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Operative survival in patients with acute aortic disease in the era of newer oral anticoagulants

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ABSTRACT

Aims The aim of this study was the analysis of the risk associated with direct oral anticoagulants (DOACs) in patients undergoing non-elective operations on the proximal aorta due to aortic disease.

Methods and results Data from the department's register of cardiac surgery was analysed retrospectively with emphasis on operative mortality. 135 non-elective operations for proximal aortic disease (October 2016 to 2018) were identified, of which 19 died during the first 90 days. DOAC use was the top-ranked risk factor in the univariate analysis with a HR of 9.6 (3.1 to 29), p=0.00007. Using a Cox proportional hazards model including the most relevant risk factors, the risk associated with DOAC use remained significant with a HR of 6.1 (1.4 to 26.3), p=0.015. We did not find increased risk associated with warfarin use.

Conclusion In patients undergoing non-elective operations on the proximal aorta due to aortic disease, the use of DOAC is associated with increased operative mortality.

Key questions

What is already known about this subject?
► In Norway, newer direct oral anticoagulants (DOACs) have now nearly replaced warfarin in patients with need for anticoagulation. DOACs are easier to use and are supposed to be safer than warfarin. Lack of access to antidote is a concern in case of bleeding and/or acute surgery.

What does this study add?
► Our study describes increased operative mortality in DOAC users undergoing non-elective operations on the proximal aorta due to aortic disease. In DOAC users, mortality was due to bleeding-related complications. To our knowledge, this is the first study indicating negative effects of DOACs on operative survival. Even though acute aortic surgery is a frequent cardiac surgical emergency, it still remains a special situation in which coagulopathy is common, both due to the disease and the surgery performed.

How might this impact on clinical practice?
► As we report increased operative mortality in DOAC users undergoing non-elective operations on the proximal aorta due to aortic disease, risk factors for aortic dissection should be taken into consideration when prescribing anticoagulant medication.

INTRODUCTION

Bleeding is a well-known complication in cardiac surgery.[1] As most patients undergoing cardiac surgery have an indication for platelet inhibitors or anticoagulant medication, cardiac surgeons develop clinical experience with these drugs. Where previously aspirin and warfarin were the repertoire, several platelet inhibitors have now demonstrated their usefulness, and in the recent years, direct oral anticoagulants (DOACs), also referred to as non-vitamin K oral anticoagulants, have challenged warfarin as the oral anticoagulant of choice. While the effect of warfarin is influenced by diet and must be monitored by blood tests (International Normalised Ratio (INR)), the DOACs are more convenient to use, as blood tests are not needed to monitor the therapeutic effect and there are no clear diet interactions. Large clinical trials have demonstrated their effectiveness in atrial fibrillation.[2–5] In Norway, DOACs have gained popularity and, of anticoagulant users in 2018, 27% used warfarin and 73% used DOAC.[6] During the DOAC era, cardiac surgeons have recognised that these drugs are potent anticoagulants, and a need for up to 10 days withdrawal prior to cardiac surgery has been suggested.[7] To evaluate our clinical experience of bleeding-related complications in DOAC users, we explored and analysed data from the register of cardiac surgery at the Department of Cardiothoracic Surgery.

METHODS

Study design and population

Following a major revision of our department's register of cardiac surgery, the use of DOAC was registered from October 2016 onward. This register is approved by

the institutional board of ethics. Recommendation in processing personal data or health information was given by the hospital's data protection officer according to institution protocol. We analysed 2658 open cardiac operations in adults from October 2016 through 2018. Survival status was updated according to information obtained by the Norwegian National Registry. Three patients were non-residents, and for these, discharge is used as the last observation. Operative survival was defined as surviving beyond 90 days after the operation and operative survival was explored by anticoagulant/platelet inhibitor and urgency. Thus, all-cause mortality is used in the analyses. Among 527 non-elective cardiac operations in adults, surgery on the proximal aorta, thoracic transplants, valve procedures and isolated coronary artery bypass surgery were the most frequent procedures. Thoracic transplant recipients were excluded as DOACs routinely are withdrawn prior to the patients being listed for transplant. For patients undergoing urgent coronary artery bypass surgery or valve surgery, the operation is postponed for a few days to allow for withdrawal of anticoagulants or dual platelet inhibitors when considered safe. Aortic disease was the indication for most non-elective operations on the proximal aorta, followed by endocarditis. A few patients suffered from other conditions. We therefore decided to analyse the effect of DOACs in non-elective operations involving the proximal aorta (root, ascending and/or arch) due to aortic disease (International Classification of Diseases-10 I71.x).

Statistical methods

Continuous variables are presented as median (IQR). To compare continuous variables Kruskal-Wallis rank sum and Wilcoxon rank-sum tests were used. Categorical variables were compared using Pearson's χ^2 contingency table test. To perform Cox proportional hazard models, categorical variables containing more than two groups were recoded with dummy variables. We performed a careful selection of variables to identify the most relevant factors for the final multivariate analysis, as there only were 19 operative deaths in this small series. Of 59 risk factors, 20 factors had more than 30% missing values due to the urgent nature of these operations and these variables were excluded from analyses because of missingness. Of the remaining variables, 33 were more than 90% completely registered. After recoding risk factors and operation types to Boolean variables and removing one variable (postinfarctseptal rupture) that was negative for all, there were 46 different risk variables. For the survival analysis, multiple imputations were used to address missing data in the remaining variables. We also analysed the data set setting missing values to 'No', however giving the same main findings. We identified 23 variables with p value ≤0.3 in the univariate analysis. As EuroSCORE, serum creatinine and estimated glomerular filtration rate had a significant number of missing values due to conversion in the register from EuroSCORE I to II during the study period, these were among the risk factors not included in the analyses. The EuroSCORE II risk factors renal impairment, pulmonary hypertension and weight of the intervention were recoded to joint variables based on EuroSCORE I using the corresponding EuroSCORE II value (eg, 'severe' or dialysis). With LASSO (least absolute shrinkage and selection operator) regression, we identified four important risk factors (DOAC use, extracardiac

Table 1 Operative data (single platelet inhibitor or less, warfarin, DAPT or DOAC)

		Single platelet inhibitor or less	Warfarin	DAPT	DOAC	
Number of operations	n	108	8	13	6	
Ascending aortic graft	n	98	8	10	6	
Aortic root replacement	n	7	0	3	0	
Aortic arch repair	n	3	0	0	0	
Duration of operation	min	175 (70)	170 (37)	248 (50)	202 (140)	* DAPT vs warfarin/less
Extracorporeal circulation	%	100	100	100	100	
Duration of extracorporeal circulation	min	107 (68)	104 (16)	173 (67)	97 (129)	* DAPT vs warfarin/less
Duration of aortic cross clamp	min	47 (35)	44 (30)	82 (52)	61 (63)	* DAPT vs less
Deep hypothermic circulatory arrest	%	100	88	92	100	*
Duration of circulatory arrest	min	15 (6)	20 (15)	16.5 (3.75)	15 (8.75)	
Antegrade selective cerebral perfusion	%	4	12	8	0	
Duration of antegrade selective cerebral perfusion	min	81 (23)	4 (0)	23 (0)	–	
Cell saver used	%	49	25	38	75	
Intraoperative haemofiltration	%	44	25	46	83	

*p<0.05
DAPT, dual anti-platelet inhibitors; DOAC, direct oral anticoagulants .

Table 2 Risk factors by anticoagulant/platelet inhibitor use (single platelet inhibitor or less, warfarin, DAPT or DOAC)

		Single platelet inhibitor or less	Warfarin	DAPT	DOAC	
Number of operations	n	108	8	13	6	
Age	y	67 (14.2)	69.5 (14.8)	51 (22)	75.5 (6.5)	* DOAC vs DAPT
Female gender	%	44	25	8	50	
Hypercholesterolaemia	%	19	33	40	17	
Diabetes on insulin	%	1	14	0	0	
Hypertension	%	61	86	92	83	
Renal failure	%	7	29	0	0	
Chronic pulmonary disease	%	15	40	23	0	
Extracardiac arteriopathy	%	19	67	38	33	*
Poor mobility	%	19	38	23	0	*
Previous cardiac surgery	%	1	38	0	0	*
Previous myocardial infarction	%	3	43	31	0	*
Myocardial infarction previous 3 months	%	0	0	38	0	*
Prior PCI	%	5	29	33	0	*
Unstable angina	%	1	0	42	0	*
Arrhythmia	%	11	57	8	67	*
History of severe ventricular arrhythmia	%	3	0	8	0	
Permanent pacemaker/CRT	%	1	12	0	0	
Left ventricular dysfunction	%	14	50	27	0	
Pulmonary hypertension	%	3	0	0	0	
Critical preoperative state	%	64	75	85	83	
Thoracic aortic aneurysm	%	70	62	77	50	
Abdominal aortic aneurysm	%	6	29	0	17	

*p<0.05
CRT, Cardiac resynchronisation therapy ; DAPT, dual anti-platelet inhibitors; DOAC, direct oral anticoagulants ; PCI, Percutaneous coronary intervention; y, years.

Table 3 Medication at admission (single platelet inhibitor or less, warfarin, DAPT or DOAC)

		Single platelet inhibitor or less	Warfarin	DAPT	DOAC	
Number of operations	n	108	8	13	6	
DOAC	%	0	0	0	100	*
Statins	%	18	25	25	17	
Nitrates	%	6	12	8	17	
Warfarin	%	0	100	0	0	*
Heparin	%	4	25	62	0	*
Corticosteroids	%	5	14	15	0	
Calcium antagonists	%	10	38	17	50	*
Beta blockers	%	18	50	8	67	*
Angiotensin receptor blockers	%	16	25	27	50	
Aspirin	%	25	50	100	17	*
Other immunosuppressants	%	2	0	0	0	
Other platelet inhibitor than aspirin	%	2	25	100	17	*
Angiotensin-converting enzyme inhibitors	%	10	14	18	0	

*p<0.05
DAPT, dual anti-platelet inhibitors; DOAC, direct oral anticoagulants.

Table 4 Postoperative data by anticoagulant/platelet inhibitor. Patients not surviving the operation were excluded from the upper part of this table. (Single platelet inhibitor or less, warfarin, DAPT or DOAC.)

		Single platelet inhibitor or less	Warfarin	DAPT	DOAC	
Number of operations	n	107	8	13	5	
PO length of stay	days	4 (2)	4.5 (3)	7 (7)	3 (1)	
PO ICU stay	days	2 (3)	2.5 (1.75)	2 (4.5)	1 (3)	
PO ventilator >24 hour	%	23	25	23	50	
PO reintubated	%	6	0	0	20	
PO renal replacement therapy	%	4	0	15	0	
PO circulatory support	%	0	0	8	0	
PO bleeding	ml	660 (990)	615 (550)	820 (870)	820 (3246)	
Any transfusion	%	96	100	92	100	
erythrocytes	units	3 (4.75)	2 (2)	5 (4)	19 (21)	
plasma	units	5 (5.75)	2.5 (3.25)	5 (4)	12 (20)	* DOAC vs warfarin
thrombocytes	units	1 (1)	1 (1.25)	1 (3)	4 (6)	
PO autotransfusion	%	32	38	15	75	
PO autotransfusion	ml	0 (450)	0 (518)	0 (0)	591 (521)	
PO nitrous oxide	%	0	0	0	0	
PO pulmonary artery catheter	%	0	0	0	20	*
PO superficial infection	%	1	0	0	0	
PO pneumonia	%	9	12	15	20	
PO other infection	%	4	12	0	0	
PO mediastinitis	%	1	0	0	0	
PO inotropic support	%	10	38	42	20	*
PO sternal dehiscence	%	0	0	0	0	
PO revision for bleeding	%	9	12	15	60	*
PO CPR	%	4	12	0	0	
PO septicaemia	%	1	0	8	0	
PO arrhythmia	%	24	50	33	40	
PO pacemaker >24 hour	%	4	0	8	0	
PO new chest tube	%	2	12	0	25	*
PO myocardial infarction	%	1	0	0	0	
PO stroke	%	9	25	15	0	
PO paraparesis	%	4	0	8	0	
PO other reoperation	%	5	0	38	20	*
PO failure in other organs	%	8	0	15	0	
PO delayed cardiac tamponade	%	3	12	8	40	*
PO return to ICU	%	7	0	0	0	
PO pressure ulcer	%	0	0	0	0	
PO mobilised <24 hour	%	70	50	54	40	
n		108	8	13	6	
PO in-department mortality	%	2	25	8	33	*
30 days mortality	%	8	25	8	67	*

*p<0.05

CPR, Cardiopulmonary resuscitation; DAPT, dual anti-platelet inhibitors; DOAC, direct oral anticoagulants ; ICU, intensive care unit; PO, postoperative.

Table 5 Univariate Cox analysis

	HR (95% CI for HR)	P value
DOAC use	9.6 (3.1 to 29)	0.000069
Extracardiac arteriopathy	6.9 (2.6 to 18)	0.000097
Abdominal aneurysm	5 (1.9 to 13)	0.0011
Angiotensin II receptor blocker use	4.3 (1.7 to 11)	0.0015
Arrhythmia	4.1 (1.7 to 10)	0.0023
Diabetes on insulin	3.6 (0.84 to 16)	0.084
Previous PCI	3.2 (1.2 to 9)	0.025
Heparin use	3.2 (1.2 to 8.9)	0.026
Calicium antagonist use	2.9 (1.1 to 7.6)	0.031
Other platelet inhibiting drugs	3.1 (1.2 to 8.1)	0.023
History of severe ventricular arrhythmia	3.1 (1.2 to 8.1)	0.023
ACE inhibitor use	2.5 (0.83 to 7.6)	0.1
Recent myocardial infarction	2.5 (0.82 to 7.4)	0.11
Previous myocardial infarction	2.2 (0.79 to 6.1)	0.13
Diabetes without insulin	2.1 (0.61 to 7.2)	0.24
Chronic pulmonary disease	2.1 (0.78 to 5.4)	0.15
Thoracic aneurysm	1.9 (0.65 to 5.9)	0.24
Critical preoperative state	2 (0.65 to 5.9)	0.23
Nitrate use	1.9 (0.56 to 6.6)	0.3
Renal failure	1.9 (0.64 to 5.8)	0.24
Hypertension	1.8 (0.67 to 5.1)	0.24
Beta blocker use	1.7 (0.64 to 4.5)	0.29
Age	1 (0.99 to 1.1)	0.15

DOAC, direct oral anticoagulants ; PCI, Percutaneous coronary intervention.

arteriopathy, angiotensin II receptor blocker use and abdominal aortic aneurysm). We then included these risk factors and age, as DOAC users seemed a bit older, as well as warfarin use (for comparison), in a Cox proportional hazards model. The proportional hazards assumption was tested for each covariate. We also performed a Cox proportional hazards model with stepwise algorithm, including the risk factors identified in the univariate analysis as covariates. This resulted in higher HR and wider CI, but the same main finding. In this analysis, DOAC use, diabetes requiring insulin, history of severe ventricular arrhythmia, use of other platelet inhibitors than aspirin and angiotensin II receptor blocker use were considered to be the most important factors. RStudio was used for the statistical analyses (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc, Boston, Massachusetts; URL: http://www.rstudio.com/).

RESULTS
A total of 135 non-elective operations on the proximal aorta for aortic disease were identified. The indication for surgery was aortic dissection in 126 and aneurysm in 9. In three operations, the aortic arch was repaired and in 10 the root was replaced. In the remaining 122 the ascending aorta was replaced with a supracoronary graft or hemi-arch procedure and in one of these, the aortic valve was also replaced (table 1). Patients using DOAC were older and patients using DOAC or warfarin more frequently had a history of cardiac arrhythmias (table 2).

In the DOAC group, 30-day mortality rate was 67% versus 9% in patients not using DOAC. All deaths among the DOAC-treated patients were bleeding related, while this was not the case in any of the other groups. Medication at admission is shown in table 3. Postoperative data are affected by early and intraoperative mortality, especially in the DOAC-treated patients where one out of five died only a few hours postoperatively (table 4). The two patients that died intraoperatively (one DOAC user and one patient using neither platelet inhibitors nor anticoagulants) are not included in the table demonstrating the postoperative observations. History of myocardial infarction and previous PCI were more common among warfarin users and in patients using dual anti-platelet inhibitors (DAPT), while DAPT users had a higher incidence of myocardial infarction during the last 3 months.

Five patients used both platelet inhibitors and anticoagulation. Among the DAPT users, there was one patient using DOAC and two patients using warfarin additionally. Two patients used aspirin in addition to warfarin. Of these five, only two of the patients survived; one was using warfarin and aspirin, and the other was using warfarin and DAPT. These patients are allocated to the respective anticoagulant group in the tables.

Thirty-eight per cent of warfarin users had previously been operated via sternotomy, vs 0.8% of patients not using warfarin (table 2). A significant number of DOAC users were reoperated due to bleeding compared with patients not using DOAC. In addition, more DOAC users were treated for late cardiac tamponade and the number of transfusions was higher (table 4).

Survival analyses
In the univariate analysis, DOAC use had the highest HR of 9.6 (3.1 to 29), p=0.00007 (table 5).

Crude survival for DOAC users and warfarin users are presented in figure 1. For the final Cox proportional hazards model age was included, as patients using DOAC were older, and warfarin use was included for comparison, in addition to the four variables identified by LASSO regression (figure 2). DOAC use was also in the multivariate analysis highly significant with a hazard rate of 6.1 (1.4 to 26.4), p=0.015. Warfarin use was not associated with increased operative mortality, neither in the univariate (HR 2.1 (0.49 to 9.1), p=0.32) nor in the multivariate (HR 1.9 (0.4 to 9.0), p=0.42) analyses. Adjusted survival curves for DOAC users and warfarin users are presented in figure 3. We also performed a multivariate analysis using the variables identified in the univariate analysis (table 5). In this model, extracardiac arteriopathy, chronic pulmonary disease and critical preoperative state
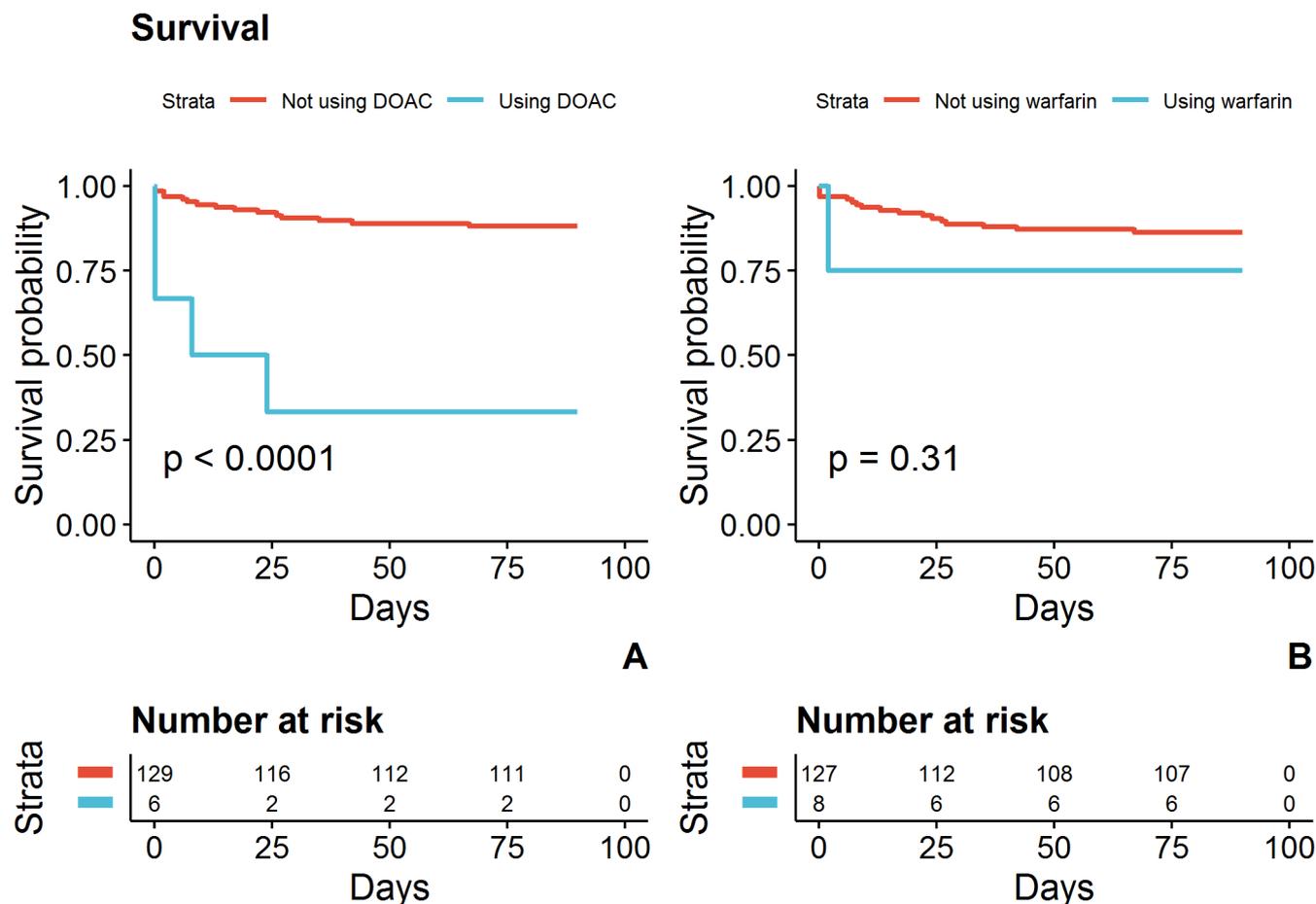
Figure 1 Unadjusted operative survival for patients using DOAC versus patients not using DOAC (A). Unadjusted operative survival for patients using warfarin versus patients not using warfarin (B). DOAC, direct oral anticoagulants.

did not meet the assumption of proportional hazards and were not included in this analysis. The analysis gave the same main finding and the results are presented in the supplement (online supplementary figure 1). We then reduced the number of covariates by stepwise selection and created a Cox model using these covariates as well as warfarin and age, and this analysis gave principally the same results as the model based on the LASSO regression. The results and are presented in the supplement (online supplementary figure 2).

DISCUSSION
Following the increased use of DOACs, we have gained experience in operating patients using these anticoagulants. In this study, including non-elective operations on the proximal aorta due to aortic disease, there was a striking and significant increase in operative mortality in DOAC users and all deaths among the DOAC treated patients were bleeding related. For dabigatran (factor IIa inhibitor), an antidote (idarucizumab) is now available, but for the factor Xa inhibitors (apixaban, rivaroxaban and edoxaban), the antidote (andexanet alfa) is not yet approved in Norway, and is not available to us. Hence, especially in the setting of acute cardiac surgery,

DOAC use has been cumbersome, as withdrawal is not an option. To analyse this clinical impression, we explored the department's quality register and identified non-elective surgery on the proximal aorta to be associated with obvious increased operative mortality. To study this effect, we performed univariate and multivariate analyses. We found the hazard rate associated with DOAC use to be significantly increased, while this was not found for warfarin.

The DOACs have gained popularity and are now the most used anticoagulants in Norway. Thus, the number of DOAC users requiring acute cardiac surgery is also likely to increase. As only 8% use dabigatran, we have yet to gain experience with the dabigatran antidote. Apixaban is the most used anticoagulant in Norway and even though plasma level analyses are available at our institution, there are no clear guidelines as to what levels would be considered therapeutic. Furthermore, as andexanet alfa may have effects on antithrombin mediated anticoagulation,[8] the safety of andexanet alfa in open heart surgery requiring full-heparinisation remains to be demonstrated. In recent cases, we have used activated recombinant coagulation factors to reduce bleeding complications in DOAC users undergoing acute cardiac
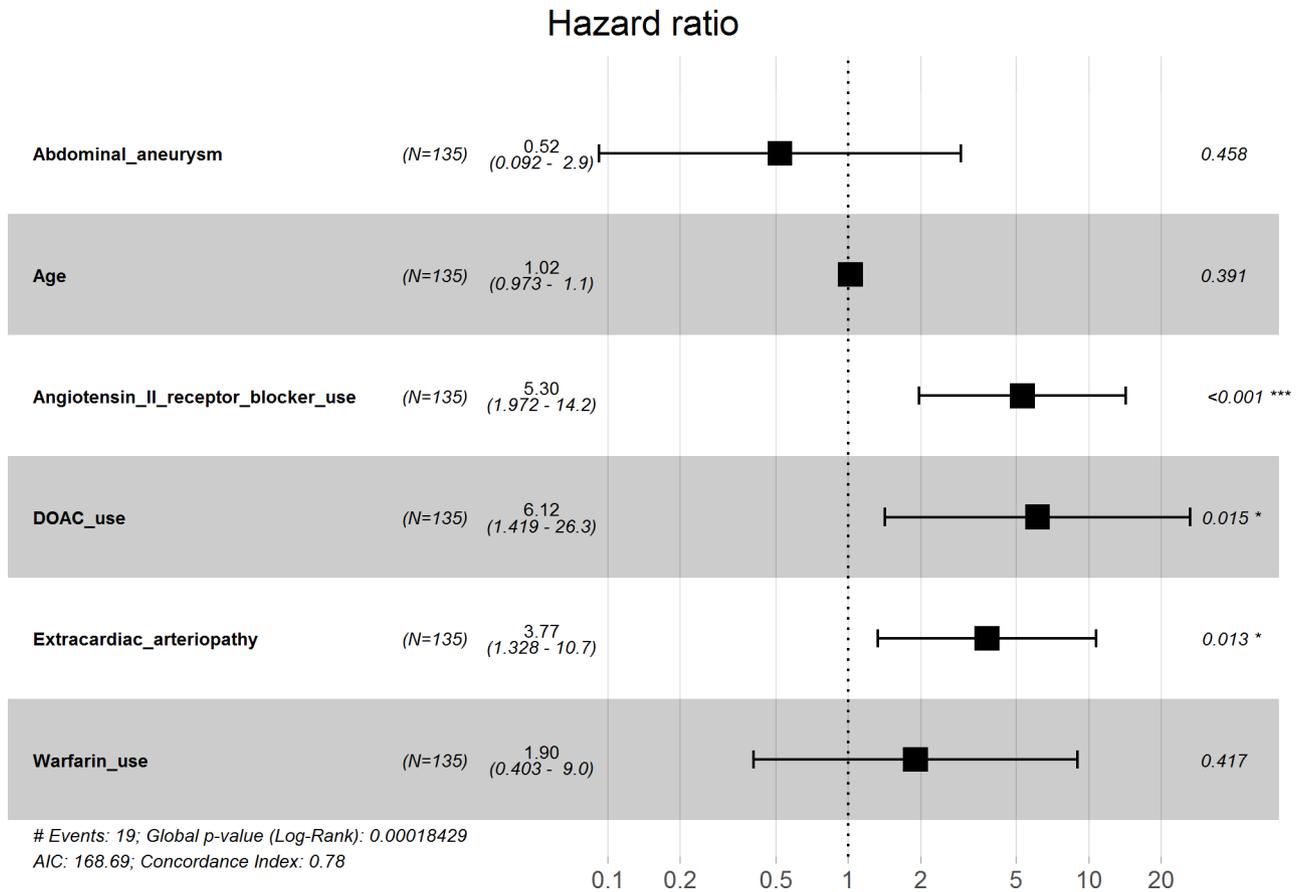
Figure 2 Forest plot from the final multivariate model. DOAC, direct oralanticoagulants. *p<0.05, ***p<0.001

surgery. We have also postponed surgery to allow for DOAC withdrawal in haemodynamically stable patients. DOACs are routinely withdrawn 5 days prior to elective surgery in our department. Even though our experience with this strategy is promising, the risk of inducing thromboembolic events or allowing for critical complications,
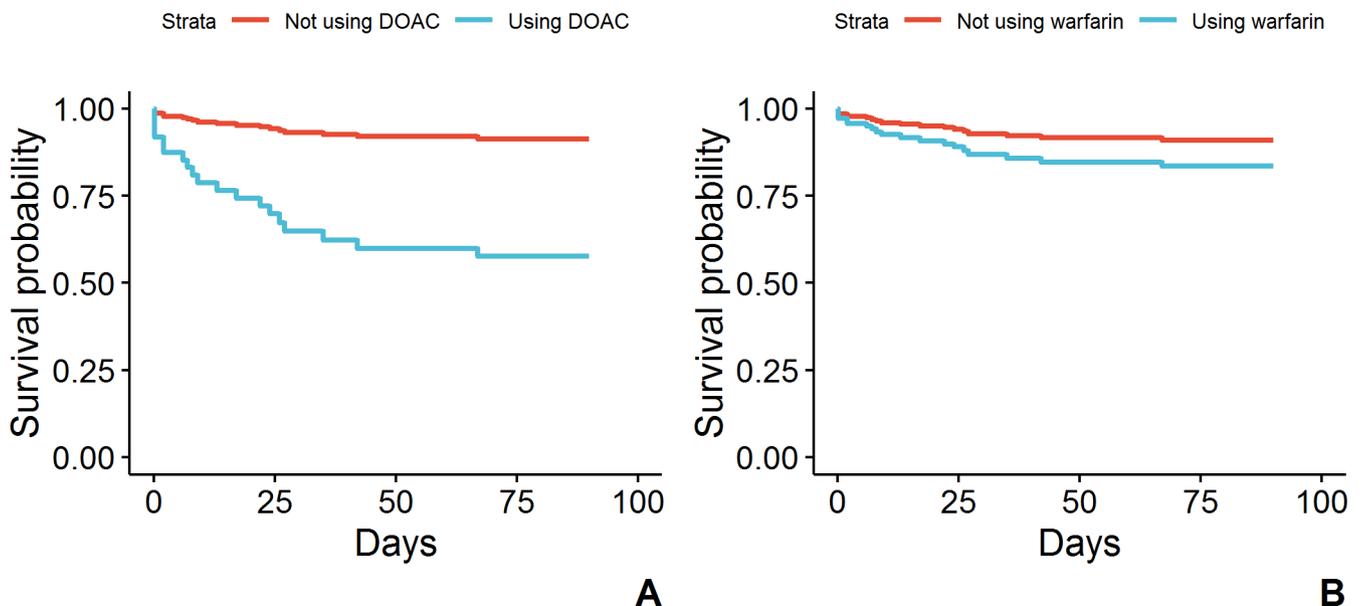
Figure 3 Adjusted operative survival for patients using DOAC versus patients not using DOAC (A). Adjusted operative survival for patients using warfarin versus patients not using warfarin (B). DOAC, direct oralanticoagulants.

such as cardiac tamponade, to develop before surgery is of concern.

In this study, we did not find any increased risk associated with warfarin use. The anticoagulant effect of warfarin can and should be measured by INR and may be corrected using vitamin K or, in case of excess bleeding, by recombinant coagulation factors or plasma. This makes warfarin an easier drug to handle for the surgeons. In this study, three out of eight of the patients using warfarin were operated after already having undergone sternotomy; however, previous sternotomy was not a risk factor in our study as all four patients with previous sternotomy survived. Warfarin treatment needs to be monitored by INR and the dose adjusted accordingly. Hence, warfarin treatment is a skill and loss of experience in dosing warfarin may diminish the warfarin treatment skills. Traditionally, warfarin treatment in Norway has been safe due to the organising of primary care and reimbursements for INR controls. In recent years, the option of INR self-testing is more widely available due to new reimbursement rules.[9] Home monitoring of INR has gained popularity, especially among younger patients.

In addition to DOACs, angiotensin II receptor blockers were in all analyses associated with increased operative risk. This medicine may be used because of hypertension, heart failure or both and 18% of the patients were registered as users of angiotensin II receptor blockers. Most patients in this material had hypertension registered as a risk factor, with 86% of warfarin users and 83% of DOAC users scored in the register. Angiotensin II receptor blockers are potent drugs, but we can, in this study, not suggest whether the increased risk is due to the drug itself or to the disease indicating the use of angiotensin II receptor blockers. However, the finding of increased risk associated with DOAC use was the only significant risk factor when performing multivariate analysis on the 20 factors identified in the univariate analysis (online supplementary figure 1).

In our material, proximal aortic surgery was the most frequent true emergency, as thoracic transplants are carefully screened and closely followed prior to transplant. Endocarditis or acute coronary syndromes are treated on an urgent basis, but the condition may allow a few days postponement to withdraw anticoagulants before surgery. Surgery for type A aortic dissections may be a special circumstance with respect to anticoagulants, as activation of the coagulation cascade inevitably occurs due to the disease. The operation requires full heparinisation and usually deep hypothermic circulatory arrest; hence, coagulopathy is a common clinical situation. However, the obvious difference in survival, revision for bleeding, and the trends for transfusions between warfarin and DOACs should warrant concern, especially in the case of type A aortic dissection. A German study of 81 consecutive patients undergoing open-heart surgery recently described effects of the DOAC withdrawal interval on postoperative bleeding, re-thoracotomy and intensive care unit stay, and recommended a need for up to 10 days withdrawal prior to cardiac surgery, in particular for patients with reduced renal function.[7] In patients using rivaroxaban or ticagrelor, the same group has also described promising effects of CytoSorb®, a whole blood adsorber for extracorporeal purification of blood that may be used with a heart-lung machine during cardiac surgery.[10] In another recent German study, warfarin use in patients surviving acute type A aortic dissection was not related to late mortality or aortic growth.[11]

Aortic dissection is not a very common disease, but it is a frequent surgical emergency in a cardiothoracic surgical department. In our region with 3 million inhabitants, 50 to 60 patients are operated for acute type A aortic dissection annually.

This study has several limitations. As an open label, non-randomised retrospective study of 135 cases, of which only six used DOAC, a firm conclusion cannot be drawn. On a yearly basis, our department treats a fair amount of aortic dissections. High volumes makes it possible to identify adverse effects observed as changes in practice for adjoining therapies occur, as for anticoagulant use in our study. Such observations require high volumes and may be difficult to identify within a reasonable time period. Thus, our caseload of aortic dissections is a strength. Hence, this study may highlight the possibility of catastrophic bleeding in patients using anticoagulants without an antidote available.

CONCLUSION

We report increased operative mortality in DOAC users undergoing non-elective operations on the proximal aorta due to aortic disease. In DOAC users, all deaths were due to bleeding-related complications. Hence, risk factors for aortic dissection, such as enlarged ascending aorta, family history, coarctation of the aorta, severe hypertension and aortic insufficiency, should be taken into consideration when prescribing anticoagulant medication.[12 13]

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