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## **Allogeneic red blood cell transfusion in coronary artery bypass surgery**

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**ALLOGENEIC RED BLOOD CELL TRANSFUSION IN  
CORONARY ARTERY BYPASS SURGERY**

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## **Preface and acknowledgements**

This PhD thesis is based on clinical and epidemiological studies carried out between 2004 and 2009 during my employment at the Department of Cardiothoracic Surgery, Aalborg Hospital, Aarhus University Hospital.

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**This PhD thesis is partly based on four scientific studies, which are referred to in the text by Roman numerals. These studies have been carried out in the period from 2004-2009:**

### **Study I**

Andreasen JJ, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary artery bypass surgery using cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2004; 26: 311-7.

DOI:10.1016/j.ejcts.2004.03.012

### **Study II**

Andreasen JJ, Westen M, Jensen S, Pallesen PA, Gorst-Rasmussen A, Johnsen SP. Transfusion practice in coronary artery bypass surgery in Denmark: a multicenter audit. *Interact Cardiovasc Thorac Surg* 2007; 6: 623-627.

DOI:10.1510/icvts.2007.154401

### **Study III**

Andreasen JJ, Riis A, Hjortdal VE, Jørgensen J, Sørensen HT, Johnsen SP. Effect of selective serotonin reuptake inhibitors on requirement for allogeneic red blood cell transfusion following coronary artery bypass surgery. *Am J Cardiovasc Drugs* 2006; 6: 243-50.

DOI: Not available

### **Study IV**

Andreasen JJ, Dethlefsen C, Modrau IS, Baech J, Schönheyder HC, Møller JK, Jacobsen C-J, Møller BK, Thomsen RW, Johnsen SP. Storage time of allogeneic red blood cells is associated with risk of severe postoperative infection after coronary artery bypass grafting.

Submitted to *Eur J Cardiothorac Surg*, December 2009.

## Abbreviations

ATP	Adenosine triphosphate
BSA	Body surface area
CABG	Coronary artery bypass grafting
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPB	Cardiopulmonary bypass
DART	Danish Register of Transfusion Risks
ECC	Extracorporeal circulation
ECG	Electrocardiography
EF	Ejection fraction
FFP	Fresh frozen plasma
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IDDM	Insulin-dependent diabetes mellitus
OPCAB	Off-pump coronary artery bypass grafting
OR	Odds ratio
PLT	Platelets
RBC	Red blood cells
RR	Relative risk
SRI	Serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TA	Tranexamic acid
WBC	White blood cells



## **Introduction**

Allogeneic blood transfusion (blood transfusion from a genetically different person) has always been an integral part of cardiac surgery including coronary artery bypass grafting (CABG). A large amount of blood is consumed since CABG has evolved to become one of the most common surgical procedures performed today. Nearly one million CABG procedures are performed throughout the world every year [1] and >2000 CABG procedures, with or without concomitant valve surgery, are performed annually in Denmark [2].

Because blood for transfusion is a scarce resource and since transfusion may even be harmful [3], there is a growing awareness among surgeons and anaesthesiologists of the benefits and risks of allogeneic blood transfusion during cardiac surgery. Several clinical guidelines on blood transfusion are published [4-12], but there is still national and international variability in transfusion practices used in patients undergoing cardiac surgery despite these guidelines [1,13-16]. These circumstances strongly suggest that much more research-based knowledge is needed to gain a better understanding of the factors that determine transfusion requirements, transfusion practices, and the effectiveness and safety of blood transfusion

This PhD thesis will focus on allogeneic red blood cell (RBC) transfusion and blood conservation among patients undergoing CABG, since CABG is the most common cardiac surgery performed and because transfusion with allogeneic RBC units is associated with adverse outcomes after CABG.

The four studies presented in this thesis will serve as an example of a multimodal approach to blood conservation in CABG with the potential to conserve blood and restrict transfusion to fewer patients. A multimodal approach to blood conservation is important because the cause of bleeding is multifactorial [11,17]. The findings of the individual studies will contribute to the pool of knowledge upon which future transfusion and blood conservation algorithms in cardiac surgery will be based.

## **Background**

### **History of blood transfusion**

The following chapter will briefly describe the history of blood transfusion from the early attempts to modern allogeneic transfusion support, which is a prerequisite for modern cardiac surgery.

Blood has always fascinated man. In ancient Rome the blood of fallen gladiators and wild animals was lapped up by men seeking vigour [18]. In 1492, a Jewish physician promised to cure the dying Pope Innocent VIII if he had access to a certain amount of juvenile human blood. Blood was taken from three boys who died soon afterwards. The physician fled and the Pope was left uncured. There are no records to support the notion that the blood was ever used for an attempted transfusion to the Pope [19].

In 1666, Dr. Richard Lower described the first direct blood transfusion, which he performed in 1665. Lower tried to transfer blood from the jugular vein of one dog to the jugular vein of a second by means of tubes between the two animals. This first attempt failed because no pump was interposed in the outer circuit. In another attempt, Lower replaced blood from an artery of one dog into the vein of a second one, thus keeping a heavily bled dog alive by transfusion from another dog [20].

The first human transfusion was performed in France by Jean-Baptiste Denis and his group in Paris. On July 15, 1667, they transfused blood from the carotid artery of a sheep into a 15 year old boy who had been bled by his physician 20 times because of violent fever. The youth recovered [21]. Another spectacular transfusion the same year was that of a blood transfusion from a calf to a 34-year-old male. The idea was to transfer the gentle character of the calf to the patient to dampen the spirits of the patient. The transfusion was repeated three times and the patient eventually died. Transfusions from animals to humans were also performed in London in 1667 [22], but a few years later animal-to-human transfusions were prohibited by the French Parliament, The Royal Society of London, and the Church of Rome due to catastrophic results.

Hereafter, a period of approximately 150 years followed before an interest in blood transfusion was revitalized. James Blundell is recognized as the pioneer of modern blood transfusion therapy [23]. Blundell performed scientific transfusion experiments and published his results [24]. He demonstrated

that only blood from the same species should be used, and he performed the first successful human-to-human blood transfusion in 1828 [18,25]. The first human-to-human transfusion in Denmark took place in Copenhagen in 1848 [26].

One of the most important findings in relation to modern blood transfusion was Landsteiner's discovery of the first three human blood groups [27]. Landsteiner received the Nobel Prize in 1930 for his work. Approximately 14–15 years later, the discovery was made that sodium citrate prevented blood from coagulating, thus permitting cold storage of blood for several days after collection [18]. These findings paved the way for establishing blood banks during the 1930's and 1940's. Cadaver blood was used initially [18], but soon blood for transfusion was only obtained from living donors. The value of prompt transfusion of blood to resuscitate wounded soldiers from haemorrhage was generally accepted by the end of World War I.

The availability of donor blood from modern blood banks set the scene for cardiac surgery to expand into a new era in the 1950's, when the heart-lung machine was invented [28]. Allogeneic blood was widely used to prime the heart-lung machine as well as for perioperative transfusions.

Nowadays, whole blood is seldom used for transfusion. Advances in transfusion medicine have made it possible to prepare different kinds of RBC units, platelet (PLT) products, plasma, and coagulation factor concentrates from whole blood [29-31], making modern allogeneic transfusion support very specific.

The following chapters will provide the theoretical framework for this PhD study by reviewing the current literature on allogeneic RBC transfusion and blood conservation in cardiac surgery.

### **Transfusion variability in CABG**

For several years, blood consumption in Denmark has in general been higher than in other countries. The average use of RBC varies considerable in different European countries. An average annual use of 35 RBC products per 1,000 inhabitants (range: 1–71) was observed in 2003 with the highest use in Denmark [32-37]. Furthermore, blood consumption varies considerably between Danish regions.

Allogeneic RBC transfusion rates between 8–100% have been reported during CABG in the past decade [1,16,38]. These wide differences in transfusion rates may be explained by a variety of reasons including different patient populations, differences in procedure-related factors, traditions, and norms. Therefore, individual centres should pay attention to their current transfusion practice.

Behavioural interventions aimed at supporting implementation of clinical guidelines, including a variety of educational initiatives, reminders, and audits are effective in changing physicians' transfusion practices, and therefore behavioural interventions with regular audits were suggested as part of a multimodal approach to blood conservation [39-41].

### **Predictors of allogeneic red blood cell transfusion during CABG**

The cause of bleeding and transfusion in CABG is multifactorial, and knowledge about predictors of bleeding and transfusion is a prerequisite for preoperative risk stratification and use of rational blood conservation techniques. Risk factors that predispose CABG patients to allogeneic blood transfusions include patient- and procedure-related factors in addition to local transfusion practices.

Several preoperative patient-related predictors of bleeding and transfusion were described in the past three decades and reviews were published [11,42]. A summary of selected studies on preoperative predictors of bleeding and allogeneic blood transfusion in cardiac surgery are shown in Table 1. Over the years, age, preoperative RBC mass, female sex, and preoperative haemoglobin concentration are consistently described as predictors of bleeding and transfusion. However, the risk profile of the patients related to bleeding and transfusion has changed over the past decade as a result of an increased use of new antiplatelet drugs, increasing age of the patients, and more comorbidities among the patients.

Few preoperative variables are modifiable. Central among modifiable factors is the preoperative intake of antiplatelet drugs. These drugs can be discontinued prior to elective surgery, or surgery can be delayed until the PLT function returns to normal.

Table 1. Preoperative variables associated with bleeding and RBC transfusion during cardiac surgery including CABG.

Reference	Number of patients	Variables associated with bleeding/transfusion
Cosgrove et al. 1985 [43]	441	Red cell volume, advanced age
Ferraris et al. 1989 [44]	159	Preoperative bleeding time, red blood cell volume
Magovern et al. 1996 [45]	2,033	Emergent and urgent surgery, cardiogenic shock, catheterization-induced coronary occlusion, low body mass index, EF <30%, age >74 years, female sex, low red cell mass, peripheral vascular disease, insulin-dependent diabetes, renal insufficiency, re-do operation.
Gammie et al. 1998 [46]	11	Preoperative administration of abciximab <12 hours
Shevde et al. 2000 [47]	253	Female sex
Karkout el al. 2001 [48]	1,007	Preoperative haemoglobin, weight, age, female sex
Ferraris et al. 2002 [49]	2,606	Intake of aspirin
Parr et al. 2003 [50]	600	Increased age, increased creatinine level, low BSA, low haematocrit, nonelective surgery.
Litmate et al. 2003 [51]	400	Left ventricular ejection fraction <0.35, age >70 years, preoperative haemoglobin <11 g/dl, IDDM, emergency operation, female sex, impaired renal function (creatinine >1.6 mg/dl), and re-operation
Scott et al. 2003 [52]	1,235	Female sex, haematocrit <35%, increasing age, decreased body weight.
Aurora et al 2004 [53]	3,046	Haemoglobin, emergent operation, renal failure, female sex, age $\geq$ 70 years, EF <0.40, re-do surgery, low BSA.
Dial et al. 2005 [54]	613	Older age, female sex, low haemoglobin, low BSA
Karkouti et al. 2006 [55]	10,667	Haemoglobin, previous sternotomy, shock, preoperative platelet count, urgency of surgery, age
Pickard et al. 2008 [56]	3,505	Intake of preoperative clopidogrel within 7 days
Ranucci et al. 2009 [57]	8,989	Age >67 years, weight (<60 kg for females and <85 kg for males), preoperative haematocrit, female sex, complex surgery

EF: Ejection fraction; BSA: Body surface area; IDDM: insulin-dependent diabetes mellitus

Large randomized clinical studies demonstrated beneficial antithrombotic effects of clopidogrel prior to percutaneous coronary angioplasty or in combination with acetylsalicylic acid in patients who had experienced a myocardial infarction [58-62]. However, some of these patients may eventually need CABG, and preoperative intake of these drugs within 5–7 days may increase the risk of perioperative bleeding and transfusion [63]. At the same time, patients may also be taking other antithrombotic or antiplatelet drugs such as glycoprotein IIb/IIIa inhibitors, low molecular weight heparins, direct thrombin inhibitors, and non-steroid anti-inflammatory drugs prior to surgery. Discontinuing antithrombotic and antiplatelet drugs in patients with stable angina 3–7 days before elective or urgent surgery is generally recommended to decrease the risk of minor and major bleeding events and transfusion [11, 63-65]. The benefit in reducing perioperative blood loss and thus perioperative transfusion by withholding clopidogrel prior to surgery, however, will be at the expense of a 1% increased risk of myocardial infarction while awaiting surgery [64].

Several procedure-related predictors of bleeding and transfusion are described. Among these are the use of cardiopulmonary bypass (CPB), which exposes blood to artificial surfaces, and mechanical trauma from the pump, time on pump, use of mild or deep perioperative hypothermia, haemodilution, use of bilateral internal mammary arteries, reduced heparin dose, and increased protamine dose after CPB, and the surgeon [11,50,54,55,66-73].

Use of specific blood conservation techniques is often based upon identified risk factors that predispose certain patients to excessive blood loss. Institution-specific protocols should, therefore, screen for high-risk patients as blood conservation interventions are likely to be most effective among these patients.

Little information is available regarding the risk of postoperative bleeding and transfusion requirements following preoperative intake of new antithrombotic drugs and other drugs with antiplatelet effects. Therefore, more clinical and epidemiological studies are needed to identify new predictors of microvascular bleeding, i.e. non-surgical bleeding during cardiac surgery.

## **Potential benefits of red blood cell transfusion in CABG**

Allogeneic blood transfusion may be given to treat life-threatening haemorrhage during surgery, but most often transfusion of blood components is given to increase the oxygen-carrying capacity of the blood or to improve haemostasis. Thus, transfusions are given in an attempt to treat or prevent a potential adverse outcome. There is, however, a lack of clear evidence regarding the benefit of RBC transfusion when it comes to enhancing the oxygen-carrying capacity of blood.

Only a few randomised trials were carried out to identify the potential benefits of RBC transfusion. A randomised, controlled study in 838 critically ill, normovolemic patients in an intensive care unit (ICU) produced equivalent results when the rates of all-cause mortality at 30 days and severity of organ dysfunction when a restrictive strategy of red-cell transfusion, i.e. haemoglobin concentration between 7–9 g/dl (4.4–5.7 mmol/l), was compared with a liberal strategy, i.e. haemoglobin concentration at 10–12 g/dl (6.3–7.5 mmol/l) [74]. The restrictive strategy of RBC transfusion was at least as effective as and possibly superior to the liberal transfusion strategy. The restrictive strategy also appeared to be safe in critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarction and unstable angina [75].

Another randomised study in 428 elective, primary CABG patients found that there were no differences in clinical outcomes, including morbidity and mortality, between two groups of patients assigned to receive RBC transfusion if the postoperative haemoglobin was <8 g/dl (5.0 mmol/l) or <9 g/dl (5.7 mmol/l), respectively [76]. The level of self-assessed fatigue was also similar in the two groups.

A randomised trial in 39 autologous blood donors undergoing elective complete myocardial revascularisation compared two different transfusion strategies for postoperative packed RBC replacement. The liberally-transfused group was transfused to achieve a haematocrit value of 32%, whereas the conservative group received transfusion for a haematocrit less than 25% [77]. A larger degree of haemodilution was not associated with significant incremental risks; however, it should be noted that

the number of patients included in this study was small and the statistical precision of the findings was, therefore, moderate.

A number of database studies in cardiac surgery reported that decreased perioperative haematocrit values is associated with decreased survival. In a study in 6,980 patients undergoing CABG, the lowest haematocrit during CPB was significantly associated with increased risk of in-hospital mortality, intra- or postoperative placement of an intraaortic balloon pump, and return to CPB after attempted separation [78]. Another study found an association between the lowest haematocrit in the ICU and adverse outcome following cardiac surgery [79]. Fang et al. [80] found a significantly increased risk of mortality only when the haematocrit levels decreased to 14%. For high-risk patients, there was a significantly increased risk of mortality for haematocrit levels  $\leq 17\%$ . These results were interpreted as supporting an aggressive effort to avoid haematocrit values  $< 20\%$  during cardiopulmonary bypass [81]. These studies, however, did not look into the effect of transfusions, and low haematocrit values may simply be markers for transfused patients. The adverse outcome in patients with low haematocrit values could potentially be caused by transfusion itself.

No “optimal” haematocrit or haemoglobin concentration is established in cardiac surgery. The classical “10/30” rule, suggesting that transfusion should be given to maintain a haemoglobin concentration of 10 g/dl (6.3 mmol/l) and a haematocrit of 30%, was abandoned several years ago [29,82]. Today, much lower haemoglobin and haematocrit values are accepted. However, there are no clinically available methods for measuring regional tissue oxygenation to identify when there is a need for RBC transfusion. Observational studies among CABG patients, who refused blood transfusions for religious reasons, suggest that survival without transfusion is possible at low haemoglobin concentrations. Mortality is first encountered at haemoglobin concentrations below 5 g/dl (3.1 mmol/l) [80,83].

During the past three decades, traditional transfusion triggers were constantly challenged. Despite published blood transfusion guidelines [4,7,9,11,82,84-86] and reviews on transfusion management in patients undergoing cardiac surgery [8,9, 87-90], there is still no consensus as to when transfusion is needed. Transfusion guidelines only rely on expert opinion and observational studies. General guidelines



from the Danish National Board of Health [12] recommend that transfusion with RBC should depend on the age of the patient, the speed at which anaemia develops, concomitant diseases, and the cause of anaemia. Furthermore, attention should be paid to physiological and clinical indicators of anaemia, i.e. hemodynamic variables such as cardiac index below 2 l/min, tachycardia, oliguria, mixed venous saturation less than 0.60, decreasing cardiac filling pressures, and decreasing systemic and pulmonary blood pressure. The guidelines also indicate that there is no documentation to support RBC transfusion when the haemoglobin concentration is >6 mmol/l, but is almost always indicated when the haemoglobin concentration is <4.5 mmol/l. Every patient should be evaluated individually, especially when the haemoglobin concentration is between 4.5–6.3 mmol/l. Similar guidelines and reviews were published abroad [29-31,91].

The potential benefits of RBC transfusion must be weighed against the risks before any decision to transfuse is made. A review regarding the risks and adverse outcomes following allogeneic RBC transfusion is presented in the next chapter.

### **Adverse outcomes following allogeneic red blood cell transfusion in CABG**

Potential immunological and non-immunological risks related to allogeneic transfusion are well described [12,29-31,92-96]. Traditional infectious risks include hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and bacteria. At the beginning of this century, the calculated risks of transfusion-related viral infections in Denmark were 1:2,000,000 for HIV, 1:500,000 for hepatitis B, and 1:250,000 for hepatitis C [95]. These rates will be further reduced when nucleic acid testing to detect viral DNA is fully established. Other non-immunological risks are acute and delayed haemolytic reaction, bleeding, volume overload, hyperkalaemia, hypocalcaemia, citrate intoxication, cooling of the heart, and iron overload. These adverse effects of transfusion may vary between different countries, especially regarding the risk of viral disease transmission [97].

Since 1999, data on transfusion complications in Denmark are collected and registered in the Danish Register of Transfusion Risks (DART) [98]. DART is part of the Danish haemovigilance system that covers the registration of collected, produced, and transfused blood components, and complications in connection with transfusion of these products. During the first nine years, the report rate to DART concerning severe risk/error in the transfusion chain was 3 per 100,000 components transfused. More than half of the severe events (56%) concerned the transfusion of an incorrect blood component. More than a third concerned immunological complications (38%). Only 6% of the reported events concerned transmitted infections. Five patients died and 47 patients experienced major morbidity [99].

An increasing number of observational studies indicate that allogeneic RBC transfusion during CABG surgery is associated with both early and long-term mortality [100-108], but conflicting results were found among other patient groups. Transfusions seem to have no effect on the long-term mortality rate after isolated valve surgery; however, transfusion is associated with increased mortality when valve surgery is combined with CABG [109]. Studies among patients undergoing surgery for hip fractures showed both increased and no association between transfusion and long-term mortality, respectively [110,111]. In a study in ICU patients, transfusions were associated with improved long-term survival [112]. These findings suggest that the type of surgery may play a role in the outcome following transfusion.

Allogeneic RBC transfusion following cardiac surgery, including CABG, was also reported to be associated with postoperative morbidity, as shown in Table 2. Only a very few studies disagree with these findings [113].

A number of observational studies indicated an association between storage time of RBC and patient outcome, both in cardiac surgery [108,123] and outside the cardiac surgical setting [123-126]. However, this association was not confirmed by other studies, and the strength and causality of this association remain uncertain [127-131]. These differences may be attributed to the heterogeneity of patient populations, transfusion of different blood products, different outcome measures, and different study designs.

Table 2. Postoperative morbidity associated with allogeneic red blood cell transfusion in cardiac surgery

Reference	Number of patients included	Outcome associated with red blood cell transfusion
Michalopoulos et al. 1998 [114]	2,615	Severe sepsis
Leal-Noval et al. 2001 [115]	738	Nosocomial pneumonia
Chelemer et al. 2002 [116]	533	Respiratory and surgical site infection
Koch et al. 2006 [117]	7,321	Reduced health-related quality of life
Koch et al. 2006 [104]	11,963	Renal failure, prolonged ventilatory support, serious infection, cardiac complications, neurologic events
Banbury et al. 2006 [118]	15,293	Septicaemia/bacteraemia, superficial and deep sternal wound infection
Koch et al. 2006 [119]	5,841	Postoperative atrial fibrillation
Rogers et al. 2007 [103]	8,518	Respiratory or wound infection or septicaemia, ischemic outcomes (myocardial infarction, stroke, renal impairment, or failure),
Rogers et al. 2007 [120]	380	Infection, pulmonary dysfunction
Whitson et al. 2007 [121]	2,691	Renal failure, prolonged ventilation time, cardiac arrest, gastrointestinal complications, atrial fibrillation, stroke, myocardial infarction
Scott et al. 2008 [107]	1,746	Increased time to extubation, increased stay in the ICU, and increased postoperative length of stay
Shander et al. 2009 [122]	455	Nosocomial infection (pneumonia, sepsis, urinary tract infection, surgical site infection, catheter-associated bacteraemia, osteomyelitis, septic arthritis, cardiovascular infection)
Koch et al. 2009 [96]	16,847	Pulmonary morbidity

ICU: Intensive Care Unit;

The reason for a potential impact of RBC transfusion on morbidity and mortality is unclear. Well described storage lesions of the blood may be involved [132-136], but there is no clear evidence to support this hypothesis. Typical storage lesions include:

1. Decreased levels of 2,3-diphosphoglycerate (2,3-DPG) reversibly, shifting the haemoglobin-oxygen dissociation curve to the left.
2. Decreased levels of adenosine triphosphate (ATP) associated with morphologic changes of the RBC.
3. The normal biconcave disc shaped form of the RBC swells to form a sphere with multiple spicules, and membrane phospholipids are lost.
4. Loss of deformability of RBC, which may disturb the flow through the microcirculation.
5. Increased adhesion of RBC to the vascular endothelium, which may lead to vascular obstruction.
6. Accumulation of proinflammatory/immunomodulating bioactive substances released from leucocytes to the storage medium.

Laboratory studies in rats indicate that transfusion does not improve oxygen delivery to tissues [137,138]. However, studies in rats are of limited relevance in relation to humans because of the faster aging of rat RBC, and the failure of stored RBC from rats to regenerate 2,3-DPG like human RBC can [139]. An association between a decrease in gastric intramucosal pH and the age of transfused blood among patients with sepsis was interpreted as development of splanchnic ischemia [140]. In contrast, transfusion of stored leucocyte-depleted RBCs caused no clinically significant adverse effects on gastric tonometry or global indexes of tissue oxygenation among euvoletic, critically-ill patients randomised to receive fresh ( $\leq 5$  days) versus older ( $\geq 20$  days) blood [141].

The immunosuppressive effects of allogeneic blood transfusion were accepted as an explanation for enhanced renal graft survival in the 1970s [142] and the immunological effects of allogeneic blood may be a part of the explanation for an increased risk for infectious post-transfusion outcomes, although any definitive mechanism has not yet been proven.

Randomised controlled studies in cardiac surgery indicate that transfusion with white blood cell (WBC)-reduced RBC units, compared with standard buffy-coat-reduced RBC transfusion, results in

lower postoperative infection and mortality rates [143-146], while other studies found no such effect [106,147-149]. This difference between studies may be a consequence of different amounts of WBCs in the non-WBC reduced blood products.

Since there is no clear evidence to support the view that transfusion actually improves patient outcome in all situations during CABG, surgeons and anaesthesiologists need further information from studies on transfusion outcome to balance the potential benefits and risks of allogeneic RBC blood transfusion.

### **Blood conservation during cardiac surgery with special reference to use of antifibrinolytic drugs**

Blood conservation during cardiac surgery is used to reduce bleeding and allogeneic blood transfusion. Reviews of recommendations for multimodal blood conservation programs are comprehensive [11,150]. Available techniques include screening for risk factors associated with bleeding, use of drugs to increase the preoperative blood volume or to decrease postoperative bleeding, devices that conserve blood (e.g. intraoperative cell saving and postoperative reinfusion of shed mediastinal blood), interventions that protect the patients' own blood from the stress of the operation, and from CPB (e.g. intraoperative normovolemic haemodilution). Most important is a multimodal approach because of the multifactorial causes of bleeding.

Among frequently used techniques for blood conservation are pharmacological strategies. Antifibrinolytic drugs have been used for almost two decades. Several reviews, including meta-analyses and Cochrane reviews, were published [151-158]. Two drugs were used equally frequently in Denmark [159]: the synthetic lysine derivate tranexamic acid (TA), and the bovine-derived aprotinin. TA acts mostly by competitive inhibition of the lysine binding sites in plasminogen, resulting in retardation of fibrinolysis [160]. Aprotinin, a serine protease inhibitor, mostly acts by inhibiting plasmin, resulting in attenuation of fibrinolysis [157]. The effects of TA and aprotinin were investigated in a large number of randomized trials. Both drugs are effective in reducing postoperative bleeding and the need for blood transfusion [153,156,158]. However, an observational study [161] in 2006 reported an association

between aprotinin and an increased risk of renal failure, myocardial infarction, heart failure, and stroke. Furthermore, a large, randomized, multicenter study in 2007 was terminated before the last patient was enrolled because of a higher death rate in high-risk patients receiving aprotinin compared with TA and aminocaproic acid [162]. In addition, aprotinin may increase the risk of saphenous vein graft occlusion in CABG [163]. Aprotinin was, therefore, withdrawn from the market in November 2007, although some investigators report that it remains a matter of speculation whether the quality and results of published data justify the withdrawal of aprotinin [164].

## **Aims and Hypotheses**

This PhD thesis deals with allogeneic RBC transfusion during CABG with special reference to predictors of transfusion, transfusion variability, outcome following transfusion, and perioperative blood conservation. The general objective of this PhD thesis was to perform four independent but related studies, which when combined will serve as an example of a multimodal approach to blood conservation during CABG. The goal was to provide institution-specific and new information to create a background for optimizing transfusion practices and the use of blood conservation techniques, thus avoiding unnecessary transfusions.

The specific aims of the individual studies were:

1. To examine whether perioperative use of prophylactic TA decreases chest tube drainage and the proportion of patients undergoing primary, elective, on-pump CABG who require perioperative allogeneic blood transfusion.
2. To audit transfusion practices during CABG in Denmark to compare transfusion practices among patients undergoing first-time CABG at different hospitals.
3. To examine whether transfusion requirements were increased in patients undergoing CABG following preoperative use of selective serotonin reuptake inhibitors (SSRIs) compared with other antidepressants.

4. To determine whether storage-time of transfused allogeneic RBC is associated with severe postoperative infections (deep sternal wound infection, bacteraemia and septicemia) among patients undergoing CABG.

Specific hypotheses were tested in four different studies (I–IV), corresponding with the papers listed previously (page 5):

1. Perioperative infusion of TA during CABG will decrease postoperative bleeding and the proportion of patients requiring perioperative allogeneic blood transfusions.
2. Allogeneic RBC transfusion rates in isolated first-time CABG vary among Danish public hospitals, and institution is an independent predictor of the use of blood products. The transfusion rate is higher in Aalborg Hospital compared with other centres in Denmark.
3. Requirements of allogeneic blood transfusions are increased in patients undergoing CABG following preoperative use of SSRIs.
4. Increased storage time ( $\geq 14$  days) of allogeneic RBC is associated with increased risk of severe postoperative infections following transfusion among patients undergoing CABG.

## **Methodology, materials and methods**

Detailed descriptions of materials and methods for each study included in this thesis can be found in the respective papers (I–IV). A summary is provided below.

### **Methodology**

The studies for this PhD thesis evolved as a part of continuing efforts to optimize the use of blood-sparing techniques, including transfusion practices in the Department of Cardiothoracic Surgery, Aalborg Hospital, Aarhus University Hospital.

The initial study (Study I) was a randomized study comparing perioperative infusion of TA and placebo to determine the efficacy of TA in decreasing chest tube drainage and the proportion of patients requiring perioperative allogeneic transfusions during primary elective CABG using CPB. The decision to perform this study was made because no perioperative drugs were routinely in use to inhibit fibrinolysis, although recurrent bleeding problems were observed in the patients. Because the effect of perioperative infusion of TA in Study I was disappointing compared with results from abroad, a comprehensive multimodal approach to blood conservation during cardiac surgery was instituted to create further institution-specific knowledge about transfusion practices and use of blood conservation techniques. Three additional studies (Studies II, III, and IV) were planned and carried out to improve the knowledge in the field.

Information from the Danish Transfusion Database indicated a liberal use of blood products in the Northern Region of Denmark. Therefore, a study (Study II) of transfusion practices in Denmark during CABG was commenced to better understand the factors that determine the use of blood products. Study III was initiated because previous studies showed that intake of SSRI, which inhibit PLT function [165,166], was associated with an increased risk of bleeding events, including bleeding and a subsequent need for blood transfusion during orthopaedic surgery [167-170]. Increasing use of new drugs inhibiting PLT, for example, may change the risk profile of patients, and Study III serves as an example of a study evaluating potential new drug-related risk factors related to bleeding and transfusion during cardiac surgery. No previous studies on the potential association between preoperative intake of SSRIs and transfusion requirements in cardiac surgery had been performed. Finally, a study (Study IV) on potential adverse outcomes following transfusion of RBC during CABG was performed. This study was based on a possible association between RBC transfusion and the development of severe postoperative infections. This study was highly relevant because periodic problems with postoperative deep sternal wound infections in our department were observed without obvious explanation.

Denmark was chosen as the unit of analysis in Study II for three theoretical reasons: firstly, there are only a few cardiothoracic centres in Denmark (five public university-affiliated units); secondly, most of



the surgeons, especially the senior surgeons, were educated in the same way through residencies in one or two of the major centres in Denmark (Rigshospitalet and/or Skejby Hospital); and finally, the patient population is very comparable and homogeneous because of the relatively small geographical area of Denmark.

Studies III and IV were population-based observational cohort studies based on data from Danish medical registries. These study designs were chosen because the possibility to perform such studies is unique in Denmark because the entire population is provided with tax-supported health care by the National Health Services. This guarantees free access to family physicians and public hospitals. Refunds are available for a variable proportion of the costs of drugs prescribed by physicians. The unambiguous linkage between population-based registers and clinical databases can be performed using the civil registry number, which is a unique permanent personal identification number given to all Danish citizens. The study units in Studies III and IV were located in two Regions in the North-Western part of Denmark because of the availability of data from unique prescription databases and microbiological databases maintained in the regions.

Several other aspects regarding perioperative blood transfusion and blood conservation in CABG related to this thesis could have been undertaken. The studies included were initiated because of ongoing clinical challenges and new questions that arose at the time the studies were commenced.

### **Ethical and legal issues**

All studies were conducted according to the guidelines of the Danish National Committee on Biomedical Research Ethics and the randomized study (Study I) was approved by the local Ethics Committee. Informed written consent was obtained from all patients included in Study I. All epidemiological studies (Studies II, III, and IV) were approved by the Danish Data Protection Agency and all studies complied with current Danish law.

## **Materials and methods**

### **Study populations**

#### Study I

The study population consisted of 46 consecutive adult patients undergoing primary, elective, on-pump CABG at Aalborg hospital. Exclusion criteria included treatment with non-steroidal anti-inflammatory drugs such as acetylsalicylic acid or other PLT inhibitors within 7 days prior to surgery, preoperative heparin administration, a history of coagulopathy, thrombocytopenia (PLT count  $<50 \times 10^9/l$ ), preoperative haemoglobin  $<6.0$  mmol/l, serum creatinine  $>115$   $\mu\text{mol/l}$ , pregnancy, and patients who refused transfusions for religious reasons.

#### Study II

We intended to include patients who underwent first-time CABG during 2004 in all public, university-affiliated hospitals in Denmark because these hospitals were comparable with regard to the staff and other resources. Skejby Hospital was, however, unable to participate in the study; therefore, the study was carried out in only four hospitals (Aalborg Hospital, Rigshospitalet, Gentofte Hospital, and Odense University Hospital). A total of 600 patients (150 consecutive patients from each hospital) were included.

#### Study III

This study was conducted within the population of the Northern and Central Denmark Regions. These regions comprise approximately 1.8 million persons or 33% of the total population of Denmark. All patients undergoing CABG, with or without concomitant cardiac surgery, at either Aalborg (January 1, 2000 to December 31, 2003) or Skejby Hospital (January 1, 1998 to December 31, 2003) were included in the study. Patients whose address was outside the regions referring patients to the two hospitals or who had lived within the regions for less than one year were excluded to ensure that data regarding the use of antidepressants and blood transfusions were available. A total of 3,516 patients

were identified. Of these, 62 patients (1.8%) had filled prescriptions for more than one type of antidepressant before the day of admission for CABG. These patients were excluded from the study, leaving 3,454 patients in the final analyses.

#### Study IV

This study was also conducted within the populations of the Northern and Central Denmark Regions. We identified 4,279 patients who underwent CABG, with or without concomitant cardiac surgery, in either Aalborg or Skejby Hospital during the study period (June 2, 2003 to July 31, 2008). Thirty-four patients were excluded because they died within 48 hours postoperatively. These patients were defined as not being at risk of developing severe postoperative infection (deep sternal infection and bacteraemia/septicaemia), which was the primary outcome of interest. Furthermore, five patients were excluded due to missing data regarding the body mass index of the patients, leaving 4,240 patients available in the final analyses.

#### **Study designs**

##### Study I

This was a double-blind, placebo-controlled trial. Patients were randomized to one of two groups. The randomization schedule was based on a random number sequence provided in sealed envelopes. Randomization and preparation of the drug/placebo was carried out just prior to anaesthesia by a staff member not involved in the treatment of the patient. One group received TA 1.5 g as a bolus, followed by a constant infusion of TA 200 mg/hour until 1.5 g was administered. The other group received placebo (0.9% saline). Routine anaesthesia, surgical, and perfusion techniques were employed. Indications for perioperative transfusion of allogeneic RBC were a haematocrit below 22% and/or mixed venous blood saturation below 65%. Allogeneic packed RBC (buffy-coat reduced RBC units) were transfused postoperatively if the haematocrit was below 25% and the mixed venous blood saturation was below 60%. Primary outcome measures were postoperative blood loss and the

proportion of patients requiring allogeneic transfusion. The postoperative chest tube output from 0–6 hours and 0–12 hours was registered.

## Study II

A retrospective review of consecutive medical records was performed. Patients were identified through the local hospital discharge registries. Pre-, peri-, and postoperative data were collected on paper forms directly from the patient records and keyed into a database afterwards. The crude and adjusted relative risks (RR) with 95% confidence intervals (CI) for transfusion requirements were calculated to compare these outcomes between hospitals. The RRs were adjusted for several possible confounding factors related to bleeding and transfusion.

## Study III

This study was a population-based cohort study. Patients were identified through the hospital discharge registries. Linkage between various registries and databases was performed using the unique civil registration number of each patient to retrieve pre-, peri-, and postoperative data. Other registries and databases used were the Central Population Registry, which has electronic records of any change of address, date of emigration, and date of death for the entire Danish population since 1968, the Danish National Hospital Registry [171], the Danish Transfusion Database, which monitors the use of blood components in Denmark ([http://www.dtdb.dk/default\\_eng.aspx](http://www.dtdb.dk/default_eng.aspx)), and prescription databases maintained in the counties [172]. All data were retrieved electronically and transferred to a study database for further analyses.

Patients were classified according to their most recent antidepressant use and as having received either none or at least one unit of any blood component. The potential association between preoperative intake of antidepressives, including SSRIs, and perioperative transfusion requirements was evaluated by calculating the RRs with 95% CIs, adjusting for several possible confounding factors.

## Study IV

This study was also a population-based cohort study. Patients were identified through the Western Denmark Heart Registry, which keeps track of all examinations and treatments regarding patients admitted for adult cardiac surgery in the western part of Denmark. Other registries and databases used were the Danish National Hospital Registry, local transfusion databases at the hospitals, local clinical biochemical databases in the central laboratories of the hospitals, the North Denmark Bacteraemia Research Database [173], and a similar local clinical microbiological database in Skejby Hospital. In case of missing electronic records, the variables were obtained manually from the medical records when possible. The association between allogeneic RBC transfusion and the development of severe infections (deep sternal wound infection and bacteraemia/septicaemia) within 90 days was evaluated, adjusting for available possible confounding factors. Stratified analyses according to transfusion and storage time of RBC were carried out, comparing crude and risk-adjusted odds ratios (OR) with 95% CI for the development of severe infection following transfusion of RBC stored for <14 days and  $\geq 14$  days using the OR for the non-transfused patients as the reference group. An evaluation of a possible risk-adjusted dose-response relationship between the number of transfused RBC units and the development of severe infection was also performed.

## Statistical methods

The statistical analyses varied in the different studies (I–IV). Descriptive statistics included mean, standard deviation, median, interquartile range, and percentage when appropriate. Groups were compared using *t*-tests, Wilcoxon's rank sum tests, or Mann-Whitney *U* test for continuous variables, and chi-squared tests or Fisher's exact tests for categorical variables. When more than two groups were compared (Study II), differences between groups were tested for statistical significance using chi-squared tests, analysis of variance, and in case of non-normality, Kruskal-Wallis tests. Sampling distributions regarding the use of blood products were not normally distributed; therefore, nonparametric statistical methods were used in these situations. Poisson regression with robust

variance was used to compare the use of allogeneic blood transfusion between the hospitals in Study II. Specifically, the RRs with 95% CI were computed for a requirement of  $\geq 1$  allogeneic blood transfusion. Poisson regression was used in Studies II and III because, in contrast with logistic regression, it may provide a more accurate estimate of adjusted RRs in cohorts with common outcomes [174]. RRs were adjusted for potential confounding factors. In Study IV, logistic regression was used to compute the OR with 95% CI.

A sample size calculation using a statistical software program (MEDSTAT, version 2.1, January 1998, Astra-gruppen A/S, Copenhagen) was carried out prior to Study I, although this was not described in the published paper. It was calculated that 46 patients should be included in the study. This number was based upon a probability of type I error ( $\alpha$ ) of 0.05, a probability of type II error ( $\beta$ ) of 0.1, an expected standard deviation of 0.1 l, and a clinically important minimal detectable difference of postoperative chest tube drainage of at least 10% (i.e. 100 ml). A  $P$ -value  $< 0.05$  was defined as the level of significance that would lead to rejection of the null hypothesis,  $H_0$ . The probabilities of the two errors  $\alpha$  and  $\beta$  can be described as  $\alpha = P(\text{reject } H_0 | H_0 \text{ is true})$  and  $\beta = P(\text{fails to reject } H_0 | H_0 \text{ is false})$ .

Several other different statistical software packages were also used; SPSS statistical software version 10 (SPSS Inc, Chicago, IL), Microsoft® Excel 2000, SAS version 8.00 (SAS Institute Inc., Cary, North Carolina, USA), and Stata Statistical Software versions 9.1 and 10.1 (Texas, USA, StataCorp LP).

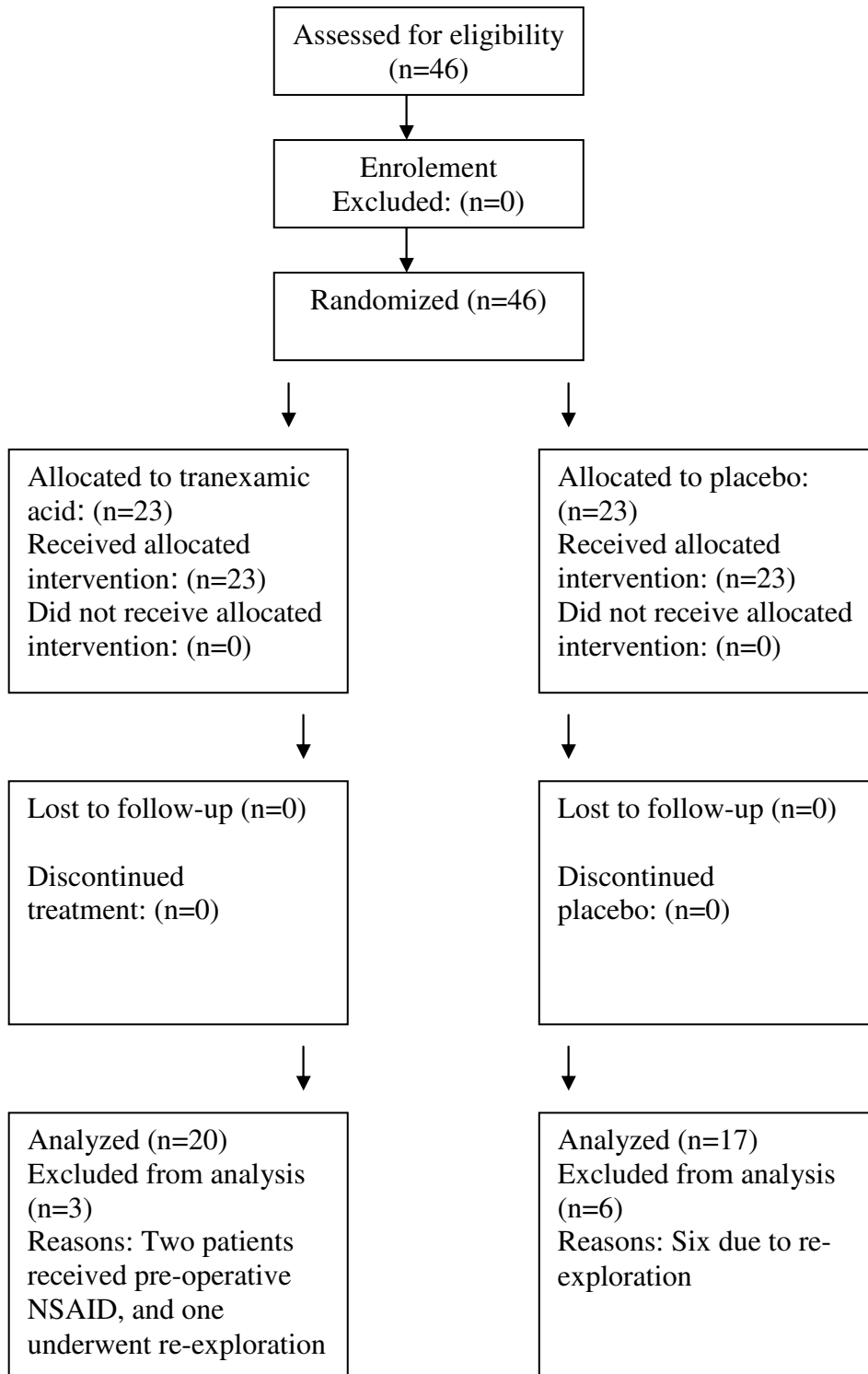
## Summary of results

### Study I

The flow chart for Study I is shown in Figure 1. The flow diagram depicts information from all four stages of the trial, i.e. enrolment, intervention allocation, follow-up, and analysis.

Patients who underwent reoperation because of bleeding were excluded from the analyses regarding chest tube output to reduce the risk of confounding by surgical bleeding. Seven patients (15%), one in the TA group and six in the placebo group, were reoperated due to excessive bleeding. Surgically-correctable bleeding was found in all but two patients in the placebo group.

Figure 1. Flowchart for Study I.



An antifibrinolytic effect following prophylactic use of TA during elective, primary CABG among patients with a low risk of postoperative bleeding was confirmed by plasma concentrations of D-dimer. Although blood loss at 6 and 12 hours postoperatively was higher in the placebo group compared with the TA group, the differences did not reach statistical significance (Table 3).

Table 3. Postoperative blood loss and transfusion requirements among patients undergoing first-time, elective coronary artery bypass grafting

Variable	Tranexamic acid n = 20	Placebo n = 17	<i>P</i> -value
Chest tube drainage, 6 hours (ml)	400 (366 – 550)	710 (460 – 950)	> 0.05
Chest tube drainage, 12 hours (ml)	730 (510 – 890)	880 (610 – 1500)	> 0.05
Autotransfusion of unwashed, shed mediastinal blood, 6 hours (ml)	300 (250 – 450)	600 (400 – 700)	> 0.05
Patients receiving any allogeneic transfusion postoperatively	6 (30%)	5 (29%)	> 0.05

Data are presented as the median and interquartile range or as number and % of patients.

The proportions of patients who received allogeneic blood transfusions postoperatively were not significantly different between the groups. There was one early sudden death in the treatment group after an initially uneventful postoperative course. No patients experienced postoperative renal insufficiency, myocardial infarction, mediastinal infection, transient ischemic attack, or stroke within 30 days.

## Study II

Baseline characteristics of the included patients were comparable between the participating hospitals except for the proportion of patients receiving surgery without discontinuing platelet inhibitors



(acetylsalicylic acid and clopidogrel) preoperatively. Perioperative differences were the frequency of off-pump techniques used, use of antifibrinolytic drugs, and lowest haemoglobin level during CPB. The percentage of patients transfused with allogeneic RBC varied from 30.0% to 64.2%, and the adjusted RR of receiving allogeneic RBC was more than twofold higher (RR: 2.1; 95% CI: 1.6 – 2.7) in the hospital with the highest transfusion rate (Hospital 1 = Aalborg Hospital) compared with the reference group (Table 4). “Hospital” was an independent predictor of allogeneic blood transfusion. The percentage of transfused patients discharged with a haemoglobin concentration >7 mmol/l, indicating unnecessary transfusions, varied between 12.1–42.7%.

Table 4. Crude and adjusted relative risks (RR) with 95% confidence intervals (CI) for allogeneic red blood cell transfusion among patients undergoing first-time coronary artery bypass grafting according to institution.

Hospital	Crude RR (95% CI)	Adjusted RR (95% CI)
1 (Aalborg)	2.2 (1.6 – 2.9)	2.1 (1.6 – 2.7)
2	1.3 (0.9 – 1.8)	1.1 (0.8 – 1.6)
3	1.6 (1.1 – 2.2)	1.7 (1.3 – 2.3)
4	1.0 (Reference)	(Reference)

RRs were adjusted for EuroSCORE, preoperative haemoglobin, preoperative platelet count, INR (international normalized ratio), preoperative use of antiplatelet drugs, use of antifibrinolytic drugs, use of CPB, CPB time, cross-clamp time, and number of distal anastomoses.

### Study III

Overall, 2,322 patients (67%) required allogeneic blood transfusion. In comparison, 2,015 of 3,025 (67%) patients who never used antidepressants required allogeneic transfusion. Similar results were found when the analyses were restricted to specific types of blood components, i.e. RBC, fresh frozen plasma (FFP), and PLT.

The number of transfusions required by patients who received blood transfusion did not differ substantially according to the use of antidepressants. The crude and adjusted RRs for transfusion

requirements with 95% CIs according to use of antidepressants are shown in Table 5. No increased requirements for blood transfusion were found, either among former users of SSRIs or among current users of non-selective SRIs and other antidepressants. The haemoglobin levels at the time of discharge did not vary among transfused users of the various types of antidepressants. The risk of re-operation due to bleeding did not appear to be associated with use of antidepressants, including use of SSRIs, and we found no clear associations between use of antidepressants and 30-day mortality.

Table 5. Crude and adjusted relative risks (RR) with 95% confidence intervals (CI) for allogeneic blood transfusion among patients undergoing coronary artery bypass grafting according to use of antidepressants.

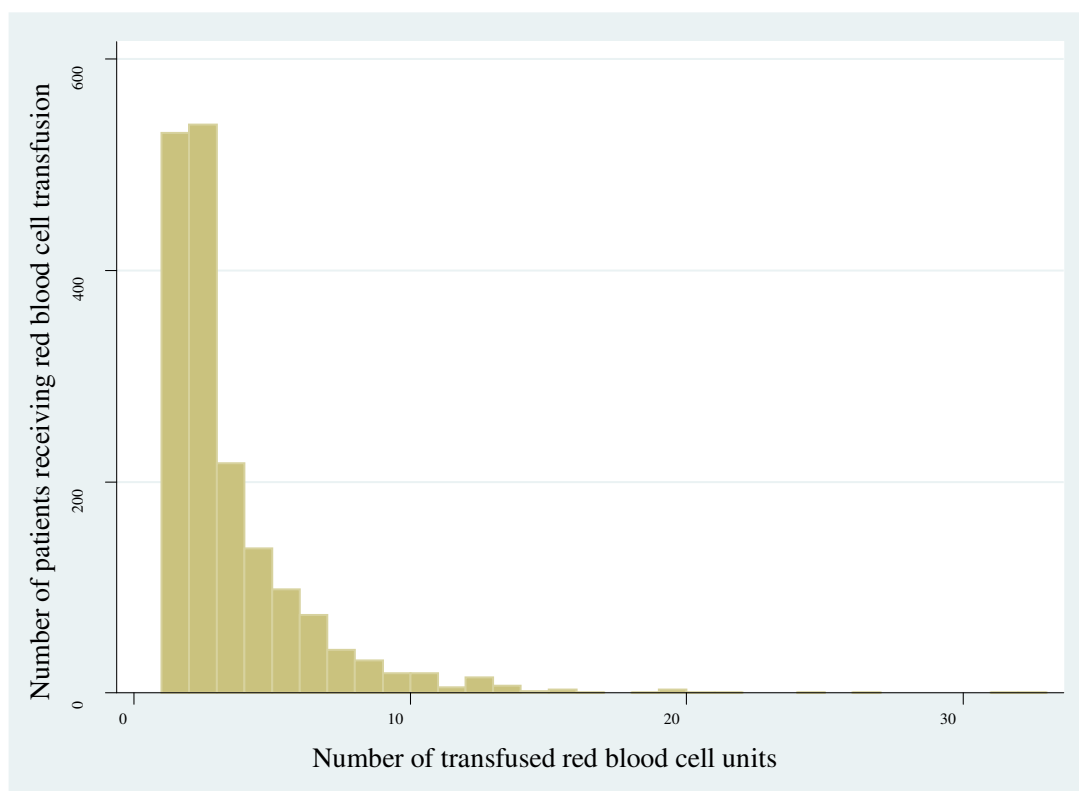
Category of use	Patients (n = 3,454)	Patients requiring transfusion (n = 2,322)	Crude RR (95 % CI)	Adjusted RR (95 % CI)
Never user	3,025	2,015	1.0 (reference)	1.0 (reference)
<b>SSRI:</b>				
-Current user	124	94	1.2 (0.9–1.4)	1.1 (0.9–1.3)
-Former user	133	90	1.0 (0.8–1.3)	1.0 (0.8–1.2)
<b>Non-selective SRI:</b>				
-Current user	40	25	0.9 (0.6–1.4)	0.9 (0.6–1.3)
-Former user	54	43	1.2 (0.6–1.6)	1.2 (0.9–1.6)
<b>Other antidepressants:</b>				
-Current user	37	27	1.1 (0.7–1.6)	1.0 (0.7–1.6)
-Former user	41	28	1.0 (0.7–1.5)	0.9 (0.6–1.4)

Category of use was defined as: Never user (no recorded prescriptions for any type of antidepressants before the day of admission for CABG), current users (filled a prescription within 0–90 days before the day of admission for CABG), and former users (filled a prescription >90 days before the day of admission for CABG). Persons using more than one category of antidepressants were excluded (n=62). SSRI, selective serotonin reuptake inhibitor; RRs were adjusted for age, sex, preoperative use of platelet inhibitors (low-dose aspirin, clopidogrel, and dipyridamole), nonsteroidal anti-inflammatory drugs and oral anticoagulants, place of surgery (Aalborg/Skejby), use of CPB, concomitant valve surgery, and Charlson comorbidity index.

#### Study IV

A total of 1,748 patients (41%) were transfused with allogeneic RBC. Figure 2 shows the number of RBC units transfused during CABG to the patients included in Study IV.

Figure 2. Number of red blood cell units transfused to each of 1,748 patients undergoing coronary artery bypass grafting, with or without concomitant cardiac surgery, at Aalborg and Skejby Hospitals.



More than half of the transfused patients received 1–2 units of RBC. The mean storage time of the RBC was 14.0 days (range, 1–35 days). A total of 165 patients (3.9%) developed severe postoperative infections. Deep sternal wound infection was identified in 96 patients (2.2%). Twenty-one of these patients (1.2%) also experienced septicaemia/bacteraemia, and 69 patients (2.1%) developed septicaemia/bacteraemia without deep sternal wound infections. Allogeneic blood transfusion was associated with an increased risk of developing severe postoperative infection compared with non-transfused patients (OR 1.6%; 95% CI: 0.9–2.8). However, patients who were exclusively transfused with RBC stored for  $\geq 14$  days were 2.5 times more likely to develop severe infections compared with those who were not transfused (Table 6). In contrast, transfusion with blood stored for  $< 14$  days was not

associated with any substantial increased risk of severe infection. There was a risk-adjusted, dose-response relationship between the number of transfused RBC units and the risk of developing severe infections. The crude risk of severe infection was increased by 17% for each transfused unit of RBC among patients who were transfused exclusively with RBC stored for  $\geq 14$  days (OR 1.17; 95% CI: 1.07–1.27). After adjusting for confounders, the risk was increased by 23% (OR: 1.23; 95% CI: 1.11–1.35) for each transfused unit. The dose-response relationship was weaker among patients exclusively transfused with RBC stored for  $<14$  days (adjusted OR: 1.09; 95% CI: 1.01–1.17).

Table 6. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) for the development of severe postoperative infection according to transfusion and storage time of red blood cells.

	All patients (n=4.240)	Patients developing severe infection (n=165)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Non-transfused	2.492	55	1.0 (reference)	1.0 (reference)
Transfused (red blood cells)	1.748	110	3.0 (2.1-4.1)	1.6 (0.9-2.8)
Storage time only $< 14$ days	953	44	2.1 (1.4-3.2)	1.2 (0.6-2.4)
Storage time only $\geq 14$ days	548	38	3.3 (2.2-5.0)	2.5 (1.2-5.4)

The ORs were adjusted for age, sex, body mass index, preoperative haemoglobin concentration, diabetes mellitus, reoperation due to bleeding, use of CPB, concomitant valve surgery, hospital of surgery, Charlson comorbidity index, number of transfused RBC units, number of transfused PLT units, ABO blood group of the patient, and minor and major ABO-incompatibility of PLT transfusions.

## **General discussion in relation to existing literature**

The value of a multimodal approach to blood conservation was pointed out by several investigators [11,175,176], supporting the fundamental idea of conducting four different but related studies for which this thesis serves as an example of a multimodal approach to blood conservation in CABG.

Study I showed that perioperative prophylactic use of TA in patients undergoing elective, primary on-pump CABG with a low risk of postoperative bleeding reduced postoperative bleeding, but the results did not reach statistical significance compared with placebo. Furthermore, transfusion requirements were not reduced. These findings highlight the need for a multimodal approach to blood conservation because prophylactic use of TA does not eliminate bleeding by itself.

Study II showed that variation in the use of allogeneic RBC transfusion during CABG between Danish hospitals could not be explained by patient- or procedure-related factors alone, but reflects real hospital-related differences in transfusion practices.

Study III focused on preoperative intake of SSRIs as a possible predictor for transfusion, but no clear association between preoperative use of antidepressants, including SSRIs, and the requirement for an allogeneic blood transfusion was identified.

Study IV showed that transfusion of allogeneic RBC was associated with a 1.6-fold increased risk of developing severe postoperative infections following CABG compared with non-transfused patients. Patients who were transfused exclusively with RBC stored for  $\geq 14$  days were 2.5 times more likely to develop severe infections compared with non-transfused patients. In contrast, no substantial increased risk was observed following transfusion exclusively with RBC units stored for  $< 14$  days. Although Study IV was an observational study with all the inherent risks of confounding with this kind of study, these results should alert surgeons and anaesthesiologist that allogeneic RBC transfusions may put patients at risk. Potential risks and the potential adverse outcomes following transfusion should be weighed against the potential benefits in every patient.

## Antifibrinolytic prophylaxis for patients undergoing CABG

Aprotinin was still on the market for cardiac surgery when Study I was commenced. TA was studied instead of aprotinin because aprotinin was more expensive and carried a risk of anaphylactic reactions [177]. Furthermore, a meta-analysis showed that there were insufficient data to conclude that aprotinin treatment would result in a better clinical outcome compared with TA [153].

Perioperative use of TA reduced postoperative bleeding in Study I compared with placebo as in most other studies [156,158], but the difference did not reach statistical significance. Differences in patient populations, dosing regimen, and the contemporary use of other kinds of blood conservation methods may have contributed to this discrepancy. We studied a group of low risk patients, but when this was taken into account most other studies still reported a statistically significant reduction in bleeding and transfusion requirements following prophylactic use of TA [178-183], with the exception of the results from another small study [184]. Based on the large volume of research showing that perioperative use of TA reduces postoperative bleeding, it is reasonable to assume that the findings in Study I may be explained by a type II error. A statistically significant reduction in bleeding following prophylactic use of TA would probably have been observed if more patients had been included in the study.

Inadequate surgical haemostasis may also have influenced the results, because the re-exploration rate due to excessive bleeding was extremely high (15%), exceeding published re-exploration rates between 2.6 – 6.6% following CABG [2,73,185,186]. Moreover, the total blood loss among patients included in Study I tended to be higher than the reported blood loss in other studies among comparable patients [180,181]. The findings from Study I indicate that meticulous efforts to achieve surgical haemostasis in a surgical department with a high re-exploration rate may be more rewarding than the use of TA by itself.

Another explanation for the findings in Study I could be related to a risk of inadequate dosing of TA. Most studies administered TA on a weight-dependent basis, and several dosing regimens are reported [187]. Initial doses often vary from 10–100 mg/kg prior to sternotomy followed by a typical maintenance infusion of  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for different time periods thereafter. However, the dosing regimen in Study I

exceeded the minimum recommended doses for prophylactic administration of TA in all patients [188], making it less likely that insufficient plasma concentrations of TA explain the negative findings in Study I.

We employed strict transfusion criteria in Study I, and found no differences in transfusion requirements when patients who received TA were compared with those who received placebo. Transfusion requirements were, however, secondary outcome measures, and the study was not powered to study any decrease in blood products used. Furthermore, transfusion requirements are not directly related to the effect of TA alone, since indications for transfusion are based on both subjective and objective measures. It is quite possible that simple changes in transfusion practices may lead to as much a reduction in the use of allogeneic blood products as any pharmacological strategy. Transfusion rates in Study I may have been reduced if indications for postoperative transfusion had been individualized.

The benefits of TA must be weighed against the risk of complications, because of the theoretical risk of thrombotic events occurring with the use of antifibrinolytic drugs. However, meta-analyses and other reviews found no evidence for increased risks of myocardial infarction, stroke, or venous thrombo-embolism following prophylactic use of TA [153,156,158]. Randomized studies on vein graft patency following prophylactic use of TA are scarce [189,190]. Administration of TA before CPB in a randomized study in 312 patients undergoing CABG did not compromise early venous graft patency rates [190]. No patients in Study I suffered from confirmed thrombo-embolic events within 30 days, but the study was not powered to evaluate such complications.

### **Transfusion variability in CABG**

Because randomized studies comparing RBC transfusion with no transfusion were never conducted to evaluate the potential benefits of allogeneic blood transfusion, all transfusion algorithms and guidelines are based on the lowest level of evidence, i.e. expert opinion. Consequently, huge variations in transfusion practices in relation to CABG were described during the past two decades [1,13-16,191-193]. Study II showed that transfusion variability also exists among public centres performing cardiac surgery

in Denmark. Considerable differences were seen among low-risk patients, even after adjusting for potential confounding factors. Several unnecessary RBC transfusions were administered in all the centres, reflecting the overall high transfusion rate in Denmark.

Methods for transfusion audits and the monitoring of transfusion practices using information technology and electronic registers are described [194-196]. These methods allow handling of large amounts of data. In Study II, we collected data manually from the patient records because the sample size was manageable, and because some clinical data, e.g. preoperative discontinuation of antiplatelet drugs, use of antifibrinolytic drugs, and information regarding the lowest perioperative haemoglobin concentration during CPB, were not available in existing databases.

Study II indicated that “hospital” was an independent predictor of allogeneic blood transfusion and this calls attention to the fact that transfusion practices need to be optimized.

### **Predictors of allogeneic red blood cell transfusion**

Large amounts of blood are consumed by patients undergoing cardiac surgery. Patients undergoing CABG are estimated to consume 20% of the blood supply worldwide [1,197]. A high risk group of patients (10–20%) consume 80% of the RBC transfused during cardiac surgery [11,150]. Cardiothoracic surgery accounts for 5.5% of the RBC transfusions in England [198]. RBC transfusion rates of 29–64% were observed at Aalborg Hospital in the study populations investigated in Studies I–IV. Therefore, it is important to be aware of predictors of bleeding and transfusion in order to identify high-risk patients preoperatively, so the appropriate blood conservation techniques can be applied in these patients. Valid clinical tools to predict the need for blood transfusion in patients undergoing cardiac surgery were developed [48,199].

Study II showed “hospital” to be an independent predictor of allogeneic RBC transfusion in Denmark after adjusting for several confounders, supporting the hypothesis of the study. This is in accordance with findings in studies from abroad, because institution was found to be an independent predictor of transfusion in several other studies, even those with transfusion rates lower than in Denmark



[191]. It is reasonable to assume that these differences are indicators of differences in traditions and norms, although differences in surgical techniques and the use of blood conservation techniques may also play a role.

New predictors of bleeding and transfusion may be identified. Study III investigated, for the first time in cardiac surgery, the potential association between preoperative intake of SSRI and transfusion requirements. Transfusion was used as a surrogate marker for bleeding. We expected to find increased transfusion rates following preoperative intake of SSRIs because SSRIs have an antiplatelet effect. However, the results of Study III did not support this hypothesis. A recent observational, multicenter study in 1,380 adults who received antidepressants before CABG in the USA is in agreement with these findings [200]. It is therefore reasonable to assume that the antiplatelet effect of SSRIs is too weak to play any significant clinical role in patients undergoing CABG with regard to bleeding and transfusion.

Study III adds important knowledge about the safety of SSRIs in patients undergoing CABG, which is of great value in relation to the well described association between depression and coronary artery disease [201,202]. Taking into account that depression was linked to an increased risk of poor outcome among patients with coronary artery disease [170, 203,204], the results of Study III do not support discontinuing ongoing SSRI treatment or other antidepressants prior to CABG. More studies are needed to investigate whether preoperative intake of SSRIs is associated with an increased risk of bleeding among subgroups of high-risk patients.

### **Severe infectious outcomes following allogeneic RBC transfusion**

Surgeons and anaesthesiologists should be aware of the risk of adverse outcomes following transfusion, particularly when the benefit of allogeneic blood transfusion is uncertain. The results from Study IV showed an association between the transfusion of RBC units and the development of severe postoperative infection, in agreement with several previous studies in patients undergoing cardiac surgery [16, 104-107,115,116,118]. More interesting was the dose-dependent increased risk of developing severe

postoperative infections following transfusion of RBC units stored for  $\geq 14$  days. This association was much weaker in patients transfused exclusively with RBC stored for  $< 14$  days.

A few studies indicated that storage time of allogeneic RBC may be an important determinant of transfusion-related postoperative morbidity and mortality during cardiac surgery, but substantial uncertainty remains since the available data are still sparse and inconsistent [108, 129-131]. The results of Study IV agree with results from a previous observational study in which 3,130 cardiac surgical patients were transfused exclusively with blood stored for  $> 14$  days, and 2,872 patients were transfused exclusively with blood stored for 14 days or less [108]. Multivariable logistic regression with propensity-score methods showed an increased risk of a composite of postoperative complications, including septicaemia following transfusion of RBC stored for  $> 14$  days.

Although Study IV and other observational studies may be criticised because of the inherent risks of residual confounding, results from observational studies are still the next best research design following randomized studies, and results from randomized trials are not yet published. The results of Study IV support the hypothesis of a possible association between RBC storage-time and development of severe infection, underlining the need for large, randomised, multicenter trials. Such studies are under way [206].

In general this thesis focused on allogeneic RBC transfusion during CABG, but other blood products, i.e. PLT and FFP, may also be associated with adverse outcomes including severe infections. However, the results in the literature are conflicting. Most studies suggest that transfusion with PLT and FFP does not confer an increased risk of morbidity or mortality [207-209].

### **Clinical implications of the studies**

Although Study I did not show any statistically significant effects regarding reduction in postoperative bleeding among patients undergoing first-time elective CABG, a decision was made to administer TA to all patients undergoing cardiac surgery in the future based upon the results in the literature. At the same time, surgical haemostasis received increased attention because the results from

Study I showed excessive bleeding and a high re-exploration rate among low risk patients, even when TA was administered.

Studies II and III increased the general attention towards predictors of bleeding. Study II identified differences between hospitals regarding several perioperative characteristics related to blood conservation, e.g. discontinuing antiplatelet drugs preoperatively, differences in the use of off-pump techniques, and different uses of antifibrinolytic drugs. These findings specifically led to alterations in our daily clinical practice. Institution-specific guidelines regarding preoperative discontinuation of antiplatelet drugs (acetylsalicylic acid and clopidogrel) prior to CABG were elaborated (Table 7) based on the literature [210]. Because of the results of Study III, patients are allowed to continue preoperative SSRI and other antidepressant intake until the day of surgery.

Table 7. Algorithm for the preoperative intake and discontinuation of acetylsalicylic acid and clopidogrel prior to CABG.

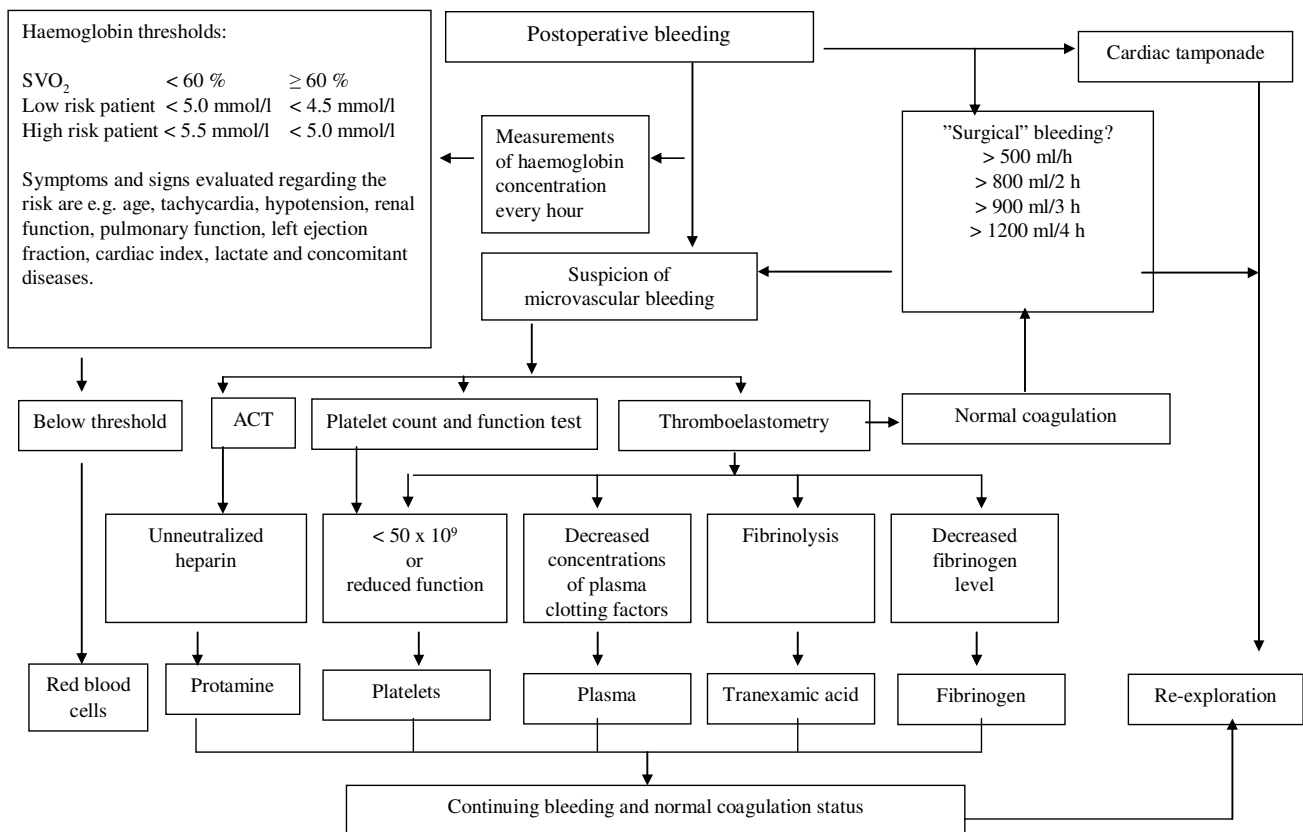
Clinical situation	Algorithm proposed
Elective CABG; stable angina pectoris; low risk plaque morphology.	Discontinue acetylsalicylic acid and clopidogrel 5 days prior to surgery.
Elective CABG; stable angina pectoris; high-risk plaque morphology, e.g. left main stenosis.	Continue acetylsalicylic acid until surgery. Discontinue clopidogrel 5 days prior to surgery.
Urgent CABG; low-risk patient (no signs of ischemia in ECG and negative troponin T).	Discontinue clopidogrel. Surgery is delayed 3–5 days if possible. Continue acetylsalicylic acid and subcutaneous low-molecular-weight heparin until the evening before surgery.
Urgent CABG; high-risk patient (recurrent or ongoing ischemia in ECG, positive troponin T).	Acetylsalicylic acid and clopidogrel are continued until surgery.

CABG: coronary artery bypass grafting; ECG: electrocardiography

Furthermore, an increased focus is directed towards transfusion practices to avoid unnecessary transfusions. An algorithm for managing postoperative bleeding in relation to cardiac surgery was developed (Figure 3). This algorithm includes the use of thromboelastometry, which has now been introduced in the hospital.

Study IV increased the attention towards potentially adverse outcomes following allogeneic blood transfusion, supporting the effort to reduce transfusions. The results of Study IV should be confirmed in randomized studies before asking blood bank services to issue only blood stored for <14 days for CABG or other kinds of cardiac surgery, since this will have significant resource implications.

**Figure 3. Postoperative management of bleeding in cardiac surgery.**



SVO<sub>2</sub>: Mixed venous oxygen saturation; ACT: Activated clotting time.

## **Strengths and limitations of the studies (I–IV)**

### **Study I**

The main strength of this study was the randomized, placebo-controlled study design. The study met most of the requirements in the CONSORT (Consolidated Standards of Reporting Trials) statement [211,212], which is an evidence-based, minimum set of recommendations for reporting randomized controlled trials, although the study protocol and paper were admittedly not written with the CONSORT statement in mind. The patient eligibility criteria are stated and the settings and locations where the data were collected are described. Precise details regarding the study interventions intended for each group are provided together with information on how and when they were actually administered. The method used to implement the random allocation sequence is stated together with information that those administering TA/placebo and those assessing the results were blinded to the group assignment. The flow of all participants through the study is accounted for.

Although Study I was a randomized study, it also has some limitations. Optimally, the study protocol and the paper should have been written according to the CONSORT statement. A description of the power analysis should have been provided in the paper, explaining how the sample size was calculated. More patients should have been included in the study to compensate for non-evaluable patients.

Patients who were re-explored because of bleeding were excluded from the final analysis. Excluding these patients from the analysis may have led to erroneous conclusions, and it is a weakness of the study that an intention-to-treat analysis was not carried out. Intention-to-treat analyses may avoid bias associated with non-random loss of study participants.

### **Study II**

The strength of Study II is the population-based, multicenter study design and the detailed data, which could not be retrieved from existing databases. Another strength was that the study focused on patients who, in principle, should be comparable within a small country.

Limitations include the retrospective study design, which resulted in missing data for some study variables. It is also a limitation that whether surgery was carried out as elective, emergent, or urgent procedure was not recorded, because non-elective surgery is a predictor of bleeding and transfusion. However, there is no reason to believe that the proportion of patients requiring non-elective surgery differed substantially between the centres. Other confounders which were not adjusted for may, at least in theory, also have influenced the results; e.g. predictors of bleeding such as a diagnosis of diabetes, peripheral arteriosclerotic disease, and surgical skills. Restriction to first-time CABG may have been done at the expense of the generalisability of the study, since this cohort of patients may not be representative of other patient groups with a higher risk of bleeding.

### Study III.

The strengths of Study III include the relatively large sample size, the use of prospectively-collected data obtained from population-based databases with complete follow-up, and the ability to study specific types of antidepressants.

However, Study III also has several limitations. Firstly, it was an observational study and as such susceptible to confounding. Although we controlled for a number of potentially important confounding factors, other factors not controlled for in the analyses may also have acted as confounding factors, e.g. use of prophylactic antifibrinolytic drugs. There was also a lack of data regarding patient's compliance in taking the antidepressants and a lack of information about the duration of any preoperative intake of these drugs. In addition, no strict transfusion algorithms were used. This study should also be interpreted carefully with regard to the risk of postoperative bleeding in relation to preoperative intake of SSRIs, because transfusion may be an imperfect surrogate marker for bleeding.

### Study IV

The major strength of this study was the population-based study design including all patients undergoing CABG in two regions of Denmark, the use of prospectively-collected, detailed data, the

complete follow-up, and the relatively large sample size with the advantage of being able to study infrequent outcomes such as severe infections. It is also a strength that Study IV only focused on severe infections because other kinds of postoperative infections may be difficult to identify in observational studies. Information regarding superficial postoperative wound infections may be incomplete. The predictive value of a correctly applied diagnosis of wound infection was only 78% in a previous study from Aalborg hospital, but a complete registration of all deep wound infections was observed during the study period [213]. The risk of misclassification of deep sternal wound infections in Study IV is assumed to be low because all patients with deep sternal wound infections are returned to either Skejby or Aalborg hospital for further surgical treatment in contrast with superficial sternal wound infections, which can be handled at local hospitals.

We could link several databases, retrieving information on a wide range of covariates, to adjust for several potential confounders not accounted for in previous studies, e.g. the Charlsons comorbidity index score. Furthermore, we were able to adjust for the number of transfused PLT units as well as for major and minor ABO-incompatible PTL transfusions. This is a strength because ABO incompatibility in PLT transfusions was associated with immune complex formation and increased morbidity including bleeding and infection after cardiac surgery [214-216].

Considering the storage time of RBC and PLTs transfused, it is important to recognise that storage times of the blood may be driven by ABO blood group type, since group O tends to have the shortest shelf time [217]. The probability of receiving blood stored for <14 days is not normally distributed according to ABO blood groups. It is therefore a strength of Study IV that ORs for development of severe infection according to storage time were adjusted for ABO blood groups. It would have been interesting to perform stratified analyses according to ABO blood groups, but the number of severe infections in each of the transfused ABO subgroups was too small to allow any meaningful evaluation of these results.

Study IV also has some limitations, which should be kept in mind when interpreting the results. Cohort studies cannot provide evidence for a cause-effect relationship, but dose-response relationships and biological plausibility, e.g. storage lesions, are elements supportive of this. Residual confounding

may be present, although we were able to adjust for several potential confounding factors. Transfused patients may be more ill and thus more susceptible to infections compared with non-transfused patients.

The results from this thesis are generalisable to some extent. The concept of a multimodal approach toward blood conservation can be applied at all centres, but the external validity from the individual studies may be affected by different patient populations and differences regarding the use of blood conservation techniques, including transfusion practices. Furthermore, the blood products used may differ. The results from Study IV may not be applicable to centres in which pre-storage WBC filtration of RBC units is performed because buffy-coat-reduced RBC units were mainly transfused in Study IV. In addition, transfusion of pooled units of random-donor, whole blood-derived PTL concentrates were predominantly performed. Apheresis PTLs, which are derived from a single donor, was very seldom used (<1.5 %).

## **Conclusions**

This PhD thesis presents an example of a multimodal approach to blood conservation during cardiac surgery. Four separate studies identified new and institution-specific information focused on transfusion variability in Denmark, predictors of bleeding, outcome following transfusion, and outcome following use of prophylactic antifibrinolytic therapy.

The main findings of the four studies are as follows below. Firstly, prophylactic TA reduced postoperative bleeding but the results did not reach statistical significance, and the proportion of patients transfused was not decreased. The findings may represent a type 2 error due to the small sample size, but inadequate surgical haemostasis may also play a role because the reoperation rate due to bleeding was high (15%). These results support the need for a multimodal approach to blood conservation. Secondly, transfusion practices vary in Denmark with regards to first-time CABG and place of surgery is an independent predictor of allogeneic RBC transfusion. The RR of receiving allogeneic RBC was approximately twice as high in Aalborg Hospital compared with the hospital with the lowest transfusion



rate. Several unnecessary RBC transfusions were administered. Thirdly, preoperative intake of SSRIs, which have an antiplatelet effect, is not associated with any substantial increase in transfusion requirements during CABG. Finally, transfusion of RBC units stored for  $\geq 14$  days are associated with a dose-dependent 2.5-fold increased risk of developing severe postoperative infections in patients undergoing CABG compared with non-transfused patients.

The results of this thesis support a multimodal approach to blood conservation in CABG and the findings are now part of the continuing multimodal efforts to optimize transfusion practices and systematic use of blood conservation techniques in the Department of Cardiothoracic Surgery, Aalborg Hospital. Potential adverse outcomes following transfusion were highlighted, but before any changes are made regarding transfusion of blood according to storage time the results from randomized trials should be obtained.

Further research in this complex research field is needed to restrict allogeneic blood transfusions to those patients who really need it.

## Future directions

Optimizing transfusion practices and use of blood-sparing techniques in cardiac surgery is an ongoing process. Any decision to transfuse allogeneic RBC should be based upon an individual evaluation of each patient with respect to the rate of blood loss, haemoglobin or haematocrit values, hemodynamic variables, symptoms, age, perioperative complications, and concomitant diseases. The decision to transfuse a specific patient should only be made after balancing the potential benefits with the risk of adverse outcomes.

Increased attention to these aspects was raised in the Department of Cardiothoracic Surgery, Aalborg Hospital, including applying the systematic use of antifibrinolytic drugs and using institutional guidelines regarding preoperative intake of antiplatelet drugs. Further interventions introduced were educational efforts, audit with feed-back, reminders, and the introduction of a new hospital form outlining transfusion guidelines. It would be of great interest to evaluate the impact of these changes. Several studies showed that behavioral interventions are effective in changing transfusion practices [41], but short-term results may be biased by the Hawthorne effects (an initial improvement in performance because of the act of observing the performance). Information on the long-term effects of the interventions is needed. A study using the before-and-after study design [218] was initiated in the Department of Cardiothoracic Surgery, Aalborg Hospital, with the objective of evaluating the attempts to decrease allogeneic blood usage during CABG. A total of 150 records from patients who underwent CABG in 2008 are being reviewed with the intention of comparing the results with the findings from the audit performed in 2004 (Study II). Preliminary results are shown in Table 8. The median total postoperative blood loss was decreased from 950 ml to 819 ml. The proportion of patients transfused with RBC was decreased from 64% to 48%, although postoperative direct reinfusion of shed mediastinal blood from the postoperative chest tube drainage was abandoned. We abandoned autotransfusion of unwashed mediastinal blood in accordance with published recommendations based on the risks associated with this technique, and the lack of clear-cut benefits [11]. The proportion of patients discharged with a

haemoglobin >7 mmol/l (over-transfusion) was reduced from 36% to 9%. A preliminary conclusion would be that the efforts to change transfusion behaviors are working.

Table 8. Postoperative blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting in 2004 and 2008.

Variable	2004 n = 141	2008 n = 147
Chest tube drainage, 6 h (ml)	560 (373–818)	460 (380–550)
Total chest tube drainage (ml)	950 (685–1298)	722 (525–975)
Patients receiving allogeneic red blood cells	64%	48%
Patients receiving allogeneic plasma	39%	31%
Patients receiving allogeneic platelets	28%	34%
Postoperative autotransfusion	72%	6%
Patients transfused with RBC and discharged with a haemoglobin concentration >7 mmol/l	36%	9%

Data on chest tube drainage are presented as the median and with the interquartile range; RBC, red blood cells.

Introduction of transfusion algorithms in other cardiac centers was done with varying success [219] and evaluation of the new transfusion algorithm (Figure 3), which includes point-of-care tests would be of great interest in optimizing the algorithm further.

Further studies should also be performed in relation to the observed associations between allogeneic RBC blood transfusion and increased morbidity and mortality from cardiac surgery. We are in the process of evaluating our study database from Study IV to investigate whether transfusion of RBC stored  $\geq 14$  days is associated with increased mortality. However, we also need well-conducted, adequately-powered, randomized studies. Studies using pre-storage WBC-filtered RBC units and PLT would be preferred because these kinds of blood products are used in an increasing number of countries. Pre-storage WBC-reduced blood products will also be used in the Northern Denmark region beginning in 2010. High-risk

patients should at best be randomized to receive exclusively either extremely old blood (storage time >30 days) or extremely fresh blood (storage time <7 days) because these extremes would be expected to send a clear message regarding the clinical impact of storage time.

Randomized studies should also be performed to compare different transfusion thresholds with respect to clinical outcomes to increase the level of strength on which recommendations in the transfusion guidelines are based.

Allogeneic RBC transfusions are given with the intent of enhancing the oxygen-carrying capacity of the blood, but there is no clear evidence supporting the view that the non-bleeding, stable patient will benefit from transfusion with RBC during cardiac surgery. However, because patients grew up with the basic principle that blood saves lives, we will probably never be able to perform the ultimate study for ethical reasons, i.e. comparing blood transfusion with other kinds of therapy.

## Summary in English

Allogeneic blood transfusion (blood transfusion from a genetically different person) has always been an integral part of cardiac surgery, but transfusion is associated with adverse clinical outcomes in cardiac surgery and a great deal of variability exists nationally and internationally regarding transfusion. The general purpose of this PhD thesis was to perform four independent but related research studies, which in total will serve as an example of a multimodal approach to blood conservation in coronary artery bypass grafting (CABG). A multimodal approach is important because bleeding during cardiac surgery is multifactorial. The goal was to produce new and institution-specific information that will contribute to the pool of knowledge upon which future transfusion and blood conservation algorithms during cardiac surgery can be based. The work evolved as a part of the continuing efforts to optimize the use of blood-sparing techniques, including transfusion practices in the Department of Cardiothoracic Surgery, Aalborg Hospital, Aarhus University Hospital.

The particular aims of the individual studies were (1) to determine whether perioperative use of prophylactic tranexamic acid (TA) would decrease chest tube drainage and the proportion of patients requiring perioperative allogeneic blood transfusion in primary elective on-pump CABG; (2) to audit transfusion practices in Denmark in patients undergoing first-time CABG at different hospitals; (3) to determine whether transfusion requirements are increased in patients undergoing CABG following preoperative use of platelet-inhibiting selective serotonin reuptake inhibitors (SSRIs); and (4) to examine whether the storage-time of allogeneic red blood cells (RBC) is associated with the development of severe postoperative infections (deep sternal wound infections and bacteraemia/septicaemia) in patients undergoing CABG.

Several other aspects regarding perioperative blood transfusion and blood conservation in CABG could have been undertaken in relation to this thesis. The studies included were initiated because of ongoing clinical challenges and new questions that arose at the time the studies were commenced.

A randomized trial and three observational studies based on detailed data from medical records, hospital discharge registries, and linkage between several clinical databases and population-based

registries were performed. The following results were found in these studies: (1) prophylactic TA reduced postoperative bleeding, as was found in most other studies, but the results were not statistically significant. The proportion of patients transfused was not decreased. Inadequate surgical haemostasis may play a role in this outcome because the reoperation rate due to bleeding was high (15%). These results support the need for a multimodal approach to blood conservation; (2) transfusion practices vary in Denmark and “hospital” was an independent predictor of allogeneic RBC transfusion. The adjusted relative risk of being exposed to RBC transfusion is approximately twice as high in Aalborg Hospital compared with the hospital with the lowest transfusion rate. Several unnecessary transfusions of RBC were administered; (3) preoperative intake of SSRIs is not associated with any substantial increase in transfusion requirements in CABG; and (4) transfusion of RBC units stored for  $\geq 14$  days is associated with a dose-dependent 2.5 fold increased risk of severe infections in patients undergoing CABG compared with non-transfused patients. This association was much weaker among patients transfused exclusively with RBC stored for  $< 14$  days.

In conclusion, the four separate studies included in this thesis provide new and institution-specific information regarding transfusion variability in Denmark, predictors of bleeding and transfusion, outcome following transfusion, and prophylactic use of antifibrinolytic therapy. These findings are now part of the continuing multimodal and multidisciplinary efforts to optimize transfusion practices and blood conservation in our department.

The results in this thesis can only be generalized to certain extent. The concept of a multimodal approach to blood conservation can be applied to all other centres, but the external validity of the individual studies may be affected by differences in patient populations, differences in blood products used, and differences regarding the ongoing use of blood conservation techniques including transfusion practices.

Further research is needed in this complex research field to restrict allogeneic blood transfusion to only those patients who really need it.

## Summary in Danish/Dansk resumé

Allogen blodtransfusion (transfusion fra et genetisk forskelligt menneske) har altid været en integreret del af hjertekirurgien, men transfusion er associeret med øget morbiditet og mortalitet efter hjertekirurgi og der er stor variation i transfusionspraksis nationalt og internationalt.

Det overordnede formål med afhandlingen var at gennemføre fire selvstændige men relaterede forskningsprojekter, som i sammenhæng fremstår som et eksempel på en multimodal tilgang til anvendelsen af blodbesparende foranstaltninger i forbindelse koronar bypass kirurgi (CABG). En multimodal tilgang til at reducere blodforbruget er vigtig fordi blødning efter hjertekirurgi er multifaktorielt betinget. Målet var at skabe ny og institutionsspecifik viden, som kan indgå i den samlede baggrundsviden som fremover vil være basis for udvikling af kliniske retningslinier med henblik på at reducere blødning og transfusion i forbindelse med hjertekirurgi.

Denne ph.d. afhandling blev skabt som led i det løbende kliniske arbejde med at optimere transfusionspraksis og brugen af andre blodbesparende foranstaltninger i forbindelse med hjertekirurgi i Hjerte-Lunge kirurgisk afdeling på Aalborg Sygehus, Aarhus Universitetshospital.

Formålet med de enkelte studier var 1) at undersøge om profylaktisk infusion af tranexamsyre (TA) reducerer postoperativ blødning via thoraxdrænene, og om andelen af patienter som får behov for blodtransfusion reduceres blandt patienter, som gennemgår en førstegangs, elektiv CABG med anvendelse af hjerte-lungemaskine. 2) at gennemføre en transfusionsaudit i Danmark med henblik på at sammenligne transfusionspraksis blandt førstegangs CABG patienter i forskellige afdelinger, 3) at undersøge om præoperativ indtagelse af trombocythæmmende selective serotoninoptagshæmmere (SSRI) øger transfusionsbehovet hos CABG patienter og 4) at undersøge om blodets lagringstid i blodbanken er associeret med udvikling af svære postoperative infektioner i form af dyb sternum infektion, bakteriæmi eller sepsis efter CABG.

Forskellige andre blodbesparende foranstaltninger kunne have været undersøgt som led i denne ph.d. afhandling. De inkluderede studier blev iværksat på baggrund af aktuelle kliniske udfordringer og nye spørgsmål i klinikken på det tidspunkt undersøgelserne blev gennemført.

Der blev gennemført et randomiseret klinisk studie og tre observationelle studier baseret på en kobling af data fra patientjournaler og forskellige populationsbaserede registre og kliniske databaser. Følgende resultater fremkom 1) Profylaktisk anvendelse af TA reducerede den postoperative blødning via drænene som i de fleste andre studier, men reduktionen i forhold til placebo var ikke statistisk significant. Andelen af patienter som blev transfunderet blev ikke reduceret. Resultatet kan være betinget af en utilstrækkelig kirurgisk hæmostase i studieperioden, da andelen af patienter, som blev reopereret for blødning, var høj (15%). Resultaterne peger på nødvendigheden af en multimodal tilgang til anvendelsen af blodbesparende foranstaltninger 2) Transfusionspraksis varierer i Danmark og ”operationssted” er en uafhængig predictor for erythrocyt transfusion. Den justerede relative risiko for at modtage en transfusion er cirka dobbelt så høj i Aalborg, som på det sygehus, hvor transfusionsraten var lavest. Der gives flere unødvendige transfusioner. 3) Præoperative indtagelse af SSRI er ikke associeret med nogen væsentlig øget risiko for transfusion i forbindelse med CABG. 4) Transfusion med erythrocytter lagret  $\geq 14$  dage er associeret med en dosisafhængig 2,5 fold øget risiko for udvikling af svære postoperative infektioner sammenlignet med patienter der ikke modtager transfusion. Sammenhængen er betydelig svagere ved transfusion med erythrocytter lagret  $< 14$  dage.

Disse fire enkeltstående undersøgelser bidrager med ny og institutions specifik viden hvad angår transfusion variabilitet i Danmark, prædiktorer for blødning og transfusion, risiko ved transfusion og effekten af profylaktisk antifibrinolytisk behandling. Resultaterne indgår nu i de løbende multimodale bestræbelser på at optimere transfusionspraksis og anvendelsen af andre blodbesparende foranstaltninger i Hjerte-Lungekirurgisk afdeling på Aalborg Sygehus, Aarhus Universitetshospital.

Resultaterne fra denne ph.d. afhandling er kun generaliserbare til en hvis grad. Den multimodale tilgang kan anvendes i alle afdelinger, men den eksterne validitet af de forskellige studier kan påvirkes af eventuelt forskellige patientpopulationer, anvendelse af forskellige blodprodukter og samtidig anvendelse af andre blodbesparende foranstaltninger.

Der er brug for flere undersøgelser indenfor dette komplekse forskningsområde for at begrænse transfusion med fremmed blod til de patienter, der virkelig har gavn af behandlingen.



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