ORIGINAL ARTICLE

Prophylaxis with enoxaparin for prevention of venous thromboembolism after lung transplantation: a retrospective study

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SUMMARY

Venous thromboembolism (VTE) is a frequent complication after solid organ transplantation (SOT) and, specifically, after lung transplantation (LT). The objectives of this study were to evaluate prophylaxis with enoxaparin and to describe risk factors for VTE after LT. We retrospectively reviewed the clinical records of 333 patients who underwent LT in our institution between 2009 and 2014. We compared two consecutive cohorts: one that received enoxaparin only during post-transplant hospital admissions and a second cohort that received 90-day extended prophylaxis with enoxaparin. Cumulative incidence function for competing risk analysis was used to determine incidence of VTE during the first year after transplantation. Risk factors were analyzed using a Cox proportional hazards regression model. The cumulative incidence of VTE was 15.3% (95% CI: 11.6–19.4). Median time from transplant to the event was 40 (p25–p75, 14–112) days. Ninety-day extended prophylaxis did not reduce the incidence of VTE. In this study, the risk factors associated with VTE were male gender and interstitial lung disease. VTE is a major complication after LT, and 90-day extended prophylaxis was not able to prevent it. Large, multicenter, randomized clinical trials should be performed to define the best strategy for preventing VTE.

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lung transplantation, venous thromboembolism

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Introduction

Venous thromboembolism (VTE) is a major complication after surgery. A previous review of the literature highlights the importance of this issue after solid organ transplantation (SOT) [1]. The incidence of VTE ranges between 2% and 14% in kidney transplantation [2], between 3% and 5% in liver transplantation [3–7], between 18% and 34% in heart transplantation, and between 8% and 29% in lung transplantation (LT) [8–14]. Different prevention strategies have been used in some of these studies, which have not been systematically studied.

Solid organ transplantation is a complex environmental risk factor for VTE and carries an inherent risk arising from surgery itself, immunosuppressive treatment,

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cytomegalovirus (CMV) infection, underlying disease, and thrombophilia. In LT, the factors associated with a higher risk of VTE include traditional factors, such as older age, diabetes mellitus, pneumonia [12], and surgery-related risk factors such as need for bypass and time to discharge [13]. The role of idiopathic pulmonary fibrosis [10] and sirolimus [15,16] has yet to be established, although both factors seem to increase the risk of VTE. The specific burden of each factor remains unknown.

No consensus has been reached on prophylactic strategies, and several protocols are used in clinical practice. Findings from the field of liver and kidney transplantation suggest that either aspirin alone [17–21] or heparin adjusted for activated clotting time [22] could be useful. Various empirical protocols are used in LT, although there is no evidence to support one over the others.

We describe the impact of a specific prophylaxis protocol with enoxaparin on the incidence of VTE and the risk factors associated with VTE in a population of LT recipients.

Materials and methods

Study population

We retrospectively reviewed the computerized clinical records of 333 consecutive adult patients who underwent LT in our institution between January 2009 and December 2014. We recorded prophylaxis, age, gender, body mass index, diabetes mellitus, previous thrombotic events, CMV status, underlying disease, transplant type, need for cardiopulmonary bypass, mechanical ventilation, length of stay, primary graft dysfunction, medication, and mobility. The study protocol was approved by the institutional Ethics board.

We identified patients with any thrombotic event during the first year after LT, including deep venous thrombosis (DVT), pulmonary embolism (PE), and treated upper extremity thrombosis (TUET). Patients receiving lifetime anticoagulation therapy prior to LT were excluded. Incidental PE (untreated subsegmental perfusion defects without clinical repercussion) was not taken into account.

As part of our standard protocol, all patients underwent a ventilation–perfusion scan (VPS) following lung transplantation immediately before discharge. No subsequent screening for VTE was performed. Patients who presented with symptoms suggestive of DVT were further studied using Doppler ultrasound (US). If PE was suspected, patients underwent either VPS or computed tomography (CT) pulmonary angiography.

Between 2009 and 2012 prophylaxis with the low-molecular-weight heparin (LMWH) enoxaparin (40 mg subcutaneously) was given once daily to all patients admitted to hospital after LT (control cohort). The prophylaxis began on postoperative day 1 if there were no formal contraindications. In January 2013, concern over the high incidence of VTE led us to change our standard protocol, and patients have since been receiving prophylactic enoxaparin up to day 90 or until full mobility is recovered (study cohort). Dosing of enoxaparin was adjusted in renal impairment and according to patient weight. We did not use any protocol to monitor enoxaparin treatment.

Data analyses

Qualitative variables are expressed as absolute numbers and percentages. Normally distributed quantitative variables are expressed as the mean and standard deviation; non-normally distributed variables are expressed as the median and interquartile range (p25–p75).

The demographic and clinical variables of patients receiving conventional prophylaxis and those receiving 90-day extended prophylaxis after LT were compared using the chi-square test for qualitative variables (or the Fisher exact test when one of the expected effects was less than 5). Normally distributed quantitative variables were compared using an unpaired *t*-test; non-normally distributed quantitative variables were compared using the Mann–Whitney test.

Cumulative incidence function for competing risk analysis was used to determine incidence of VTE through the formulas proposed by Gooley *et al.* [23] and Greewood (cited in Marubini *et al.* [24]) using the STATA syntax *stcompet*; both for the entire group and according to type of anticoagulant prophylaxis. Death and retransplant without previous VTE were treated as competing risks.

Cox proportional hazards regression was applied by modeling time from LT to the first event, with VTE as the outcome measure. We first conducted univariate analyses based on the Cox proportional hazards model using each of the potential predictors of VTE as independent variables and VTE as the dependent variable. Then, we performed a stepwise multivariable Cox regression with a backward elimination (*P*-value criterion of 0.20) fitted with all candidate variables, after adjusting for type of anticoagulant prophylaxis.

Data were analyzed using STATA software (StataCorp. 2011, release 12.1 College Station, TX, USA: StataCorp LP).

Results

Comparison between study and control cohorts

The study group (90-day extended prophylaxis) comprised 138 patients, and the control group 195 patients. The demographic characteristics of both cohorts are shown in Table 1. Older age, interstitial lung disease as the underlying disease, diabetes mellitus prior to transplantation, and hemodynamic instability (defined as the need for vasoactive drugs) were more frequent in the study cohort. However, the incidence of thromboembolic events was not significantly different between the protocols (Table 1). Thirteen patients in the study group did not receive the prophylaxis protocol due to diverse reasons, but none of them developed VTE.

Thromboembolic events

Fifty patients developed VTE and 52 died during the first year after LT. The cumulative incidence of VTE during this period was 15.3% (95% CI: 11.6–19.4) in the entire group; 16.1% (95% CI: 11.3–21.6) in the cohort receiving conventional prophylaxis and 14.1% (95% CI: 8.9–20.6) in cohort receiving 90-day extended prophylaxis, with no differences between the two cohorts (Fig. 1). The events are classified in Table 2. Median time from transplant to the event was 40 days (p25–p75 14–112). Twenty-nine events (58%) took place before hospital discharge (Table 1 and Fig. 2); of the other 21 events, 11 (22%) were within the first 90 days after LT and 10 (20%) were between postoperative day 90 and the first year (Table 1). There were 22 events in single LT patients, nine (41%) of them localized in the graft.

Pulmonary embolism and deep venous thrombosis of the lower extremities

Forty-one PE and two DVT were diagnosed during the first year after LT. We considered six asymptomatic subsegmental PE to be incidental events that were not treated; therefore, they were not taken into account for the purposes of the study. The final sample was 35 PE. The clinical characteristics of the events are shown in Fig. 3.

Four single LT recipients due to interstitial lung disease did not have CT angiography to confirm the diagnosis. In three of these four cases, a high probability VPS was considered enough for the diagnosis of PE. The last case had an intermediate probability VPS coinciding with a femoral vein DVT.

No patients fulfilled the criteria for massive PE. Thirteen patients underwent echocardiography close to the event, and three presented right ventricular dilatation. Coagulation assays revealed one lupus anticoagulant-positive patient and one patient with mild factor VII deficiency.

In 24 (68.6%) of the 35 patients with PE, VPS was performed between 7 and 857 days after the event (median time of 172 days). Partial reperfusion of the defects was reported in 10 patients and persistent perfusion defects in two. One patient had a new perfusion defect (detected by VPS 145 days after the event) No patients developed pulmonary hypertension after PE.

There were 12 deaths (32.4%), 11 of which were considered not directly related to the thrombotic event. The causes of death were chronic allograft dysfunction (four cases), respiratory infection (three cases), sepsis (two cases), melanoma (one case), and multiple organ failure (one case). During the follow-up [median 659 (p25–p75 138–1337) days], eight of the 37 patients (21.6%) developed chronic allograft dysfunction (five cases of bronchiolitis obliterans syndrome and three cases of restrictive allograft syndrome).

Treated upper extremity thrombosis

Treated upper extremity thrombosis alone was diagnosed in 12 patients. As it was related to intravenous devices, most cases were diagnosed in the ICU. Only one patient presented at the emergency department 5 days after discharge with swelling of the left arm that had begun 3 days earlier. All the cases were symptomatic, and thrombus extension was evaluated using ultrasound to confirm the diagnosis and the need for anticoagulant treatment.

Safety

There were two mild bleeding events in patients under prophylactic doses of LMWH. Only one patient in the study cohort receiving anticoagulation at treatment doses suffered a massive epistaxis with airway obstruction that required invasive mechanical ventilation and admission to intensive care unit.

In the control cohort there were four bleeding events in patients receiving anticoagulation treatment: hemothorax (two cases), hematoma (one case), and thrombocytopenia (one case).

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Table 1. Characteristics of lung transplantation (LT) recipients according to anticoagulant prophylaxis. Bold values indicate statistically significant correlations.

	All *n* = 333	Control cohort *n* = 195	Study cohort *n* = 138	*P*
Pretransplant variables				
Age, mean (SD)	52.0 (11.4)	50.2 (11.8)	54.5 (10.5)	**<0.001**
Sex: male, *n* (%)	201 (60.4)	119 (61.0)	82 (59.4)	0.768
BMI, *n* (%) [*n* = 327]				
<20 kg/m^2, *n* (%)	33 (10.1)	23 (12.1)	10 (7.3)	0.199
20–24.9 kg/m^2, *n* (%)	110 (33.6)	58 (30.5)	52 (38.0)	
≥25 kg/m^2, *n* (%)	184 (56.3)	109 (57.4)	75 (54.7)	
Diagnosis, *n* (%)				
Interstitial lung diseases (ILD)	143 (42.9)	74 (38.0)	69 (50.0)	**0.029**
COPD, bronchiectasis, or BO	123 (36.9)	73 (37.4)	50 (36.2)	0.823
Cystic fibrosis	25 (7.5)	16 (8.2)	9 (6.5)	0.566
Pulmonary arterial hypertension	17 (5.1)	13 (6.7)	4 (2.9)	0.138
LAM	5 (1.5)	3 (1.5)	2 (1.5)	0.989
Other	20 (6.0)	16 (8.2)	4 (2.9)	0.989
Pretransplant diabetes mellitus, *n* (%)	52 (15.6)	22 (11.3)	30 (21.7)	**0.010**
Pretransplant VTE, *n* (%)	10 (3.0)	8 (4.1)	2 (1.5)	0.205
Pretransplant CMV serology (positive), *n* (%)	282 (84.7)	161 (82.6)	121 (87.7)	0.201
Peritransplant variables				
Type of lung transplant, *n* (%)				
Bilateral	201 (60.4)	116 (59.5)	89 (64.6)	0.699
Single	132 (39.6)	79 (40.5)	53 (38.4)	
Extracorporeal circulation, *n* (%)	75 (22.5)	49 (25.1)	26 (18.8)	0.176
Reintervention, *n* (%)	32 (9.6)	15 (7.7)	17 (12.3)	0.158
Surgical complications, *n* (%)	38 (11.4)	23 (11.8)	15 (10.9)	0.794
Hemodynamic instability, *n* (%)	213 (64.0)	135 (69.2)	78 (56.5)	**0.017**
Days on mechanical ventilation, median (p25–p75)	13 (2–37)	13 (2–42)	12 (2–36)	0.571
Days of hospitalization, median (p25–p75)	37 (25–60)	38 (25–65)	36 (24–56)	0.228
Primary graft dysfunction, *n* (%)	114 (34.3)	71 (36.4)	43 (31.4)	0.343
Post-transplant variables				
Treatment with mTOR, *n* (%)	7 (2.1)	3 (1.5)	4 (2.9)	0.454
Reduced mobility 3 months post-transplant, *n* (%) [*n* = 258]*	41 (15.9)	19 (12.7)	22 (20.4)	0.169
CMV disease, *n* (%)	20 (6.0)	14 (7.2)	6 (4.4)	0.284
Incidence of thromboembolic events				
Total thromboembolic events, *n* (%)	50 (15.0)	31 (15.9)	19 (13.7)	0.592
Before discharge	29 (58.0)	19 (9.7)	10 (7.3)	0.426
After discharge [*n* = 261]†	21 (8.1)	12 (7.8)	9 (8.3)	0.886
<90 days after discharge [*n* = 261]†	11 (22.0)	7 (4.6)	4 (3.7)	0.730
>90 days after discharge [*n* = 240]‡	10 (20.0)	5 (3.7)	5 (4.9)	0.749

BMI, body mass index; COPD, chronic obstructive pulmonary disease; BO, bronchiolitis obliterans; LAM, lymphangioleiomyomatosis; VTE, venous thromboembolism; CMV, cytomegalovirus.

*Patients at risk of a thromboembolic event at 3 months after transplant.

†Patients at risk of a thromboembolic event after hospital discharge.

‡Patients at risk of a thromboembolic event 90 days after hospital discharge.

Study of risk factors

Table 3 shows the influence of the variables included in the univariate Cox analysis on the incidence of VTE. Multivariable Cox proportional hazards analysis revealed that male gender (HR 2.72; 95% CI 1.25–4.03; $P = 0.007$) and interstitial lung disease (HR 2.25; 95% CI 1.25–4.03; $P = 0.007$) were significantly related to VTE, after adjusting for type of anticoagulation prophylaxis (Table 4). Ninety-day extended prophylaxis did not seem to protect from VTE in the study population.

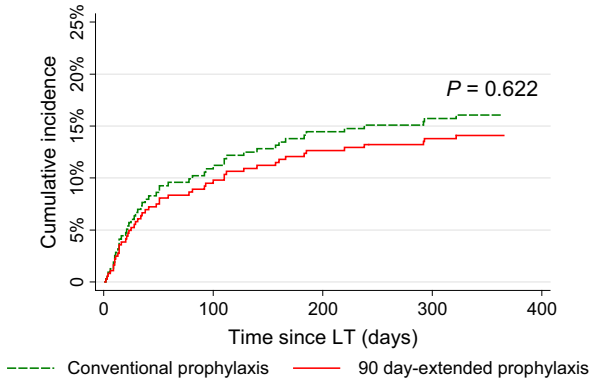

Figure 1 Cumulative incidences of thromboembolic event according to anticoagulant prophylaxis (n = 333).

Table 2. Classification of the thromboembolic events recorded during the first year after lung transplantation (LT).

	Patients with a thromboembolic event n = 50 (%)
Deep venous thrombosis (DVT) of the lower extremities	2 (4.0)
Pulmonary embolism (PE)	35 (70.0)
PE + DVT	5/35
Treated upper extremity thrombosis	12 (24.0)
Atrial thrombosis	1 (2.0)

Discussion

Our results show that VTE is a relevant complication following LT, mainly in the early postoperative period and that 90-day extended prophylaxis seems unable to prevent it.

The 15% incidence of VTE in our cohort is similar to that reported for LT recipients in the literature, namely 8–29% [8–11,13,25,26]. The single case of atrial thrombosis in 333 LT patients we recorded is within the expected range; we interpreted this problem as being directly related to the surgical procedure. It is difficult to explain the high incidence of VTE in LT, although the various potentially involved factors include increased vascular trauma, higher levels of immunosuppression, and worse preoperative functional status [13]. The variations in incidence found in epidemiologic studies may be due to differences in methodology (i.e., follow-up time, VTE screening protocol, and prophylactic treatment), which hamper comparison between studies. One study [8] reports data on patients under periodical surveillance by VPS, but there is no information regarding the incidence of asymptomatic events. In our study, 10 of the 35 PE were asymptomatic events detected in the protocol VPS, thus highlighting the role of this test to assess graft vasculature after surgery. DVT is not routinely screened for, although some groups have recently implemented routine assessment of DVT and 3-month prophylaxis with enoxaparin after reporting a 39% incidence of DVT and 15% incidence of PE in patients where only suspected events were investigated [26]. Less is known about the impact of VTE on survival. From the few small series published, mortality attributable to VTE seems to be low (between 7% and 14%), [8–10] as is the frequency of chronic graft allograft dysfunction following VTE (7–15%) [8–12]. Nevertheless, VTE seems to be more frequent in frail patients and therefore is associated with poorer prognosis. Following this line of argument, Evans *et al.* [26] described DVT as a risk factor for patient survival (HR 2.43; 95% CI, 1.29–4.64), and Lingaraju *et al.* [15] found VTE to be associated with poorer survival 3 months after LT.

Data on risk factors in LT in the literature are inconsistent. The present study found male patients and patients with interstitial lung disease to be more susceptible to VTE in the adjusted analysis. Nathan *et al.* [10] pointed out the role of idiopathic pulmonary fibrosis as a risk factor in a small cohort of 72 lung recipients. The authors detected 7 VTE events, all of them in patients with idiopathic pulmonary fibrosis. Susceptibility was attributed to inherent disease factors, because other circumstances (i.e., functional status and length of stay) were similar in both groups. This possibility was also explored by Navaratnam *et al.* [27] in a study that compared 211 incident cases of idiopathic pulmonary fibrosis and 256 age- and sex-matched controls. The authors found that a prothrombotic state—defined as any acquired or inherited clotting defect—was four times more common in idiopathic pulmonary fibrosis patients than in controls. Although other authors have suggested age as a confounding factor in the association between idiopathic pulmonary fibrosis and VTE [12], the results of Navaratnam *et al.* support the idea of pretransplant idiopathic pulmonary fibrosis as a risk factor for VTE.

In our study, we evaluated 90-day extended prophylaxis with enoxaparin and found that this strategy did not protect against VTE. To our knowledge, this is the first study to evaluate a prophylaxis protocol in LT. Prophylaxis protocols have been evaluated in kidney and liver transplantation, although most studies were retrospective and analyzed few patients, and only two are randomized [28,29]. These studies showed

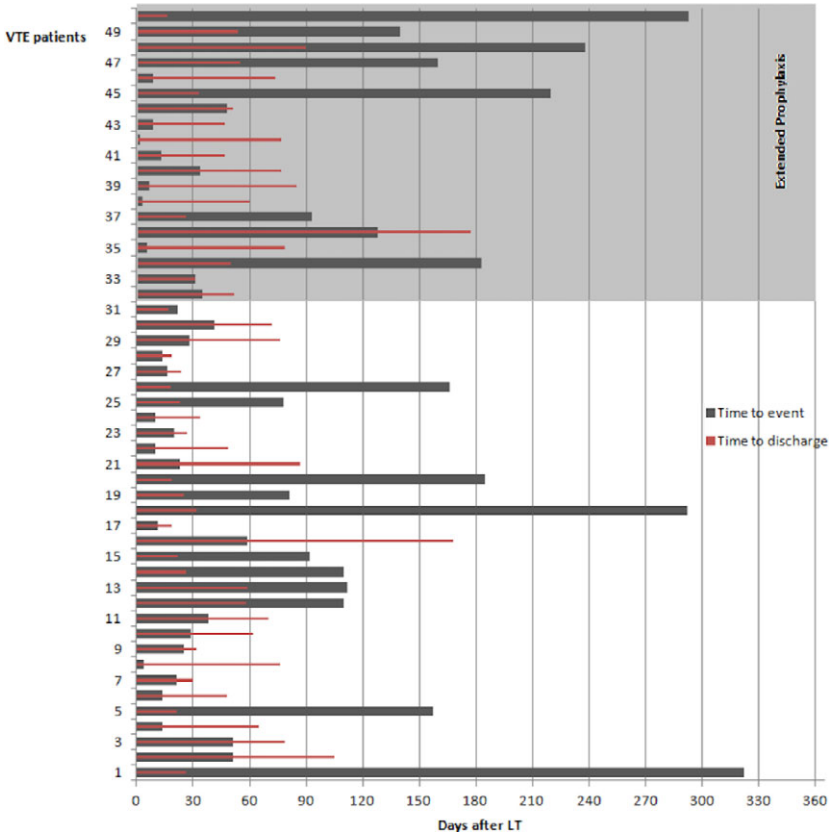

Figure 2 Time to event and hospital discharge of all patients with venous thromboembolism (VTE).

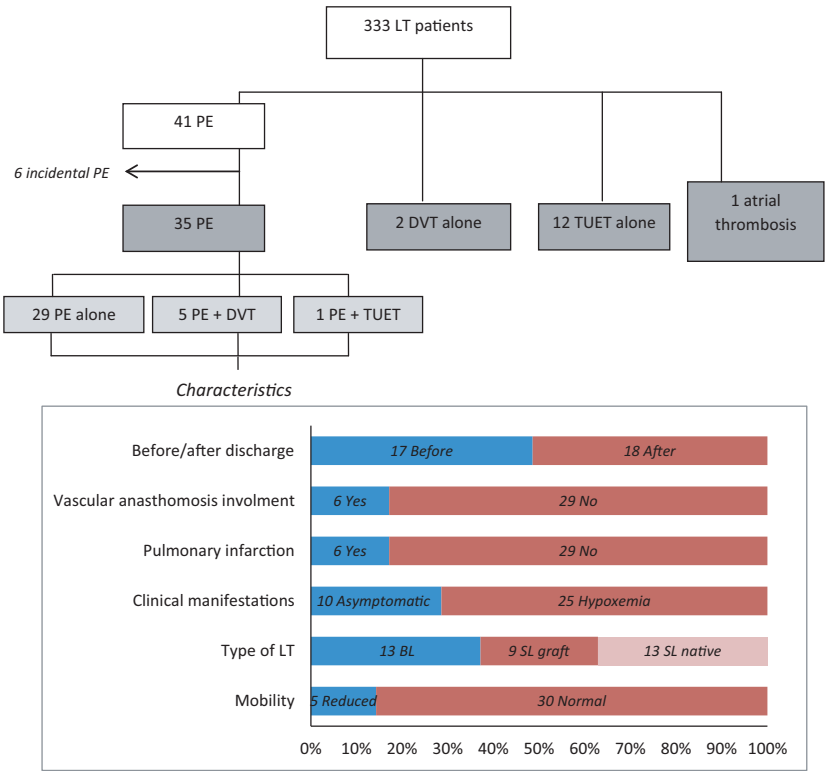

Figure 3 Flow chart and characteristics of the thrombotic events.

Table 3. Univariate predictors of VTE (univariate Cox models).

	Hazard ratio (95% CI)	*P*
Pretransplant variables		
Age (years)	1.01 (0.99–1.04)	0.322
Sex: male	3.00 (1.45–6.18)	0.003
BMI (kg/m^2)	0.99 (0.93–1.06)	0.822
Interstitial lung disease	2.40 (1.34–4.27)	0.003
COPD, bronchiectasis, or BO	0.58 (0.31–1.09)	0.092
Cystic fibrosis	0.22 (0.03–1.62)	0.138
Pulmonary arterial hypertension	0.45 (0.06–3.24)	0.426
LAM	2.47 (0.34–17.9)	0.371
Pretransplant diabetes mellitus	0.70 (0.30–1.66)	0.426
Pretransplant VTE	1.24 (0.30–5.13)	0.760
Pretransplant CMV serology (positive)	1.46 (0.62–3.42)	0.386
Peritransplant variables		
Single lung transplant	1.67 (0.96–2.91)	0.069
Extracorporeal circulation	0.85 (0.41–1.75)	0.663
Reintervention	1.12 (0.40–3.10)	0.830
Surgical complications	1.10 (0.93–3.05)	0.860
Hemodynamic instability	1.25 (0.69–2.24)	0.461
Days on mechanical ventilation	0.99 (0.99–1.00)	0.953
Days of hospitalization	1.00 (0.99–1.00)	0.453
Primary graft dysfunction	1.44 (0.82–2.53)	0.208
Post-transplant variables		
Treatment with mTOR	0.84 (0.12–6.01)	0.860
Reduced mobility 3 months after transplant*	0.89 (0.26–3.01)	0.848
CMV disease	0.95 (0.29–3.04)	0.927
Extended prophylaxis	0.87 (0.49–1.54)	0.628

BMI, body mass index; COPD, chronic obstructive pulmonary disease; BO, bronchiolitis obliterans; LAM, lymphangioleiomyomatosis; VTE, venous thromboembolism; CMV, cytomegalovirus.

*Patients at risk of a thromboembolic event at 3 months after transplant $n = 258$.

Table 4. Best model of independent predictors of venous thromboembolism (VTE) after lung transplantation (LT) by stepwise multivariable Cox regression analysis, after adjusting for type of anticoagulation prophylaxis.

	Hazard ratio (95% CI)	*P*
90-day extended prophylaxis	0.77 (0.43–1.38)	0.386
Sex (male)	2.72 (1.25–4.03)	0.007
Diagnosis (ILD)	2.25 (1.25–4.03)	0.007

inconsistent results for the balance between bleeding risk and thrombotic events. Heparin implies a significant increase in bleeding complications in both kidney and liver transplantation [28–33], but treatment with dalteparin adjusted for activated clotting time in liver transplantation seems to be safe [22]. Prophylaxis of renal or liver allograft thrombosis with aspirin alone seems to be another good option that does not increase the frequency of bleeding complications [17–21], although doses differ between studies. Furthermore, one of the strengths of our study is the long follow-up of our patients, out to 1 year.

In our study, we did not use any protocol to monitor enoxaparin prophylaxis or treatment. Guidelines about antithrombotic treatment for VTE recommend enoxaparin monitorization in pregnancy, children, and renal impairment and only when receiving anticoagulation treatment, not prophylaxis [34]. There are three studies assessing this issue in solid organ transplantation [35–37]. All of them use antifactor Xa to monitor enoxaparin activity in transplanted patients receiving therapeutic anticoagulation. Standard dosing of enoxaparin was associated with high incidence of supratherapeutic anti-Xa levels in all three studies. Although we do not have evidence regarding the monitorization of prophylactic protocols, these studies suggest that standard doses of enoxaparin might be supratherapeutic and, thus, the lack of effect of our protocol might not be dose-related.

Venous thromboembolism is more frequent in the postoperative period; however, we did not find an association between VTE and surgical factors, such as need for bypass and time to discharge, as reported in Kahan *et al.* [13]. We were unable to replicate the results reported by Yegen *et al.* [12], who showed an association between traditional risk factors such as older age, diabetes mellitus, and pneumonia and a higher risk of VTE.

Therapy with mammalian target of rapamycin (mTOR) inhibitors has been considered a risk factor for thrombosis since the United States Food and Drug Administration warning in 2002, which alerted to a possible association with hepatic artery thrombosis among liver recipients [38]. In kidney transplantation, Baas *et al.* [39] reported increased endothelial activation, thrombin formation, and impaired fibrinolysis with everolimus. Subsequent studies have been unable to reproduce these results, either in liver or kidney transplantation [40–44]. Two studies report an increased risk of VTE in LT recipients with sirolimus [15,16]. Ahya *et al.* [16] performed a prospective, multicenter, randomized, open-label trial comparing the incidence of VTE in 181 LT patients who received a regimen based on tacrolimus, sirolimus, and prednisone or on

tacrolimus, azathioprine, and prednisone. The higher incidence of VTE in the sirolimus cohort persisted after adjusting for pretransplant diagnosis and after stratifying by transplant center. As only seven patients in our study received mTOR inhibitors during the first year after LT, it is not possible to draw conclusions.

Our study is subject to a series of limitations. First, it was a retrospective analysis performed in a single center. Second, we did not track the use of mechanical devices for thromboprophylaxis in the intensive care unit. Third, as no routine VTE screening was performed (US was performed only in symptomatic patients), we may have under-diagnosed thrombotic events, and the relatively short number of VTE events may have limited the detection of risk factors. Moreover, the effect of our protocol could have been diminished by the fact that we compared two consecutive cohorts that differed in terms of age and number of patients with pretransplant interstitial lung disease and diabetes and peritransplant hemodynamic instability. Although the two eras of our study did not differ in terms of the diagnostic protocol, it is not possible to dismiss a higher suspicion in the study cohort that could have lead to a higher detection rate and, consequently, to an infraestimation of the effect of the prophylactic treatment.

We conclude that VTE is a major complication after LT and that 90-day extended enoxaparin prophylaxis seems unable to prevent it. In our study, males and patients with interstitial lung disease were at higher risk of thrombotic events, even if no association was detected between this complication and other classic risk factors, surgical factors, or the use of mTOR inhibitors. Despite its limitations—retrospective and comparing two different eras—this study highlights the relevance of this complication, and the need for randomized clinical trials to identify the best strategies for preventing VTE in LT recipients.

Authorship

BSG: researched the data and wrote the article. JP and AF: participated in the data collection. CB, HS, MLM, VM, CD and AS: critically reviewed the article. MAR: performed the statistical analysis and reviewed the article. SG and AR: designed the study.

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Conflict of interest

The authors declare no conflict of interests.

REFERENCES

1. Saez-Gimenez B, Berastegui C, Loor K, *et al.* Deep vein thrombosis and pulmonary embolism after solid organ transplantation: an unresolved problem. *Transplant Rev (Orlando)* 2015; **29**: 85.
2. Kazory A, Ducloux D. Acquired hypercoagulable state in renal transplant recipients. *Thromb Haemost* 2004; **91**: 646.
3. Ishitani M, Angle J, Bickston S, *et al.* Liver transplantation: incidence and management of deep venous thrombosis and pulmonary emboli. *Transplant Proc* 1997; **29**: 2861.
4. Salami A, Qureshi W, Kuriakose P, *et al.* Frequency and predictors of venous thromboembolism in orthotopic liver transplant recipients: a single-center retrospective review. *Transplant Proc* 2013; **45**: 315.
5. Forrat R, Ferrera R, Boissonnat P, *et al.* High prevalence of thromoembolic complications in heart transplant recipients. Which preventive strategy? *Transplantation* 1996; **61**: 757.
6. Miriuka SG, Langman LJ, Evrovski J, *et al.* Thromboembolism in heart transplantation: role of prothrombin G20210A and factor V Leiden. *Transplantation* 2005; **80**: 590.
7. Garcia-Herrera JM, Rabago G, Herreros J, Paramo JA. Peripheral thromboembolic complications in heart transplantation: prevalence and review of the literature. *Rev Med Univ Navarra* 2001; **45**: 11.
8. Kroshus TJ, Kshettry VR, Hertz MI, Bolman RM III. Deep venous thrombosis and pulmonary embolism after lung transplantation. *J Thorac Cardiovasc Surg* 1995; **110**: 540.
9. Izbicki G, Bairey O, Shitrit D, Lahav J, Kramer MR. Increased thromboembolic events after lung transplantation. *Chest* 2006; **129**: 412.
10. Nathan SD, Barnett SD, Urban BA, *et al.* Pulmonary embolism in idiopathic pulmonary fibrosis transplant recipients. *Chest* 2003; **123**: 1758.
11. Garcia-Salcedo JA, de la Torre MM, Delgado M, *et al.* Complications during clinical evolution in lung transplantation: pulmonary embolism. *Transplant Proc* 2010; **42**: 3220.
12. Yegen HA, Lederer DJ, Barr RG, *et al.* Risk factors for venous thromboembolism after lung transplantation. *Chest* 2007; **132**: 547.
13. Kahan ES, Petersen G, Gaughan JP, Criner GJ. High incidence of venous thromboembolic events in lung transplant recipients. *J Heart Lung Transplant* 2007; **26**: 339.
14. Tabarelli W, Bonatti H, Tabarelli D, *et al.* Long term complications following 54 consecutive lung transplants. *J Thorac Dis* 2016; **8**: 1234.
15. Lingaraju R, Blumenthal N, Mendez J, *et al.* Venous thromboembolic disease after lung transplantation: special focus on sirolimus. *Open Transplant J* 2010; **4**: 1.
16. Ahya VN, McShane PJ, Baz MA, *et al.* Increased risk of venous thromboem-

bolism with a sirolimus-based immunosuppression regimen in lung transplantation. *J Heart Lung Transplant* 2011; **30**: 175.
17. Robertson AJ, Nargund V, Gray DW, Morris PJ. Low dose aspirin as prophylaxis against renal-vein thrombosis in renal-transplant recipients. *Nephrol Dial Transplant* 2000; **15**: 1865.
18. Shay R, Taber D, Pilch N, *et al.* Early aspirin therapy may reduce hepatic artery thrombosis in liver transplantation. *Transplant Proc* 2013; **45**: 330.
19. Murphy GJ, Taha R, Windmill DC, Metcalfe M, Nicholson ML. Influence of aspirin on early allograft thrombosis and chronic allograft nephropathy following renal transplantation. *Br J Surg* 2001; **88**: 261.
20. Stechman MJ, Charlwood N, Gray DW, Handa A. Administration of 75 mg of aspirin daily for 28 days is sufficient prophylaxis against renal transplant vein thrombosis. *Phlebology* 2007; **22**: 83.
21. Vivarelli M, La BG, Cucchetti A, *et al.* Can antiplatelet prophylaxis reduce the incidence of hepatic artery thrombosis after liver transplantation? *Liver Transpl* 2007; **13**: 651.
22. Uchikawa Y, Ikegami T, Masuda Y, *et al.* Administration of dalteparin based on the activated clotting time for prophylaxis of hepatic vessel thrombosis in living donor liver transplantation. *Transplant Proc* 2009; **41**: 3784.
23. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999; **18**: 695.
24. Marubini E, Valsecchi MG. *Analysing Survival Data from Clinical Trials and Observational Studies*. Chichester, UK: John Wiley & Sons, 1995.
25. Burns KE, Iacono AT. Pulmonary embolism on postmortem examination: an under-recognized complication in lung-transplant recipients? *Transplantation* 2004; **77**: 692.
26. Evans CF, Iacono AT, Sanchez PG, *et al.* Venous thromboembolic complications of lung transplantation: a contemporary single-institution review. *Ann Thorac Surg* 2015; **100**: 2033.
27. Navaratnam V, Fogarty AW, McKeever T, *et al.* Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: a population-based case-control study. *Thorax* 2014; **69**: 207.
28. Ubhi CS, Lam FT, Mavor AI, Giles GR. Subcutaneous heparin therapy for cyclosporine-immunosuppressed renal allograft recipients. *Transplantation* 1989; **48**: 886.
29. Bakkaloglu H, Salmaslioglu A, Tunca F, *et al.* Is heparinization necessary in the early postoperative period of renal transplantation from cadaveric donors? *Transplant Proc* 2012; **44**: 1690.
30. Friedman GS, Meier-Kriesche HU, Kaplan B, *et al.* Hypercoagulable states in renal transplant candidates: impact of anticoagulation upon incidence of renal allograft thrombosis. *Transplantation* 2001; **72**: 1073.
31. Alkhunaizi AM, Olyaei AJ, Barry JM, *et al.* Efficacy and safety of low molecular weight heparin in renal transplantation. *Transplantation* 1998; **66**: 533.
32. Murashima M, Konkle BA, Bloom RD, *et al.* A single-center experience of preemptive anticoagulation for patients with risk factors for allograft thrombosis in renal transplantation. *Clin Nephrol* 2010; **74**: 351.
33. Kaneko J, Sugawara Y, Tamura S, *et al.* Coagulation and fibrinolytic profiles and appropriate use of heparin after living-donor liver transplantation. *Clin Transplant* 2005; **19**: 804.
34. Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; **149**: 315.
35. Singer JP, Huang MY, Hui C, *et al.* Supratherapeutic anticoagulation from low-molecular-weight heparin in lung transplant recipients. *J Heart Lung Transplant* 2010; **29**: 1009.
36. Sofjan AK, Iuppa JA, Bain KB, *et al.* Evaluation of enoxaparin dosing as a risk factor for bleeding in lung transplant recipients. *Ann Pharmacother* 2016; **50**: 824.
37. Moten MA, Gaber AO, Putney D, Patel SJ. Low molecular weight heparin dosing and monitoring in solid organ transplant recipients. *Clin Transplant* 2013; **27**: 852.
38. Massoud O, Wiesner RH. The use of sirolimus should be restricted in liver transplantation. *J Hepatol* 2012; **56**: 288.
39. Baas MC, Gerdes VE, Ten Berge IJ, *et al.* Treatment with everolimus is associated with a procoagulant state. *Thromb Res* 2013; **132**: 307.
40. Langer RM, Kahan BD. Sirolimus does not increase the risk for postoperative thromboembolic events among renal transplant recipients. *Transplantation* 2003; **76**: 318.
41. Molinari M, Berman K, Meeberg G, *et al.* Multicentric outcome analysis of sirolimus-based immunosuppression in 252 liver transplant recipients. *Transpl Int* 2010; **23**: 155.
42. McKenna GJ, Trotter JF. Sirolimus – it doesn't deserve its bad Rap(a). *J Hepatol* 2012; **56**: 285.
43. Dunkelberg JC, Trotter JF, Wachs M, *et al.* Sirolimus as primary immunosuppression in liver transplantation is not associated with hepatic artery or wound complications. *Liver Transpl* 2003; **9**: 463.
44. Levy G, Schmidli H, Punch J, *et al.* Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; **12**: 1640.