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ORIGINAL RESEARCH

Burden of Atherosclerosis and Outcomes of Acute Pulmonary Embolism: A Post Hoc Analysis of the Hokusai-VTE Trial

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BACKGROUND: The burden of atherosclerosis may have prognostic implications for patients affected by venous thromboembolism (VTE). We aimed to assess the association of the presence and extent of atherosclerotic disease with long-term clinical outcomes in patients with acute pulmonary embolism (PE).

METHODS: In patients with PE from the Hokusai-VTE trial, we assessed the association between the presence of atherosclerotic disease in multiple (polyvascular disease), one, or no vascular territories (coronary, cerebral, and/or peripheral arteries) and 1-year risk of VTE or PE recurrence, major bleeding, and all-cause death. We used univariable and multivariable Cox regression analysis, with adjustment for relevant comorbidities and anticoagulation modeled as a time-varying covariate.

RESULTS: Of 2800 patients, 67 (2.4%) had polyvascular and 357 (12.7%) had single vascular atherosclerotic disease. During 12-month follow-up, recurrent VTE was reported for a total of 356 patients, including 208 PE events. A total of 52 patients had a major bleeding event and 91 deaths were recorded. Polyvascular atherosclerotic disease was strongly associated with VTE (adjusted hazard ratio,1.91 [95% CI, 1.05–3.49]) and PE recurrence (adjusted hazard ratio, 2.06 [95% CI, 1.03–4.16]). Polyvascular and single vascular disease were associated with major bleeding and all-cause death in univariable analysis; however, these associations attenuated after adjustment.

CONCLUSIONS: The pre-existing burden of atherosclerosis may have prognostic value with respect to secondary prevention in patients who experienced an acute PE. Optimization of overall cardiovascular risk may be considered by management studies in the follow-up of this patient population.

REGISTRATION: URL: www.clinicaltrials.gov; Unique identifier: identifier: NCT00986154

Key Words: atherosclerosis ■ prognosis ■ pulmonary embolism ■ recurrence ■ venous thromboembolism

Venous thromboembolism (VTE) and, in particular, pulmonary embolism (PE), is the third most frequent cardiovascular cause of death following acute myocardial infarction and ischemic stroke.[1] The burden of PE on patients and health care systems is substantial: its incidence is high and increasing, it can be fatal in the acute phase,[2,3] and it is often associated with persisting symptoms and long-term sequelae.[4–6]

Those who survive acute PE have a high risk of recurrence and of other adverse events linked to its treatment, such as bleeding, or to the baseline risk profile and comorbidities.[1] The risk of these events may be associated with overall vascular health in general, and the burden

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CLINICAL PERSPECTIVE

What Is New?

- Using data from a randomized clinical trial with pre-defined follow-up, we demonstrated that pre-existing polyvascular disease worsens the overall prognosis of other acute cardiovascular disease.
- The burden of atherosclerosis, as assessed by the number of affected vascular territories (coronary, cerebral, and peripheral arterial circulations) in the medical history at the time of pulmonary embolism, is associated with an increased long-term risk of pulmonary embolism recurrence, bleeding, and all-cause mortality.

What Are the Clinical Implications?

- Assessment of overall cardiovascular risk, encompassing arterial and venous vessels, may play a role in the long-term management of patients recovering from acute pulmonary embolism.

Nonstandard Abbreviation and Acronym

ISTH	International Society on Thrombosis and Hemostasis

of atherosclerosis in particular, at the time of the acute PE. This association is likely due to pathophysiological pathways and risk factors shared by arterial and venous thrombosis, including but not limited to endothelial injury, metabolic derangement, or systemic inflammation and hypercoagulopathy.[7] These abnormalities typically result in a prothrombotic state, reflecting a bidirectional relation between VTE and atherosclerosis.[8–10] Indeed, on the one hand VTE seems to be associated with concomitant or subsequent atherosclerosis;[11,12] on the other hand, post hoc analyses of trials have suggested that the greater the burden of atherosclerosis, the higher the VTE risk.[13] The latter is independently related to the number of the affected vascular territories (ie, coronary, cerebral, or peripheral arteries).[13,14]

The number of arterial territories involved by atherosclerosis may represent a plausible proxy of the burden of atherosclerosis and may lead to site-specific complications.[13] Atherosclerosis in different territories shares the same risk factors but with different strength of association and with some evidence of interaction with regard to atherogenic potential.[15] In this perspective, the larger the number of these territories, the worse vascular involvement can be assumed to be across multiple pathophysiological pathways. Accordingly, we hypothesized that, among patients presenting with acute PE, the burden of coexisting atherosclerosis, assessed by the number of affected territories, may be associated with the risk of subsequent complications, particularly recurrence. If confirmed, this association would offer an additional prognostic tool for post-PE assessment and imply that optimizing atherosclerosis management might improve PE-specific outcomes as well.

Therefore, in the present study, we performed a post hoc analysis to test the association between the burden of atherosclerosis, as reflected by the number of affected vascular territories, with PE or VTE recurrence, bleeding, and death in the population of a large randomized trial on anticoagulant treatment of VTE.[16]

METHODS

The design and methods of the Hokusai-VTE study have been previously described (ClinicalTrials.gov identifier: NCT00986154).[16,17] Briefly, Hokusai-VTE was a phase III, randomized, double-blind, double-dummy, noninferiority, event-driven trial that compared edoxaban with warfarin in 8292 adult patients with acute, symptomatic deep vein thrombosis (DVT) or PE, and led to the approval of edoxaban for this indication. The primary efficacy outcome was symptomatic recurrent VTE and the principal safety outcome was major or clinically relevant nonmajor bleeding. All participants provided written informed consent before randomization and the study was approved by the institutional review board of each participating center.

Patients were excluded if, among others, they had clinically significant liver disease or severe renal function impairment, contraindications to heparin or warfarin, or another indication for therapy with a vitamin K antagonist. A full list of the inclusion and exclusion criteria is provided in the original study protocol. Initially, all enrolled patients received open-label unfractionated heparin or enoxaparin for at least 5 days, after which they were started on edoxaban or warfarin. Treatment duration with the trial medication was at least 3 months for all patients and extended up to 12 months at the physician's discretion. Regardless of the total treatment duration, all patients were followed for a total of 12 months.

Study Population

For this analysis, we only included patients diagnosed with acute PE as the index event, irrespective of history of prior VTE and the presence of concomitant DVT, and provided that they had available follow-up data.[16] PE was defined as (1) at least 75% perfusion defect of a segment with a local ventilation result on a perfusion/ventilation lung scan, (2) an intraluminal filling defect in (sub) segmental or more proximal branches on a spiral computed tomography scan, (3) an intraluminal filling defect or a sudden cut-off of vessels greater in diameter than 2.5 mm on a pulmonary angiogram, or (4) identification of DVT on a lower-extremity compression ultrasound or venography in case of an inconclusive lung scan.[17]

Definitions

We classified all patients into 3 distinct groups according to the number of vascular territories affected by atherosclerosis, based on the medical history recorded by the Hokusai VTE investigators at the time of the index PE: (1) patients with polyvascular atherosclerotic disease, defined as those with at least 2 affected territories out of the following ones: coronary arterial circulation (symptomatic coronary artery disease including acute myocardial infarction or angina or intervention with these indications); cerebrovascular circulation (ischemic stroke, endovascular intervention for stroke or carotid artery stenosis, or transient ischemic attack); and peripheral arterial circulation (symptomatic peripheral artery disease or intervention for peripheral artery disease); (2) patients with single vascular atherosclerotic disease; and (3) patients without medical history of symptomatic atherosclerosis or intervention with this indication.

The outcomes of interest were VTE recurrence, PE recurrence, major bleeding, and all-cause death as reported by the investigators during the follow-up period of the original trial. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis criteria.[18]

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as medians with interquartile range. The date of the index PE was considered the start of follow-up.

Univariable and multivariable Cox proportional hazards regression models for the association of clinical variables with time to first occurrence (or censoring) of each of the 4 outcomes were used to estimate hazard ratios (HRs) with corresponding 95% CIs. For each outcome, we constructed 3 models. Model 1 was univariable and included the number of vascular territories affected by atherosclerosis (classified as polyvascular, single vascular territory, or none, the latter serving as reference) as only explanatory variable. We generated the corresponding Kaplan–Meier curves and Cox survival curves. Model 2 was additionally adjusted for age, sex, and anticoagulation modeled as a binary time-varying covariate. Model 3 was adjusted for all variables included in Model 2 and additionally for renal failure (creatinine clearance <50 mL/min), heart rate >110 beats per minute, history of previous VTE, anemia, cancer, chronic lung disease, chronic heart failure, diabetes, and the use of antiplatelets or statins, all at baseline. The anticoagulation period was defined as the initial phase with heparin followed by the duration under the trial medication (edoxaban or warfarin) plus 3 days, as described in the study protocol.[17] Patients were considered to be using antiplatelets or statins at baseline if they had initiated these medications either before the start of follow-up or, to account for late recording of baseline medication, within 2 days thereafter.

We performed the following model checks. First, we checked the proportional hazards assumption using scaled Schoenfeld residuals. Model fit was examined using martingale residuals and cumulative hazard plots of the Cox-Snell residuals. Because all covariates were categorical, nonlinearity was not an issue. Finally, we investigated the influence of single observations by calculating approximate delta-betas based on score residuals. Originally, we also tested a model in which anticoagulation was modeled as a continuous variable in days rather than as a binary time-varying covariate. However, we found that for this variable, the hazard ratio increased with time from a value <1 to a value >1, violating the proportional hazards assumption. This may have been due to confounding introduced by the clinical severity and prognostic features that affected the medical decision on the length of anticoagulation in individual patients. Therefore, we did not include this model in the final analysis.

For the primary analysis, patients with missing data on vascular territories were assumed to have no affected territories (0 affected territories). Additionally, a sensitivity analysis was conducted in which patients with missing values were excluded. A second sensitivity analysis was performed, stratifying VTE events as provoked or unprovoked, according to the definitions used in the original Hokusai VTE data collection.[16]

Two-tailed P values of <0.05 were considered significant. Statistical analysis was performed using R (R Foundation for Statistical Computing).[19]

Data Availability Statement

All data from Hokusai VTE study have been made available in anonymized form at the Vivli – Center for Global Clinical Research Data repository and can be accessed after approval of a data request by the data contributor at https://vivli.org.[20]

RESULTS

Study Populations

Of the 8292 patients included in the Hokusai VTE study, 8240 received at least 1 dose of the trial medication (4118 edoxaban versus 4122 warfarin). For post hoc analyses, data were available for 7541 individuals after de-identification/anonymization according to regulatory requirements. Of these, 2800 (37.1%) with an acute PE as the index event were included in the current study; concomitant DVT was diagnosed in 962 (34.4%) patients.

Table 1. Baseline Characteristics of N=2800 Patients With Pulmonary Embolism From the Hokusai VTE Trial

N=2800	Polyvascular disease (N=67)	Single vascular artery disease (N=357)	No vascular disease (N=2376)
Males, n (%)	38 (57)	197 (55)	1262 (53)
Age (y), median (IQR)	72 (62.5–80)	69 (62.0–76.0)	57 (44.0–69.0)
Weight (kg), median (IQR)	79 (69.2–93.0)	76 (65.5–90.0)	81.6 (69.0–95.0)
Risk factors, n (%)			
Diabetes	17 (25)	73 (20)	206 (9)
Arterial hypertension	57 (85)	255 (71)	894 (38)
Active cancer	2 (3)	14 (4)	60 (3)
History of VTE	7 (10)	50 (14)	328 (14)
Recent surgery/immobilization	12 (18)	78 (22)	459 (19)
Hormonal treatment	0 (0)	9 (3)	95 (4)
Known thrombophilias	4 (6)	6 (2)	127 (5)
Arterial disease, n (%)			
Ischemic heart disease	58 (87)	221 (62)	0 (0)
Cerebrovascular disease	49 (73)	100 (28)	0 (0)
Peripheral artery disease	33 (49)	36 (10)	0 (0)
Comorbidities, n (%)			
Atrial fibrillation	13 (19)	28 (8)	67 (3)
Chronic heart failure	16 (24)	43 (12)	92 (4)
Chronic lung disease	25 (37)	104 (29)	367 (15)
Obstructive sleep apnea syndrome	8 (12)	22 (6)	57 (2)
Liver steatosis	3 (5)	22 (6)	82 (4)
Chronic kidney disease	18 (27)	46 (13)	130 (6)
Concomitant medications, n (%)			
Corticosteroids	8 (12)	47 (13)	223 (9)
NSAIDs	6 (9)	35 (10)	296 (13)
Antiplatelets	35 (52)	142 (40)	239 (10)
Statins	34 (51)	127 (36)	238 (10)
Clinical presentation			
HR, median	77 (70.0–87.5)	80 (70.0–88.0)	80 (71.0–88.5)
RR, median	18 (16.2–20.0)	19 (17.0–21.0)	18 (16.0–20.0)
Concomitant DVT, n (%)	19 (28)	89 (25)	854 (36)

Known thrombophilias included Factor V Leiden, hyperhomocysteinemia, prothrombin gene mutation, protein S deficiency, protein C deficiency, antithrombin deficiency, antiphospholipid antibody syndrome, and other unspecified thrombophilic conditions. DVT indicates deep vein thrombosis; HR, heart rate; IQR, interquartile range; RR, respiratory rate; and VTE, venous thromboembolism.

Polyvascular and single vascular artery disease were present in 67 (2.4%) and 357 (12.7%) patients, respectively. In both groups, ischemic heart disease was most common (87% in polyvascular and 62% in single vascular artery disease, respectively), followed by cerebrovascular disease (73% and 28%) and peripheral artery disease (49% and 10%). The baseline characteristics of the included patients are presented in Table 1. During a follow-up of 12 months, recurrent VTE was reported for a total 356 patients, including 208 PE events; a total of 52 (1.9%) patients had a major bleeding event and 91 (3.2%) deaths were recorded.

Association of Burden of Atherosclerotic Disease With Clinical Outcomes

The presence of polyvascular atherosclerotic disease was strongly associated with recurrent VTE and PE, even after adjusting for multiple confounders. For recurrent VTE, the HR for polyvascular disease (versus no vascular disease) was 1.91 (95% CI, 1.05–3.49) in the fully adjusted model (Model 3); for recurrent PE, the HR was 2.06 (95% CI, 1.03–4.16). In contrast, single vascular atherosclerotic disease was not associated with either outcome in any model.

As regards major bleeding, the association was present in univariable analysis for both polyvascular

(HR vs. no vascular disease, 3.84 [95%, CI, 1.36–10.9]) and single vascular disease (HR vs. no vascular disease, 2.47 [95% CI, 1.31–4.67]). However, its strength progressively diminished with additional adjustments and was no longer present in Model 3 (HR, 1.39 [95% CI, 0.45–4.31] for polyvascular disease; HR, 1.04 [95% CI, 0.51–2.10] for single vascular disease). Both polyvascular and single vascular disease were associated with mortality in univariable analysis (HR versus no vascular disease 2.78 [95% CI, 1.12–6.90] and HR, 2.43 [95% CI, 1.53–3.92], respectively). However, the association weakened and was no longer statistically significant after adjustment, with the HR for polyvascular disease decreasing to 1.57 (95% CI, 0.60–4.13) and for single vascular disease to 1.31 (95% CI, 0.77–2.21) in Model 3 (Table 2).

The Kaplan–Meier curves and the Cox survival curves for the crude association of polyvascular atherosclerotic disease with each outcome is shown in Figures S1–S4.

Sensitivity Analysis

The first sensitivity analysis tested the assumption that a missing report of vascular disease at baseline implied absence of vascular disease. This led to the exclusion of 155/2800 (5.5%) patients with no reported presence or absence or vascular disease. The association of the burden of atherosclerosis with the 4 clinical outcomes of interest was comparable to the one observed in the main analysis for all models (Table S1). In the second sensitivity analysis, polyvascular disease was associated with recurrent PE in patients with unprovoked VTE in model 2; however, this association attenuated with multiple adjustment (Table S2).

Table 2. Cox Proportional Hazards Regression Analysis of the Association of Burden of Atherosclerosis With 1-Year Recurrent VTE, Recurrent PE, Major Bleeding, and All-Cause Death in 2800 Patients With PE From the Hokusai-VTE Study

N=2800	Polyvascular disease HR (95% CI) vs. no vascular disease	Single vascular artery disease HR (95% CI) vs. no vascular disease
Recurrent VTE (N=356)		
Model 1 (univariable)	1.54 (0.88–2.69)	0.98 (0.72–1.35)
Model 2	2.14 (1.21–3.80)*	1.19 (0.86–1.65)
Model 3	1.91 (1.05–3.49)*	1.07 (0.76–1.52)
Recurrent PE (N=208)		
Model 1 (univariable)	2.03 (1.07–3.85)*	0.97 (0.63–1.47)
Model 2	2.70 (1.39–5.25)*	1.14 (0.74–1.76)
Model 3	2.06 (1.03–4.16)*	0.92 (0.58–1.46)
Major bleeding (N=52)		
Model 1 (univariable)	3.84 (1.36–10.9)*	2.47 (1.31–4.67)*
Model 2	2.94 (1.02–8.51)*	1.81 (0.94–3.50)
Model 3	1.39 (0.45–4.31)	1.04 (0.51–2.10)
All-cause death (N=91)		
Model 1 (univariable)	2.78 (1.12–6.90)*	2.43 (1.53–3.92)*
Model 2	2.41 (0.95–6.09)	1.57 (0.96–2.59)
Model 3	1.57 (0.60–4.13)	1.31 (0.77–2.21)

*Results are statistically significant for P <0.05.

Hazard ratios (95% CI) are calculated vs. no vascular disease as reference. Explanatory variables in each model: Model 1: number of vascular territories affected by atherosclerosis (univariable). Model 2: Model 1+age, sex, time-varying anticoagulation yes/no. Model 3: Model 2+renal failure (creatinine clearance <50 mL/min), prior VTE, anemia, cancer, chronic lung disease, chronic heart failure, heart rate >110 beats per minute, diabetes, antiplatelets, statins. HR indicates hazard ratio; PE, pulmonary embolism; and VTE, venous thromboembolism.

DISCUSSION

Our post hoc analysis of a randomized clinical trial showed that the burden of atherosclerosis, as assessed by the number of affected vascular territories (coronary, cerebral, and peripheral arterial circulations) at the time of PE, is associated with increased long-term risk of PE recurrence, bleeding, and all-cause death.

Polyvascular disease, defined as the presence of atherosclerosis in multiple arterial beds or territories, has emerged as a potentially relevant marker of the burden of atherosclerosis. It reflects a greater vascular compromise than single-vessel atherosclerosis. In patients with atherosclerosis in >1 territory, the severity of atherosclerosis in each territory is higher than in patients with atherosclerosis in only 1 territory, and atherosclerotic plaques have distinct characteristics.[21–24] Because different risk factors for atherosclerosis have a different impact on atherosclerosis at each vascular bed, polyvascular disease may reflect a worse risk profile across several of the pathophysiologic pathways leading to atherosclerosis.[15]

The association between polyvascular disease and adverse outcomes after PE may be explained by several mechanisms. Although a direct link between atherosclerosis and VTE remains uncertain, several risk factors are thought to be common, worsening the overall prognosis.[10,25] Well-studied shared modifiable risk factors include obesity, diabetes, and hypertension,[26,27] particularly if the constellation of the metabolic syndrome is present.[28,29] Indeed, lipid-lowering drugs have been reported, in addition to their atheroprotective effects, to be associated with a lower risk of VTE.[30–33] A possibly nonmodifiable component of the shared risk that clusters within families has also been described.[34] Accordingly, there is a growing consensus on the importance of optimizing the management

of cardiovascular risk after a first episode of VTE.[35] Atherosclerosis is also associated with bleeding, a major complication of VTE treatment, both indirectly through common risk factors and directly, through the risk of bleeding imposed by a history of stroke.[36]

The worse prognosis of patients post-PE with polyvascular arterial disease may also be driven by complications and treatment side effects. Polyvascular disease is associated with increased multiorgan damage, particularly renal disease, which makes the management of medical therapy complex.[37] Furthermore, in patients with polyvascular disease, the treatment of PE needs to be harmonized with the pre-existing therapy of atherosclerosis and its risk factors, especially when it comes to the reassessment of the bleeding risk and the switch across antithrombotic and anticoagulant treatment.[38,39] Other cardiovascular drugs, such as antihypertensive drugs, often need to be discontinued or modified in the acute stage of PE treatment, and nonmedical factors such as patient compliance, health care literacy, or access to health care may also affect prognosis.[35,40–42]

Last, PE may exacerbate the pre-existing burden that, in patients with polyvascular arterial disease, multimorbidity imposes on the patient's psychological well-being, functional status, and self-management abilities.[43–46]

Our findings extend those of several recent studies showing that existing polyvascular disease worsens the overall prognosis of other acute cardiovascular disease. It increases the risk of complications in patients with atrial fibrillation and ischemic stroke and of patients hospitalized for acute heart failure.[47,48]

The association observed in this study suggests that assessment of overall vascular health may play a role in the long-term management of patients recovering from PE. In addition, a medical history of polyvascular disease is readily available to physicians, and patients with arterial disease are likely to already be under long-term management, facilitating risk optimization and secondary prevention for PE.

Despite the use of data from a randomized clinical trial and multivariable adjustment including the modeling of anticoagulation as a time-varying variable, this nonprespecified analysis may have a number of limitations. First, the definition of polyvascular disease as number of territories involved by atherosclerotic conditions in the medical history was limited to known medical diagnoses and may not have captured subclinical atherosclerosis. However, this potential misclassification would only result in a loss of specificity (those classified as without atherosclerotic disease may have had subclinical atherosclerosis), but not of sensitivity (the past diagnoses in our definition ensured the ascertainment of atherosclerosis). In addition, the definition we used corresponds to the information available to a physician treating a patient after PE, and makes our finding generalizable to clinical practice. Second, the study protocol does not explicitly specify whether compression ultrasound of the lower limb was performed systematically in patients with acute PE and therefore, the proportion of concomitant DVT may be underestimated. Third, certain associations attenuated with multivariable adjustment. While this attenuation does not remove the potential prognostic implications in a real-life setting, it may be due to the relatively small number of events and subsequent low power in the context of an unplanned post hoc multivariable analysis. This may especially apply to the association with major bleeding, the outcome with the smallest number of events. Of note, the exclusion criteria in the original trial may have led to the underrepresentation of polyvascular disease in our sample, although this is unlikely to have affected the direction of the associations that we observed.

In conclusion, the pre-existing burden of atherosclerosis may have prognostic value with respect to secondary prevention in patients who experienced an acute PE. Optimization of overall cardiovascular risk may be considered by management studies in the follow-up of this patient population.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figures S1–S4

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