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Original Article

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Effectiveness of oral anticoagulants in precapillary pulmonary hypertension associated with systemic sclerosis: a EUSTAR cohort study

Nicola Farina[1,2,‡], Silvia Bellando Randone[1,‡], Hilde Jenssen-Bjørkekjær[3], Sebastien Sanges[4,5], Patricia Carreira[6], Paolo Airò[7], Serena Guiducci[2], Dilia Giuggioli[8], Gabriela Riemekasten[9], Carmen-Pilar Simeón Aznar[10], Christina Bergmann[11], Elise Siegert[12], Ivan Castellví[13], Lesley Ann Saketkoo[14], Jeska de Vries-Bouwstra[15], Philipp Klemm[16], Ulf Müller-Ladner[16], Alexandra Balbir-Gurman[17], Vanessa Smith[18], Florenzo Iannone[19], Luca Idolazzi[20], Christopher Denton[21], Edoardo Rosato[22], Britta Maurer[23], Yannick Allanore[24], Yoshiya Tanaka[25], Elisabetta Zanatta[26], Marie-Elise Truchetet[27], Masataka Kuwana[28], Mickaël Martin[29], Alberto Cauli[30], Kamal Solanki[31], Francesco Del Galdo[32], Ana Maria Gheorghiu[33], Branimir Anic[34], Gonçalo Boleto[35], Gábor Kumánovics[36], Kristofer Andréasson[37], Simona Rednic[38], Lorinda S Chung[39], Susana Oliveira[40], Marius Cadar[41], Addolorata Corrado[42], Carolina de Souza Müller[43], Vivien M. Hsu[44], Yair Levy[45], Gianluca Moroncini[46], Jörg Henes[47], Andra Balanescu[48], Ellen De Langhe[49], Carlomaurizio Montecucco[50], Petros P. Sfikakis[51], Michele Iudici[52], Stefan Heitmann[53], Madelon C. Vonk[54], Anna-Maria Hoffmann-Vold[55], Oliver Distler[56], Marco Matucci Cerinic[2,57,58], Cosimo Bruni[1,56,*]

[1]Department of Experimental and Clinical Medicine, Scleroderma Unit, Division of Rheumatology, University of Florence, Azienda Ospedaliera Universitaria Careggi, Florence, Italy
[2]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy
[3]Department of Rheumatology, Hospital of Southern Norway, Kristiansand, Norway
[4]National Reference Center for Pulmonary Arterial Hypertension (Pulmotension), Lille, France
[5]Inserm, CHU Lille, Department of Internal Medicine and Clinical Immunology, Reference Center for Rare Autoimmune and Autoinflammatory diseases (CERAINOM), U1286 – INFINITE—Institute for Translational Research in Inflammation, University of Lille, Lille, France
[6]Rheumatology Department, Hospital Universitario, Madrid, Spain
[7]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy
[8]Scleroderma Unit, Rheumatology Unit, University Hospital of Modena and Reggio Emilia, Modena, Italy
[9]Klinik für Rheumatologie und klinische Immunologie, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany
[10]Department of Internal Medicine, Systemic Autoimmune Diseases Unit, Hospital Universitario Vall d'Hebron, Barcelona, Spain
[11]Department Internal Medicine 3, University Hospital Erlangen, Erlangen, Germany
[12]Department of Rheumatology, Charité University Hospital, Berlin, Germany
[13]Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[14]New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, United States
[15]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[16]Department of Rheumatology and Clinical Immunology Center, JLU Giessen, Bad Nauheim, Germany
[17]Rheumatology Institute, Rambam Health Care Campus, Haifa, Israel
[18]Department of Rheumatology, University of Ghent, Ghent, Belgium
[19]Rheumatology DiMePReJ, University of Bari School of Medicine, Bari, Italy
[20]Section of Rheumatology, Department of Medicine, University of Verona, Verona, Italy
[21]Centre for Rheumatology, Royal Free London and University College London Medical School, London, United Kingdom
[22]Department of Translational and Precision Medicine, Azienda Ospedaliero-Universitaria Policlinico Umberto 1-Centro di riferimento regionale per la sclerosi sistemica, Sapienza University of Rome, Rome, Italy
[23]Department of Rheumatology and Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[24]Rheumatology Department, Université Paris Cité, Cochin Hospital, Paris, France
[25]Department of Molecular Targeted Therapeutics, First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyūshū, Japan
[26]Rheumatology Unit, Padova University Hospital, Padova, Italy
[27]Rheumatology Department, CHU de Bordeaux, Bordeaux, France

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[28]Nippon Medical School Hospital, Tokyo, Japan
[29]Department of Internal Medicine, Poitiers University Hospital, Poitiers, France
[30]Department of Medical Sciences and Public Health, Rheumatology Unit, AOU and University of Cagliari, Monserrato, Cagliari, Italy
[31]Rheumatology Unit, Te Whatu Ora Health NZ – Waikato, Waikato School of Medicine, Hamilton, New Zealand
[32]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds Raynaud's and Scleroderma Program, NIHR Biomedical Research Centre, Leeds, United Kingdom
[33]Internal Medicine and Rheumatology Department, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Ion Cantacuzino Hospital, Bucharest, Romania
[34]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Zagreb, School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia
[35]Department of Rheumatology, Faculdade de Medicina, ULS Santa Maria, Centro Académico de Medicina de Lisboa, Universidade de Lisboa, Lisbon, Portugal
[36]Department of Rheumatology and Immunology, University of Pécs, Medical School, Pecs, Hungary
[37]Section of Rheumatology, Department of Clinical Sciences, Lund University, Lund, Sweden
[38]Clinica Reumatologie, University of Medicine and Pharmacy Iuliu Hatieganu Cluj, Cluj-Napoca, Romania
[39]Department of Medicine, Stanford University School of Medicine, Stanford, United States
[40]Department of Medicine IV, Systemic Immunomediated Diseases Unit, Fernando Fonseca Hospital, Amadora, Portugal
[41]Rheumatology Clinic, Sapienza University of Rome, Rome, Italy
[42]Rheumatology Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy
[43]Rheumatology Division, Hospital de Clinicas da Universidade Federal do Parana, Curitiba, Brazil
[44]Rutgers—RWJ Scleroderma Program, New Brunswick, United States
[45]Meir Medical Center, Tel-Aviv University, Kfar-Saba, Israel
[46]Department of Internal Medicine, Marche University Hospital, Clinica Medica, Ancona, Italy
[47]Department for Internal Medicine II (Haematology, Oncology, Rheumatology and Clinical Immunology), University Hospital Tuebingen, Tuebingen, Germany
[48]Department of Internal Medicine and Rheumatology, "Carol Davila" University of Medicine and Pharmacy, "Sf. Maria" Hospital, Bucharest, Romania
[49]Department of Development and Regeneration, University Hospital Leuven, Laboratory of Tissue Homeostasis and Disease, KU Leuven, Leuven, Belgium
[50]Rheumatology Unit, Università di Pavia e IRCCS Fondazione Policlinico S. Matteo, Pavia, Italy
[51]Rheumatology Unit, Athens University Medical School, First Propaedeutic and Internal Medicine, Athens, Greece
[52]Division of Rheumatology, Geneva University Hospitals, Hôpital Beau-Séjour, Geneva, Switzerland
[53]Department of Rheumatology, Marienhospital Stuttgart, Stuttgart, Germany
[54]Department of Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands
[55]Department of Rheumatology, Oslo University Hospital, Oslo, Norway
[56]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[57]Inflammation, Fibrosis and Ageing Initiative (INFLAGE), IRCCS San Raffaele Hospital, Milan, Italy
[58]Medical Faculty, Vita-Salute San Raffaele University, Milan, Italy
[‡]N.F. and S.B.R. contributed equally.
*Correspondence to: Cosimo Bruni, Department of Rheumatology, University Hospital Zurich, University of Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. E-mail: cosimo.bruni@usz.ch

Abstract

Objectives: **The role of anticoagulation in systemic sclerosis (SSc) with precapillary pulmonary hypertension (PH) remains controversial, with conflicting evidence regarding its impact on survival, including potential harmful effects. Aiming to address this research gap, we evaluated both mortality and PH worsening in a large SSc-precapillary PH cohort, additionally accounting for SSc-specific risk factors in our analyses, to better inform individualized treatment decisions.**

Methods: **This retrospective cohort study included SSc patients from the European Scleroderma Trials and Research database with precapillary PH confirmed by right heart catheterization (RHC). The association of oral anticoagulants (OAC) use with survival and PH worsening was assessed using Kaplan–Meier estimates and multivariable Cox regression models. To minimize confounding, propensity score matching was additionally performed.**

Results: **Among 614 patients included, 143 (23%) received OAC at the time of RHC. At baseline, patients on OAC had worse hemodynamic parameters. No significant association was found between OAC use and survival (HR 0.983 95%CI 0.724–1.334) or PH worsening (HR 1.070 95%CI 0.811–1.412). These findings remained consistent after propensity score matching and in the subgroup of 230 SSc patients with precapillary PH without interstitial lung disease.**

Conclusion: **In this large SSc cohort with precapillary PH, we did not observe any clinical benefit associated with OAC, neither in terms of survival nor of PH worsening. Further prospective studies are needed to determine whether specific patient subgroups may benefit from anticoagulation therapy.**

Keywords systemic sclerosis, pulmonary hypertension, anticoagulant, real-world

***Rheumatology* key messages**

- In a large cohort of patients with systemic sclerosis and precapillary precapillary pulmonary hypertension, oral anticoagulation showed no benefit on survival or clinical worsening.
- Our data question routine anticoagulation in this clinical setting, highlighting the need to individualize therapy based on standard thromboembolic indications and bleeding risk.

Introduction

Precapillary pulmonary hypertension (PH), and particularly pulmonary arterial hypertension (PAH), represents a severe and life-threatening manifestation of systemic sclerosis (SSc), characterized by progressive pulmonary vascular remodeling, inflammation and endothelial dysfunction, culminating in increased pulmonary vascular resistance, right heart failure and eventual death [1]. Among the factors implicated in the pathogenesis of PAH, the presence of microthrombosis within the pulmonary vasculature has emerged as a key contributor [2]. Thrombotic lesions in small pulmonary arteries are thought to exacerbate vascular remodeling and contribute to disease progression, highlighting the potential relevance of anticoagulation therapy in managing this condition [3].

Historically, oral anticoagulants (OAC) have been a cornerstone in the management of idiopathic PAH, where their use has been associated with improved survival [4, 5]. However, the role of anticoagulation in SSc-associated precapillary PH remains controversial and incompletely understood. While abnormal coagulation processes and a hypercoagulable state are recognized as part of the disease's pathophysiology [3, 4], existing studies have yielded conflicting results regarding the benefits of anticoagulation in SSc-associated PAH.

The COMPERA registry reported improved survival with OAC among incident idiopathic PAH patients, though findings were less favorable in SSc-associated PAH, showing a non-significant increase in mortality [5]. In contrast, the REVEAL registry found no survival benefit of warfarin in idiopathic PAH and suggested worse outcomes in SSc-PAH patients receiving OAC [6]. Similarly, Johnson *et al.* [7] and the recent French Pulmonary Hypertension Registry study by Bertoletti *et al.* [8]—analysing 1597 PAH patients—demonstrated no association between OAC and survival across all subgroups, including connective tissue disease-associated PAH. Other studies have suggested potential benefits in specific contexts. For instance, Morrisroe *et al.* [9] observed improved survival with combined PAH-specific therapy and OAC, while Ngian *et al.* [10] reported better outcomes with OAC in connective tissue disease-associated PAH, highlighting ongoing controversy. More recently, the SPHInX randomized controlled trial evaluated apixaban in SSc-associated PAH but included only 25 patients with SSc-PAH and was underpowered for its primary end point; it found no benefit on time to clinical worsening or survival [11].

The heterogeneity of these findings stresses the complexity of precapillary PH associated with SSc and the challenges of applying uniform treatment strategies [12]. Differences in study design, patient selection and the inherent heterogeneity of SSc populations likely contributed to the divergent outcomes.

In fact, current European guidelines for the diagnosis and treatment of PH explicitly discourage the routine use of anticoagulation in SSc-associated PAH. In particular, the long-term risk/benefit profile of OAC in SSc is stated to be unfavorable due to an increased bleeding risk associated with gastrointestinal vascular abnormalities [13].

In the current study, we analysed real-world data to evaluate the impact of OAC on mortality and worsening in SSc patients with precapillary PH. Using a large, longitudinal cohort, we aimed to provide robust, clinically relevant evidence to inform treatment decisions and to optimize management strategies in this challenging population. Unlike prior research mainly focused on mortality, our analysis evaluates both mortality and PH worsening in a large SSc cohort. We also incorporate SSc-specific risk factors in adjusted analyses, addressing key gaps to better inform individualized treatment decisions.

Methods

Study design and population

This post-hoc cohort study using both prospectively and retrospectively collected data from the European Scleroderma Trial and Research (EUSTAR) database until 2 June 2022. EUSTAR includes comprehensive clinical, laboratory and outcome data from patients with SSc, as described previously [14]. The study was approved by the EUSTAR board (CP111—Amendment B). In our analysis, we included patients:

- classified as SSc according to the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [15];
- diagnosed with precapillary PH according to the 2022 hemodynamic definition [13]: mean pulmonary arterial pressure >20 mmHg, with pulmonary vascular resistance (PVR) >2 WU and pulmonary wedge pressure (PWP) ≤ 15 mmHg;
- with complete information on OAC exposure status up to the date of right heart catheterization (RHC) and afterwards; and
- with at least 3 months of observation following RHC.

Baseline was defined as the visit of the first diagnostic RHC. To avoid immortal time bias, we excluded patients who initiated OAC after RHC. At this timepoint, data were collected regarding demographic and clinical features, including age, sex, disease duration from the first non-Raynaud's phenomenon sign or symptom, cutaneous subset, autoantibody profile. RHC measurements covered mean, systolic and diastolic pulmonary arterial pressure (mPAP, sPAP and dPAP, respectively), PVR, PWP, cardiac index (CI) and cardiac output (CO).

Regarding treatment, we collected data about the exposure to vasoactive-vasodilating drugs (VVD, including endothelin receptor antagonists, PDE5 inhibitors and prostanoids), immunosuppressive therapies and OAC at the time of RHC. With specific focus on OAC as our main predictor of interest, we included in this category both vitamin K antagonists and direct anticoagulants, considering as 'exposed' patients who received OAC at the time of RHC, for at least 3 months.

Outcome variables at the last available visit included the combination of all-cause mortality and PH worsening. PH worsening was defined by the occurrence of any of the following: a decrease in the 6-min walk test (6MWT) distance of at least 15% from baseline, worsening of PH symptoms [at least one between a change from baseline to a higher New York Heart Association (NYHA) functional class (or no change in patients who were in NYHA functional class IV at baseline) or the appearance or worsening of signs of right heart failure that did not respond to oral diuretic therapy], the need for additional treatment for PH or for lung transplantation, as previously proposed [16].

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as mean ± standard deviation or median (interquartile range), while categorical variables as absolute frequencies and percentages. Differences between patients receiving and not receiving OAC were assessed using appropriate statistical tests based on the distribution and variance of the data. The student's t test was used for normally distributed variables; otherwise, for non-normally distributed variables, the Mann–Whitney test was utilized. For categorical variables, associations were evaluated using the χ^2 test, with Fisher's correction where required.

To evaluate the association between OAC exposure and outcome variables, survival analyses were conducted using Kaplan–Meier estimates, and the log-rank test was used to compare survival curves between groups. A multivariable Cox regression model was performed to identify statistically significant predictors, with a random effect for the country to account for variability across different health systems. Each model was adjusted for covariates associated with severity and the prognosis of precapillary PH, chosen according to published literature and expert consensus by the co-authors, including: age, sex, disease duration, reduced 6MWT distance (<440 meters) [12], reduced CI (<2.5 l/min/m^2) [13], increased levels of brain natriuretic peptide (BNP) (>50 ng/l) or N-terminal (NT) proBNP (>300 ng/l) [13], NYHA functional class III-IV, mPAP on RHC, interstitial lung disease on high resolution computed tomography, diffusion capacity of the lung for carbon oxide on single breath (DLCO/SB) [17], and the use of VVD at the time of RHC as monotherapy or combination. Missing data were handled by sequential single imputation using random Forest models in SAS (PROC HPFOREST; 100 trees) [18]. The proportional hazards assumption was assessed by visual inspection of log-survival plots. Model adequacy was evaluated through inspection of residual plots and dfbeta statistics. Overall model fit was assessed using likelihood ratio statistics.

The survival analyses and regression models were first conducted considering the combined dependent variable (death or PH worsening), then exploring them as individual outcomes. Additionally, sub-analyses were performed to investigate the associations between independent variables and each specific determinant of PH worsening [16].

A sensitivity analysis was conducted excluding patients with any ILD to assess the association between OAC exposure and outcome variables, aiming to isolate a PAH subgroup and improve comparability with idiopathic PAH [5].

Finally, to further minimize confounding and account for differences in baseline characteristics between patients receiving and not receiving OAC, we performed propensity score matching. The propensity score was calculated using a logistic regression model that included the same relevant covariates considered for multivariable Cox regression models, in addition to SSc subset and cigarette smoking ever. A 1:1 nearest-neighbour matching algorithm without replacement was applied, using a caliper width of 0.1 times the standard deviation of the logit of the propensity score, to derive balanced groups of OAC exposed and non-exposed patients. Kaplan–Meier survival analyses were repeated in the matched cohort to validate the robustness of the findings.

All analyses were performed with SPSS v. 31.0.2.0, with type I error set to $< 5\%$.

Results

Study population

Among 19 331 patients with SSc in the EUSTAR cohort, 614 were eligible for this study (flow diagram for cohort selection is shown in Supplementary Fig. S1). Baseline demographics, disease features and RHC data are reported in Table 1, which also compares patients receiving OAC with those not receiving OAC. Notably, patients who received OAC were older, more frequently Caucasian and were characterized by a higher prevalence of ACA positivity, telangiectasias, as well as worse hemodynamic parameters on RHC.

Survival analysis and multivariable regression model

Over mean follow-up of 51 (± 35) months after RHC date, 401 (65%) patients presented with the combined prognostic outcome. In details, 295 (48%) patients experienced PH worsening, and 245 (40%) died. Among these, data about cause of death were available for 89 (36%) patients: 46 died due to PH progression, three due to gastrointestinal bleeding events and 40 due to other causes.

Patients receiving OAC had higher rates of death and PH worsening compared with those not receiving OAC (Table 2), while cause of death did not significantly differ between groups (data not shown). Most individual components of the PH worsening end point/outcome were also more frequent among OAC-treated patients. Despite these findings, survival analysis showed no significant difference in the combined outcome between patients with and without OAC exposure (log-rank $P = 0.535$; Supplementary Fig. S2). Similar results were observed for death (log-rank $P = 0.385$) and PH worsening (log-rank $P = 0.211$) alone. Sub-analyses evaluating single determinants of

Table 1 Data on demographics, disease features, treatment exposure, functional and hemodynamic parameters, and outcome variables, compared between patients who received oral anticoagulants and those who did not.

	All patients (*n* = 614)	**Patients not exposed to OAC (*n* = 471)**	**Patients exposed to OAC (*n* = 143)**	***P*-value**
Female sex	507 (83%)	389 (83%)	118 (83%)	0.536
Age (years)	63 ± 15	62 ± 15	65 ± 10	**0.038**
Caucasian	466 (76%)	350 (89%)	116 (98%)	**<0.001**
Smoking ever	202 (32%)	158 (34%)	44 (31%)	0.264
Diffuse SSc	173 (28%)	149 (32%)	24 (14%)	0.487
Disease duration (years)	10 ± 9	11 ± 9	10 ± 9	0.604
ACA positivity	295 (48%)	215 (46%)	80 (56%)	**0.028**
ATA positivity	140 (23%)	109 (23%)	30 (21%)	0.649
Digital ulcers, ever	208 (34%)	162 (37%)	46 (35%)	0.835
Gastroesophageal symptoms	442 (72%)	347 (74%)	95 (67%)	0.067
Telangiectasias	474 (77%)	353 (75%)	121 (86%)	**0.011**
Renal crisis, ever	20 (4%)	18 (4%)	2 (1%)	0.184
ILD on HRCT	384 (62%)	302 (64%)	82 (57%)	0.086
Dyspnea (NYHA class ≥ III)	318 (52%)	239 (51%)	79 (56%)	0.586
Increased NTproBNP/BNP	220 (35%)	151 (32%)	69 (48%)	**<0.001**
6MWT distance (m)	343 ± 117	348 ± 117	325 ± 116	**0.047**
VVD monotherapy	147 (24%)	117 (25%)	30 (21%)	0.467
VVD dual therapy	87 (14%)	70 (15%)	17 (12%)	
VVD triple therapy	45 (7%)	32 (7%)	13 (9%)	
Immunosuppressants	310 (51%)	232 (50%)	78 (55%)	0.339
FVC (% predicted)	84 ± 24	84 ± 24	84 ± 21	0.790
DLCO/SB (% predicted)	42 ± 15	43 ± 15	42 ± 14	0.695
sPAP on RHC (mmHg)	55 ± 19	54 ± 18	60 ± 20	**0.003**
dPAP on RHC (mmHg)	20 ± 9	20 ± 8	22 ± 10	**0.009**
mPAP on RHC (mmHg)	34 ± 11	34 ± 11	37 ± 12	**0.003**
PVR (Wood Units)	6 ± 5	6 ± 5	7 ± 5	**0.018**
CO (L/min)	4.8 ± 1.9	4.8 ± 1.4	4.6 ± 3.0	0.342
PWP (mmHg)	10 ± 3	9 ± 3	10 ± 3	0.252
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.8 ± 0.8	2.9 ± 0.8	2.6 ± 0.9	**0.001**

Categorial and continuous variables are reported as absolute numbers (%) and mean (standard deviation), respectively. Bold represents statistical significance with *P*-value < 0.05. ACA: anti-centromere antibodies; ATA: anti-topoisomerase antibodies; BNP: brain natriuretic peptide; CI: cardiac index; CO: cardiac output; DLCO/SB: diffusion lung capacity of carbon monoxide on single breath; dPAP: diastolic pulmonary arterial pressure; FVC: forced vital capacity; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; mPAP: mean pulmonary arterial pressure; NT: N-terminal; NYHA: New York Heart Association; PVR: pulmonary vascular resistance; PWP: pulmonary wedge pressure; RHC: right heart catheterization; SSc: systemic sclerosis; sPAP: systolic pulmonary arterial pressure; VVD: vasoactive-vasodilating drugs ongoing at the time of RHC; 6MWT: 6-min walking test.

Table 2 Data on outcome variables, including specific determinant of pulmonary hypertension worsening, compared between patients who received oral anticoagulants and those who did not.

	All patients (*n* = 614)	**Patients not exposed to OAC (*n* = 471)**	**Patients exposed to OAC (*n* = 143)**	***P*-value**
Combined outcome	401 (65%)	298 (63%)	103 (72%)	**0.033**
Deaths	245 (40%)	176 (37%)	69 (48%)	**0.025**
PH worsening	295 (48%)	213 (45%)	82 (57%)	**0.013**
Decrease in the 6MWT distance	130 (21%)	94 (20%)	36 (25%)	0.112
Worsening of NYHA class	195 (32%)	134 (28%)	61 (43%)	**0.001**
Right heart failure	91 (15%)	62 (13%)	29 (20%)	**0.027**
Additional PH therapy	178 (29%)	123 (26%)	55 (38%)	**0.003**
Lung transplantation	20 (3%)	15 (3%)	5 (3%)	0.849

Categorial variables are reported as absolute numbers (%). Bold represents statistical significance with *P*-value < 0.05. NYHA: New York Heart Association; OAC: oral anticoagulants; PH: pulmonary arterial hypertension; 6MWT: 6-min walking test.

PH worsening showed no significant associations with OAC (data not shown).

In multivariable Cox regression analyses, OAC was not significantly associated with any of the primary (panel a of Fig. 1) or secondary (panels b and c of Fig. 1) outcome variables.

Propensity score matching

Propensity score matching identified 120 case-control matched pairs. The overall balance between the two groups was achieved in terms of the main demographic and clinical characteristics, except for ethnicity (Supplementary Table S1). Kaplan–Meier survival analysis performed in this matched population did not show any significant association between OAC exposure and death or PH worsening, both in combination (panel a of Fig. 2) or as individual events (panels b and c of Fig. 2), nor with the specific PH worsening features.

Sensitivity analysis

After excluding SSc patients with any extent of ILD, we identified 230 patients with precapillary PH (namely, PAH). Of them, 61 (27%) had received OAC at the time of RHC (Supplementary Table S2). Clinically, the patients in this sub-cohort resembled the whole study population, except for a higher prevalence of Caucasian ethnicity (more prevalent in patients treated with OAC) and ACA positivity, the latter well-distributed between the two groups.

In this group I PAH cohort, survival analysis did not show a higher risk of death among OAC-exposed patients (log rank $P = 0.097$; Cox regression HR 1.303, 95%CI 0.769–2.107), but it did so for PH worsening at univariable analysis (log rank $P = 0.018$), even though this was not confirmed by multivariable Cox regression (HR 1.606, 95%CI 1.016–2.536). Likewise, when looking at single components of the worsening end point, while log-rank test showed and association for the need for additional PH treatment (log rank $P = 0.038$) and the appearance or worsening of signs of right heart failure (log rank $P = 0.003$) with OAC exposure, this was not confirmed by Cox regression adjusted for confounders (additional PH treatment: HR 1.486, 95%CI 0.872–2.532; right heart failure: HR 1.294, 95%CI 0.613–2.173).

Discussion

In this large, multicentre cohort study analysing real-world data from the EUSTAR database, we investigated the association between OAC use and prognosis of SSc patients with precapillary PH. Unlike prior research focused solely on mortality, our analysis evaluates both mortality and PH worsening in a large cohort. We also incorporate SSc-specific risk factors in adjusted analyses, addressing key gaps to better inform individualized treatment decisions. Our findings did not demonstrate any significant association between OAC use and survival, nor did they show a protective effect against PH worsening. Consistent results were observed after adjustment for confounding factors using propensity score matching, with no meaningful differences in outcomes between patients receiving and not receiving OAC. These findings suggest that routine oral anticoagulation in SSc patients with precapillary PH may not provide a clear clinical benefit, although the absence of OAC-related safety data limits the generalizability of our findings.

The result of our study aligns with the complex risk-benefit balance previously observed in SSc-associated PAH and further clarifies the conflicting results of previous studies on smaller SSc cohorts [5–12].

Although *in situ* thrombosis has been implicated in PAH pathophysiology [2, 3], our findings demonstrate that in an unselected SSc population with precapillary PH, OAC exposure was associated with neutral or worse clinical outcomes. Considering that patients with SSc may be more prone to bleeding complications due to underlying vasculopathy and gastrointestinal involvement [19], these results are further reinforced by the recently published SPHInX randomized controlled trial. In SPHInX, apixaban showed no benefit over placebo on time to clinical worsening or survival in SSc-PAH and was associated with a high frequency of iron-deficiency anaemia, suggesting that the risks of anticoagulation may outweigh any potential benefit [11]. Accordingly, our data do not support routine OAC initiation for precapillary PH in SSc patients, though OAC remains indicated for established, non-PH-related cardiovascular comorbidities such as atrial fibrillation or venous thromboembolism [20, 21].

A key observation in our study was that patients receiving OAC had worse baseline hemodynamic parameters, suggesting that OAC were more frequently prescribed in patients with more severe PH features. Interestingly, this did not reflect in a different distribution between groups of VVD administration (either in monotherapy or combination).

Despite this, the results of our analyses, well-adjusted for confounders, did not show any survival advantage in patients receiving OAC, nor did they suggest a meaningful reduction in precapillary PH worsening. Importantly, our multivariable models did not identify OAC as a protective factor against death or PH worsening, and sub-analyses of individual determinants of PH worsening similarly failed to reveal significant associations.

To minimize bias, we also repeated our analysis after propensity score matching, ensuring that key baseline characteristics were balanced between anticoagulated and non-anticoagulated patients. Despite this rigorous adjustment, still no association was observed between OAC and survival outcomes. This strengthens the validity of our findings and suggests that the absence of benefit is not merely due to differences in disease severity or treatment strategies.

Even in the sensitivity analysis restricted to SSc patients without ILD—representing a subgroup of pure vascular PAH class 1—no beneficial effect of anticoagulation was observed. Indeed, we noted a tendency—although not confirmed by multivariable analysis—for OAC-treated patients to more frequently need additional PH therapy, as a proxy for worsening, in line with data previously shown by the REVEAL registry [6]. Overall, these data might not be interpretable as a negative effect related to OAC, but instead as a lack of therapeutic, beneficial effect of this category of medication in SSc patients. This contrasts with findings from the COMPERA registry [5], which reported improved survival with anticoagulation in idiopathic PAH.

Overall, our findings are consistent with current guideline recommendations [13], which advise against the routine use of anticoagulation in SSc-associated PAH, although several

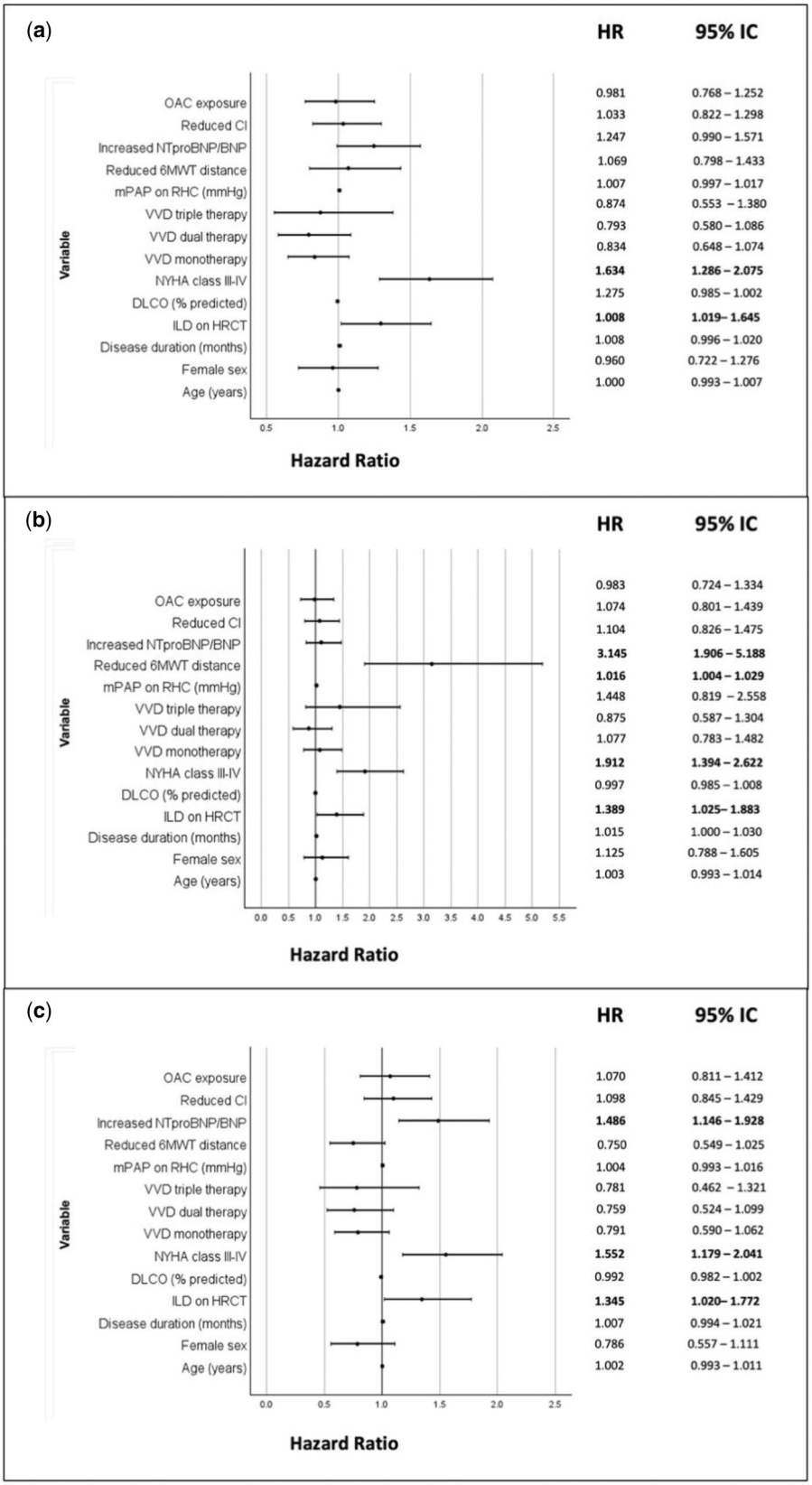

Figure 1 Forest plots of multivariable regression models testing the association between exposure to oral anticoagulants and the prognosis (panel a primary end point, panel b death, panel c pulmonary hypertension worsening) of patients with pulmonary arterial hypertension at right heart catheterization. BNP: brain natriuretic peptide; CI: cardiac index; DLCO: diffusion lung capacity of carbon monoxide; HR: hazard ratio; HRCT: high resolution computed tomography; ILD; interstitial lung disease; mPAP: mean pulmonary arterial pressure; NYHA: New York Heart Association; PH: pulmonary hypertension; VVD: vasoactive vasodilating drugs ongoing at right heart catheterization; 6MWT: 6-minute walking test. Bold represents statistical significance with *P*-value < 0.05

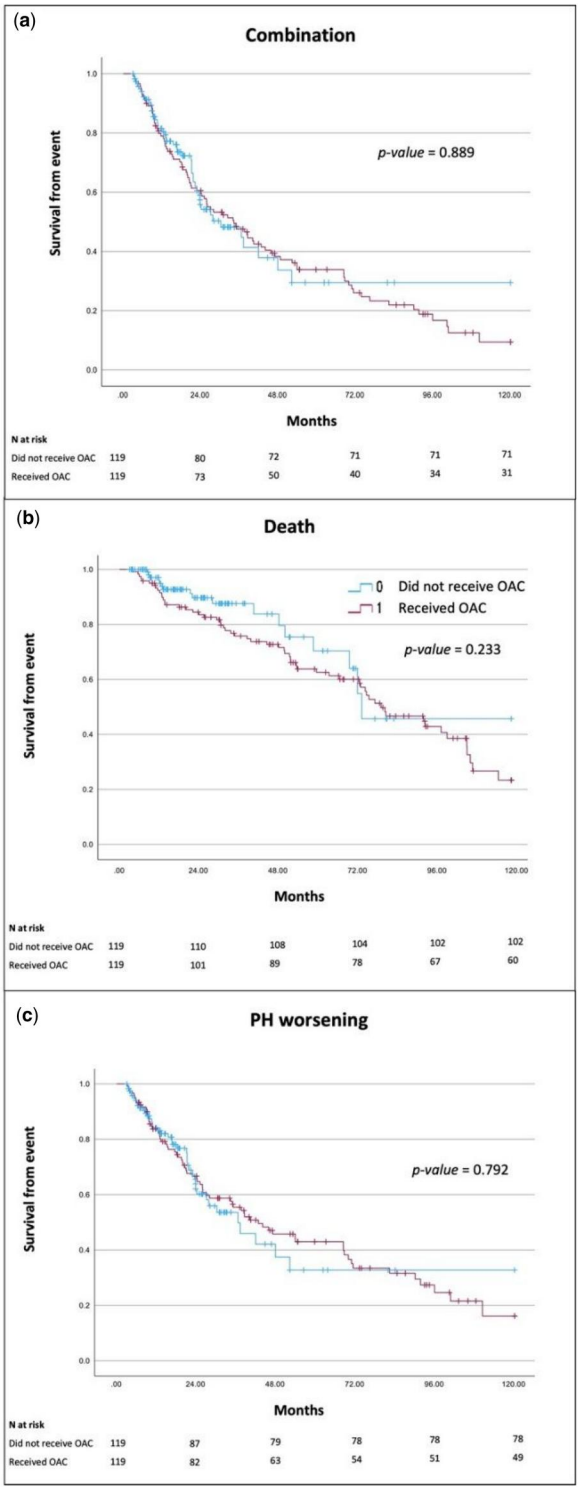

Figure 2 Survival curves for different outcome variables according to the exposure status to oral anticoagulants (blue line: not exposed; red line: exposed) in the match-control population identified using propensity score matching, for the combined outcome (panel a), death alone (panel b) or PH worsening alone (panel c). OAC: oral anticoagulants; PH: pulmonary hypertension

limitations should be acknowledged regarding our study. We could not differentiate between anticoagulant types, as the specification of vitamin K antagonists *vs* direct OAC is not part of the original dataset and this may have different risk-benefit profiles. Additionally, we did not have data about cause of death for all patients and we lacked information about adverse events, including bleeding complications or predisposing SSc features (such as gastric antral vascular ectasia), which would provide further insight into the safety concerns associated with OAC in SSc-PAH. In addition, we also lacked information regarding the SSc-unrelated conditions (including trombophilic-related factors) for initiating OAC: concomitant cardiovascular comorbidities might indeed have had an impact on the overall prognosis of our patients independently of SSc and precapillary PH status. Notably, compared with prior studies [22, 23], our cohort exhibited a higher event rate for PH worsening, possibly attributable to less intensive treatment in earlier years and our use of a single criterion definition [16], *vs* composite endpoints used in other studies [23]. Finally, despite the fact that we adjusted for as many features as possible and performed PSM, the more severe baseline status of the patients treated with OAC might still limit the interpretation of our findings.

In conclusion, significant clinical benefit associated with exposure to OAC could not be detected in our large, international cohort of SSc patients with precapillary PH. Further prospective studies taking also into consideration OAC safety outcomes and indications are needed to clarify whether any subset of patients with SSc-associated PH may benefit from anticoagulation therapy. Until such data becomes available, the decision to initiate OAC should be made on a case-by-case basis, carefully weighing the potential risks and benefits based on cardiovascular and pro-thrombotic comorbidities, according to appropriate guidelines [20, 21].

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data will be shared on reasonable request to the corresponding author, subject to approval by EUSTAR and in accordance with applicable data protection and governance policies.

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