbete I** visades att preoperativa fibrinogennivåer korrelerar till postoperativ blödning. Preoperativa fibrinogennivåer, kvinnligt kön och lång operationstid var också oberoende prediktorer för transfusion av röda blodkroppar. I **delarbete II** visades att det föreligger en markant spridning av koagulationsfaktoraktiviteten efter hjärtkirurgi. Bara plasmakoncentrationen av fibrinogen och

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faktor XIII-aktiviteten korrelerade till postoperativ blödning. I **delarbete III** visades att introduktionen av ett enkelt strukturerat blodbespringsprogram minskar blodtransfusioner till hjärtkirurgiska patienter utan att äventyra den medicinska säkerheten, samtidigt som de transfusionsrelaterade kostnaderna minskar. I **delarbete IV** visades att behandlande läkare följde klinikens riktlinjer för blodtransfusioner i anmärkningsvärd låg utsträckning.

Slutsatser: Pre- och postoperativa fibrinogennivåer och faktor XIII-aktivitet predikterar postoperativ blödningsvolym efter kranskärlskirurgi, och skulle därför kunna användas för att identifiera patienter med ökad risk för blödning. Införandet av ett strukturerat blodbesparingsprogram är medicinskt säkert och minskar användandet av blodprodukter inom hjärtkirurgi. Behandlande läkare följer klinikens riktlinjer för blodtransfusioner i låg utsträckning.

Abbreviations

ACT	Activated clotting time
ADP	Adenosine diphosphate
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AT	Antithrombin
CABG	Coronary artery bypass grafting
CI	Confidence interval
CPB	Cardiopulmonary bypass
ECC	Extracorporeal circulation
EVF	Erythrocyte volume fraction
Hb	Haemoglobin
HCT	Haematocrit
ICU	Intensive care unit
LMWH	Low molecular weight heparin
NOAC	Non-vitamin K oral anticoagulants
OR	Odds ratio
PCI	Percutaneous coronary intervention
PFT	Platelet function test
PLG	Plasminogen
RBC	Red blood cells
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitors
TEM	Thromboelastometry
TF	Tissue factor
tPA	Tissue plasminogen activator
uPA	Urokinase plasminogen activator
vWF	von Willebrand factor
WHO	World Health Organization

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Introduction

In his textbook 'The surgery of the chest' from 1896, Sir Stephen Paget, a British surgeon, remarked that *"Surgery of the heart has probably reached the limit set by Nature to all surgery: no new method and no new discovery can overcome the natural difficulties that attend a wound to the heart."* (1). Ten years later, the German surgeon Ludwig Rehn repaired a right ventricle stab wound (2). This is commonly referred to as the first successful heart operation and the birth of cardiac surgery. Today cardiac surgery is the standard treatment in many congenital and acquired heart diseases.

In Sweden the number of procedures in cardiac surgery has decreased steadily since the turn of the millennium. The main reason is the development of percutaneous coronary interventions (PCI), leading to a decrease in coronary artery bypass grafting surgery (CABG) procedures. In 2000, more than 9000 cardiac surgical procedures were performed in Sweden, with a 30-day mortality of 3.6% (3). In 2013, only 5685 procedures were reported. The overall 30-day mortality is still low (2.9%), although patients now are older and more critically diseased than previously (4).

Even though cardiac surgery is constantly developing, there are still risks of severe complications such as stroke (5), infections (6), myocardial infarction and heart failure (7), renal insufficiency (8), and pulmonary dysfunction (9). Severe postoperative bleeding is a serious complication after cardiac surgery, resulting in increased morbidity and mortality (10, 11). This thesis considers some clinical aspects of bleeding and transfusion in cardiac surgery. More specifically, the importance of different coagulation factors for postoperative bleeding and transfusions was determined, the effects of a blood conservation programme on utilisation and costs of blood products were evaluated, and indications for blood transfusions and adherence to transfusion guidelines were assessed.

Cardiac surgery and bleeding

Bleeding after cardiac surgery is multifactorial, and can be caused by both impaired haemostasis and surgical factors (10). Impaired haemostasis may be related to coagulopathy caused by the exposure of blood to artificial surfaces, haemodilution, platelet dysfunction, enhanced fibrinolysis and the surgical trauma (12). Antiplatelet drugs are widely used in the treatment of patients with coronary artery

disease, and preoperative medication with platelet inhibitors (clopidogrel, ticagrelor, prasugrel and glycoprotein IIb/IIIa blockers) and medications affecting the coagulation cascade (low molecular heparin, warfarin and non-vitamin K oral anticoagulants [NOACs]) may contribute to increased postoperative bleeding (13-15).

Bleeding is one of the most common and serious complications after cardiac surgery. The average cardiac surgery patient bleeds 500-1200 ml postoperatively, and about 5% of all cardiac surgery patients are re-explored due to excessive bleeding or tamponade (11). Re-exploration for bleeding is defined as a necessary re-opening of the surgical wound, to achieve haemostasis in patients with sudden massive bleeding or persisting bleeding that cannot be explained by coagulation dysfunction. There is convincing evidence that re-exploration is an independent risk factor for morbidity and mortality in cardiac surgery (10, 16, 17).

Identifying patients at risk of excessive postoperative bleeding would offer the possibility to optimise perioperative management. If patients with increased risk were identified, countermeasures could be initiated. An impaired haemostasis status can be treated with pro-coagulant substances or blood products, but the methods may be associated with increased risk for thromboembolic complications. Change in surgical approach or postponing the operation are other possible preventive actions.

Prior to cardiac surgery there is a widespread use of laboratory tests. Routine screening tests such as activated thromboplastin time (aPTT), prothrombin time (PT) and platelet count, have no or limited ability to identify patients with increased bleeding risk (18-20). When the work with this thesis began there was no explicit laboratory test for predicting bleeding after cardiac surgery.

Haemostasis

Upon vascular damage there is an immediate reflex that promotes vasoconstriction, diminishing blood loss. The first step in haemostasis is when platelets adhere to the exposed subendothelium. Platelets undergo change in shape and degranulation and release cytoplasmic granules containing serotonin, ADP and thromboxane A2 (21). The ADP attracts more platelets and thromboxane A2 promotes platelet aggregation, degranulation and vasoconstriction. ADP and thromboxane A2 promote additional platelet aggregation and consequently more ADP and thromboxane A2 (22). This promotes the formation of a platelet plug, the second step in haemostasis, followed by plasma coagulation, the final haemostatic mechanism.

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Coagulation

The coagulation cascade has two possible initiation pathways leading to thrombin generation. In the extrinsic or tissue factor system, (the physiological one), subendothelial structures and monocytes expose tissue factor (TF) upon vascular damage. Circulating FVIIa binds to TF, and this complex activates FX and additional FVII and FIX. On the surface of activated platelets, FXa together with FVa activate prothrombin into thrombin. Thrombin is central in the coagulation and is responsible for several critical reactions, by cleaving fibrinogen into fibrin, activating platelets, playing an important role in positive feedback activation of coagulation, and being critical for clot formation (23, 24). The intrinsic or contact system pathway is initiated by the activation of contact system and FXII on foreign surfaces. Activation of FXII is followed by activation of FXI and FIX. The intrinsic and extrinsic pathways converge into the final common pathway at the level of FX activation (25). FXIII, when activated by thrombin, builds cross-links between the fibrin strands to form a stable clot.
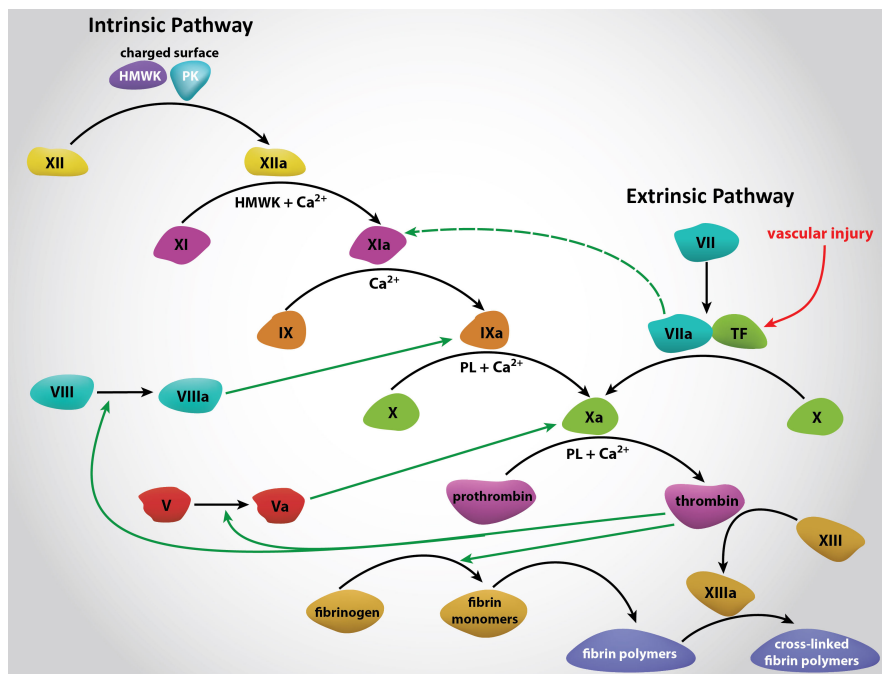

Figure 1. The coagulation cascade. Reproduced with permission of themedicalbiochemistrypage, LLC.

Fibrinolysis

To avoid widespread thrombosis, the fibrin clot is degraded soon after formation, a mechanism called fibrinolysis. Under physiological conditions, coagulation and fibrinolysis are in perfect balance. Plasmin is the major fibrinolytic enzyme. Its precursor, plasminogen (PLG) is a circulating plasma protein and can be converted into plasmin by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) (26). Fibrin regulates its own degradation by binding PLG and tPA on its surface. Once formed, plasmin cleaves the fibrin strands, generating degradation products cleared by other proteases and the liver and kidneys.

Fibrinogen

Fibrinogen, or coagulation factor I, is a key protein in achieving and maintaining haemostasis. It is a soluble plasma glycoprotein synthesised and secreted by the liver, with a molecular weight of 340 kDa. In a healthy individual, plasma concentration of fibrinogen ranges from 2.0 to 4.5 g/L (27). Daily turnover of fibrinogen is 2-5 g and half-life in plasma is 5 days. After bleeding, baseline level of fibrinogen is restored within 12 hours (28-30).

Fibrinogen is a dimeric molecule with each part consisting of three chains linked by disulphide bridges. Thrombin cleaves the chains to release the fibrinopeptides from the aminoterminal ends. After fibrinopeptide release, the fibrin monomers undergo polymerisation, and are stabilised by FXIII to form an insoluble fibrin clot. Fibrinogen also plays an important role in platelet aggregation by cross-linking activated platelets. Activated platelets express on their surface the activated platelet membrane glycoprotein receptor GP IIb/IIIa, which binds fibrinogen. There are studies indicating that low plasma fibrinogen levels are associated with an increased risk of bleeding (31).

Physiological as well as pathological and lifestyle factors influence fibrinogen concentration. Elevated levels due to ageing, in female gender, in pregnant and menopausal women (32), and during treatment with oral contraceptives (33) have been observed. Fibrinogen is an acute phase reactant that increases considerably in response to pro-inflammatory agents (34). Fibrinogen concentration is a strong independent risk factor for cardiovascular disorders, and associations between increased fibrinogen levels and risk for coronary heart disease, stroke, peripheral arterial disease and total mortality have been shown (35, 36).
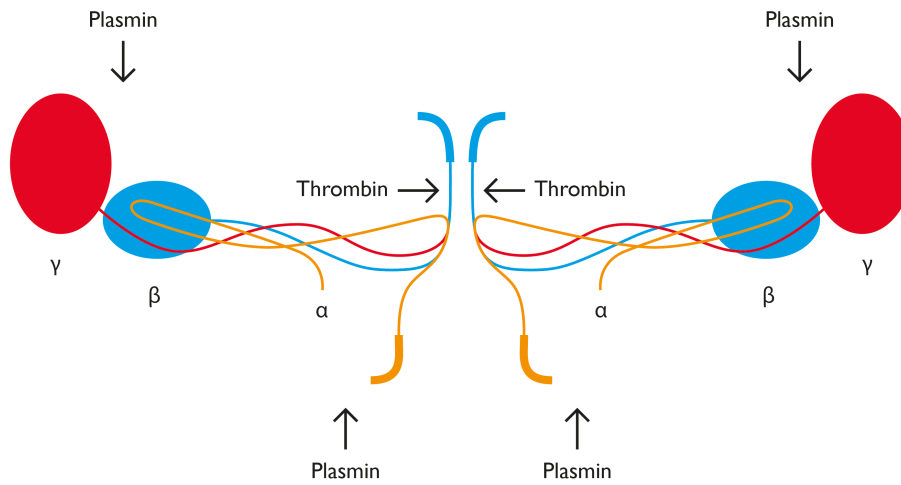
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Figure 2. Schematic representation of the fibrinogen molecule.

In massive bleeding, fibrinogen concentration may be more important than previously assumed. An inverse correlation between plasma fibrinogen concentration and perioperative bleeding in cardiac and scoliosis surgical patients has been demonstrated (37-40). A human fibrinogen concentrate has been on the market since 1986. Initially the product was approved for treatment and prophylaxis of haemorrhagic diatheses in congenital and acquired fibrinogen deficiency, but recently the same product has been made available for treatment of acute bleeding in patients with congenital fibrinogen deficiency. Recent studies have shown that administration of human fibrinogen results in improved clot strength, as measured by thromboelastometry (TEM) (41), and human fibrinogen concentrate to be effective in reducing bleeding and the number of transfusions in surgical procedures (27, 42-44).

Coagulation factor XIII

FXIII is a protransglutaminase present in plasma and in the cytoplasm of platelets, monocytes and macrophages (45). In plasma, almost all FXIII is bound to fibrinogen in an inactivated form, and comprises two potentially active subunits and two carrier subunits. The activation of FXIII occurs in the final phase of the coagulation cascade by the action of thrombin and in the presence of $Ca2^+$. The main function of FXIII is to cross-link fibrin into polymer structure. Fibrin cross-linking stabilises fibrin and makes it more resistant to shear stress and fibrinolysis. FXIII is essential for maintaining haemostasis, and severe deficiency leads to bleeding diathesis (46).

FXIII is essential for haemostasis, but recent studies have also proved its importance in wound healing and angiogenesis (46). There are studies indicating that FXIII is required for maintaining pregnancy (45), and recent studies suggest that elevated FXIII level is a gender-specific risk factor of coronary artery disease and peripheral arterial disease in women (47). In cardiac surgery there is conflicting evidence as to whether levels of FXIII are associated with increased bleeding after CPB or not. In a study on cardiopulmonary bypass patients, no association was found between FXIII activity and extent of postoperative bleeding (39). Regarding administration of FXIII, studies indicate supplementation of FXIII in patients with subnormal levels reduces postoperative blood loss and blood transfusions after coronary surgery (48). In contrast, some recent studies do not show any effect of FXIII substitution on transfusion requirements or re-exploration in cardiac surgery patients (49).
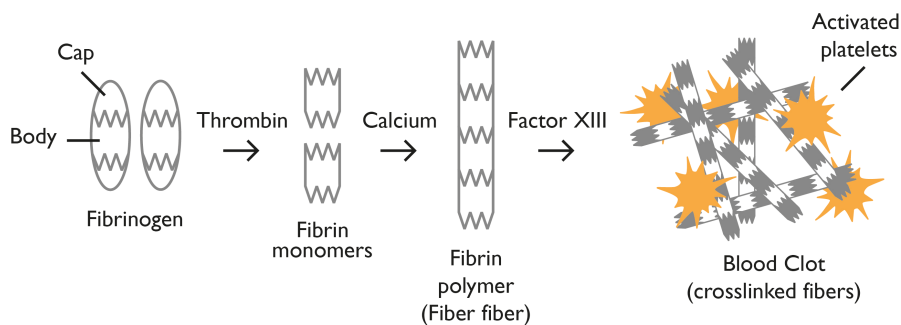

Figure 3. Fibrin monomers polymerise to form fibres. The fibrin fibres form a meshwork stabilised by coagulation factor XIII.

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Platelets

Platelets play a crucial role in both normal haemostasis and pathological bleeding and thrombosis (50). Platelets are the smallest of the many cell types in the circulation, averaging 2.0-5.0 μm in diameter, and have a life span of 7-10 days. Platelets possess important secretory functions. They contain α-granules enclosing, for example, von Willebrand Factor (vWF) and FV, dense granules, and lysosomes (51). Platelet exocytosis releases molecules at sites of vascular injury to activate other cells or to facilitate cellular adhesion. During activation, granule proteins are expressed and adhesive proteins, coagulation factors and growth factors are released. Upon vascular damage, platelet attachment to subendothelial structures is dependent on vWF, fibronectin, and different types of collagen (52). Platelets contribute to the haemostatic process, through the formation of a haemostatic plug, and by being the procoagulant surface for plasma coagulation.

Antiplatelet therapy is the cornerstone of treatment and prevention of ischemic events in patients with coronary artery disease. However, antiplatelet therapy is also associated with an increased risk of bleeding complications, especially in trauma and surgery. Newer antiplatelet drugs are more potent and produce more consistent inhibition of platelet aggregation via the P2Y12 ADP platelet receptor (53).

Platelet function tests (PFT) may be used pre- and perioperatively to predict bleeding and to monitor the efficacy of the various types of prohaemostatic therapies. In cardiac surgery, evidence indicates a reduction in blood transfusions when PFT is used (54). Recently developed point-of-care tests of platelet function have many advantages, including whole blood analyses, low sample volume, rapid availability of the results bedside, and no requirement for a skilled technician.

Platelet transfusions are commonly utilised during or after cardiac surgery with CPB (55). The effects of CPB on platelets include platelet activation due to exposure to surfaces of the heart lung machine, platelet fragmentation, and impaired aggregation (12, 56, 57). There is convincing evidence that patients who have received antiplatelet therapy, such as aspirin, GPIIb/IIIa or P2Y12 receptor inhibitors preoperatively, are at increased risk of bleeding (58-60).
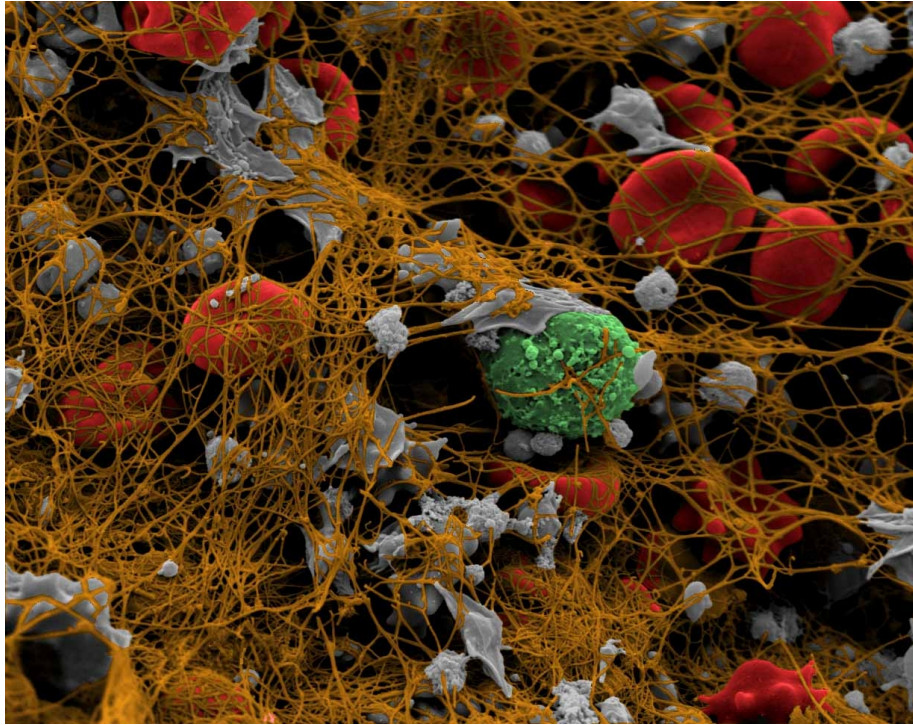
Figure 4. Scanning electron microscopy of a coronary artery thrombus. Fibrin fibres are brown, platelet aggregates are grey, red blood cells are red and leukocytes are green. Image courtesy of John W. Weisel, PhD, Dept. of Cell & Developmental Biology, Perelman School of Medicine, University of Pennsylvania.

Blood transfusions

In the beginning of the 17th century, the British physician William Harvey discovered the blood circulation. The first successful blood transfusions between dogs and from sheep to humans were described in the end of the 17th century (61), but in most cases, transfusions from animals resulted in death and were outlawed by the Paris Society of Physicians in 1678. During the 19th century, attempts were made with transfusion of milk (62). Later, milk was replaced by saline due to adverse reactions to milk.

Figure 5. Richard Lower transfusing blood from lamb to man. Painting from 1692 by the German surgeon M G Purmann, held at Paris Faculty of Medicine.

The discovery of the AB0 blood group system by the Austrian physician Karl Landsteiner in the early 20th century made blood transfusions a therapeutic possibility (63). In 1940 the Rh blood group system was discovered (64), and was soon known to be the cause of the majority of transfusion reactions. During and shortly after the Second World War, blood transfusions became routine treatment.

In the 1970s, the Swedish professor Claes Högman developed a system for separating and preserving the different blood components (65), and the use of whole blood was abandoned in most situations.

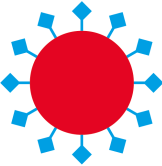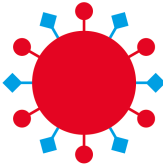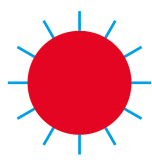|	Group A	Group B	Group AB	Group 0
Erythrocytes				
Antibodies	Anti-B	Anti-A	none	Anti-A Anti-B
Antigenes	A antigen	B antigen	A & B antigen	none

Figure 6. The AB0 blood group system.

Risks with blood transfusions

Transfusion of blood products saves lives and improves health, but unnecessary transfusions may expose patients to considerable risks and adverse effects. Blood transfusions are associated with a small, but not negligible risk of transmission of pathogens. Transfusion of blood products can result in immune response modulation, with an increased risk of infections and malignancies (66-68). Data has been published suggesting transfusion with blood products as an independent risk factor for short- and long-term mortality after cardiac surgery (69-71). A recent study demonstrated that each unit of transfused red blood cells (RBC) in CABG patients was associated with increased morbidity and mortality (70).

According to WHO, around 108 million blood donations are collected globally every year (72). In Sweden, about 500,000 units of blood are donated annually (73). Nevertheless, blood products are a scarce resource and unnecessary transfusions reduce the availability of blood products for patients who are in need. The use of blood products is associated with considerable costs for society, and studies have shown that costs to society are markedly higher than institutional prices (74-76).

Blood conservation programmes

Blood conservation programmes have been introduced successfully in a variety of specialties. In cardiac surgery there is compelling evidence that such programmes are effective in reducing postoperative transfusions (77-80). DeAnda et al. described the implementation of a blood conservation programme in 2006, where the key component of success was believed to be the result of a multidisciplinary approach (80). Xydas et al. showed that a systematic implementation of a comprehensive blood conservation algorithm in cardiac surgery patients, led to significant reductions in the use of blood products (81). In 2013, LaPar et al. reported a successful implementation, at state-wide level, of a multi-institutional blood conservation programme in CABG patients (82).

Transfusion guidelines

The prevalence of perioperative transfusions in cardiac surgery varies widely, both between and within institutions (83, 84). The differences between institutions are probably due to differences in transfusion practice, guidelines and attitudes, as well as differences in patient characteristics. A multicentre European study revealed that transfusion rates depend less on type of procedure, patient population or hospital, than on the individual physician (85). Trigger and target haemoglobin (Hb) thresholds for transfusions of red blood cells (RBC) are crucial for reducing the use of blood products. Studies of Jehovah's Witnesses prove that moderate

anaemia of 80-100 g/L is not harmful if normovolemia is maintained (86, 87). There are still clinicians who transfuse patients to maintain a Hb level >100 g/L, despite the fact that a perioperative Hb level of 60 g/L may be tolerated as suggested in the guidelines from the Society of Thoracic Surgeons and the Society of Cardiac Anaesthetists 2007 (78).

Adherence to guidelines

Even though the indications may be clear, the final decision on whether or not to transfuse a patient is made by the physician responsible. There is little information on which indication or combination of indications leads to transfusion in cardiac surgery patients, and on how often the decisions adhere to institutional guidelines. Low adherence to guidelines has been reported in orthopaedic patients (88), in patients with postpartum bleeding (89, 90), and in various kinds of intensive care patients (91). Adherence in cardiac surgery patients has been found to be high if a liberal transfusion regimen is used, but markedly lower if a more restrictive attitude is adopted (92).

Study objectives

Massive bleeding after cardiac surgery is a serious complication associated with increased morbidity and mortality (10, 11). The bleeding is multifactorial and influenced by both surgical factors and an impaired haemostasis (12). Identification of patients with increased risk for excessive bleeding and transfusion of blood products offer the possibility to take countermeasures. An inverse correlation was observed between plasma fibrinogen concentration and amount of postoperative bleeding in patients undergoing CABG in a small study from our group (38). In **Paper I** we designed a larger prospective non-interventional observational study on patients undergoing first-time elective isolated CABG. The relationship between preoperative fibrinogen plasma concentration and bleeding volume in the first 12 postoperative hours was investigated.

Enhanced fibrinolysis, platelet dysfunction or loss, haemodilution and the surgical trauma are all factors that contribute to the impaired haemostasis in cardiac surgery patients (12). Consumption of coagulation factors during CPB has also been suggested as contributing to coagulopathy after cardiac surgery (13, 93), but it is not evident whether all coagulation factors respond similarly to CPB and surgical trauma. In **Paper II,** the objective was to describe the activity of individual coagulation factors in relation to haemodilution during and after cardiac surgery with CPB, and to investigate whether activity of any plasma coagulation factor corre-

lated to bleeding after surgery. First-time elective CABG patients operated with CPB were enrolled in a prospective descriptive non-interventional study.

Transfusion of blood products can be lifesaving, but, as mentioned earlier, there are considerable risks and adverse effects related with the usage of all blood products (66-68). Recent data suggests that transfusion of blood products is an independent risk factor for both short- and long-term mortality after cardiac surgery (69-71, 94, 95). The decision to transfuse is based on multiple patient factors, but also on guidelines and attitudes. In 2009, 61% of the cardiac surgery patients in our institution were transfused with blood products. At that time there were no written transfusion guidelines. Because of this high transfusion prevalence, a blood conservation programme was initiated, with the intention to reduce transfusions by 30%. In **Paper III** we evaluated the effects of this blood conservation programme on transfusion prevalence and volumes, cost of blood products, and potential effects on early complication rates. The effects were studied over a 24-month period after the project was completed.

A number of recent studies have shown that the implementation of more restrictive institutional guidelines for blood transfusions in cardiac surgery results in a reduced transfusion prevalence, an improved or unchanged clinical outcome, and reduced costs (77, 82, 96-98). In the light of these data we studied the prevalence of and indications for red blood cell transfusion in cardiac surgery patients, and assessed the adherence to our institutional transfusion guidelines (**Paper IV**).

Aims

I. To investigate the relationship between preoperative levels of plasma fibrinogen, and postoperative bleeding and transfusions after CABG.

II. To describe the activity of individual coagulation factors before and after CABG in relation to haemodilution and postoperative bleeding.

II. To study the effects of a structured blood conservation programme to reduce transfusions and transfusion-associated costs in cardiac surgery.

IV. To describe prevalence and indications for red blood cell transfusion in cardiac surgery patients.

V. To assess the adherence to local transfusion guidelines.

Patients and Methods

Patients

The Regional Research Ethics Committee approved all studies. In studies I and II, patients were included after written informed consent. The Ethics Committee waived the requirement for individual patient consent in studies III and IV. The studies were performed at the Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

Paper I

During 2005 and 2006, 175 patients undergoing primary elective isolated CABG with CPB were included in a prospective non-interventional observational study. Exclusion criteria were emergency CABG, known liver or kidney disease, and a surgical site of bleeding at re-exploration. Aspirin was not discontinued before surgery. The last dose of low molecular weight heparin (LMWH) was given the evening before surgery. Clopidogrel and Warfarin were discontinued at least 5 days prior to surgery. Additional medication with, for example, naturopathic drugs and selective serotonin reuptake inhibitors (SSRI) were not taken into consideration. Five patients were excluded due to re-exploration for surgical bleeding, leaving 170 patients in the study (Table 1).

Paper II

Fifty-nine consecutive patients undergoing primary elective isolated CABG with CPB were initially included in a prospective descriptive non-interventional study. Patients with known bleeding disorders were excluded. Aspirin was not discontinued before surgery. Clopidogrel was discontinued at least three days before surgery. Two patients were excluded, one due to changed surgical approach and one due to ongoing treatment with clopidogrel, leaving 57 patients in the study (Table 1).

Paper III

All adult patients undergoing cardiac surgery from February 2009 to January 2011 at our institution were included in the study. The patients were divided into two groups. The first group comprised all patients undergoing surgery during the 12 months prior to the blood conservation programme started (n=1128). The second

group comprised all patients undergoing surgery after the start of the programme (n=1034) (Table 1).

Paper IV

All 1034 patients in the second group in **Paper III** (n=1034) were included in the study.

	Study I	Study II	Study III before intervention	Study III after intervention and Study IV
n	170	57	1128	1034
Age (years)	67 ± 9	65 ± 7	65 ± 12	65 ± 12
Gender (male %)	75	77	75	75
BMI (kg/m^2)	27 ± 3.9	27 ± 3.4	27 ± 7.2	27 ± 4.2
Euroscore I		2 (1-4)	5 (3-7)	5 (3-7)
CABG (%)	100	100	53	50
Valve surgery (%)			25	28
CABG + valve (%)			10	10
Others (%)			12	12
Hb (g/L)	140 ± 14	148 ± 14	137 ± 15	136 ± 15
PLT count (x10^9/L)	265 ± 70	279 ± 64	259 ± 78	262 ± 79
Fibrinogen (g/L)	4.2 ± 0.9	3.7 ± 0.9	3.9 ± 1.1	3.7 ± 1.0
Aortic clamp time (min)	43 ± 15	44 ± 17	67 ± 35	65 ± 34
ECC time (min)	73 ± 25	72 ± 27	99 ± 45	99 ± 50
Postoperative bleeding (mL/12 h)	360 (250-510)	380 (300-515)	465 (350-660)	450 (335-650)

Table 1. Patients characteristics in the four studies. Mean ± standard deviation, median and 25th and 75th percentiles or number (%)

Clinical management

Paper I – IV

Anaesthesia was induced with fentanyl and thiopentone followed by pancurionium, and maintained with sevoflurane. During CPB, anaesthesia was maintained with propofol. Heparin was given (300 units/kg) to keep an activated clotting time (ACT) of more than 480 seconds. After CPB, heparin was reversed with protamine to an ACT of less than 130 s. All patients received 2 g tranexamic acid at induction of anaesthesia and at the end of surgery. Aprotinin was not used in any of the patients.

The CPB circuit included a membrane oxygenator and roller pumps. Non-pulsatile CPB technique with haemodilution was used. Cardioprotection was attained with cold blood cardioplegia. Weaning off CPB was performed after rewarming to a bladder temperature of 36°C.

Study design and analyses

Paper I

The following pre- and perioperative variables were registered: age, gender, BMI, number of grafts, unstable angina, extracorporeal circulation time, aortic clamp time, and anticoagulation therapy. Hb concentration, PLT count, aPTT, PT, and fibrinogen were analysed the day before surgery. APTT was analysed with a routine assay (STA-R, STA-PTT Automat 5 reagent, Diagnostica Stago). PT was analysed with a prothrombin complex assay (STA-R, SPA 50 Reagent, Diagnostica Stago). Plasma fibrinogen concentration was measured by the modified method of Clauss (99), where excess thrombin is added to diluted, low-fibrinogen-containing plasma, to determine the amount of clottable protein.

Postoperative bleeding volume was defined as the total amount of chest tube drainage during the first 12 postoperative hours. Drainage volumes until re-exploration for bleeding were recorded. Definition of a surgical bleeding was a specific bleeding controlled by surgical means. Transfusions of red blood cells, platelets, and plasma during the first 24 postoperative hours were recorded. Preoperative fibrinogen concentration was unknown for the treating physician.

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Paper II

The following pre- and perioperative variables were registered: age, gender, BMI, Euroscore, type of angina, preoperative medication, number of grafts, CPB-time and aortic clamp time. Plasma concentration of fibrinogen and plasma activity of coagulation factor II (FII), FV, FVII, FVIII, FIV, FX, FXI, and FXIII were analysed the day before surgery, 2 and 24 hours after surgery. At the same points Hb, HCT, and PT were analysed. Chest drainage during the first 12 postoperative hours was recorded.

All samples were analysed at the coagulation laboratory at Sahlgrenska University Hospital. Fibrinogen was measured by the modified method of Clauss as in study I. Activity of FII (reference range 70-130%), FV (reference range 60-140%), FVII (reference range 50-160%), FVIII (reference range 50-200%), FIX (reference range 45-190%), FX (reference range 70-130%), and FXI (reference range 60-140%) were determined using one stage clotting assay with specific factor deficient plasma samples on the instrument STA-R (Diagnostica Stago, Asnieres, France). Activity of FXIII was measured using the Cobas Mira instrument (Roche, Basel, Switzerland) by a photometric method (reference range 70-140%). Coagulation factor activity was reported as absolute values and values adjusted for haemodilution according to the formula: adjusted activity = absolute activity X (preoperative haematocrit / actual haematocrit) (99). Haemoglobin concentration, haematocrit and platelet count were analysed with clinical standard methods as in study I.

Paper III

The following variables were registered: preoperative: age, gender, BMI, additive Euroscore, antiplatelet therapy, preoperative Hb, aPTT, platelet count, serum creatinine and plasma fibrinogen concentration; peri- and postoperative: surgical procedure, CPB-time, aortic clamp time, acuteness, number of red blood cells, plasma and platelet transfusions during hospital stay, re-exploration for bleeding during the first 24 hours postoperatively, chest drain amounts during the first 12 hours postoperatively or until re-exploration, length of stay in ICU, length of stay in hospital, ventilation time, mediastinitis, highest postoperative serum creatinine, haemoglobin levels day 4 after surgery. Data were compared between the two groups and in subpopulations on the basis of gender, age, surgical procedure and preoperative Hb level. The institutional price list for blood products from 2009 was used to make cost calculations for both years (RBC concentrate: €102/unit; plasma: €35/unit; platelets: €290/unit).

The blood conservation programme consisted of three parts:

1   Training. All staff involved in the care of the patients was given training about the risks and benefits of blood transfusions and the new transfusion guidelines in a 45-minute lesson.

2.   Guidelines. According to the new guidelines, indications for red blood cell transfusion should be based on clinical assessment of the patient´s haemo-dynamic status, and/or signs of low oxygen delivery with mixed venous saturation below 55%. Absolute indications were Hb<60g/L, but in patients with ongoing significant bleeding an Hb level of >100 g/L was the target. Plasma was transfused in patients with ongoing bleeding (>200ml/h) and/or prolonged coagulation time in the absence of sustained heparin effect, indicating coagulation factor deficiency. Platelets were transfused in patients with ongoing bleeding (>200ml/h) and/or low platelet count (<100x10^9/L) and/or suspected platelet dysfunction. The decision to transfuse or not was always at the discretion of the physician responsible.

3.   Transfusion log. In a transfusion log added to the patient records, all transfusion episodes were recorded, together with time and type of transfusion, number of units, indication and patient status. Fig 7.

Paper IV

The transfusion log described in **Paper III** was used. When the indications for red blood cell transfusion were assessed, only transfusion episodes with red blood cells alone were included to avoid confusion as to whether the indication for transfusion included plasma or platelets. Complete log records with red blood cells only were found in 351 transfusion episodes in 256 patients. Transfusion of red blood cells was considered to adhere to guidelines in patients with ongoing bleeding, Hb <60g/L, signs of impaired oxygen delivery (SvO2 < 55%), heart failure, renal failure or cerebral deoxygenation indicated by INVOS (Somanetics INVOS Oxymeter, Covidien, Mansfield, MA, USA). The degree of adherence to guidelines, based on the transfusion log, was assessed by two observers (AJ and LT).

Transfusion log

	Date						
	Time						
	Ward						

Indication	Ongoing bleeding						
	Anemia						
	Hypovolemia						
	Heart failure						
	Other						

Product	Blood						
	Plasma						
	Platelets						

Status	Hb						
	EVF						
	SvO$_2$						
	Blood pressure						
	Pulse						
	TEG (Y/N)						

	Name and signature of prescribing doctor						

Key: EVF; Erythrocyte Volume Fraction, Hb; Haemoglobine, SVO2; Venous Oxygen Saturation, TEG; Thromboelastogram

Figure 7. The transfusion log, in which indication for transfusion, type of blood product, patient status and laboratory variables were recorded.

Statistical analyses

Paper I

The relationship between haematological and demographic data and the volume of postoperative bleeding were analysed with simple linear regression. Multiple linear regression using forward selection was then used to identify factors independently associated with bleeding volume. Groups were compared using two sample t-tests for continuous data and with chi-square tests for categorical data. Independent predictors for transfusion were analysed with multiple regression. Results are expressed as mean and standard deviation, or number and percentage. Statistical significance was defined as a p-value of < 0.05.

Paper II

All statistical analyses involving bleeding were performed with non-parametric tests. Intergroup comparisons were performed with the Mann-Whitney test, Kruskal-Wallis test or chi-square test. For correlation testing, Pearson´s test (normally distributed data) or Spearman rank sum test were used. Correlation between coagulation factor activity and postoperative bleeding was performed on absolute activities, without correction for haemodilution, and coagulation factor activity after surgery was compared to baseline with paired T-test. Results are expressed as mean and standard deviation, or number and percentage. Statistical significance was defined as a p-value of < 0.05.

Paper III

To compare normally distributed continuous variables, the independent sample t-test was used, and to compare non-normally distributed continuous variables the Mann-Whitney U-test was used. Categorical variables were compared with a chi-square test. The Kolmogorov-Smirnov test was used to test distribution of data. Results are expressed as mean and standard deviation and/or median and 25th and 75th percentiles, or as number and percentage. Statistical significance was defined as a p-value < 0.05.

Paper IV

Univariable and multivariable predictors of red blood cell transfusion were calculated with logistic regression. The distribution of data was displayed with histograms with normal curve and tested with Kolgomorov-Smirnov. Most continuous data were not normally distributed, so these were reported as median with 25th and 75th percentiles. Data for pre- and perioperative fibrinogen levels was missing in 4.3%, and in remaining variables data was missing in $< 1.7\%$. Statistical significance was defined as a p-value < 0.05.

Results

Paper I

One of the 170 patients died of multiorgan failure 9 days after surgery. Four patients were re-explored for postoperative bleeding within 12 hours after surgery. Median postoperative bleeding was 360 mL/12 hours (range 110-2085 mL), and 29 patients (17%) received blood transfusion during the first 24 postoperative hours.

Mean preoperative fibrinogen plasma concentration was 4.2 ± 0.9 g/L (range 2.4-8.1 g/L). One-hundred-and-sixteen (68%) patients had normal concentrations of plasma fibrinogen (2.0-4.5 g/L), while the remaining 54 patients (32%) had higher concentrations. Mean Hb concentration was 140 ± 14 g/L. PLT count, aPTT, and PT values were all within the normal range.

Significant inverse correlations were found between postoperative bleeding and plasma fibrinogen concentration, PLT count, and Hb concentration. There were no correlations between bleeding and aPTT or between bleeding and PT. In multivariate testing, preoperative fibrinogen concentration was the only factor independently associated with postoperative bleeding ($r=-0.53$, $p < 0.001$).
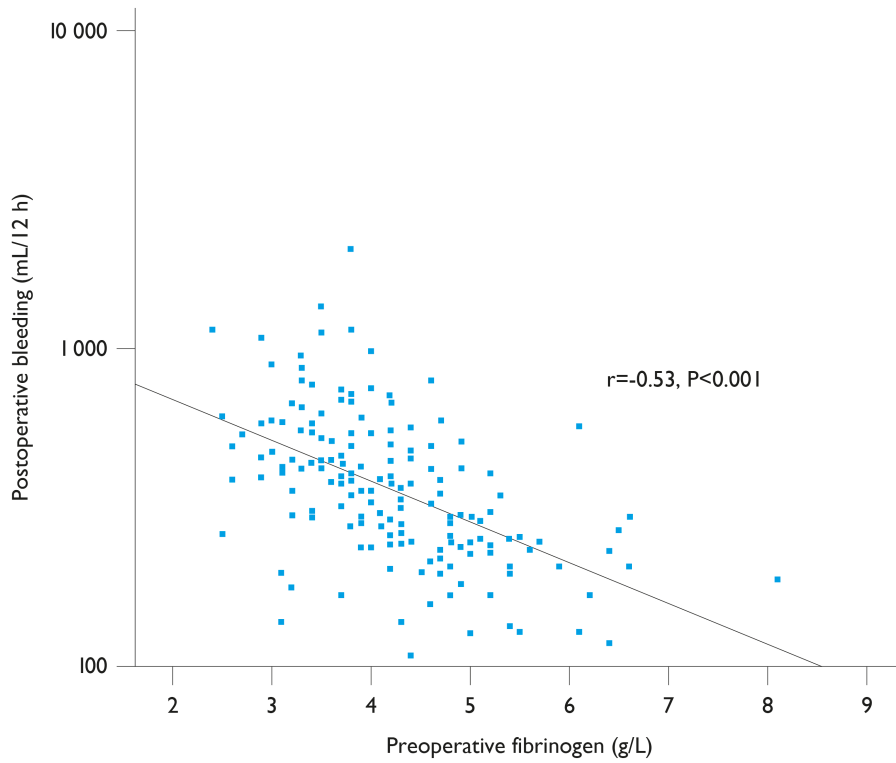
Figure 8. Correlation between preoperative fibrinogen concentration and bleeding after CABG. There was a significant correlation between the two factors (r=-0.53, p < 0.001).

Significant independent predictors of transfusion in a logistic regression model were preoperative fibrinogen concentration, female gender, and aortic clamp time. The absolute risk for transfusion of blood products in relation to gender and fibrinogen concentration is shown in Figure 9.
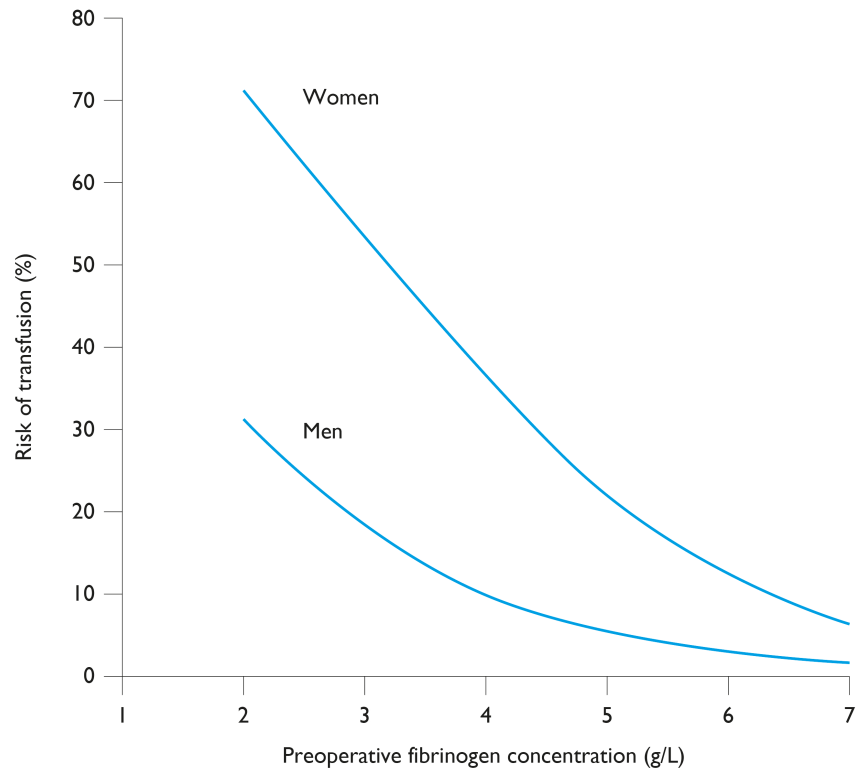
Figure 9. Absolute risk for transfusion of blood products during the first 24 postoperative hours in men and women with different preoperative plasma concentrations of fibrinogen.

Paper II

Coagulation factor activity was above the lower normal range in 56/57 patients, and a significant number of patients had coagulation factor activity over the upper normal range: 2 to 35 % for the individual coagulation factors. The unadjusted plasma factor activity was significantly reduced two hours after surgery in all factors, except for FIX. Twenty-four hours after surgery, unadjusted fibrinogen levels and FVIII activity increased compared to preoperatively, while FIX activity did not differ significantly. The activity of all other factors was reduced in comparison to preoperatively.

In Fig 10, the changes from baseline activity after adjustment for haemodilution are shown. Mean plasma concentration of fibrinogen and activity of FII, FV, FX and FXII significantly decreased two hours after surgery, while activity of FVII and FXI did not differ, and activity of FVIII and FIX significantly increased. Twenty-four hours after surgery the plasma concentration for fibrinogen and activity of FVIII and FIX had increased significantly. Plasma activity of FV, FVII, FX, FXI, and FXIII decreased significantly, and activity of FII did not differ from baseline.
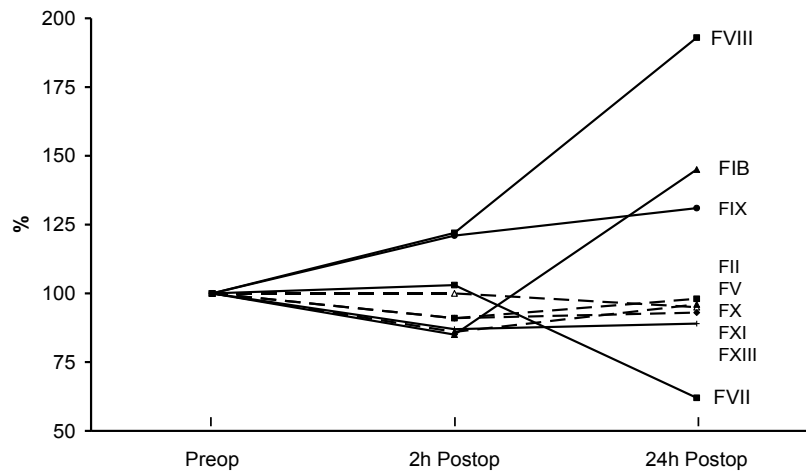

Figure 10. Plasma concentrations of fibrinogen and plasma activity of FII, FV, FVII, FVIII, FIX, FX, FXI and FXIII before surgery and 2 and 24 hours after surgery, in % of the preoperative value.

There were significant inverse correlations between postoperative bleeding volume and postoperative concentration of fibrinogen (r=-0.33, p=0.019) and pre- and postoperative activity of FXIII (r=-0.34, p=0.009 and r=-0.41, p=0.003, respectively), but not with any of the other coagulation factors.

Paper III

The proportion of patients transfused with any blood product was 60.9% before the programme was started, and 48.3, 54.0, and 50.7%, 1-3 years after initiation.

The first year after the programme was initiated, the proportion of patients transfused with red blood cells decreased by 21.8%, plasma by 37.4%, and platelets by 21% (Figure 12). Re-explorations for bleeding, early complication rate, and 30-day mortality did not change after introduction of the programme (Table 2). The savings on blood products were €161,623 during the first 12 months after the programme was initiated (Table 3).
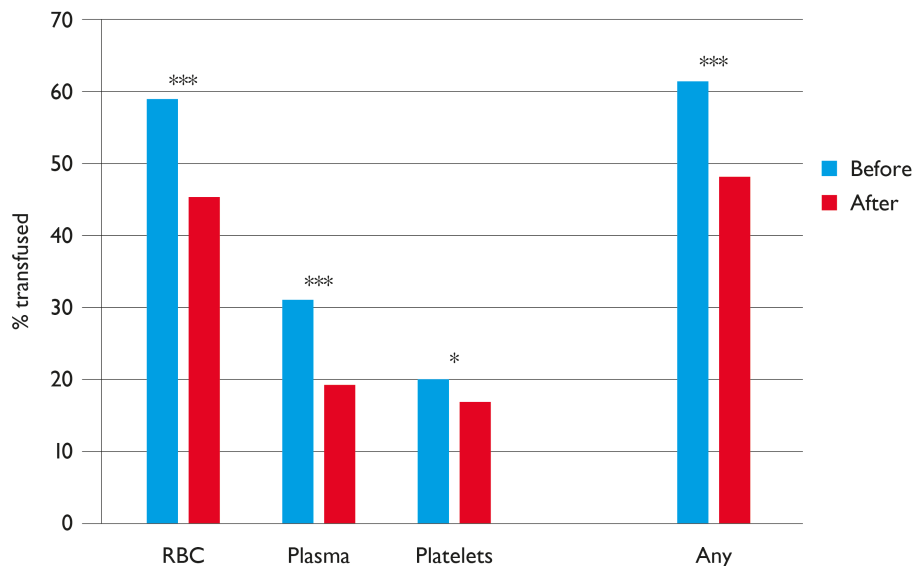

*Figure 11. Percentage of patients transfused with red blood cells, plasma, platelets and any blood product before and after initiation of the blood conservation programme. *P <0.05, ***P <0.001.*

	Before start (n = 1128)	After start (n = 1034)	P-value
Postoperative drain loss (ml/12 h)	587 ± 416	553 ± 350	0.04
Reoperation for bleeding	65 (5.8%)	52 (5.0%)	0.45
Postoperative serum creatinine	107 ± 67	108 ± 72	0.55
Postoperative dialysis	31 (2.7%)	29 (2.8%)	0.94
Stroke	12 (1.1%)	18 (1.7%)	0.18
Mediastinitis	17 (1.5%)	15 (1.5%)	0.91
Ventilation time (h)	3 (2–5)	3 (2–6)	<0.001
ICU stay (days)	2 (2–2)	2 (2–2)	0.07
Hb at Day 4 (g/l)	100 ± 11	98 ± 12	<0.001
Hospital stay (days)	7 (6–9)	7 (6–8)	0.013
30-day mortality	28 (2.5%)	27 (2.6%)	0.95

Table 2. Outcome variables before and after the start of the blood conservation programme.

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	Units saved/patient	Total units saved	Price/unit (Euros)	Total amount (Euros)
RBCs	0.78	806	102	82 185
Plasma	0.54	558	35	19 524
Platelets	0.20	207	290	59 914
Total savings				161 623

Table 3. Cost (in Euros) for blood products during a 12-month period after the start of the blood conservation programme.

Paper IV

The prevalence of re-exploration for bleeding was 5.0% and median postoperative blood loss was 450 mL/12h. Thirty-day mortality was 2.6%. Of 1034 patients, 470 (46%) were transfused with red blood cells. Twenty-five percent of the patients received red blood cells alone, and 21% received red blood cells in combination with plasma and/or platelets. The most common self-reported indication (69%) for transfusion of red blood cells alone was anaemia. Hypovolemia was reported in 56%, heart failure in 19%, and ongoing bleeding in 7% of the cases (Figure 13). Mean haemoglobin level was 81 g/L before blood transfusion. Only 43% of the red blood cell transfusions were administered in accordance with institutional guidelines.
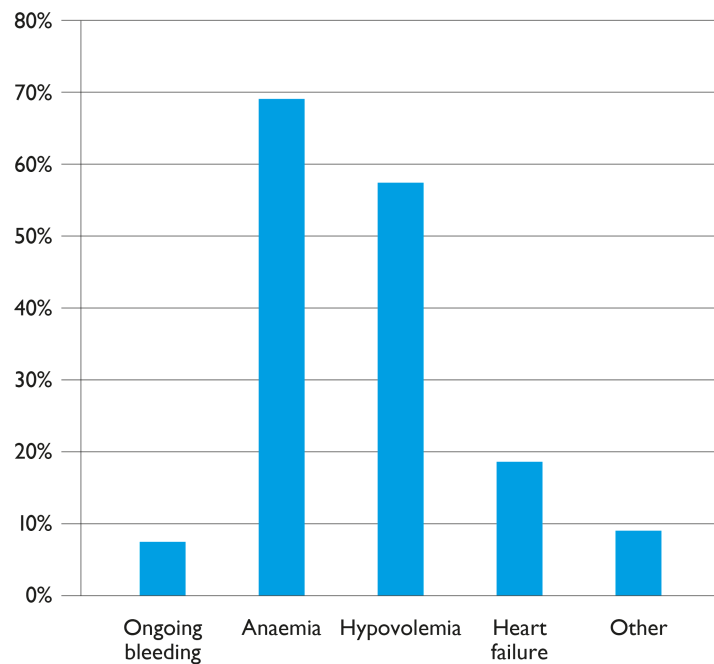

Figure 12. Self- reported indications for transfusion with red blood cells only in 351 transfusion occasions in cardiac surgery patients.
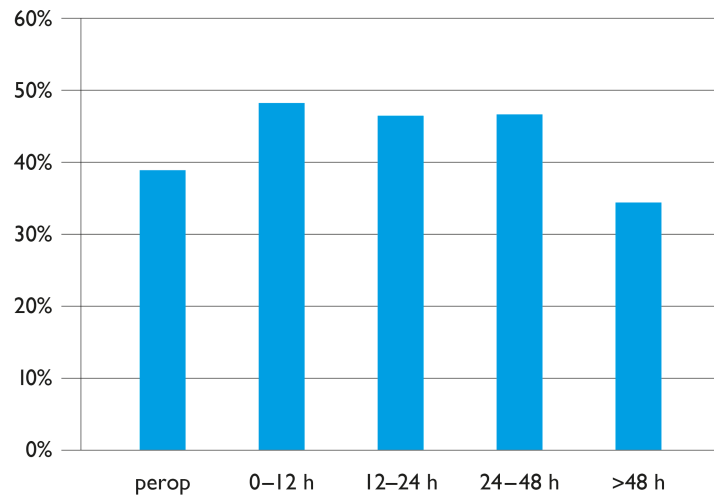
Figure 13. Adherence to guidelines for red blood cell transfusion at different periods of time.

Discussion

Plasma fibrinogen level, bleeding and transfusion

Knowledge of fibrinogen and its role in bleeding and coagulation has increased steadily. In the early part of our studies, it was suggested that plasma fibrinogen levels of higher than 1.0 g/L were sufficient to ensure that the coagulation was not limited by the fibrinogen concentration (100), and guidelines recommended administration of fibrinogen to maintain plasma fibrinogen levels <0.5-1.0 g/L (101). In Study I, mean plasma concentration of fibrinogen was 4.2 ± 0.9 g/L, and 32% of the 170 elective CABG patients had a preoperative fibrinogen concentration above the upper normal limit of 4.5 g/L. This is explained by the association between elevated levels of fibrinogen in ageing (32) and in cardiovascular risk (35, 36). In Study I, the results indicate that a fibrinogen level of 1g/L is not sufficient for haemostasis when the coagulation system is defied by cardiac surgery, the use of CPB, and haemodilution. Our conclusion is that plasma fibrinogen concentration is a limiting factor for postoperative haemostasis, and that fibrinogen levels, even in the normal range, may be too low to ensure appropriate coagulation during and after major surgical procedures. This is confirmed in more recent studies in cardiac (102) and scoliosis (40, 102) surgery. Consistent with these findings, European guidelines on the management of severe bleeding in the perioperative setting and in trauma patients now recommend using fibrinogen concentrate if significant bleeding is accompanied by plasma concentrations <1.5-2.0 g/L (103, 104).

Identifying patients at risk of excessive postoperative bleeding would offer the possibility to optimise perioperative management. If patients at increased risk for postoperative bleeding were identified, countermeasures could be initiated. Prior to cardiac surgery there is a widespread use of laboratory tests. Routine screening tests such as activated thromboplastin time (aPTT), prothrombin time (PT) and platelet count, have no or limited ability to identify patients with increased bleeding risk (18-20). In study I we found no correlation between bleeding and aPTT and PT. However the correlation between plasma fibrinogen level and postoperative bleeding volume was significant (r=-0.53). A significant, but less prominent correlation was also found between bleeding and PLT count (r=-0.26). Fibrinogen alone was independently associated with bleeding in the multivariate test. The results suggest that preoperative measurement of fibrinogen concentration in CABG patients provides additional information about bleeding and transfusions, and may be measured, particularly in patients with other risk factors of increased bleeding. Moreover, recent studies on fibrinogen levels in postoperative cardiac

surgery patients have shown a predicted risk of postoperative bleeding (105, 106). In study II, there was a significant correlation between fibrinogen, measured 2 hours postoperatively, and postoperative bleeding. However, there was no correlation between preoperative fibrinogen levels and postoperative bleeding, which may be explained by the small study population. The strong correlation between preoperative fibrinogen levels and postoperative bleeding suggests that the time-point when fibrinogen is measured is of less importance. A meta-analysis from 2014 on both pre- and postoperative fibrinogen levels showed a weak to moderate significant correlation between fibrinogen and bleeding in cardiac surgery (31).

In study I, an association was shown between preoperative fibrinogen concentration and transfusion of red blood cells. These results could not be reproduced in a larger study from our group (102). One reason might be that, in study I, we only registered transfusions during the first 24 postoperative hours, whereas the study by Walden et al. (97) included all transfusions given during hospital stay. Indications for red blood cell transfusions are multifactorial, especially after the immediate postoperative period, as was also shown in **Paper IV**.

Correlation between postoperative bleeding, and fibrinogen and coagulation factor XIII

Of all the coagulation factors analysed in study II, only postoperative fibrinogen and pre- and postoperative FXIII were associated with postoperative blood loss. The association between FXIII activity and bleeding volume has been investigated in a few studies, with varying results. In a study by Blome in 2005, a marked decrease in plasma activity of FXIII during CPB was not associated with postoperative bleeding (39). However, the results may not be comparable since the patients in their study were treated with aprotinin. Conversely, there are studies pointing to the importance of FXIII levels for maintaining clot strength and reducing postoperative blood loss (107), and studies suggesting replacement therapy with FXIII to be considered in postoperative bleeding (48). However, conflicting results have been published recently (49).

Together with the activity measurements, our results indicate that coagulation factors involved in the first steps of the coagulation cascade (before thrombin generation) do not reach critically low levels after CABG with limited bleeding and limited operation time. In contrast, two factors involved in the end of the coagulation cascade, fibrinogen and FXIII, correlated to postoperative blood loss. This indicates that clot stability may be more critical than clot initiation for haemostasis after uncomplicated cardiac surgery. This speculation is supported in a study by Solomon et al., where fibrin formation was more impaired than thrombin

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generation and platelet function immediately after CPB (108). Furthermore, in a study on paediatric surgery patients, where transfusions were guided by intraoperative thromboelastometry (TEM), the results demonstrated that clot formation was the main limiting factor for postoperative haemostasis and that the use of TEM led to a marked reduction in plasma transfusions, while transfusions of fibrinogen and platelets increased (109). This supports the theory that impaired coagulation after cardiac surgery with CPB, most probably is a consequence of impaired clot stability rather than compromised clot initiation. Additional studies support the fact that fibrinogen and FXIII are crucial for the quality of the clot (110-112).

The effects of a blood conservation programme

Transfusions of blood products can be lifesaving but are associated with considerable risks (66-68). In cardiac surgery, transfusions have been associated with increased mortality (69-71). In 2009, 61% of the patients undergoing cardiac surgery at our institution were transfused with blood products. This high prevalence initiated a blood conservation programme, to reduce transfusions and transfusion-related costs, where a more restrictive approach to transfusion than before was advocated. In **Paper III** the effects of the programme were studied. The results demonstrated that a structured blood conservation programme reduces transfusion prevalence and costs for blood products, and that the reduction prevalence was maintained for at least 3 years. This was achieved without compromising patient safety.

The difference in patient mix between the years suggests that there in fact may have been an increased need for blood transfusions during the year the programme was introduced. Preoperative levels of fibrinogen were significantly lower and, in addition, the proportion of patients undergoing acute surgery was higher, though not significantly, during the programme year. Both factors have been shown to correlate with increased postoperative bleeding and transfusions after cardiac surgery (66, 77, 102). Despite this, the proportion of patients who received RBC was reduced by 22%, plasma by 37% and platelets by 21%. The proportion of patients who received any type of blood transfusion was reduced by 21%.

Prior to the introduction of the blood conservation programme, three simple steps were taken. The clinic's guidelines for blood transfusions were revised, all staff with patient contact underwent a 45-minute lesson on the benefits and risks of blood transfusions, and the clinic's new guidelines were reviewed. All patients received a transfusion log, where status, indication, and type of blood transfusion were recorded. With these very simple, neither time-consuming nor costly

measures, the utilisation of blood products could be reduced by 21% and the total saving for blood products was €161,623.

As mentioned earlier, there are studies indicating increased mortality in cardiac surgery patients after transfusion of as little as 1-2 units of red blood cells (69, 70). A study by Paone et al. showed that 1-2 units were administered to 26% of the total population, corresponding to 50% of all patients receiving blood transfusions (70). In most cases, transfusions at this level are probably redundant. In our material 37% of the patients were transfused with 1-2 units of red blood cells before the programme was initiated. Before the introduction of the programme, we believed that transfusions of 1-2 units would be significantly reduced and that the greatest savings of blood products would come from this subgroup of patients. Surprisingly, there was no decrease at all in this group (37% vs. 41%), although the overall transfusion prevalence decreased. This suggests there is room for further reduction in transfusion prevalence than that was achieved with the programme.

After the introduction of the programme, almost 1,600 units of blood products were saved during a 12-month period. These blood products could be used for patients who were in greater need of them. The financial savings were substantial (Table 3) although the net saving was slightly lower as the reduced use of plasma resulted in an increase in the use of albumin and other plasma expanders. On the other hand, previous studies have shown that the cost of blood products for society is significantly higher than institutional prices (74-76).

Adherence to transfusion guidelines

In **Paper IV** the prevalence and timing, as well as the indications for and predictors of red blood cell transfusion in cardiac surgery patients, were studied. Adherence to guidelines was also analysed. Transfusion of red blood cells was considered to adhere to guidelines when given to patients with Hb <60 g/L, signs of impaired oxygen delivery (SvO2 < 55%), ongoing bleeding, heart failure, renal failure or cerebral deoxygenation indicated by INVOS. A haemoglobin level of <60 g/L might be considered low, but in our institutional guidelines we tried to avoid transfusion of red blood cells based only on haemoglobin levels, and instead base the decision to transfuse on clinically significant anaemia. Our transfusion policy was based on the recommendations of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (66).

In our study, only 43% of RBC transfusion episodes adhered to institutional guidelines. Similar rates have been reported in intensive care unit patients, in

patients with postpartum bleeding, and in orthopaedic patients (88, 90, 91). In cardiac surgery patients, a high adherence to guidelines (84%) was seen when a liberal transfusion policy was used (Hb <95 g/L). The adherence was markedly lower (41%) with a more restrictive policy (Hb <70 g/L during and <75 g/L after surgery) (92). This last study is not directly comparable since different transfusion triggers and definitions of adherences were used. However, the results were surprisingly similar (43% vs. 41% adherence).

This is the first study to report the prescriber´s indication for red blood cell transfusion in cardiac surgery. In this patient group, the most common indication for red blood cell transfusion was anaemia, followed by hypovolemia. The anaemia was an expected finding, but the fact that RBC was prescribed for hypovolemia was a surprise. However hypovolemia alone was rarely an indication for RBC transfusions; instead a combination of hypovolemia and another indication was common. One explanation is that patients with a clinical requirement for volume substitution and medium to low haemoglobin levels were prescribed RBC transfusions, with an intention to solve both problems. Ongoing bleeding was a rare indication for transfusing only red blood cells. However, during ongoing bleeding, transfusion of RBC and plasma and/or platelets is often prescribed. In our material this was the case in approximately 20% of the operated patients during the study period.

Limitations

There are important limitations in studies I and II. The studies are single-centre experiences. Transfusion thresholds, haematological practice, use of thromboelastography, discontinuation of anticoagulants, and the use of perioperative antifibrinolytics may not be applicable to other centres. However, all patients were treated with tranexamic acid and this may well reflect the real world, since tranexamic acid today is used in the vast majority of cardiac surgery patients in Sweden and probably also in centres worldwide. Furthermore, there are numerous factors beyond coagulation status influencing postoperative bleeding volume, so bleeding volume is not an optimal endpoint. However transfusion requirement, another possible endpoint, is also multifactorial, possibly even more so.

In study III, factors not related to the transfusion policy may have changed during the study period. Non-adherence to transfusion guidelines may also have influenced the results, but this issue was addressed in study IV.

In **Paper III**, higher-quality data for the second period may have introduced bias since these data were collected prospectively, while data for the period before the

start of the project were retrieved from prospective registers. However, prospective collection during the first period would also have biased the results since all staff would have been aware of the upcoming changes. This could have influenced decision-making regarding blood transfusions.

The fact that **Paper IV** is a single-centre study raises the question of whether the experience can be applied to other institutions. The patients had the same risk factors for transfusions as previously reported, indicating the results could be relevant to other institutions. Since the transfusion log did not allow us to distinguish between indications for red blood cells, plasma and platelets, indications for transfusions were analysed in patients receiving only red blood cells, which could be considered a limitation.

Conclusions

I.   Pre- and postoperative fibrinogen concentration and factor XIII activity correlates to postoperative bleeding volume after CABG, and may be used to identify patients with increased risk of bleeding (**Papers I & II**).

II.   There is a marked disparity of clotting factor activity after cardiac surgery with CPB (**Paper II**).

III.   The introduction of a structured blood conservation programme in cardiac surgery is safe, and reduces the use and costs of blood products (**Paper III**).

IV.   Transfusions of red blood cells are given to cardiac surgery patients not only because of anaemia, but also because of other indications (**Paper IV**).

V.   The adherence to transfusion guidelines among treating physicians is low (**Paper IV**).

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Acknowledgements

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