RESEARCH LETTER

Safety of minimally invasive procedures in patients with lung diseases treated with non–vitamin K antagonist oral anticoagulants: a single-center case series

Sabina Wołoch[1], Joanna Kurnik[1], Artur Szlubowski[2], Maciej Gnass[2], Marek Koprowski[1], Anetta Undas[1,3,4]

1 Department of Civilization Diseases and Pulmonary Diseases, John Paul II Hospital, Kraków, Poland
2 Endoscopy Unit, John Paul II Hospital, Kraków, Poland
3 Department of Experimental Cardiac Surgery, Anesthesiology, and Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
4 Krakow Center for Medical Research and Technologies, John Paul II Hospital, Kraków, Poland

Introduction Direct oral anticoagulants (DOACs) are commonly used in the prevention of stroke associated with atrial fibrillation as well as in the prevention and treatment of venous thromboembolism. The effectiveness of DOACs is similar or even higher than that of vitamin K antagonists, with adequate safety and convenient administration.[1,2] The use of all anticoagulants is associated with increased risk of bleeding, including that observed after invasive procedures. It is recommended to take the last dose of a DOAC 24 hours before the elective procedure with a low bleeding risk in patients with normal kidney function. In patients on dabigatran and with a creatinine clearance (CrCl) of less than 80 ml/min, graded interruption should be considered. Similarly, in patients taking a FXa inhibitor (eg, rivaroxaban or apixaban) and with a CrCl of 15 to 29 ml/min, the last DOAC dose should be taken 36 hours or more before surgery. Before invasive procedures with high bleeding risk it is recommended that the last DOAC dose should be taken 48 hours or more before surgery.[3]

Douketis et al[4] confirmed in 2019 that the standardized perioperative management approach depending on bleeding risk related to the procedure, type of DOAC, and CrCl, is safe. They reported the rate of major bleeding of less than 2% and thromboembolic risk of less than 1%, without heparin bridging or perioperative coagulation function testing.[4] Little is known about the safety of such a strategy in real-life patients with lung diseases undergoing invasive procedures, such as standard bronchoscopy, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), or pleural puncture.

Our objective was to investigate the risk of bleeding in DOAC-treated patients with lung diseases qualified to invasive procedures in association with preprocedural DOAC measurements.

Patients and methods This was a retrospective case series of consecutive hospitalized patients with lung diseases who received a DOAC on a long-term basis and underwent invasive procedures at the Department of Civilization Diseases and Pulmonary Diseases, John Paul II Hospital, Kraków, Poland, between January and April 2021. The total number of procedures performed in this period was: 159 EBUS, 129 bronchoscopies, and 32 pleural punctures. The inclusion criteria were: age of 18 years or more, declared use of apixaban, rivaroxaban, or dabigatran for at least one month, and the consent to undergo an invasive procedure. We excluded patients who stopped anticoagulation for more than 96 hours prior to the procedure. Definitions of comorbidities were provided previously.[5]

In accordance with the current recommendations and the approach published by Douketis et al,[4] we developed a protocol based on the CrCl value and the risk of bleeding according to the summaries of product characteristics. We stopped rivaroxaban and apixaban 48 hours before the procedure if CrCl was greater than 30 ml/min and 72 to 96 hours if CrCl was

Correspondence to:
Marek Koprowski, MD, PhD, Department of Civilization Diseases and Pulmonary Diseases, John Paul II Hospital, ul. Prądnicka 80, 31-202 Kraków, Poland, phone: +48 12 614 35 20, email: marek.koprowski@kopalnia.pl
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TABLE 1 Patients with lung diseases undergoing invasive procedures: comparison depending on preprocedural direct oral anticoagulant concentrations

Variable			Concentration <30 ng/ml	Concentration >30 ng/ml	*P* value
Total			14 (73.7)	5 (26.3)	–
Age, y, mean (SD)			73.6 (6.1)	72.2 (3.4)	0.64
Men			8 (57.1)	2 (40)	0.63
BMI, kg/m^2, mean (SD)			28.36 (4.94)	26.40 (4.39)	0.45
Indication for the use of DOAC		Atrial fibrillation/AFL	11 (78.6)	5 (100)	–
		Venous thromboembolism	1 (7.1)	0	
		Other	2 (14.3)	0	
CHA_2DS_2VASc			4 (3–4)	4 (4–5)	0.44
HAS-BLED			2.5 (2–3)	3 (1–3)	0.81
Congestive heart failure			2 (14.3)	0	0.53
Arterial hypertension			11 (78.6)	4 (80)	0.73
Diabetes mellitus			1 (7.1)	2 (40)	0.16
Prior stroke/transient ischemic attack			4 (28.6)	0	–
Prior hemorrhagic stroke			2 (14.3)	0	–
Peripheral arterial disease			5 (35.7)	0	–
Creatinine, μmol/l			80 (75–93)	95 (89–110)	0.19
GFR, ml/min/1.73 m^2			70.5 (68–77)	57 (50–58)	0.11
GFR ≤50 ml/min/1.73 m^2			1 (7.1)	1 (20)	0.47
Platelet count, × 10^3/μl			231.5 (189–286)	279 (187–384)	0.55
Patients receiving ASA			1 (7.1)	0	–
Type of DOAC		Rivaroxaban	10 (71.4)	0	–
		Dabigatran	3 (21.4)	3 (60)	0.26
		Apixaban	1 (7.1)	1 (20)	0.47
DOAC dose		Full dose	10 (71.4)	2 (40)	0.31
		Reduced dose	4 (28.6)	3 (60)	
Time since last dose, h, mean (SD)			59.5 (18.8)	51.8 (16.9)	0.43
Hemorrhagic complications		Minor bleeding	2 (14.3)	1 (20)	0.81
		Clinical relevant nonmajor bleeding	1 (7.1)	0	
Procedure	Pleural puncture		1 (7.1)	1 (20)	–
	EBUS	Without TBNA	1 (7.1)	0	
		With TBNA	7 (50)	0	
	Bronchoscopy	Without EBB	4 (28.6)	3 (60)	
		With EBB	1 (7.1)	1 (20)	

Data are expressed as median (interquartile range) or number (percentage) unless otherwise indicated.

Abbreviations: AFL, atrial flutter; ASA, acetylsalicylic acid; BMI, body mass index; DOAC, direct oral anticoagulants; EBB, endobronchial biopsy; EBUS, endobronchial ultrasound; GFR, glomerular filtration rate; TBNA, transbronchial needle aspiration

less than 30 ml/min. Dabigatran was stopped 48 hours before the procedure in patients with ClCr greater than 50 ml/min, 96 hours if ClCr was 30 to 50 ml/min, and 6 days if CrCl was less than 30 ml/min.

On the day of the procedure, we measured the DOAC concentration and the value of less than 50 ng/ml was arbitrarily set as a cutoff point for safe performance of an invasive procedure. In patients with higher values, the decision was taken on an individual basis.

Apixaban and rivaroxaban concentrations were measured using a chromogenic assay (HYPHEN BioMed, Neuville-sur-Oise, France).[6] The dabigatran concentration was measured using a clotting method based on the inhibition of a constant and defined concentration of thrombin (Siemens, Marburg, Germany).[7] Measurement of the DOAC levels on the 24/7 basis has been available at our hospital for more than 6 years.[8]

The risk of postprocedural hemorrhagic complications was estimated as low in the case of thoracentesis, EBUS-TBNA, and bronchoscopy without biopsy, and as intermediate for bronchoscopy with endobronchial biopsy, according to Abuqayyas et al[9] and Ault et al.[10]

Statistical analysis Data were analyzed with STATISTICA 13.5 (Statsoft, Tulsa, Oklahoma, United States). Continuous data are presented as means (SDs) or medians and interquartile ranges, as appropriate. The distribution was assessed using skewness and kurtosis analysis. Qualitative data were analyzed using the Fisher exact test.

Quantitative data were analyzed with the *t* test or the Mann–Whitney test. A *P* value of less than 0.05 was considered statistically significant. This was a retrospective study, and therefore, it did not require the approval of a bioethics committee.

Results We enrolled 19 patients (5.9% of patients undergoing the procedures over the period of 4 months), aged 73 (5) years, including 10 men (53%). The reasons for therapy with DOAC were as follows: 16 patients (84.2%) had atrial fibrillation, 1 patient (5.3%) following venous thromboembolism, and 2 patients (10.5%) were treated for other causes (intracardiac thrombi). Eleven patients (57.9%) received rivaroxaban, 6 (31.6%) dabigatran, and 2 (10.5%) apixaban. The number of patients with glomerular filtration rate of 59 ml/min/1.73 m^2 or less was 6 (31.6%); none of them had stage G4 chronic kidney disease.

The range of preprocedural DOAC concentrations was 0 to 54 ng/ml. In 5 patients (26.3%), drug concentration was greater than 30 ng/ml, in one case (5.3%) it was greater than 50 ng/ml. We performed 2 therapeutic pleural punctures, 7 EBUS-TBNA, 1 EBUS without TBNA, 2 bronchoscopies with conventional endobronchial biopsy due to suspected lung cancer, and 7 bronchoscopies with the sole purpose of microbiological diagnostics.

The percentage of all endoscopic procedures with biopsy followed by hemorrhagic complications (ie, 2 bronchoscopies with endobronchial biopsy and 7 EBUS-TBNA procedures) was 44.4%. No major bleeding events were observed (**TABLE 1**).

Discussion The present study shows that typical invasive diagnostic procedures performed in patients with lung disease who were treated with DOACs could be performed using the recommended protocol, which states that 24 to 48 hours since the last dose of the anticoagulant without any bridging with heparin, are sufficient. In line with the study by Douketis et al,[4] we observed low DOAC concentrations prior to the procedure without association between the DOAC levels and mostly minor bleeding events. In the study by Douketis et al,[4] there were no patients undergoing invasive diagnostic procedures, and therefore, this report provided additional evidence for the safety of the assessed protocol.

We did not observe major bleeding complications and only a single clinically relevant hemorrhagic complication. The present study confirms that DOACs could be stopped prior to the invasive diagnostic procedure without DOAC measurement or heparin bridging which has been demonstrated to increase risk of bleeding without any impact on thromboembolic risk.

The study has several limitations. A retrospective study performed in a small sample of patients requires confirmation in a larger patient group. We were not able to assess risk factors for hemorrhagic events and our findings cannot be easily extrapolated to patients with advanced chronic kidney disease, those receiving antiplatelet agents concomitantly or those with thrombocytopenia, who are known to be at increased bleeding risk.[8,11] As expected, bronchoscopic procedures without biopsy (used mostly for microbiological diagnostics) were not complicated with bleeding. This may suggest that continuation of NOACs during such procedures will not increase the risk of bleeding nor that of thromboembolic events.

In conclusion, we provided real-life data supporting the strategy of DOAC withdrawal prior to invasive procedures performed in patients with lung diseases.

ARTICLE INFORMATION

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