Direct oral anticoagulants and cardiac surgery: A descriptive study of preoperative management and postoperative outcomes

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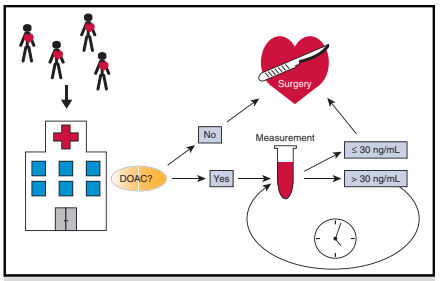
ABSTRACT

Objective: Recommendations for perioperative management of direct oral anticoagulant (DOAC) treatment in cardiac surgery are lacking. To establish a standardized approach for these patients, we compared hemorrhagic complications and clinical outcomes in patients on DOAC medication, patients on vitamin K antagonists (VKA), and patients without preoperative anticoagulation.

Methods: All 3 groups underwent major cardiac surgery and were retrospectively analyzed: patients on DOAC were advised to take their last DOAC dose 4 days before hospital admission, and DOAC plasma levels were measured the day before surgery. In patients with plasma levels of >30 ng/mL, surgery was postponed until plasma level was below this threshold level. Postoperative chest tube drainage, bleeding complications, use of blood products, and thromboembolic events were collected for all groups.

Results: A total of 5439 patients no anticoagulation, 239 patients on VKA, and 487 patients on DOAC medication were included between April 2014 and July 2017. Adjusted postoperative chest tube drainage did not differ between the DOAC and VKA groups for the strategy applied in this study (380 mL/12 hours vs 360 mL/12 hours). Moreover, secondary endpoint measures, such as rethoracotomy (30 [6.16%] vs 15 [6.28%]), 30-day-mortality 12 [2.46%] vs 7 [2.93%]), blood-product use, and stroke, were not significantly different through implementation of our standardized study management ($P > .05$).

Conclusions: Our standardized management for perioperative discontinuation of DOAC therapy may provide a safe approach to minimize hemorrhagic complications in cardiac surgery in patients on DOACs. (J Thorac Cardiovasc Surg 2021;161:1864-74)



Timing of cardiac surgery in DOAC patients depending on the preoperative DOAC levels.

CENTRAL MESSAGE

A standardized management of preoperative direct oral anticoagulation (DOAC) medication in cardiac surgery patients may help to prevent perioperative hemorrhagic complications.

PERSPECTIVE

With today's broad use of direct oral anticoagulation (DOAC) medication, handling of these drugs in a perioperative setting has become a challenge, and recommendations are limited. Standardized measurement of DOAC plasma levels and timing of surgery may help to decrease hemorrhagic complications. We describe a method of preoperative DOAC management to decrease hemorrhagic complications postoperatively.

See Commentaries on pages 1875 and 1876.

With the broad and growing use of direct oral anticoagulants (DOACs), eg, for patients with nonvalvular atrial fibrillation[1] and as secondary prevention against thromboembolic events,[2] management of these drugs in a perioperative setting has become a challenge. It is feared that perioperative bleeding complications in high-risk surgery will result.

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Abbreviations and Acronyms

ASA = acetylsalicylic acid
DOAC = direct oral anticoagulant
EuroSCORE = European System for Cardiac Operative Risk Evaluation
GFR = glomerular filtration rate
non-OAC = no anticoagulation
VKA = vitamin K antagonists

Scanning this QR code will take you to the table of contents to access supplementary information.

In the current literature, there are only limited recommendations available for perioperative management of patients receiving DOAC treatment.[3,4]

Some authors recommend DOAC discontinuation 3 to 5 days before any kind of surgery, a period calculated using the estimated half-lives of DOAC and renal function.[5,6] A prospective study in patients treated with dabigatran suggests discontinuing dabigatran 24 hours to 6 days before surgery, depending on renal function and bleeding risk during surgery.[7] Other recommendations for drug discontinuation vary between 1 and 4 days before surgery, depending on the kind of drug, bleeding risk during surgery, and renal function.[8]

Some authors suggest applying a DOAC plasma concentration threshold of 30 ng/mL,[9-11] proposing the feasibility of surgery only then. Importantly, these suggestions are based on mainly laboratory data, but this hypothesis has yet to be clinically tested.[9-11] The European Stroke Organization has recently updated its thrombolysis guidelines, which now also include a safe-for-treatment threshold of 30 ng/mL for all DOAC, but this suggested threshold has likewise yet to be validated in daily clinical use. Some authors propose a plasma level <20 ng/mL for dabigatran to keep the risk of bleeding complications low in patients undergoing surgery.[12] Moreover, it is still unclear whether plasma level measurement of DOAC is useful for perioperative monitoring in general.[13]

At present, there is still a lack of reliable data for a secure DOAC discontinuation scheme in cardiac surgery, representing a type of surgery associated with a high risk of hemorrhagic complications. At our institution, we investigated an approach for the management of all DOAC-treated patients who were referred for major cardiac surgery. We used a single concentration (≤30 ng/mL) as a threshold for DOAC before performing the surgical procedure, regardless of the DOAC used (Figure 1). If plasma levels were >30 ng/mL the day before surgery, the operation was postponed until the threshold was accomplished. The present descriptive study aimed to investigate whether our procedure is appropriate with respect to perioperative chest tube drainage, and we also sought to compare operative morbidity and 30-day mortality, depending on the type of anticoagulation used preoperatively. In particular, the hypothesis of our descriptive study was to examine the 2 clinically relevant groups, DOAC and vitamin K antagonists (VKAs), regarding their bleeding complications when undergoing cardiac surgery (Video 1).

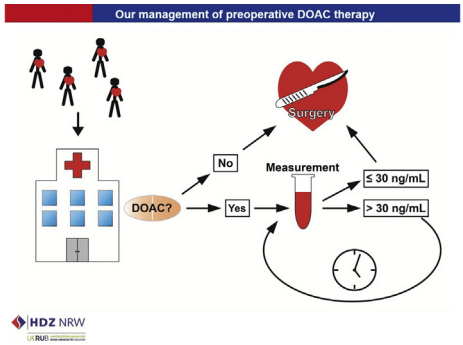
MATERIALS AND METHODS

Study Design and Patient Selection

All patients who underwent cardiac surgical procedures at our institution between April 2014 and July 2017 were eligible for inclusion (Figure 2). We performed a single-center retrospective database analysis. We limited our data analysis to patients aged >18 years undergoing elective cardiac surgical procedures, such as coronary artery bypass grafting (alone or in combination with arrhythmia surgery or carotid thromboendarterectomy), heart valve surgery, aortic surgery, surgical ablation, septal myectomy, pericardiectomy, resection of ventricular aneurysms, surgery for congenital heart disease, or combinations of these procedures. Exclusion criteria were emergency surgery, implantation of a ventricular assist device, heart transplantation, transcatheter aortic valve implantation, pacemaker and defibrillator implantation, known cases of von Willebrand disease, and leukemia. Moreover, patients with activated partial thromboplastin time values >37 seconds and international normalized ratio values >1.3 were excluded from data analysis. Patients undergoing bridging therapy with any type of heparin or fondaparinux were also excluded (Figure 2).

We had 3 groups of patients with different preoperative anticoagulation schemes within all patients meeting our inclusion criteria: one group received DOAC therapy preoperatively, another group was on VKA medication, and the third group had no preoperative anticoagulation therapy.

Some of our patients received medication with platelet inhibitors preoperatively. Acetylic salicylic acid (ASA) and other platelet inhibitor intake like clopidogrel or ticagrelor was continued until hospital admission. Platelet inhibitor management was identical in all 3 patient groups.



VIDEO 1. Presentation on the course of the study: intention, results and outlook. Video available at: https://www.jtcvs.org/article/S0022-5223(19)37170-3/fulltext.

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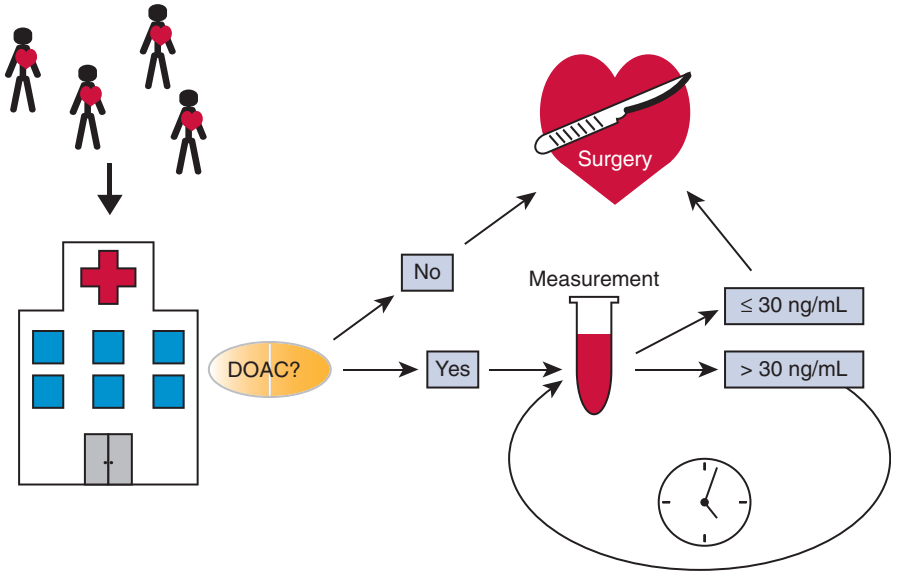

FIGURE 1. Procedure for surgery management. DOAC level measurement was performed on the day before surgery. If level was >30 ng/mL, surgery was postponed until threshold was reached. *DOAC*, Direct oral anticoagulation.

The study was performed in accordance with the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) for cohort studies (www.strobe-statement.org/). Informed consent was waived since our study was retrospective. The study was approved by the Ethics Committee of the Ruhr-University Bochum in Bad Oeynhausen, Germany (Reg.-No. 58/2015).

Perioperative Hemostatic Control

With regard to preoperative DOAC management, we used a standardized procedure: patients were advised to take the last DOAC dose 4 days before hospital admission. Plasma levels of DOAC were measured on admission, which was usually the day before surgery. Cardiac surgery was only performed if plasma level was ≤30 ng/mL. If the drug concentration was >30 ng/mL, it was measured daily and the heart surgery was delayed until the plasma level reached ≤30 ng/mL. None of the patients received DOAC antidotes because authority approval applies to life-threatening bleeding and emergency operations only.

Regarding preoperative VKA management, we advised patients to stop VKA medication 7 days before admission. Bridging with heparin, be it low molecular weight or unfractionated, was not permitted. In patients with complex heart surgery (eg, re-OP, long cardiopulmonary bypass time), a bolus of tranexamic acid (1 g) was administered with skin incision. Five hundred milligrams of tranexamic acid was loaded into the extracorporeal circuit, and infusion with tranexamic acid (200 mg/h) was administered until weaning from the extracorporeal circuit. All other patients received a bolus of 1 g with skin incision.

Our bleeding management algorithm consists of conservative coagulation optimization, but for more than 1000 mL, chest tube drainage rethoracotomy was considered.

Measurement of DOAC Concentration

The measurements were performed using an ACL TOP 700 system from April 2014 to February 2016 (Instrumentation Laboratory, Munich Germany), and a Sysmex CS-5100 System from March 2016 to July 2017 (Siemens Healthineers, Erlangen, Germany). For more information, see Appendix E1.

Dabigatran plasma concentrations were determined using HEMOCLOT Thrombin Inhibitors (CoaChrom Diagnostica, Maria Enzersdorf, Austria) and the anti-Xa activity of samples containing rivaroxaban, apixaban, or edoxaban was measured using the COAMATIC Heparin (Chromogenix, Forest Park, Ga) after calibration with drug-specific calibrators. A diluted thrombin time is measured for dabigatran determination. The clotting procedure is initiated by adding a constant amount of highly purified human thrombin. The clotting time measured is directly related to the concentration of dabigatran in the tested plasma.

The principle of anti-Xa measurement is based on an excess of FXa. If an FXa inhibitor is present, part of the FXa is inhibited and the remaining active factors cleave a chromogenic substrate in the following step. The signal from the dye is inversely proportional to the drug concentration.

If a laboratory has only an anti-Xa test calibrated for heparin, the latter can only be used to a limited extent with regard to its specificity. For a value of 0 IU/mL in the heparin test, it can be assumed that less than 30 ng/mL of the corresponding DOAC is present in the sample.

Endpoints

The primary endpoint was chest tube drainage within the first 12 postoperative hours. In accordance with Dyke and colleagues,[14] we applied the parameters used in this expert review specifically for cardiac surgery, which were postoperative chest tube drainage within 12 hours (milliliters), red blood cells (units), platelets (units), and fresh-frozen plasma (units). Secondary endpoints were postoperative bleeding events, stroke, low cardiac output syndrome, acute kidney injury, and 30-day mortality. A bleeding event was considered present in rethoracotomy cases that were necessary due to bleeding and/or pericardial tamponade, intracranial hemorrhage, and gastrointestinal bleeding. A stroke was considered present when a clinically manifest motoric, sensory, or cognitive neurologic deficit was detected due to a cerebrovascular event. All patients showing a neurologic deficit lasting longer than 12 hours underwent a postoperative computed tomography scan. Low cardiac output syndrome was defined as a cardiac index ≤2.5 L/min/m^2 or mixed venous oxygen blood saturation ≤55% requiring high-dose inotropic support and/or temporary mechanical circulatory support. Myocardial infarction was considered to have occurred in cases of new persistent

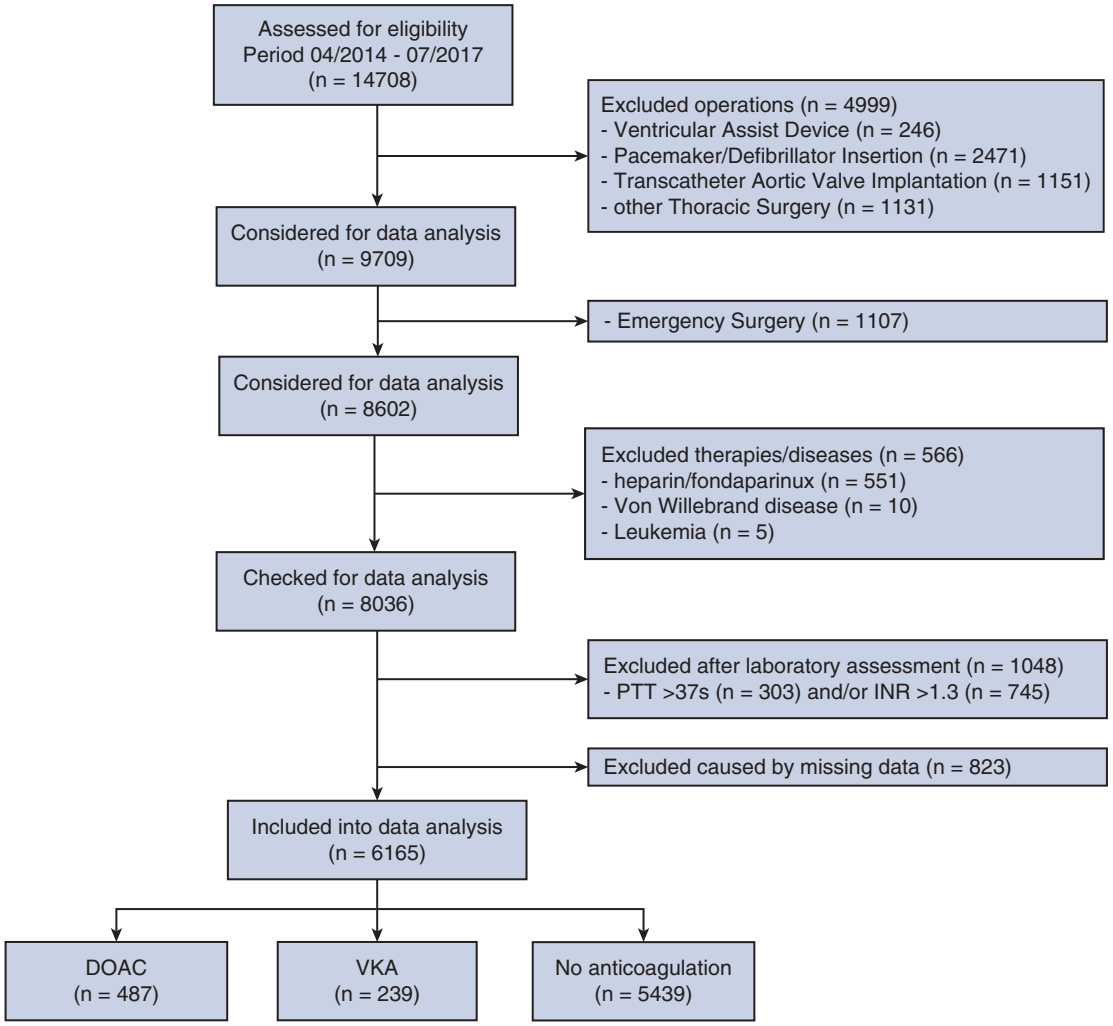

FIGURE 2. Study flow chart. This flow chart demonstrates the way of proving inclusion and exclusion criteria for all patients undergoing surgery in our center between April 2014 and July 2017. *PTT*, Partial thromboplastin time; *INR*, international normalized ratio; *DOAC*, direct oral anticoagulation; *VKA*, vitamin K antagonist.

ST-segment changes in combination with a rise in cardiac troponin values and/or imaging evidence of new regional wall motion abnormalities. Renal-replacement therapy via continuous venovenous hemofiltration was initiated in cases of acute renal failure refractory to pharmacologic therapy (repetitive boluses of 0.5-1 mg/kg furosemide intravenously), leading to uremia, hyperkalemia, and excessive volume overload. All secondary endpoints were assessed until the patient's discharge.

Statistical Analysis

Categorical variables are summarized as percentages and number of observations. Continuous variables are presented as medians and interquartile ranges, as they were not normally distributed (Shapiro–Wilk test, $P < .05$). We used the χ^2 test, Fisher exact test, and the Kruskal–Wallis test to assess group-specific differences in categorical variables and continuous variables of the baseline parameters. To estimate the association of the 3 study groups with the outcomes, linear, logistic, and negative binomial regression models were used with the 3 study groups as categorical predictors. To evaluate the association of the study groups with the incidence rates of the clinical endpoints, multivariable logistic regression was used.

The number of units of red blood cells, platelets, and fresh-frozen plasma administered, as well as the number of days of intensive care unit stay, were analyzed by negative binomial regression models as a highly significant overdispersion could be observed, preventing the use of standard Poisson models ($P < .001$ for all count models, test for overdispersion as implemented in the function "dispersiontest" in the R package AER). To account for this overdispersion, negative binomial regression models were used. Drainage volume, cut time, and postoperative minimal hemoglobin were analyzed using linear regression models where non-normally distributed continuous variables were log transformed. All models were adjusted for the following baseline covariates: age, sex, European System for Cardiac Operative Risk Evaluation (EuroSCORE), left ventricular ejection fraction, preoperative glomerular filtration rate (GFR), off-pump surgery, treatment with platelet inhibitors, preoperative hemoglobin, type of surgery, and atrial fibrillation, selected according to medical expert knowledge.

For the primary end point, pairwise comparisons between the 3 study groups were performed by post hoc analysis using Tukey's method, as implemented in the 'multcomp' package in R.[15] For secondary endpoints, multiple testing correction was performed over contrasts and number of

TABLE 1. Baseline characteristics of the study groups

Demographic variables and comorbidities	Non-OAC (n = 5439)	VKA (n = 239)	DOAC (n = 487)	Total (n = 6165)	*P* value (all 3 groups)	*P* value (VKA vs DOAC)
Age, y, median (IQR)	68 (58, 75)	74 (67, 78)	73 (66.5, 77)	69 (59, 76)	<.001	.548
Sex, female, n (%)	1613 (29.66%)	95 (39.75%)	170 (34.91%)	1878 (30.46%)	<.001	.214
Body mass index, median (IQR)	27.44 (24.8, 30.48)	27.63 (24.53, 31.59)	27.08 (24.19, 30.45)	27.43 (24.73, 30.49)	.19	.279
Atrial fibrillation, n (%)	153 (2.81%)	130 (54.39%)	272 (55.85%)	555 (9%)	<.001	.692
Preoperative GFR, mL/min/1.73 m^2, median (IQR)	78 (64, 90)	64 (48, 80)	67 (53.5, 81)	77 (62, 89)	<.001	.061
Risk factors						
Left ventricular ejection fraction, %, median (IQR)	60 (52, 65)	59 (50, 66)	56 (50, 62)	60 (50, 65)	<.001	.021
EuroSCORE, median (IQR)	3.7 (1.96, 7.16)	11.7 (5.97, 23.49)	9.32 (4.96, 17.38)	4.06 (2.08, 8.44)	<.001	.007
Preoperative bleeding-related variables						
Preoperative minimum hemoglobin, g/dL, median (IQR)	14.2 (13.1, 15.2)	13.2 (12.15, 14.35)	13.8 (12.6, 14.9)	14.1 (13, 15.1)	<.001	<.001
Platelet inhibitors					<.001	.013
P2Y12 inhibitors	507 (9.32%)	12 (5.02%)	8 (1.64%)	527 (8.55%)		
ASA	2579 (47.4%)	33 (13.8%)	51 (10.5%)	2663 (43.2%)		
PTT, s, median (IQR)	28 (24, 30)	29 (26, 32)	27 (24, 30)	28 (25, 30)	<.001	<.001
INR, median (IQR)	1.00 (1.00, 1.00)	1.10 (1.00, 1.20)	1.00 (1.00, 1.10)	1.00 (1.00, 1.00)	<.001	<.001
Platelet count, $\times 10^3/\mu L$, median (IQR)	123 (88, 166)	105 (71, 149)	119 (77, 168)	122 (86, 166)	<.001	.016
Preoperative bleeding-related variables						
Type of surgery					<.001	.304
Isolated AVR/MVR	1891 (34.77%)	130 (54.39%)	242 (49.69%)	2263 (36.71%)		
Isolated CABG	2129 (39.14%)	25 (10.46%)	45 (9.24%)	2199 (35.67%)		
CABG and AVR/MVR	806 (14.82%)	38 (15.9%)	83 (17.04%)	927 (15.04%)		
CABG and other*	75 (1.38%)	21 (8.79%)	69 (14.17%)	165 (2.68%)		
Aortic surgery	503 (9.25%)	23 (9.62%)	45 (9.24%)	571 (9.26%)		
Congenital	35 (0.64%)	2 (0.84%)	3 (0.62%)	40 (0.65%)		
Bypass time, min, median (IQR)	80 (0.00, 118.00)	114.50 (77.75, 149.00)	107 (72.00, 148.00)	83 (0.00, 122.00)		
Surgery off-pump	1868 (34.34%)	35 (14.64%)	85 (17.45%)	1988 (32.25%)	<.001	.344

non-OAC, No anticoagulation; *VKA*, vitamin K antagonists; *DOAC*, direct oral anticoagulants; *IQR*, interquartile range; *GFR*, glomerular filtration rate; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *P2Y*, P2Y-inhibitor; *ASA*, acetylic salicylic acid; *PTT*, partial thromboplastin time; *INR*, international normalized ratio; *AVR*, aortic valve repair/replacement; *MVR*, mitral valve repair/replacement; *CABG*, coronary artery bypass grafting. *Other = arrhythmia surgery and/or carotid thrombendarterectomy.

end points using Holm's method.[16] *P* values <.05 were considered statistically significant. A statistical power calculation revealed that the study would have 90% power to detect a relative difference of 30 mL in the primary endpoint in the DOAC group compared with the VKA group, given a total sample size of 700 patients, a standard deviation of 120 mL, and using a 2-sided alpha level of 0.05. We used the SPSS statistical software package, version 21 (IBM Corp, Armonk, NY) and R (version 3.2.2)[17] to perform the analyses.

RESULTS

Baseline Characteristics and Operative Data

A total of 6165 patients were included in our study (Figure 2). Of these 6165 patients, 487 patients had regular preoperative medication (DOAC group) consisting of apixaban (227 patients), dabigatran (36 patients), rivaroxaban (214 patients), or edoxaban (10 patients). An additional 239 patients were on regular VKA medication (VKA group), whereas 5439 patients did not take any anticoagulation (non-OAC group) preoperatively. In total, 344 patients with a DOAC drug level <30 ng/mL on admission stated the date and time of their last DOAC intake.

The characteristics of the study groups are provided in Table 1. Patient groups in the focus of our hypothesis (VKA vs DOAC) did not show statistically significant differences in baseline characteristics for age, sex, GFR values, atrial fibrillation, body mass index, or type of surgery. The group without preoperative oral anticoagulation was, on average, younger and had greater

left ventricular ejection fraction compared with the VKA and DOAC groups. Furthermore, preoperative hemoglobin concentrations and GFR values were greater in the non-OAC group. Atrial fibrillation was significantly lower in the non-OAC group than in both OAC groups (2.8 vs 54.4/55.9%). However, none of our patients suffered from any thromboembolic event preoperatively while they discontinued anticoagulant therapy before cardiac surgery. Baseline characteristics reveal numerical differences for P2Y12-inhibitors (P2Y)/ASA between DOAC and VKA group and potential interactions of antiplatelet medications with DOACs have been addressed. No statistically significant differences on the drainage volume between P2Y/ASA-treated DOAC and VKA groups and patients without platelet inhibitors were identified ($P = .10$).

Overall, surgical procedures performed (eg, coronary artery bypass grafting, valve replacement) were not statistically different between our focused clinically relevant DOAC and VKA groups. Mean interval between last DOAC intake and drug level measurement was 3.8 days in this study (N = 381, median: 3.828 days, Q1, Q3: 2.455, 4.794). In 75 patients, plasma level was >30 ng/mL. Surprisingly, 52 of 75 patients (69%) with increased DOAC levels had taken their DOAC despite their physicians advising them otherwise. In this context in particular, the importance of our study becomes clear since

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TABLE 2. Chest tube drainage, use of blood products, rethoracotomy rate, postoperative minimal hemoglobin concentration, skin-to-skin operative time, low output syndrome, stroke, gastrointestinal bleeding, acute kidney injury, stay on intensive care unit, and 30-day-mortality by study group

Outcome variables for bleeding	non-OAC (n = 5439)	VKA (n = 239)	DOAC (n = 487)	Total (n = 6165)
Drainage volume/12 h Postoperative, mL, median (IQR)	350 (250, 500)	360 (250, 550)	380 (272.5, 560)	350 (250, 510)
Red blood cells, units				
0	2303 (42.3%)	66 (27.6%)	165 (33.9%)	2534 (41.1%)
1-2	1389 (25.5%)	52 (21.8%)	108 (22.2%)	1549 (25.1%)
3-5	917 (16.9%)	38 (15.9%)	100 (20.5%)	1055 (17.1%)
6-19	717 (13.2%)	69 (28.9%)	99 (20.3%)	885 (14.4%)
≥20	113 (2.1%)	14 (5.9%)	15 (3.1%)	142 (2.3%)
Platelets, units				
0	4323 (79.5%)	154 (64.4%)	356 (73.1%)	4833 (78.4%)
1-2	844 (15.5%)	63 (26.4%)	87 (17.9%)	994 (16.1%)
3-5	181 (3.3%)	10 (4.2%)	29 (6.0%)	220 (3.6%)
6-19	78 (1.4%)	8 (3.3%)	11 (2.3%)	97 (1.6%)
≥20	13 (0.2%)	4 (1.7%)	4 (0.8%)	21 (0.3%)
Fresh-frozen plasma, units				
0	3432 (63.1%)	120 (50.2%)	268 (55.0%)	3820 (62.0%)
1-2	1093 (20.1%)	43 (18.0%)	104 (21.4%)	1240 (20.1%)
3-9	753 (13.8%)	55 (23.0%)	85 (17.5%)	893 (14.5%)
10-49	154 (2.8%)	20 (8.4%)	30 (6.2%)	204 (3.3%)
≥50	7 (0.1%)	1 (0.4%)	0 (0.0%)	8 (0.1%)
Fibrinogen dose, g				
0	4884 (89.8%)	215 (90.0%)	426 (87.5%)	5525 (89.6%)
1	31 (0.6%)	1 (0.4%)	2 (0.4%)	34 (0.6%)
2-5	477 (8.8%)	18 (7.5%)	52 (10.7%)	547 (8.9%)
≥6	47 (0.9%)	5 (2.1%)	7 (1.4%)	59 (1.0%)
Rethoracotomy	183 (3.36%)	15 (6.28%)	30 (6.16%)	228 (3.7%)
Other outcome variables				
Postoperative Hb, min, g/dL, median (IQR)	9.6 (8.9, 10.3)	9.4 (8.8, 9.95)	9.4 (8.7, 10.1)	9.5 (8.9, 10.3)
Skin-to-skin operative time, min, median (IQR)	195 (163, 234)	210 (176, 250)	207 (170, 247)	197 (164, 236)
Low output syndrome	230 (4.23%)	28 (11.72%)	46 (9.45%)	304 (4.93%)
Stroke	85 (1.56%)	9 (3.77%)	14 (2.87%)	108 (1.75%)
Gastrointestinal bleeding	46 (0.85%)	3 (1.26%)	7 (1.44%)	56 (0.91%)
Acute kidney injury	315 (5.79%)	34 (14.23%)	47 (9.65%)	396 (6.42%)
Stay on intensive care unit, h, median (IQR)	23 (19, 49)	36 (22, 94)	36 (21, 81)	23 (19, 59)
30-d mortality	66 (1.21%)	7 (2.93%)	12 (2.46%)	85 (1.38%)

Values are shown as the median (IQR) or the percentage. *Non-OAC*, No anticoagulation; *VKA*, vitamin K antagonists; *DOAC*, direct oral anticoagulants; *IQR*, interquartile range; *Hb*, hemoglobin.

TABLE 3. Multivariable regression models for secondary outcomes: estimate denotes log rate ratios for red blood cells [units], thrombocytes [units], fresh-frozen plasma [units], fibrinogen dose [g] and stay on intensive care unit [h], changes in log(minutes) for skin-to-skin operative time [min], and changes in Hb for postoperative min Hb [g/dL]

Outcome variables for bleeding	Estimate	SE	*P* value	Deviance/ R^2
Drainage volume/12 h postoperative				
VKA – non-OAC	0.007	0.043	.986	
DOAC – non-OAC	0.066	0.034	.119	0.062
DOAC – VKA	0.059	0.046	.405	
Red blood cells				
VKA – non-OAC	0.015	0.097	>.99	
DOAC – non-OAC	–0.212	0.078	.275	6449.700
DOAC – VKA	–0.227	0.105	>.99	
Platelets				
VKA – non-OAC	0.268	0.184	>.99	
DOAC – non OAC	−0.212	0.151	>.99	3301.225
DOAC – VKA	−0.480	0.200	.647	
Fresh-frozen plasma				
VKA – non-OAC	0.141	0.145	>.99	
DOAC – non-OAC	−0.202	0.116	>.99	4939.527
DOAC – VKA	−0.343	0.157	>.99	
Fibrinogen dose				
VKA – non-OAC	−0.385	0.315	>.99	
DOAC – non OAC	−0.290	0.246	>.99	1711.389
DOAC – VKA	0.095	0.339	>.99	
Rethoracotomy				
VKA – non-OAC	0.000	0.315	>.99	
DOAC – non OAC	0.139	0.251	>.99	1830.597
DOAC – VKA	0.140	0.335	>.99	
Other outcome variables				
Postoperative, min, Hb				
VKA – non-OAC	0.010	0.072	>.99	
DOAC – non-OAC	–0.068	0.057	>.99	0.193
DOAC – VKA	–0.078	0.078	>.99	
Skin-to-skin operative time				
VKA – non-OAC	0.051	0.018	.245	
DOAC – non-OAC	0.034	0.014	.699	0.151
DOAC – VKA	–0.017	0.020	>.99	
Low output syndrome				
VKA – non-OAC	0.080	0.260	>.99	
DOAC – non-OAC	−0.094	0.224	>.99	2016.907
DOAC - VKA	−0.174	0.276	>.99	
Stroke				
VKA – non-OAC	0.088	0.427	>.99	
DOAC – non-OAC	–0.172	0.367	>.99	994.027
DOAC – VKA	–0.260	0.444	>.99	
Gastrointestinal bleeding				
VKA – non-OAC	–0.849	0.679	>.99	
DOAC – non-OAC	–0.444	0.511	>.99	580.933
DOAC – VKA	0.405	0.715	>.99	
Acute kidney injury				
VKA – non-OAC	–0.324	0.264	>.99	
DOAC – non-OAC	–0.369	0.224	>.99	2103.708
DOAC – VKA	–0.045	0.283	>.99	
Stay on intensive care unit				
VKA – non-OAC	0.15	0.07	.410	
DOAC – non-OAC	0.02	0.06	>.99	6939.431
DOAC – VKA	–0.13	0.08	.900	
30-d mortality				
VKA – non-OAC	0.002	0.472	>.99	
DOAC – non-OAC	0.081	0.388	>.99	769.363
DOAC – VKA	0.078	0.505	>.99	

(Continued)

TABLE 3. Continued

Corresponding standard error, *P* values, and deviance (or R^2 for linear models for postoperative min Hb and skin-to-skin operative time) are given. *P* values have been multiple testing corrected using Holm's method. *SE*, Standard error; *VKA*, vitamin K antagonists; *non-OAC*, No anticoagulation; *DOAC*, direct oral anticoagulants.

such patients may have undergone regular cardiac surgery and could have faced high bleeding risk.

Primary and Secondary Endpoints

After adjustment for baseline covariates, no significant differences in the 12-hour drainage volume (primary endpoint) between the patients without anticoagulation and the patients with VKA or DOAC treatment could be detected (Tables 2 and 3). Similarly, analysis of the secondary endpoints yielded no significant differences overall in the pairwise comparison between the study groups after multivariable statistically adjusted analysis (Tables 2 and 3). Furthermore, we investigated the incidence rates of clinical events (low-output syndrome, rethoracotomy rate, number of strokes, gastrointestinal bleeding, acute kidney failure, 30-day mortality). No significant differences could be observed in the pairwise comparison of the individual groups (Tables 2 and 3). With regard to postoperative myocardial infarctions, the number of events was so small that it was not statistically evaluable (n = 25).

Proportions of >500 mL/12 hours drainage volume and <500 mL/12 hours drainage volume showed no differences in pairwise comparisons (Figure 3, *A*). Comparable with the main analysis, this yielded no significant differences in particular for the clinically relevant DOAC and VKA groups (Figure 3, *A*). In addition, multivariable analysis was conducted to identify variables of influence for red blood cell use (Figure 3, *B*) and prolonged stay in the intensive care unit (Figure 3, *C*). Blood-based product use is shown in Figure E1.

Moreover, pharmacokinetics of all DOACs were addressed by separate testing of chest tube drainage volume for each DOAC (dabigatran, edoxaban, rivaroxaban, and

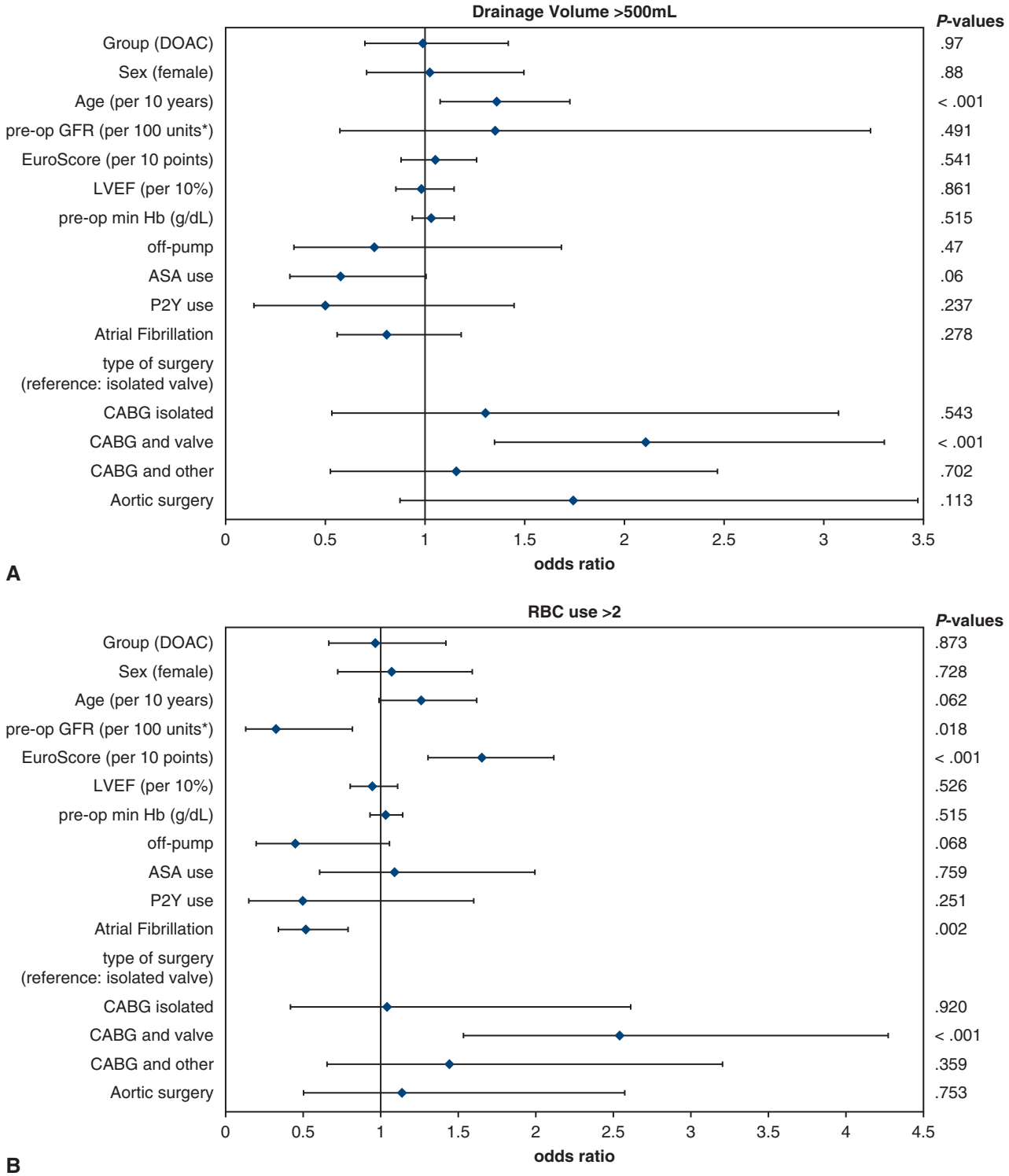

FIGURE 3. A, Chest tube drainage greater than 500 mL in 12 hours (in patients with preoperative DOAC or VKA anticoagulation) by subgroup analysis. B, Use of more than 2 RBC units (in patients with preoperative DOAC or VKA anticoagulation) by subgroup analysis. C, ICU stay >72 hours (in patients with preoperative DOAC or VKA anticoagulation) by subgroup analysis. A-C, Results are presented as odds ratio with 95% confidence intervals. Reference for type of surgery: isolated AVR/MVR. *RBC*, Red blood cell; *DOAC*, direct oral anticoagulation; *GFR*, glomerular filtration rate; *LVEF*, left ventricular ejection fraction; *Hb*, hemoglobin; *ASA*, acetylic salicylic acid; *P2Y*, P2Y-inhibitor; *CABG*, coronary artery bypass grafting; *ICU*, intensive care unit. *mL/min/1.73m^2

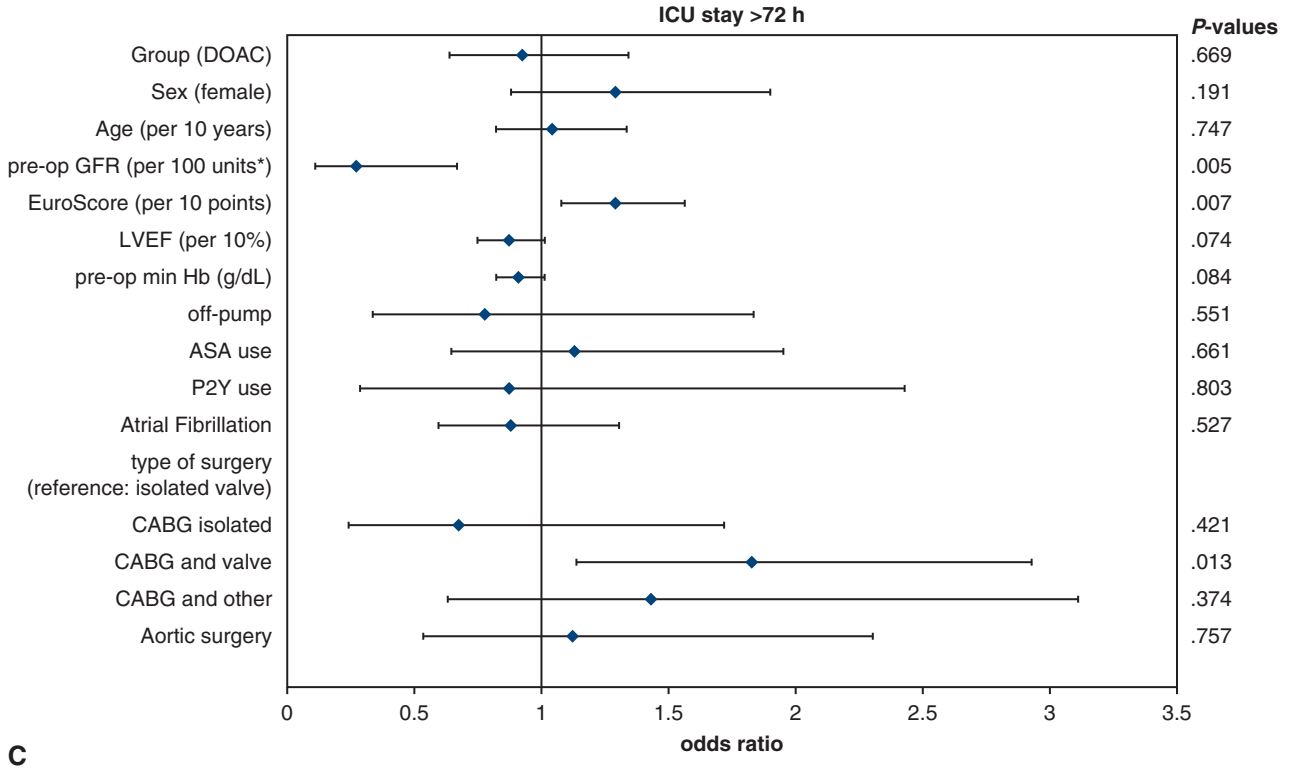

FIGURE 3. (*continued*).

apixaban), yielding no significant difference between the individual DOAC. We also assigned preoperative DOAC concentrations to specific operations. Table 4 shows what the actual drug levels were for patients going for different operations and what numbers of people were on which drug.

DISCUSSION

This descriptive study tested the hypothesis that DOAC drug level measurement and implementation of a threshold of <30 ng/mL, which was a median of 3.8 days without DOAC (regardless of the drug used), results in comparable perioperative chest tube drainage and hemorrhagic events in patients on DOAC compared with established VKAs. Enrolling a total of 6165 patients (239 on previous VKA and 487 on DOAC) undergoing cardiac surgery, our data indicate no increased perioperative risk regarding perioperative chest tube drainage, rethoracotomy, gastrointestinal bleeding, acute kidney injury, or administering blood products with this approach. To the best of our knowledge, this is the first study to describe perioperative management of DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) in comparison with VKA or non-OAC patients in cardiac surgery using standardized management for interruption of oral anticoagulants.

In this context, DOAC plasma level measurement has been increasingly discussed in the present literature.

TABLE 4. Concentration of the respective DOAC in relation to the type of surgery

	Isolated CABG (n = 18)	Isolated AVR/MVR (n = 116)	CABG and AVR/MVR (n = 33)	Aortic surgery (n = 14)	CABG and other* (n = 29)	Congenital (n = 2)	Total (n = 212)
DOAC concentration							
Median (Q1, Q3)	0 (0, 16.5)	0 (0, 8.5)	0 (0, 13)	0 (0, 9.75)	0 (0, 18)	23.5 (22.75, 24.25)	0 (0, 12.25)
DOAC							
Dabigatran	2 (11.1%)	5 (4.3%)	2 (6.1%)	0 (0.0%)	3 (10.3%)	0 (0.0%)	12 (5.7%)
Edoxaban	0 (0.0%)	4 (3.4%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)
Rivaroxaban	9 (50.0%)	53 (45.7%)	15 (45.5%)	7 (50.0%)	9 (31.0%)	0 (0.0%)	93 (43.9%)
Apixaban	7 (38.9%)	54 (46.6%)	15 (45.5%)	7 (50.0%)	17 (58.6%)	2 (100.0%)	102 (48.1%)

CABG, Coronary artery bypass grafting; *AVR*, aortic valve repair/replacement; *MVR*, mitral valve repair/replacement; *DOAC*, direct oral anticoagulants; *Q1*, quartile 1; *Q3*, quartile 3. *Other = arrhythmia surgery and/or carotid thrombendarterectomy.

Douketis and colleagues[18] have shown that the incidence of major bleeding events for patients with dabigatran medication after elective surgery of any kind (bridged with heparin and not bridged) was 6.5% and 1.8%, respectively. Some authors state that a dabigatran plasma level of >200 ng/mL and an edoxaban level >150 ng/mL may be associated with increased bleeding,[19] whereas some reports mention a threshold of 400 ng/mL, which has been claimed to be associated with elevated bleeding risk in high-risk surgery.[20] Similar results were shown for patients with VKA medication (bridged with heparin and not bridged) before surgical procedure with hemorrhagic events of 6.8% and 1.6%, respectively.[18] A meta-analysis published by Siegal and colleagues[21] included 34 studies on the surgical outcome of patients on VKA treatment (bridged or not bridged) and reported major bleeding events of 4.2% and 0.9%, respectively. For patients with atrial fibrillation using rivaroxaban for stroke prevention, the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study described an event rate for major bleeding per 30 days of 0.99% (0.97% under warfarin) during temporary interruption for surgical procedures.[22] Data from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial also reported no differences in major bleeding rates between patients treated with apixaban versus warfarin during surgical procedures.[23] Several studies have been published on bleeding events under VKA treatment,[21] but they are mostly substudies of DOAC-approval trials.[18,23] Their findings are in line with our data showing comparable bleeding risk between patients on VKA or DOAC, which is of daily clinical relevance.

Nevertheless, the current literature exploits the fact that no standardized approach or method is available on how to handle DOAC plasma thresholds.[20] In terms of patient safety and practicability, we aimed to establish an easy-to-use threshold for all DOAC for daily clinical routine. Whether the 30 ng/mL concentration used in our approach is optimal, or whether a 50 ng/mL concentration, as suggested by Tripodi and colleagues,[24] may be superior, needs to be investigated by future studies. In general, Tripodi and colleagues[25,26] stated that DOAC concentration measurement in patients undergoing surgical or invasive procedures appears to be superior in terms of patient safety. Hassan and colleagues[27] recently speculated about a beneficial 10-day discontinuation of DOAC before elective cardiac surgery, but residual DOAC drug levels were not measured in this study. Furthermore, the length of DOAC withdrawal before surgery was estimated from the 24-hour drainage volume. That study does not provide data on thromboembolic events during the transition period. Since our study groups were comparable in terms of drainage volume, clinical bleeding tendency, and thromboembolic events and our patients even had greater median EuroSCORE and continuous acetylsalicylic acid intake, we consider Hassan and colleague's proposed 10-day discontinuation of DOAC therapy unjustified because we could show comparable bleeding events after a median of 3.8 days, making 10 days of discontinuation unnecessary and implicating a greater risk of thromboembolic events. Moreover, contrary to the suggestions of Hassan and colleagues, the 2018 European Heart Rhythm Association recommendation includes a discontinuation of DOAC of only 2 days for high-risk procedures.[28] Random EuroSCORE and platelet inhibitor use reached statistical significance in our baseline characteristics, but for the wide variety of patients investigated this incidental statistical finding is believed to have no clinical impact.

In summary, our standardized management of preoperative discontinuation of DOAC therapy may provide a safe approach to minimize hemorrhagic complications in cardiac surgery in patients on DOACs. Our study management facilitates identification of such incompliant patients who otherwise would have faced preventable very high bleeding risk. The potential benefit of our proclaimed study management is to provide an easily practicable approach to improve perioperative handling of cardiac surgery patients on DOAC since it addresses individual DOAC drug levels. Therefore, we encourage our colleagues in heart surgery to integrate a DOAC measurement protocol to increase perioperative safety in heart surgery.

Limitations

There are limitations within this study, including its retrospective, single-center study design, which is why we cannot prove prospective safety but can suggest a reliable methodology. Our aim was to compare clinically relevant bleeding complications in DOAC-treated patients versus VKA patients. Hence, our heterogenous collective is representative of a usual population undergoing cardiac surgery, including the broad spectrum of cardiac procedures performed in centers today. However, some centers may not be able to measure drug levels, and larger studies are needed to further investigate the safety and efficacy of DOAC handling in cardiac surgery, as well as to find the optimal time to stop DOAC preoperatively.

Conflict of Interest Statement

Ingvild Birschmann received speaker's honoraria from Aspen Germany GmbH, Bristol-Myers Squibb/Pfizer, Siemens Healthcare, and CSL Behring and reimbursement for congress traveling and accommodation from Aspen

and Bristol-Myers Squibb and performed contract research for Siemens Healthcare. Ingvild Birschmann is a member of the advisory board of LFB biomedicaments. All other authors have nothing to disclose with regard to commercial support.

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Key Words: direct oral anticoagulation, vitamin K antagonists, cardiac surgery, chest tube drainage, perioperative management, hemorrhagic complications

ADULT

APPENDIX E1. SUPPLEMENT METHODS

Data Collection

Demographic data, preoperative and perioperative clinical data, as well as postoperative morbidity and mortality data, were obtained from a database using the cardiac surgery acquisition program, THGQIMS (Münster, Germany). Biochemical parameters were obtained from Lauris (SWISSLAB, Berlin, Germany). All preoperative blood samples were analyzed 1 day before cardiac surgery to determine hemostatic functions, DOAC plasma levels (or several times if the concentration was >30 ng/mL, see Methods section), and other biochemical parameters.

Measurement and Perioperative Procedure of Hemostatic Parameters

The measurements were performed using an ACL TOP 700 system from April 2014 to February 2016 (Instrumentation Laboratory, Munich Germany; RecombiPlasTin 2G, SynthASil), and a Sysmex CS-5100 System from March 2016 to July 2017 (Siemens Healthineers, Erlangen, Germany; Dade Innovin, Actin FS). On the day before surgery, the activated partial thromboplastin time (aPTT) time and international normalized ratio values were routinely measured, and all patients in our 3 study groups with aPTT values >37 seconds and international normalized ratio values >1.3 were excluded to prevent any other influences through out-of-range coagulation for any reason. After a change of the laboratory automation system and a change of the reagents, the cut-off of the aPTT changed to >29 seconds. This was taken into account in the evaluation of the data. Perioperative heparin management for off-pump procedures was performed using target-activated clotting times of >300 seconds, whereas >480 seconds was used for on-pump procedures. Unfractionated heparin was started 6 hours after surgery unless there were bleeding complications. Two chest tubes are routinely inserted: mediastinal and pericardial. In case of an accidentally opened pleural cavity, additional pleural tubes are inserted.

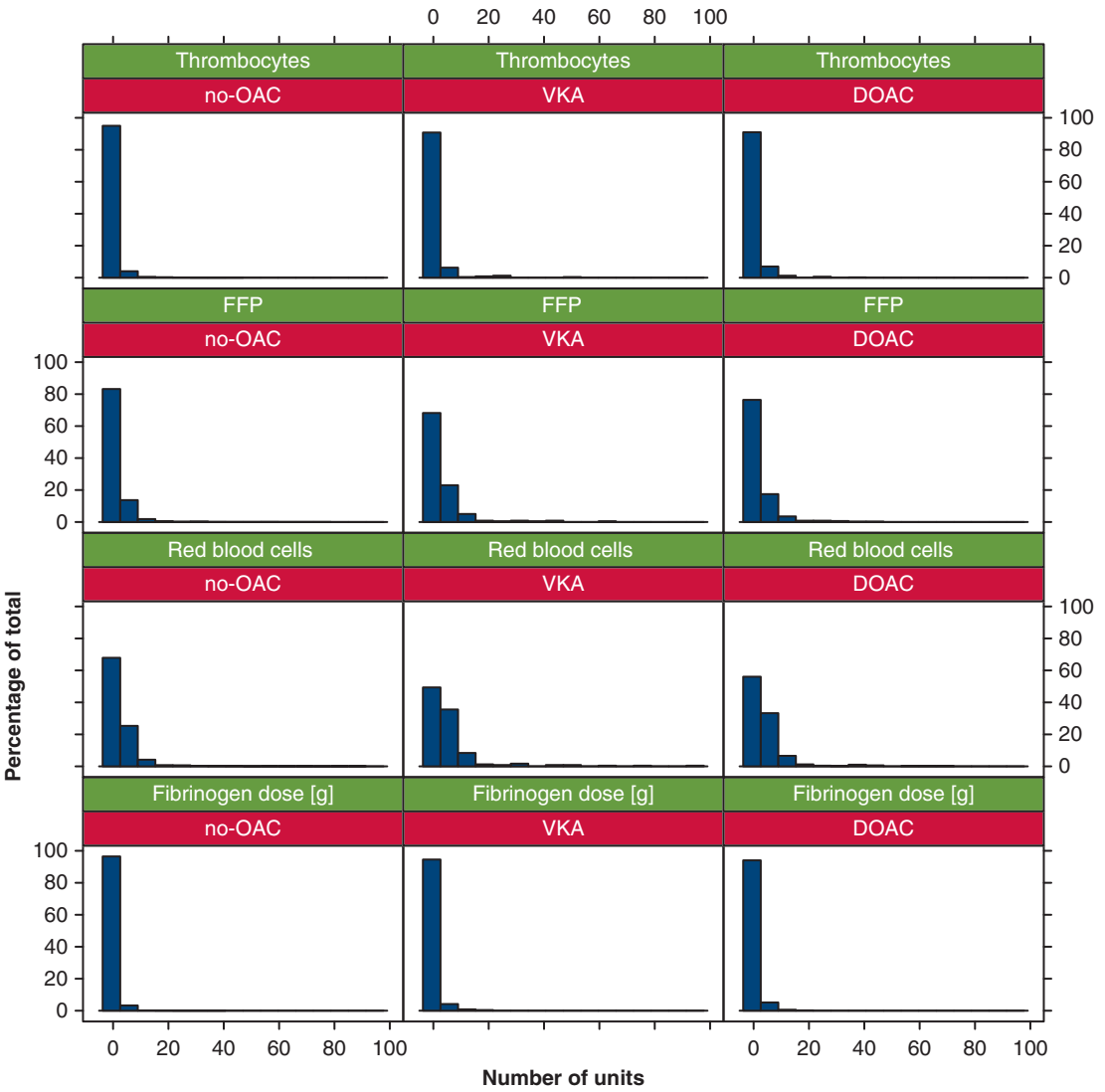

FIGURE E1. Histograms of number of units for RBC, platelets and FFP, and fibrinogen dosage. *non-OAC*, No anticoagulation; *VKA*, vitamin K antagonist; *DOAC*, direct oral anticoagulation; *FFP*, fresh-frozen plasma.