

Effect of Direct Oral Anticoagulants on bleeding and blood product usage in cardiac surgery compared to Warfarin and controls

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Abstract

In this retrospective, single-centre, observational study, we assessed 1) Use of anticoagulant and antiplatelet (AP) therapy, 2) The duration of DOAC discontinuation 3) renal function and 4) PT and APTT as predictors of bleeding and blood product usage; in adults (>18 years) undergoing major cardiac surgery from 01.01.2015 to 31.12.2018. Comparisons were made between each treatment group (warfarin, DOAC and DOAC + AP) and untreated controls and between warfarin and DOAC. A total of 2928 patients were included for analysis. Median (range) DOAC discontinuation was 5 days (1-22) for DOAC and 5 days (2-7) for DOAC + AP. There were no differences in bleeding between anticoagulant groups vs control or DOAC vs warfarin. There were no differences in blood product use between DOAC and warfarin patients. The duration of DOAC discontinuation but not the creatinine clearance influenced bleeding and blood products use. Thrombosis occurred in 0.7% and 3.1% in controls and patients on warfarin respectively ($P=0.099$) with none among patients on DOAC or DOAC + AP. The PT/APTT had no predictive value. Median 5-day discontinuation of DOAC +/- AP irrespective of renal function prevents an increase in bleeding compared to patients on warfarin or controls with no increase in thrombosis.

Key words: cardiac surgery; direct acting oral anticoagulant; warfarin; bleeding; thrombosis

Introduction

Major bleeding (>150ml of thoracic or mediastinal drainage per hour) is a significant complication of cardiac surgery which affects approximately 10% of patients (Charlesworth and Arya 2018; Lopes et al. 2016). Major bleeding is associated with higher mortality, longer stays in Intensive Care Units (ICU), increased blood product usage and higher postoperative complication rates resulting in increased NHS cost and poorer patient outcomes (Lopes et al. 2016). Use of anticoagulant or antiplatelet (AP) therapy prior to surgery, should insufficient time be given to allow the drug to clear from the circulation and in the case of AP therapies, for platelets to be replaced, can significantly influence the risk of bleeding. The optimal duration of anticoagulant discontinuation prior to surgery depends on the type of anticoagulant, the indication for treatment, the patient's renal function, the estimated risk of thrombosis without anticoagulation and the expected risk of bleeding.

There are no universally accepted guidelines on the optimum period of direct acting oral anticoagulant (DOAC) discontinuation prior to major cardiac surgery. Several guidelines, based on pharmacokinetic properties, renal function and operative bleeding risk, recommend a period of 2-7 days for dabigatran and 2-5 days for apixaban and rivaroxaban with edoxaban appearing to require a similar regimen depending on the renal function and the predicted risk of bleeding related to the surgery (Douketis et al. 2018; Keeling et al. 2016; Steffel et al. 2018). However, the CORIDA study showed that neither the preprocedural DOAC level [DOAC] nor the period of DOAC discontinuation were independent risk factors for bleeding events, although the predictive value specifically for cardiac surgery was not shown (Godier et al. 2017).

In a meta-analysis of 9 randomised controlled studies including 15,880 patients undergoing surgical interventions, there were no differences in perioperative major bleeding or mortality rates in patients on apixaban, rivaroxaban or dabigatran vs warfarin (He et al. 2018). However, only 2.57% of patients underwent major cardiac surgery. The CORIDA study showed renal function to be an independent predictor of both preprocedural [DOAC] and bleeding

complications (Godier et al. 2017). The recently published PAUSE trial used a standardised protocol based on operative bleeding risk, pharmacokinetic properties and, in the case of dabigatran, the patients' renal function, without low-molecular-weight heparin (LMWH) bridging. With an interruption period of 36-42hr for low-risk procedures and 60-68hr high-risk procedures (prolonged intervals for those on dabigatran with renal impairment), only the dabigatran cohort demonstrated a major bleeding rate <2%. However, only 37.2% of cases were cardiothoracic with effects specifically among high risk cardiothoracic procedures unknown (Douketis et al. 2019). Overall, with a high-bleeding-risk procedure, the rates of major bleeding were 2.96% (95%CI, 0%-4.68%) in the apixaban cohort and 2.95% (95%CI, 0%-4.76%) in the rivaroxaban cohort.

There are few data available in respect of bleeding events among patients on combined anticoagulant and AP therapy undergoing major cardiac surgery. In a study of patients on warfarin plus single or dual AP therapy undergoing transcatheter aortic valve implantation there was a significantly higher risk of major or life-threatening bleeding compared to those on vitamin-K antagonist (VKA) monotherapy (Abdul-Jawad Altisent et al. 2016).

Although prothrombin time (PT) and activated partial thromboplastin time (APTT) may be used to exclude [DOAC] above therapeutic ranges, they lack the sensitivity to distinguish between negligible and therapeutic concentrations (Dale, Chan, and Eikelboom 2016; Godier et al. 2017). The utility of these tests is also known to vary depending on the reagents used (Dale, Chan, and Eikelboom 2016). Despite these limitations, and contrary to guidelines, PT and APTT are still frequently performed prior to surgery (Steffel et al. 2018).

The main aim of this study was to determine the effect of oral anticoagulant +/- AP therapy on the risk of bleeding and blood product usage during the first 48-hours from the start of surgery in adults undergoing cardiac surgery.

Patients and Methods

This was a single centre, retrospective observational study in a major cardiothoracic referral centre in UK. The study was approved by the Research Ethics Committee and the local Research and Development Office (Reference number: 19/NW/0474). Data were extracted from the Clinical Data Warehouse and patient electronic records. Patients' demographics, laboratory data, surgical and clinical data including EuroSCORE II data were collected, EuroSCORE II is a cardiac risk model for predicting mortality following cardiac surgery and is an update of the logistic EuroSCORE model (Nashef et al. 2012). It is derived from a data set which includes extracardiac arteriopathy, pulmonary disease, and preoperative state of the patient in addition to patient demographics and cardiac risk factors.

Patients

Patients with age ≥ 18 years undergoing major cardiac surgery (procedures that require at least opening of chest cavity through sternal incision) from 01.01.15 – 31.12.2018 who fulfilled the study inclusion criteria were included. Patients on an anticoagulant prior to surgery, with or without AP therapy, comprised the study groups and patients not on any anticoagulant or AP prior to surgery were taken as controls.

Anticoagulant management prior to surgery

Patients on warfarin stopped therapy 5 days prior to surgery with those considered to be at high risk of thrombosis receiving bridging with either unfractionated heparin (UFH) infusion or LMWH. UFH was stopped 4-6 hours prior to the surgery. The last dose of therapeutic dose LMWH was given 24hrs prior to surgery and prophylactic dose at 12hrs prior. P2Y12 inhibitors were stopped 5-7 days before surgery and aspirin was continued throughout surgery. DOACs were discontinued based on patient's renal function as per the pre-specified protocol for the study centre. Patients on apixaban or rivaroxaban stopped either ≥ 48 hrs, 48-72hrs or ≥ 72 hrs based patient's calculated creatinine clearance (CrCl) of >50 ml/min, 30-50ml/min and <30 ml/min respectively. Dabigatran was stopped ≥ 48 hrs, 48-72hrs or ≥ 96 hrs if the calculated CrCl was >80 ml/min, ≥ 50 -80ml/min and ≥ 30 - <50 ml/min respectively. This is in keeping with

the British Society for Haematology guidelines and differs from the European Society of Cardiology guidelines which recommend a longer discontinuation period in the presence of impaired renal function (Steffel et al. 2018; Keeling et al. 2016). For this study, the period of discontinuation was defined as the period, in days, from the time of last dose of anticoagulant to time of surgery.

Inclusion criteria

Patients $\geq$ 18yrs old undergoing major cardiac surgery with full blood count within 14 days prior to the surgery.

Exclusion criteria

Patients who returned to theatre following the surgery owing to bleeding that was clearly surgical in origin or with no data distinguishing surgical from bleeding related to coagulopathy or if patients had any of the following characteristics which influence bleeding: suffering a cardiac arrest, cardiogenic shock, use of IV nitrates, heparin or inotrope, aortic balloon pump insertion, use of a ventricular assist device or any other preoperative support device or thrombolysis within 24hrs of surgery, were excluded from analysis. Patients on single or dual AP alone prior to surgery were excluded from the study.

Statistical analysis

Results are presented as percentages for categorical data, and median and ranges for continuous data. Groups were compared using the Chi-squared test for categorical data, and the T-test, Mann-Whitney test or Kruskal-Wallis test for continuous data (as appropriate). P values <0.05 were considered statistically significant. Analyses were performed using SPSS version 24 software (IBM Corp., Armonk, NY, USA).

Results

A total of 6072 adults underwent cardiac surgery during the study period with 2928 patients meeting the inclusion criteria: 2819 control, 32 warfarin, 64 DOAC and 13 DOAC + AP (Figure

1). During the study period, there were only 3 patients on Warfarin + AP undergoing surgery and thus we deemed this to be insufficient for comparison. DOAC + AP was reported as the regimen is naturally different from DOAC alone and we thought differences should be analysed. Baseline characteristics for the study cohort are summarised in Table 1. There are significant differences between groups including age and comorbidity reflecting their different reasons for surgery. The baseline haematological parameters differed only in respect to platelet count ($P=0.007$) with the DOAC group having a lower count than controls ($181.5 [99 - 420] \times 10^9$ vs $203 [35 - 652] \times 10^9$, $P=0.002$). The median (range) discontinuation period was 5 (1-22) days for DOAC patients and 5 (2-7) days for DOAC + AP.

. Although patients on warfarin had significantly longer duration of surgery [280 (150 - 540) mins] compared to control group [250 (35 - 760) mins], $p=0.028$, there was no difference in the duration surgery between four groups (4-way $P = 0.127$). Table 2 summarises the details of the cardiac surgeries within study groups. There were no differences in the type of cardiac surgery between the four groups (0.946). Due to small numbers of patients in individual cardiac surgery groups, especially in patients on DOAC+_AP, comparisons were not performed for individual type of cardiac surgeries between groups. Indications for anticoagulation on patients on warfarin, DOAC and DOAC + AP are presented in table 3. Out of 13 patients on DOAC +AP, 9/13 were on DOAC + aspirin and 4/ 13 were on DOAC + P2Y12 inhibitors (clopidogrel or Prasugrel). P2Y12 inhibitors were stopped 5-7 days before surgery and aspirin was continued throughout surgery in all 9 patients.

Indicators of bleeding and relationship to anticoagulants

There were no differences in direct or indirect signs or measures of bleeding between any of the treatment groups and controls or between warfarin and DOAC patients during the perioperative period (Table 4).

Blood product usage

Intra-operative

Patients on warfarin received significantly more units of platelets, cryoprecipitate and FFP compared to others (controls, DOAC and DOAC +AP, 4-way P-values: 0.038, 0.024 and 0.045 for each product respectively). Furthermore, patients on warfarin had larger volumes of salvaged cells returned ($p=0.002$) and also a higher proportion of warfarin patients received salvaged cells ($P=0.002$) intra-operatively compared to other groups. Although there was no difference in the proportion of patients receiving platelets in the DOAC group vs the controls, more units of platelets were used per DOAC patient, $P=0.048$. However, the absolute difference was small (mean increase of 0.2 units of platelets per patient). The only other difference between DOAC and control was the proportion of patients receiving salvaged cells (83.6% vs 70.2%, $P=0.023$). . Despite no differences in the renal function, history of previous cardiac surgery, duration and type of the surgery between study groups, patients on DOAC + AP were less likely to receive packed red cells (PRC) intra-operatively than the control group (0% vs 25.8%, $P=0.034$) with fewer units of PRC used per DOAC + AP patient (0.67 units per patient $P=0.036$). Greater volumes of salvaged cells were returned per DOAC + AP patient vs control (median [range]) 530 [0-981] ml vs (381 [0-7659] ml, $P= 0.014$). A higher proportion of patients on warfarin received platelets and cryoprecipitate compared to control (46.9% and 18.8% vs 30.4% and 6.9%), $P = 0.044$ and 0.009 respectively. In addition, the number of units of platelets and cryoprecipitate given per patient was also higher in the warfarin group compared to controls ($P = 0.035$ and 0.009). There was a trend towards receiving more FFP units per patient on warfarin compared to controls, $P=0.05$. Patients on warfarin received a larger volume of cell salvage: (median [range]) 582 [90-1461] ml) compared to control (381 [0-7659] ml), $P= 0.017$. There were no differences in intra-operative blood product administration between patients on warfarin compared to DOAC.

Post-operative

There was no difference in the post-operative blood product administration between patients on any anticoagulant vs control, between warfarin vs DOAC or between any of the study groups.

Overall (peri-operative) (Fig 2)

The peri-operative period is defined as the first 48hrs after the first surgical incision of the chest. Patients on warfarin had significantly higher number of units of cryoprecipitate administered ($P=0.021$), volume of salvaged cells returned ($P=0.003$) and proportion of patients receiving salvage cells ($P=0.002$) during the peri-operative period (Figure 2). A higher proportion of patients on DOACs received cryoprecipitate vs control (18.8% vs 10.8%, $P=0.04$) but the absolute difference small (0.14 more units of cryoprecipitate per DOAC patient). In addition, more patients on DOAC received salvaged cells compared to controls; (83.6% vs 70.4%, $P=0.025$). The only difference observed between the DOAC + AP group and controls was the larger median (range) volume of salvaged cells administered per DOAC + AP patient: 530 (0-981) vs 383.5 (0-7659), $P=0.015$. Compared to controls, patients on warfarin were more likely to receive platelets (56.3% vs 38.4%, $p=0.039$) and cryoprecipitate (21.9% vs 10.8%, $p=0.046$). More units of platelets and cryoprecipitate and also larger volumes of salvaged cells were given per warfarin patient ($P=0.022$, 0.042 and 0.019) vs control. There was no difference in overall peri-operative blood products use between patients on warfarin and DOAC.

Post-op management and clinical outcomes

Anticoagulant +/- AP therapy had no impact on the initial location of post-operative care. Differences in length of hospital stay were observed ($P=0.021$). Warfarin patients stayed longer in hospital than controls and patients on DOAC: 11.5 (6-79) days vs 10 (3-174) days and 9.5 (6-44) days, $P=0.006$ and 0.03 respectively. No differences were seen between either the DOAC or DOAC + AP groups vs control. Thrombotic events occurred in 0.7% and 3.1% in controls and patients on warfarin respectively ($P=0.099$) with no TE among patients on DOAC or DOAC + AP; $P=0.51$ and 0.77 respectively vs control. There was no difference in

TE between warfarin and DOAC patients within 30 days, $P=0.155$. There were no differences in 30-day mortality between groups.

Sub-group analysis

Effect of DOAC discontinuation period on bleeding and blood product usage

Discontinuation period data was available for 58/64 DOAC patients. The period of DOAC discontinuation had no effect on intra-operative or post-operative blood product administration. However, overall during the peri-operative period, a higher proportion of patients who stopped DOACs <48hrs received FFP, $P=0.039$ and there was trend towards receiving more cryoprecipitate ($p=0.05$) compared to those who stopped > 48hrs (Table 5). However, there were no significant differences in the indicators of bleeding between patients who stopped DOAC < 48hrs vs those who stopped them > 48hrs (Table 5).

Effect of renal function on bleeding and blood products usage

Renal function data was available for all 64 DOAC patients. Differences between those with normal or mildly impaired (>50 ml/min), moderately impaired (30-50 ml/min) or severely impaired (<30ml/min) renal function respectively were seen in respect of post-op fibrinogen (2.85 [1.5-4.3] vs 2.5 [1.3-4.1] vs 1.8 [1.5-3.1], $P=0.007$) and the percentage of lead surgeon for the procedure being a consultant (88.5% vs 86.2% vs 28.6%, $P=0.006$). Renal function had no effect on blood product administration, either intra-operatively, post-operatively or peri-operatively, nor any indicator of bleeding.

Coagulation tests as a predictor for bleeding and blood products usage

56/64 DOAC patients had preoperative PT and APTT results available. There were no differences in the indicators of bleeding or use of blood products in patients with normal or abnormal coagulation test results.

Discussion

We report the effect of anticoagulant therapy on indicators of bleeding and blood product usage compared to patients not on anticoagulants in adult patients undergoing major cardiac surgery. This is the first study to make comparisons between those on DOAC +/- AP therapy vs controls and between DOAC vs warfarin monotherapy specifically in the setting of major cardiac surgery.

The main finding of our study is the lack of significant difference in measured indicators of bleeding between any of the anticoagulated groups and when compared to controls. This is notable given the increased age and lower pre-operative platelet count in patients on DOACs which are factors associated with an increased bleeding risk (Lopes et al. 2016; Lopes et al. 2015).

The results are in contrast to a previous meta-analysis that reported significantly lower rate of overall bleeds, major bleeds and minor bleeds in patients on DOAC (apixaban, rivaroxaban and dabigatran) compared to warfarin but prior to less invasive cardiac procedures (cardiac ablation) (Zhao et al. 2017). As our study did not separate DOAC patients into drug-specific groups, we could not determine the effect of each specific DOAC in major cardiac surgery.

With respect to warfarin vs control analysis, Oh et al, reported no difference in intra or 24hr post-operative blood product use between warfarin and control groups undergoing cardiac surgery on by-pass (Oh et al. 2015). In contrast, we noticed increased platelet and cryoprecipitate use overall in the warfarin group. Whilst the differences may be explained by the increased age of the warfarin patients and longer operating times vs control within our study, it is also possible that, as a tertiary cardiothoracic centre, the operations were of higher complexity than those in the Oh study group and that for such procedures, warfarin patients require greater intervention than controls.

Despite a higher EuroSCORE 2 score (Nashef et al. 2012), the warfarin, DOAC and DOAC + AP groups had no associated increase in 30-day mortality following cardiac surgery vs control;

there were also no differences between the warfarin and DOAC groups. This is yet another positive finding in favour of DOAC use.

Our study was not designed to determine the optimum period of DOAC discontinuation but support the CORIDA study in recommending that 48hrs is insufficient time to remove DOAC anticoagulant effect at time of surgery (Godier et al. 2017) as in the 0-48 hrs cohort, a significantly higher proportion of patients received FFP over the perioperative period and had a trend towards a larger drop in platelet count and receiving more cryoprecipitate compared to those who stopped DOACs >48hrs. The PAUSE study also suggests that a discontinuation period of 60-68hrs for major cardiac surgery may not be sufficient for patients on rivaroxaban or apixaban. The indicators of safety in the PAUSE study were a 30-day perioperative major bleeding rate of 2% and an arterial thromboembolism rate of 1.5%. Although no statistical analyses were performed, rates of major bleeding were higher following high bleeding risk procedures vs low bleeding risk procedures: 2.96 (0-4.68) % vs 0.59 (0-1.2) % for apixaban patients and 2.95 (0-4.76) % vs 1.27 (0-2.17) % for rivaroxaban patients. However, the perioperative regimen was not dependent on renal function for rivaroxaban and apixaban patients with 85.4% and 93.1% achieving [DOAC] <30ng/ml at time of surgery although, as mentioned, this was not shown to be predictive of bleeding risk. This led the authors to conclude further study was required for this regimen in high risk procedures, such as in our study cohort (Douketis et al. 2019). Although, it was not our study aim to assess the duration of discontinuation of DOACs prior to major cardiac surgery, the absence of any TE event within the DOAC cohorts, indicates that the median discontinuation of DOAC 5 days prior to major cardiac surgery is safe and effective. However, some patients stopped DOACs for less than 5 days (around 50% of the patients stopped DOACs <5 days) but showed no difference in the indicators of bleeding or use of blood products except FFP; indicating that not all patients need to discontinue DOACs 5 days prior to major cardiac surgery.

In our study, moderate or severe renal impairment had no impact on any indicator of bleeding or blood product usage, either intraoperatively, postoperatively or perioperatively. This

appears to contradict findings of the CORIDA study but the median period of DOAC discontinuation was 5 (1-22), 5 (1-18) and 5 (1-7) for normal, moderate and severe respectively, exceeding that recommended by local, British and European guidelines for those with moderate or severe impairment and those included in the CORIDA cohort which was 66hrs (1-218) (Godier et al. 2017; Keeling et al. 2016; Steffel et al. 2018). It is possible that any effect of renal impairment was thus negated by this prolonged period of DOAC discontinuation. The small number of patients with severe impairment and the small number of patients on dabigatran, which is affected more by renal impairment than rivaroxaban or apixaban, limits the reliability of this finding.

There was no value in assessing PT/APTT prior to major cardiac surgery in patients on DOACs, as these tests did not predict the bleeding or use of blood products in patients undergoing major cardiac surgery.

The main limitation of this study was its retrospective, observational design with small sample sizes in the treatment groups. Differences in baseline characteristics were present but these are likely to be present in any anticoagulant group. Furthermore, pre-specified transfusion guidelines were not implemented meaning surgical bias may have occurred. Variability in surgical skill may have also impacted on bleeding and product usage although we anticipate this effect to be minimal due to the highly specialised and experienced nature of the surgeons operating at a tertiary cardiothoracic centre (Lopes et al. 2015). Although we have not measured the [DOAC], after discontinuation of the drug a median of 5 days prior to surgery we would expect the levels to be undetectable with drug specific assays. In hindsight, it supports the conclusion that measurement of drug levels is unnecessary prior to major cardiac surgery if the drug is stopped with an appropriate time to clear from the circulation.

The strengths of the study include a comparison of the DOAC group to both control and warfarin patients as well as inclusion of those on DOAC + AP with both COX and P2Y12 inhibitors included in the AP regimes. Almost all relevant clinical and laboratory data were available for analysis. We analysed several indicators of bleeding, thrombotic events and

blood product administration, both in different clinical settings and overall during the perioperative period.

In conclusion, discontinuing DOAC with a median 5 days prior to major cardiac surgery +/- AP therapy or renal impairment may be sufficient to avoid an increase in bleeding with minimal to no increase in blood product usage and no increased in thrombotic events or 30-day mortality. This suggests the local guidelines combining the British and European guidelines regarding the time of last DOAC intake prior to cardiac surgery are safe and effective (Keeling et al. 2016; Manning et al. 2017; Steffel et al. 2018). Whilst our study was not designed to assess the optimum period of discontinuation, the findings emphasise that, for high risk procedures, this is unlikely to be within 48hrs of surgery (Godier et al. 2017). Finally, PT and APTT were not useful as predictors of bleeding and blood product usage in those on DOAC undergoing surgery. However, prospective studies to generate high quality evidence is required to confirm our findings.

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Authorship

CL performed the data collection, analysis and writing the first draft of the manuscript. D.J.A involved in the design of the study, interpretation of the data and revising the manuscript.

RS analysed the data. TA collected the data. ML interpreted the data and reviewed manuscript. All authors reviewed and approved the final manuscript

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Legends to figures

Table 1. Baseline characteristics of study groups.

Table 2. Details of the cardiac surgeries of the study groups

Table 3: Indications for anticoagulant therapy

Table 4. Measured indicators of bleeding between study groups

Table 5. Blood product usage for patients on direct acting oral anticoagulant (DOAC) stratified by period of DOAC discontinuation prior to surgery.

Figure 1: Patient inclusion and exclusion criteria for the study

Figure 2: Blood product usage for the control and treatment groups overall during the perioperative period. Graphs indicate the percentage of patients receiving each product and tables the median (range) number of products given per patient. * indicates a significant difference vs Control: $<0.05 = *$, $<0.01 = **$ and $<0.001 = ***$. † indicates significance between Warfarin and DOAC groups: $<0.05 = †$, $<0.01 = ††$ and $<0.001 = †††$. Figure 1: Patient inclusion and exclusion criteria

Table 1. Baseline characteristics of study groups.

Baseline Characteristics								
	Control	Warfarin	P value*	DOAC	P value*	DOAC+AP	P value*	4-way P value
Male sex (%)	71.7	62.5	0.285	75	0.561	84.6	0.302	0.481
Age (yrs)	67 (15 - 94)	72.5 (37 - 81)	0.046	72 (38 - 83)	<0.001	72 (60 - 82)	0.082	<0.001
BMI (kg/m ²)	27.3 (15.4 - 62.1)	28.1 (21.3 - 41.1)	0.603	27.5 (19.6 - 45.4)	0.353	27.6 (21.1 - 40.6)	0.441	0.565
Previous cardiac surgery (%)	7.6	15.6	0.092	3.1 †	0.177	0.0	0.300	0.245
LVEF >50% (%)	82.3	84.4	0.550	75.0	0.075	53.8	0.011	0.009
Extracardiac arteriopathy (%)	6.2	12.5	0.148	7.8	0.609	15.4	0.175	0.132
Neurological dysfunction (%)	2.9	0.0	0.328	6.3	0.120	0.0	0.533	0.519
Pulmonary disease (%)	13.0	12.5	0.931	7.8	0.219	15.4	0.800	0.391
Previous MI (%)	15.0	3.1	0.146	15.6	0.773	46.2	0.007	0.381
Diabetes (%)	21.1	15.6	0.447	17.2	0.443	30.8	0.397	0.722

EuroSCORE 2	1.52 (0.5 - 64.35)	3.21 (0.5 - 16.54)	0.001	2 (0.5 - 14.56)	0.021	3.26 (0.92 - 9.35)	0.017	<0.001
Hb (g/L)	134 (62 - 188)	133 (84 - 163)	0.998	139 (99 - 163)	0.108	137 (98 - 171)	0.866	0.462
MCV (fl)	89 (55 - 120)	89 (66 - 100)	0.648	90.7 (79.8 – 112)	0.019	91.3 (85.2 - 97.2)	0.066	0.017
PCV	0.40 (0.18 - 0.55)	0.41 (0.25 - 0.46)	0.514	0.41 (0.31 - 0.49)	0.028	0.40 (0.29 - 0.51)	0.918	0.162
Platelet count (x10 ⁹)	203 (35 - 652)	188 (68 - 304)	0.075	181.5 (99 - 420)	0.002	186 (91 - 350)	0.874	0.007
Minimum post-op fibrinogen (g/L)	2.60 (0.4-7.0)	2.35 (1.5-4.0)	0.100	2.55 (1.3-4.3)	0.776	2.60 (1.7-3.8)	0.870	0.422
Creatine clearance (ml/min)	85.7 (4.99 – 261)	81.5 (30.0 - 282)	0.119	73.4 (25.9 - 199.2)	0.103	79.0 (45 - 144)	0.343	0.123
Elective (%)	75.6	65.6	0.192	82.8	0.183	69.2	0.594	0.678
On by-pass (%)	80.1	90.6	0.137	78.1	0.696	76.9	0.775	0.948
Duration of surgery (minutes)	250 (35 - 760)	280 (150 - 540)	0.028	260 (150 - 425)	0.716	275 (130 - 400)	0.381	0.127
Patient status – Stable (%)	73.6	75.0	0.859	79.7	0.274	61.5	0.325	0.702
Lead surgeon -Consultant (%)	79.0	78.1	0.909	80.6	0.746	92.3	0.238	0.389
TXA use (%)	73.8	87.5	0.079	68.6 †	0.366	69.2	0.710	0.656

Aprotinin use (%)	5.3	3.1	0.586	3.1	1	7.7	0.699	0.586
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Total	2819	32		64		13		
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Data presented as median (min – max) or % were appropriate. *P-values represent differences to control group unless stated. † indicates significance between Warfarin and DOAC groups: † = 0.026 and 0.046 respectively. Δ DOAC + AP differed significantly to control, warfarin and DOAC, P=0.01, <0.001 and 0.012 respectively.

DOAC = direct acting oral anticoagulant; AP = antiplatelet; MI = myocardial infarction; BMI = body mass index; Hb = haemoglobin; MCV = mean cell volume; PCV = packed cell volume; TXA = tranexamic acid; AF = Atrial Fibrillation; VTE = Venous thromboembolism; MHV = Mechanical heart valve; CAD = Coronary Artery Disease;;LVEF = Left ventricular ejection fraction

Table 2: Details of the cardiac surgeries of the study groups

Cardiac Surgery	Control	Warfarin	DOAC	DOAC + AP
Aortic repair/replacement	68	0	1	0
CABG alone	855	1	10	3
CABG + other*	38	1	3	2
CABG + valve	273	12	8	6
Valve alone	1029	5	18	1
Valve + other**	459	10	17	1
Others***	97	3	7	0
Total	2819	32	64	13

CABG = cardiopulmonary bypass graft; DOAC = direct acting oral anticoagulant; AP = antiplatelet; * this includes heart or lung transplant, Wash-out, removal of packs and closure and Myxoma/mass resection; ** this includes ascending aorta replacement (AAR), full-maze procedure, or pulmonary vein isolation (PVI).

*** This includes Atrial appendage resection and closure of atrial septal defects, Carotid graft, superior vena cava reconstruction and open thrombectomy.

Table 3: Indications for anticoagulant therapy in study groups

Indication for anticoagulant	Warfarin	DOAC	DOAC +AP
Atrial Fibrillation	28/32 (88%)	60 (94%)	11 (85%)
Venous thromboembolism	1 (3%)	2 (3%)	0 (0%)
Mechanical heart valves	3 (9%)	0 (0%)	0 (0%)
Coronary heart disease	0 (0%)	2 (0%)	2 (15%)

DOAC = direct acting oral anticoagulant; AP = antiplatelet

Table 4 Measured indicators of bleeding between study groups

Indicators of Bleeding								
	Control	Warfarin	P value*	DOAC	P value*	DOAC + AP	P value*	4-way P value
Hb (g/L)	-34 (-106 - 31)	-34 (-70 - 34)	0.780	-32.5 (-71 - -1)	0.510	-33 (-60 - - 6)	0.943	0.914
PCV	-0.1 (-0.31 - -0.09)	-0.11 (-0.21 - -0.10)	0.661	-0.10 (-0.22 - 0.00)	0.676	-0.10 (-0.18 - -0.03)	0.971	0.945
Platelet count (x10 ⁹)	-67 (-420 – 166)	-72.5 (-142 – 62)	0.995	-60.5 (-264 – 25)	0.197	-70 (-142 – 58)	0.588	0.585
Volume of red cells salvaged (ml)	1818.5 (0 - 17112)	1948 (0 - 6458)	0.150	2018.5 (0 - 7562)	0.263	2214 (0 - 4333)	0.721	0.170
24-hr Surgical drain volume (ml)	550 (0 - 3640)	550 (100 - 2750)	0.537	500 (0 - 2000)	0.726	537.5 (75 - 1900)	0.721	0.889
Total	2819	32		64		13		

Data presented as median (min – max) or % were appropriate. *P-values represent differences to control group. Hb = haemoglobin; PCV = packed cell volume; DOAC = direct acting oral anticoagulant; AP = antiplatelet

Table 5 Blood product usage for patients on direct acting oral anticoagulant (DOAC) stratified by period of DOAC discontinuation prior to surgery.

<u>Intra-operative</u>					
	0 – 48 hrs (n =12)	48< - 96 hrs (n=17)	96< - 144 hrs (n=17)	144< hrs (n=12)	<u>P Value</u>
Packed red cell units	0 (0 - 2)	0 (0 - 4)	0 (0 - 3)	0 (0 - 3)	0.56
Platelet units	0 (0 - 3)	0 (0 - 2)	0 (0 - 2)	0 (0 - 1)	0.74
Cryoprecipitate units	0 (0 - 3)	0 (0 - 1)	0 (0 - 1)	0 (0 - 2)	0.67
FFP units	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)	0 (0 - 0)	0.11
Volume Cell Salvage (mL)	550 (0 - 1124)	310 (0 - 849)	450 (0 - 828)	309.5 (0 - 1146)	0.19
Packed red cell (%)	41.7	23.5	35.3	16.7	0.34
Platelets (%)	41.7	35.3	47.1	33.3	0.90
Cryoprecipitate (%)	16.7	5.9	5.9	8.3	0.50
FFP (%)	41.7	23.5	35.3	0	0.06
Cell Salvaged (%)	91.7	70.6	93.3	75	0.70
<u>Post-Operative</u>					
	0 – 48 hrs (n =12)	48< - 96 hrs (n=17)	96< - 144 hrs (n=17)	144< hrs (n=12)	<u>P Value</u>
Packed red cell unit	0.5 (0 - 4)	0 (0 - 2)	0 (0 - 1)	0 (0 - 2)	0.10
Platelet units	0 (0 - 2)	0 (0 - 1)	0 (0 - 0)	0 (0 - 1)	0.12
Cryoprecipitate units	0 (0 - 2)	0 (0 - 1)	0 (0 - 0)	0 (0 - 1)	0.11
FFP units	0 (0 - 7)	0 (0 - 4)	0 (0 - 5)	0 (0 - 3)	0.63

Volume Cell Salvage (mL)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	1
Packed red cell(%)	50	17.6	17.6	33.3	0.40
Platelets (%)	25	5.9	0	8.3	0.12
Cryoprecipitate (%)	25	5.9	0	8.3	0.12
FFP (%)	25	11.8	11.8	8.3	0.28
Cell Salvaged (%)	0	0	0	0	1
<u>Overall</u>					
	0 – 48 hrs (n =12)	48< - 96 hrs (n=17)	96< - 144 hrs (n=17)	144< hrs (n=12)	<u>P Value</u>
Packed red cell units	2 (0 - 4)	0 (0 - 4)	0 (0 - 4)	0 (0 - 3)	0.18
Platelet units	1 (0 - 3)	0 (0 - 2)	0 (0 - 2)	0 (0 - 1)	0.53
Cryoprecipitate units	0 (0 - 3)	0 (0 - 1)	0 (0 - 1)	0 (0 - 2)	0.05
FFP units	1.5 (0 - 7)	0 (0 - 4)	0 (0 - 5)	0 (0 - 3)	0.07
Volume Cell Salvage (mL)	550 (0 - 1124)	310 (0 - 849)	450 (0 - 828)	309.5 (0 - 1146)	0.19
Packed red cell (%)	75	35.3	41.2	41.7	0.17
Platelets (%)	58.3	41.2	47.1	41.7	0.53
Cryoprecipitate (%)	41.7	11.8	5.9	16.7	0.10
FFP (%)	58.3	35.3	47.1	8.3	0.04
Cell Salvaged (%)	91.7	70.6	93.3	75	0.70

Data presented as median (range) or percentages were appropriate. FFP = fresh frozen plasma.

Figure 1

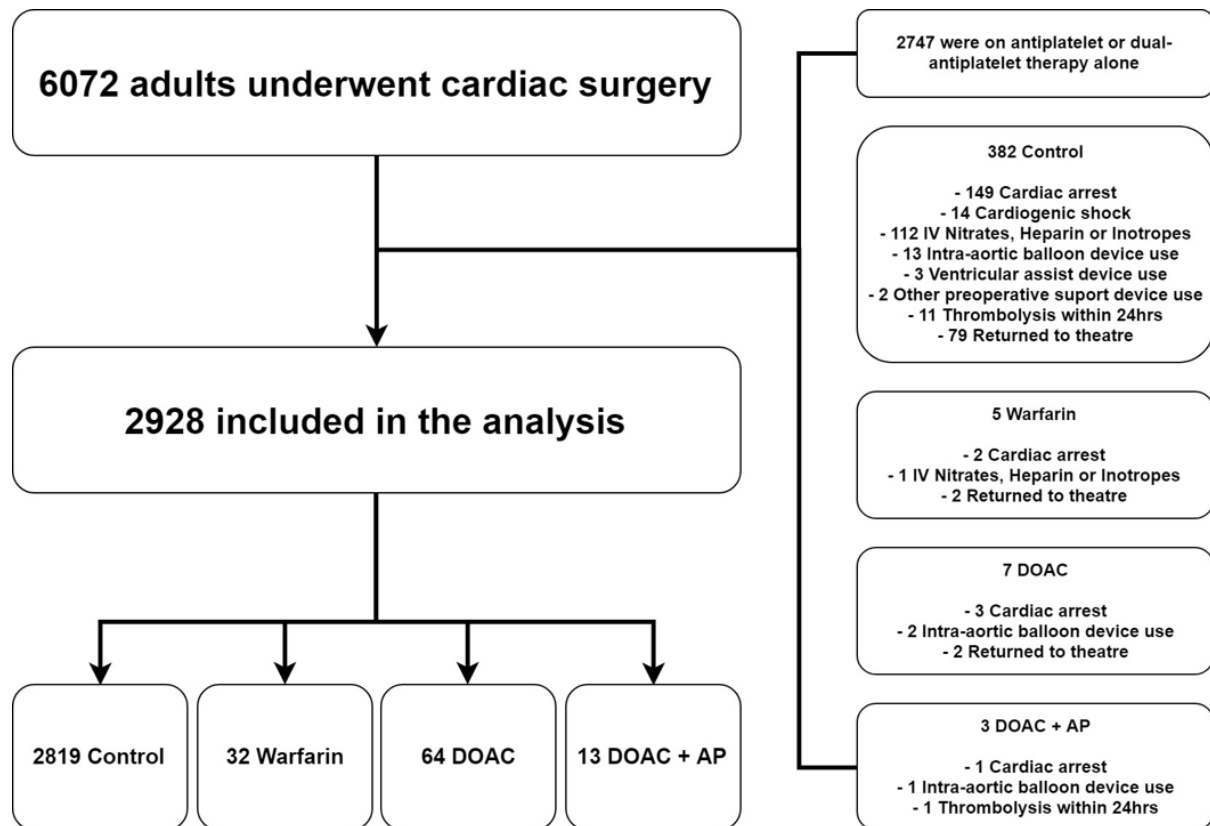
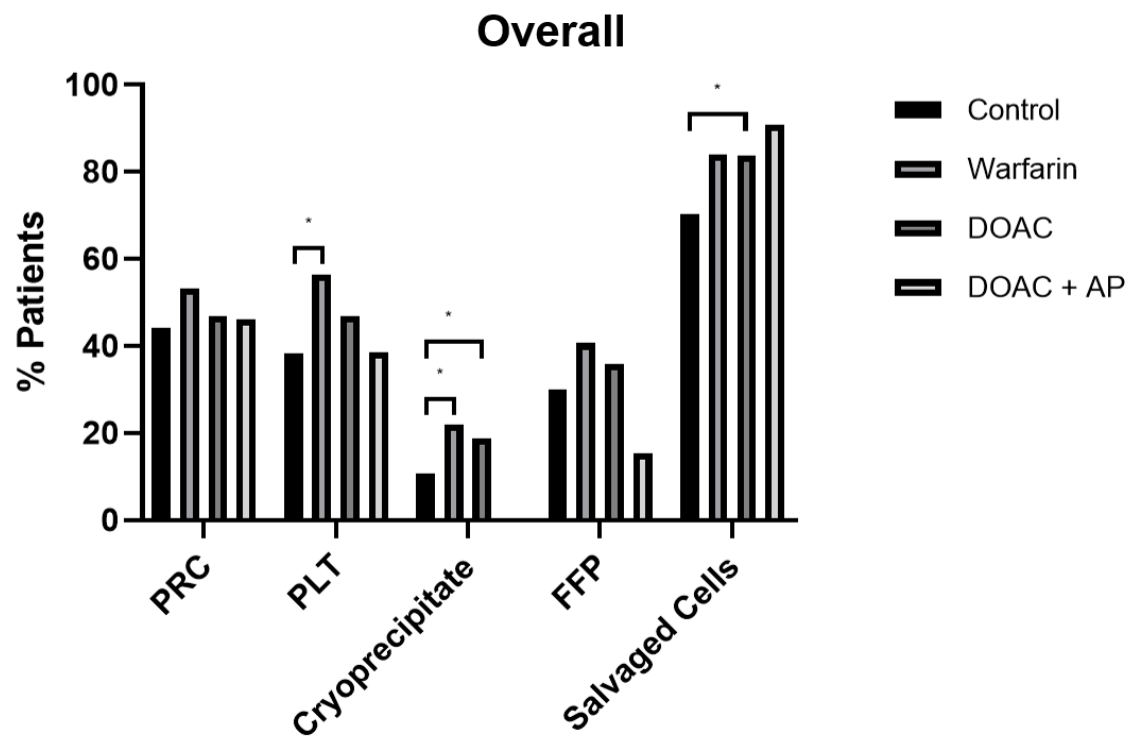


Figure 2



	Control n=2819	Warfarin n=32	DOAC n=64	DOAC+AP n=13
PRC (Units)	0 (0-27)	1 (0-6)	0 (0-4)	0 (0-3)
Platelet (Units)	0 (0-9)	1 (0-5) *	0 (0-4)	0 (0-2)
Cryoprecipitate (Units)	0 (0-6)	0 (0-4) *	0 (0-3) *	0 (0-0)
FFP (Units)	0 (0-16)	0 (0-12)	0 (0-7)	0 (0-2)
Volume Cell Salvage (ml)	383.5 (0-7659)	582 (0-1461) *	438 (0-1146)	530 (0-981) *