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ORIGINAL ARTICLE

Quality of life in patients with pulmonary embolism treated with edoxaban versus warfarin

Roisin Bavalia MD¹  | Ingrid M. Bistervels MD^{1,2}  | Wim G. Boersma MD, PhD³ |
 Isabelle Quere MD, PhD⁴  | Dominique Brisot MD⁵ | Nicolas Falvo MD⁶ |
 Dominique Stephan MD, PhD⁷ | Francis Couturaud MD, PhD⁸  |
 Sebastian Schellong MD, PhD⁹ | Jan Beyer-Westendorf MD, PhD¹⁰ |
 Karine Montclair MD¹¹ | Waleed Ghanima MD, PhD¹² | Marije ten Wolde MD, PhD² |
 Michiel Coppens MD, PhD¹ | Emile Ferrari MD, PhD¹³ | Olivier Sanchez MD, PhD¹⁴ |
 Patrick Carroll MD¹⁵ | Pierre-Marie Roy MD, PhD¹⁶ | Susan R. Kahn MD, MSc¹⁷  |
 Karina Meijer MD, PhD¹⁸  | Simone Birocchi MD¹⁹ | Michael J. Kovacs MD²⁰ |
 Amanda Hugman MD²¹ | Hugo ten Cate MD, PhD²²  | Hilde Wik MD, PhD²³  |
 Gilles Pernod MD, PhD²⁴ | Marie-Antoinette Sevestre-Pietri MD, PhD²⁵ |
 Michael A. Grosso MD²⁶ | Minggao Shi PhD²⁶ | Yong Lin PhD²⁶ |
 Barbara A. Hutten PhD²⁷  | Peter Verhamme MD, PhD²⁸  |
 Saskia Middeldorp MD, PhD^{1,29}   | the Hokusai post-PE study investigators

¹Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

²Department of Internal Medicine, Flevo Hospital, Almere, The Netherlands

³Department of Pulmonology, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands

⁴Department of Vascular Medicine, Montpellier University Hospital, University of Montpellier, Montpellier, France

⁵Department of Vascular Medicine, Clinique du Parc, Castelnau Le Lez, France

⁶Department of Internal Medicine and Immunology, Centre Hospitalier Regionale Universitaire Dijon, Dijon, France

⁷Department of Hypertension, Vascular Disease and Clinical Pharmacology, Regional University Hospital, Strasbourg, France

⁸Department of Pulmonology, Centre Hospitalier Regionale Universitaire Brest, Brest, France

⁹Medizinische Klinik, Städtisches Klinikum Dresden, Dresden, Germany

¹⁰Division of Hematology and Hemostasis, Department of Medicine I, Thrombosis Research, University Hospital "Carl Gustav Carus" Dresden, Dresden, Germany

¹¹Department of Cardiology, Centre Hospitalier Le Mans, Le Mans, France

¹²Department of Research, Østfold Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway

¹³Department of Cardiology, Centre Hospitalier Universitaire de Nice, Nice, France

¹⁴Department of Pulmonology, Hôpital Européen Georges-Pompidou, Paris, France

¹⁵Department of Vascular Medicine, Redcliffe Hospital, Redcliffe, Qld, Australia

¹⁶Department of Emergency Medicine, Centre Hospitalier Universitaire d'Angers, Angers, France

¹⁷Department of Medicine, McGill University, Montreal, QC, Canada

¹⁸Department of Hematology, University Medical Centre Groningen, Groningen, The Netherlands

¹⁹Internal Medicine II, San Paolo Hospital, Milan, Italy

Roisin Bavalia and Ingrid M. Bistervels authors contributed equally to this work.

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²⁰Department of Hematology and Thrombosis, London Health Sciences Centre, Victoria Hospital, London, ON, Canada

²¹Department of Haematology, St George Hospital, Sydney, NSW, Australia

²²Thrombosis Expertise Centre, Heart+Vascular Center, Maastricht University Medical Centre, Maastricht, The Netherlands

²³Department of Haematology, Oslo University Hospital, Oslo, Norway

²⁴Department of Medicine, Centre Hospitalier Regionale Universitaire de Grenoble-Alpes, Grenoble, France

²⁵Department of Medicine, Centre Hospitalier Regionale Universitaire d'Amiens, Amiens, France

²⁶Daiichi Sankyo Pharma Development, Basking Ridge, NJ, USA

²⁷Department of Epidemiology and Data Sciences, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

²⁸Department of Vascular Medicine and Hemostasis, University Hospital Leuven, Leuven, Belgium

²⁹Department of Internal Medicine & Radboud Institute of Health Sciences (RIHS), Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence

Saskia Middeldorp, Department of Internal Medicine & Radboud Institute of Health Sciences (RIHS), Radboud University Medical Center, Nijmegen, The Netherlands.

Email: saskia.middeldorp@radboudumc.nl

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Abstract

Background: Long-term sequelae of acute pulmonary embolism (PE) include decreased quality of life (QoL). Evidence suggests that adequacy of initial anticoagulant treatment in the acute phase of venous thrombosis has a key impact on late post-thrombotic complications. We hypothesize that patients with acute PE treated with edoxaban for acute PE experience have improved QoL compared to those treated with warfarin.

Methods: Patients with PE who participated in the Hokusai-VTE trial were contacted between June 2017 and September 2020 for a single long-term follow-up visit. Main outcomes were the generic and disease-specific QoL measured by the 36-Item Short Form Health Survey (SF-36) and Pulmonary Embolism Quality of Life questionnaire.

Results: We included 251 patients from 26 centers in eight countries, of which 129 (51%) had been assigned to edoxaban and 122 (49%) to warfarin. Patient- and thrombus-specific characteristics were similar in both groups. Mean time since randomization in the Hokusai-VTE trial was 7.0 years (standard deviation, 1.0). No relevant or statistical differences were observed in the QoL for patients treated with edoxaban compared to patients treated with warfarin. The mean difference between patients treated with edoxaban and patients with PE treated with warfarin was 0.8 (95% confidence interval [CI], -1.6 to 3.2) for the SF-36 summary mental score and 1.6 (95% CI, -0.9 to 4.1) for summary physical score.

Conclusion: Our findings indicate that patients with an index PE treated with edoxaban or warfarin have a similar long-term QoL. Since our study was a follow-up study from a well-controlled clinical trial setting, future studies should be designed in a daily clinical practice setting. We suggest a longitudinal design for investigation of changes in QoL over time.

KEYWORDS

edoxaban, pulmonary embolism, quality of life, warfarin

Essentials

- Decreased quality of life (QoL) is a long-term complication of pulmonary embolism (PE).
- This is a follow-up study of the Hokusai-VTE trial. We assessed general and PE-related QoL.
- Seven years after index PE, 251 patients were included in 25 centers in eight countries.
- We observed no difference in QoL in patients treated with edoxaban vs warfarin.

1 | INTRODUCTION

Long-term complications in patients who experienced acute pulmonary embolism (PE) occur in about 25% to 50% of patients despite adequate anticoagulant treatment.¹ These comprise symptoms such as dyspnea, exercise intolerance, and functional limitations, which persist after the acute phase and are called post-PE syndrome.^{2,3} The complaints vary from mild symptoms present during exercise only to severe symptoms at rest.⁴ Diseases correlated to the post-PE syndrome comprise chronic thromboembolic diseases, with chronic thromboembolic pulmonary hypertension as the most feared complication due to its poor prognosis.⁵ The underlying pathology is thought to be a combination of inadequate thrombus resolution, persistent elevated pulmonary artery pressure, and/or right ventricular dysfunction.^{4,6} In addition, anxiety and deconditioning may also contribute to the development of the post-PE syndrome.⁴ The proposed definition for diagnosing post-PE syndrome comprises a combination of suggestive symptoms, objectified worsening of cardiac or pulmonary function, and a deterioration of functional status after a PE.³

The Evaluation of Long-Term Outcomes After PE (ELOPE) study, a prospective multicenter Canadian study suggested that quality of life (QoL), dyspnea, and exercise capacity in patients with PE improve after 1 year of experiencing the PE.⁷ However, two Dutch studies suggest that the QoL in patients with PE, 2 to 3 years after the event, is worse in comparison with the QoL of a representative sample of the general Dutch population, adjusted for sex and age. These QoL assessments were all performed relatively shortly after the index PE. Assessment of long-term QoL after acute PE may be an important patient outcome that reflects the presence of post-PE syndrome.^{3,8,9}

At present, therapeutic options of post-PE syndrome are limited to treatment of preexistent pulmonary and cardiac comorbidities and psychological support.⁴ In analogy with the postthrombotic syndrome in patients with deep vein thrombosis (DVT), quality of anticoagulation may be a risk factor for the development of post-PE syndrome.¹⁰ Hence, it is plausible that adequate anticoagulant management in the acute phase of PE is important for prevention of post-PE syndrome and thus influences QoL. All of the reported studies mentioned above included only patients treated with vitamin K antagonists (VKAs).^{7,11,12} In the past decade, direct oral anticoagulants (DOACs) have replaced VKAs as the drug of first choice in most patients with acute venous thromboembolism (VTE).¹³ DOACs are pharmacologically more stable than VKA and do not require therapeutic drug monitoring or dose adjustments. Hence, quality of anticoagulation may be higher for DOACs than with VKAs, particularly in the days to weeks after discontinuation of the heparin lead-in in patients with acute VTE. Edoxaban is a direct factor Xa inhibitor that is as effective as warfarin for treatment of acute VTE, and safer with regards to serious bleeding.¹⁴

In this study, we assessed whether patients with acute PE who were treated with edoxaban had a better QoL than those who were initially treated with warfarin.

2 | METHODS

2.1 | Study design and population

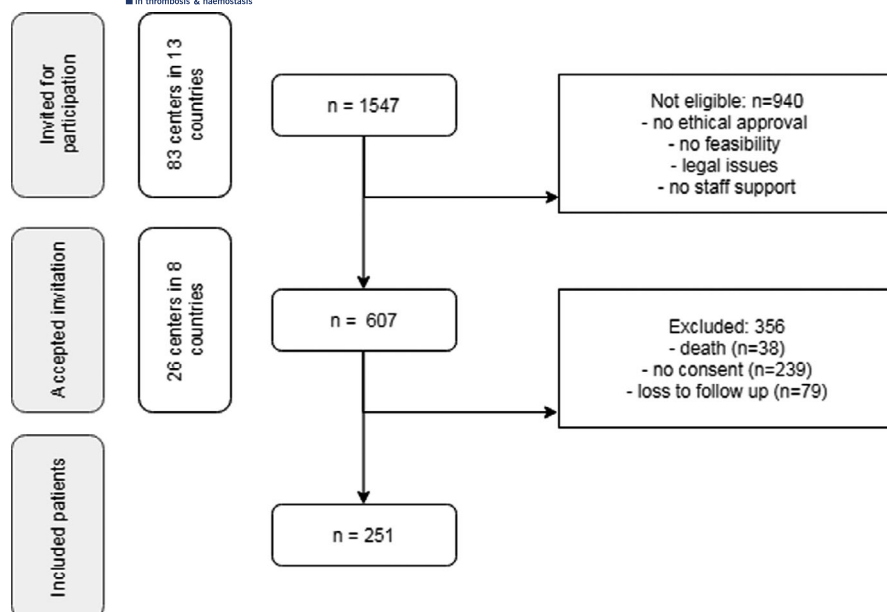
The source population for this cohort study comprised the participants of the Hokusai-VTE trial (NCT00986154).¹⁴ In summary, the Hokusai-VTE trial was an international, randomized, double-blind, noninferiority trial evaluating the efficacy and safety of edoxaban (30 or 60 mg daily) versus warfarin (target international normalized ratio [INR] between 2.0 and 3.0) in patients with acute symptomatic VTE. In total, 8292 patients (3319 patients with PE) were included between January 2010 and October 2012, and all patients received initial therapy with subcutaneous enoxaparin for at least 5 days. Treatment with edoxaban or warfarin was continued for at least 3 months and for a maximum of 12 months. The last trial visit for all patients was scheduled 12 months after randomization.

For the current study (the Hokusai post-PE study), we selected centers based on the number of patients included in the original Hokusai-VTE trial (>10 patients) and language (QoL questionnaires were available only in Roman and Germanic languages).^{15,16} Patients were eligible for the current follow-up study if they were recruited in one of these study centers and treated for PE (with or without DVT) as their index event for participation in Hokusai-VTE trial. In 2016, we approached 83 study centers located in Austria, Australia, Belgium, Canada, Denmark, France, Germany, Italy, the Netherlands, New Zealand, Norway, United Kingdom, and United States to participate in the Hokusai post-PE study. Patients were approached for participation in the study by their own study center. During a single telephone visit, information on VTE-related medical history along with comorbidity and comedication was collected. After the telephone visit, the questionnaires on disease-specific and generic health-related QoL were sent to patients' homes; patients were asked to fill these out and to return them by regular mail in a postage-paid return envelope. Additionally, the original Hokusai-VTE trial database was accessed, and data on patient characteristics during trial inclusion (VTE history, thrombus characteristics, and management of PE) as well as allocation of treatment were retrieved.

The study protocol was approved by the institutional review board of Amsterdam UMC, University of Amsterdam (NL587525.018.16), and local review boards in all participating centers. The study was registered at ClinicalTrials.gov (NCT04007653). All participants provided written informed consent. The study was conducted according to the revised principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act.

An overview of the study timeline is presented in Appendix S1, Figure S1.

FIGURE 1 Flowchart of invited participating centers and included patients



2.2 | Study outcomes

2.2.1 | Outcomes

The generic health-related QoL was assessed by the 36-Item Short Form Health Survey (SF-36) questionnaire, which reflects overall health perceptions regardless of underlying diseases. The SF-36 comprises 36 items and assesses generic well-being during the previous 30 days. It contains eight dimensions and two summary measures for physical and emotional well-being. The eight dimensions are physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general health. Scores are expressed on a 0 to 100 scale, with higher values indicating better QoL.¹⁷

The disease-specific QoL was assessed by the disease-specific Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire.^{9,15,16} The PEmb-QoL questionnaire is a validated questionnaire that measures the disease-specific QoL during the previous 4 weeks and consists of nine questions, with a total of 40 items summarized in six subscales: frequency of complaints, limitations in activity of daily life, work-related problems, social limitations, intensity of complaints, and emotional complaints. The minimum score for all dimensions was 1 (indicating no complaints), and the maximum scores were 5, 3, 2, 5, 6, and 6, respectively. Scores were expressed on a 0 to 100 scale, with higher values indicating a better QoL.

2.3 | Statistical analysis

Differences in baseline characteristics between both groups were evaluated by means of the two-sample *t* tests for normally distributed variables and the Mann-Whitney test for skewed distributions; chi-square tests were applied for categorical data.

The association between QoL scores (SF-36, PEmb-QoL) and treatment group (edoxaban, warfarin) was assessed using linear

regression analyses, for each dimension separately. We explored the effect of potential confounders in two different ways. First, potential confounders were assigned by clinical relevance by multiple assessors (RB, IB, BH) and were taken into a full model. Second, we determined the univariable association between patient characteristics (potential confounders) and treatment allocation (determinant), as well as between patient characteristics and QoL scores (outcome). Characteristics that had a *P* value <.25 for both univariable associations were considered as a potential confounder and were included in a second full model. For both full models, we applied stepwise backward elimination based on the largest *P* value and created a final model (that always contained the variable “treatment allocation”), consisting of variables with a *P* value <.1.

P values <.05 were considered statistically significant. All analyses were conducted using statistical software SPSS, version 26 (SPSS Inc; Chicago, IL, USA).

We performed a sensitivity analysis in the subgroup of patients who were unaware of treatment allocation during the Hokusai-VTE trial at the moment of filling out the QoL questionnaires.

2.4 | Data sharing statements

All data relevant to the study are included in the article or uploaded as supporting information. Data are available upon reasonable request.

3 | RESULTS

Between June 2017 and September 2020, 251 patients were included in the Hokusai post-PE study. Figure 1 represents the flowchart of patient inclusions in this study. The Hokusai-VTE trial included 3319 patients in 439 centers with a PE.¹⁴ Of all approached

TABLE 1 Demographic and clinical characteristics at inclusion of the Hokusai post-PE study

	Total (n = 251)	Edoxaban (n = 129) ^a	Warfarin (n = 122) ^a
Mean age, y (SD)	64 (13.7)	64 (14.7)	65 (13)
Male sex, n (%)	138 (55)	73 (58)	65 (53)
Mean weight, kg, SD	84 (17.6)	84 (16.8)	85 (18.4)
Mean BMI, kg/m ² (SD)	28.1 (5.0)	28.0 (4.6)	28.2 (5.5)
Smoking, n (%)	28 (11)	14 (11)	14 (11)
≥2 VTE in medical history, n (%) ^b	51 (20)	28 (22)	23 (19)
Comorbidities, n (%)			
Cardiovascular disease ^c	140 (56)	73 (57)	67 (55)
Malignancy	21 (8)	8 (6)	13 (11)
Musculoskeletal disease	31 (12)	13 (10)	18 (15)
Neurological disease	9 (3)	7 (5)	2 (2)
Psychiatric disorder	13 (5)	4 (3)	9 (7)
Concomitant medication use, n (%)			
Any concomitant medication use, n (%)	185 (74)	95 (74)	90 (74)
Chronic analgesic use ^d	39 (16)	12 (9)	27 (22)
Chronic anticoagulant use	88 (35)	45 (35)	43 (36)
DOAC	45 (51)	25 (56)	20 (48)
VKA	38 (43)	18 (40)	20 (48)
Other	5 (6)	2 (4)	3 (4)
Years since randomization in Hokusai-VTE trial, mean (SD)	7.3 (1.0)	7.2 (1.0)	7.2 (1.0)
Informed about treatment allocation during Hokusai-VTE trial, n (%)	86 (34)	41 (33)	45 (38)

Note: Missing for age, 1; missing for weight, 8; missing for BMI, 17; missing for years since randomization Hokusai-VTE trial, 5; missing informed treatment allocation, 5; missing for chronic anticoagulant use, 2.

BMI, body mass index; DOAC, direct oral anticoagulant; PE, pulmonary embolism; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aBoth edoxaban and warfarin treatment were preceded by enoxaparin.

^bTwo or more VTEs in medical history implies these patients had a history of VTE before their index PE of the Hokusai-VTE trial and/or a recurrent VTE after randomization in the Hokusai-VTE trial.

^cCardiovascular disease included coronary heart disease, cerebral vascular stroke, hypertension, diabetes mellitus, and dyslipidemia.

^dChronic analgesic use was self-reported and comprised nonsteroidal anti-inflammatory drugs, paracetamol, and opioids.

83 centers (1547 Hokusai-VTE trial patients), 58 centers (940 Hokusai-VTE trial patients) were not eligible for participation for logistical reasons. In the remaining 26 centers, 356 of the original 607 patients were excluded due to death, loss to follow-up, or no consent for participation, leaving 251 of 3319 (7.6%) patients from 26 centers in eight countries for inclusion. The included countries were Australia, Belgium, Canada, France, Germany, Italy, Norway, and the Netherlands.

3.1 | Patients and treatment

The mean (standard deviation [SD]) time from randomization in the Hokusai-VTE trial to inclusion in the Hokusai post-PE study

was 7 (1) years in both groups. Of the 251 patients, 129 (51%) patients had been allocated to edoxaban during the Hokusai-VTE trial, and 122 (49%) had been allocated to warfarin. Demographic and clinical characteristics at inclusion of the Hokusai post-PE study were comparable for patients treated with edoxaban and patients treated with warfarin (Table 1). The mean (SD) age at time of inclusion in the present study was 64 (14) and mean (SD) body mass index was 28 (5) kg/m². The proportion of comorbidities did not differ between both groups and 51 (20%) of included patients had a history of recurrent VTE. A significant difference was observed in the proportion of chronic analgesic use between patients treated with edoxaban and patients with PE treated with warfarin (9% vs 27%; $P = .005$). Following routine unblinding at the end of Hokusai-VTE trial in some centers, 86 (34%) patients

TABLE 2 Characteristics of index PE at randomization of Hokusai-VTE trial

	Total (n = 251)	Edoxaban (n = 129) ^a	Warfarin (n = 122) ^a
Specific characteristics of PE			
Location of index PE, n (%)			
Central	67 (33)	39 (32)	28 (24)
Segmental	100 (52)	47 (38)	53 (45)
Subsegmental	67 (27)	34 (27)	33 (28)
Bilateral PE, n (%)	167 (67)	86 (68)	81 (69)
Anatomical extent of PE, ^b n (%)			
Extensive	125 (50)	62 (48)	63 (52)
Intermediate	93 (37)	51 (40)	42 (34)
Limited	15 (6)	5 (4)	10 (8)
Not assessable	18 (7)	11 (9)	7 (6)
Median NT-proBNP, pg/mL (IQR)	110 (45–307)	111 (44–289)	109 (49–361)
Right ventricular dysfunction, ^c n (%)	27 (11)	13 (10)	14 (11)
Unprovoked PE, n (%)	177 (71)	97 (75)	80 (67)
Concomitant DVT, n (%)	80 (32)	39 (30)	41 (34)
Treatment of PE			
Median duration of anticoagulant treatment during Hokusai-VTE trial, mo (IQR)	8.7 (6.0–12.0)	9.8 (6.1–12.0)	8.0 (6.0–12.0)
≥80% compliance with assigned treatment, n (%)	249 (99.6)	128 (100)	121 (99.2)
Mean percentage of time spent in therapeutic range, ^d SD	NA	NA	72
Mean percentage of time spent in range INR < 2, SD	NA	NA	10
Patients receiving 30 mg of edoxaban at randomization, ^e n (%)	NA	15 (12)	NA
Use of concomitant medication, n (%)			
Antiplatelet treatment	36 (14)	21 (16)	15 (12)
NSAIDs	28 (11)	15 (12)	13 (11)

Abbreviations: DVT, deep vein thrombosis; INR, international normalized ratio; IQR, interquartile range; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aBoth edoxaban and warfarin treatment were preceded by enoxaparin.

^bAmong patients with PE, limited refers to involvement of ≤25% of the vasculature of a single lobe; intermediate, involvement of >25% of the vasculature of a single lobe or multiple lobes with involvement of ≤25% of the entire vasculature; and extensive, involvement of multiple lobes with ≥25% of the entire vasculature.

^cRight ventricular function was assessed by calculating the ratio of the right ventricular diameter to the left ventricular diameter on a four-chamber view of the qualifying index PE on a computed tomographic scan.

^dTime to therapeutic range was calculated by linear interpolation.¹⁴ Patients with a body weight <60 kg or a creatinine clearance of 30–50 mL/min, as well as patients who were receiving concomitant P-glycoprotein inhibitors such as verapamil or quinidine, received 30 mg instead of 60 mg of edoxaban to maintain similar exposure to the cohort receiving 60 mg. Missing values: location PE, 8; bilateral, 8; NT pro BNP, 26; duration treatment, 1.

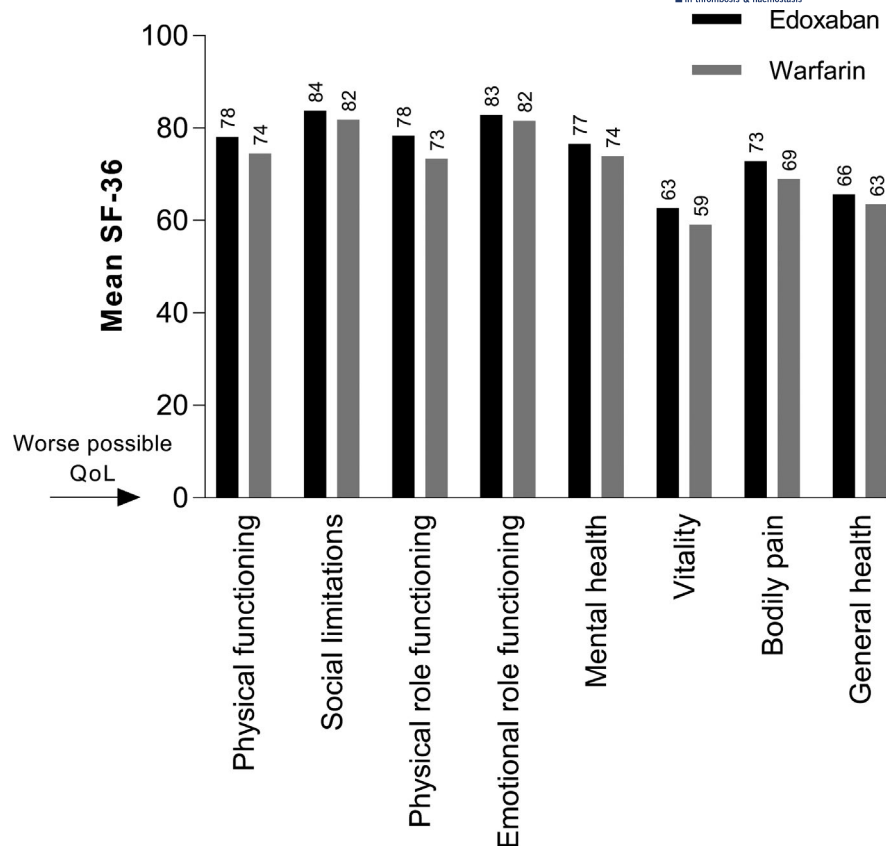
^ePatients with a body weight below 60 kg or a creatinine clearance of 30 to 50 ml per minute, as well as patients who were receiving concomitant P-glycoprotein inhibitors such as verapamil or quinidine, received 30 mg instead of 60 mg of edoxaban to maintain similar exposure to the cohort receiving 60 mg.

were aware about treatment allocation during the Hokusai-VTE trial at the time of filling out the questionnaires for the present Hokusai post-PE study. Of 129 patients allocated to edoxaban, 45 (35%) and of the 122 patients allocated to warfarin, 43 (36%), were still in use of an anticoagulant drug at the time of filling out the questionnaire.

PE-related aspects (ie, location and extent of PE), and management of PE during the Hokusai-VTE trial were comparable in patients treated with edoxaban and patients treated with warfarin

(Table 2). In the edoxaban-treated patients, 39 (34%) had central PE, compared to 28 (24%) in patients treated with warfarin. Mean N-terminal pro-brain natriuretic peptide was 110 pg/mL for all patients and was similar in both groups. The majority (71%) of all 251 patients experienced unprovoked PE, with no significant difference between patients treated with edoxaban or with warfarin (75% vs 67%; $P = .14$). Median duration of anticoagulant treatment for the index PE was 9 months (interquartile range, 5–11) and almost all patients were compliant with the assigned drug during the Hokusai-VTE trial,

FIGURE 2 Generic quality of life in patients with pulmonary embolism treated with edoxaban or warfarin. Mean SF-36 scores of patients with a history of acute pulmonary embolism in patients on edoxaban ($n = 129$) and warfarin ($n = 122$), stratified per dimension. SF-36, 36-Item Short Form Health Survey



which was defined as an adherence rate of $\geq 80\%$. Concomitant antiplatelet and nonsteroidal anti-inflammatory drug treatment was used in 64 (25%) patients.

Appendix S1 shows the corresponding characteristics for all patients included in the Hokusai-VTE trial at the time of randomization (Appendix S1, Table S1). In our study, the overall proportion of patients with an unprovoked PE and a concomitant DVT was slightly larger than in the Hokusai-VTE trial. The proportion of right ventricular dysfunction and mean percentage of time spent in the INR range < 2 , on the other hand, was slightly lower in our study. All other characteristics were similar between the subset of patients included in our study and all patients included in the Hokusai-VTE trial.

3.2 | Quality of life—SF-36

Scores of the eight dimensions and the two summary scores of the SF-36 for patients treated with edoxaban and patients treated with warfarin are shown in Figure 2 and Table 3. In all eight dimensions, the SF-36 score was slightly higher in patients treated with edoxaban in comparison with patients treated with warfarin (Figure 3), but none of the mean differences were statistically significant. After adjustment for all variables in the final regression models 1 and 2, the adjusted mean difference for the eight dimensions did not change substantially. The included variables in the adjusted models are presented in detail in Appendix S1 (Table S2).

3.3 | Quality of life—PEMB-QOL

PEmb-QoL scores of the six dimensions for patients treated with edoxaban and patients treated with warfarin are reported in Figure 4 and Table 3. None of the six dimensions showed significant or clinically relevant differences between patients treated with edoxaban and patients treated with warfarin (Figure 5). After adjustment for all variables in the final regression models 1 and 2, the adjusted mean difference for the six dimensions did not change substantially. The included variables in the adjusted models are presented in detail in Appendix S1 (Table S3).

A sensitivity analysis in 160 patients who were unaware of their allocation treatment during the Hokusai-VTE trial during filling out the QoL questionnaires did not show any large differences in comparison to the analysis in all 251 patients (Appendix S1, Table S4). In an additional analysis, we stratified patients still using anticoagulants at the time of filling out the QoL questionnaire and patients who stopped their anticoagulant drug after the Hokusai-VTE trial (Appendix S1, Tables S5 and S6).

4 | DISCUSSION

In this follow-up study of a selected population of patients with acute, symptomatic PE, the generic health and the disease-specific QoL 7 years after index PE was not different in patients treated with edoxaban or warfarin. After adjustment for possible confounders, we observed no substantial decrease or increase in

TABLE 3 Crude and adjusted mean differences for quality of life for patients with index PE in the Hokusai-VTE trial treated with edoxaban and warfarin

Outcome	Edoxaban (n = 129)	Warfarin (n = 122)	Crude mean difference (95% CI)	Adjusted mean difference ^a (95% CI)	Adjusted mean difference ^b (95% CI)
SF-36, mean (SD)					
Physical functioning	78.0 (24.1)	74.4 (25.7)	3.6 (−2.6 to 9.8)	1.8 (−4.4 to 8.0)	1.1 (−4.4 to 6.6)
Social functioning	83.7 (20.4)	81.8 (22.2)	1.9 (−3.4 to 7.2)	−0.1 (−5.3 to 5.2)	−0.4 (−5.6 to 4.7)
Role physical complaints	78.3 (34.7)	73.3 (40.7)	5.1 (−4.4 to 14.5)	1.5 (−7.8 to 10.8)	0.5 (−8.4 to 9.5)
Role emotional complaints	82.8 (31.9)	81.5 (35.2)	1.3 (−7.1 to 9.6)	−1.0 (−9.4 to 7.4)	−2.0 (−10.1 to 6.2)
Mental health	76.6 (18.6)	73.9 (19.2)	2.6 (−2.1 to 7.4)	3.0 (−1.6 to 7.6)	2.9 (−1.6 to 7.4)
Vitality	62.4 (21.2)	59.1 (20.9)	3.3 (−1.9 to 8.6)	1.5 (−3.7 to 6.7)	2.1 (−2.9 to 7.1)
Bodily pain	72.8 (24.7)	69.0 (28.3)	3.8 (−2.8 to 10.4)	0.6 (−5.7 to 7.0)	−0.5 (−6.8 to 5.9)
General health	65.6 (20.9)	63.4 (20.4)	2.1 (−3.1 to 7.3)	1.4 (−3.8 to 6.7)	1.4 (−3.8 to 6.5)
Summary mental score	51.7 (9.1)	50.9 (10.1)	0.8 (−1.6 to 3.2)	0.9 (−1.5 to 3.2)	1.0 (−1.4 to 3.5)
Summary physical score	47.1 (9.6)	45.6 (10.4)	1.6 (−0.9 to 4.1)	0.4 (−2.0 to 2.9)	0.0 (−2.3 to 2.3)
PEmb-QoL, mean (SD)					
Frequency of complaints	85.1 (18.6)	86.8 (19.1)	−1.7 (−6.4 to 3)	−1.8 (−8.0 to 4.4)	−1.1 (−6.6 to 4.4)
ADL limitations	81.6 (22.6)	81.5 (23.1)	0.1 (−5.6 to 5.8)	0.1 (−5.2 to 5.3)	0.4 (−4.7 to 5.6)
Work-related problems	81.7 (34.8)	83.4 (33.1)	−1.7 (−10.2 to 6.9)	−1.5 (−10.8 to 7.8)	−0.5 (−9.5 to 8.4)
Social interference	92.5 (16.2)	91.7 (18.1)	0.8 (−3.5 to 5.1)	1.0 (−7.4 to 9.4)	2.0 (−6.2 to 10.1)
Intensity of complaints	79.1 (21.7)	80.2 (22.6)	−1.2 (−6.7 to 4.3)	−3.0 (−7.6 to 1.6)	−2.9 (−7.4 to 1.6)
Emotional complaints	85.4 (14.5)	85.6 (16.2)	−0.3 (−4.1 to 3.6)	−3.3 (−8.6 to 1.9)	−2.1 (−7.1 to 2.9)

Note: Missing frequency of complaints, 3; missing ADL, 3; missing work related, 6; missing social interference, 4; missing intensity of complaints, 3; missing emotional complaints, 3; missing physical functioning, 3; missing social functioning, 3; missing role physical complaints, 3; missing role emotional, 3; missing mental, 4; missing vitality, 4; missing pain, 3; missing general health, 5; missing mental score, 6; missing physical score, 6.

Abbreviations: ADL, activities of daily living; CI, confidence interval; PE, pulmonary embolism; SD, standard deviation.

^aAdjusted by variables from model 1 (clinical reasoning) as described in the Methods section.

^bAdjusted by variables derived by model 2 ($P < .25$) as described in the Methods section. Details on the included variables per model are presented in Appendix S1. A negative mean difference implies a difference in favor of warfarin, a positive mean difference implies a difference in favor of edoxaban.

the mean QoL difference between both treatment arm groups. Our adjusted models showed that sex, body mass index, and the use of analgesics were prevalent confounders in the association between the treatment arm and the different dimensions of QoL. None of the confounders, however, changed the lack of significance of the crude mean difference. Factors known to influence the degree of thrombus resolution, such as location and anatomic extent of PE, did not influence the association between treatment arm and QoL.^{3,18}

We assessed the outcome QoL as a surrogate for the post-PE syndrome.³ However, as we did not assess objective indicators of the post-PE syndrome (eg, ergometrics or spirometrics or persistent thrombus on imaging), it is uncertain whether our results also reflect a lack of difference in incidence of post-PE syndrome between patients with PE treated with edoxaban and patients with PE treated with warfarin. If QoL is associated with the post-PE syndrome, in part as a result of thrombus resolution, our findings may imply that in a well-controlled clinical trial setting (ie, a clinical trial setting such as the Hokusai-VTE trial in which patients adhered to a protocol, including drug accountability), thrombus resolution in both treatment arms is equally achieved.^{4,6} This could be explained by the common

initial lead-in of heparin for at least 5 days in both the edoxaban and warfarin arms. However, this is speculative, as we did not investigate anatomic or physiological outcomes.

The differences in QoL between patients with PE treated with edoxaban and patients with PE treated with warfarin has not been previously assessed. In fact, the outcome QoL in general has rarely been investigated in patients who experienced a PE.^{7,19} This study contributes to this important topic and may be a foundation for further research on the pathophysiology of the post-PE syndrome. Studies that have addressed QoL after acute PE have been conducted in patients on VKA only and have mostly focused on a relatively short follow-up period of 1 to 4 years after the acute PE.^{7,11,12} We suggest future research to focus on development of the post-PE syndrome over time for different anticoagulant treatments. A longitudinal study with a yearly QoL assessment after the index PE would be an adequate design to evaluate the impact of time on the QoL.

The long-term follow-up of patients who were included in a randomized trial is a strength of this study. The design of this study also has limitations. First, we were not able to adjust for QoL at baseline of the Hokusai-VTE trial because those data were not available.

FIGURE 3 Mean difference of generic quality of life in patients with pulmonary embolism treated with edoxaban or warfarin. Mean difference and 95% confidence interval; of SF-36 scores of patients with a history of acute pulmonary embolism in patients on edoxaban ($n = 129$) and warfarin ($n = 122$), stratified per dimension. This graph is not corrected for any baseline characteristics. The dotted purple line is the minimal clinically important difference of 10 points as described in the Methods section. SF-36, 36-Item Short Form Health Survey

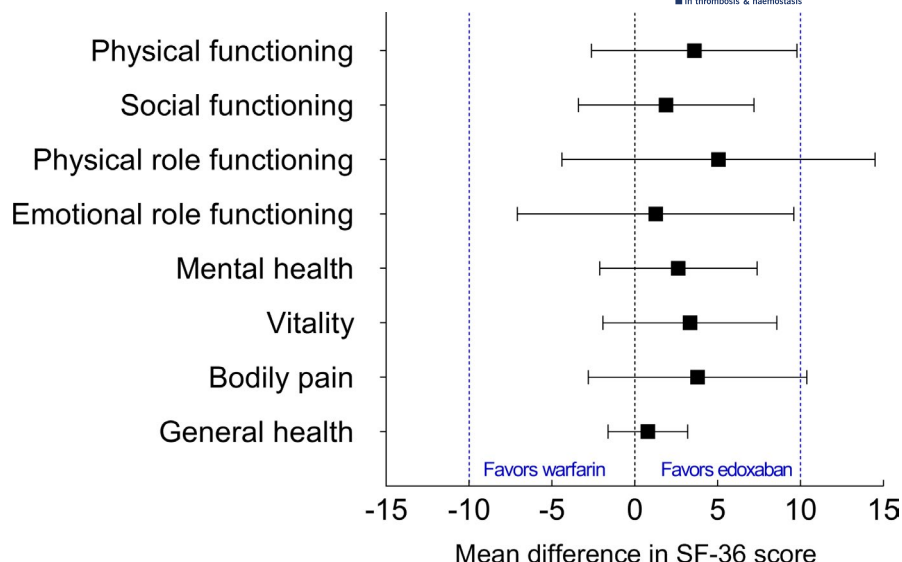
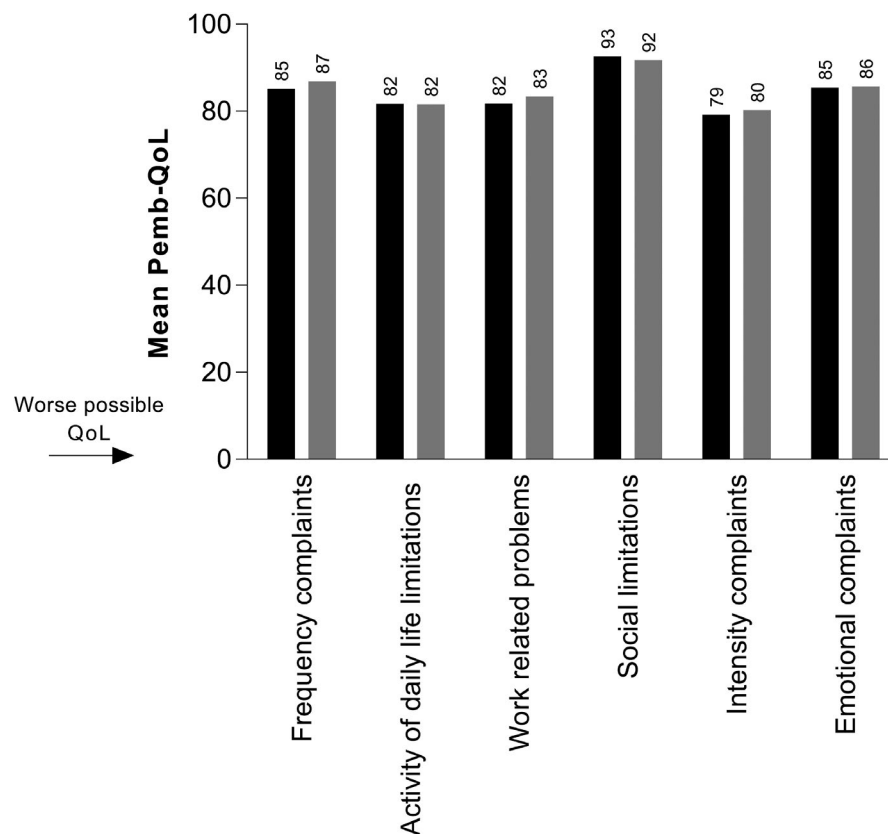


FIGURE 4 Pulmonary embolism-specific quality of life in patients with pulmonary embolism treated with edoxaban or warfarin. Results of the PEmb-QoL scores of patients with a history of acute pulmonary embolism in patients on edoxaban ($n = 129$) and warfarin ($n = 122$) Scores are presented as means. Higher PEmb-QoL scores indicate improved quality of life. PEmb-QoL, Pulmonary Embolism Quality of Life



Additionally, we have selected a sample of a trial population, potentially leading to limitations in generalizability. The high adherence rates in both treatment arm groups imply that these observed results account for patients in a well-controlled trial setting. As we know that the QoL in atrial fibrillation patients with well-controlled VKA therapy was not different from patients treated with DOAC therapy, these high adherence rates may explain why we did not observe a difference between both treatment arm groups.²⁰ Therefore, we need to bear in mind that our findings may not reflect daily clinical practice in which patients on both anticoagulant

drugs have lower adherence rates. Corresponding with the high adherence rate in a well-controlled setting, our study may comprise a selection of relatively healthy PE patients, who were mentally and physically healthy enough to fill out the questionnaires anticipated. In addition, Hokusai-VTE trial excluded patients with high-risk PE according to the European Society of Cardiology classification. In addition hereto, recently published guidelines recommend indefinite anticoagulation for most of the patients after acute PE.^{13,21} Therefore, patients at highest risk for post-PE syndrome were underrepresented in Hokusai-VTE trial and in our subset of patients

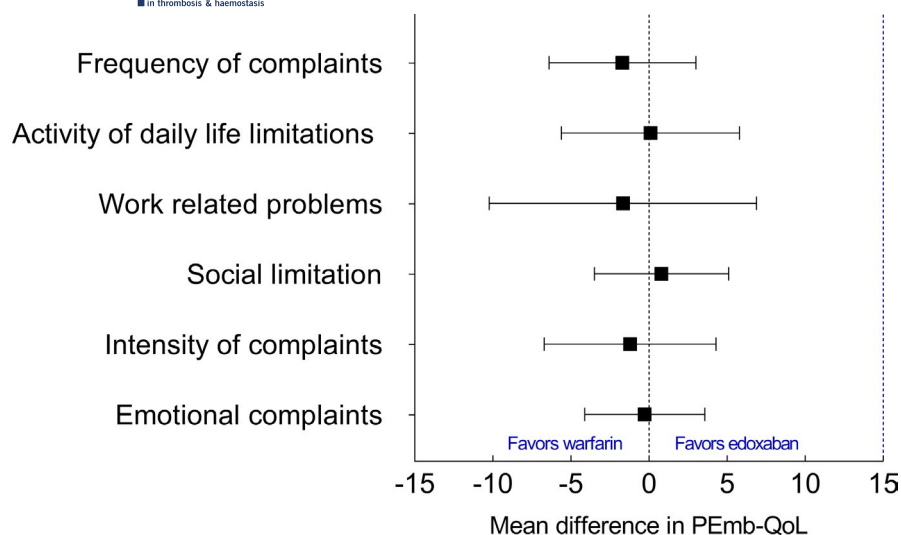


FIGURE 5 Mean difference of pulmonary embolism-specific quality of life in PE patients treated with edoxaban or warfarin. Mean differences of the six dimensions of the PEmb-QoL scores in patients with a history of acute pulmonary embolism treated with edoxaban ($n = 129$) and warfarin ($n = 122$). Scores are presented as mean differences between both groups with 95% confidence interval. The dotted purple line is the minimal clinically important difference of 15 points as described in the methods section. PEmb-QoL, Pulmonary Embolism Quality of Life

so that our findings may not be generalizable to patients with more severe PE. In line herewith, we were not able to account for the competing risk bias of mortality and had no information on treatment allocation in the eligible patients who did not participate in this study. This might have potentially led to attrition bias. However, this seems unlikely as the demographic and clinical characteristics of our included patients are similar to the baseline characteristics in the original Hokusai-VTE trial.

In conclusion, this study suggests that, in a well-controlled setting, there is no difference in long-term QoL in patients who experienced a PE treated with edoxaban or warfarin. Future studies should focus on a cohort with adherence rates in both groups, mimicking daily clinical practice.

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AUTHOR CONTRIBUTIONS

The steering committee (IMB, RB, JBW, PV, SM [executives]) designed the study. All Hokusai post-PE study investigators recruited patients and collected data. BH, MS, YL, IMB, and RB contributed to the data analysis. IMB and RB wrote the first draft of the manuscript, and all authors critically reviewed and revised the manuscript. The final manuscript was approved by all authors.

RELATIONSHIP DISCLOSURE

HtC received funding from Bayer and Pfizer and consulting fees from Portola and Alveron; he is a stockholder in Coagulation Profile. JBW reports personal fees and other from Bayer HealthCare, Boehringer Ingelheim, BMS/Pfizer, CSL Behring, Daiichi Sankyo, and LEO Pharma, outside the submitted work. FC reports grants from BMS/Pfizer; personal fees and other from Bayer, AstraZeneca,

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ORCID

Roisin Bavalia  <https://orcid.org/0000-0002-1806-1050>
 Ingrid M. Bistervels  <https://orcid.org/0000-0002-1155-4143>
 Isabelle Quere  <https://orcid.org/0000-0002-1492-9764>
 Francis Couturaud  <https://orcid.org/0000-0002-1855-8032>
 Susan R. Kahn  <https://orcid.org/0000-0002-5667-8916>
 Karina Meijer  <https://orcid.org/0000-0001-9447-0465>
 Hugo ten Cate  <https://orcid.org/0000-0001-7796-4463>
 Hilde Wik  <https://orcid.org/0000-0002-1035-5521>
 Barbara A. Hutten  <https://orcid.org/0000-0002-9243-0037>
 Peter Verhamme  <https://orcid.org/0000-0001-8698-2858>
 Saskia Middeldorp  <https://orcid.org/0000-0002-1006-6420>

TWITTER

Saskia Middeldorp  @MiddeldorpS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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