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BRIEF COMMUNICATION

Oral anticoagulants (NOAC and VKA) in chronic thromboembolic pulmonary hypertension

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EXPERT was an international, multicenter, prospective, uncontrolled, non-interventional cohort study in patients with pulmonary hypertension treated with riociguat. Patients were followed for 1−4 years, and the primary outcomes were adverse events (AEs) and serious AEs (SAEs), including embolic/thrombotic and hemorrhagic events. Here we report data on patients with chronic thromboembolic pulmonary hypertension (CTEPH) receiving a vitamin K antagonist (VKA; n = 683) or a non-vitamin K antagonist oral anticoagulant (NOAC; n = 198) at baseline. AEs and SAEs were reported in 438 patients (64.1%) and 257 patients (37.6%), respectively, in the VKA group, and in 135 patients (68.2%) and 74 patients (37.4%) in the NOAC group. Exposure-adjusted hemorrhagic event rates were similar in the two groups, while exposure-adjusted embolic and/or thrombotic event rates were higher in the NOAC group, although the numbers of events were small. Further studies are required to determine the long-term effects of anticoagulation strategies in CTEPH.

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Lifelong anticoagulation is recommended for patients with chronic thromboembolic pulmonary hypertension (CTEPH).[1,2] Vitamin K antagonists (VKAs) have traditionally been used, but are limited by food and drug interactions, need for frequent monitoring, and bleeding risk.[3,4] Non-vitamin K antagonist oral anticoagulants (NOACs) were developed to overcome some of these limitations, but few data have been published in CTEPH. The EXPosurE Registry RiociguaT in patients with pulmonary hypertension (EXPERT) was an international, prospective, non-interventional registry to monitor the long-term safety of riociguat in clinical practice.[5,6] The objective of the current study was to compare the safety of NOACs with VKAs, particularly regarding hemorrhagic and embolic/thrombotic events, in patients with CTEPH in EXPERT.

EXPERT ran from May 2014 to March 2018 as described previously.[5,6] Patients were followed for 1−4 years from enrollment or until 30 days after stopping riociguat, with data collected approximately every 3−6 months. The primary safety outcomes were adverse events (AEs) and serious adverse events (SAEs). Data were also captured on anticoagulant use and safety, including embolic and/or thrombotic and hemorrhagic events. Details of methods are shown in the Supplementary Material (online). EXPERT was conducted in accordance with good pharmacovigilance practices. Protocol approvals were obtained from independent ethics committees or institutional review boards at all participating centers. Informed written consent was obtained from all patients.

Of 956 patients with CTEPH, 198 (20.7%) were receiving a NOAC at baseline (rivaroxaban, n = 164; apixaban, n = 23; dabigatran, n = 10; edoxaban, n = 1) and 683 (71.4%) were receiving a VKA (warfarin, n = 269; phenprocoumon, n = 237; acenocoumarol, n = 177). Another 27 patients (2.8%) were receiving unfractionated heparin or low-molecular-weight heparin, and 48 (5.0%) had no reported anticoagulation. The present analysis included only patients receiving VKA or NOACs at baseline. In total, 87.6% and 82.3% of patients receiving concomitant VKAs and NOACs, respectively, completed the study (Figure S1).

Baseline characteristics are shown in Table 1. Mean disease duration was shorter in the NOAC group, the distribution of disease types differed significantly between the groups, and riociguat monotherapy was less common in the VKA group. Comorbidities are shown in Table S1.

Median (range) duration of observation was 532 (0−1,367) days in the VKA group and 465 (0−1,344) days in the NOAC group. Discontinuation of anticoagulation was recorded in 48 (7.0%) patients in the VKA group and 30 patients (15.2%) in the NOAC group. In the VKA group, approximately 50%−55% of patients with data available were in the therapeutic range for international normalized ratio (INR) (2−3) (Table S2).

"General" AEs were reported in 438 patients (64.1%) in the VKA group and in 135 patients (68.2%) in the NOAC group, and SAEs in 257 patients (37.6%) and 74 patients (37.4%), respectively. The most common AEs are listed in Table S3.

Absolute rates of hemorrhagic and embolic/thrombotic events, numbers of events, and exposure-adjusted rates are shown in Table 2.

Absolute rates of both type of event were comparable in the two groups. Exposure-adjusted bleeding rates were similar in the two groups, while exposure-adjusted rate of embolic and/or thrombotic events was higher with NOACs than with VKAs. Demographics and disease characteristics of patients who experienced hemorrhagic or embolic/thrombotic events (Table S5) showed no clear differences from the overall populations.

When AEs reported after discontinuation of VKAs or NOACs were excluded (Table S4), the absolute event rates were similar to the main analysis. Safety results for patients receiving no anticoagulation at baseline are presented in Table S6.

In both groups, the most common hemorrhagic events were epistaxis and hemoptysis, and the most common embolic and/or thrombotic event was pulmonary embolism (Table 3). Serious hemoptysis was more common in the VKA group than the NOAC group. No hemorrhagic or embolic/thrombotic events were reported in patients with antiphospholipid syndrome in either group.

Estimated Kaplan−Meier survival rates (95% confidence interval) at 1, 2, and 3 years were 95% (91−98), 90% (82−94), and 80% (65−89) in the NOAC group and 95% (92−96), 85% (81−88%), and 80% (74−85) in the VKA group (Figure S2).

AEs reported during the acute post-procedural phase of pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty are described in the Supplementary Material.

NOACs are not currently recommended for patients with CTEPH.[2] It is not clear why so many patients received NOACs in our study, but increasing use of these agents has also been reported elsewhere.[7,8] This may reflect the recommendation for NOACs in pulmonary embolism guidelines.[9] Other studies in CTEPH have reported similar or lower bleeding rates with NOACs than with VKAs, while results for venous thromboembolism recurrence have been inconsistent.[7,10,11] Our results show similar absolute and exposure-adjusted rates of hemorrhagic events with VKAs and NOACs, while exposure-adjusted rates of embolic and/or thrombotic events were higher with NOACs. However, the numbers of events were small and the excess of embolic and/or thrombotic events could be a chance observation or related to differences in baseline characteristics between the 2 groups. Questions regarding the use of NOACs in CTEPH have been reviewed elsewhere.[8]

The higher rate of discontinuation of NOACs (15.2%) versus VKAs (7.0%) in the current study may have contributed to the excess of embolic and/or thrombotic events. Renal function (Table 1), concomitant diseases (Table S1), and use of pulmonary hypertension-approved therapies (Table 1) were similar in the 2 groups; it therefore seems unlikely that the differences in outcomes were related to preference for VKAs in patients with renal impairment, or to imbalances in concomitant diseases or use of pulmonary hypertension-approved therapies. These questions are discussed further in the Supplementary Material.

Table 1 Baseline Demographics and Disease Characteristics in the VKA and NOAC Groups

	VKA group (n = 683)	NOAC group (n = 198)	p value[a]
Age, years	66.5±13.6 [69.0; 58, 77]	66.0±14.5 [69.5; 56, 78]	0.924
Age group, years			0.836
<65	260 (38.1)	72 (36.4)	
65 to <75	186 (27.2)	58 (29.3)	
≥75	237 (34.7)	68 (34.3)	
Female sex	404 (59.2)	123 (62.1)	0.453
BMI, kg/m^2	28.9±17.5 [27.0; 24, 30.7]	28.0±6.6 [27.1; 23.9, 31.1]	0.890
Smoking status			0.075
Never	421 (61.6)	134 (67.7)	
Former	237 (34.7)	53 (26.8)	
Current	25 (3.7)	11 (5.6)	
CTEPH type			0.033
Inoperable	306 (44.8)	87 (43.9)	
Persistent PH following PEA	164 (24.0)	36 (18.2)	
Persistent PH following BPA	13 (1.9)	11 (5.6)	
Other[b]	161 (23.6)	50 (25.3)	
Missing	39 (5.7)	14 (7.1)	
Disease duration of initial CTEPH diagnosis, years	3.9±4.2 [2.7; 0.9, 5.8] (n = 645)	2.2±3.4 [1.1; 0.3, 2.7] (n = 196)	<0.001
WHO FC, % (I/II/III/IV/unknown)	4/38/51/2/5	4/38/47/6/5	0.706
6MWD, m	368±128 [378; 285, 455] (n = 591)	360±128 [361; 262, 450] (n = 160)	0.501
mPAP, mmHg	43±12 [43; 34, 51] (n = 612)	42±11 [41; 33, 49] (n = 175)	0.080
PVR, dyn·s·cm^{-5}	656±521 [561; 400, 818] (n = 554)	635±457 [530; 351, 786] (n = 160)	0.209
PAWP, mmHg	11±5 [10; 8, 14] (n = 586)	11±5 [11; 8, 14] (n = 163)	0.771
Cardiac index, L/min/m^2	2.7±3.0 [2.4; 2.0, 2.9] (n = 543)	2.5±0.8 [2.3; 2.0, 2.8] (n = 157)	0.624
RAP, mmHg	9±6 [8; 5, 12] (n = 509)	8±5 [8; 5, 11] (n = 151)	0.213
SvO_2 (%)	64±9 [64; 59, 69] (n = 434)	64±10 [66; 58, 71] (n = 139)	0.411
Renal impairment at baseline			
No	548 (80.2)	160 (80.8)	
Yes	120 (17.6)	30 (15.2)	
Unknown	5 (0.7)	1 (0.5)	
Missing	10 (1.5)	7 (3.5)	
Severity of renal impairment			
Mild (CrCl 50−80 mL/min)	46 (6.7)	13 (6.6)	
Moderate (CrCl 30−49 mL/min)	50 (7.3)	12 (6.1)	
Severe (CrCl <30 mL/min)	18 (2.6)	2 (1.0)	
Missing	6 (0.9)	3 (1.5)	
PH treatment at baseline			0.027
Riociguat monotherapy	530 (77.6)	168 (84.9)	
Riociguat + ERA and/or prostanoid	153 (22.4)	30 (15.2)	
Antiplatelet agents	28 (4.1)	12 (6.1)	0.243

Abbreviations: 6MWD, 6-min walking distance; BMI, body mass index; BPA, balloon pulmonary angioplasty; CrCl, creatinine clearance (by Cockroft−Gault formula); CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; mPAP, mean pulmonary artery pressure; NOAC, non-vitamin K antagonist oral anticoagulant; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; SvO_2, saturated venous oxygen; VKA, vitamin K antagonist; WHO FC, World Health Organization functional class.

Data for continuous variables are mean ± SD, number (%), and [median; 25th percentile, 75th percentile]. Data for other variables are n (%). Values are for all patients unless otherwise stated.

[a]Includes surgically accessible operability under investigation or PEA or surgical assessment declined by the patient.

[b]A Mann−Whitney U test was used for continuously distributed data and a χ^2 test for categorical data in order to compare patients treated with VKAs and NOACs.

Survival at 3 years—80% in both groups—was similar to patients with CTEPH in EXPERT overall (79%),[5] and to intermediate-risk patients in the COMPERA registry (78%),[12] but higher than in non-operated patients in older registries.[5,13] The apparent improvement in survival may reflect advances in CTEPH management, or differences in patient characteristics between studies.

Study limitations include those common to registries, such as missing values and lack of randomization, meaning that the two groups were not balanced in sample size or disease characteristics. Most patients in the NOAC group received rivaroxaban; our results are therefore mainly applicable to rivaroxaban and other Factor Xa inhibitors. Dosages of anticoagulants and their indications were not

Table 2 Absolute and Exposure-adjusted Rates of Hemorrhagic and Embolic/Thrombotic Events in the VKA and NOAC Groups.

	Hemorrhagic events		Embolic/thrombotic events	
Rates, *n* (%)	VKA group (*n* = 683)	NOAC group (*n* = 198)	VKA group (*n* = 683)	NOAC group (*n* = 198)
Any event	78 (11.4)	24 (12.1)	15 (2.2)	6 (3.0)
Drug discontinuation due to event	2 (0.3)	0 (0)	1 (0.1)	0 (0)
Any serious event	40 (5.9)	11 (5.6)	14 (2.0)	5 (2.5)
Discontinuation due to serious event	2 (0.3)	0 (0)	1 (0.1)	0 (0)
Event-related death	8 (1.2)	1 (0.5)	2 (0.3)	0 (0)
Number of events [exposure-adjusted rates][a]				
Any event	99 [9.5]	34 [12.1]	18 [1.7]	13 [4.6]
Drug discontinuation due to event	3 [0.3]	0 [0]	1 [0.1]	0 [0]
Any serious event	52 [5.0]	12 [4.3]	17 [1.6]	8 [2.9]
Discontinuation due to serious event	3 [0.3]	0 [0]	1 [0.1]	0 [0]

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.
[a]Number of events (rate per 100 patient-years, calculated by the number of events observed divided by [total drug exposure in years/100]).

Table 3 Most Common Hemorrhagic and Embolic/Thrombotic Events in the VKA and NOAC Groups.

Patients with event, *n* (%)	VKA group (*n* = 683)	NOAC group (*n* = 198)
Hemorrhagic events		
Epistaxis	19 (2.8)	7 (3.5)
Hemoptysis	19 (2.8)	5 (2.5)
Contusion[a]	4 (0.6)	0
Gastrointestinal hemorrhage	4 (0.6)	1 (0.5)
International normalized ratio increased[a]	3 (0.4)	0
Lower gastrointestinal hemorrhage	3 (0.4)	0
Subcutaneous hematoma	3 (0.4)	0
Abdominal wall hematoma	2 (0.3)	0
Hematuria	2 (0.3)	0
Post-procedural hemorrhage	2 (0.3)	0
Hematemesis	2 (0.3)	2 (1.0)
Hemoglobin decreased	1 (0.1)	2 (1.0)
Menorrhagia	0	3 (1.5)
Hematoma	0	2 (1.0)
Serious hemorrhagic events		
Hemoptysis	12 (1.8)	1 (0.5)
Gastrointestinal hemorrhage	4 (0.6)	1 (0.5)
Lower gastrointestinal hemorrhage	3 (0.4)	0
Abdominal wall hematoma	2 (0.3)	0
Epistaxis	2 (0.3)	1 (0.5)
Hematuria	2 (0.3)	0
Hematemesis	2 (0.3)	0
Hemoglobin decreased[a]	0	2 (1.0)
Embolic/thrombotic events		
Pulmonary embolism	7 (1.0)	4 (2.0)
Acute myocardial infarction	2 (0.3)	0
Coronary angioplasty	2 (0.3)	0
Deep vein thrombosis	2 (0.3)	0
Serious embolic/thrombotic events		
Pulmonary embolism	7 (1.0)	3 (1.5)
Coronary angioplasty	2 (0.3)	0
Deep vein thrombosis	2 (0.3)	0

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.
Table shows events reported in >1 patient in either group.
[a]SAEs were reported in EXPERT according to Medical Dictionary for Regulatory Activities (MedDRA) terms using Standardized MedDRA Query (SMQ). The SMQ "Hemorrhages" includes terms such as "hemoglobin decreased" that might not be considered hemorrhagic events in the clinical setting.

routinely recorded, and INRs were not available for all patients.

In conclusion, hemorrhagic event rates appear similar in patients with CTEPH receiving VKAs or NOACs, but there may be a signal for increased embolic and/or thrombotic events with NOACs. These results are hypothesis-generating, and further studies are required to determine the long-term effects of various anticoagulation strategies in CTEPH.

Disclosure statement

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Jens Klotsche has no conflicts of interest relevant to the EXPERT study.

Christian Meier is an employee of Bayer AG.

Marius M. Hoeper reports personal fees from Bayer AG, during the conduct of the study; personal fees from Acceleron, Actelion, Jansen, MSD, and Pfizer, outside the submitted work.

Author contributions

Marc Humbert. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Gérald Simonneau. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

David Pittrow. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; project administration; approval of final draft for submission.

Marion Delcroix. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

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Joan A. Barberà. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Jens Klotsche. Conceptualization; methodology; software; validation; formal analysis; resources; data curation; writing – review & editing; visualization; approval of final draft for submission.

Christian Meier. Conceptualization; methodology; validation; writing – review & editing; supervision; project administration; funding acquisition; approval of final draft for submission.

Marius M. Hoeper. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Data sharing statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations and Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing, pertaining to scope, time point, and process of data access. Bayer commits to sharing upon request from qualified scientific and medical researchers' patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union as necessary for doing legitimate research. This commitment applies to data on new medicines and indications that have been approved by the European Union and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to do further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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Supplementary materials

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References

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC) International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.

2. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J 2021;57: 2002828.
3. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.
4. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373-498.
5. Ghofrani HA, Gomez Sanchez MA, Humbert M, et al. Riociguat treatment in patients with chronic thromboembolic pulmonary hypertension: final safety data from the EXPERT registry. Respir Med 2020;178:106220.
6. Hoeper MM, Gomez Sanchez MA, Humbert M, et al. Riociguat treatment in patients with pulmonary arterial hypertension: final safety data from the EXPERT registry. Respir Med 2020;177:106241.
7. Bunclark K, Newnham M, Chiu YD, et al. A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. J Thromb Haemost 2020;18:114-22.
8. Porres-Aguilar M, Hoeper MM, Rivera-Lebron BN, Heresi GA, Mukherjee D, Tapson VF. Direct oral anticoagulants in chronic thromboembolic pulmonary hypertension. J Thromb Thrombolysis 2021;52:791-6.
9. Konstantinides SV, Meyer G. The 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2019;40:3453-5.
10. Sedhom R, Megaly M, Gupta E, Amanullah A. Use of direct oral anticoagulants in chronic thromboembolic pulmonary hypertension: a systematic review. J Thromb Thrombolysis 2021. https://doi.org/10.1007/s11239-021-02501-8.
11. Sena S, Bulent M, Derya K, et al. Real-life data of direct anticoagulant use, bleeding risk and venous thromboembolism recurrence in chronic thromboembolic pulmonary hypertension patients: an observational retrospective study. Pulm Circ 2020;10:2045894019873545.
12. Delcroix M, Staehler G, Gall H, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J 2018;52:1800248.
13. Gall H, Felix JF, Schneck FK, et al. The Giessen Pulmonary Hypertension Registry: survival in pulmonary hypertension subgroups. J Heart Lung Transplant 2017;36:957-67.