Reija Mikkola

DETERMINANTS AND CLINICAL IMPLICATIONS OF BLEEDING RELATED TO CORONARY ARTERY BYPASS SURGERY
ACTA UNIVERSITATIS OULUENSIS
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REIJA MIKKOLA

DETERMINANTS AND CLINICAL IMPLICATIONS OF BLEEDING RELATED TO CORONARY ARTERY BYPASS SURGERY

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Abstract
Coronary artery bypass grafting (CABG) is the treatment of choice for patients with three-vessel disease or left main stenosis. However, it is associated with considerable risk of perioperative complications such as myocardial infarction, stroke, infections, and mortality to which excessive bleeding is a contributing factor. This thesis aims to determine the factors involved in and clinical implications of bleeding after CABG.

The 1st study evaluated the effects of preoperative ASA discontinuation on the patient’s outcome after CABG. The results showed that late or no discontinuation of low-dose ASA before CABG may decrease the risk of postoperative stroke without increasing the risk of postoperative bleeding.

In the 2nd study the use of warfarin was found to be a safe during CABG with no excess bleeding nor other major complications.

The 3rd study estimated the impact of surgeons’ performances on blood loss and need for re-exploration after CABG. With 2001 study patients, this study clearly demonstrated that an individual surgeon is a powerful determinant of postoperative bleeding and need for re-exploration after CABG.

Using systematic review and meta-analysis, we estimated the risk of complications related to re-exploration for bleeding after CABG. In literature search in 2011, 8 articles with 557 923 patients fulfilled the inclusion criteria. Re-exploration for bleeding after cardiac surgery carries a significantly increased risk of postoperative mortality and morbidity, and thus has a major impact on the patient’s immediate postoperative outcome.

We also studied the impact of transfusion of blood products on the development of post-operative stroke after CABG. Of the study population of 2 226 CABG patients, stroke occurred postoperatively in 53 patients (2.4%). The statistical analysis showed that transfusion of blood products after CABG has a strong, dose-dependent association with the risk of stroke. The use of Octaplas® and platelet transfusions seem to have an even larger impact on the development of stroke than red blood cell transfusions.

The 6th study investigated the impact of transfusion of blood products on intermediate outcome after CABG in 2001 patients. The findings indicated that transfusion of any blood product is associated with a significant risk of all-cause and cardiac mortality after CABG.

Keywords: anticoagulation, aspirin, bleeding, blood transfusion, coronary artery bypass surgery, fresh frozen plasma, platelets, re-exploration, red blood cells, resternotomy, stroke
Tiivistelmä

Sepelvaltimotauti on yleisin kuolinsyy ja sepelvaltimoiden ohitusleikkaus hyviline pitkäaikaistuloksineen on todettu parhaaksi hoidoksi potilailla, joilla on monen suonen tai vasemman päärungon tauti. Ohitusleikkaukseen liittyy kuitenkin verenvuodon sekä näihin kytkeytyvien komplikaatioiden riski. Tämän vääristä vointi tuottaa voinottelua ohitusleikkauskseen vähentää aivoinfarktien riskiä lisäämättä silti verenvuodon riskiä.

Verenhyytymistä estävien lääkkeiden tiedotus liittyy verenvuodon riskiin. Ensimmäinen tutkimus osoitti, että ASA:n jatkaminen keskeyttää ohitusleikkauskseen vähentää aivoinfarktien riskiä lisäämättä silti verenvuodon riskiä.

Toiseksi tutkimus osoitti kirurgin taidon merkityksen verenvuotojen ja uusintaleikkausten määrään 2001 potilailla. Verenvuotojen vaikutus teräväväntä uusintaleikkausten negatiivinen vaikutus on todettu yksiselitteisesti useissa tutkimuksissa.

Kolmas tutkimus osoitti kirurgin taidon merkityksen verenvuotojen ja uusintaleikkausten määrään 2001 potilailla. Verenvuotojen vaikutus teräväväntä uusintaleikkausten negatiivinen vaikutus on todettu yksiselitteisesti useissa tutkimuksissa.

Vuonna 2011 tehdyllä systemaattisella kirjallisuuskatsauksella ja meta-analyysillä selvitimme yhteensä 557 923 ohitusleikkauskapotilaan aineistosta, että verenvuodon jälkeisiin uusintaleikkauskoihin liittyy huomattava kuoleman ja komplikaatioiden riski.

To My Family
Acknowledgments

This study was carried out at the Department of Surgery, Division of cardiothoracic and Vascular Surgery, University of Oulu during the years 2009 to 2017.

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Finally, my deepest gratitude belongs my beloved husband Heikki for his endless support and patience throughout these years. He, together with our boys Eetu and Oiva, have brought so much happiness, love and laughter to my life.

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Oulu, 1.12.2017

Reija Mikkola
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ACT</td>
<td>activated clotting time</td>
</tr>
<tr>
<td>ANH</td>
<td>acute normovolemic hemodilution</td>
</tr>
<tr>
<td>ASA</td>
<td>acetylsalicylic acid, aspirin</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CPB</td>
<td>cardiopulmonary bypass</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>EACA</td>
<td>epsilon-aminocaproic acid</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
</tr>
<tr>
<td>FFP</td>
<td>fresh frozen plasma</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>HBD</td>
<td>hereditary inherited bleeding disorder</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>ITP</td>
<td>idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>LMWH</td>
<td>low-molecular weight heparin</td>
</tr>
<tr>
<td>NOAC</td>
<td>new oral anticoagulant</td>
</tr>
<tr>
<td>OPCAB</td>
<td>off-pump coronary artery bypass surgery</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAD</td>
<td>preoperative autologous blood donation</td>
</tr>
<tr>
<td>PCC</td>
<td>prothrombin complex concentrate</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>ROTEM</td>
<td>thromboelastometry</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>TEG</td>
<td>thrombelastography</td>
</tr>
<tr>
<td>TF</td>
<td>tissue factor</td>
</tr>
<tr>
<td>TOAC</td>
<td>therapeutic oral anticoagulation</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractioned heparin</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonist</td>
</tr>
<tr>
<td>VWD</td>
<td>von Willebrand’s disease</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
</tbody>
</table>
List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

Coronary artery disease (CAD) is the leading cause of death in western countries, and in Europe it is still responsible for over 1.8 million deaths per year (Nichols et al. 2015). In CAD, the myocardial ischemia is a result from a weakened oxygen supply due to stenosis or occlusion in coronary arteries. Despite the awareness and optimal conservative treatments, mechanical revascularization with percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG) or both, is often required for patients with significant CAD or symptoms (Iqbal and Serruys 2014, Davierwala & Mohr 2014). CABG is preferred in patients with three vessel disease, left main stenosis, left ventricular systolic dysfunction and/or diabetes, as it is associated with improved survival, reductions in cardiovascular events and reductions in repeat revascularization when compared to PCI (Iqbal and Serruys 2014, Sipahi et al. 2014, Davierwala & Mohr 2014, Deb et al. 2013).

CABG surgery is associated with a considerable risk of perioperative complications such as myocardial infarction, stroke, major bleeding, acute kidney injury, respiratory problems, infections, and mortality (Stone et al. 2012). Excessive bleeding has been found to contribute to these complications (Alström et al. 2012) and there is a growing body of evidence suggesting that a transfusion of blood products is also an independent risk factor for these complication (Biancari & Kinnunen 2012, Stone et al. 2012). Furthermore, reoperation for bleeding represents an important complication in CABG patients and is strongly associated with greater morbidity and mortality (Mehta et al. 2009). For these reasons, identification of factors associated with an increased risk of bleeding is essential.

This thesis evaluated the impact of perioperative bleeding and the transfusion of blood products on the outcome of patients undergoing isolated CAGB. Furthermore, risk factors for major bleeding and re-exploration for bleeding were estimated.
2 Review of the literature

2.1 Bleeding in coronary artery bypass surgery

Coronary artery bypass surgery is a major procedure associated with a considerable risk of perioperative bleeding. Studies of hemostatic complications in cardiac operations are summarized in table 1. According to these studies, reoperation for bleeding is required in 1.3% to 5.9% patients undergoing coronary artery bypass graft surgery.

Table 1. Studies of hemostatic complications in cardiac operations.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>No. of patients</th>
<th>Percentage of patients who received blood products</th>
<th>Percentage of re-sternotomy for bleeding</th>
<th>Amount of blood loss in ICU (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sellman et al.</td>
<td>1997</td>
<td>8 563</td>
<td>-</td>
<td>4.4% (378)</td>
<td>-</td>
</tr>
<tr>
<td>Unsworth-White</td>
<td>1995</td>
<td>2 221</td>
<td>-</td>
<td>3.8% (85)</td>
<td>median 2 156 ml, range 1 440–2 435 ml</td>
</tr>
<tr>
<td>Moulton et al.</td>
<td>1996</td>
<td>6 015</td>
<td>-</td>
<td>4.2% (253)</td>
<td>-</td>
</tr>
<tr>
<td>Karthik et al.</td>
<td>2004</td>
<td>2 898</td>
<td>-</td>
<td>3.1% (89)</td>
<td>-</td>
</tr>
<tr>
<td>Mehta et al.</td>
<td>2009</td>
<td>528 686</td>
<td>59.2% (312 819)</td>
<td>2.39% (12 652)</td>
<td>-</td>
</tr>
<tr>
<td>Choong et al.</td>
<td>2007</td>
<td>3 220</td>
<td>-</td>
<td>5.9% (191)</td>
<td>mean 1 236 ml, range 100–10 661 ml</td>
</tr>
<tr>
<td>Dacey et al.</td>
<td>1998</td>
<td>8 586</td>
<td>-</td>
<td>3.6% (305)</td>
<td>-</td>
</tr>
<tr>
<td>Alström et al.</td>
<td>2012</td>
<td>3 000</td>
<td>-</td>
<td>2.5% (76)</td>
<td>-</td>
</tr>
<tr>
<td>Biancari &amp; Kinnunen</td>
<td>2012</td>
<td>140</td>
<td>47.9% (67)</td>
<td>2.1% (3)</td>
<td>901 ± 35 ml</td>
</tr>
<tr>
<td>Stone et al.</td>
<td>2012</td>
<td>1 491</td>
<td>41.0% (612)</td>
<td>1.3% (20)</td>
<td>-</td>
</tr>
</tbody>
</table>

2.2 Description of coagulation cascade

Hemostasis include three phases: initiation, amplification, and propagation. The coagulation cascade starts via its intrinsic or extrinsic activation. The coagulation factor enzymes are sequentially activated in the cascade and the final steps involve the conversion of soluble plasma fibrinogen into fibrin by thrombin (Figure 2). The coagulation cascade starts with an initiation phase in which the resting endothelium is stimulated to become an activated surface via injury (tissue factor release) or exposure to a signaling molecule. Despite the difference in the activation mechanism, the two pathways converge on a common pathway leading to clot
formation. During the amplification and propagation of the thrombus, activated platelets adhere to the endothelium, facilitated by von Willebrand factor (vWF) via glycoprotein Ib receptors. The thrombin thus formed activates additional platelets and a positive feedback cycle increases the generation of thrombin. Thrombin also converts fibrinogen to a fibrin monomer, which is then polymerized into a clot stabilizer by thrombin-activated factor XIII. The coagulation process is limited to the site of vascular injury by serine protease inhibitors including protein C and S, tissue factor pathway inhibitor, and antithrombin. The fibrinolytic system activates concurrently, and removes the clot on coordination with wound healing and tissue remodeling.

2.3 Impact of antithrombotic drugs on perioperative bleeding

Over the last decade there have been several changes in the practice of the preoperative use of antithrombotic and antiplatelet drugs in cardiac surgery. The relationship between antiplatelet therapy at the time of coronary artery bypass grafting and perioperative bleeding complications is still under debate and requires further examination. Nowadays, cardiac surgeons are faced with an increasing number of patients referred to operations while being treated with one or more antithrombotic and/or antiplatelet agents. Because of the risk of bleeding, the proper timing of operation has to be carefully considered before any surgical intervention.

The different types of antithrombotic drugs (Figure 1) can be classified by their pharmacological effect (Figure 2).
Fig. 1. Antithrombotic drugs.

Fig. 2. Coagulation cascade via intrinsic and extrinsic activation. Pharmacological effects of antithrombotics.
2.3.1 ASA

Acetylsalicylic acid (ASA) inhibits thromboxane A2 synthesis, which in result inhibits the aggregation of blood platelets. ASA is an integral part of pharmacologic therapy in patients with coronary artery disease and one of the mainstay treatments to prevent graft occlusion after CABG. Several studies have shown that preoperative ASA increases the postoperative bleeding, RBC transfusion requirements, and reoperation for bleeding in patients undergoing CABG (Unsworth-White et al. 1995, Jacob et al. 2011, Ma et al. 2014, Hastings et al. 2015). However, in a subgroup analysis of 8 randomized controlled trials, Ma et al. (2014) demonstrated that ASA given at doses ≤100 mg/d might not increase postoperative bleeding. Traditionally, the administration of ASA is discontinued within seven days before coronary artery bypass surgery to reduce the risk of postoperative bleeding complications. In the last few years, however, some studies have suggested that continuing ASA until the time of surgery does not increase bleeding or increase the need for allogeneic blood transfusion in coronary artery surgery (Gulbins et al. 2009, Hijazi 2011). Continued ASA treatment has also been shown to reduce oxidative and inflammatory responses among CABG patients (Berg et al. 2013). Performing CABG on ASA may also decrease the long-term risk of major cardiac events such as cardiovascular death, infarction, or repeat revascularization (Deja et al. 2012).

2.3.2 Clopidogrel

Clopidogrel belongs to the group of thienopyridines, which are prodrugs whose active metabolites inhibit platelet aggregation and activation by irreversibly antagonizing the P2Y12 adenosine diphosphate receptor on the surface of platelets. Current guidelines recommend that dual antiplatelet therapy with aspirin and a thienopyridine is the basis in treatment for prevention of thrombosis after PCI in ACS patients.

The increased risk of bleeding and reoperation in CABG patients with clopidogrel treatment is irrespective of whether surgery is performed on- or off-pump (Berger et al. 2012). Those patients who used clopidogrel within 5 days of robotic-assisted CABG had greater postoperative bleeding (Vainrub et al. 2014, Daniel et al. 2014) and a higher incidence of blood transfusion (Daniel et al. 2014), even though robotic-assisted CABG is considered to be less invasive as it does not involve sternotomy.

There is evidence that combined therapy using ASA and clopidogrel has no significant increase in the postoperative bleeding risk and blood transfusion when compared to monotherapy using clopidogrel alone (Badreldin et al. 2009). Current guidelines recommend that clopidogrel should be discontinued 5 days prior to CABG (Vainrub et al. 2014) to reduce bleeding complications. The optimal timing for discontinuation of clopidogrel before surgery is under debate, however, as some studies have demonstrated that bleeding complications are similar in patients that stopped clopidogrel at 3 days preoperatively when compared to those that discontinued at 5 days preoperatively (Firanescu et al. 2009).

2.3.3 Prasugrel

Prasugrel is the most recent addition to the available thienopyridine antiplatelet agents used to prevent ischemic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Prasugrel has been shown to exert a more powerful antiplatelet effect and a more effective inhibition of platelet activation than clopidogrel, but the clinical benefits are counterbalanced by an increase in bleeding risk compared with clopidogrel (Martin et al. 2011). The current American College of Cardiology Foundation/American Heart Association guidelines recommend a discontinuation of ADP antagonists at least 5 days before surgery for clopidogrel and at least 7 days before surgery for prasugrel to minimize bleeding complications. In a prospective study of 143 patients, Drews et al. (2015) reported an increase in the need for platelet transfusion and surgical re-exploration after CABG in patients pretreated with prasugrel, when compared to clopidogrel. In a subset of the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38), Smith et al. (2012) demonstrated that the preoperative use of prasugrel lowers the rate of death after CABG compared with clopidogrel, despite an increase in bleeding, platelet transfusion, and surgical re-exploration for bleeding.
2.3.4 Ticagrelor

Concerns regarding clopidogrel’s delayed onset of action, variability in antiplatelet effects, and prolonged recovery of platelet function after discontinuation have driven the development of direct P2Y(12) receptor antagonists such as ticagrelor (Cheng 2012). Current evidence suggests that ticagrelor or prasugrel plus ASA should be the dual antiplatelet therapy of choice in patients with acute coronary syndrome undergoing percutaneous coronary intervention (Clemmensen et al. 2013). Compared to clopidogrel, ticagrelor has been shown to reduce thrombotic events and the risk of cardiovascular death, myocardial infarction, and stroke in ACS patients, even when treated with CABG (Held et al. 2010, Held et al. 2011, Cheng 2012). Ticagrelor also has a faster onset and offset of action than clopidogrel, and therefore, it appears that platelet function recovers faster on discontinuation of therapy (Held et al. 2010, Schotola et al. 2014). In GABG patients on dual antiplatelet medication up to the day of surgery, however, ticagrelor + ASA therapy is associated with more bleeding complications (higher blood loss, higher use of blood products and coagulation factors, higher incidence of resternotomy for bleeding) compared to those who were treated with clopidogrel + ASA (Hansson et al. 2014, Schotola et al. 2014). There was no difference in major bleeding complications overall when ticagrelor or clopidogrel was used in accordance with guidelines (Hansson et al. 2014). The protocol recommends that ticagrelor be withheld for 24 to 72 h preoperatively (Held et al. 2011). At times, however, the usage of these drugs cannot be discontinued before coronary artery bypass grafting due to the risk of stent thrombosis or in the case of emergency operations. One of the downsides in using ticagrelor is the twice-a-day maintenance dose, elevations in serum creatinine and uric acid, and dyspnea (Wallentin et al. 2009).

2.3.5 Heparins

Unfractioned heparin (UFH) catalyzes the anticoagulant effect of antithrombin (AT), which is an inhibitor of factors IIa (thrombin) and Xa (Figure 2). Secondly, it catalyzes the anticoagulant properties of heparin cofactor II. Low-molecular weight heparins (LMWH) are fragments of unfractioned heparin, and have a greater activity against factor Xa (Handeland et al. 1990). In a retrospective study of almost 2 900 patients, Karthik et al. (2004) found preoperative heparin to be a risk factor for re-exploration for bleeding after on-pump coronary artery surgery. Furthermore,
the early postoperative use of UFH was also associated with a significant increase in re-exploration for postoperative bleeding (Jones et al. 2005).

Systemic heparinization is used to prevent the accumulation of thrombus in the cardiopulmonary bypass circuit and minimize the activation of the coagulation system. A common practice during CPB is administering a fixed, weight-based heparin dose and measuring the activated clotting time (ACT) for targeting a level considered adequately safe for surgery. Unfractionated heparin has long been the anticoagulant of choice in surgery with CPB as it is effective, inexpensive, and easily reversed.

### 2.3.6 Warfarin

Warfarin decreases blood coagulation by inhibiting vitamin K epoxide reductase, which affects the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. Its activity is monitored by blood testing for the international normalized ratio (INR). Its pharmacologic action can be reversed by vitamin K. The most common indications for anticoagulation therapy are atrial fibrillation, valvular heart disease, and thromboembolic disease.

There are only a limited number of studies analyzing the bleeding outcome after CABG in patients on oral anticoagulation. Preoperative, long-term warfarin therapy is assumed to increase bleeding complications with respect to surgical procedures and it is recommend that it is discontinued for 7 days before surgery (Torosian et al. 1978). In a case-control study of 162 matched CAGB patients pairs, Biancari et al. (2010) discovered that a short preoperative pause (median, 2 days) in warfarin treatment does not increase the risk of bleeding complications (postoperative blood loss, need of red blood cell transfusion, reoperation for bleeding) when compared to CABG patients without preoperative warfarin. This was the case even when the operative risk of warfarin-treated patients was higher (p = 0.001) than in the control patients. In the Oulu University Hospital, it is a practice to pause oral anticoagulation 2 days before CABG. There is increasing evidence, however, that there is no difference in bleeding complications when comparing patients undergoing diagnostic coronary angiography during uninterrupted therapeutic warfarin treatment to patients with preprocedural warfarin discontinuation (Annala et al. 2008). Gunn et al. (2014) demonstrated in his study that, despite oral anticoagulation, bleeding events are infrequent after both PCI and CABG and should not affect the treatment choice.
2.3.7 New oral anticoagulants

In recent years, new oral anticoagulants (NOACs) have been released in the Finnish market. Dabigatran (©Pradaxa) is a direct thrombin inhibitor used for the prevention of venous thromboembolism after elective knee or hip arthroplasty, for the treatment of acute venous thromboembolism, and for the prevention of ischemic stroke in patients with atrial fibrillation. Rivaroxaban (©Xarelto) and apixaban (©Eliquis) are direct factor X inhibitors used for the same indications as dabigatran. Of these, only dabigatran has a specific antidote at this time. All these novel anticoagulants have a short half-life, which may add some value in acute care settings such as coronary artery bypass surgery in patients with a high risk of bleeding. The lack of scientific evidence regarding the preoperative discontinuation and the impact on perioperative bleeding, however, has limited the preoperative use of these drugs in CAGB patients.

2.4 Comorbidities

2.4.1 BMI

As the incidence of obesity increases in western populations, more attention is being focused on the effect of obesity on surgical outcomes. Obesity is often classified according to body mass index (BMI) and is grouped into five categories by the World Health Organization: underweight (BMI < 18.5), normal weight (BMI 18.50 to 24.99), overweight (BMI 25 to 29.99), obese (BMI 30 to 39.9), and morbidly obese (BMI ≥ 40). Johnson et al. (2015) studied 78,762 patients undergoing CABG or combined CABG/aortic valve replacement surgery. They found overweight and obese patients to have lower rates of mortality and adverse outcomes (e.g. postoperative bleeding) after cardiac surgery compared with normal weight, underweight and morbidly obese patients. Similar findings have been made in other studies; for example in a retrospective study of 290 CABG surgery patients, Nolan et al. (2013) found overweight and obese BMI to be a significant independent predictor of decreased intraoperative transfusion and postoperative blood loss. Engel et al. also concluded that obese BMI was not an independent predictor of morbidity or mortality after CABG, despite the comorbidities that are often present with obesity. The exact mechanism behind these positive effects is unknown.
A lower BMI, on the other hand, has been shown to be a risk factor for re-exploration for bleeding after CABG (Karthik et al. 2004, Mehta et al. 2009, Johnson et al. 2015). CAGB patients with an underweight BMI also have the greatest risk of mortality, prolonged ventilation, reoperation for bleeding, and renal failure (Engel et al. 2009, Johnson et al. 2015).

2.4.2 Renal failure

Patients can be classified into four chronic kidney disease (CKD) stage classes by estimated glomerular filtration rate calculated using the Cockcroft-Gault formula (Table 2). Several studies have demonstrated that even a mild level of preoperative renal dysfunction is an independent predictor of in-hospital and late mortality in adult patients undergoing cardiac surgery (Litmathe et al. 2009, Howell et al. 2008, Zakeri et al. 2005, Ix et al. 2005). The same type of effect has been noticed in postoperative renal function; Brown et al. (2008) found in a study population over 13 500 patients that those with moderate to severe acute kidney injury after CABG surgery have a worse 5-year survival compared to patients with normal or near-normal renal function. In a study population of over 7 600 patients, Howell et al. (2008) also detected a higher incidence in re-exploration for bleeding in patients with decreased renal function.

Controversial conclusions have, however, also been made; Van Straten et al. (2009) studied over 10 000 patients to determine how preoperative renal function affects long-term survival after isolated coronary artery bypass. They classified patients into 4 groups according to preoperative renal function, and found that only patients with a creatinine clearance less than 30 ml/min showed a worse outcome when compared with expected survival.

When compared to on-pump CABG, off-pump surgery is associated with a reduced risk of postoperative renal dysfunction (Abu-Omar et al. 2012, Garg et al. 2014).
Table 2. GFR\(^1\) categories in CKD\(^2\).

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (ml/min/1.73 m(^2))</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥ 90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>Mildly decreased(^3)</td>
</tr>
<tr>
<td>G3</td>
<td>30–59</td>
<td>Moderately decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

\(^1\) GFR, glomerular filtration rate. \(^2\) CKD, chronic kidney disease. \(^3\) Relative to young adults’ level. In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

2.4.3 Anemia

The World Health Organization definition for anemia is a hemoglobin (Hb) level under 130 g/l in men and under 120 g/l in women. Low preoperative hemoglobin levels are common in patients undergoing cardiac operations and are often caused by hospital acquired blood loss, iron-deficiency anemia, and anemia due to chronic disease (that are unrelated to the operative procedure), all of which are readily diagnosable and treatable (Engoren et al. 2014). Reasons for perioperative and/or postoperative anemia related to surgical procedures are intraoperative blood loss and hemodilution due to the use of cardiopulmonary bypass.

In coronary artery bypass surgery, when compared to a nonanemic group of surgical patients, patients with preoperative anemia have a worse risk profile before surgery: older age, higher EuroScore values, lower ejection fraction, lower estimated glomerular filtration rate, and higher rates of diabetes mellitus, acute myocardial infarction, and cardiogenic shock (Boening et al. 2011, Matsuda et al. 2013). Even when taking these risks into consideration, preoperative anemia in CABG patients is associated with an increased postoperative mortality (Kulier et al. 2007, van Straten et al. 2009, Boening et al. 2011). In patients undergoing coronary artery bypass surgery, preoperative anemia is also associated with longer lengths of stay in icu and hospital (Riera et al. 2009).

Apart from the distinct detrimental effects on outcomes of anemia, it is also important because it is the driving force behind transfusions of red blood cells and is frequently treated by RBC transfusions, which is associated with an increase in late mortality (see more in chapter 2.8.1). Taken together, preoperative anemia and RBC transfusion have been associated with an increased hazard of late mortality when compared with transfusion in nonanemic CABG patients (Engoren et al. 2014).
2.4.4 Thrombocytopenia

Thrombocytopenia is defined as a platelet count of under 150/nl. Thrombocytopenic ICU patients have been reported to have a higher prevalence of bleeding and greater transfusion requirements even with mild thrombocytopenia (Strauss et al. 2002). The bleeding risk was observed to increase with the decrease in platelet count (Strauss et al. 2002). CABG surgery was shown to be an independent risk factor for ICU-acquired thrombocytopenia in a large, over 20,000 patients cohort study, in which thrombocytopenia was defined as a platelet count > 100/nl (Williamson et al. 2013). The same study also found both prevalent and incident thrombocytopenia in the ICU to be associated with an increased risk of major bleeding and mortality.

Idiopathic thrombocytopenic purpura (ITP) is a relatively rare autoimmune disorder with a low platelet count that may predispose to bleeding. Concomitantly, these patients display an increased risk for thrombosis and atherosclerosis related to a high presence of hemostatic factors and chronic steroid therapy (Russo et al. 2011). In a review article of 32 CABG patients with ITP, Russo et al. (2011) reported a 12.5% rate of significant bleeding, and an approximately 3% rate of surgical re-exploration, which indicates a moderate increase in bleeding risk compared to the general population.

2.4.5 Age

As the human lifespan has increased over the decades, the incidence of coronary artery bypass grafting surgery in elderly patients has also been increasing. When compared to younger CABG patients (age 70 years or younger), the elderly patients had postoperative complications more frequently, such as pulmonary complications, inotropic drug use, intra-aortic balloon pump use, and infection (Sabzi et al. 2013). Older age is also associated with an increased likelihood of intraoperative transfusions (Nolan et al. 2013). Preoperative surgical risks such as chronic obstructive pulmonary disease, myocardial infarction, and emergent surgery were also more frequent in elderly patients (Sabzi et al. 2013).

2.4.6 Bleeding disorders

Inherited hemostatic abnormalities in coagulation factors or platelet function causes improper blood clotting. It is estimated that up to 1% of the general
population has a congenital bleeding disorder (Mensah & Gooding 2015). The majority of these hereditary inherited bleeding disorders (HBDs) include the hemophilias, von Willebrand’s disease, and inherited qualitative platelet defects. The rest of the bulk is distributed between much rarer conditions.

The most common of the HBDs is von Willebrand’s disease (VWD), which involves either a quantitative (type 1, 75% of all cases) or a qualitative (type 2) defect in von Willebrand factor (vWF) or a marked decrease or absence of vWF (type 3, rare). In primary hemostasis, the vWF is a multifunction protein that mediates platelet to platelet and platelet to collagen adhesions and serves as a carrier protein for circulating factor VIII. Hemophilias (Hemophilia A [Hem A] and Hemophilia B [Hem B] being the most common types) are inherited, X-linked recessive clotting factor deficiencies, which result in a deficiency of factor VIII and factor IX. The severity of clinical expression is largely dependent on the baseline factor level, by which hemophilia can be divided into severe (factor VII or IX > 1%), moderate (1–5%) or mild (> 5%) types (Mensah & Gooding 2015).

There are no commonly accepted guidelines for the peri-operative treatment of cardiac surgery patients with inherited bleeding disorders, nor are there many recent studies on the matter. Bhave et al. (2015) retrospectively examined seventeen patients with HBDs (hemophilia or VWD) who underwent cardiac surgery. These patients underwent perioperative individualized factor replacement protocol depending on their underlying condition, its severity, the cardiac procedure performed, and postoperative events. They found that patients with HBDs have more reoperations due to bleeding than non-HBD patients, but HBD was not found to increase mortality. In conclusion, a successful surgical treatment of HBD patients can be carried out safely with careful preoperative planning employing a multidisciplinary approach (Bhave et al. 2015, Mensah & Gooding 2015).

2.4.7 Diabetes

Zhang et al. (2011) studied 100 217 patients undergoing CABG in a quantitative meta-analysis; they concluded that patients with diabetes mellitus (DM) are at increased risk of mortality, stroke, renal failure, sternal infection and blood transfusion when compared to those without DM, despite evolving definitions of DM and practice patterns.
2.5 Technical factors

2.5.1 Off-pump vs. on-pump surgery

Several studies have found off-pump coronary artery bypass surgery to decrease the need for transfusion and reoperation for bleeding when compared with conventional coronary artery bypass grafting with cardiopulmonary bypass (CPB) (Puskas et al. 2003, Lemma et al. 2012, Cakir et al. 2014, Dhurandhar et al. 2015). Repeat CABG patients have higher transfusion rates when compared to patients with primary surgery (Bracey et al. 1995). Dohi et al. (2015), however, found that the off-pump technique decreased the need for blood transfusion in redo CABG.

2.5.2 Surgeon

Training cardiac surgeons have the potential to lead to longer operating times and poorer patient outcomes because of the complexity and lack of minor cases in cardiac surgery. Trainee surgeons have been shown to have longer perfusion and crossclamp times (Yap et al. 2009, Bakaeen et al. 2012, Saxena et al. 2013). Senior-level cardiac surgeons have been found to perform more complex cases than surgeons-in-training, but no differences were found in clinical short- or long-term outcomes (eg. bleeding, sternal infection, renal failure, stroke) were not found (Stoicka et al. 2008, Saxena et al. 2013, Almassi et al. 2015). Yap et al. (2009) found trainee surgeons to have an increased risk for early postoperative myocardial infarction, but they also concluded that CABG surgery performed by trainee within a supervised program is a safe procedure with acceptable short- and midterm outcomes. In addition, training has been demonstrated to not compromise graft patency (Bakaeen et al. 2012).

An individual surgeon’s performance has, however, been found to independently predict excessive bleeding in patients undergoing cardiac surgery (Vuylsteke et al. 2011, Dixon et al. 2014).

2.5.3 Cardiopulmonary bypass (CPB)

Perioperatively, CPB affects the blood coagulation system via several mechanisms; the contact between the blood and the extracorporeal circuit activates the intrinsic pathway of coagulation (Davidson 2014); hemodilutional coagulopathy is caused
by fluid administration and the use of cardioplegia and CPB prime (Davidson 2014); the use of CPB pumps increase platelet activation and the risk of clot formation (Besser et al. 2015); the administration of heparin increases coagulopathy (Davidson 2014, Besser et al. 2015); the washing of shed blood removes the activation products of hemostasis and re-transfusion of this shed blood can cause further activation of coagulation system (Davidson 2014). A longer CPB duration has been reported as an independent risk factor of re-exploration for bleeding (Choong et al. 2007).

A minimized extracorporeal circulation has been developed in order to reduce the negative effects associated with cardiopulmonary bypass (CPB). According to Abdel et al. (2011), the mini-cardiopulmonary bypass (mini-CPB) system decreased postoperative blood loss and blood transfusion when compared to conventional CPB. Koivisto et al. (2010) found mini-CPB to be associated with improved cerebral protection in high risk (EuroSCORE ≥ 6) CABG patients, but found no statistical difference in postoperative bleeding or need for transfusion. In a meta-analysis of 13 randomized trials, Biancari and Rimpiläinen (2009) found that mini-CBP may be associated with a lower risk of postoperative stroke and blood losses; due to the large heterogeneity of methods and the small number of studies and patients, however, no clear conclusion could be drawn in that study.

2.5.4 Other technical factors/aspects

A prolonged operation/CPB time has been found to increase blood loss (Dixon et al. 2014). Also, the priority of the surgery has been proven to be associated with the severity of postoperative bleeding; the bleeding risk increases in urgent/emergency operations when compared to elective surgery (Vuylsteke et al. 2011, Dixon et al. 2014). In addition, combined surgery (coronary artery bypass + valve operation) has been found to increase bleeding when compared to a single type of operation (Vuylsteke et al. 2011).

2.6 Blood conservation strategies

2.6.1 Preoperative autologous blood donation

Preoperative autologous blood donation (PAD) is a procedure where the patient’s own blood is preoperatively collected and stored and then transfused in elective
surgery if needed. Over the last several years, there has been a significant downward trend in the use of PAD. This can be explained by a combination of several factors, including a decreasing real and perceived risk of disease transmission through allogeneic transfusion, the adoption of better patient blood management practices that have reduced the need for perioperative transfusion, and the increasing logistical and cost constraints of PAD programs (Vassallo et al. 2015). The potential benefits and risks of PAD are listed in table 3. Vassallo et al. (2015) recommend that PAD should be exclusively considered for patients with RBC alloantibodies necessitating rare blood unavailable in volumes likely to be required; those at serious psychological risk for refusal of necessary allotransfusion; and, possibly, selected healthy individuals planning procedures with at least a 50% risk of requiring 3 or more units of RBCs.

Table 3. Potential benefits and risks in using preoperative autologous blood donation (PAD), modified from an article by Vassallo et al. 2015.

<table>
<thead>
<tr>
<th>Potential benefits in using PAD</th>
<th>Potential risks in using PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminates risk of transmitting allogeneic diseases</td>
<td>Increases risk of perioperative anemia and transfusion events</td>
</tr>
<tr>
<td>Preserves the allogeneic blood supply during shortages</td>
<td>Potential unit loss due to administrative issues, cold agglutinins, and leukoreduction filtration failure or other production losses</td>
</tr>
<tr>
<td>Decreases likelihood of procedural delay during shortages (because of the unit expiration date)</td>
<td>Adds risk of significant donation reactions for patients with cardiopulmonary and other disease states</td>
</tr>
<tr>
<td>Reduces or abolishes risk of many allogeneic immunologic and allergic adverse reactions and eliminates risk of alloimmunization</td>
<td>Increasing donor inconvenience with fewer available sites at greater distances as collection volumes decline</td>
</tr>
<tr>
<td>Promotes transfusion acceptance in patients at psychological risk for refusal of blood</td>
<td>An expensive resource</td>
</tr>
<tr>
<td>May fulfill rare blood needs for patients with high-frequency or multiple alloantibodies</td>
<td>Catastrophic consequences for misadministration of marker-positive banked units</td>
</tr>
</tbody>
</table>

2.6.2 Acute normovolemic hemodilution

In acute normovolemic hemodilution (ANH), whole blood is removed, collected and stored from a patient after induction of anesthesia and before the heparinization. As blood is collected, the ANH volume is replaced with sufficient volumes of
colloid and/or crystalloid fluid to maintain hemodynamic stability and normovolemia. The main benefit of ANH is the availability of whole blood containing RBCs, clotting factors and platelets for reinfusion when necessary. In a couple of small studies, ANH was found to be ineffective in reducing the need for allogenic transfusion and postoperative bleeding (Casati et al. 2002, Höhn et al. 2002). However, Goldberg et al. (2015) concluded in a 13 534 patient’s prospective study that there is a significant association between ANH and reduced perioperative RBC transfusion in cardiac surgery patients. They also found that a larger volume of ANH provided the most profound reduction in RBC transfusions.

2.6.3 Intraoperative cell salvage

In cell salvage, the blood is collect from the surgical site and then the whole blood or only the RBCs are infused back into patient. There are several methods for achieving this, and some devices even perform centrifugal washing for removing non-cellular material before reinfusion. Several studies have demonstrated a reduction in postoperative blood loss (Carless et al. 2010, Vonk et al. 2013) and transfusion requirements (Klein et al. 2008, Wang et al. 2009, Carless et al. 2010, Vonk et al. 2013) in cardiac surgery patients when using intraoperative cell salvage. In coronary artery surgery, autologous blood transfusion with cell saver use reduces the use of intraoperative packed red blood cells and has been demonstrated to have no (negative) effect on postoperative morbidity (Niranjan et al. 2006, Carless et al. 2010).

2.6.4 Mediastinal shed blood transfusion

In cardiac surgery, reinfusion of shed mediastinal blood is used to conserve allogenic blood components. Sirvinskas et al. (2007 and 2005) found postoperative re-infusion of autologous RBCs processed from shed mediastinal blood to not increase bleeding tendency and to reduce the requirement for allogeneic transfusion when compared to those patients whose mediastinal blood was discarded. They also concluded that re-infusion was effective in reducing the rate of infective complications and the length of postoperative in-hospital stay.

Similar findings were reported by Folkersen et al. (2011), who concluded in their study that, in over 620 consecutive cardiac surgery patients receiving reinfusion of shed mediastinal blood, the amount of postoperative drainage and the allogenic blood transfusion (but no FFP or platelets transfusion) was decreased.
2.7 Pharmacological interventions for bleeding

2.7.1 Antifibrinolytics

Aprotinin

Diffuse microvascular bleeding is usually treated with antifibrinolytics in or after cardiac procedures. Aprotinin is a broad-spectrum serine protease inhibitor, which was withdrawn from the market in some countries due to its serious side-effects, e.g. increased risk of mortality (Fergusson et al. 2008). Aprotinin is known, however, to have the highest potential in antifibrinolytics to reduce perioperative blood loss, the amount of blood transfusion, and re-exploration for bleeding and there some rise in criticism over its withdrawal has been seen (Dhir 2013, Beckerman et al. 2013).

Tranexamic acid

Epsilon-aminocaproic acid (EACA) and tranexamic acid are synthetic lysine analogues that prevent fibrinolysis by inhibiting the plasmin-plasminogen system. Tranexamic acid dosing varies between 30 to 100 mg per kilogram. In a large systematic review, lysine analogues effectively reduced blood loss and the need for RBC transfusion, but they did not decrease reoperation rate (Henry et al. 2011). These positive effects were also found in the use of low-dose tranexamic acid (Ghaflari Nejad et al. 2012, Esfandiari et al. 2013). No significant difference was observed when comparing the efficacy of EACA and tranexamic acid together (Henry et al. 2011, Raghunathan et al. 2011). In a study of over 4 600 CAGB patients, Myles et al. (2017) found tranexamic acid to be associated with a lower risk of bleeding than placebo, without a higher risk of death or thrombotic complications within 30 days after surgery. In a meta-analysis of ten studies, however, tranexamic acid was found to be associated with a higher risk of postoperative seizures and the incidence rate of seizures increased when the dose levels increased (Lin & Xiaovi 2016).

There has been increasing evidence that the topical application of aminocaproic acid may decrease postsurgical bleeding after major surgical procedures, but further data is needed regarding the safety of this hemostatic approach (Ipema & Tanzi 2012).
2.7.2 Protamine

Protamine sulfate binds heparin and is a standard therapy for reversing heparin anticoagulation during cardiac surgery. Hemodynamic responses to protamine are common, ranging from minor perturbations to cardiovascular collapse, and are related to in-hospital mortality after coronary artery bypass surgery (Welsby et al. 2005, Wang et al. 2013). These responses occur in slightly over 2% of patients after CPB (Wang et al. 2013).

Protamine administration can be administered as a fixed dose based on ACT and the amount of heparin given, or by titrating the dosage according to plasma heparin concentration. In a meta-analysis of four randomized controlled trials with 507 patients undergoing cardiac surgery with CPB, Wang et al. (2013) found titrated protamine dosing to be associated with significantly lower postoperative blood loss and need for RBC transfusion when compared to standard protamine dosing. Similar findings were made by Vonk et al. (2014), who concluded that individualized heparin and protamine management decreases the protamine-to-heparin ratio, thereby improving postbypass thromboelastometric hemostatic parameters, and reducing the incidence of severe blood loss.

2.7.3 PCC

Prothrombin complex concentrates (PCCs) are derived from a plasma pool, containing vitamin K-dependent coagulation factors (II, VII, IX and X), and are mainly used for the reversal of the anticoagulant effect of vitamin K antagonists (VKAs, e.g. warfarin). Due to the limited amount of controlled clinical studies, PCCs are not yet recommend by guidelines. However, PCCs are used in some countries in addition to or instead of fresh frozen plasma (FFP) (Arnekian et al. 2012).

In a small, retrospective study, Arnekian et al. (2012) found that an administration of PCC significantly decreases postoperative bleeding after CPB with no association of thromboembolic complications. In a small, randomized study, Demeyere et al. (2010) compared intraoperative administration of PCC to FFP in reversing anticoagulant effect of warfarin, and found PCC to be safer, faster and to cause less bleeding than FFP. Goldstein et al. (2015) also studied patients needing VKA reversal for urgent surgical or invasive interventions in a randomized, open label study and found PCC to be non-inferior and superior to plasma for rapid INR reversal and effective hemostasis.
2.7.4 Cryoprecipitate

Cryoprecipitate is a cold insoluble portion of fresh frozen plasma (FFP) that precipitates from controlled thawing of FFP at 1–6 degrees of Celsius. It is an allogeneic blood product containing higher molecular weight proteins such as Factor VIII, von Willebrand’s Factor, fibronectin, Factor XIII and fibrinogen. Cryoprecipitate (CPP) is most commonly used to replenish fibrinogen levels in patients with acquired coagulopathy, such as in clinical settings with hemorrhage including cardiac surgery, trauma, liver transplantation, or obstetric hemorrhage. CPP is recommended for supplementation when plasma fibrinogen levels decrease below 1 g/l; however, this threshold is empiric and is not based on solid clinical evidence (Nascimento et al. 2014).

Because cryoprecipitate is a pooled product that does not undergo pathogen inactivation, its administration has been associated with a number of adverse events such as transmission of infectious diseases, transfusion-associated circulatory overload, and transfusion-related acute lung injury (Nascimento et al. 2014). There are only a small number of studies concerning the use of CPP in cardiac surgery, even though it is most commonly used in cardiac patients. In a retrospective analysis of 1 714 propensity-matched cardiac surgery patients, Shaw et al. (2014) found blood transfusion, specifically cryoprecipitates, to be independently associated with an increased 5-year mortality. Because of these safety concerns, along with an increasing use of other alternative fibrinogen preparations, CPP has been withdrawn from use in a number of European countries.

2.7.5 rFVIIa

Recombinant factor VIIa (rFVIIa) is used in patients with hemophilia and inhibitors to coagulation factors VIII or IX, FVII deficiency, and acquired hemophilia for the prevention and/or treatment of surgical related bleeding. Activated factor VII involves the generation of thrombin by initial binding to tissue factor and subsequent activation of factor X on the platelet surface; activated factor X in combination with factor V leads to localized thrombin formation (Despotis et al. 2005).

Several small studies have demonstrated that rFVIIa decreases bleeding (Diprose et al. 2005, Karkouti et al. 2005, Raivio et al. 2005, Filsoufi et al. 2006, Pavani et al. 2015) and the need for transfusion (Raivio et al. 2005, Filsoufi et al. 2006, Masud et al. 2009). There is some increasing concern over a small increase
in the number of critical serious adverse events, including stroke, in patients treated with rFVIIa (Raivo et al. 2005, Gill et al. 2009). These findings are not, however, statistically significant, and the issue still requires further examination.

2.8 Use of blood products

2.8.1 Red blood cells


Perioperative RBC transfusion after CABG is associated with an increased risk of mortality during a 1-year follow-up period, with a large proportion of deaths occurring within 30 days. (Kuduvalli et al. 2005)

Several studies suggest that RBC transfusion may be harmful by increasing the risk of

- mortality (Surgenor et al. 2005, Koch et al. 2006, Paone et al. 2014),
- renal failure (Koch et al. 2006, Stone et al. 2012, Paone et al. 2014),
- initial ventilator time (> 8 h) (Paone et al. 2014),
- prolonged ventilatory support (Koch et al. 2006, Stone et al. 2012, Paone et al. 2014),
- serious infection (Koch et al. 2006, Möhnle et al. 2011, Stone et al. 2012),
- cardiac complications (Koch et al. 2006, Möhnle et al. 2011, Stone et al. 2012),
– increased troponin I release (Biancari & Kinnunen 2014),
– neurologic events (Koch et al. 2006),
– permanent stroke (Paone et al. 2014),
– vasoplegia (Alfirevic et al. 2011),
– atrial fibrillation (Stone et al. 2012, Paone et al. 2014),
– reoperation for bleeding (Paone et al. 2014),
– reoperation (Stone et al. 2012),
– repeat revascularization (Stone et al. 2012),
– total ICU time (> 24 h) (Stone et al. 2012, Paone et al. 2014),
– postoperative length of stay (> 7 days)/increased duration of total hospitalization (Stone et al. 2012, Paone et al. 2014).

In spite of the evidence suggesting a significant morbidity associated with blood transfusions, the use of blood and blood products remains high in cardiac surgery. Some reports have described a dose-dependent relationship between the number of RBC units transfused and mortality after cardiac surgery (Whitson et al. 2010, van Straten et al. 2010, Stone et al. 2012, Paone et al. 2014). The data is conflicting however, as to whether a threshold exists at which this association emerges. Surgenor et al. (2005) and Paone et al. (2014) reported that even 1 to 2 U of transfused RBCs was significantly associated with increased morbidity and mortality, whereas van Straten et al. (2010) found that only transfusion of ≥ 3 U correlated with reduced survival.

Bracey et al. (1999) speculate that lowering the hemoglobin threshold for RBC transfusion from 90 to 80 g/l after coronary artery bypass graft surgery would reduce blood use without adversely affecting patient outcome.

2.8.2 Fresh frozen plasma

Fresh frozen plasma (FFP) is obtained from whole blood and frozen within 8 hours of collection. It contains procoagulant factors such as fibrinogen and factors II, V, VII, VIII, IX, X and XI. It also contains anticoagulants such as protein C, protein S and antithrombin, along with a large number of proteins (e.g. immunoglobulins, albumin, and acute phase proteins). In cardiac surgery, FFP is administered to reduce bleeding prophylactically or therapeutically. Kasper et al. (2001), however, found no evidence supporting the prophylactic administration of a therapeutic dose of autologous FFP after CPB for preventing bleeding or transfusion of blood.
Octaplas® is a form of solvent-detergent-treated, virus-inactivated fresh frozen plasma. It is used for patients specifically requiring replacement of the labile clotting factors or other proteins with poor storage stability. It was made with the aim of reducing the risk of transmitting lipid-enveloped viruses and transfusion-related acute lung injury through blood transfusions.

In a systematic review, Desborough et al. (2015) found no significant difference in blood loss, need for re-operation or mortality between cardiac surgery patients who received FFP and those that did not.

### 2.8.3 Platelets transfusion

The decision of transfusion of platelets is often made empirically if microvascular bleeding persists after adequate heparin reversal after CPB. Furthermore, preoperative antiplatelet medication reduces the clinical threshold.

Platelet transfusion has been reported to increase morbidity and mortality after cardiac surgery (Spiess et al. 2004) but prior studies were limited by confounding variables including red blood cell (RBC) transfusions. McGrath et al. (2008) published a prospective study of platelet transfusion and patient’s outcome in 32,298 patients who underwent CABG, isolated valve, or combined CABG and valve procedure. After risk adjustment with both multivariable regression and propensity methods, platelet transfusion was not found to increase morbid events after cardiac surgery, even though these patients returned to the operating room for bleeding more frequently. Furthermore, Welsby et al. (2010) found no association between platelets storage age (currently limited to 5 days) and short-term outcome, survival, or postoperative infections.

### 2.9 Monitoring of coagulation

#### 2.9.1 ACT

Activated clotting time (ACT) represents whole blood clotting time and is linearly related to the concentration of heparin in the blood specimen. The ACT test is a gold standard assay for monitoring anticoagulation during extracorporeal life support in cardiac theatres because of its advantages over laboratory tests (Spinler et al. 2005): shorter time between sampling and results; smaller blood sample size; availability to have test performed by non-lab personnel; reduced errors associated
with sample mislabeling/mishandling; decreased risk of sample degradation with time. The target level for ACT is 400s in cardiac surgery.

Heparin resistance is defined as the inability to achieve the target ACT using an adequate, weight-based heparin dose. Any value below the ideal ACT value raises the concern that the patient is not fully anticoagulated, which may in turn result in excessive activation of the hemostatic system by the CPB (Finley & Greenberg 2013). Due to the complex nature of cardiac surgery and the multiple variables present, ACT does not solely depict heparin’s anticoagulant effect. Variables which can alter ACT results include hypothermia, hemodilution, aprotinin, platelets, etc. (Horton & Augustin 2013), all of which are commonly seen in cardiac surgery. A small prospective randomized study found ACT-based heparin and protamine dosing to have the same effect on hemostasis than individual titration curves (Radulovic et al. 2015).

2.9.2 Thrombelastography (TEG) or thromboelastometry (ROTEM)

Peri-operative platelet dysfunction is thought to be one of the main causes of postoperative bleeding (Corredor et al. 2015). Point-of-care (POC) platelet function tests, such as the TEG and ROTEM, have been devised to detect platelet dysfunction. They provide a graphic representation of clot formation and the subsequent lysis (Johansson et al. 2012). Blood in a heated cup is incubated at 37 °C and within the cup a pin is suspended connected to a detector system (a torsion wire in TEG and an optical detector in ROTEM). The cup and pin are rotated relative to each other through an angle of 4°45’. The movement is initiated either from the cup (TEG) or the pin (ROTEM). As fibrin forms between the cup and pin, the transmitted rotation from the cup to pin (TEG) or the impedance of the rotation of the pin (ROTEM) are detected at the pin and a trace generated (Johansson et al. 2009). The trace differs according to different pathological states. Different values can be determined from the trace: clotting time corresponding to the initiation phase of hemostasis, clot formation time reflecting the amplification phase, and clot strength and stability.

In cardiac surgery, TEG and ROTEM have been used to predict blood loss and transfusion requirements. Two prospective, randomized studies showed that the use of a TEG-guided algorithm reduced the consumption of blood products in CABG surgery (Agarwal et al. 2015, Ak et al. 2009). Corredor et al. (2015) reached the same conclusion in their systematic review and meta-analysis; the inclusion of POC platelet function tests into transfusion management algorithms is associated with a
reduction in blood loss and transfusion requirements in cardiac surgery patients. TEG has also been found to be useful for the identification of post-CPB bleeding complications (Hertfelder et al. 2005). Venema et al. (2010) found that TEG and ROTEM measurements are not interchangeable.

2.10 Clinical implications of severe bleeding

Excessive bleeding after cardiac surgery and its treatment are associated with the risks related to exposure to allogeneic blood and with significant use of hospital resources. Major bleeding is an independent risk factor for increased 30-day mortality (Ranucci et al. 2013). Re-exploration after cardiac surgery is a dreaded bleeding-related complication, as it is associated with significant mortality and morbidity (Moulton et al. 1996, Karthik et al. 2004, Ranucci et al. 2008). Centofanti et al. (2007) found that early reoperation for bleeding was independently associated with an increased risk of sternal wound infection, which causes considerable extra morbidity, mortality and costs after cardiac surgery, but also prolonged time for re-exploration is associated with a higher risk of complications after CAGB surgery (Karthik et al. 2004).
3 Aims of the present research

The aim of this study was to determine the risk factors and effects of perioperative bleeding and blood transfusion in isolated CABG patients. The detailed aims of the original articles were

I to evaluate the effects of preoperative ASA discontinuation on the patient’s outcome after CABG.
II to assess the safety of therapeutic oral anticoagulation (TOAC) in patients undergoing CABG surgery.
III to estimate the impact of individual surgeon’s performances on blood loss and need for re-exploration after CABG.
IV to evaluate the impact of re-exploration for bleeding after cardiac surgery on the patient’s immediate postoperative outcome.
V to study the impact of blood transfusion on the development of post-operative stroke after CABG.
VI to investigate the impact of the transfusion of blood products on intermediate outcome after CABG.
4 Material and methods

Table 4. Characteristics of the studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Study period</th>
<th>Study hospitals</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose ASA discontinuation</td>
<td>859</td>
<td>2008–2010 OYS, TYKS, Vaasa</td>
<td>Retrospective</td>
<td></td>
</tr>
<tr>
<td>TOAC discontinuation</td>
<td>270</td>
<td>2004–2009 OYS, TYKS</td>
<td>Retrospective</td>
<td></td>
</tr>
<tr>
<td>Individual surgeons’ impact</td>
<td>2,001</td>
<td>2006–2011 OYS</td>
<td>Prospective clinical registry</td>
<td></td>
</tr>
<tr>
<td>Re-exploration for bleeding</td>
<td>557 923</td>
<td>2011 -</td>
<td>Meta-analysis</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2,226</td>
<td>2008–2010 OYS, TYKS, Vaasa</td>
<td>Prospective clinical registry</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion and intermediate survival</td>
<td>2,001</td>
<td>2006–2011 OYS</td>
<td>Prospective clinical registry</td>
<td></td>
</tr>
</tbody>
</table>

In our studies, the EuroSCORE risk analysis was used to assess the patients’ operative risk. Intravenous heparin was used after sternotomy and was neutralized at the end of the procedure with protamine sulfate. If necessary, protamine was administered for bleeding during closure of the chest or within the first postoperative hour according to the ACT. Aprotinin was not used. Tranexamic acid was used intraoperatively according to the anesthesiologist’s orders and in Turku University Hospital postoperatively for bleeding. Enoxaparin was started postoperatively according to the patient’s weight on the evening of the day of surgery. ASA was restarted on the first postoperative day. Warfarin was started on the first postoperative day in patients on chronic oral anticoagulation or started de novo in case of persistent atrial fibrillation. Clopidogrel was used postoperatively in these patients only in case of allergy to ASA or recent percutaneous coronary intervention. In the ASA study, clopidogrel was not used postoperatively. All blood lost during the operation was collected in the cell saver reservoir, and washed, salvaged RBCs were autotransfused during or at the completion of the operation. Mediastinal blood/fluid was collected after surgery in a sterile collection chamber connected to 15 cm H²O wall suction via an underwater seal and then discarded. Platelets and FFP were transfused according to the quantity of bleeding, the patient’s INR, and platelet count. On the day of the operation, RBC transfusion threshold was set at 90 g/l. Later, RBCs were transfused if hemoglobin was under 80 g/l. Stroke was defined as a new neurologic deficit following surgery and lasting over 24 hours accompanied by new structural changes in computed tomography or magnetic resonance imaging. In the absence of structural changes at imaging, the diagnosis of stroke was made clinically by a neurologist. Renal failure was defined as postoperative renal failure requiring temporary or prolonged dialysis. Low-
cardiac-output syndrome was defined as a postoperative cardiac index of 2.0 l/min/m² or less, measured at 2 different times. Follow-up was complete for all patients, and data on causes and date of death were acquired from the Finnish National Registry Statistics Finland.

For more details, see the original articles.

4.1 Study I

The study of low-dose ASA discontinuation compared patients who used ASA (100 mg/day) within 3 days before CAGB surgery to those whose ASA was discontinued more than 3 days before surgery. The cutoff for the timing of ASA discontinuation was based on a preliminary analysis of the overall series. The exclusion criteria for the study population were preoperative use of other antiplatelet or anticoagulant drugs than ASA and only elective CABG patients were included. ASA was restarted during the first postoperative day. The primary outcome measurements were in-hospital death, stroke, new-onset renal failure requiring dialysis, re-exploration for excessive bleeding, use of blood products, and length of stay in the intensive care unit. Turku University Hospital also measured the release of troponin I among the other secondary outcome end-points. The composite outcome end-point included in-hospital death, low-cardiac-output syndrome, de novo dialysis, stroke, re-exploration for excessive bleeding, or an intensive care unit stay ≥ 5 days.

Statistical analyses were performed using the PASW 18 statistical software (IBM SPSS, Inc, Chicago, IL). Continuous variables are reported as mean standard deviations and as median when indicated. For univariate analysis, the Mann-Whitney test, Kruskal-Wallis test, Pearson’s chi-squared test, and Fisher exact test were used. The treatment groups were likely to differ markedly with respect to the pretreatment covariates. Thus, such differences were accounted for by developing a propensity score for the timing of ASA discontinuation. Logistic regression with backward selection was performed to calculate the risk, the so-called propensity score, of these patients to be included in the study groups. Variables having a p-value < 0.2 at univariate analysis were included in the logistic regression model. Variables included in the regression analysis were also chosen for clinical considerations to avoid over fitting of the regression model. Therefore, hypertension and type of graft were not included in the model, as these parameters were deemed unlikely to affect the immediate outcome of these patients. In addition, as there was a major imbalance between the study groups in the number of patients
who underwent surgery with epiaortic ultrasound and this likely affected the detection of a diseased ascending aorta, only epiaortic ultrasound was included in the regression analysis. To elucidate this issue further, a separate analysis of the outcome of these patients was performed based on the status of the ascending aorta as determined by epiaortic ultrasound.

ROC curve analysis was used to estimate the area under the curve of the model predicting the probability of being included in any of the study groups. The calculated propensity score was used for 1-to-1 matching, to adjust for other variables in estimating their impact on the postoperative outcome at multivariate analysis and for stratification, i.e., analysis of outcome events in quartiles of propensity score. The latter analysis was performed by defining quartiles, i.e., in 4 equal parts, of the propensity score. In fact, the propensity score can be stratified usefully, as it can balance the distribution of the preoperative covariates in the treatment groups in ordered subclasses of propensity score without excluding any patient from the analysis as otherwise occurs in 1-to-1 propensity score matching. In our study, stratification in quintiles could not be used because of the limited size of the database. We performed one-to-one propensity score matching between study groups according to a difference in the propensity score of 0.005 among patients in the study groups. Logistic regression with backward selection was used to adjust the effect of preoperative aspirin discontinuation on the propensity score. The impact of preoperative ASA discontinuation on postoperative troponin I release was evaluated using repeated-measures test.

### 4.2 Study II

The TOAC discontinuation study compared 103 patients who underwent CAGB during therapeutic oral anticoagulation (TOAC group, INR 2.0–3.5) to a control group of 81 patients in whom preoperative INR was subtherapeutic (INR ≤ 1.5). Stroke risk was estimated using the CHADS2 index (Gage et al. 2001), in which 1 point is given for congestive heart failure, 1 point for hypertension, 1 point for age over 75 years, 1 point for diabetes and 2 points for prior stroke or transient ischemic attack. CHADS2 was used, even though it has mainly been validated for patients with atrial fibrillation (Gage et al. 2001). The most common strategy in elective surgery is to discontinue warfarin two days prior to surgery with no preoperative heparins. Only selected patients with acute coronary syndrome or with a prior mechanical heart valve used preoperative enoxaparin. ASA and/or clopidogrel were discontinued for 5 to 7 days when feasible, i.e. when the patient’s condition was
stable enough to allow a delay in surgery for a few days. Warfarin was restarted on the first postoperative day if significant bleeding did not occur.

The primary in-hospital outcomes were death, stroke, myocardial infarction, new onset renal failure, and resternotomy due to postoperative hemorrhage. The composite of major adverse events was defined as any of the above complications during the index hospitalization. Consumption of blood products and length of stay in the intensive care unit and total hospital stay were also evaluated.

All data were analyzed using the SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, Ill., USA). Following a test of statistical normality, continuous variables are shown as mean ± standard deviation or median and 25th–75th interquartile range (IQR) as appropriate. Spearman's test, chi-square test, Fisher exact test, and the Mann-Whitney test were used for univariate analysis. Logistic regression with backward selection was performed to calculate the risk of these patients being included in either the TOAC or the control group. Variables with a p < 0.2 at univariate analysis have been included in the regression model. ROC curve analysis was also used to assess the impact of continuous variables on dichotomous outcome end-points. Logistic regression was used to adjust the impact of TOAC on the outcome end-points for other variables. A p < 0.05 was considered statistically significant.

4.3 Study III

The study of individual surgeons’ impact on the outcome included 12 surgeons. Two surgeons had about 2 years of post-residency experience and the others had 9 years of post-residency experience. Neither the surgeons or the anesthesiologists were aware of the study at the time of surgery. Patients were allocated to surgeons in order to achieve a homogenous caseload for each staff member without matching the operative risk to the experience of a particular surgeon. A higher operative risk was expected, however, in patients whose surgeries were performed by surgeons who were on call more frequently during the study period. Because of this potential bias, emergency surgery, additive EuroSCORE, and other important clinical variables were chosen to adjust the impact of individual surgeons.

Patients who were on long-term anticoagulation and referred for elective surgery had warfarin discontinued 2 days before surgery, and enoxaparin was only used preoperatively in patients with an acute coronary syndrome or with a mechanical heart valve. Clopidogrel and/or ASA were discontinued for 5 and 7 days, respectively, when feasible.
Re-exploration was indicated in occurrences of

1. drainage > 500 ml during the first postoperative hour, > 400 ml during each of the first 2 hours, > 300 ml during each of the first 3 hours, or > 1 000 ml in total during the first 4 hours;
2. continuous bleeding throughout the first 12 hours, leading to total bleeding > 100 ml/h;
3. sudden massive bleeding;
4. obvious signs of cardiac tamponade secondary to active or previous bleeding;
5. cardiac arrest of a patient who continued to bleed; and
6. excess bleeding despite the correction of coagulopathies.

According to these criteria, re-exploration performed a few days after surgery because of cardiac tamponade caused by a significant amount of intrapericardial hematoma and/or frank blood was considered re-exploration for excessive bleeding.

For this study, the primary outcome measurement was the re-exploration for excessive bleeding. The secondary outcome measurements were the amount of postoperative blood loss from surgical drains, 30-day mortality, low-cardiac-output syndrome, new-onset renal failure requiring dialysis, stroke, resternotomy for mediastinitis, and length of stay in the intensive care unit. Postoperative blood loss was defined as the amount of blood lost from surgical drains measured on the morning of the first postoperative day or in the afternoon/evening in patients who underwent night-time surgery. Postoperative blood loss was dichotomized according to 95th percentiles of postoperative blood loss (1 600 ml).

All data were analyzed using the PASW 18 statistical software (IBM SPSS, Inc, Chicago, IL). Continuous variables are reported as mean standard deviation or median and interquartile range. The Pearson chi-squared test, the Fisher exact test, and the Monte Carlo method were used as appropriate for the univariate analysis of nominal and ordinal variables. The Kruskal-Wallis and Mann-Whitney tests were used for the univariate analysis of continuous variables. Survival analyses were performed using the Kaplan-Meier test. Logistic and linear regression with backward selection was used for the multivariate analysis to identify the independent predictors of the immediate postoperative outcome. Only variables with a p-value < 0.20 at univariate analysis were included in the regression model.
4.4 Study IV

The meta-analysis on re-exploration for bleeding was performed in accordance with the Cochrane Handbook for Systematic Reviews (Higgins & Altman 2008). An English-language literature review was performed through PubMed, Scopus, Science Direct, and Cochrane Library for any study up to January 2011 evaluating outcome after re-operation for bleeding subsequent to adult cardiac surgery. The words used in the search were: ‘re-exploration’, ‘reoperation’, ‘resternotomy’, and ‘bleeding’ combined with ‘coronary artery bypass’, ‘coronary bypass’, ‘myocardial revascularization’, ‘aortic valve’, ‘mitral valve’, ‘ascending aorta’, and ‘cardiac surgery’.

The reference lists of the articles obtained were also searched. For this analysis, we considered both prospective and retrospective observational studies published in the English language as full-length articles and reporting on the outcome of patients who underwent re-exploration for bleeding after adult cardiac surgery. Studies including re-exploration for causes other than major postoperative bleeding were excluded. We restricted this analysis to studies published after year the 1980 to avoid any major bias in terms of medical and surgical-treatment approaches. We did not include unpublished data or data reported in only abstract form in this study. We applied the guidelines for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al. 2000).

The primary outcome end-point was immediate postoperative mortality defined as any death occurring during in-hospital stay or during the 30-day postoperative period. The secondary outcome end-points were stroke, acute renal failure, need of intra-aortic balloon pump, sternal wound infection, and prolonged mechanical ventilation. Sternal wound infection was defined as any deep wound infection or mediastinitis. Acute renal failure was defined as an increase in postoperative serum concentration of creatinine > 200 μmol/l or need of dialysis. Prolonged mechanical ventilation and stroke were reported, as originally defined by the authors.

Statistical analysis was performed using Review Manager 5.0.18 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) (Stroup et al. 2000). Differences in continuous variables were reported as mean differences with 95% confidence interval (95% CI). Differences in preoperative and outcome dichotomous variables were reported as risk differences (RD) with 95% CI. The pooled risk of adverse event was expressed as a risk ratio (RR) with 95% CI. The natural logarithm of adjusted odds ratio (OR) and the estimated
standard error of each study were entered into Review Manager to estimate pooled adjusted OR for in-hospital mortality by generic inverse variance analysis. The standard error of each retrieved adjusted OR was estimated using the following formula: ln SE = (ln of upper confidence limit – ln of lower confidence limit)/3.92. Generic inverse variance analysis was first performed for adjusted ORs obtained from the multivariate analysis only, and then by also including unadjusted ORs estimated from propensity score-matched pairs. Heterogeneity has been assessed by using the I² statistic. An I² < 40% was considered as nonimportant heterogeneity. In cases of important heterogeneity, we used the random-effects analysis; otherwise we used fixed-effect analysis. Because of the small number of studies included herein, we did not perform meta-regression analysis. Instead, sensitivity analysis was performed according to the type of surgery, mid-date of studies, and timing of re-exploration.

4.5 Study V

This study evaluated the impact of blood transfusion on the development of postoperative stroke after CABG. ASA was discontinued preoperatively in most of the patients undergoing elective surgery and administered until the day of surgery in patients with acute coronary syndrome.

The main outcome end-point was stroke. Secondary outcome end-points were in-hospital death, new onset renal failure requiring dialysis, re-exploration for excessive bleeding, use of blood products and duration of stay in the intensive care unit. A composite outcome end-point included in-hospital death, stroke, low cardiac output syndrome, re-exploration for excessive bleeding, de novo dialysis, or an intensive care unit stay ≥ 5 days. Statistical analysis was performed using the PASW version 18 statistical software (IBM SPSS Inc., Chicago, IL, USA). Continuous variables are reported as the mean ± standard deviation. Pearson’s chi-square test, Fisher’s exact test and Mann-Whitney’s test were used for univariate analysis. Correlations between continuous variables were assessed by Spearman’s test. Logistic regression with the help of backward selection was used for multivariate analysis. Only variables with a p < 0.050 at univariate analysis were included in the logistic regression model.

We estimated the prognostic impact of blood transfusion by defining a priori classes of increasing amount of transfused blood products according to the type of blood product (red blood cells units: 0, 1–2 units, or > 2 units; platelet units: 0, 1–8 units, or > 8 units; Octaplas units: 0, 1–4 units, or > 4 units). The sum of these
classes was used to estimate the overall amount of blood products and to identify those patients who received large amount of blood products. This was done assuming that only patients who received > 2 units of red blood cells, > 4 units of Octaplas and/or > 8 units of platelets were those at higher risk of transfusion-related adverse events. These cut-off values were later confirmed by classification and regression tree analysis (CART). CART analysis was performed to identify independent risk factors for post-operative stroke. Validation of the classification tree procedure was assessed by cross-validation through 25 folds. The minimum number of patients for the parent node was set at 30 and the minimum for the child node was 1. The maximum classification tree depth was 5. Gini’s method was used to measure impurity, which is the extent to which a node does not represent a homogenous subset of cases. A minimum change in improvement was set at 0.0001. ROC curve analysis was used to estimate the area under the curve of probabilities values estimated by the CART analysis model outcome. We observed that patients who received all three types of blood products had a significantly higher risk of stroke compared to those who did not receive any blood transfusion. These two groups differed markedly with respect to pre-operative co-variables; such differences between the study groups, i.e. patients who did not receive any blood product and those who received red blood cells, Octaplas and platelet transfusion, were accounted for by developing a propensity score for the treatment method. Propensity score analysis was used to control for all known patients’ factors that might be related to the decision to administer blood products, and thus potentially to the outcome of interest. The propensity score was calculated by logistic regression with backward selection by including clinical variables with a certain difference between the study groups as indicated by \( p < 0.050 \) in univariable analysis. ROC curve analysis was used to estimate the area under the curve of the model, predicting the probability of being included in the study groups. The calculated propensity score was only employed for one-to-one matching, as our purpose was to identify two study groups with similar characteristics in order to fulfill the criteria of comparability. One-to-one propensity score matching between study groups was performed according to a difference in the logit of propensity score of less than 0.04 between each pair of patients in the study groups. Such a caliper width was equal to 0.2 of the standard deviation of the logit of the herein calculated propensity score. Standardized differences were estimated to compare the means of continuous and binary variables between the study groups. Standardized differences less than 0.1 were taken to indicate a negligible difference in the mean or prevalence of covariates between the study groups. The propensity
score was used to adjust transfusion of all three types of blood products in predicting postoperative stroke.

4.6 Study VI

In this study, we collected data on the use of blood products (RBC, platelets, FFP, and Octaplas®) during the operation day up to 30 days after surgery from a prospective computerized database (VerSo).

The primary outcome end-points of this study were all-cause and cardiac mortality. Secondary outcome end-points were 30-day mortality, low cardiac output syndrome (cardiac index < 2.0 l/min/m² at least twice), postoperative use of inotropes for more than 12 h, stroke, and de novo dialysis.

All data were analyzed using the PASW v. 18 statistical software (IBM SPSS Inc., Chicago, IL, USA). Continuous variables are reported as the mean ± standard deviation. We evaluated the correlation between continuous variables by Spearman’s test. Logistic regression was used to adjust transfusion of any blood product for additive the EuroSCORE. Survival analyses were performed using Kaplan–Meier’s method and Cox’s regression method with backward selection. Only variables with a p < 0.05 at univariate analysis have been included in the regression model.
5 Results

5.1 Low-dose ASA discontinuation

The aim of the present study was to evaluate the effects of preoperative ASA discontinuation on patient outcome after CABG. A sensitivity analysis of different timings of discontinuation of ASA showed that discontinuing ASA \( \leq 3 \) days before surgery was associated with the most beneficial effects compared with more a prolonged pause in ASA treatment, at least in the postoperative stroke rate. Therefore, a cutoff timing of \( > 3 \) days of ASA discontinuation was chosen for this analysis (Table 5). A similar amount of postoperative blood loss and a similar rate of re-exploration for excessive bleeding were observed in the study groups with different timings of preoperative ASA discontinuation. A more frequent use of blood products was observed, however, in patients whose ASA treatment was discontinued \( > 7 \) days, but this was clearly related to interhospital differences in the use of blood products (logistic regression, \( p < 0.0001 \)). The only evident, but not statistically significant, difference was the higher rate of postoperative stroke (1.9% v 0.4%, \( p = 0.13 \)) observed in patients whose ASA treatment was discontinued \( > 3 \) days before surgery. This finding was not related to interhospital differences (logistic regression, \( p = 0.474 \)).

ASA discontinuation \( > 3 \) days was associated with a trend towards a higher postoperative stroke rate versus no ASA discontinuation after off-pump (1.9% v 0%, \( p = 0.58 \)) and on-pump (2.0% v 0.6%, \( p = 0.46 \)) surgery, but such differences did not achieve statistical significance. No stroke occurred in patients in whom the ascending aorta was left untouched. In patients undergoing surgery with epiaortic ultrasound, the stroke rate was higher in patients with ASA discontinued \( > 3 \) days (2.2% v 0%, \( p = 0.13 \)). Such a difference was also observed in 307 patients with an ascending aorta free of atherosclerosis (1.9% v 0%, \( p = 0.25 \)). An analysis of 32 patients with a diseased ascending aorta showed that ASA discontinued \( > 3 \) days was associated with a nonsignificant increase of stroke risk (4.3% v 0%, \( p = 1.00 \)).

Data on the troponin I serum concentration, as measured with the same technique, on the day before surgery and on the first and third postoperative days, were available in 206 patients who underwent surgery at Oulu University Hospital. A repeated measures test showed no significant differences in the postoperative troponin I release between the study groups (test of between-subjects effects, \( p = 0.90 \)).
Table 5. Adverse Events During In-Hospital Stay After Coronary Artery Bypass Graft Surgery According to Different Timings of ASA Discontinuation.

<table>
<thead>
<tr>
<th>Outcome Endpoint</th>
<th>Late Use of ASA (n = 240)</th>
<th>ASA Pause 4–7 d (n = 273)</th>
<th>Pause &gt; 7 d (n = 346)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1 (0.4)</td>
<td>5 (1.8)</td>
<td>7 (2.0)</td>
<td>0.236</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>2 (0.8)</td>
<td>2 (0.7)</td>
<td>4 (1.2)</td>
<td>0.907</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>18 (7.5)</td>
<td>24 (8.8)</td>
<td>19 (5.5)</td>
<td>0.259</td>
</tr>
<tr>
<td>Postoperative blood loss (ml)</td>
<td>782 ± 432</td>
<td>940 ± 748</td>
<td>775 ± 392</td>
<td>0.015</td>
</tr>
<tr>
<td>Resternotomy for bleeding</td>
<td>10 (4.2)</td>
<td>15 (5.5)</td>
<td>4.6 (5.0)</td>
<td>0.770</td>
</tr>
<tr>
<td>Resternotomy for &quot;surgical&quot; bleeding</td>
<td>6 (2.5)</td>
<td>9 (3.3)</td>
<td>14 (4.0)</td>
<td>0.619</td>
</tr>
<tr>
<td>RBC1 units transfused</td>
<td>0.9 ± 1.7</td>
<td>0.9 ± 2.4</td>
<td>1.2 ± 1.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FFP2 units transfused</td>
<td>0.3 ± 0.8</td>
<td>0.4 ± 1.5</td>
<td>0.5 ± 1.4</td>
<td>0.060</td>
</tr>
<tr>
<td>Platelet units transfused</td>
<td>0.5 ± 1.9</td>
<td>0.7 ± 3.5</td>
<td>1.0 ± 2.7</td>
<td>0.010</td>
</tr>
<tr>
<td>De novo dialysis</td>
<td>2 (0.8)</td>
<td>3 (1.1)</td>
<td>1 (0.3)</td>
<td>0.451</td>
</tr>
<tr>
<td>ICU3 stay ≥ 5 d</td>
<td>9 (3.8)</td>
<td>18 (6.6)</td>
<td>13 (3.8)</td>
<td>0.206</td>
</tr>
<tr>
<td>Composite adverse end-point4</td>
<td>29 (12.1)</td>
<td>45 (16.5)</td>
<td>48 (13.9)</td>
<td>0.368</td>
</tr>
</tbody>
</table>

1 RBC, red blood cell, 2 FFP, fresh frozen plasma, 3 ICU, intensive care unit, 4 In-hospital death, low-cardiac-output syndrome, de novo dialysis, stroke, re-exploration for excessive bleeding, or intensive care unit stay ≥ 5 days.

Evaluation of the immediate outcome in patients with and without ASA discontinuation > 3 days was likely biased by the major differences existing in the baseline variables of the study groups. A propensity score was therefore calculated for 135 pairs and the area under the receiver operating characteristics curve was 0.793 (95% confidence interval [CI] 0.755–0.831, p < 0.0001). Among these pairs matched by the propensity score, a similar amount of postoperative blood loss, a similar rate of re-exploration for excessive bleeding, and a similar use of blood products were observed. Also, patients whose ASA treatment was discontinued > 3 days before surgery had a significantly higher rate of postoperative stroke (5.9% v 0.7%, p = 0.02) and tended to have a higher risk for the composite adverse end-point (19.6% v 12.4%, p = 0.09).

ASA discontinuation > 3 days before surgery tended to be associated with postoperative stroke when adjusted for the propensity score (p = 0.10). Similarly, a trend toward an increased risk of stroke after ASA discontinuation > 3 days was observed in 3 quartiles of the propensity score (Figure 3). When adjusted for the propensity score, ASA continued until the day of surgery or discontinued ≤ 3 days...
before surgery was not associated with an increased risk of re-exploration for excessive bleeding ($p = 0.99$), red blood cell transfusion ($p = 0.80$), the composite outcome end-point ($p = 0.43$), and in-hospital mortality ($p = 0.37$). No difference in red blood cell transfusions was observed in the quartiles of the propensity score (Figure 4).

**Fig. 3.** Postoperative stroke rates after coronary artery bypass surgery according to ASA discontinuation and propensity score quartiles. The observed differences between study groups were not statistically significant.

**Fig. 4.** Rates of red blood cell transfusion after coronary artery bypass surgery according to the timing of ASA discontinuation and propensity score quartiles. The observed differences between the study groups were not statistically significant.
5.2 TOAC discontinuation

The TOAC group consisted of 103 patients in whom CABG was performed during therapeutic oral anticoagulation (INR 2.0–3.5). The control group consisted of 81 patients in whom preoperative INR was subtherapeutic (INR ≤ 1.5). CABG was performed in the entire population after a mean cessation of warfarin of 2.4 days and the mean INR at the time of operation was 1.9 (range from 1.0 to 5.7). CABG was performed with uninterrupted warfarin (≤ 1 day pause) in 63 patients (23%). In 24 patients (9%), the exact time of warfarin interruption was not available. In both groups, the most common indication for warfarin was atrial fibrillation, followed by a history of stroke. Acute myocardial infarction tended to be a more common indication for CABG in the TOAC group leading to more common emergency operations in this group. Emergency surgery (OR 4.09, 95% CI 1.13–14.76; p = 0.03) was the only variable significantly different on logistic regression. This finding confirmed the homogeneity of the study groups and prevented a propensity score analysis, and because of this, we used the additive EuroSCORE (OR 1.17, 95% CI 1.05–1.30; p = 0.004) when included into logistic regression to adjust clinical variables for the outcome analysis. In the TOAC group, the mean INR on the day of surgery was 2.4.

Enoxaparin was used until surgery in 34 control patients (44.2%) and in 54 TOAC patients (52.9%) (chi-square test, p = 0.24). ASA was discontinued for a mean of 8.3 ± 8.0 days before CABG and was used preoperatively ≤ 5 days prior to CABG in 35 control patients (43.2%) and in 39 TOAC patients (37.9%) (p = 0.46). Six control patients (7.4%) and 7 TOAC patients (6.8%) were treated with clopidogrel ≤ 5 days prior to CABG (p = 0.60).

In-hospital mortality was comparable in the TOAC and control groups (4.9% versus 2.5%, p = 0.40, adjusted for EuroSCORE: p = 0.49). Similarly, there were no significant differences between the groups in the other major complications or in the number of patients suffering from any major adverse event (Table 6). The need for red blood cell transfusions was comparable between the groups, but postoperative blood loss was higher in the TOAC group (941 ± 615 vs. 754 ± 610 ml, p < 0.01) and they also needed a longer stay in the intensive care unit and more fresh frozen plasma transfusions than the controls (Table 6). There were no significant independent predictors for any of the major complications. Clopidogrel use within 5 days of CABG and the preoperative use of enoxaparin were the only significant independent predictors for the incidence of the composite end-point (OR 4.8, 95% CI 1.4–16.2, p = 0.01 and OR 2.6, 95% CI 1.1–6.5,
p = 0.04, respectively). There were 4 patients with subtherapeutic perioperative oral anticoagulation (INR N3.5). In this subgroup of patients, none of patients died or required an intensive care unit stay longer than 3 days. Reoperation for bleeding was required for one patient.

Table 6. Immediate postoperative outcome in patients with therapeutic (TOAC group) and subtherapeutic (Control group) oral anticoagulation who underwent coronary artery bypass surgery (CABG).

<table>
<thead>
<tr>
<th>Postoperative outcome</th>
<th>Whole study population (n = 270)</th>
<th>TOAC group INR 2.0–3.5 (n = 103)</th>
<th>Control group INR ≤ 1.5 (n = 81)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>10 (3.7)</td>
<td>5 (4.9)</td>
<td>2 (2.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.7)</td>
<td>2 (1.9)</td>
<td>0 (0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (3.7)</td>
<td>4 (3.9)</td>
<td>3 (3.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>4 (1.5)</td>
<td>2 (1.9)</td>
<td>2 (2.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Reoperation</td>
<td>23 (8.5)</td>
<td>12 (11.7)</td>
<td>5 (6.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Combined adverse outcome³</td>
<td>27 (10.0)</td>
<td>18 (17.5)</td>
<td>9 (11.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Prolonged need for inotropics</td>
<td>137 (50.7)</td>
<td>57 (55.3)</td>
<td>34 (42.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Postoperative hemoglobin</td>
<td>100 ± 14</td>
<td>100 ± 15</td>
<td>100 ± 17</td>
<td>0.96</td>
</tr>
<tr>
<td>Patients requiring red blood cell transfusion</td>
<td>155 (57.4)</td>
<td>63 (61.2)</td>
<td>46 (56.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Postop. drainage bleeding (ml)</td>
<td>857 ± 618</td>
<td>941 ± 615</td>
<td>754 ± 610</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Red blood cell units</td>
<td>2.1 ± 3.1</td>
<td>2.1 ± 2.8</td>
<td>2.1 ± 3.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Fresh frozen plasma units</td>
<td>2.1 ± 2.7</td>
<td>2.8 ± 3.0</td>
<td>1.3 ± 2.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Platelet units</td>
<td>1.1 ± 2.8</td>
<td>1.2 ± 3.1</td>
<td>1.2 ± 3.1</td>
<td>0.53</td>
</tr>
<tr>
<td>Intensive care unit stay (days)</td>
<td>3.3 ± 4.1</td>
<td>3.7 ± 3.9</td>
<td>2.7 ± 3.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>In-hospital stay (days)</td>
<td>8.8 ± 5.4</td>
<td>9.1 ± 5.0</td>
<td>8.6 ± 5.8</td>
<td>0.15</td>
</tr>
</tbody>
</table>

³Death, myocardial infarction, stroke, acute renal failure or reoperation; Values are reported as mean ± standard deviation or absolute numbers with related percentages in parentheses.

5.3 The impact of the individual surgeon

Of the entire study group of 2001 CABG patients, one hundred thirteen (5.3%) underwent re-exploration for excessive bleeding and in 83 patients (73.5%) the bleeding site was identified as being surgical. The sources of bleeding are listed in table 7. At univariate analysis, patients who underwent re-exploration had a significantly higher risk of 30-day mortality (6.2% v 2.6%, p = 0.038), low-cardiac-output syndrome (22.1% v 11.6%, p = 0.001), prolonged need of inotropes (43.4% v 26.1%, p < 0.0001), atrial fibrillation (51.3% v 41.3%, p = 0.039), and an intensive care unit stay ≥ 5 day (11.2% v 5.0%, p < 0.0001) but not of stroke (2.7%
v 2.1%, p = 0.732) or re sternotomy for mediastinitis (3.5% v 1.2% p = 0.062). When adjusted for the additive EuroSCORE, re-exploration for bleeding was only associated with an increased risk of low-cardiac-output syndrome (OR 2.239, 95% CI 1.328–3.777, p = 0.003), prolonged need of inotropes (OR 1.894, 95% CI 1.198–2.994, p = 0.006), and an intensive care unit stay ≥ 5 days (OR 2.129, 95% CI 1.202–3.770, p = 0.010). Patients who underwent re-exploration for excessive bleeding had a similar 5-year overall survival to those who did not undergo re-exploration (87.1% v 87.9%, p = 0.445, log-rank test).

According to individual surgeons, re-exploration rates ranged from 1.4% to 11.7% and such differences were statistically significant (p < 0.0001). This was observed in patients who did not use clopidogrel preoperatively (Figure 5). Re-exploration rates were significantly different among surgeons after elective and urgent/emergency procedures (Figure 6) and after off-pump surgery (p = 0.003) and conventional surgery (p = 0.003).

Fig. 5. Incidence of re-exploration for excessive bleeding after coronary artery bypass grafting according to individual surgeons in patients with and without a preoperative exposure to clopidogrel. Re-exploration rates differed significantly among individual surgeons only in cases not exposed to clopidogrel.
Logistic regression showed that an individual surgeon (p < 0.0001), a preoperative body mass index < 25 kg/m² (OR 2.733, 95% CI 2.145–3.481, p < 0.0001), and an estimated glomerular filtration rate < 30 ml/min/1.73 m² (OR 3.891, 95% CI 1.669–9.076, p = 0.002) were independent predictors of re-exploration for excessive bleeding (c-statistic 0.695, 95% CI 0.647–0.743, p = 0.970, Hosmer-Lemeshow test). When 6 surgeons with a re-exploration rate higher than the mean of the overall series were included in the regression model, they were associated with a significant increased risk of re-exploration for excessive bleeding (OR 3.283, 95% CI 2.128–5.064, p < 0.0001).

Data on postoperative blood loss were available in 1 915 patients (95.7%) and a blood loss > 1 600 ml was observed in 102 patients (5.1%). An individual surgeon was associated significantly with the amount of postoperative blood loss (p < 0.0001, Kruskal-Wallis test). Postoperative blood losses > 1 600 ml ranged from 1.5% to 10.9% according to individual surgeons (p = 0.002). Logistic regression showed that an individual surgeon (p = 0.001), male sex (OR 2.126, 95% CI 1.134–3.983, p = 0.019), a body mass index < 25 kg/m² (OR 2.157, 95% CI 1.404–3.314, p < 0.0001), previous peripheral vascular surgery (OR 2.805, 95% CI 1.385–5.679, p = 0.004), emergency surgery (OR 2.236, 95% CI 1.135–
4.403, \( p = 0.020 \), and an estimated glomerular filtration rate < 30 ml/min/1.73 m² (OR 3.721, 95% CI 1.113–12.441, \( p = 0.033 \)) were independent predictors of postoperative blood loss > 1 600 ml (c-statistic 0.717, 95% CI 0.667–0.767, \( p = 0.942 \), Hosmer-Lemeshow test).

Table 7. Sources of bleeding Requiring Re-Exploration after CABG.

<table>
<thead>
<tr>
<th>Source of bleeding</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evident bleeding source</td>
<td>26</td>
</tr>
<tr>
<td>Internal mammary artery harvest site</td>
<td>23</td>
</tr>
<tr>
<td>Sternal edges</td>
<td>22</td>
</tr>
<tr>
<td>Internal mammary artery branch</td>
<td>13</td>
</tr>
<tr>
<td>Sternum (metallic wire)</td>
<td>13</td>
</tr>
<tr>
<td>Vein graft branch</td>
<td>14</td>
</tr>
<tr>
<td>Neck vessel</td>
<td>9</td>
</tr>
<tr>
<td>Pericardial artery</td>
<td>9</td>
</tr>
<tr>
<td>Aortic proximal anastomosis</td>
<td>6</td>
</tr>
<tr>
<td>Diffuse bleeding</td>
<td>4</td>
</tr>
<tr>
<td>Distal anastomosis</td>
<td>4</td>
</tr>
<tr>
<td>Myocardium</td>
<td>4</td>
</tr>
<tr>
<td>Surgical drain insertion site</td>
<td>2</td>
</tr>
<tr>
<td>Pacemaker wire insertion site</td>
<td>2</td>
</tr>
<tr>
<td>Ascending aorta (cannulation site)</td>
<td>1</td>
</tr>
<tr>
<td>Right atrium</td>
<td>1</td>
</tr>
<tr>
<td>Brachiocephalic vein branch</td>
<td>1</td>
</tr>
</tbody>
</table>

Note. Multiple sources of bleeding were identified in 33 patients.

5.4 Re-exploration for bleeding

The aim of this review was to evaluate the impact of re-exploration for bleeding after cardiac surgery on the immediate postoperative outcome.

The decision to perform re-exploration was made according to varying criteria, but, in all studies, re-operation was carried out for severe postoperative bleeding and/or cardiac tamponade.

Patients requiring re-exploration were older, more frequently male, more often had peripheral vascular disease and preoperative exposure to ASA, and more frequently underwent urgent/emergency surgery. As data on these variables were not reported in all studies, however, this analysis may be biased. Furthermore, no data regarding the timing of exposure to ASA were available and data regarding other anti-thrombotic agents were scanty for specific analysis. In spite of this, a risk
difference of 9% (95% CI 2–19%) was observed among these risk factors in terms of urgent/emergency surgery in the 538,553 patients reported in six studies. Apart from its well-recognized impact on postoperative mortality, an increased incidence of resternotomy for bleeding after urgent/emergency operation suggests that these patients were more likely exposed preoperatively to anti-platelet/anticoagulant agents. Re-exploration for bleeding was associated with a significantly increased risk of immediate postoperative mortality (Figure 6), stroke, need for intra-aortic balloon pump, acute renal failure, sternal wound infection, and prolonged mechanical ventilation. The negative prognostic impact of re-exploration on immediate postoperative mortality was consistent in all studies, but was the least significant factor for this (Figure 7). Four studies (Moulton et al. 1996, Karthik et al. 2004, Choong et al. 2007, Ranucci et al. 2008) reported on adjusted ORs of the impact of re-exploration for bleeding on the immediate postoperative mortality. The pooled RR of these studies was 2.56 (95% CI 1.46–4.50, $I^2 = 55\%$, random effect analysis, $p = 0.001$) (Figure 7). ORs were extracted in two of these studies from propensity-matched pairs’ analysis (Karthik et al. 2004, Ranucci et al. 2008). When only adjusted ORs obtained from multivariate analysis were included in the analysis (Moulton et al. 1996, Choong et al. 2007), the pooled RR for immediate postoperative mortality was 2.35 (95% 1.62–3.38, $I^2 = 7\%$, fixed-effect analysis, $p < 0.00001$). The increased risk of stroke after re-exploration was another observation of particular concern (RR 2.18, 95% CI 1.96–2.43). This finding was consistent across all studies, but no data was available to assess whether or not re-exploration was an independent risk factor for cerebrovascular complications.
Fig. 7. Forest plot showing the pooled risk ratio for immediate postoperative mortality after re-exploration for bleeding after cardiac surgery.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Re-exploration</th>
<th>No re-exploration</th>
<th>Risk Difference</th>
<th>Year</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsworth-White 1995</td>
<td>19 85 117</td>
<td>2 136</td>
<td>0.17 [0.08, 0.26]</td>
<td>1995</td>
<td>0.06 [0.03, 0.10]</td>
</tr>
<tr>
<td>Moulton 1996</td>
<td>27 253</td>
<td>5 762</td>
<td>0.06 [0.03, 0.10]</td>
<td>1996</td>
<td>0.03 [0.00, 0.05]</td>
</tr>
<tr>
<td>Selman 1997</td>
<td>22 378</td>
<td>8 185</td>
<td>0.03 [0.00, 0.05]</td>
<td>1997</td>
<td>0.06 [0.03, 0.10]</td>
</tr>
<tr>
<td>Dacey 1998</td>
<td>29 305</td>
<td>8 281</td>
<td>0.06 [0.03, 0.10]</td>
<td>1998</td>
<td>0.03 [0.00, 0.05]</td>
</tr>
<tr>
<td>Karthik 2004</td>
<td>1 84</td>
<td>3 84</td>
<td>-0.02 [-0.07, 0.02]</td>
<td>2004</td>
<td>0.09 [0.04, 0.13]</td>
</tr>
<tr>
<td>Choong 2007</td>
<td>21 191</td>
<td>67 3 029</td>
<td>0.09 [0.04, 0.13]</td>
<td>2007</td>
<td>0.11 [0.06, 0.16]</td>
</tr>
<tr>
<td>Ranucci 2008</td>
<td>33 232</td>
<td>8 232</td>
<td>0.11 [0.06, 0.16]</td>
<td>2008</td>
<td>0.07 [0.07, 0.08]</td>
</tr>
<tr>
<td>Mehta 2009</td>
<td>1 212</td>
<td>12 652</td>
<td>11 115 5 160 34</td>
<td>18.2%</td>
<td>0.07 [0.07, 0.08]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14 180</td>
<td>543 743</td>
<td>100.0%</td>
<td>0.06 [0.04, 0.09]</td>
<td>0.06 [0.04, 0.09]</td>
</tr>
</tbody>
</table>

Total events 1 364 12 073

Heterogeneity: Tau^2 = 0.00; Chi^2 = 38.32, df = 7 (P < 0.00001); I^2 = 82%
Test for overall effect: Z = 4.90 (P < 0.00001)

Favors re-exploration 0.06 [0.04, 0.09]

Favors no re-exploration -0.2 -0.1 0 0.1 0.2
Fig. 8. Forest plot showing the pooled risk ratio of studies reporting adjusted odds ratios for immediate postoperative mortality after re-exploration for bleeding after cardiac surgery.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Year</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moulton 1996</td>
<td>0.693</td>
<td>0.242</td>
<td>36.8 %</td>
<td>1996</td>
<td>2.00 [1.24, 3.21]</td>
</tr>
<tr>
<td>Karthik 2004</td>
<td>-1.123</td>
<td>1.165</td>
<td>5.4 %</td>
<td>2004</td>
<td>0.33 [0.03, 3.19]</td>
</tr>
<tr>
<td>Choong 2007</td>
<td>1.089</td>
<td>0.296</td>
<td>32.6 %</td>
<td>2007</td>
<td>2.97 [1.66, 5.31]</td>
</tr>
<tr>
<td>Ranucci 2008</td>
<td>1.551</td>
<td>0.404</td>
<td>25.1 %</td>
<td>2008</td>
<td>4.72 [2.14, 10.41]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td></td>
<td>2.56 [1.46, 4.50]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\hat{\tau}^2 = 0.17$; $\hat{\chi}^2 = 6.72$, df= 3 ($P < 0.08$); $I^2 = 55\%$

Test for overall effect: $Z = 3.26$ ($P = 0.001$)
Two studies (Karthik et al. 2004, Choong et al. 2007) reported on the mortality rates after re-exploration for bleeding performed within 12 h or later. When performed more than 12 h after surgery, re-exploration for bleeding was associated with a significantly increased risk of mortality (21.5% vs 5.1%; 14/65 vs 11/215 patients) (RR 5.22, 95% CI 2.43–11.21, I² = 0%, fixed-effect analysis, p < 0.00001; RD 18%, 95% CI 8–29%, I² = 2%, fixed-effect analysis, p = 0.0007). When analyzing the studies including only patients, who underwent isolated coronary artery bypass surgery (Dacey et al. 1998, Karthik et al. 2004, Mehta et al. 2009), a significantly higher risk of postoperative mortality was observed among patients who underwent re-exploration for bleeding (RR 3.23, 95% CI 1.88–5.55, I² = 81%, random-effect analysis, p < 0.00001). A pooled analysis of studies including procedures other than isolated coronary artery bypass operations (Moulton et al. 1996, Sellman et al. 1997, Ranucci et al. 2008) also demonstrated a higher risk of mortality (RR 3.24, 95% CI 2.25–4.65, I² = 67%, random-effect analysis, P < 0.00001). Studies published during the last decade (Karthik et al. 2004, Choong et al. 2007, Ranucci et al. 2008, Mehta et al. 2009) had a higher pooled RR for mortality (RR 4.30, 95% CI 2.06–8.56, I² = 52%, random-effect analysis, P < 0.00001) than those published in the 1990s (Unsworth-White et al. 1995, Moulton et al. 1996, Sellman et al. 1997, Dacey et al. 1998) (RR 2.75, 95% CI 2.06–3.66, I² = 67%, random-effect analysis, P < 0.00001).

### 5.5 Blood transfusion and stroke

This study investigated the impact of blood transfusion on the development of post-operative stroke after CABG. Of the study population, stroke occurred postoperatively in 53 patients (2.4%). These strokes were regarded of ischaemic origin. Since there was a strong correlation between the amount of transfused red blood cell units and transfused platelet units (rho: 0.467, p < 0.0001) as well as transfused Octaplas® units (rho: 0.423, p < 0.0001), all these three risk factors were analysed further. The area under the ROC curve for predicting post-operative stroke was 0.653 (95% CI 0.570–0.736) or red blood cell units, 0.627 (95% CI 0.543–0.712) for Octaplas® units and 0.618 (95% CI 0.532–0.703) for platelet units.

Figure 9 summarizes the unadjusted rate of post-operative stroke according to increasing amount of red blood cell units (0, 1–2 units, or > 2 units), platelets units (0, 1–8 units, or > 8 units) and Octaplas® units (0, 1–4 units, or > 4 units) transfused (p < 0.0001 adjusted for pre-operative hemoglobin and post-operative blood loss). When the use of all blood products was summed, a dose-dependent
increase of post-operative stroke was observed (when adjusted for pre-operative hemoglobin and post-operative blood loss: OR 1.474, 95% CI 1.262–1.720, p < 0.0001). Similarly, the increase in the use of blood product types ranging from no transfusion to combined transfusion of red blood cells, platelets and Octaplas® was associated with a significantly increased rate of post-operative stroke (when adjusted for pre-operative hemoglobin and post-operative blood loss: OR 1.727, 95% CI 1.350–2.209, p < 0.0001, Figure 10).

Fig. 9. Post-operative stroke rates according to increasing amount of red blood cell (RBC) units (0 = none, 1 = 1–2 units, 2 = > 2 units; p = 0.002), platelets units (0 = none, 1 = 1–8 units, 2 = > 8 units; p < 0.0001) and Octaplas® units (0 = none, 1 = 1–4 units, 2 = > 4 units; p < 0.0001) transfused.
Logistic regression showed that extracardiac arteriopathy (OR 2.344, 95% CI 1.133–4.847), preoperative atrial fibrillation (OR 2.409, 95% CI 1.149–5.052), preoperative creatinine (OR 1.003, 95% CI 1.000–1.006), and the number of packed red blood cell units transfused (OR 1.121, 95% CI 1.065–1.180) were significantly associated with postoperative stroke. When the various blood product transfusions instead of transfused units were included in the multivariable analysis, solvent/detergent treated plasma (Octaplas®) transfusion (OR 2.149, 95% CI 1.141–4.047), but not red blood cell transfusion, was significantly associated with postoperative stroke along with preoperative creatinine, preoperative atrial fibrillation and extracardiac arteriopathy. Stroke rate was not significantly different between the three hospitals (p-values ranging from 0.186 to 0.820) when the hospitals were in the regression models. Renal failure, preoperative atrial fibrillation and extracardiac arteriopathy were included in the CART model along with classes of increasing amount of transfused red blood cells, Octaplas® and platelets. This model showed that increasing amount of transfused Octaplas®, platelets and history of extracardiac arteriopathy were significantly associated with post-operative stroke (area under the ROC curve for this predictive model: 0.631, 95% CI 0.546–0.716). The propensity score estimated the risk of receiving
transfusion of all types of blood products (red blood cells, Octaplas® and platelets). Logistic regression showed that patient's age, preoperative hemoglobin, preoperative exposure to clopidogrel, chronic use of warfarin, previous cardiac surgery, recent myocardial infarction, emergency operation, critical operative status, no diabetes and no intraoperative use of tranexamic acid were significantly associated with perioperative use of all types of blood products (Hosmer-Lemeshow's test \( p = 0.731 \)). The area under the ROC curve for this predictive model was 0.820 (95% CI 0.791–0.848). When use of all three types of blood products was adjusted for the propensity score, the former was significantly associated with post-operative stroke (OR 4.832, 95% CI 2.370–9.851).

One-to-one propensity score matching allowed us to get 210 pairs of patients who did not receive any blood transfusion and patients who received transfusion of red blood cells, Octaplas® and platelets. It is noteworthy that despite the optimal area under the ROC curve of the propensity score as well as adequate goodness of fit for this logistic regression model, there were still a few differences between the study groups as denoted by standardized differences. Patients who did not receive blood products had a post-operative stroke rate of 1.0%, whereas it was 6.7% in patients who received all three types of blood products (\( p = 0.004 \)).

Logistic regression showed that, when adjusted for different institutions (p-values ranging from 0.277 to 0.537), transfusion of all three blood products was associated with a rather high postoperative stroke risk (OR 9.497, 95% CI 1.949–46.265). Overall, transfusion of all three types of blood products was associated with a remarkably higher risk of all major adverse postoperative end-points (Table 8) except in-hospital mortality, for which the difference did not reach statistical significance (2.4% vs. 5.7%, \( p = 0.08 \)). Since certain differences persisted between study groups in the propensity score matching analysis, we assessed the immediate postoperative outcome in patients with increasing operative risk as estimated by additive EuroSCORE classes (additive EuroSCORE 0–5, 6–9 and > 9 points). This sensitivity analysis confirmed the major impact of transfusion of all three types of blood products on the development of stroke as well as other major adverse events (Table 9). Logistic regression including additive EuroSCORE classes, amount of post-operative bleeding, different institutions and transfusion of all three blood products, showed that the last variable was the only independent predictor of post-operative stroke (\( p < 0.0001 \), OR 4.212, 95% CI 2.053–8.643). Use of blood products ranging from no transfusion (stroke rate 1.6%) to combined transfusion of red blood cells, platelets and Octaplas® was associated with a significant increase in postoperative stroke incidence (6.6%, adjusted analysis: OR 1.727,
Patients who received > 2 units of red blood cells, > 4 units of Octaplas® units and > 8 units of platelets had the highest stroke rate of 21%.

Table 8. Adverse events during the immediate postoperative period after coronary artery bypass surgery in 210 propensity score matched pairs of patients who did not receive any blood transfusion and those who received all three types of blood products. Results of univariable and multivariable analyses for prediction of postoperative stroke are reported.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No blood transfusion</th>
<th>Transfusion of RBC, Octaplas® and platelets</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>5 (2.4)</td>
<td>12 (5.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1.0)</td>
<td>14 (6.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>14 (6.7)</td>
<td>46 (21.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Post-operative blood loss (ml)</td>
<td>683 ± 347</td>
<td>1 385 ± 910</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Re-sternotomy for bleeding</td>
<td>3 (1.4)</td>
<td>57 (27.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>&quot;Surgical bleeding&quot;</td>
<td>2 (1.0)</td>
<td>41 (19.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>De novo dialysis</td>
<td>1 (0.5)</td>
<td>12 (5.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>64 (30.6)</td>
<td>92 (43.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>ICU stays (days)</td>
<td>1.1 ± 3.0</td>
<td>3.2 ± 4.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ICU stay ≥ 5 days</td>
<td>4 (1.9)</td>
<td>36 (17.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Composite outcome end-point^3</td>
<td>20 (9.5)</td>
<td>108 (51.4)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Continuous variable are reported as mean ± standard deviation or counts (%). 1 RBC: red blood cells. 2 ICU: intensive care unit. 3 Composite end-point: in-hospital death, low cardiac output syndrome, de novo dialysis, stroke, re-sternotomy for excessive bleeding, or intensive care unit stay ≥ 5 days.
Table 9. Adverse events during the immediate postoperative period after coronary artery bypass surgery in patients who did not receive any blood transfusion and those who received all three types of blood products. Results are according to increasing additive EuroSCORE classes.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Additive EuroSCORE 0–5</th>
<th>Additive EuroSCORE 6–9</th>
<th>Additive EuroSCORE &gt; 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No blood transfusion</td>
<td>Transfusion of RBC, Octaplas® and platelets</td>
<td>No blood transfusion</td>
</tr>
<tr>
<td></td>
<td>804 patients</td>
<td>117 patients</td>
<td>142 patients</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1 (0.1)</td>
<td>2 (1.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (1.6)</td>
<td>6 (5.1)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>32 (4.0)</td>
<td>18 (15.4)</td>
<td>10 (7.0)</td>
</tr>
<tr>
<td>Post-operative blood loss (ml)</td>
<td>723 ± 395</td>
<td>1 546 ± 970</td>
<td>650 ± 366</td>
</tr>
<tr>
<td>Re-sternotomy for bleeding</td>
<td>7 (0.9)</td>
<td>37 (31.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>“Surgical bleeding”</td>
<td>4 (0.5)</td>
<td>27 (23.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>De novo dialysis</td>
<td>3 (0.4)</td>
<td>2 (1.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>221 (27.5)</td>
<td>43 (36.8)</td>
<td>48 (33.8)</td>
</tr>
<tr>
<td>ICU stays (days)</td>
<td>1.4 ± 2.1</td>
<td>2.5 ± 3.9</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>ICU stay ≥ 5 days</td>
<td>18 (2.2)</td>
<td>11 (9.4)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Composite outcome end-point²</td>
<td>58 (7.2)</td>
<td>53 (45.3)</td>
<td>14 (9.9)</td>
</tr>
</tbody>
</table>

Continuous variable are reported as mean ± standard deviation or counts (%). ¹RBC: red blood cells, ²ICU: intensive care unit, ³Composite end-point: in-hospital death, low cardiac output syndrome, de novo dialysis, stroke, re-sternotomy for excessive bleeding, or intensive care unit stay ≥ 5 days, ⁴p < 0.050.
5.6 Blood transfusion and intermediate survival

The aim of this study was to investigate the impact of transfusion of blood products on intermediate outcome after CABG. In this series of 2001 patients, 2.8% died during the 30-day postoperative period, 12.2% had low cardiac output syndrome, 27.0% required use of inotropics for more than 12 h, 2.1% suffered stroke, and 1.4% required de novo dialysis. Re-exploration for bleeding was needed in 5.6% of patients. When adjusted for additive EuroSCORE, transfusion of any blood product was associated with significantly higher risk of 30-day mortality (p = 0.048, OR 4.496, 95% CI 1.012–19.972), low cardiac output syndrome (p < 0.0001, OR 2.691, 95% CI 1.728–4.191), prolonged use of inotropics (p < 0.0001, OR 3.273, 95% CI 2.387–4.486), and stroke (p = 0.016, OR 3.763, 95% CI 1.286–11.011). It also tended to be associated with de novo dialysis (p = 0.057). The mean follow-up was 2.5 ± 1.5 years. Three-year all-cause mortality was 9.5% and cardiac mortality was 5.8%.

All blood products were associated with significantly higher risk of all-cause mortality. The impact of FFP/Octaplas® on all-cause mortality was particularly evident (p < 0.0001). Multivariable analysis showed that patient’s age, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction, emergency operation, and any blood product transfusion (RR 1.678, 95% CI 1.087–2.590) were independent predictors of all-cause mortality. When RBC transfusion, platelets transfusion, and FFP/Octaplas® transfusion were included in this regression model, FFP/Octaplas® transfusion was the only blood product associated with increased risk of all-cause mortality (RR 1.692, 95% CI 1.222–2.344). Only 64 patients received FFP, and when these patients were compared to those who received Octaplas®, no significant differences were observed in terms of all-cause mortality (p = 0.631) and cardiac mortality (p = 0.703). RBC transfusion was marginally associated with all-cause mortality (RR 1.503, 95% CI 0.986–2.291). When the units of blood products were entered in this regression model, FFP/Octaplas® units (RR 1.066, 95% CI 1.014–1.121) and RBC units (RR 1.045, 95% CI 1.010–1.082) were independent predictors of all-cause mortality. The additive effect of blood products was particularly evident when the sum of each blood product was included in the regression analysis (p < 0.0001, RR 1.401, 95% CI 1.203–1.630). Univariate analysis showed that age (p < 0.0001), eGFR (p < 0.0001), number of distal anastomoses (p = 0.005), diabetes (p = 0.018), extracardiac arteriopathy (p < 0.0001), prior cardiac surgery (p < 0.0001), recent
myocardial infarction (p < 0.0001), left ventricular ejection fraction (p < 0.0001), emergency operation (p < 0.0001), critical preoperative status (p < 0.0001), atrial fibrillation (p = 0.005) as well as any kind of blood product transfusion (for all products: p < 0.0001) were associated with any cardiac mortality.

Cox regression analysis showed that any blood product transfusion was associated with significantly increased risk of cardiac mortality (p = 0.040, RR 1.893, 95% CI 1.030–3.478). When each blood product at once was entered into the regression model, RBC transfusion (p = 0.027, RR 1.950, 95% CI 1.078–3.526), FFP/Octaplas® transfusion (p < 0.0001, RR 2.292, 95% CI 1.533–3.426), and platelet transfusion (p = 0.002, RR 1.913, 95% CI 1.265–2.893) were predictive of cardiac mortality. When all the three blood products were entered into the Cox regression model along with the other covariates, FFP/Octaplas® was the only blood product associated with increased risk of cardiac mortality (p < 0.0001, RR 2.125, 95% CI 1.414–3.194). The synergic effect of blood products was evident when the sum of each blood product was included in the regression analysis (p < 0.0001, RR 1.553, 95% CI 1.273–1.895).

The effect of blood product transfusion was particularly marked during the first three postoperative months (Figure 11). When the follow-up was truncated at 3 months, any blood product transfusion was a significant predictor of all-cause mortality (p = 0.040, RR 2.998, 95% CI 1.053–3.537). In order to exclude a possible effect of transfusion only on the early outcome, we evaluated the outcome of 1880 patients who survived or had at least 3 months of potential follow-up. In this patient population, transfusion of any blood product was associated with all-cause and cardiac mortality only at univariable analysis, but not at multivariable analysis (all-cause mortality: p = 0.148, RR 1.430, 95% CI 0.880–2.323; cardiac mortality: p = 0.470, RR 1.329, 95% CI 0.614–2.877). The inclusion of each single blood product in the analysis did not significantly affect intermediate outcome of this subgroup of patients.
Fig. 11. Kaplan-Meier’s estimate of all-cause mortality hazard in patients who received or did not receive any type of blood product transfusion.
6 Discussion

6.1 Low-dose ASA discontinuation

In two meta-analyses on preoperative exposure to ASA before CABG, an increased risk of bleeding and need for blood transfusion was reported with late or no discontinuation of ASA (Sun et al. 2008, Alghamdi et al. 2013). These analyses included studies that were performed over three decades, however, and contained a wide variation in operative and anesthesiology methods and pharmacologic treatments, and there was no information on important outcome end-points, such as immediate postoperative mortality and cardiovascular morbidity, which can be considered as a major limitation. In addition, the quality of the studies, the dosages of ASA, and the timing of discontinuation varied in a wide range, making the pooling of analysis more complicated. In a single-center study of 1,519 propensity matched pairs, Jacob et al. (2011) reported an increased need for transfusions in patients with late use of preoperative ASA in CABG, but no difference was detected in cardiovascular morbidity or mortality. Several studies have, however, demonstrated the harmful effect of blood transfusion (see more in chapter 2.8.1). Apart from the optimal methodology adopted in this study, it remains unclear as to whether patients undergoing urgent surgery were included in the analysis. It is also noteworthy that patients receiving adenosine diphosphate inhibitors, heparin, and warfarin were not excluded, which complicated the analysis of these data.

In a large series of cardiac surgery patients, Ferraris et al. (2002) observed a higher risk of bleeding in patients with a history of ASA ingestion within 12 hours of surgery. Due to the lack of specific data, the results may have been affected by the inclusion of patients who also underwent valve surgery and those who underwent urgent/emergency surgery and were therefore likely at an increased risk to be exposed to antithrombotic drugs. Furthermore, the investigators did not report data on postoperative cardiovascular morbidity and mortality (Ferraris et al. 2002). Similarly, the study by Bybee et al. (2005) likely included patients who underwent urgent/emergency surgery as indicated by the large number of patients with a history of recent myocardial infarction. Moreover, data on the use of other antithrombotic medication were not reported.

Antiplatelet drugs are an integral part of the pharmacologic therapy for patients with acute coronary syndromes. For this reason, the issue of whether or not to discontinue ASA before CABG should mainly affect those patients with stable
coronary artery disease undergoing elective surgery. Our study showed that avoiding the early interruption of low-dose ASA before elective CABG did not increase postoperative blood loss or the use of blood products. Furthermore, the immediate postoperative outcome was not impaired by late or no discontinuation of ASA. Indeed, the present observations suggested that this strategy might have a positive impact in preventing postoperative stroke. According to our speculation, the preoperative discontinuation of antiplatelet treatment may expose patients to thrombotic events as observed in patients not undergoing surgery. Surgery may thus increase the risk. Unfortunately, most previous studies on this topic have not reported data on the occurrence of postoperative stroke after CABG. However, a pooled analysis of the data of 5330 patients included in 3 available studies (Ferraris et al. 2002, Srinivasan et al. 2003, Bybee et al. 2005) and the present study showed a trend toward an increased risk of postoperative cerebrovascular events in patients with an early discontinuation of ASA before CABG (RR 1.34, 95% CI 0.83–2.14, p = 0.23; Figure 12). The lack of data on preoperative events potentially occurring after the discontinuation of ASA before CABG is one major limitation of our and all previous studies. In addition to clinical experience and the sporadic reports on the adverse events after the discontinuation of ASA in patients scheduled for CABG (Matsuzaki et al. 1999), there is a well-established increased risk of cardiovascular events in patients with coronary disease who discontinue or do not adhere to ASA treatment (HR 1.82, 95% CI 1.52–2.18, p < 0.00001) (Biondi-Zoccai et al. 2006). García Rodríguez et al. (2011) found that discontinuation of ASA for the secondary prevention of cardiovascular events was associated with a significantly higher risk of stroke/transient ischemic attack compared with continued ASA use (RR 1.40, 95% CI 1.03–1.92). Patients with a previous diagnosis of cerebrovascular disease had an even higher risk (RR 2.79, 95% CI 2.05–3.80). These findings are in line with a study by Maulaz et al. (2005) who observed a particularly high risk of stroke/transient ischemic attack in patients with coronary artery disease and no adherence to ASA treatment. Although the retrospective nature of our study may represent a limitation, the data was mostly collected from local institutional clinical registries which prospectively collected information in computerized databases and electronic files.
Fig. 12. Forest plot showing a trend toward a lower risk of cerebrovascular events after coronary artery graft bypass surgery in patients who used aspirin until surgery or in whom aspirin was discontinued a few days previously compared with those in whom aspirin was earlier discontinued prior to surgery.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early aspirin discontinuation Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Late use of aspirin Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srinivasan 2003</td>
<td>0</td>
<td>170</td>
<td>1</td>
<td>0.33 [0.01, 8.13]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jawob 2011</td>
<td>14</td>
<td>1519</td>
<td>12</td>
<td>1.17 [0.54, 2.51]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bybee 2005</td>
<td>12</td>
<td>320</td>
<td>36</td>
<td>1.37 [0.72, 2.60]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>12</td>
<td>619</td>
<td>1</td>
<td>4.65 [0.61, 35.59]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2628</td>
<td>3245</td>
<td>100.0%</td>
<td>1.34 [0.83, 2.14]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>38</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.20 (P = 0.23)

Heterogeneity: Tau² = 0.00; Chi² = 2.33, df = 3 (P = 0.51); I² = 0%

-0.02 -0.1 1 10 50

Favors early aspirin discontinuation  
Favors late aspirin use
In conclusion, the late use (within 3 days) or no discontinuation of low-dose ASA before CABG may decrease the risk of postoperative stroke without significantly increasing postoperative bleeding or the need for blood transfusions. These findings coupled with the risk of cardiovascular events possibly occurring at the time of its discontinuation before surgery, suggest that the use of ASA until the day of elective coronary surgery may be beneficial.

6.2 TOAC discontinuation

This study shows that a simple strategy of performing CABG during therapeutic oral anticoagulation lead to an operative outcome comparable to that of the more complicated strategy of performing CABG after achieving a near-normal INR level. Unexpectedly, the bleeding complications were relatively rare in both patient groups and were not related to perioperative INR levels. On the other hand, the use of clopidogrel and enoxaparin together with therapeutic warfarin was associated with an adverse operative outcome.

Due to underlying chronic medical conditions, Serruys et al. (2009) estimated that more than 5% of patients undergoing CABG require long-term oral anticoagulation. There are no randomized trials comparing different strategies to manage long-term oral anticoagulation in patients undergoing CABG. Torosian et al. (2010) suggested that continued warfarin treatment increases the risk of perioperative bleeding, and the only contemporary trial addressing this complicated issue is a recent case-control study by Biancari et al. (2010) which suggested that the outcome is not affected by oral anticoagulation, although there was more a frequent need for fresh frozen plasma. The importance of this issue is further emphasized by the fact that the magnitude of this problem is increasing with the growing number of elderly patients referred for cardiac surgery.

Minimizing the risk for perioperative bleeding in CABG patients is important due to the increased risk for death and other adverse outcome in patients who require blood transfusion during the perioperative period (Surgenor et al. 2009). Unexpectedly, there were no significant differences in bleeding events between the study groups. The rate of bleeding events or need for blood products other than fresh-frozen plasma were also not related to INR levels. This again is in agreement with the findings reported in the case-control study by Biancari et al. (2010), where chronic warfarin treatment was not associated with an increased incidence of any bleeding events or other major perioperative complications, even when controlled with a propensity score analysis. On the other hand, when enoxaparin treatment
was combined with therapeutic oral anticoagulation, bleeding events and operative complications were common and concomitant clopidogrel treatment appeared to be even more hazardous.

The degree of perioperative anticoagulation administered should be balanced with the risks of bleeding and thromboembolic complications in the patient. We observed a relatively high incidence of postoperative strokes in both groups, but this was unrelated to the intensity of oral anticoagulation as measured by INR. In the light of the observed association of bleeding risk to high CHADS2 score (Poli et al. 2007, Hylek et al. 2007), the intrinsic liability for stroke in patients with chronic atrial fibrillation and other co-morbidities may also be crucial with reference to postoperative stroke risk and should be taken into account when planning perioperative antithrombotic treatment. It is noteworthy that we did not observe any increase in strokes in the patients with preoperative warfarin cessation without heparin bridging. This finding, however, must be interpreted with caution given the limited number of patients exposed and the lack of data on potential preoperative strokes.

Patients on long-term warfarin therapy are significantly less likely to undergo coronary angiography and coronary interventions, and their waiting times for these procedures are longer than in patients not on warfarin (Wang et al. 2008). This may be related to the fear of perioperative problems and to the common practice to discontinue or fully reverse warfarin if CABG is planned. Uninterrupted warfarin treatment or a short discontinuation of warfarin may, however, shorten the risky waiting time and help to avoid the transient prothrombotic state caused by warfarin reinitiation. Another option, bridging therapy with heparin, is currently recommended for patients considered to be at increased risk of thromboembolism. More recently, the safety and efficacy of bridging therapy has been questioned in patients undergoing various cardiac interventions due to a high incidence of bleeding problems (Wazni et al. 2004, Tolosana et al. 2009, Karjalainen et al. 2008, Airaksinen et al. 2010). The findings of the SYNERGY trial, where bleeding was observed to be higher in those patients who crossed over from one anticoagulant to the other, may also be relevant in this context (White et al. 2006). Thus, it is unsurprising that perioperative anticoagulation strategies differ widely between different hospitals and operators. In the present cohort, short preoperative heparin bridging was mainly employed in patients with a mechanical heart valve or with acute coronary syndromes. In many cases, the oral anticoagulation was still at a therapeutic level during heparin use.
Our study carries all the inherent limitations of a retrospective cohort study. On the other hand, the strength of our analysis is that we could identify and include all consecutive warfarin-treated patients from the records and avoid the potential selection bias inherent to prospective studies. The outcome assessment was not blinded and it was not possible to retrospectively gather reliable information on e.g. mild bleeding complications from patient records. We tried to take confounding factors into account by using multivariable analysis, but the possibility remains that residual confounders may remain and more studies are required to confirm our findings. Potential selection bias and the small sample size limit the conclusions that can be drawn from these results, especially concerning the effects of clopidogrel and enoxaparin treatments. In spite of these limitations, we feel that our data may be used to guide the treatment of patients with an indication of long-term oral anticoagulation undergoing CABG. It may also be helpful in planning future prospective studies on this topic.

In conclusion, our study suggests that CABG is a safe procedure during TOAC with no excess bleeding or major complications. To confirm this observation, and to compare different types of treatment strategies in CABG patients on long-term warfarin therapy, prospective cohorts and randomized trials are needed in the future.

6.3 The impact of the individual surgeon

Excessive bleeding is associated with an increased risk of major complications and its treatment requires significant human and medical resources, with marked incremental costs, making it one of the most vexing problems in cardiac surgery. The most important determinant of major bleeding is the preoperative use of anticoagulant and antiplatelet drugs. As was found in our meta-analysis (study IV), the preoperative discontinuation of clopidogrel has been considered an effective measure against such a severe complication. On the contrary, the preoperative discontinuation of ASA may expose patients to preoperative (Rodriguez et al. 2011, Llinas et al. 2011) and postoperative thrombotic events (study I). Even if the preoperative use of potent antiplatelet drugs results in significant, diffuse, intra- and postoperative bleeding, the present study indicates that an individual surgeon’s performance may be an even more powerful determinant of excessive blood loss and need for re-exploration. Papachristofi et al. (2014) found a low-power proof that cardiac surgeons with low monthly operation volume coupled with high average case-mix risk may increase the chance of in-hospital death. Simulation training in robotic cardiac surgery has been found to be beneficial for surgeons in
training (Valdis et al. 2016). Derivated from these findings, surgeons with low operation volume should do simulation training to improve patient outcome.

A recent meta-analysis of 10 944 CABG patients on preoperative exposure to clopidogrel reported pooled rates of re-exploration for bleeding of 3.2%, 4.9% in patients exposed to clopidogrel, and 2.0% in controls (RR 1.88, 95% CI 1.37–2.58) (Nashef et al. 1999). Among these series, the re-exploration rates have ranged from 0% (Filsoufi et al. 2008) to 6% (Ascione et al. 2005). Even if preoperative exposure to clopidogrel was not an independent predictor of re-exploration (probably because of a type-II error), our study shows that the re-exploration rates for excessive bleeding were markedly and uniformly higher in all surgeons operating on patients with exposure to clopidogrel (Figure 5). Nevertheless, in patients not exposed preoperatively to clopidogrel (Figure 5) or in elective cases (Figure 13), the scattered high re-exploration rates by individual surgeons strengthens the present finding of a marked impact of the quality of individual surgeons’ skills on postoperative bleeding. Importantly, this study confirmed previous findings on the type of surgical bleeding sites (Unsworth-White et al. 1995, Moulton et al. 1996, Dacey et al. 1998). Our meta-analysis regarding re-exploration for bleeding (study IV) found that diffuse bleeding was the cause for re-exploration in 20% of patients, whereas bleeding from vein graft branches, internal mammary artery branches, and anastomoses were responsible for half the re-explorations. The present study found almost 75% of re-explorations to be caused by “surgical” bleeding and were therefore possibly preventable by employing a meticulous surgical technique during graft harvesting and anastomosing. The definition of “surgical” bleeding is imperfect, but without doubt most significant hemorrhages from surgical sites are preventable at the time of the primary surgery. Indeed, a decrease of re-exploration for excessive bleeding can be expected by specifically addressing this problem because this complication is potentially associated with further adverse events (Wolfe et al. 2007).
Fig. 13. Incidence of re-exploration for excessive bleeding after coronary artery bypass grafting according to individual surgeons in patients undergoing an elective or an urgent/emergency procedure. Re-exploration rates differed significantly after elective and urgent/emergency procedures.

One limitation of our study is its retrospective nature. Although all surgeons tended to follow the same policy for re-exploration for severe bleeding, the indication for re-exploration may have varied among surgeons. Nevertheless, we believe that the analysis of severe bleeding (postoperative blood loss ≥ 600 ml) is a reliable indicator of significant postoperative bleeding. Secondly, the rather limited study interval prevents an analysis of time trends in excessive postoperative bleeding. However, the authors had access to files that accurately and systematically reported important pre-, intra-, and postoperative variables during this period. Furthermore, a relatively aggressive preoperative antiplatelet drug policy was uniformly adopted during this study period by the cardiologists at the Oulu University Hospital. In addition, all surgeons included in the present analysis had adequate experience, but the fact remains that, a minimal number of performed procedures by some surgeons may have introduced a bias. The power analysis indicated, however, that the number of patients evaluated to detect a significant difference in the re-exploration rate between “high-risk” and “low-risk” surgeons was adequate. In fact, to detect a significant difference between these 2 groups of surgeons (re-exploration rate 8.5% vs 2.9%), 303 patients would be needed in each study group (type-I error 0.05,
power 80%). The number of patients needed to compare surgeons with a low postoperative re-exploration rate (about 2%) with those having a high re-exploration rate (about 11%) was even smaller (138 patients per study group, type-I error 0.05, power 80%).

According to our study, the individual surgeon has a major impact on postoperative bleeding, since - among other things - the site of bleeding was identified as being surgical in three-fourths of CABG patients who underwent re-exploration for excessive bleeding. For this reason, a meticulous surgical technique can be expected to significantly decrease the incidence of this severe complication. In conclusion, the present results suggest that the individual surgeon’s quality of skills may be as important as the preoperative discontinuation of antiplatelet and anticoagulation drugs in decreasing the risk of excessive postoperative blood loss.

6.4 Re-exploration for bleeding

This meta-analysis of cardiac surgery patients provides evidence that excessive bleeding requiring re-exploration is associated with increased morbidity and mortality. Even though the results are derived from observational, mainly retrospective studies, their quality appears to be satisfactory (Table 10).
Table 10. Characteristics of observational studies included in this meta-analysis on the impact of re-exploration for excessive bleeding after cardiac surgery. Proportions of adverse events are reported for patients who underwent re-exploration versus control patients, respectively.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Isolated CABG (%)</th>
<th>Re-exploration for bleeding (%)</th>
<th>Immediate mortality (%)</th>
<th>Sternal wound infection (%)</th>
<th>Need for IABP (%)</th>
<th>Acute renal failure (%)</th>
<th>Stroke (%)</th>
<th>Prolonged mechanical ventilation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsworth-White 1995</td>
<td>P</td>
<td>2,221</td>
<td>70.4</td>
<td>3.8</td>
<td>22.4 vs. 5.5</td>
<td>-</td>
<td>14.1 vs. 3.1</td>
<td>9.4 vs. 3.3</td>
<td>-</td>
<td>14.1 vs. 3.1</td>
</tr>
<tr>
<td>Moulton 1996</td>
<td>R</td>
<td>6,015</td>
<td>68.6</td>
<td>4.2</td>
<td>10.7 vs. 4.2</td>
<td>2.4 vs. 0.9</td>
<td>-</td>
<td>15.8 vs. 3.8</td>
<td>3.6 vs. 1.9</td>
<td>24.5 vs. 8.6</td>
</tr>
<tr>
<td>Sellman 1997</td>
<td>R</td>
<td>8,563</td>
<td>80.5</td>
<td>4.4</td>
<td>5.8 vs. 3.0</td>
<td>1.9 vs. 1.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dacey 1998</td>
<td>P</td>
<td>8,586</td>
<td>100</td>
<td>3.6</td>
<td>9.5 vs. 3.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Karthik 2004</td>
<td>P</td>
<td>168</td>
<td>100</td>
<td>PSA</td>
<td>1.2 vs. 3.4</td>
<td>9.5 vs. 4.8</td>
<td>8.3 vs. 2.4</td>
<td>9.5 vs. 2.4</td>
<td>6.0 vs. 3.6</td>
<td>32.1 vs. 7.1</td>
</tr>
<tr>
<td>Choong 2007</td>
<td>P</td>
<td>3,220</td>
<td>81.9</td>
<td>5.9</td>
<td>11.0 vs. 2.2</td>
<td>-</td>
<td>26.2 vs. 6.1</td>
<td>4.2 vs. 0.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ranucci 2008</td>
<td>R</td>
<td>4,64</td>
<td>39.7</td>
<td>PSA</td>
<td>14.2 vs. 3.4</td>
<td>-</td>
<td>10.8 vs. 3.0</td>
<td>17.7 vs. 6.9</td>
<td>0.9 vs. 0</td>
<td>4.7 vs. 3.0</td>
</tr>
<tr>
<td>Mehta 2009</td>
<td>P</td>
<td>528,686</td>
<td>100</td>
<td>2.4</td>
<td>9.5 vs. 2.2</td>
<td>1.7 vs. 0.3</td>
<td>19.2 vs. 9.8</td>
<td>-</td>
<td>2.6 vs. 1.2</td>
<td>42.4 vs. 9.3</td>
</tr>
</tbody>
</table>

1 P: Prospective study, 2 R: retrospective study, 3 PSA: propensity score analysis, only matched pairs reported, 4 CABG: coronary artery bypass grafting.
The results are consistent throughout the studies and outcome end-points. Only one study reported a lower mortality rate after re-exploration for excessive bleeding compared with controls (Karthik et al. 2004); but this study was of a relatively small size and was not powered enough to reliably detect differences in terms of mortality. The evaluation of all other major outcome end-points, however, displayed the unfavorable results associated with re-exploration (Karthik et al. 2004). The mechanisms behind the poor outcome after re-exploration for excessive bleeding are likely multifactorial. Patients requiring re-exploration have multiple, preoperative, high-risk features. Their operation is also performed more often on an urgent/emergency basis, which certainly contributes to the major bleeding complications. Despite these considerations, logistic regression found re-exploration for bleeding to be an independent predictor of immediate postoperative mortality in two studies (Choong et al. 2007, Moulton et al. 1996). Two further studies (Karthik et al. 2004, Ranucci et al. 2008) reported the results of propensity score-matched pairs’ analysis, and were, thus, valuable in estimating the prognosis in patient populations with a similar operative risk. The pooled RR of adjusted ORs reported in these studies (Figure 8, see chapter 5.4) provides clear evidence that re-exploration for bleeding has an independent negative impact on postoperative mortality. Furthermore, Moulton et al. (1996) found that re-exploration for bleeding increases mortality even in low-risk patients (4.8% vs 1.2%, adjusted OR 4.4, p = 0.03). Mortality risk also appears to increase with an increasing number of transfused red blood cell units in both re-exploration and control patients (Ranucci et al. 2008, Moulton et al. 1996), thus providing further indirect evidence of the prognostic impact of severe bleeding. The quality of the data on preoperative anti-thrombotic treatment was, however, suboptimal. The study periods are also rather prolonged, during which period anti-platelet/anticoagulation strategies have changed markedly, becoming increasingly aggressive. More importantly, we were not able to retrieve sufficient data on pre, intra- and postoperative anti-thrombotic medication, and this may represent a serious limitation in the interpretation of these data. Thus, it is not clear whether cardiac, pulmonary, renal, and cerebrovascular complications were related mostly to the severity of postoperative as well as intraoperative bleeding, to the preoperative operative risk profile of the patient, to suboptimal surgical treatment or to technical complications. Importantly, a pooled analysis of two studies (Karthik et al. 2004, Choong et al. 2007) showed a markedly increased mortality (RD 18%) in patients undergoing re-exploration > 12 h after surgery. Such a markedly increased risk cannot probably be explained by increased blood loss and/or amount of red blood cells’ unit.
transfusions (Ranucci et al. 2008, Choong et al. 2007). Despite a similar blood loss and extent of pericardial hematoma, we can speculate that patients undergoing late re-exploration might have more a compromised baseline or postoperative cardiac function, making bleeding and cardiac tamponade less ‘tolerable’. The data available suggests, however, that late re-exploration may contribute to most of re-exploration-related deaths. This is one of the main reasons that re-exploration should be carried out as soon as excessive bleeding and/or cardiac tamponade-related hemodynamic instability becomes evident.

The present findings should be viewed as background for further studies, as re-exploration for excessive bleeding revealed itself as being an important and preventable complication. Moreover, the potential for significant improvement in the outcome of adult cardiac surgery and for marked savings of hospital resources should not be forgotten. In our opinion, future research on this topic should focus on:

- the risk of re-exploration for bleeding and related outcome according to different types of cardiac procedures;
- the prognostic impact of re-exploration for bleeding on stroke;
- the prognostic impact of ‘surgical’ versus diffuse ‘non-surgical’ source of bleeding at re-exploration;
- the prognostic impact of timing of re-exploration, focusing on pre- and postoperative cardiac function;
- an evaluation of long-term outcome after re-exploration for bleeding; and
- a propensity score analysis: the use of propensity score matching, stratification as well as regression adjustment are advised for an adequate adjustment of baseline and operative variables (D’Agostino et al. 1998) particularly for an appropriate evaluation of the results of observational series.

In conclusion, re-exploration for bleeding after cardiac surgery seems to carry a significantly increased risk of immediate postoperative mortality and morbidity, despite the limitations related to the nature of the studies included in this meta-analysis. In view of these findings, any effort to avoid excessive bleeding requiring re-exploration may lead to a marked improvement in outcome after adult cardiac surgery.
6.5 Blood transfusion and stroke

In cardiac surgery, stroke can be considered one of the most severe and feared complications occurring postoperatively as it has significant impact on the patient's immediate and late outcome and quality of life (Filsoufi et al. 2008, Tarakji et al. 2011). The etiopathogenesis of stroke is complex, multifactorial and related to many peri-operative factors and patient comorbidities (Carrascal et al. 2010). Intraoperative embolism is considered the most important mechanism of post-operative stroke, but the role of various contributing factors is difficult to ascertain or to investigate. Atherosclerosis of the ascending aorta is found to be a risk factor for postoperative stroke in cardiac surgery (van der Linden et al. 2001). In such cases, the use of off-pump surgery and a no-touch aorta technique may reduce the risk of post-operative stroke (Biancari & Yli-Pyky 2011, Biancari et al. 2007). The incidence of postoperative stroke and the significance of minor modifications in surgical technique in view of the epiaortic ultrasound information is not clear (van der Linden et al. 2001). It is, however, a common practice to use epiaortic ultrasound in coronary operations in our institution. If there is found arteriosclerotic lesions in ascending aorta, there may be same kind of lesions also in cerebral arteries because of the universal nature of arteriosclerotic disease. One can speculate, that this cerebral arteriosclerosis may be one etiological factor of postoperative stroke in coronary artery bypass patients.

Other measures which may considerably reduce the risk of post-operative stroke are improving cardiopulmonary bypass techniques and materials (Carrascal et al. 2010, Biancari & Rimpiläinen 2009), reducing cardiopulmonary bypass time (Nissinen et al. 2009), and avoidance of peri-operative arrhythmias (Lahtinen et al. 2004), hypoperfusion (Haugen et al. 2007) as well as hemodilutional anemia (Karkouti et al. 2005).

As shown in our meta-analysis, excessive bleeding requiring re-exploration is associated with a high risk of post-operative stroke, an observation which confirms that acute surgical anemia is a major determinant of neurological events (Bahrainwala et al. 2011, Karkouti et al. 2005). Indeed, a study by Kulier et al. (2007) also found evidence of an increased risk of post-operative stroke in CABG patients with pre-operative anemia, but this finding was not confirmed by the present or other previous studies (Bahrainwala et al. 2011, Bell et al. 2008, Boening et al. 2011). This is probably because preoperative anemia is now actively corrected before or at the start of surgery. Severe perioperative hemodilutional anemia, however, may certainly induce significant cerebral ischemia. Experimental
data indicates that under moderate or profound hypothermic conditions, severe cerebral ischemia develops when hematocrit sinks below 10–15% (Duebener et al. 2001, Miura et al. 2007). In accordance with this, clinical data indicates that the risk of post-operative neurological events increases in adult cardiac surgery patients with hematocrit levels < 20–22% (Karkouti et al. 2005, Habib et al. 2003), thereby confirming the importance of avoiding excessive bleeding during cardiac surgery. These findings do not, however, take into consideration the amount of postoperative bleeding and immediate post-operative anemia, which can be even more profound than intra-operatively.

On the other hand, the use of blood products to correct anemia and restore coagulation may also contribute to the development of neurological events (Bahrainwala et al. 2011, Whitson et al. 2007). Bahrainwala et al. (2011) also provided strong evidence on the independent prognostic impact of both post-operative hemoglobin levels and the need for intra-operative red blood cell transfusion on the risk of post-operative stroke. In our study, logistic regression showed the amount of transfused packed red blood cells to be an independent predictor of stroke. In the detailed analysis of type of transfused blood products, however, it was demonstrated that the need for Octaplas® transfusion is an independent predictor of stroke, whereas the transfusion of red blood cells was not. This finding was also confirmed by CART analysis, which showed the significant impact of transfusion of Octaplas® > 4 units and platelets > 8 units (stroke rate, 19.4%). Similar findings were observed by Whitson et al. (2007), who indicated that the risk for stroke and mortality, as well as other important adverse events, is increased by the need for excessive blood product transfusion. Correspondingly, Figure 10 in the present series (chapter 5.5) demonstrates that the transfusion of all three types of blood products was dose-dependently associated with stroke risk. Importantly, this risk was evident when Octaplas® > 4 units and platelets > 8 units were transfused, but also to a much lesser extent when red blood cell > 2 units were transfused (Figure 9 in chapter 5.5). In the absence of data on peri-operative hemoglobin and hematocrit nadir, we may speculate that the need for transfusion of all three types of blood products certainly indicates significant bleeding, even if the amount of post-operative blood loss was not associated with post-operative stroke. The evidence of an increased risk of postoperative stroke in cardiac surgery patients receiving recombinant activated factor VII (Ponschab et al. 2011) suggests that the beneficial hemostatic effects of coagulation-promoting drugs could be counterbalanced by severe atherothrombotic events. Although this may be purely speculative, large amounts of transfused blood products may also induce a
prothrombotic status. There is no specific data on the clinical impact of Octaplas® transfusion in patients undergoing cardiac surgery, but De Maistre et al. (2009) observed an increased risk of venous thromboembolism after transfusion of fresh-frozen plasma in patients who underwent abdominal aortic surgery. Buchta et al. (2004) reported a concern about a lower level of protein S in Octaplas® compared with FFP. Administration of solvent/detergent-treated plasma has been shown to be associated with decreased protein S activity (Haubelt et al. 2002, De Silvestro et al. 2007), which may be detrimental in patients with congenital or acquired protein S deficiency. We, therefore, suspect that the prothrombotic status may be further enhanced by solvent/detergent-treated plasma in patients undergoing major surgery.

There is limited data indicating that platelet transfusion may be associated with an increased risk of thromboembolism (Khorana et al. 2008). A propensity score matched analysis by McGrath et al. (2008) did not demonstrate an increased morbidity risk with the use of platelet transfusion in adult cardiac surgery. The authors did not take into account the amount of platelet units transfused, however, and therefore, there was no report on patients who received large numbers of platelet units. It is known, however, that platelet storage is associated with microparticles (Simak & Gelderman 2006) and the possible association of such microparticles with thrombotic risk is a very active area of investigation.

Several factors may have affected our findings. First is the retrospective nature of our study, where data was collected from three hospitals with different peri-operative approaches. Second, the omitted data on intra- and post-operative levels of hemoglobin and hematocrit would have been useful to confirm the independent impact of blood products on post-operative neurological events. Third, we do not have data on the possible use of procoagulant drugs other than tranexamic acid. However, these potent procoagulants such as recombinant factor VII are only rarely used in our institutions and mainly in the treatment of severe bleeding occurring after valve and aortic surgery. Fourth, the impact of patient's comorbidities as well as operative technique are not easily assessable because of the complexity of the etiopathogenesis of stroke and the interaction of variables resulting in excessive bleeding and at the same time in a prothrombotic state. Table 6 (chapter 5.5) shows, however, that the rate of post-operative stroke and other major adverse events after transfusion of all three types of blood products is so high that patients' comorbidities and peri-operative anemia cannot be the only determinants of these complications. This is further confirmed by the sensitivity analysis of different additive EuroSCORE classes (Table 7 in chapter 5.5). In conclusion, our results
indicate that transfusion of large amounts of blood products after CABG is associated with a very high risk of postoperative stroke. It is of particular interest that the use of Octaplas® and platelet transfusions seems to have an even larger impact on the development of stroke than does the transfusion of red blood cells.

6.6 Blood transfusion and intermediate survival

Several studies have shown that blood transfusion during cardiac surgery significantly increases the risk of postoperative complications and mortality. Much research has focused on the impact of RBC transfusion and the data as to whether other blood products were administered has been missing, which may introduce a bias. This does suggest to some extent, however, that the individual impact of perioperative anemia and blood transfusion is not easily discernible, and both these risk factors may independently contribute to the patients’ recovery. As the use of FFP, Octaplas®, and platelet transfusions promotes coagulation and may thus potentially induce thrombotic complication, they may also affect outcome after cardiac surgery. Our results suggest that using any allogeneic blood product may contribute negatively to the prognosis of CABG patients. At this stage, it is not clear whether patients receiving all three blood products are at the highest risk of mortality because of the additive negative effects of each different type of allogeneic blood products or the severity of bleeding. We can assume, however, that the evaluation of the prognostic impact of blood transfusion should not be limited to transfusions of allogeneic RBCs. Several studies have shown blood transfusion to decrease long-term survival after CABG (Murphy et al. 2007, Koch et al. 2006, Engoren et al. 2002). Koch et al. (2006) also showed that RBC and platelet transfusions have a negative impact on the health-related quality of life 6–12 months after cardiac surgery. This study and other studies have failed, however, to confirm these findings. After evaluating 1841 patients who survived longer than 60 days after CABG, Weightman et al. (2009) did not find any association between the transfusion of blood products and all-cause mortality up to 10 years after surgery. Using a similar approach, Surgenor et al. (2009) showed that RBC transfusion had a significant impact on mortality up to 6 months, but during the late phase (6 months to 5 years), there was no significant association between allogeneic RBC exposure and mortality. Also Van Straten et al. (2010) did not find a significant association between RBC transfusion and late mortality (> 30 days) after CABG. Similarly, among patients with a follow-up of at least 3 months, we found that the perioperative use of any blood product was associated with a slight
increase in the risk of late mortality, but this was not statistically significant. Possible differences in the study populations and different transfusion policies can explain these controversial findings. Furthermore, during the last few years, potent antiplatelet drugs have been introduced in the perioperative treatment of patients undergoing CABG, and the use of aprotinin has been discontinued in most hospitals. This latter change may have significantly contributed to changes in the severity of bleeding, the need for transfusion, and the occurrence of cardiovascular events, as well as possibly the prognosis of these patients. Another important concept is the age of transfused RBCs. Koch et al. (2008) found in a propensity-matched analysis that transfusion of RBCs that had been stored for more than 2 weeks was associated with an increased risk of postoperative complications as well as reduced short-term and long-term mortality.

Pre- and perioperative anemia in CABG patients is associated with increased postoperative mortality and morbidity, and it is also driving force behind transfusions of red blood cells. However, at the critical level of anemia, transfusion of RBCs is lifesaving. The present results provide further evidence on the need for a re-engineering of preoperative management of anemia, the prevention of intra- and postoperative bleeding, and a more sparing use of blood products in patients undergoing CABG. This can be achieved by preoperative recognition and treatment of anemia, a preoperative discontinuation of potent antiplatelet drugs, the use of acute normovolemic hemodilution, the use of thromboelastometry, the intraoperative use of tranexamic acid, and an avoidance of overtransfusion (Shander et al. 2012, Andreasen et al. 2012). As was demonstrated in our study on individual surgeon’s role in reducing the amount of perioperative bleeding (study III), a meticulous surgical technique remains as major goal to reduce the need for blood transfusion. Any of these measures may significantly reduce the need of blood transfusion with a possibly improved clinical outcome and a decrease in costs.

The negative prognostic impact of the use of FFP/Octaplas® in these patients is a concern, as we earlier observed an increased risk of stroke associated with its use during CABG (study IV). There is no specific data on the clinical impact of Octaplas® transfusion in patients undergoing cardiac surgery, but De Maistre et al. (2009) observed an increased risk of venous thromboembolism after FFP transfusion in patients who underwent abdominal aortic surgery. Buchta et al. (2004) reported a concern about a lower level of protein S in Octaplas® compared with FFP. While undergoing major surgery, patients with congenital or acquired protein S deficiency may find the administration of solvent-/detergent-treated plasma detrimental, as it has been shown to be associated with decreased protein S
activity (Haubelt et al. 2002, De Silvestro et al. 2007). Therefore, we may expect that a prothrombotic status may be further enhanced by solvent-/detergent-treated plasma in patients undergoing major surgery.

In conclusion, the significantly increased risk of all-cause and cardiac mortality associated with transfusion of any blood product seems to be limited to the early postoperative period and diminish later. Among different kind of blood products, the main determinant of mortality seems to be the perioperative use of FFP or Octaplas®.
7 Conclusions

The results of these studies can be summarized as follows:

I Late or no discontinuation of low-dose aspirin before CABG may decrease the risk of postoperative stroke without increasing the risk of postoperative bleeding.

II CABG is a safe procedure during therapeutic oral anticoagulation (TOAC) with no excess bleeding or major complications.

III An individual surgeon has a major impact on postoperative bleeding and need for re-exploration after CABG.

IV Re-exploration for bleeding after cardiac surgery carries a significantly increased risk of postoperative mortality and morbidity.

V Transfusion of blood products after CABG has a strong, dose-dependent association with the risk of stroke. The use of Octaplas® and platelet transfusions seem to have an even larger impact on the development of stroke than red blood cell transfusions.

VI Transfusion of any blood product is associated with a significant risk of all-cause and cardiac mortality after CABG.
References


Original publications


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