Outcome after Procedures for Retained Blood Syndrome in Coronary Surgery

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ABSTRACT

OBJECTIVES: Incomplete drainage of blood from around the heart and lungs can lead to retain blood syndrome (RBS) after cardiac surgery. The aim of this study was to assess the incidence and outcome after procedures for RBS in patients undergoing isolated coronary artery bypass grafting (CABG).

METHODS: 2764 consecutive patients who underwent isolated CABG from 2006 to 2013 were investigated retrospectively. Patients undergoing any procedure for RBS were compared with patients who did not undergo any procedure for RBS. Multivariate analyses were performed to assess the impact of procedures for RBS on the early outcome.

RESULTS: 254 patients (9.2%) required at least one procedure for RBS. Multivariate analysis showed that RBS requiring procedure for blood removal was associated with significantly increased 30-day mortality (8.3% vs. 2.7%, OR 2.11, 95%CI 1.15-3.86). Procedures for RBS were independent predictors of need of postoperative antibiotics (51.6% vs. 32.1%, OR 2.08, 95%CI 1.58-2.74), deep sternal wound infection/mediastinitis (6.7% vs. 2.2%, OR 3.12, 95%CI 1.72-5.66), KDIGO acute kidney injury (32.7% vs. 15.3%, OR 2.50, 95%CI 1.81-3.46), length of stay in the intensive care unit (mean 8.3 vs. 2.0 days, beta 1.74, 95%CI 1.45-2.04) and composite major adverse events (21.3% vs. 6.9%, OR 3.24, 95%CI 2.24-4.64). These findings were confirmed also in a subgroup of patients without any pre- or postoperative unstable hemodynamic conditions.

CONCLUSION: RBS requiring any procedure for blood removal from pericardial and pleural spaces is associated with an increased risk of severe complications after isolated CABG.

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KEYWORDS: Coronary artery bypass grafting; coronary artery bypass surgery; bleeding; retained blood; reoperation; thoracentesis; pleural drainage.

IINTRODUCTION

Excessive blood loss is known to be associated with a number of complications after cardiac surgery [1-3]. Evacuation of shed blood from the pericardium during the early postoperative period by chest tubes is of particular importance. Recently, an interest in retained blood as a possible predictor of adverse effects after cardiac surgery has arisen. Bloody fluid collection in the pericardium and pleura caused by excessive bleeding, clogging of drains [4-7] or other mechanisms are hypothesized to generate a continuum of complications, which Boyle et al. [4] named as retained blood syndrome (RBS). RBS is defined as an acute, sub-acute or chronic collection of blood or hematoma requiring removal from the pericardial or pleural spaces. In the acute phase, RBS can manifest as cardiac tamponade and/or hemothorax usually requiring urgent resternotomy. Bloody pericardial and pleural effusions characterize the syndrome in the sub-acute phase, which is treated by pleural drainage, thoracentesis and pericardial fenestration. Chronic phase includes fibrothorax and constrictive pericarditis induced by effusion and inflammation resulting from stagnant leftover blood. [4] Recent studies have shown that retained blood can be observed in as many as one fifth of patients undergoing cardiac surgery [4,5,8] and in up to 64% of patients undergoing urgent cardiac operation [8]. RBS seems to be associated with poor postoperative outcome [8]. However, studies addressing this issue are scarce. The purpose of the present study was to evaluate the incidence of procedures performed for retained blood and to assess the impact of procedures for RBS on the outcome after coronary artery bypass grafting (CABG).

MATERIALS AND METHODS

Patient population

This is a retrospective observational, single center study including 2764 consecutive patients who underwent isolated CABG from June 2006 to December 2013 at the Oulu University Hospital, Finland. Complete data on pre- intra- and postoperative variables were available in all these patients as

obtained from an institutional electronic cardiac surgery registry collecting data on baseline and operative variables as well as on immediate postoperative adverse events. Data on preoperative use of antithrombotics were retrospectively collected. Data on the types and amount of transfused blood products such as red blood cells (RBCs), platelets and solvent/detergent-treated plasma (Octaplas; Octapharma AG, Lachen, Switzerland) was retrieved from a prospective electronic hospital registry. Data on the amount of chest drainage output at 12 hours after surgery was retrieved from a prospective electronic registry of the intensive care unit. Clinical variables were defined according to the EuroSCORE II definition criteria [9]. Glomerular filtration rate (eGFR) was estimated by the Modification of Diet in Renal Disease (MDRD) formula [10]. Bleeding risk was estimated according to the Papworth Bleeding Risk Score [11]. The E-CABG bleeding classification [12] was employed to stratify the severity of perioperative bleeding according to the following criteria: Grade 0, no RBC transfusion or transfusion on one units of RBCs; Grade 1, transfusion of platelets, fresh frozen plasma or Octaplas and/or of 2-4 units of RBCs; Grade 2, transfusion of 5-10 units of RBCs and/or reoperation for bleeding; Grade 3, transfusion of > 10 units of RBCs. Data on patients' death were provided up to January 31st, 2016 from the Finnish Population Registry Center (Väestörekisteri), which collects the certificates of death of all inhabitants of Finland. We assume that there are no missing data on any immediate and late death of this study population.

Perioperative antithrombotic treatment

In this series, acetylsalicylic acid was interrupted for at least seven until 2012, whilst it was continued until the procedure later on. Vitamin K antagonist was interrupted at least 2 days before the procedure and heparin bridging was not adopted. Patients with acute coronary syndrome or mechanical heart valve received enoxaparin preoperatively. P2Y12 inhibitors were discontinued for at least 5 days when feasible. Heparin (3.0 mg/kg) was administered intravenously during the operation to maintain an activated coagulation time of longer than 450 seconds. Protamine sulphate (3.0 mg/kg) was given at the end of procedure to neutralized heparin. These patients did not receive aprotinin. Tranexamic acid

was administered intraoperatively at discretion of the anesthesiologist. RBCs were transfused on the operation day if hemoglobin < 90 g/L and later if hemoglobin < 80 g/L. Octaplas® and platelets were transfused according to the severity of perioperative bleeding, INR levels and platelet count. rFVIIa was used only in cases of unrelenting massive bleeding.

Patients received enoxaparin 40-80 mg once-a-day since the evening of the operation day is chest drainage output was less than 1000 mL. Aspirin 100 mg was restarted on the first postoperative day. Warfarin was restarted on the first postoperative day in those patients under chronic anticoagulation. P2Y12 inhibitors were administered after surgery only in case of allergy to aspirin or recent percutaneus coronary intervention.

Operative techniques and management of chest drainages

Intermittent antegrade and retrograde cold blood cardioplegia was employed for myocardial protection in patients undergoing on pump coronary surgery. Octopus stabilizer (Medtronic, Minneapolis, MN) as well as intracoronary shunts were routinely used in patients who underwent off-pump surgery.

Blood lost intraoperatively was collected into a cell-saver reservoir and was reinfused during or at the completion of the procedure.

One 24 Fr pericardial drainage and one 30 Fr mediastinal drainage were inserted in all patients. Pleural drainages of 28 Fr in size were inserted when mediastinal pleura was accidentally opened, when prophylactic pericardial fenestration was made or in case on preoperative lung edema and/or pleural effusion. Mediastinal and pleural blood was collected after surgery in a sterile collection chamber connected to 15 cm H_2O wall suction via an underwater seal and then discarded. Mediastinal drainages were cleared by the nurses milking them regularly during the postoperative period and were removed within 24 hours after surgery. No active clearance device was used in these patients. Pleural

drainages were removed along with mediastinal drainages or, in case of postoperative blood loss > 1000 mL, as soon as the drainage output was < 200 mL/day.

Diagnosis and treatment of retained blood syndrome

Retained blood syndrome or RBS was defined as any condition requiring reopening the surgical incision and washout of the pericardial and pleural spaces, pericardial window, insertion of a chest tube and/or thoracentesis to remove blood from the pericardial or pleural space within 30 days from the index procedure. Only patients with frank blood effusion were considered having retained blood. Resternotomy was performed on the same operation day in case of excessive bleeding for hemostasis and removal of retained blood. Bleeding in to the pericardium and/or pleural spaces was suspected in case of a drop > 10 g/L of hemoglobin level compared to a previous postoperative measurement (hemoglobin levels were routinely monitored at least once-a-day) and/or unstable cardiorespiratory conditions. In such cases, chest X-ray and echocardiography were performed to diagnose excessive pericardial and pleural fluid and the diagnosis of RBS was confirmed when frank blood was removed. Resternotomy or pericardial fenestration was performed for removal of retained blood when patients' oxyhemodynamic conditions were suboptimal and/or in presence of pericardial effusion/hematoma with signs of tamponade at echocardiography. Thoracoscopic fenestration was usually performed when excessive retained blood was detected more than two weeks after surgery and cardiorespiratory conditions allowed selective right bronchial intubation and lateral position on the operating table. Otherwise, pericardial blood was removed through a sub-xiphoid access. Pleural drainage was inserted or thoracentesis performed when excessive pleural effusion was detected at chest-X ray and/or patient's oxygen saturation was suboptimal.

Outcomes

The primary outcomes of this study were all-cause in-hospital and 30-day mortality. Secondary outcomes were the length of intensive care unit stay, stroke, atrial fibrillation, ventricular fibrillation or asystole, postoperative use of antibiotics, deep sternal wound infection, mediastinitis, low cardiac output syndrome, repeat revascularization, surgery for gastrointestinal complications, acute kidney injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [13], nadir hemoglobin level during the postoperative period, chest drain output 12 hours after surgery, severity of bleeding according to the E-CABG bleeding classification as well as the E-CABG complication score and E-CABG complication grade 3 (renal failure requiring renal replacement therapy, mediastinitis, stroke, early repeat myocardial revascularization, ventricular fibrillation/asystole, surgery for gastrointestinal complication and/or extracorporeal membrane oxygenation) as composite outcome measures [12]. For the purpose of this study, bleeding-related parameters, i.e. use of blood products and reoperation for bleeding, were excluded from these composite outcomes. Low cardiac output syndrome was defined as postoperative cardiac index < 2.0 L/min/m^2 as measured at least twice. The other outcomes were defined according to the E-CABG definition criteria as previously described [12].

Ethical considerations

This study was approved by the Institutional Review Board of the Oulu University Hospital. This study was not financially supported.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 23.0, IBM Corporation, New York, USA). Continuous variables are reported as mean and standard deviation. Nominal variables are reported as counts and percentages. Risk estimates are reported as beta coefficient or

odds ratio (OR) with 95% confidence interval (95%CI). No attempt to replace missing values was made. The Fisher's exact test and Chi-square test were used to evaluate the differences of nominal variables between study groups. The Mann-Whitney test was used to evaluate differences of continuous variables between study groups. Logistic, linear and ordinal regression analyses were performed to adjust the effect of baseline variables on outcomes. The impact of procedures for retained blood on the outcomes was adjusted in logistic, linear and ordinal regression analyses for those variables with $p<0.05$ in univariate analysis: patient's age, body mass index, recent myocardial infarction, critical preoperative status, dialysis, and urgency status. Predictors of RBS were identified in logistic regression including covariates with $p<0.05$ in univariate analysis as listed in Table 1. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

RESULTS

Procedures for retained blood syndrome

In overall, 254 patients (9.2%) required at least one procedure for removal of retained blood in the pericardial or pleural cavity. Characteristics of these patients compared with those not requiring removal of retained blood are summarized in Tables 1 and 2. One procedure for removal of retained blood was performed in 211 patients (7.6%), two procedures in 39 patients (1.4%), three procedures in three patients (0.1%) and five procedures in one patient (0.03%). Resternotomy for removal of retained blood was performed in 181 patients (6.5%) after a mean of 1.8±4.1 days. Forty-five of these patients (24.9%) had resternotomy after ≥ 2 days after the index procedure. Pericardial fenestration was performed in 40 patients (1.4%), pleural drainage in 50 patients (1.8%, in three patients it was done twice) and thoracentesis in 25 patients (0.9%, in three patients it was done twice). Pericardial fenestration was performed in one patient thoracoscopically and in 39 patients through the sub-xiphoid access. In these patients, hemodynamic signs and symptoms of pericardial tamponade were observed in 32 patients and echocardiographic findings of tamponade without oxyhemodynamic instability in 25

patients. Excluding patients who underwent resternotomy, procedures for RBS were performed in 73 patients (2.6%). During follow-up, surgery for pericarditis was performed in two patients and one of them has had resternotomy for RBS. No patients required surgery for fibrothorax in this series. Predictors of procedures for RBS in univariate analysis are listed in Tables 1 and 2. Logistic regression (Hosmer-Lemeshow's test: p=0.286) identified age (p=0.03, OR 1.02, 95%CI 1.00-1.03), preoperative dialysis (p=0.001, OR 4.93, 95%CI 2.00-12.33) and critical preoperative status (p=0.006, OR 1.77, 95%CI 1.18-2.66) as independent predictors of RBS.

Impact of retained blood syndrome on the immediate outcome

Patients with RBS had a significantly lower nadir hemoglobin (mean, 76±10 g/L vs. 84±13 g/L, p<0.0001) compared to those who did not require any procedure for RBS. Such a difference was observed also when patients who underwent resternotomy for bleeding were excluded from the analysis (mean, 78±11 g/L vs. 84±13 g/L, p<0.0001). However, chest drain output was significantly higher in the overall group of patients who underwent procedures for RBS (mean, 965±732 mL vs. 456±305 mL, p<0.0001), but not in those with RBS who did not require resternotomy (mean, 480±368 mL vs. 456±305 mL, p=0.95). Procedures for RBS were performed more frequently in patients with severe bleeding as stratified by the E-CABG bleeding severity classification (Tab. 3).

Multivariate analysis of the overall series showed that RBS requiring procedure for blood removal was an independent predictor of increased in-hospital and 30-day mortality (Tab. 3). A subanalysis excluding patients who required resternotomy for RBS showed that procedures for RBS other than resternotomy were associated with an increased risk of early death, but such a difference did not reach statistical significance in multivariate analysis (Tab. 3).

Procedures for RBS were independent predictors for most of secondary outcomes (Tab. 3). These patients had a significantly lower nadir hemoglobin level than patients who did not require procedures for RBS. Analysis excluding patients who underwent resternotomy for RBS showed that retained

blood requiring pericardial fenestration , thoracentesis and/or pleural drainage was associated with an increased risk new atrial fibrillation, need of postoperative antibiotics as well as deep sternal wound infections and mediastinitis, acute kidney injury and gastrointestinal complications (Tab. 3). Such increased rate of adverse events in patients with RBS translated in to a prolonged stay in the intensive care unit.

Procedures for RBS, either including resternotomy or not, were associated with a significantly increased risk of composite outcome defined as E-CABG complication grades and score (Tab. 3). The excessive risk of E-CABG grade 3 complications in patients who underwent procedure for RBS (21.3% vs. 6.9%, p<0.0001, adjusted OR 3.22, 95%CI 2.24-4.64) compared to those patients who did not have RBS is worth noting. Such an increased risk of E-CABG grade 3 complications associated with procedures for RBS was observed also when excluding from the analysis those patients who underwent resternotomy (19.2% vs. 6.4%, p<0.0001, adjusted OR 2.80, 95%CI 1.48-5.32).

Impact of resternotomy for bleeding on the immediate outcome

Comparative analysis of the outcome of patients who underwent resternotomy for bleeding and those who did not experience RBS showed that resternotomy for bleeding was associated with increased risk of in-hospital death (7.2% vs. 2.0%, adjusted OR 2.55, 95%CI 1.18-5.51) and 30-day death (10.5% vs. 2.7%, adjusted OR 3.00, 95%CI 1.56-5.74). Furthermore, resternotomy for bleeding was an independent predictor of a number of other adverse events (Tab. 3), most notably KDIGO acute kidney injury (30.9% vs. 15.3%, adjusted OR 2.42, 95%CI 1.64-3.52), low cardiac output (20.4% vs. 13.1%, adjusted OR 1.73, 95%CI 1.16-2.59), E-CABG complication grade 3 (22.1% vs. 6.9%, adjusted OR 3.40, 95%CI 2.24-5.17) and increased E-CABG complication score (mean 5.7 vs. 3.0, adjusted beta 2.16, 95%CI 1.53-2.78) (Tab. 3).

Impact of retained blood syndrome on the immediate outcome of patients with preoperative and postoperative stable hemodynamic conditions.

Since it is difficult to disentangle the impact of RBS from that of critical hemodynamic conditions on adverse events occurring after CABG, we performed a separate analysis in a subgroup of patients without critical preoperative status such as those receiving inotropes, experiencing out-of-hospital cardiac arrest or ventricular arrhythmias, with intra-aortic balloon pump as well as without postoperative low cardiac output, prolonged need of inotropes, need of intra-aortic balloon pump or who required further myocardial revascularization immediately after CABG. In this hemodynamically stable patient population, procedures for RBS were performed in 112 (6.3%), and 83 (4.7%) patients underwent resternotomy for bleeding. RBS was associated with an increased risk of KDIGO acute kidney injury (20.2% vs. 8.6%, adjusted OR 2.66, 95%CI 1.53-4.63), deep sternal wound infection/mediastinitis (6.3% vs. 2.1%, adjusted OR 3.04, 1.21-7.64), E-CABG complication grade 3 (10.7% vs. 3.4%, adjusted OR 2.74, 95%CI 1.30-5.82) and increased E-CABG complication score (mean 3.7 vs. 2.0, adjusted beta 1.19, 95%CI 0.64-1.74) (Tab. 4).

DISCUSSION

In the present study the incidence of RBS was 9.2% which was lower than in previous studies reporting a rate of RBS of about 19% [5,8]. Herein, we observed that procedures for removal of retained blood were performed more often in patients suffering from severe bleeding as assessed by the E-CABG bleeding severity classification and were associated with several postoperative complications. Most importantly, in-hospital and 30-day mortality were significantly increased in patients who had undergone any procedure for RBS. However, when patients who required resternotomy were excluded, procedures other than resternotomy were associated with an increased risk of in-hospital death (4.1% vs. 2.0%), which did not reach statistical significance in multivariate analysis. Balzer et al. [8] investigated patients undergoing CABG and/or valve operation and observed

that procedures for evacuation of retained blood (including resternotomy) were associated with increased in-hospital mortality (OR 4.04, 95% CI 2.59-6.35) [8]. They reported a rate of in-hospital mortality of 19.7% in patients with RBS [8], which is much higher than that observed in the present study (6.3%).

This study showed that procedures for RBS, either including resternotomy or not, were independent predictors of the need of postoperative antibiotics, deep sternal wound infection/mediastinitis, acute kidney injury, length of stay in the intensive care unit, and composite adverse events defined as E-CABG complication score and grading. Of particular interest is the excessive risk of E-CABG grade 3 complications in patients who underwent any procedure for RBS, even in patients who did not require resternotomy and among those with stable hemodynamic conditions. Similar results on the detrimental effect of procedures for RBS on the outcome after cardiac surgery have been reported by other investigators as well [4,5,8].

We observed that chest drain output was significantly larger in patients who needed resternotomy than in control patients. On the contrary, chest drain output in RBS patients was similar to control patients when resternotomies were excluded from the analysis. This observation suggests that in some cases, blood is retained in the pericardium after chest tubes clog up. However, we suspect that bleeding may still occur into the pericardium or pleural spaces after the removal of chest tubes. Although this study was not planned to assess this issue, the role of individual surgeon must be emphasized. Indeed, individual surgeon has been shown to have a significant impact on chest tube output as well as on resternotomy for excessive bleeding [14,15]. Importantly, most of the sources of bleeding requiring resternotomy can be classified as surgical [3,14,16]. Excessive blood loss requiring resternotomy can be considered a remarkable adverse event as resternotomy for bleeding is associated with a number of severe complications [3,14,17].

Another possible cause for retained blood is clogging of drainage tubes. The lumen of the drain may get occluded because of thrombosis within the drainages when clearance is not optimal or even because of kinking or malposition of the drain. The clot usually develops inside the chest, which can

make difficult to recognize it [4]. In a survey conducted by Shalli et al. [7], 100% of surgeons had encountered clogged chest tubes and 88% were aware that it could lead to adverse effects. Chest tube occlusion is a surprisingly common problem. It can be present in as many as 36% of patients. Clogging of chest tubes are more frequently associated with non-elective operation, renal failure, increased number of transfused RBCs during the operation and postoperative platelet administration [6]. Occlusion of the drainages can be prevented by active suction devices. Sirch et al. [5] investigated this issue and found that when active clearance of the chest tubes was used after cardiac surgery, the prevalence of RBS decreased from 19.5% to 11.3%. The suction apparatus also reduced chest tube output and mechanical ventilation hours [5]. When detected, manipulating the drain could clear the occlusion, although it is not always advisable [7]. Ege et al. [18] reported on cases of cardiac tamponade as a result of clogged pericardial drain.

Drainage tube clogging seems to be associated with an increased risk of atrial fibrillation [5,6], which is one of the most frequent adverse effects after cardiac surgery. Its incidence is at least around 20% according to different authors [19,20]. The prevalence of atrial fibrillation can be reduced by proper clearance of pericardial fluid collections [5,18,21]. Atrial fibrillation and other supraventricular arrhythmias are reduced also in patients who undergo posterior pericardiotomy [20]. The present results demonstrated that retained blood in the pericardium is associated with an increased risk of postoperative atrial arrhythmias.

As suggested by Boyle et al. [4], pericardial and pleural effusions characterize sub-acute RBS. The prevalence of pericardial effusion has been reported to be between 1.5% and 22% in cardiac surgery patients [22,23]. Early effusions are more common after CABG [23], but late pericardial effusions and cardiac tamponade were more common after valvular operations [22-24]. A large proportion of patients with significant pericardial effusion have been reported to develop cardiac tamponade later on [22,24]. In the study conducted by Light et al. [25], the prevalence of pleural effusion in CABG patients at four weeks was as high as 62.4% with no difference to patients who underwent combined CABG and valve procedures. Pleural fluid aspirates within 30 days of the index operation contained

large amounts of red blood cells indicating retained blood [25], but later effusions are usually classified as chronic inflammation [26].

Retained blood could be the stimulus for postpericardiotomy syndrome (PPS), which is characterized by friction rub, fever without any evidence of infection, pleuritic chest pain, pleural effusion and new or worsening pericardial effusion [4]. The incidence of PPS varies according to diagnostic criteria, but the majority of cases present within the first month [27]. In some patients, this condition can progress to fibrosis and constrictive pericarditis [27], as hypothesized also by Boyle et al. [4]. However, in our series, surgery for pericarditis was performed in only two patients and one of them has had resternotomy for RBS.

Some limitations related to this study should be acknowledged. First, most of data were collected retrospectively and the nature of fluid collection was defined by the operating surgeon and not confirmed by any specific laboratory test. Second, a problem lies in the analysis of outcomes and their relation to the needed reintervention without referring to the timing of the adverse events. An analysis of the timing of occurrence of these adverse events is anyway complex and not feasible in a retrospective study. However, some adverse events such as sternal wound infection develop a few days after surgery, whilst other complications such as acute kidney injury may develop before RBS is recognized. The strength of the present analysis is that the amount of blood loss and that of blood products were recorded in prospective clinical registries. This makes the estimation of severity of perioperative bleeding reliable.

In conclusion, RBS requiring any procedure for blood removal from the pericardial and pleural spaces is a relatively common complication after CABG and is associated with an increased risk of severe adverse events.

CONFLICT OF INTEREST

None to declare.

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Table 1: Baseline characteristics.

Baseline variables	*Overall series No. 2764*	*No procedure for RBS No. 2510*	*Procedure for RBS No. 254*	*P-value*	*Procedure for RBS excluding resternotomy No. 73*	*P-value*
Age (years)	67.0±9.1	66.9±9.1	68.2±9.2	0.02	69.2±10.0	0.02
Females	582 (21.1)	539 (21.5)	43 (16.9)	0.09	10 (13.7)	0.11
Body mass index	28.1±4.5	28.1±4.5	27.4±4.5	0.01	27.6±4.9	0.13
Hemoglobin (g/L)	137±16	137±16	137±16	0.71	135±17	0.45
Platelets (10^9/L)	242±75	241±74	254±106	0.73	254±106	0.74
eGFR (mL/min/1.73 m^2)	86±25	86±25	83±28	0.06	80±29	0.03
Dialysis	22 (0.8)	15 (0.6)	7 (2.8)	<0.01	3 (4.1)	0.01
Pulmonary disease	274 (9.9)	249 (9.9)	25 (9.8)	0.97	10 (13.7)	0.29
Diabetes	788 (28.5)	714 (28.4)	74 (29.1)	0.82	22 (30.1)	0.75
Stroke	95 (3.4)	84 (3.3)	11 (4.3)	0.41	3 (4.1)	0.72
Extracardiac arteriopathy	265 (9.6)	238 (9.5)	27 (10.6)	0.55	10 (13.7)	0.23
Atrial fibrillation	282 (10.2)	252 (10.0)	30 (11.8)	0.37	12 (16.4)	0.08
Previous PCI	201 (7.3)	188 (7.5)	13 (5.1)	0.17	4 (5.5)	0.52
Previous cardiac surgery	46 (1.7)	42 (1.7)	4 (1.6)	1.00	1 (1.4)	1.00
Left ventricular ejection fraction ≤50%	699 (25.3)	625 (25.9)	74 (30.5)	0.12	26 (37.1)	0.03
Recent myocardial infarction	1319 (47.7)	1181 (47.1)	138 (54.3)	0.03	41 (56.2)	0.15
Critical preoperative status	217 (7.9)	186 (7.4)	31 (12.2)	0.01	13 (17.8)	<0.01
Preoperative IABP	11 (0.4)	9 (0.4)	2 (0.8)	0.30	0	1.00
Recent ventricular tachycardia	83 (3)	73 (2.9)	10 (3.9)	0.36	6 (8.2)	0.01
Cardiac massage	43 (1.6)	38 (1.5)	5 (2.0)	0.58	3 (4.1)	0.11
Potent antiplatelet drugs within 5 days from surgery*	512 (18.5)	456 (18.2)	56 (22.0)	0.13	18 (24.7)	0.16
Warfarin within 2 days from surgery	77 (2.8)	67 (2.7)	10 (3.9)	0.24	3 (4.1)	0.46
Papworth bleeding score	1.0±0.8	1.0±0.8	1.2±0.8	<0.01	1.3±0.8	<0.01

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. RBS: retained blood syndrome; PCI: percutaneous coronary intervention; IABP: intra-aortic balloon pump; GFR: glomerular filtration rate; *: it referes to clopidogrel, ticagrelor and prasugrel; p-values refer comparison with patients who did not undergo procedures for retained blood.

Table 2: Operative data.

Operative variables	*Overall series No. 2764*	*No procedure for RBS No. 2510*	*Procedure for RBS No. 254*	*P-value*	*Procedure for RBS excluding resternotomy No. 73*	*P-value*
Urgency status						
Elective	1260 (45.6)	1161 (46.3)	99 (39.0)	<0.01	27 (37.0)	0.29
Urgent	1306 (47.3)	1180 (47.0)	126 (49.6)		40 (54.8)	
Emergency	198 (7.2)	169 (6.7)	29 (11.4)		6 (8.2)	
Off-pump surgery	1449 (52.4)	1319 (52.5)	130 (51.2)	0.68	44 (60.3)	0.36
Bilateral mammary artery graft	221 (8.0)	204 (8.1)	17 (6.8)	0.42	6 (8.2)	1.00
Number of distal anastomoses	4.0±1.1	3.9±1.1	4.0±1.1	0.25	4.0±1.2	0.45
Cross-clamping time (min)	85±29	85±29	88±29	0.07	77±37	0.80
CPB time (min)	111±38	110±38	116±37	0.02	101±46	0.75
Length of the operation (min)	249±69	248±70	258±60	0.04	256±50	0.25
Any pleural drainage	1449 (52.4)	1310 (52.3)	139 (53.5)	0.71	28 (38.4)	0.02
Bilateral pleural drainage	452 (16.4)	402 (16.0)	50 (19.7)	0.13	12 (16.4)	0.92
Prophylactic pericardial window	157 (5.7)	143 (5.7)	14 (5.5)	0.90	5 (6.8)	0.68

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. RBS: retained blood syndrome; CPB: cardiopulmonary bypass; p-values refer comparison with patients who did not undergo procedures for retained blood.

Table 3: Outcomes.

	Overall series No. 2764	*No procedure for RBS No. 2510*	*Procedure for RBS No. 254*	*Univariate analysis P-value*	*Adjusted risk estimate (95%CI)*	*Resternotomy for bleeding No. 175*	*Univariate analysis P-value*	*Adjusted risk estimate (95%CI)*	*Procedure for RBS excluding resternotomy No. 73*	*Univariate analysis P-value*	*Adjusted risk estimate (95%CI)*
In-hospital death	66 (2.4)	50 (2.0)	16 (6.3)	<0.01	**2.26, 1.14 -4.48**	13 (7.2)	<0.01	**2.55, 1.18-5.51**	3 (4.1)	0.20	1.77, 0.48-6.66
30-day mortality	89 (3.2)	68 (2.7)	21 (8.3)	<0.01	**2.11, 1.15-3.86**	19 (10.5)	<0.01	**3.00, 1.56-5.74**	2 (2.7)	1.00	0.52, 0.10-2.58
ICU stay (days)	2.2±2.5	2.0±2.1	3.4±4.4	<0.01	**1.74, 1.45-2.04**	3.7±4.1	<0.01	**1.53, 1.20-1.85**	4.6±5.1	<0.01	**2.32, 1.82-2.81**
Stroke	58 (2.1)	48 (1.9)	10 (3.9)	0.03	1.57, 0.75-3.32	8 (4.4)	0.02	1.83, 0.80-4.21	2 (2.7)	0.65	0.95, 0.22-4.18
New atrial fibrillation	946 (38.1)	843 (37.3)	103 (46.0)	0.01	**1.33, 1.01-1.75**	87 (44.1)	0.11	1.19, 0.86-1.64	33 (54.1)	0.01	**1.80, 1.04-3.09**
Ventricular fibrillation/asystole	49 (1.8)	39 (1.6)	10 (3.9)	0.01	1.97, 0.93-4.19	7 (3.9)	0.02	2.01, 0.88-4.97	3 (4.1)	0.11	1.88, 0.50-7.00
Low cardiac output syndrome	383 (13.9)	328 (13.1)	55 (21.7)	<0.01	**1.74, 1.24-2.45**	37 (20.4)	<0.01	**1.73, 1.16-2.59**	18 (24.7)	<0.01	1.71, 0.94-3.08
Repeat CABG or PCI	14 (0.5)	9 (0.4)	5 (2.0)	<0.01	**5.72, 1.87-17.43**	4 (2.2)	<0.01	6.78, 2.04-22.49	1 (1.4)	0.25	3.49, 0.41-29.60
Postop. use of antibiotics	937 (33.9)	806 (32.1)	131 (51.6)	<0.01	**2.08, 1.58-2.74**	80 (44.2)	<0.01	**1.51, 1.09-2.09**	51 (69.9)	<0.01	**4.78, 2.80-8.14**
Deep SWI/mediastinitis	72 (2.6)	55 (2.2)	17 (6.7)	<0.01	**3.12, 1.72-5.66**	8 (4.4)	0.06	2.01, 0.89-4.54	9 (12.3)	<0.01	**6.01, 2.68-13.47**
Surgery for gastroint. compl.	32 (1.2)	22 (0.9)	10 (3.9)	<0.01	**3.80, 1.67-8.64**	6 (3.3)	<0.01	**3.17, 1.16-8.71**	4 (5.5)	<0.01	**5.94, 1.86-18.97**
Acute kidney injury	457 (16.9)	377 (15.3)	80 (32.7)	<0.01	**2.50, 1.81-3.46**	54 (30.9)	<0.01	**2.42, 1.64-3.52**	26 (37.1)	<0.01	**2.81, 3.103-8.82**
Nadir hemoglobin (g/L)	83±13	84±13	76±10	<0.01	**-6.31, -7.80- -4.83**	75±8	<0.01	**-7.49, -9.17- -5.71**	78±11	<0.01	**-3.41, -6.11- -0.71**
Blood loss at 12 hours (mL)	503±394	456±305	965±732	<0.01	**503.3, 455.5-551.0**	1167±752	<0.01	**707, 653-761**	480±368	0.95	20.52, -50.21-91.26
E-CABG bleeding grades				<0.01	**-3.24, -3.54- -2.93**		<0.01	**-4.34, -4.78- -3.90**		<0.01	**-1.13, -1.58- -0.68**
Grade 1	1117 (40.4)	1091 (43.5)	26 (10.2)			0			26 (35.6)		
Grade 2	506 (18.3)	332 (13.2)	174 (68.5)			153 (84.5)			21 (28.8)		
Grade 3	68 (2.5)	31 (1.2)	37 (14.6)			28 (15.5)			9 (12.3)		
E-CABG compl. grade 3	186 (7.2)	172 (6.9)	54 (21.3)	<0.01	**3.24, 2.24-4.64**	40 (22.1)	<0.01	**3.40, 2.24-5.17**	14 (19.2)	<0.01	**2.80, 1.48-5.32**
E-CABG compl. score*	3.3±4.7	3.0±4.2	6.1±7.0	<0.01	**2.51, 1.96-3.06**	5.7±6.8	<0.01	**2.16, 1.53-2.78**	7.1±7.4	<0.01	**3.44, 2.49-4.40**

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. Risk estimates are beta coefficients or odds ratios with 95% confidence intervals. Risk estimates in bold indicate statistical significance in multivariate analysis; RBS: retained blood syndrome; ICU: intensive care unit; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; SWI: sternal wound infection; *: excluding bleeding-related outcomes. P-values and adjusted estimates refer to comparison with patients who did not undergo procedures for retained blood.

Table 4: Impact of retained blood syndrome on the outcome of patients without preoperative or postoperative unstable hemodynamic conditions.

	No procedure for RBS No. 1657	*Procedure for RBS No. 112*	*Univariate analysis P-value*	*Adjusted risk estimate (95%CI)*
In-hospital death	12 (0.7)	4 (3.6)	0.02	3.46, 0.66-18.09
30-day mortality	20 (1.2)	4 (3.6)	0.06	0.64, 0.08-5.46
ICU stay (days)	1.4±1.5	2.2±1.7	<0.01	**0.55, 0.32-0.77**
Stroke	20 (1.2)	2 (1.8)	0.65	0.69, 0.09-5.36
New atrial fibrillation	589 (35.5)	39 (34.8)	0.88	0.92, 0.60-1.42
Ventricular fibrillation/asystole	10 (0.6)	2 (1.8)	0.17	3.02, 0.62-14.74
Low cardiac output syndrome	0	0	-	-
Repeat CABG or PCI	0	0	-	-
Postop. use of antibiotics	435 (26.3)	49 (43.8)	<0.01	**2.05, 1.37-3.08**
Deep SWI/mediastinitis	34 (2.1)	7 (6.3)	<0.01	**3.04, 1.21-7.64**
Surgery for gastroint. compl.	5 (0.3)	1 (0.9)	0.33	0, 0-0
Acute kidney injury	140 (8.6)	22 (20.2)	<0.01	**2.66, 1.53-4.63**
Nadir hemoglobin (g/L)	86±12	77±10	<0.01	**-6.84, -9.06- -4.61**
Blood loss at 12 hours (mL)	460±258	1025±780	<0.01	**551, 490-612**
E-CABG bleeding grades			<0.01	**-3.78, -4.26 - -3.30**
Grade 1	670 (40.4)	9 (8.0)		
Grade 2	122 (7.4)	85 (75.9)		
Grade 3	6 (0.4)	7 (6.3)		
E-CABG compl. grade 3	56 (3.4)	12 (10.7)	<0.01	**2.74, 1.30-5.82**
E-CABG compl. score*	2.0±2.9	3.7±5.2	<0.01	**1.19, 0.64-1.74**

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. Risk estimates are beta coefficients or odds ratios with 95% confidence intervals. Risk estimates in bold indicate statistical significance in multivariate analysis; RBS: retained blood syndrome; ICU: intensive care unit; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; SWI: sternal wound infection; *: excluding bleeding-related outcomes.