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[1] Title Page

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Platelet transfusion is not associated with increased mortality or morbidity in patients undergoing cardiac surgery.

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[2] Abstract:

Background: Transfusion of platelets is common in cardiac surgery and while there are guidelines for their use, there are concerns about potential risks. We aimed to assess the impact of platelet transfusion on mortality, thrombosis and infection in this patient group.

Study Design and Methods: A retrospective cohort study of all patients at St Vincent's Hospital Melbourne who underwent a first cardiac surgery procedure from June 2001 to June 2014. A propensity-weighted analysis was performed to examine the association between intra-operative platelet transfusion and outcomes.

Results: 5233 patients met inclusion criteria, 531 (10.15%) received intraoperative platelet transfusion (median 2 platelet doses, IQR 1-17). Patients receiving platelets were older, had higher body mass index, lower rates of diabetes and dyslipidaemia, higher rates of infective endocarditis, recent myocardial infarction and unstable angina, and exposure to aspirin or clopidogrel. On univariable analysis, platelet transfusion was associated with increased 30-day mortality (2.4% vs. 10.55%, p<0.001), return to theatre for bleeding (3.23% vs. 13.37%, p<0.001) and rates of any infection (9.26% vs. 19.17%, p<0.001). After adjusting for confounders, platelet transfusion was not associated with increased risk of 30-day mortality or infective complications. Platelet transfusion was associated with higher rates of return to theatre (relative risk [RR] 2.46; CI 1.42, 4.04, p=0.001) and decreased risk of thromboembolic events (RR 0.28; CI 0.15, 0.51, p<0.001).

Conclusion: Platelet transfusion was not associated with increased mortality or infective complications following first cardiac surgery. Further prospective studies are required to identify patients most likely to benefit from platelet transfusion.

Key words: platelet transfusion, cardiac surgery, thrombosis, inflammation, infection.

[3] Text

3.1 Introduction

Cardiac surgery accounts for a significant proportion of red blood cell (RBC), platelet and other non-red blood cell product use with several studies linking increased transfusion to higher rates of morbidity and mortality. [1] [2] [3] Bleeding in cardiac surgery is often multifactorial and contributing factors include pre-operative thrombocytopenia and/or anti-platelet medication use, acquired platelet dysfunction secondary to exposure to the cardiopulmonary bypass (CPB) circuit, heparin exposure, hypothermia, acidosis and dilutional and consumptive coagulopathy, in addition to other patient and procedural risk factors. For any individual patient, an increased number of these risks results in increased bleeding and transfusion requirement.

Marked thrombocytopenia, defined as a platelet count of $<50x10^9$/L, acquired and congenital qualitative platelet defects are thought to be modifiable risk factors for peri-operative bleeding. While the use of aspirin in the immediate pre-operative period may not be associated with excessive bleeding,[4] the use of other anti-platelet agents such as clopidogrel increases this risk.[5] There is trial evidence and recommendations for use of RBC transfusion in cardiac surgery, with some favoring a liberal and others a more restrictive approach; however there is minimal guidance on platelet transfusion in cardiac surgery.[6] [7] In addition, the American Association of Blood Banks (AABB) provides expert consensus recommendations based on very low quality evidence recommending against prophylactic platelet transfusion for patients with a normal platelet count while suggesting transfusion in patients with peri-operative bleeding and thrombocytopenia and/or evidence of platelet dysfunction.[8] The paucity of evidence to guide the use of platelets in cardiac surgery may contribute to the significant variability in transfusion practice for patients having coronary artery bypass graft (CABG) surgery,[9] [10] as evidenced by a multi-center study reporting overall platelet transfusion rates in the range of 0-36%.[11]

Furthermore, there are conflicting reports on the effects of platelet transfusion and patient outcomes with some studies suggesting an association with mortality and morbidity and others reporting no such associations.[12] [13] [14] We aimed to determine the possible association between intra-operative platelet transfusion with outcomes including mortality, infection and thrombosis.

3.2. Materials and Methods

3.2.1. Study Design

We conducted a retrospective analysis of patients who underwent cardiac surgery at St. Vincent's Hospital Melbourne (SVHM) from June 2001 to June 2014 inclusive. We limited the analysis to the first cardiac procedure at SVHM.

3.2.2. Data Sources

3.2.2.1. Cardiac surgery database

We obtained prospectively collected information on all cardiac surgery procedures from our institutional cardiac surgery database. This included patient demographics (age, gender, height, weight), cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, diabetes mellitus and family history of ischemic heart disease (IHD)), co-morbidities (history and type of acute coronary syndrome (ACS), congestive cardiac failure, cerebrovascular disease, infective endocarditis, chronic lung disease, peripheral vascular disease, pre-operative renal function and dialysis status), peri-operative aspirin and clopidogrel use and surgical factors (type and urgency of surgery).

Patient outcomes were return to theatre due to on-going bleeding, post-operative infection (deep sternal wound or thoracotomy infection, pneumonia, septicemia), thromboembolism (pulmonary embolism, TIA, or CVA), and 30 day mortality.

3.2.2.2. SVHM Laboratory Information System (LIMS)

We used the SVHM LIMS (PLS; Kestral Computing Pty Ltd) to extract pre-operative full blood examination (FBE) results to identify patients with pre-operative thrombocytopenia. The SVHM transfusion laboratory product issue data was extracted from the LIMS and used to determine the time of issue of blood products, including platelets.

3.2.2.3. SVHM Health Information Service (HIS) records

We accessed local HIS records to obtain the time of admission to hospital as well as surgery day, start and finish times.

3.2.3. Exposure/outcome definitions

We defined platelet transfusion as the administration of a single adult dose or bag of platelets. **The Australian Red Cross Blood Service (ARCBS) is our national blood service that provides all fresh blood components, including platelets. During the study period, both single donor and apheresis platelets in plasma and platelets obtained from buffy coats from ABO identical donors and re-suspended in platelet additive solution (pooled platelets) were transfused.** Universal leucoreduction and irradiation of platelet bags was initiated by the ARCBS in **August 2008. Prior to this time platelets were either non-leucodepleted or leucodepleted, with a progressive increase in the proportion of**

leucodepleted units issued in the preceding years (approximately 40% of units in 2003-04 and 85% of units in 2007-08 were leucodepleted).[15] We defined pre-operative transfusion as occurring within 24 hours prior to the start of surgery and intra-operative transfusion defined as occurring during the time of surgery as recorded in the HIS records.

All outcomes measured occurred following surgery, that is post potential exposure to platelets, and within 30 days of surgery. We defined deep sternal wound infection as infection involving the muscle and bone with or without mediastinal involvement as demonstrated by surgical exploration and deep thoracotomy wound infection as an infection involving a thoracotomy or parasternal incision site. We defined pneumonia by positive cultures of sputum or trans-tracheal aspirate and consistent clinical findings including radiological changes. We defined septicaemia as positive blood cultures supported by at least two of fever, increased white cell count, elevated and increasing C-reactive protein or elevated and increasing erythrocyte sedimentation rate (ESR). A pulmonary embolism was diagnosed by either a V/Q scan or CT angiogram.

3.2.4. Statistical analysis

Summary statistics are presented as mean and standard deviation or median and interquartile range as appropriate. Categorical variables are presented as proportions. We performed statistical significance testing of baseline characteristics using Student's t-test, Wilcoxon rank sum, Fisher's exact test or chi-squared tests as appropriate.

To estimate the causal effect of an intervention in an observational study, logistic regression of all clinically relevant covariates was applied to predict the risk of platelet transfusion for each patient. The dependent baseline variables assessed include age, gender, pre-operative platelet count, smoking status, diabetes status and type, hyperlipidemia, renal

replacement, respiratory disease, estimated glomerular filtration rate, hypertension, cerebrovascular disease, peripheral vascular disease, infective endocarditis, recent myocardial infarction, use of bypass (including aortic cross-clamp time and cardiopulmonary bypass time), angina type, congestive heart failure, circulatory shock, arrhythmia, inotrope infusion, intravenous nitrates, steroid medication, previous cardiothoracic intervention, body mass index, left main coronary artery disease, surgical urgency, transfer from cardiac catheter laboratory, type of surgery (coronary artery bypass, valvular surgery, aortic surgery or other) and use of intra-aortic balloon pump or ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO). Baseline variables with greater than 10% missing values were excluded to prevent a large reduction in sample size. Continuous variables were categorized according to centiles or clinically accepted criteria.

Associations between binary outcomes and platelet transfusion were modeled using a generalized linear model (GLM) with inverse propensity weighing. **Firstly, imbalance between baseline variables was assessed using standardized differences (SD). The unweighted SD is a ratio of the mean value in the platelet exposed cohort minus the mean value in the platelet unexposed cohort divided by the pooled SD; and any value that is greater than 10% is considered to be an imbalanced variable. The inverse of the probability of each patient receiving a platelet transfusion obtained from logistic regression was then applied to reweigh the observations seen in order to balance the two populations to have the same proportion such that following propensity matched weighing, all assessed variables had a SD less than 10%, meaning baseline variables were balanced in the two cohorts, akin to what can be expected when comparing two groups enrolled in a randomised clinical trial.** The common support condition was imposed, meaning that observations were removed if there were no patients of comparable propensity score in the other group. A binomial distribution with log link function was used to report results as relative risks.

All calculations were performed using STATA® Version 14 (StataCorp, Texas USA).

The study was reviewed and approved (QA 073/14) by the SVHM Quality Assurance Sub-committee of Human Research Ethics Committee (HREC)-A.

3.3. Results

3.3.1. Baseline demographics and variables by platelet transfusion status

Of the 5896 cardiac surgery events recorded in the institutional database, 5233 met the inclusion criteria with 531 (10.2%) having at least one adult dose of platelets transfused either within 24 hours before surgery (15 patients) or during the intra-operative period (525 patients); the median number of adult doses transfused was 2 (IQR 1, 3) with range of 0-17. Within the first 48 hours following surgery, platelets were transfused in a total of 721 patients (13.8%). The median number of units transfused was 1 (IQR 1, 2) with range 0-17.

Patients were excluded if data necessary for the propensity model were missing (n=253) and to impose the common support condition (n=75) (Figure 1.). After inverse propensity weighting, all baseline variables were well balanced between the two groups with all standardised differences < 10% (see Appendix I). **A total of 93.7% of the cohort was matched and included in the final analysis.**

Table 1 summarizes the distribution of baseline demographics, cardiovascular risk factors, co-morbidities, details concerning IHD history, anti-coagulant and anti-platelet medication use and operative variables by platelet transfusion status. As outlined, on univariable analysis, multiple factors were associated with an increased likelihood of having a platelet transfusion.

3.3.2. Pre-operative platelet count and platelet transfusion status

Pre-cardiac surgery, the vast majority of patients (4976; 95.1% of cohort) had a platelet count of ≥ $150x10^9$/L. Of the 257 patients with thrombocytopenia, 91% had a mild thrombocytopenia (100-149 $x10^9$/L), 8% had moderate thrombocytopenia (50-99 $x10^9$/L) and <1% patients had a platelet count of <50 $x10^9$/L. Only 2% of patients (5/257) with pre-

operative thrombocytopenia received pre-operative platelet transfusions including both patients with marked thrombocytopenia at baseline, 2 of the 21 with moderate thrombocytopenia and 1 of 234 patients with a platelet count of 100-149 $x10^9$/L.

Overall, the median preoperative platelet count was 242 $x10^9$/L (IQR: 62, 755). Patients receiving any platelet transfusion had a median platelet count of 236 $x10^9$/L (IQR: 181.5, 292) compared to 243 $x10^9$/L (IQR: 201, 293) in patients who did not receive platelet transfusion (p=0.018).

3.3.3. Pre-operative use of aspirin and clopidogrel by platelet transfusion status

Aspirin was continued pre-operatively in 2134 patients (40.8%) with 91.3% of these having aspirin at least two days prior to the surgery and 185 patients (8.7%) having aspirin within 3-7 days prior to the surgery. Clopidogrel was continued in 271 (6.8%) patients; 35.4% of whom had clopidogrel within 48 hours of surgery while 74.6% stopped clopidogrel only 3-7 days prior to the surgery. On univariable analysis, pre-operative continuation of aspirin or clopidogrel was associated with increased likelihood of platelet transfusion (p=0.01 for aspirin and p=0.001 for clopidogrel).

3.3.4. Blood and blood product (other than platelets) use by platelet transfusion status

Of the 2745 patients (52.5%) who received a RBC transfusion, detailed transfusion laboratory data with respect to the number of RBC transfused was available for 2352 patients. The median number of RBC units transfused was 3 (IQR: 2-5) with the maximum number of units issued to a single patient being 65. Non-RBC (NRBC) products (fresh frozen plasma (FFP) and cryoprecipitate) were transfused in 28.4%, while 1300 (24.8%) patients received both RBC and NRBC products and 2301 patients (43.9%) did not receive any blood or blood products.

86.8% of patients who received one or more platelet transfusions also had a RBC transfusion and 94.6% had either FFP or cryoprecipitate in addition to the platelet transfusion. On univariable analysis, there was an association between platelet transfusion and likelihood of also receiving either RBC or NRBC products.

3.3.5. Patient outcomes by platelet transfusion status

Patient outcomes by platelet transfusion, specifically concerning mortality, risk of infection and thrombosis are summarized in Table 2. On univariable analysis, risk of 30-day mortality, return to theatre for bleeding, risk of postoperative infection including risk of pneumonia and septicaemia were all higher in patients receiving platelet transfusions. Following propensity weighting, risk of return to theatre for bleeding remained higher in patients having platelet transfusion (risk ratio (RR) 2.46, confidence interval (CI) 1.42 – 4.04, p=0.001). In addition, risk of any thromboembolic events and permanent CVA was lower in this group of patients with relative risk (RR) 0.28 (CI 0.15, 0.51; p<0.001) and RR 0.24 (CI 0.11, 0.49; p<0.001) respectively.

Leucoreduction of platelets issued by the Australian Red Cross Blood Service was introduced gradually with universal leucoreduction mandatory from August 2008 onwards. There was no evidence in the data that universal leucoreduction caused a significant reduction in the risk of mortality after August 2008 (see Appendix II).

3.4. Discussion

In our cohort study of all cardiac surgery patients, we found a rate of intra-operative platelet transfusion of 10.2%. Although platelet transfusion was associated with mortality, infection and thrombosis on univariable analysis, after adjusted analysis, there was no increased risk of 30-day mortality or infective complications in patients who received platelet transfusion intra-operatively. Furthermore, after adjustment, we found no evidence of increased risk of thromboembolic complications, but rather a decreased risk, in those patients who received platelet transfusion.

To date, there have been at least three observational studies on the effect of platelet transfusion on patient outcomes in cardiac surgery. The two largest studies suggest either no association or a decreased risk of mortality, infection and neurological outcomes in those who received platelet transfusion.[16 17] The first of these compared 1848 propensity matched pairs and found no difference in mortality or a composite outcome of mortality, organ failure and infection. The largest study to date included 29,487 patients from 1993 to 2006, of whom approximately 12% received platelet transfusion either intra- or post-operatively. In this study, a propensity matched analysis was performed on 5488 patients, and reported decreased risk of mortality, infection and neurological outcomes in those who received platelets. Both of these studies did not differentiate between intra-operative or post-operative platelet exposure (which therefore may have occurred after some of the outcomes of interest) and both used propensity matching which excluded more than 80% of their patient cohorts, potentially introducing bias. The third study included 1720 patients enrolled in six randomised clinical trials of aprotinin from 1990 to 1994 and reported a 4.76 times higher odds of death on multivariable regression. [2] In comparison to these studies, we limited our analysis to platelet transfusion immediately prior to or during surgery, to ensure the exposure occurred before the outcome, and included over 90% of our patient cohort in our propensity analysis.

With regard to infection and platelet transfusion in cardiac surgery, there are contradicting reports with studies not adjusting for confounders concluding there to be an increased risk of infection.[2 16 18 19] Similar to our findings, studies by Karkouti *et. al.* and Sreeram *et. al.* assessing patients receiving non-leucoreduced and leucoreduced cellular blood products respectively, reported no association between transfusion and infection.[16 18] In contrast, a recent study assessing platelet transfusion in critically ill intensive care patients demonstrated that after adjustment for patient severity and other blood component use, platelet transfusion in this patient population was independently associated with ICU-acquired infection. [20]

Leucocyte-mediated transfusion-related immunomodulation (TRIM) is a transient immunosuppression which may occur following transfusion of allogeneic blood.[21] While the exact mechanisms, and many are proposed, are not yet established it is hypothesised that leucocyte release of cytokines modules the balance between a Type 1 and Type 2 immune response leading to increased rates in post-operative bacterial infections, organ dysfunction and length of stay.[22]

Universal leucoreduction and pre-storage bacterial screening was introduced by the Australian Red Cross Blood Service in August 2008 and our cohort includes patients from both pre- and post this time, although as noted previously, there was a progressive increase in the proportion of platelets leucoreduced in Australia prior to August 2008. Comparing exposure prior to and after universal leucoreduction, we found no difference in 30-day mortality between the two groups.

It has been proposed that as the age of stored platelets increases, pro-inflammatory proteins and pro-thrombotic mediators like soluble CD40 ligand (sCD40L) are increased, partially compensating for decreased haemostatic potential of stored platelets but potentially contributing to thrombosis. [23] We did not find an increased risk of thrombosis in our cohort receiving one or more doses of platelets, although we did find a lower risk of thromboembolic complications overall, and lower CVA events. This may be a chance finding as the total number

of CVA events in both groups was small, and we performed multiple comparisons. Of note however, the largest observational study to date also reported decreased risk of neurological outcomes in patients who received platelet transfusion. [17] Proteomic analysis of pooled buffy-coat platelet concentrates reveals many bioactive proteins including increased levels of brain derived neurotrophic factor (BDNF), which has been shown to have a neuroprotective role in hypoxic ischaemic brain injury. [24 25] Furthermore, platelets have a diverse transcriptome and release many microparticles including microparticle-associated microRNAs which are being increasingly recognised as capable of influencing intercellular signalling and gene expression modulating various aspects biology and pathophysiology. [26] It is possible that the platelet storage lesion modulates the thrombotic milieu and it would be of interest to confirm our findings in other prospective studies.

The strengths of our study lie in its large cohort, use of a comprehensive clinical database coupled with detailed data on platelet transfusion, limiting assessment to intraoperative episodes, and performing a propensity weighted analysis, which allowed us to include over 90% of our study cohort in the analysis. The major limitation of our study is its observational and single-centre design. We cannot exclude the possibility that we have not accounted for unmeasured confounders. Information regarding specific indications for platelet transfusion, particularly whether given as prophylaxis or for treatment of bleeding, was not available. **Furthermore, while our subgroup analysis demonstrates no effect of universal leucodepletion on mortality, our study does not categorically compare patients receiving leucodepleted products to non-leucodepleted products.** Within these limitations, this is a large cohort study of contemporary transfusion practice in cardiac surgery. To our knowledge, there are no randomised clinical trial data in this field of transfusion medicine.

3.5. Conclusion

We found no evidence that platelet transfusion is associated with increased risk of mortality, infection or thrombotic complications. There is a lack of consensus guidelines or strong evidence base on which to guide platelet transfusion, which is a common intervention in cardiac surgery, and future prospective studies are warranted to define which patients are most likely to benefit from platelet transfusion.

[4] Acknowledgments

SN, ZM and MCS developed study concept and design. SN and ZM performed data cleaning. SN, ZM and RG performed statistical analysis. SN wrote the initial manuscript. All authors contributed to and approved the final version of the manuscript. The authors also extend their thanks to Mr Mark Rose for IT support and Dr Rosemary L Sparrow her for discourse on the platelet storage lesion.

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Table 1

		No Platelet Transfusion (n=4702)	Platelet Transfusion (n=531)	P-value ‡	Standardized Difference	
					Unweighted	Weighted
Male		3482 (74.1%)	380 (71.6%)	0.22	-5.6	0.50
*Age, median (IQR)		68 (60, 75)	70 (60, 76)	0.015	4.72	0.63
Age Category	<30 years	26 (0.6%)	6 (1.1%)	<0.001	6.32	-1.44
	30-59 years	1125 (23.9%)	121 (22.8%)		-2.70	-3.02
	60-79 years	3162 (67.2%)	334 (62.9%)		-9.12	6.57
	>80 years	389 (8.3%)	70 (13.2%)		15.91	-5.53
*BMI, mean (SD)		28.7 (5.2)	27.7 (5.3)	<0.001		
BMI	<18.5	44 (0.9%)	9 (1.7%)	<0.001	6.67	-0.77
	18.5-24.9	1096 (23.3%)	163 (30.8%)		16.74	2.58
	25-29.9	1881 (40.1%)	208 (39.2%)		-1.66	-8.81
	30-39.9	1529 (32.6%)	134 (25.3%)		-16.10	5.25
	>40	146 (3.1%)	16 (3.0%)		-0.52	5.11
Smoking status	Ex-smoker	2390 (50.8%)	247 (46.5%)	0.14	-8.63	2.76
	Smoker	708 (15.1%)	92 (17.3%)		-6.16	-6.75
	Never Smoked	1604 (34.1%)	192 (36.2%)		4.28	2.28
Diabetes		1479 (31.5%)	143 (26.9%)	0.033	-12.95	1.89
Diabetes control	Diet	291 (6.2%)	31 (5.8%)	0.053	-2.38	-6.96
	Insulin	338 (7.2%)	41 (7.7%)		2.03	1.71
	OHG	850 (18.1%)	71 (13.4%)		1.91	-4.45
Hypercholesterolemia		3368 (71.7%)	339 (64.0%)	<0.001	-16.5	-3.02
Dialysis		21 (0.4%)	14 (2.6%)	<0.001	17.83	-6.94
Hypertension		3498 (74.4%)	390 (73.4%)	0.63	-2.19	1.14
CVD		522 (11.1%)	68 (12.8%)	0.24	5.23	-6.98
PVD		501 (10.7%)	60 (11.3%)	0.65	2.05	-4.98
Respiratory disease		643 (13.7%)	80 (15.1%)	0.38	3.96	7.53
Infective endocarditis		85 (1.8%)	37 (7.0%)	<0.001	25.38	-5.35
Myocardial Infarction		2003 (42.6%)	240 (45.2%)	0.25	5.24	5.78
MI-when	<6 hours	16 (0.3%)	4 (0.8%)	0.005	10.17	-3.36

	6-24 hours	49 (1.0%)	13 (2.4%)		-1.24	0.24
	1-7 days	397 (8.4%)	61 (11.5%)		5.60	-3.30
	8-21 days	505 (10.7%)	55 (10.4%)		-4.61	8.77
	>21 days	1036 (22.0%)	107 (20.2%)		-5.23	4.49
Angina-type	None			<0.001	-29.79	-7.67
	Stable	2304 (49.0%)	183 (34.5%)		7.47	2.60
	Unstable	1122 (23.9%)	144 (27.1%)		24.19	5.29
Left Main stenosis >50%		1031 (22.0%)	103 (19.6%)	0.21	-5.81	3.14
Congestive heart failure		1470 (31.3%)	228 (42.9%)	<0.001	24.33	2.90
Shock		82 (1.7%)	45 (8.5%)	<0.001	30.90	-1.40
Arrhythmia		826 (17.6%)	142 (26.7%)	<0.001	22.22	0.28
Inotropes		92 (2.0%)	45 (8.5%)	<0.001	29.61	-1.02
IV nitrates		295 (6.3%)	57 (10.7%)	<0.001	16.03	0.24
Steroids		67 (1.4%)	11 (2.1%)	0.24	4.93	-0.27
Anticoagulants		1062 (22.6%)	168 (31.6%)	<0.001	20.46	-3.11
Aspirin-days	3-7 Days	169 (3.6%)	16 (3.0%)	0.012	-3.25	-5.94
	≤2 Days	1720 (36.6%)	229 (43.1%)		13.39	0.85
	>7 Days or never	2813 (59.8%)	286 (53.0%)		-12.06	1.32
Clopidogrel-days	3-7 Days	147 (3.1%)	28 (5.3%)	0.001	10.71	0.36
	≤2 Days	64 (1.3%)	32 (6.0%)		24.91	5.72
	>7 Days or never	4491 (95.5%)	471 (88.7%)		-25.45	-4.06
Platelet glycoprotein IIb/IIIa Antagonist	≤2 Days	0 (0.0%)	4 (0.8%)	<0.04	12.31	1.05
	>3 Days or never	4702 (100%)	527 (99.2%)		-12.31	-1.05
Aggrostat	3-7 Days	12 (0.3%)	1 (0.2%)	0.07	-1.42	-3.96
	≤2 Days	48 (1.0%)	12 (2.3%)		9.76	-3.64
	>7 Days or never	4642(98.7%)	518 (97.6%)		-8.67	4.92
Antiplatelet other than aspirin		251(5.5%)	54(11.1%)	<0.001	25.10	2.48

* Baseline platelet count 10^9/L, median (IQR)		243 (201, 293)	236 (181.5, 292)	0.018		
Platelet count	<100	9 (0.20)	14 (2.82)	<0.001	21.63	-6.57
	>=100	4561 (99.8%)	482 (97.2%)		-21.63	6.57
* EGFR, median (IQR)		78.1 (59.4, 101.7)	69.2 (48.1, 96.5)	<0.001		
	<15	21 (0.4%)	3 (0.6%)	<0.001	1.68	-2.69
	15-29.99	10.3 (2.2%)	17 (3.2%)		6.27	-5.04
	30-59.99	1085 (23.1%)	193 (36.4%)		29.44	1.36
	60-89.99	1780 (37.9%)	158 (29.8%)		-17.11	-0.41
	>90	1710 (36.4%)	159 (30.0%)		-13.60	1.19
Previous cardiothoracic intervention		847 (18.0%)	136 (25.6%)	<0.001	18.47	-5.36
Cross clamp	<80 mins	1597 (34.5%)	121 (23.0%)	<0.001	-25.61	2.58
	80-106 mins	1586 (34.2%)	124 (23.5%)		-23.74	-0.59
	>106 mins	1452 (31.3%)	282 (53.5%)		46.04	-1.81
† Bypass duration (min), Median (IQR)	117 (96, 142)	117 (96, 142)	156 (119, 203)	<0.001	83.32	-5.49
	<104 mins	1627 (35.1%)	79 (15.0%)	<0.001	-47.70	5.34
	105-136 min	1616 (34.9%)	108 (20.5%)		-32.53	-2.59
	>137 min	1392 (30.0%)	340 (64.5%)		73.56	-2.28
Surgical status	Elective	3128 (66.5%)	279 (52.5%)	<0.001	-28.77	-0.92
	Emergency	287 (6.1%)	77 (14.5%)		27.87	1.39
	Salvage	17 (0.4%)	20 (3.8%)		24.10	-7.98
	Urgent	1270 (27.0%)	155 (29.2%)		4.85	2.01
Transfer from cath lab		67 (1.4%)	20 (3.8%)	<0.001	14.76	-0.33
CABG		3705 (78.8%)	375 (70.6%)	<0.001	-18.88	2.93
Valve		1543 (32.8%)	277 (52.2%)	<0.001	39.89	-2.15
Other cardiac procedure		574 (12.2%)	114 (21.5%)	<0.001	24.93	-0.73
Aortic procedure		202 (4.3%)	91 (17.1%)	<0.001	42.41	2.0

Other non-cardiac procedure		67 (1.4%)	28 (5.3%)	<0.001	21.50	-1.83
CPB used		4597 (97.8%)	526 (99.1%)	0.049	10.34	-1.60
IABP used		230 (4.9%)	95 (17.9%)	<0.001	41.77	-1.54
VAD/ECMO		21 (0.4%)	8 (1.5%)	0.002	10.79	0.51

***Table 1**: Baseline demographics, cardiovascular risk factors, co-morbidities, details about coronary artery disease and cardiac surgery by platelet transfusion status. IQR: interquartile range, BMI: body mass index, SD: standard deviation, OHG: oral hypoglycaemic, CVD: cerebrovascular disease, PVD: peripheral vascular disease, MI: myocardial infarction, eGFR: estimated glomerular filtration rate, CABG: coronary artery bypass grafting, CPB: cardio-pulmonary bypass, IABP: intra-aortic balloon pump, VAD/ECMO: ventricular assist device/extracorporeal membrane oxygenation. * The log odds for these variables were not linear in the continuous form; thus the categorical form of these variables was used in the propensity models. † To improve balance both the continuous and categorical forms of this variable were used. ‡Statistical comparison with two sample Wilcoxon rank-sum and Pearson's χ^2 where appropriate.*

Outcome	No Platelet Transfusion	Platelet Transfusion	Unweighted		Propensity Weighted	
	N=4702	N=531	Risk Ratio (95% CI)*	P-value	Risk Ratio (95% CI)*	P-value
30 Day Mortality	113 (2.40%)	56 (10.55%)	4.39 (3.23, 5.97)	<0.001	1.06 (0.55, 2.03)	0.85
Return to theatre for bleeding	152 (3.23%)	71 (13.37%)	4.14 (3.17, 5.40)	<0.001	2.46 (1.42, 4.04)	0.001
Any infection	435 (9.26%)	101 (19.17%)	2.07 (1.70, 2.52)	<0.001	1.20 (0.83, 1.73)	0.33
Pneumonia	369 (7.85%)	92 (17.46%)	2.22 (1.80, 2.74)	<0.001	1.41 (0.98, 2.05)	0.06
Septicemia	82 (1.75%)	27 (5.12%)	2.94 (1.92, 4.50)	<0.001	0.92 (0.39, 2.21)	0.87
Deep sternal infection	34 (0.72%)	5 (0.95%)	1.31 (0.52, 3.34)	0.57	1.03 (0.25, 4.21)	0.97
Deep thoracotomy wound infection	8 (0.17%)	1(0.19%)	1.11 (0.14, 8.90)	0.92	NA	NA
Wound infection either	42 (0.90%)	4 (0.82%)	1.27 (0.54, 3.0)	0.56	0.84 (0.20, 3.44)	0.81
Thromboembolism (any)	170 (3.62%)	22 (4.17%)	1.15 (0.75, 1.78)	0.52	0.28 (0.15, 0.51)	<0.001
Pulmonary embolism	31 (0.66%)	2 (0.38%)	0.58 (0.14, 2.40)	0.45	0.59 (0.14, 2.52)	0.48

Perioperative AMI	37 (0.79%)	6 (1.14%)	1.45 (0.61, 3.41)	0.40	0.37 (0.11, 1.27)	0.11
TIA	25 (0.53%)	2 (0.38%)	0.71 (0.17, 3.00)	0.65	0.26 (0.05, 1.23)	0.09
CVA permanent	86 (1.83%)	14 (2.66%)	1.45 (0.83, 2.54)	0.19	0.24 (0.11, 0.49)	<0.001

Table 2: *Patient outcomes by platelet transfusion status with both propensity unweighted and weighted analysis. TIA: transient ischemic attack, CVA: cerebrovascular accident, CI: confidence interval. * Risk ratios computed using binary regression.*

Figure 1: Flowchart of patient selection and propensity score matching analysis construction.

Appendix 1: Logistic regression was used to generate propensity scores based on baseline patient characteristics.

Variable		Odds Ratio	95% CI	p-value
Bypass duration (min) Median (IQR)	117 (96, 142)	1.021	1.010, 1.031	0.000
	<104 mins	Reference		
	105-136 min	1.096	0.634, 1.896	0.743
	>137 min	1.642	0.796, 3.389	0.180
Cross clamp	<80 mins	Reference		
	80-106 mins	0.379	0.075, 1.907	0.239
	>106 mins	0.761	0.161, 3.584	0.730
Age Category	<30 years	Reference		
	30-59 years	1.195	0.349, 4.091	0.777
	60-79 years	1.243	0.356, 4.340	0.733
	>80 years	1.735	0.472, 6.375	0.406
Male		0.933	0.722, 1.206	0.595
Platelet Count	<100	Reference		
	>=100	0.082	0.030 , 0.226	0.000
Smoking current	Ex-smoker	Reference		
	Smoker	1.213	0.881, 1.670	0.237
	Never Smoked	1.157	0.903, 1.482	0.248
Diabetes control	Diet	Reference		
	Insulin	1.116	0.631, 1.974	0.705
	OHG	0.775	0.471, 1.274	0.315
	No Diabetes	0.986	0.635, 1.531	0.950

Hypercholesterolemia			0.881	0.680, 1.142	0.337
Dialysis			9.298	2.802, 30.85	0.000
Hypertension			1.104	0.842, 1.446	0.474
Cerebrovascular Disease			0.906	0.648, 1.266	0.564
Peripheral vascular Disease			0.987	0.699, 1.393	0.939
Respiratory Disease			1.027	0.756, 1.394	0.867
Infective Endocarditis			2.416	1.385, 4.215	0.002
AMI	<6 hours		Reference		
	6-24 hours		0.881	0.552, 1.404	0.593
	1-7 days		0.729	0.144, 3.685	0.702
	8-21 days		0.996	0.624, 1.590	0.987
	>21 days		0.302	0.086, 1.058	0.061
		No AMI	0.854	0.546, 1.335	0.487
Angina		Stable	Reference		
		Unstable	0.871	0.565, 1.344	0.533
		No Angina	1.121	0.831, 1.511	0.454
Congestive Heart Failure			1.090	0.851, 1.396	0.495
Shock			0.977	0.400, 2.389	0.960
Arrhythmia			0.881	0.659, 1.177	0.390
Inotropes			0.758	0.346, 1.662	0.489
IV nitrates			1.296	0.825, 2.037	0.261
Steroids			0.973	0.437, 2.161	0.946
Aspirin-days	3-7 Days		Reference		
	≤2 Days		1.584	0.862, 2.913	0.139
	>7 Days or never		1.060	0.577, 1.947	0.851

Other Antiplatelet		2.489	1.637, 3.787	0.000
Anticoagulants		1.176	0.814, 1.700	0.388
Previous cardiothoracic intervention		1.136	0.872, 1.481	0.344
BMI	<18.5	Reference		.
	18.5-24.9	1.156	0.627, 2.132	0.642
	25-29.9	0.962	0.501, 1.847	0.908
	30-39.9	1.128	0.464, 2.741	0.790
EGFR	<15	Reference		
	15-29.99	3.750	0.616, 22.830	0.152
	30-59.99	5.962	1.009, 35.220	0.049
	60-89.99	3.785	0.632, 22.650	0.145
	>90	3.837	0.630, 23.359	0.145
Left Main Stenosis >50%		0.854	0.637, 1.144	0.290
Surgical status	Elective	Reference		
	Emergency	1.695	1.010, 2.845	0.046
	Salvage	6.558	1.551, 27.732	0.011
	Urgent	1.330	1.001, 1.765	0.049
Transfer from cathlab		0.571	0.205, 1.587	0.283
CABG		1.094	0.760, 1.574	0.628
Valve surgery		1.381	1.016, 1.876	0.039
Other cardiothoracic surgery		1.125	0.826, 1.532	0.454
Aortic Procedure		2.587	1.760, 3.803	0.000
Other non-cardiac procedure		2.685	1.491, 4.837	0.001
CPB used		0.108	0.018, 0.642	0.014
IABP used		1.892	1.278, 2.800	0.001

ECMO	0.816	0.227, 2.935	0.755
constant	0.074	0.003, 1.576	0.095

Appendix II – 30-day mortality before and after universal leucoreduction (August 2008) showing no evidence of impact on mortality; *CI – confidence interval.

Crude 30-Day Mortality	Platelet transfusion N (%)	No platelet transfusion N (%)	Risk Ratio (95% CI)*	P-Value
Before August 2008	30 (11.7%)	61 (2.5%)	4.67 (95% CI 3.1, 7.1)	<0.001
After August 2008	26 (9.5%)	52 (2.3%)	4.12 (95%CI 2.62, 6.5)	<0.001
Risk after Aug 2008 compared to before			0.87 (95%CI 0.65, 1.17)	0.37