Original Article

Early postoperative bleeding impacts long-term survival following first-time on-pump coronary artery bypass grafting

Thomas Senage[1,2], Caroline Gerrard[1], Narain Moorjani[1], David P. Jenkins[1], Jason M. Ali[1]

[1]Department of Cardiothoracic Surgery, Royal Papworth Hospital, Cambridge, UK; [2]SPHERE (MethodS in Patient-Centred Outcomes and Health Research), University of Nantes, Nantes, France

Contributions: (I) Conception and design: All authors; (II) Administrative support: C Gerrard, T Senage, JM Ali; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: T Senage, C Gerrard, JM Ali; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jason M. Ali, PhD. Department of Cardiothoracic Surgery, Royal Papworth Hospital, Cambridge CB20AY, UK.
Email: ja297@cam.ac.uk.

Background: Significant bleeding following cardiac surgery is a recognised complication, associated with a requirement for re-exploration and blood transfusion, both associated with increased morbidity and early mortality. The aim of this study was to examine the impact of the volume of early postoperative bleeding on long-term survival for patients undergoing coronary artery bypass grafting (CABG).

Methods: A retrospective analysis was performed of patients undergoing first-time isolated CABG at a single centre between January 2003 and April 2013, conditional from 30-day survival.

Results: Six thousand two hundred and sixty-five patients were analysed, with a mean Logistic EuroSCORE of 4.9%. The mean age was 67.8 years. Median follow-up was 11.5 years. The overall 10- and 15-year survival was 70.6% and 51.9% respectively. Following surgery, 4.6% (n=291) required return to theatre for re-exploration, and 43.6% (n=2,733) received at least one red cell transfusion. In multivariable analysis, the strongest correlates of mortality were age, smoking history, BMI, COPD, renal impairment, preoperative left ventricular function and preoperative haemoglobin (Hb) level. Twelve-hour blood loss was an additional predictor of inferior long-term survival. Five-year survival was 89.6% for patients with <500 mL blood loss, 86.8% for 500–1,000 mL and 83.8% for >1,000 mL. Re-exploration and receiving blood transfusion were not associated with reduced long-term survival.

Conclusions: Significant 12-hour blood loss is associated with inferior long-term survival following CABG. This observation supports efforts aimed at improving intra-operative haemostasis and aggressive management of patients with early signs of bleeding.

Keywords: Bleeding; re-exploration; outcomes; coronary artery bypass grafting (CABG)

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Introduction

Although there are many strategies employed with the aim of reducing postoperative bleeding after cardiac surgery, such as intraoperative haemostasis checklists (1) and point of care monitoring of coagulation status (2), bleeding remains an important complication.

Significant postoperative bleeding is associated with re-exploration and blood transfusion, both associated with inferior outcomes (3,4). A recent review concluded that patients who bleed significantly and undergo re-exploration have increased mortality and experience greater morbidity (5). Similarly, studies have demonstrated an association between blood transfusion and increases in short- and long-term mortality, with a correlation between

the amount of blood transfused and morbidity (6,7). These studies have driven a shift from more liberal use of blood products to a more restrictive and goal-directed approach.

There is also evidence that bleeding itself is harmful, independently of re-exploration and significant blood transfusion, with studies demonstrating association with increased postoperative mortality risk (8-11). To date though, there is little evidence exploring the impact of significant bleeding on longer term survival.

The aim of our study was to examine the impact of early postoperative bleeding volume on long-term survival for patients undergoing coronary artery bypass grafting (CABG).

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-1241).

Methods

Patient population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Royal Papworth Hospital Clinical Governance Department and individual consent for this retrospective analysis was waived. This was a retrospective observational study conducted at a single institution. All patients undergoing CABG at Royal Papworth Hospital between January 2003 and April 2013 were included. Demographic, intra-operative and post-operative outcome data were collected prospectively, and a full dataset was available for every patient. Mortality information was obtained from the UK National Health Service patient administration system and was therefore available for all patients included in the study. The hospital Clinical Research Ethics Committee provided approval for the study.

Patient exclusion

The following patients were excluded from analysis due to there being small numbers in each group:

- Previous cardiac surgery.
- Single coronary artery bypass graft.
- Minimally invasive direct CABG.
- Off-pump CABG.
- End-stage renal failure undergoing haemodialysis.

In this series there were few patients who underwent single coronary bypass grafting, many of whom underwent hybrid revascularisation. They represent a different group of patients from the majority of our practice, hence their exclusion.

The aim was to assess the impact of postoperative blood loss on long-term survival independent of severe postoperative complications, and therefore patients who died within the first 30-day following surgery (considered perioperative mortality) were also excluded from the analysis.

Patient management

The operating techniques and mode of myocardial preservation were left to the 16 operating surgeon's discretion. A common surgical approach via median sternotomy with extracorporeal bypass was adopted, with proximal anastomoses performed after cross-clamp release. For elective patients during this era, anti-platelet and anticoagulant medications were discontinued in advance of admission: aspirin 5-day, clopidogrel 7-day and warfarin 5-day. For urgent and emergency operations aspirin was continued until surgery whilst clopidogrel was discontinued once the prospect of surgery was identified.

The decision to re-explore patients was at the operating surgeon's discretion. During the era of this study the unit policy was a transfusion trigger of 80 g/L.

Study endpoint

The primary outcome measure was long-term survival. The impact of postoperative bleeding on survival was examined, defining significant bleeding on the basis of:

- Mediastinal drainage within the first 12 hours, as a categorical variable: <500 mL, between 500 and 1,000 mL, and >1,000 mL.
- Requirement for re-exploration for suspected bleeding within the first 48 hours.
- Red blood cell transfusion, as a categorical variable: none, <2 units, and >2 units (including intra-operative and post-operative period).

For the blood loss continuous variable, the log-linearity assumption was not confirmed (checked by using the quartiles of the variable). Therefore, a transformation of the variable in a categorical variable was performed. The 500 and 1,000 thresholds were chosen following clinical judgment.

Statistical analysis

Statistical analysis was performed using R 2.15.0 (R Core Team, Vienna, Austria). Quantitative data are expressed as mean ± standard deviation, while categorical variables are expressed as a frequency. For comparison, continuous variables were analysed with the Mann-Whitney U test if not normally distributed and with the students *t*-test (or one-way ANOVA test) if normally distributed. categorical variables were analysed with the Chi-squared test. A P value ≤0.05 was considered statistically significant.

The main outcome of this study was the time between surgery and patient death. A first selection of covariates was performed with the use of the, including covariates associated with the blood loss variable (P<0.20) and/or the main outcome (Kaplan-Meier estimator and log-rank test, P<0.20). Continuous covariates have been transformed if the log-linearity assumption was not confirmed (checked by using the quartiles of the covariate).

The following perioperative data were considered as possible correlates of death: operative age (years), sex, body mass index (BMI), family history, high blood pressure history, diabetes mellitus, smoking history, dyslipidaemia, obesity, chronic obstructive pulmonary disease (COPD), preoperative creatinine clearance, left ventricular function, surgery priority, preoperative haemoglobin (Hb), cardiopulmonary bypass (CPB) time, cross clamping time, number of grafts, type of grafts, final Hb in theatre, re-exploration for bleeding in the first 48 hours, blood transfusion, and, finally, blood loss in the first 12 hours.

For the multivariable analysis, a Cox proportional hazards regression model have been performed. Age and blood loss have been forced into the model. Hazards proportionality was checked graphically by plotting log-minus-log survival curves and by testing the scaled Schoenfeld residuals, and no violation was observed. A backward elimination was performed, manually variable by variable. This procedure allowed us the identification of possible confounding factors (variation of blood loss regression coefficient of >20%).

Results

Patient population

Over the period of study 16,109 patients underwent surgery, of whom 7,927 patients underwent CABG. Of these, 6,265 patients met inclusion criteria. The 30-day mortality of this cohort was 1.2% (n=72), leaving a final cohort of 6,265 who had 30-day conditional survival. The preoperative characteristics of these patients are detailed in *Table 1*. The mean age was 67.8 (SD=9.4) years. Cardiovascular risk factors were prevalent: 71.9% (n=4,112) with smoking history, 75.5% (n=4,678) with hypertension, 32.8% with obesity (n=2,009), and 24.8% (n=1,557) with diabetes. In 77.8% (n=4,876) surgery was performed electively. The mean Logistic EuroSCORE was 4.9% (SD=6.2, range, 0.88–80.25).

Operative characteristics

Details of the surgery are summarised in *Table 2*. The majority had three or more bypass grafts (85.8% n=5,811), with the majority using the left internal mammary artery (LIMA) and saphenous vein graft (SVG) (85.2%, n=5,340). The radial artery was harvested in 5.3% (n=331) of patients and only 1.5% (n=96) had bilateral internal mammary arteries harvested. The mean cross clamp and bypass times were respectively 46 and 82 minutes.

Bleeding and patient outcomes

Bleeding outcomes are summarised in *Table 2*. Following surgery, 4.6% (n=291) required re-exploration, and 43.6% (n=2,733) received at least one red cell transfusion. Blood loss within the first 12 hours was <500 mL in 71.2% (n=4,462) of patients, between 500 and 1,000 mL in 22.4% (n=1,403) and >1,000 mL in 6.4% (n=400) (*Figure 1*).

The median follow-up was 11.5 years (ranging from 0.1 to 16.0) after surgery. There were 2,139 deaths during follow-up (34.1%). The 10- and 15-year survival rates were 70.6% and 51.9% respectively.

Long term survival

The multivariable Cox model for mortality is shown in *Table 3*. Concordance of the final multivariable model =0.683 (se =0.007). The preoperative and patient variables found to be independently correlated with inferior survival were: age, smoking history, BMI, chronic pulmonary disease (CPD), diabetes, creatinine clearance, left ventricular ejection fraction, and preoperative Hb level.

Twelve-hour blood loss was found to be associated with an increased risk of long-term mortality if the blood loss was >500 mL (P=0.025) and >1,000 mL (P=0.001). Re-exploration and receiving blood transfusion were not independent predictors of long-term survival. Volume of bleeding was retained as an independent predictor even

Table 1 Patient demographic data—correlates of long-term survival: univariable analysis

Clinical data	Patients, n=6,265	HR	P value
Female (%)	1,174 (18.7)	1.260	<0.001
Age, years (ref <60)	67.8±9.4 [28–91]		
<60 (%)	1,226 (19.6)	–	–
60–70 (%)	2,075 (33.1)	1.547	<0.001
70–80 (%)	2,420 (38.6)	3.003	<0.001
>80 (%)	549 (8.8)	5.381	<0.001
Smoker (%)	4,112 (71.9)	1.144	0.011
Hypertension (%)	4,678 (75.5)	1.271	<0.001
BSA, kg/m² (range)	1.98±0.20 (1.33–3.00)	0.554	<0.001
BMI, m² (ref =20–25)	28.5±4.7 (13.3–59.5)		
<20 (%)	82 (1.3)	1.568	0.006
20–25 (%)	1,252 (20.4)	–	–
25–30 (%)	2,787 (45.5)	0.847	0.004
30–40 (%)	1,883 (30.7)	0.932	0.252
>40 (%)	126 (2.1)	1.003	0.986
CPD (ref = none)			
No pulmonary disease (%)	5,491 (88.1)	–	–
COPD (%)	450 (7.2)	1.708	<0.001
Asthma (%)	289 (4.6)	1.142	0.202
Diabetes (ref = not diabetic)			
Not diabetic (%)	4,713 (75.2)	–	–
Diet controlled (%)	58 (0.9)	0.734	0.383
Oral therapy (%)	1,033 (16.5)	1.236	<0.001
Insulin (%)	466 (7.4)	1.816	<0.001
Creatinine clearance, mL/min (ref >60)	76.5±27.7 [16–250]		
<30 (%)	115 (1.9)	3.564	<0.001
30–60 (%)	1,630 (27.0)	2.013	<0.001
>60 (%)	4,303 (71.1)	–	–
Left ventricular function (ref = good)			
Good LV (%)	3,381 (55.4)	–	–
Moderate LV (%)	2,165 (35.4)	1.275	<0.001
Poor LV (%)	562 (9.2)	1.913	<0.001
Priority (ref = urgent or emergency)			
Elective (%)	4,876 (77.8)	0.766	<0.001
Urgent (%)	1,307 (20.8)	–	–
Emergency (%)	87 (1.4)	–	–

Table 1 (*continued*)

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Clinical data	Patients, n=6,265	HR	P value
Log EuroSCORE, % [range]	4.9±6.2 [0.88–80.25]	1.04	<0.001
Preoperative Hb, g/L (ref >120)	124±15 [80–193]		
80–100 (%)	451 (7.2)	3.141	<0.001
100–120 (%)	1,853 (29.6)	1.809	<0.001
>120 (%)	3,958 (63.2)	–	–

Percentages quoted are for the patients with data available for that particular variable. BMI, body mass index; CPD, chronic pulmonary disease; COPD, chronic obstructive pulmonary disease; LV, left ventricle; Hb, haemoglobin.

Table 2 Patient surgical data—correlates of long-term survival: univariable analysis

Surgery	Patients, n=6,265	HR	P value
CPB time, min [range]	82±24 [27–263]	1.002	0.084
Cross clamping time, min [range]	46±15 [13–158]	0.999	0.530
Number of grafts (ref =2)			
2 (%)	874 (13.9)	–	–
3 (%)	3,149 (50.2)	1.050	0.458
4+ (%)	2,247 (35.8)	0.962	0.471
Type of grafts for CABG ≥2 (ref = LIMA + SVG)			
SVG (%)	503 (8.0)	1.153	0.056
LIMA + SVG (%)	5,340 (85.2)	–	–
LIMA + radial (%)	331 (5.3)	0.791	0.018
BIMA (± SVG or radial) (%)	96 (1.5)	0.598	0.014
Re-exploration (%)	291 (4.6)	0.907	0.359
Blood loss in the first 12 hours (ref <500)			
<500 mL (%)	4,462 (71.2)	–	–
500–1,000 mL (%)	1,403 (22.4)	1.171	0.002
>1,000 mL (%)	400 (6.4)	1.262	0.007
Blood transfusion (ref = none)			
None (%)	3,537 (56.4)	–	–
1 to 2 unit(s) (%)	1,475 (23.5)	1.056	0.301
>2 unit(s) (%)	1,258 (20.1)	0.988	0.838

Percentages quoted are for the patients with data available for that particular variable. CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; SVG, saphenous vein graft; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery.

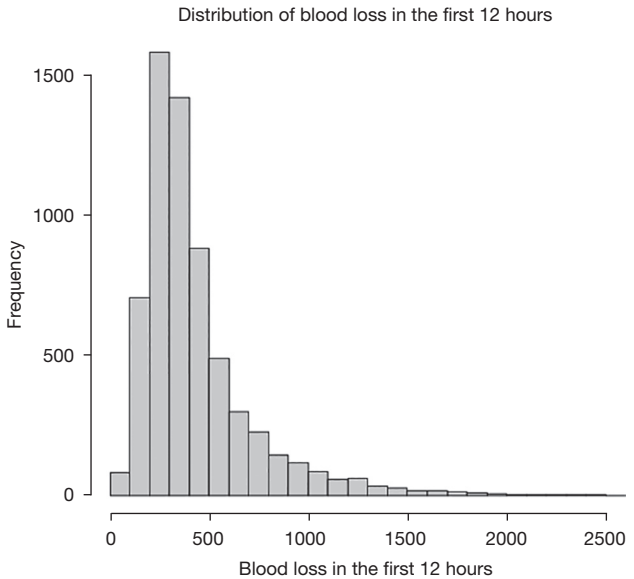

Figure 1 Histogram showing the incidence and volume of 12-hour blood loss.

Table 3 Multivariable Cox model analysis of long-term survival

Clinical data	HR (95% CI)	P value
Age, years (ref <60)		
<60	–	–
60–70	1.479 (1.247–1.753)	<0.001
70–80	2.567 (2.174–3.033)	<0.001
>80	3.760 (3.044–4.645)	<0.001
Smoker	1.199 (1.076-1.336)	0.001
BMI, m² (ref =20–25)		
<20	1.106 (0.783–1.563)	0.568
20–25	–	–
25–30	1.021 (0.901–1.156)	0.744
30–40	1.209 (1.053–1.388)	0.007
>40	1.773 (1.262–2.490)	0.001
CPD (ref = no pulmonary disease)		
No pulmonary disease	–	–
COPD	1.432 (1.222–1.676)	<0.001
Asthma	1.044 (0.840–1.299)	0.694
Diabetes (ref = not diabetic)		
Not diabetic	–	–
Diet controlled	0.658 (0.328–1.321)	0.239
Oral therapy	1.138 (1.007–1.285)	0.039
Insulin	1.544 (1.317–1.810)	<0.001
Creatinine clearance, mL/min (ref >60)		
<30	1.351 (1.009–1.808)	0.043
30–60	1.177 (1.047–1.323)	0.006
>60	–	–
Left ventricular function (ref = good LV)		
Good LV	–	–
Moderate LV	1.176 (1.062–1.301)	0.002
Poor LV	1.593 (1.376–1.844)	<0.001
Preoperative Hb, g/L (ref >120)		
80–100	2.181 (1.864–2.552)	<0.001
100–120	1.384 (1.245–1.538)	<0.001
>120	–	–
Blood loss in the first 12 hours (ref <500)		
<500 mL	–	–
500–1,000 mL	1.134 (1.016–1.265)	0.025
>1,000 mL	1.339 (1.118–1.602)	0.001

CI, confidence interval; CPD, chronic pulmonary disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LV, left ventricle; Hb, haemoglobin.

when conditional survival was extended to 1-year. The same results were seen for the entire cohort including those patients who died within 30 days (Figure S1).

Blood loss within the first 12 hours

Table 4 presents the patient characteristics divided by blood loss category. More significant bleeding was associated with male gender, increasing age, operative urgency and increasing logistic EuroSCORE. Patients going on to bleed had a lower Hb on arrival in the ICU. There was no association between 12-hour blood loss and the incidence of

Table 4 Cohort characteristics according to the first 12-hour blood loss

Clinical data	Blood loss in the first 12 hours			P value
	<500 mL (n=4,462)	500–1,000 mL (n=1,403)	>1,000 mL (n=400)	
Female (%)	908 (20.3)	206 (14.7)	59 (14.7)	<0.001
Age, years	67.5±9.4 [28–91]	68.6±9.5 [38–89]	68.6±9.1 [39–89]	0.001
<60 (%)	906 (20.3)	247 (17.6)	71 (17.8)	
60–70 (%)	1,520 (34.1)	428 (30.5)	124 (31.0)	
70–80 (%)	1,668 (37.4)	581 (41.4)	171 (42.7)	
>80 (%)	368 (8.2)	147 (10.5)	34 (8.5)	
Smoker (%)	2,971 (72.6)	876 (69.1)	261 (72.3)	0.052
Hypertension (%)	3,339 (75.7)	1,050 (75.6)	286 (72.6)	0.391
BSA, m²	1.98±0.2 [1.33–3.00]	1.98±0.2 [1.36–2.89]	1.96±0.2 [1.36–2.56]	0.102
BMI, kg/m² (ref =20–25)	28.8±4.7 [13.3–59.5]	27.9±4.3 [16.6–52.2]	27.8±4.7 [16.6–44.6]	0.045
<20 (%)	49 (1.1)	23 (1.7)	10 (2.5)	
20–25 (%)	832 (19.1)	328 (24.0)	91 (23.1)	
25–30 (%)	1,967 (45.1)	629 (46.0)	188 (47.7)	
30–40 (%)	1,415 (32.4)	371 (27.2)	96 (24.4)	
>40 (%)	102 (2.3)	15 (1.1)	9 (2.3)	
CPD				0.732
No disease (%)	3,904 (87.9)	1,227 (88.3)	356 (89.7)	
COPD (%)	320 (7.2)	102 (7.3)	27 (6.8)	
Asthma (%)	215 (4.8)	60 (4.3)	14 (3.5)	
Diabetes				0.048
Not diabetic (%)	3,319 (74.4)	1,085 (77.3)	305 (76.2)	
Diet controlled (%)	34 (0.8)	17 (1.2)	7 (1.8)	
Oral therapy (%)	761 (17.1)	210 (6.5)	61 (15.3)	
Insulin (%)	348 (7.8)	91 (6.5)	27 (6.7)	
Creatinine clearance, mL/min	77.2±27.6 [17–250]	74.7±27.5 [16–197]	74.9±28.2 [17–211]	0.237
<30 (%)	78 (1.8)	29 (2.1)	8 (2.1)	
30–60 (%)	1,125 (26.2)	395 (29.1)	109 (27.9)	
>60 (%)	3,092 (72.0)	934 (68.8)	273 (70.0)	
Left ventricular function				0.450
Good (%)	2,421 (55.8)	729 (53.3)	228 (57.7)	
Moderate (%)	1,526 (35.2)	507 (37.1)	131 (33.2)	
Poor (%)	393 (9.1)	132 (9.6)	36 (9.1)	

Table 4 (*continued*)

Table 4 (*continued*)

Clinical data	Blood loss in the first 12 hours			P value
	<500 mL (n=4,462)	500–1,000 mL (n=1,403)	>1,000 mL (n=400)	
Priority				<0.001
Elective (%)	3,537 (79.3)	1,072 (76.4)	264 (66.0)	
Urgent (%)	873 (19.6)	309 (22.0)	123 (30.8)	
Emergency (%)	52 (1.2)	22 (1.6)	13 (3.2)	
Log EuroSCORE, % (range)	4.7±6.2 [0.88–80.25]	5.1±6.3 [0.88–62.2]	5.6±6.6 [0.88–45.6]	0.008
Preop Hb, g/L	124±15 [80–193]	123±15 [80–178]	122±16 [80–166]	0.115
80–100 (%)	298 (6.7)	113 (8.1)	39 (9.8)	
100–120 (%)	1,328 (29.8)	406 (29.0)	115 (28.9)	
>120 (%)	2,831 (63.5)	883 (63.0)	244 (61.3)	
Surgery				
CPB time, min [range]	81±24 [27–263]	83±24 [27–180]	84±27 [28–228]	0.031
Cross clamping time, min [range]	46±15 [13–158]	46±15 [15–126]	47±16 [15–158]	0.538
Number of grafts				0.003
2 (%)	657 (14.7)	164 (11.7)	53 (13.3)	
3 (%)	2,254 (50.5)	715 (51.0)	179 (44.7)	
4+ (%)	1,551 (34.8)	524 (37.3)	168 (42.0)	
Type of grafts for CABG ≥2				0.001
SVG (%)	367 (8.2)	98 (7.0)	38 (9.5)	
LIMA + SVG (%)	3,821 (85.6)	1,191 (84.9)	324 (81.0)	
LIMA + radial (%)	219 (4.9)	87 (6.2)	24 (6.0)	
BIMA (± SVG/radial) (%)	55 (1.2)	27 (1.9)	14 (3.5)	
Final Hb in theatre	96±13 [50–167]	95±14 [65–167]	93±13 [59–167]	0.002
<80 (%)	394 (9.3)	163 (12.1)	52 (13.6)	
80–100 (%)	2,224 (52.7)	726 (53.9)	212 (55.4)	
100–120 (%)	1,413 (33.5)	400 (29.7)	106 (27.7)	
>120 (%)	188 (4.5)	59 (4.4)	13 (3.4)	
Re-exploration <48 h (%)	205 (4.6)	63 (4.5)	23 (5.7)	0.548
Blood transfusion				0.241
None (%)	2,554 (57.2)	773 (55.1)	208 (52.0)	
1 to 2 unit(s) (%)	1,029 (23.1)	342 (24.4)	102 (25.5)	
>2 unit(s) (%)	879 (19.7)	288 (20.5)	90 (22.5)	
No blood transfusion (%)	2,554 (57.2)	773 (55.1)	208 (52.0)	0.067

Percentages quoted are for the patients with data available for that particular variable. BSA, body surface area; BMI, body mass index; CPD, chronic pulmonary disease; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; SVG, saphenous vein graft; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery.

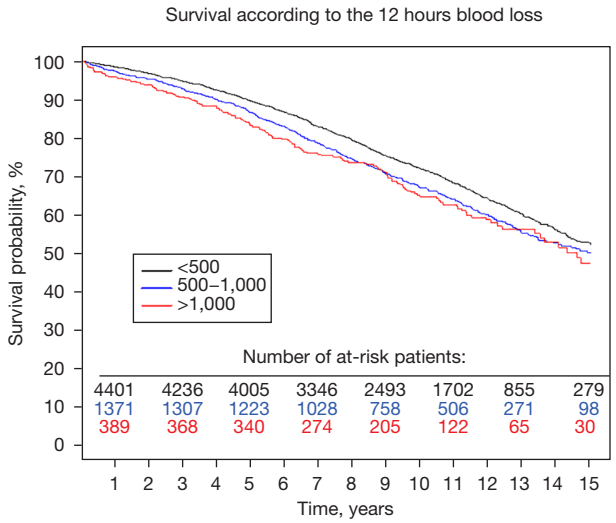

Figure 2 Impact of postoperative bleeding on long term survival for patients with 30-day conditional survival.

re-exploration or the administration of blood transfusions, although there was a trend—and this may reflect the absence of guidelines protocolising these and the different thresholds of individual surgeons to re-explore.

The impact of bleeding on long-term survival is demonstrated in *Figure 2*. The 5-year survival rates for postoperative blood loss <500 mL, between 500 and 1,000, and >1,000 mL respectively, were: 89.6%, 86.8% and 72.2%, and 10-year survival rates 83.8%, 67.2% and 65.1%. The impact of receiving blood transfusion on long-term survival was also explored. There were no significant differences in the long-term survival comparing those who received or did not receive transfusion, respectively HR =1.04 [95% confidence interval (CI), 0.87–1.23] and 0.98 (95% CI, 0.72–1.35) in the >500 and >1,000 mL bleeding groups (*Figure 3*).

Outcomes following aortic valve replacement (AVR)

To examine if this observation was unique to the CABG population, we repeated the analysis for the 3,689 patients who underwent isolated AVR during the same period (Table S1). Blood loss 500–1,000 and >1,000 mL were both significant on univariable analysis (P<0.001) as being predictors of long-term survival. However, on multivariable analysis (Table S2) neither blood loss 500–1,000 or >1,000 mL were identified as being associated with inferior long-term survival (P=0.646 and P=0.123, respectively). This analysis identified that the same patient factors (except preoperative creatinine clearance) are independently associated with inferior long-term survival following AVR as for CABG. There was reduced 12-hour blood loss following AVR likely relating to the antiplatelet medication in the CABG population.

Discussion

In this large study of 6,265 patients, we have been able to demonstrate that significant 12-hour blood loss is associated with inferior long-term survival following CABG. By imposing 30-day conditional survival we were able to examine the effect of bleeding on long-term survival, excluding those patients who experienced significant early complications—including bleeding, but succumbed during the early post-operative period. As a result, we have a large population of patients who survived 30 days and therefore in whom bleeding and other complications did not result in early mortality.

It is notable in this analysis that re-exploration for mediastinal bleeding and units of blood transfusion were not found to be independently associated with long-term survival in this cohort of patients with 30-day conditional survival. That is despite studies which demonstrate both of the these to be significantly associated with early post-operative mortality.

In terms of re-exploration for bleeding, studies have demonstrated that return to theatre is associated with a 2–4-fold increase in postoperative mortality, but also a significant increase in postoperative complications, including stroke, renal failure, prolonged ventilation, sternal wound infection, pulmonary complications and gastrointestinal complications (4,8-10,12-14). It is notable that several of these studies have observed that outcomes are superior for patients who are re-explored early following surgery, suggesting that delayed re-exploration is detrimental—perhaps (12-14). This may be related to the on-going blood-loss that occurs in these patients, associated with haemodynamic compromise and increased blood transfusion. The lack of association when considering long term outcomes in this study likely relates to exclusion of those who suffer mortality within 30 days—likely to be the more severe cases.

Regarding blood transfusion, there are a series of studies demonstrating the detrimental impact on postoperative outcomes (3,7). For example, Koch *et al.* identified

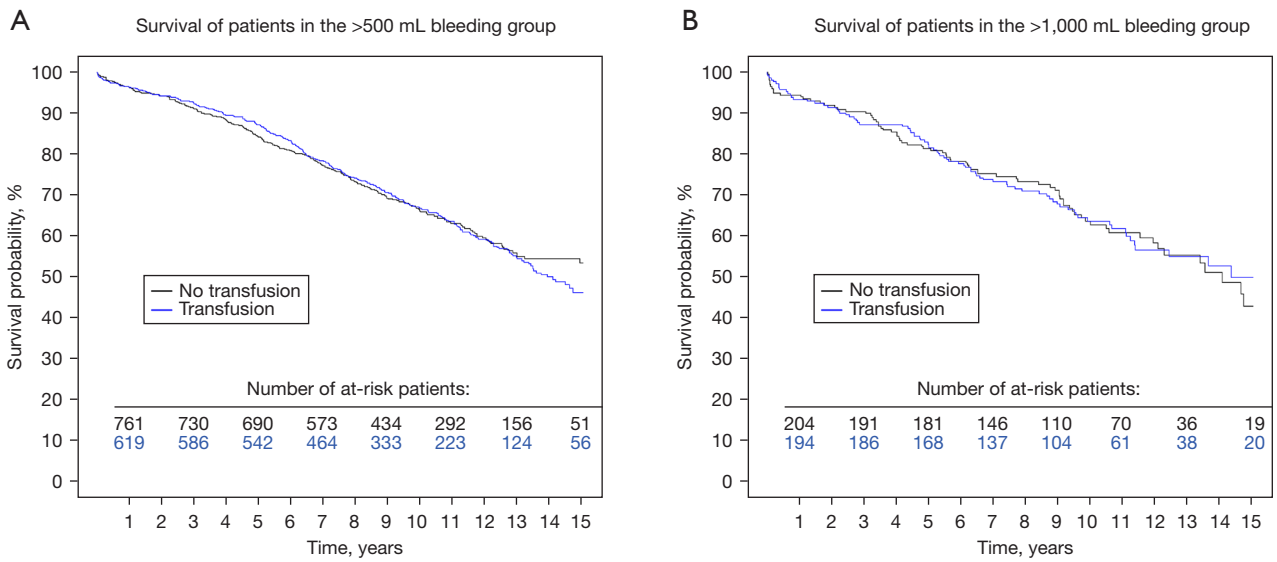

Figure 3 Impact of receiving blood transfusion on long-term survival for patients with >500 or >1,000 mL 12-hour blood loss.

perioperative blood transfusion as the single most reliable factor associated with postoperative morbidity (6). They described an increase in mortality (OR, 1.77; 95% CI, 1.67–1.87; P<0.0001), renal failure (OR, 2.06; 95% CI, 1.87–2.27; P<0.0001), prolonged ventilator support (OR, 1.79; 95% CI, 1.72–1.86; P<0.0001), severe infection (OR, 1.76; 95% CI, 1.47–1.63; P<0.0001), cardiac complications (OR, 1.76; 95% CI, 1.47–1.63; P<0.0001), and neurologic events (OR, 1.37; 95% CI, 1.30–1.44; P<0.0001). Of note, in a different analysis, they also observed that there was an association between transfusion and late survival following CABG (6). Why blood transfusion should have an impact on long-term survival is not clear, but it has been suggested that this may relate to immunomodulatory effects of blood transfusion that are thought to persist for many months (15). A more recent study has sought to examine this potential long-term impact of transfusion following CABG and initially made a similar observation of a long-term survival impact (16). It is worth also highlighting that there is now a trend towards 'restrictive' rather than 'liberal' transfusion following cardiac surgery and a recent meta-analysis concluded that early outcomes are not negatively impacted by restrictive transfusion (17). Longer term outcomes are not really addressed in that study, but it will be interesting to hypothesise that these may be improved with the restrictive protocols, at least for the CABG population. Unfortunately, discharge Hb was not available for our patients, but it would have been interesting to see if this correlated with long-term outcome.

Our data agree that for patients who are re-explored or receive blood transfusion, if they survive to 30 days their long-term outcomes are unaffected by this early insult. This implies that once patients recover there are no long-term impacts of having been re-explored or receiving blood transfusion, and that the negative effects of these are both focused in the early post-operative period. This is not the case for bleeding though, which does appear to have an impact. This then, raises a further question: why does significant bleeding have an adverse influence on long-term survival? It is recognised that 12-hour blood loss is associated with increased incidence of complications including stroke, renal failure and low cardiac output, that contribute to the increased early mortality (18). However, these can also be a contributing factor to the long-term survival impact we have observed—since non-fatal sequelae of these complications could certainly account for increased long-term morbidity. Furthermore, it is well recognised that peri-operative anaemia is associated with inferior long-term outcomes and it may be that a persistent anaemia, if untreated, may contribute to the inferior long-term survival (19). As such elective patients at our centre with pre-operative anaemia are reviewed by a haematologist for pre-operative optimisation.

It is notable that the association between blood loss and inferior long-term survival was not seen in our patients undergoing isolated AVR. These patients had significantly lower

levels of cardiovascular comorbidity—for example, incidence of smoking was 17.3% lower, hypertension 22.2% lower and diabetes was 60% less prevalent. Patients undergoing CABG would therefore be more likely to suffer from a generalised vasculopathy that perhaps would render them more susceptible to the blood-loss and consequent anaemia.

It was also observed in our study that re-exploration and blood transfusion were not strongly associated with 12-hour blood loss in our series, which is interesting since it would be predicted that those experiencing significant bleeding would be more likely to be re-explored and/or receive blood transfusion. Regarding re-exploration, this may reflect that the threshold to return a patient to theatre varies between consultant surgeons, with some preferring to re-explore patients early when it is apparent, they may be bleeding—before they have experienced significant blood-loss. In terms of blood-transfusion, this lack of association with bleeding may reflect acceptance of a range of preoperative Hb levels during this period. For example, 36.5% of patients in the <500 mL bleeding group had a preoperative Hb of <120 g/dL and were anaemic. As such, it is likely that many of these patients would have received blood transfusion as a consequence of haemodilution during CPB and intraoperative blood loss. Therefore, the extent of blood transfusion may not necessarily reflect bleeding in this patient cohort. It is now recognised that preoperative anaemia is an independent predictor of inferior outcome following cardiac surgery (20,21). As such there are now efforts to treat anaemia preoperatively, with evidence that this improves outcomes (22).

Our multivariable analysis also identified other factors that are associated with inferior long-term survival following CABG: age, smoking history, raised BMI, CPD, diabetes, impaired preoperative renal function, impaired left ventricular function and low preoperative Hb level. These factors are concordant with those identified by other studies examining long-term outcomes following CABG (23,24). In addition, some studies identify use of arterial grafts to be associated with improved long-term survival (25). At our centre over this period the use of arterial grafts was comparatively low and as such our study was not powered to examine this.

Identifying that postoperative bleeding can have a negative impact on long-term survival emphasises the importance of intraoperative haemostasis and taking steps to minimise postoperative bleeding. Some centres, including ours, have introduced a haemostasis checklist which is designed to reduce post-operative bleeding complications (1,26). Introduction of this simple checklist at our centre has been associated with a significant reduction in mean 12-hour blood loss and an associated 42% reduction in re-exploration rate, and a substantial saving on the use of blood products (1). In addition to these early benefits, it can be appreciated that this intervention will also be associated with improved longer-term survival. In this study we also performed a propensity matched analysis which demonstrated a more than double 30-day mortality in patients who experience significant port-operative bleeding highlighting the impact of bleeding on early outcomes.

Limitations

This is a single centre retrospective study which has inherent limitations including the inability to demonstrate causality. In order to examine long-term outcomes our patient cohort underwent surgery from 2003–2013. We acknowledge that some practices during this period may not reflect contemporary practice and this must be considered when thinking about the generalisability of the results—however this enables us to consider long term outcomes. Unfortunately, we could not retrieve detailed information on preoperative antiplatelet and other anticoagulant medications as these may have had an impact on bleeding outcomes and as such we could not risk adjust for this—furthermore, the nature of the perioperative antiplatelet treatment has evolved with newer medications now available. Similarly, we did not have information on preoperative coagulation screens or renal function (other than those who were dialysis dependent) which could also influence postoperative bleeding. Additionally, factors such as hepatic cirrhosis and tricuspid valve regurgitation may also impact coagulation status and are variables that we have been unable to account for. We could also not access coagulation screen results. We have also not been able to retrieve cause of death during follow-up in order to understand potential links between bleeding and inferior survival. Furthermore, we do not have data on myocardial viability, perioperative myocardial infarction or the presence of ischaemic mitral regurgitation—all of which may also impact on early and late outcomes following surgery. In this study we have focused on patients with 30-day conditional survival and as such this will limit the generalisability of the findings. Despite these limitations we have a large cohort of patients from a single centre providing sufficient data to perform robust statistical analyses.

Conclusions

With a large dataset and long-term follow-up, we have been able to demonstrate that 12-hour postoperative blood loss volume is an independent predictor of long-term survival in patients undergoing CABG. It has been long recognised that bleeding impacts on early outcomes, but less focus has been placed on longer term outcomes. Having an insight into the longer-term impact of bleeding, further emphasises the importance of intra-operative haemostasis, and strategies aimed to minimise post-operative bleeding.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Royal Papworth Hospital Clinical Governance Department and individual consent for this retrospective analysis was waived.

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