Diplomarbeit

Lipoprotein(a) as a prognostic biomarker for the severity and course of venous thromboembolism

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Moritz Pechtold

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unter der Anleitung von

Dr. med. univ. et Dr. sci. med. Paul Gressenberger

Assoz. Prof. Priv.- Doz. Dr. med. univ. Thomas Gary

Graz, am 08.06.2023

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DISCLOSURES

The current diploma thesis was the basis for the preparation of a manuscript. A subgroup analysis has been published in the journal “Frontiers in Cardiovascular Medicine”. Therefore, significant parts of the diploma thesis are similar to the published manuscript. It was accepted on 6th of January 2022. The article was published under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0, available from http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided appropriate credit to the original authors and the source is given, a link to the Creative Commons license is given, and changes made are indicated.

Authors: Paul Gressenberger MD[1,2], Florian Posch MD[3], Moritz Pechtold[1], Katharina Gütl MD[1], Viktoria Muster MD[1], Philipp Jud MD[1], Jakob Riedl MD[3], Günther Silbernagel MD[1], Ewald Kolesnik MD[4], Johannes Schmid MD[5], Reinhard B. Raggam MD[1], Marianne Brodmann MD[1], Thomas Gary MD[1]

1) Division of Angiology, Department of Internal Medicine, Medical University of Graz, Austria
2) Department of Dermatology, Medical University of Graz, Austria
3) Division of Oncology, Department of Internal Medicine, Medical University of Graz, Austria
4) Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz, Austria
5) Division of General Radiology, Department of Radiology, Medical University of Graz, Graz, Austria

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All co-authors have explicitly agreed to the use of their data in the thesis.
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ABBREVIATIONS

(s)PESI	(simplified) Pulmonary Embolism Severity Index
°C	Degrees Celsius
Apo(a)	Apolipoprotein(a)
ApoB	Apolipoprotein B-100
aPTT	activated partial thromboplastin time
ASCVD	Atherosclerotic cardiovascular disease
ASO	Antisense oligonucleotide
BNP	Brain natriuretic peptide
CI	confidence interval
CRP	C-reactive protein
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
CUS	Compression ultrasound
CV	Contrast venography
CVI	Chronic venous insufficiency
DOAC(s)	Direct oral anticoagulant(s)
DVT	Deep vein thrombosis
e.g.	exempli gratia
FDA	U.S. Food and Drug Administration
FVL	Factor V Leiden
FXI	Factor XI
GalNAc3	Triantennary *N*-acetyl galactosamine
HIT	Heparin-induced thrombocytopenia

HoFH	Homozygous familial hypercholesterolemia
IL-6	Interleukin-6
INR	International normalized ratio
LA	Lipoprotein apheresis
LDL-C	Low density lipoprotein cholesterol
LMWH	Low molecular weight heparin
Lp(a)	Lipoprotein(a)
Mg	milligram
Min	minute
mmHg	millimeter Mercury
MRA	Magnetic resonance angiography
NOAC(s)	Non-vitamin K antagonist oral anticoagulant(s)
O2	Oxygen
OxPL	Oxidized phospholipids
OxPL-apo(a)	Oxidised phospholipids associated with apo(a)
OxPL-apoB	Oxidised phospholipids associated with apoB
P	Wald test p-value
PCSK 9	Proprotein convertase subtilisin/kexin type 9
PE	Pulmonary embolism
PTS	Post-thrombotic syndrome
RCT	Randomized controlled trial
rtPA	recombinant tissue-type plasminogen activator
RV	Right ventricle
t-PA	tissue-type plasminogen activator

TTE	Transthoracic echocardiography
UFH	Unfractionated heparin
VKA	Vitamin K antagonists
VTE	Venous Thromboembolism

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ZUSAMMENFASSUNG

Hintergrund

Lipoprotein(a) ist ein bekannter Risikofaktor für atherosklerotische Herz-Kreislauf-Erkrankungen (ASCVDs). Aufgrund der Plasminogen-ähnlichen Struktur von Lp(a), die auf eine antifibrinolytische Wirkung hinweist, wird vermutet, dass es auch die Entstehung und den Verlauf von venösen Thromboembolien (VTEs) beeinflusst. Mehrere Studien haben bereits den Zusammenhang zwischen erhöhtem Lp(a)-Spiegel und dem Risiko für VTEs untersucht und erhielten widersprüchliche Ergebnisse.

Zielsetzung

Diese Arbeit soll zeigen, ob es eine Korrelation zwischen der Lp(a)-Konzentration und dem Schweregrad von Lungenembolien gibt.

Methoden

Es wurde eine retrospektive Datenanalyse von Patient*innen durchgeführt, die an der klinischen Abteilung für Angiologie der Universitätsklinik Graz, Österreich, aufgrund einer Lungenembolie behandelt wurden. Patient*innen mit der Diagnose Lungenembolie und mit zumindest einmal gemessener Lp(a)-Konzentration wurden eingeschlossen. Für die statistische Auswertung wurden die Lungenembolie-Fälle in Übereinstimmung mit den 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism nach Schweregrad in 4 Gruppen unterteilt:

- low-risk,
- intermediate low-risk,
- intermediate-high-risk und
- high-risk.

Der Studienzeitraum umfasst die Zeit vom 1. Januar 2002 bis 1. August 2020.

Ergebnisse

Wir analysierten 1.171 Patienten mit Lungenembolie (LE), von denen 450 (38 %) eine LE von niedrigem Risiko, 508 (43 %) eine LE von niedrigem bis mittlerem Risiko, 104 (9 %) eine LE von mittlerem bis hohem Risiko und 109 (9 %) eine LE von hohem Risiko hatten. Die mittlere Lp(a)-Konzentration betrug in der ersten Gruppe 15 mg/dL [25. bis 75. Perzentil: 10-34], in der zweiten 15 mg/dL [10-33], in der dritten 13 mg/dL [10-41] und in der vierten ebenfalls 13 mg/dL [10-29].

Schlussfolgerung

Wir konnte keine Korrelation zwischen der Lp(a)-Konzentration und dem Schweregrad von Lungenembolien beobachten.

ABSTRACT

Introduction

Lipoprotein(a) is a known risk factor for atherosclerotic cardiovascular diseases (ASCVDs). Because of the plasminogen-like structure of Lp(a), which indicates an antifibrinolytic effect, it is thought to also influence the development and course of venous thromboembolism (VTEs). Several studies have already investigated the association between elevated Lp(a) levels and the risk of VTEs and obtained inconsistent results.

Objective

This work aims to show whether there is a correlation between Lp(a) concentration and the severity of pulmonary embolism.

Methods

We conducted a retrospective data analysis from the medical registry of patients treated for pulmonary embolism at the Department of Angiology, University Hospital Graz, Austria. Patients with a diagnosis of pulmonary embolism and with measured Lp(a) concentration were included. For statistical analysis, pulmonary embolism cases were divided into 4 groups based on severity in accordance with the 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism:

- low-risk,
- intermediate-low-risk,
- intermediate-high-risk, and
- high-risk.

The study period was from January 1, 2002, to August 1, 2020.

Results

We analyzed 1,171 patients with PE, of whom 450 (38%) had low-risk PE, 508 (43%) had intermediate-low-risk PE, 104 (9%) had intermediate-high-risk PE, and 109 (9%) had high-risk PE, respectively. Median Lp(a) concentrations were 15 mg/dL [25th-75th percentile: 10-34], 15 mg/dL [10-33], 13 mg/dL [10-41], and 13 mg/dL [10-29], respectively.

Conclusion

We did not observe a correlation between Lp(a) concentration and pulmonary embolism severity.

1 INTRODUCTION

1.1 Venous thromboembolism overview

1.1.1 Definition

The term venous thromboembolism (VTE) describes the occlusion of a blood vessel by a blood clot originating in a vein. It includes deep vein thrombosis (DVT) and pulmonary embolism (PE) (1).

DVT is the formation of a thrombus in a deep subfascial vein resulting in its partial or complete obstruction. It most frequently affects veins localized in the legs or pelvis, but can also occur in veins of the upper extremities or internal organs (2). Depending on the location, a distinction can be made between distal and proximal DVT. Distal DVT involves the veins of the lower leg. Proximal DVT includes thromboses of the popliteal, femoral or iliac veins, or the inferior vena cava (2).

PE is the embolic occlusion of a pulmonary artery, which may be induced by blood clots, fat, air, or foreign materials. The result is a disturbance of blood circulation and gas exchange in the lungs. The abruption and migration of a venous thrombus through the bloodstream and the right heart to the lungs is the most frequent cause for PE. PE therefore usually occurs as a complication of DVT. PE may involve the main pulmonary artery or its lobar, segmental, or subsegmental branches (2).

1.1.2 Epidemiology

VTE is a common disease with an average annual incidence rate of approximately 104 to 183 per 100,000 persons of European ancestry, which increases distinctly with age. The incidence of VTE is highly variable for hospitalization-related and community occurrence with 330 versus 8 per 100,000 person-years, respectively (3). The incidence rate of VTE for men (130 per 100,000) is generally higher than for women (110 per 100,000) except for the childbearing age, when women are more often affected (4). The risk for women is particularly high in the postpartum period (5). In comparison to the number of cases in adults the incidence of pediatric VTE is much lower, averaging 2.9 per 100,000 person-years (6). The

prevalence of VTEs also differs among different ethnic groups. African Americans are on average more likely to develop VTEs than Caucasians and Hispanics, while Asians are the least affected (7). Approximately 60% of all VTE cases are DVTs alone, while the remaining 40% present as PEs with or without DVT (8). In patients who have been affected by VTE more than once, the recurrence rate is very high with 30% at 3 years (9). Outcome in VTE patients is still very poor with a 30-day mortality of 3% for DVT and 31% for PE, respectively (10).

1.1.3 Etiology and risk factors

Rudolf Virchow described three essential factors that are involved in the pathogenesis of venous thrombosis and therefore predispose an individual to this disease. It is accordingly known as Virchow's triad and consists of

- hypercoagulability through abnormal blood constituents,
- reduced blood flow and
- endothelial injury (11).

Consequently, any condition which influences one or more factors of Virchow's triad may increase the probability of developing venous thrombosis. A distinction is drawn between hereditary or genetic and acquired or environmental risk factors (8). An event of VTE may be categorized as provoked or unprovoked. Provoked VTE is associated with a transient or permanent environmental risk factor, while unprovoked ones occur in the absence of any known environmental risk factor. Provoked and unprovoked each account for approximately half of all VTEs (12).

Hereditary risk factors associated with hypercoagulability include thrombophilias such as

- factor V Leiden (FVL) mutation,
- prothrombin G2021A mutation,
- protein C, protein S, and antithrombin deficiencies and
- antiphospholipid antibody syndrome (8,13).

Acquired risk factors that may lead to hypercoagulability comprise:

- surgery and trauma,

- pregnancy and the postpartum period,
- oral contraception and hormonal replacement therapy,
- paraneoplastic syndrome and chemotherapy,
- inflammation,
- infection,
- heparin-induced thrombocytopenia (13,14).

Other acquired risk factors cause reduced blood flow and thereby contribute to VTE development:

- immobilisation due to hospitalisation, older age or long distance travelling,
- little physical activity,
- varicose veins and valvular dysfunction,
- congestive heart failure,
- prior venous thrombosis (13,15).

Damage to the endothelium may be caused by:

- vascular inflammation,
- hypertension,
- surgery and trauma,
- central venous catheters (13).

Risk factors that cannot be modified and cannot be assigned to the other categories:

- older age,
- male sex,
- ethnicity (8,13).

1.1.4 Pathophysiology

Virchow's hypothesis, according to which the presence of one or more of the three factors hypercoagulability, reduced blood flow, and damage to the vessel wall promote VTE, is still widely acknowledged as the underlying pathogenic mechanism of this disease. While one risk factor alone may not be of concern, the

combination of multiple risk factors, in particular, increases the likelihood of a VTE event (16).

Naturally, muscle contractions support the venous return to the heart through repetitive compressions of the veins. In immobile patients, this effect is absent and blood flow slows down (16). In patients with varicose veins, blood flow is not only slowed down, but also more turbulent. The result is an accumulation of clotting factors in areas of low blood flow velocity. Consequently, an imbalance between coagulation and fibrinolysis forms, increasing the likelihood of thrombus formation.

Sustained or at least reduced outflow due to occlusion or stenosis of a deep vein leads to acute congestion distal to the thrombosis, resulting in venous hypertension. The volume overload and overstretching of deep vein segments leads to both the development of edema in the surrounding tissue and venous valvular dehiscence and insufficiency. This is followed by the opening of collaterals via the superficial venous system. Although this mechanism drains the congested vein section, the collateral veins themselves become overstretched and insufficient. Secondary varicosis of the superficial veins develops as a result (2).

Blood clots that form in veins are usually red thrombi. Since, unlike white thrombi, they do not adhere firmly to the vessel wall, the risk of embolization is high. In many cases, the blood clot then travels via blood stream to a pulmonary artery resulting in PE. When the embolus then occludes an artery, pulmonary vascular resistance suddenly increases and so does the afterload for the right ventricle of the heart. In addition to the mechanical obstruction, vasoconstrictor mediators such as thromboxane and serotonin are released by the thrombus and in the affected vascular bed, leading to a further increase in resistance. The pulmonary arterial pressure thereby increases from about 10 mmHg to up to 30-40 mmHg (17). However, the muscle-weak right heart is adapted to much lower pressures and can only respond to the pressure increase with a limited increase in contractility. Dilation and insufficiency of the right ventricle subsequently occur. Dilation of the right ventricle additionally causes a shift of the septum toward the left ventricle, impairing its filling in diastole (18). An increasing alveolar dead space due to reduced blood flow to the lungs is another effect of the arterial occlusion, resulting in hypoxemia. The combination of right ventricular failure, impaired left

ventricular filling and inadequate oxygen supply to the myocardium leads to forward failure and subsequent cardiogenic shock (17,19). Eventually, death occurs due to multiple organ failure (20). Merely 10 percent of all PEs are associated with a pulmonary infarction. Due to anastomoses between the pulmonary and bronchial arteries, the lung tissue is still sufficiently supplied. Only embolisms of small segmental arteries distal to the anastomoses can lead to haemorrhagic pulmonary infarction, especially when there is concomitant left heart failure (19).

1.1.5 Clinical symptoms

Overall, DVT and PE present with nonspecific symptoms. The typical symptom triad of DVT consists of pain, swelling, and cyanosis of the affected body part. However, this triad occurs in only ten percent of all cases. Other symptoms of DVT include tenderness and hyperthermia of the affected region and pressure pain along the deep veins. Occasionally, fever and elevated inflammation levels are measured. As a result of venous outflow obstruction and collateralization, there may also be increased venous drawing, known as Pratt's sign. A frequent late complication of DVT is the post-thrombotic syndrome (PTS), which is the most common cause of chronic venous insufficiency (CVI). Recurrent thrombosis and development of PE represent further complications (19).

Small PEs are often asymptomatic. The leading symptoms of greater PEs include dyspnoea, tachypnoea, and respiratory chest pain. Other common symptoms include tachycardia, cough, and sometimes haemoptysis. In severe haemodynamically relevant PEs, syncope and circulatory shock may also occur (17,19). The occurrence of haemorrhagic pulmonary infarction is a possible complication of PE, which may also subsequently lead to the development of infarction related pneumonia. Another complication and the main cause for fatal outcome that occurs as a result of pulmonary hypertension is right heart failure. The risk of recurrence of PEs without anticoagulation therapy is high at 30%. Recurrent PEs but also persistent arterial occlusions due to lack of recanalization may result in chronic thromboembolic pulmonary hypertension (CTEPH). In CTEPH, fibrosis of the emboli occurs resulting in chronic pulmonary hypertension

with a mean pulmonary artery pressure of >25 mmHg (19). It presents with exertional dyspnea, fatigue and syncope and can lead to right ventricular failure (21).

1.1.6 Assessment of clinical probability and diagnostic algorithm

Since the symptoms of PE are nonspecific, it is reasonable to use diagnostic tools following an algorithm. This algorithm is based on the patient's physical condition and the pre-test probability (17).

The first diagnostic step for a potential pulmonary embolism event should be conducted depending on the patient's circulatory status. If the patient is haemodynamically unstable, for example, with persistent hypotension or symptoms of shock, CTPA or echocardiography should be performed immediately (19). In such patients it is useful to perform echocardiography at the beginning. It serves to detect RV dysfunction. If RV dysfunction is present and CTPA is not available or feasible due to the patient's condition, reperfusion therapy may be initiated immediately. If CTPA is available and feasible though, it should subsequently be used to detect emboli and when positive therapy should be initiated. In case RV dysfunction is not observed or CTPA is negative, another cause of the shock symptoms must be sought (22). **Figure 1** illustrates the decision-making process as described above.

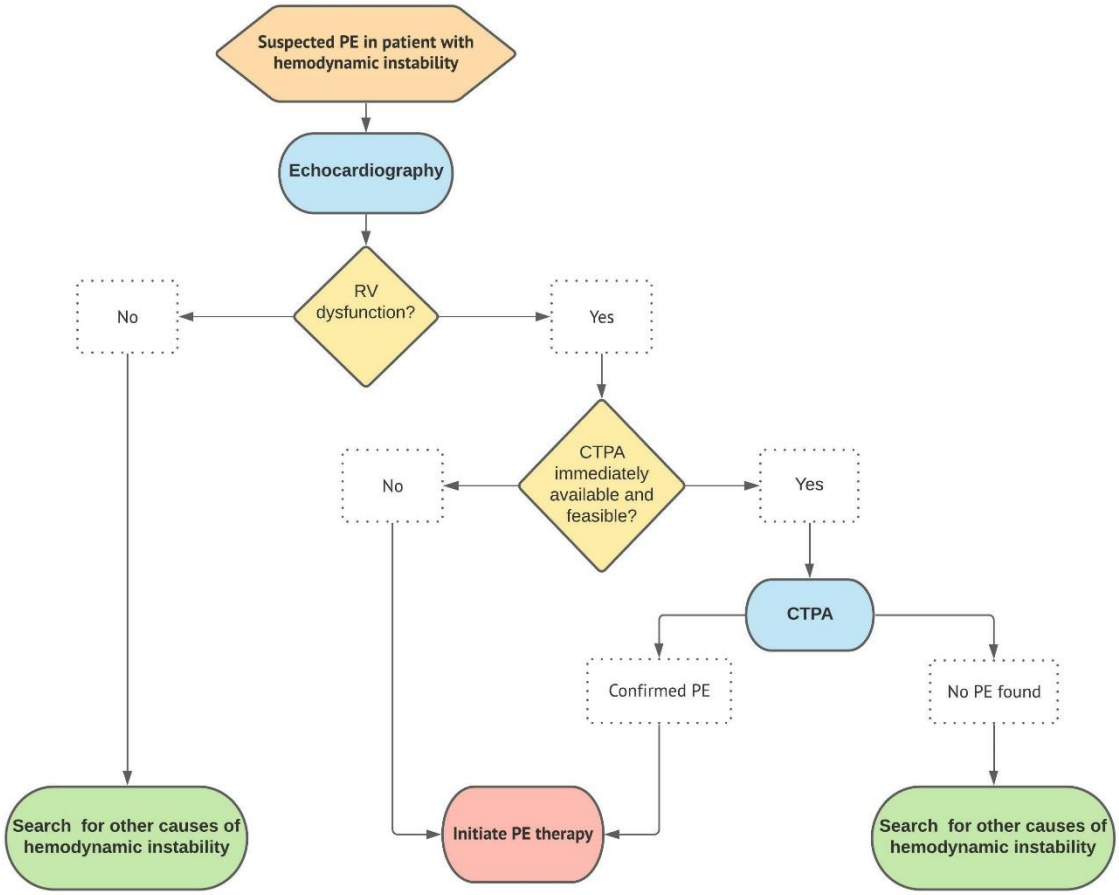

Figure 1: Diagnostic algorithm for suspected PE in patients with haemodynamic instability. Own figure.

In a patient without haemodynamic instability, the pre-test probability is determined first. The Wells-Score, as seen in **Table 1**, is a proven tool for this purpose. It is based on anamnestic and clinical factors and is suitable for determining the pre-test probability of DVT as well as PE (19,23).

Table 1: Estimation of the clinical pre-test probability for PE – Wells-Score.

Criteria	**Score**
Clinical signs of recent DVT	3,0
Other diagnoses are less likely than PE	3,0
Heart rate > 100/min	1,5

Immobilization (at least 3 days) or surgery in the last 4 weeks	1,5
Prior DVT or PE	1,5
Haemoptysis	1,0
Neoplasia (under therapy or diagnosed within the last 6 months)	1,0
Probability for PE	**Total score**
Low	< 2,0
Intermediate	2,0 – 6,0
High	> 6,0

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; min, minute. Own table based on Herold (19).

Another well-established scoring system for determining the likelihood of a PE event is the revised Geneva-Score, which is shown in **Table 2**. In contrast to the Wells score, it is based completely on objective criteria (23).

Table 2: Estimation of the clinical pre-test probability for PE - Revised Geneva-Score.

Criteria	**Score**
Age > 65 years	1
Prior DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Haemoptysis	2
Heart rate	
75-94/min	3
≥ 95/min	5
Pain on lower limb deep venous palpation and unilateral edema	4
Probability for PE	**Total score**
Low	0-3
Intermediate	4-10

High	≥ 11

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; min, minute. Own table based on Le Gal et al. (24).

Both the Wells and the Geneva scores also exist in a simplified form, which can be used to minimize calculation errors in an acute situation. Both scores allow a classification into low, intermediate, and high probability of PE depending on the total score (23). The risk assessment determines the next diagnostic step. In case of a low or intermediate risk, the next step is the measurement of D-dimers in the blood serum. If the result of this test is negative (D-dimers not elevated), pulmonary embolism can be ruled out with a high certainty and no further PE diagnostics are required. However, if the clinical probability of PE is high or the D-dimer test result is positive (D-dimers elevated), computed tomographic pulmonary angiography (CTPA) imaging should be performed next. In the case the CTPA examination confirms the presence of a thrombus in pulmonary arteries and therefore confirms PE, appropriate therapeutic measures will have to follow depending on PE severity. Is the pre-test probability high however and CTPA results are negative, further diagnostic tests should be considered (17). The algorithm described is illustrated in **Figure 2**.

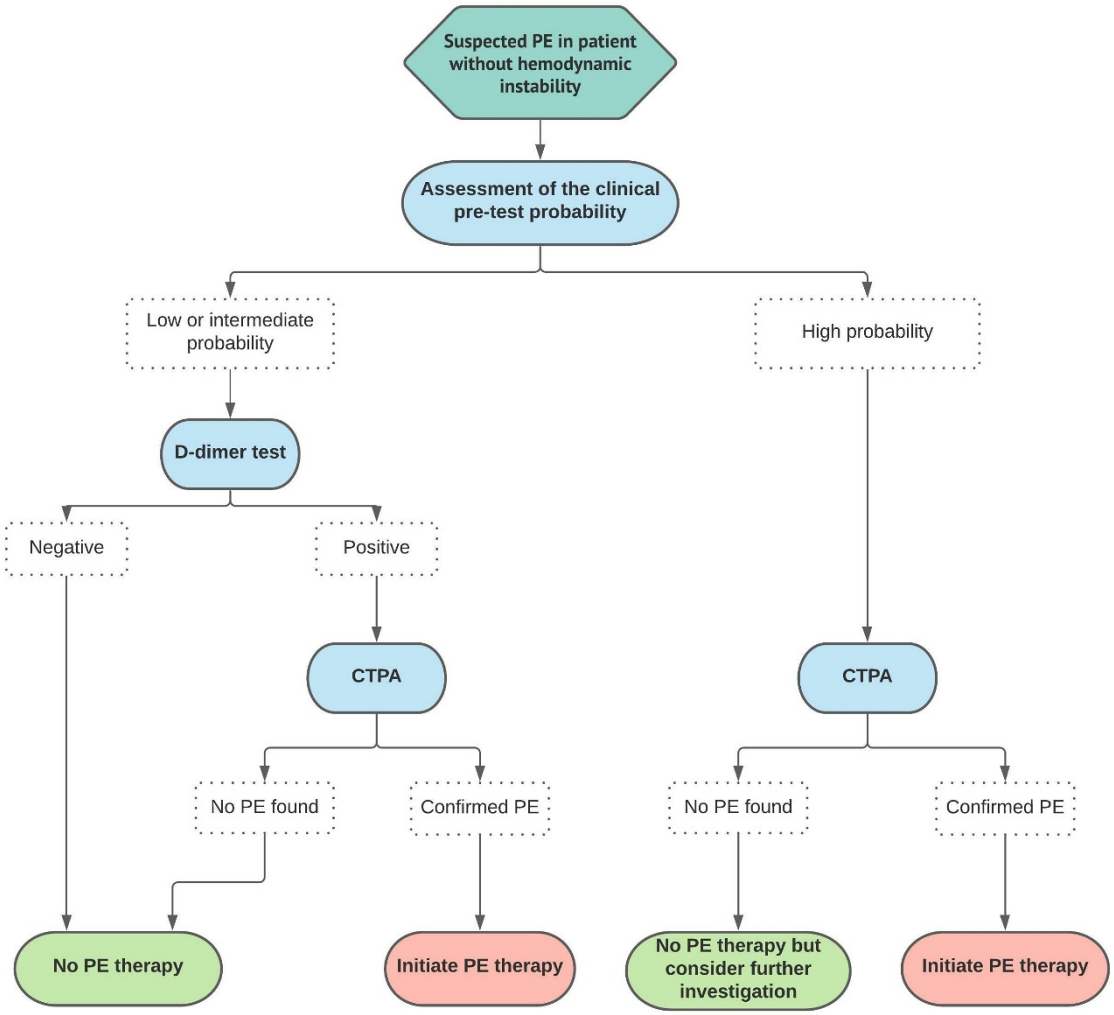

Figure 2: Diagnostic algorithm for suspected PE in patients without haemodynamic instability. Own figure.

1.1.7 Laboratory testing

D-dimers accumulate when fibrin is broken down and are therefore elevated in plasma during DVT or PE. The sensitivity of D-dimers is very high at over 80% for DVT and over 95% for PE. However, because the specificity of a D-dimer test is low, it is primarily useful for ruling out VTE. Accordingly, VTE can be excluded with a very high probability if the D-dimer test is negative. An elevation of D-dimers, however, does not necessarily mean that DVT or PE is present, but may be due to various causes such as malignancy, pneumonia, recent surgery or trauma, sepsis or pregnancy (20).

Two other biomarkers that have prognostic relevance in PE are cardiac troponin and brain natriuretic peptide (BNP). Troponin and BNP both reflect increased myocardial stress. Therefore, a negative troponin test and a physiological BNP level in confirmed PE indicate a mild course (19,20).

1.1.8 Imaging

1.1.8.1 Venous compression ultrasonography (CUS)

While a normal vein already collapses under slight compression, a vein affected by DVT cannot be compressed due to resistance of the thrombus. This fact is used in an examination with venous compression ultrasound (CUS) to detect thrombosis. As the pressure is applied via the transducer, the thrombus can be visualized in the ultrasound image at the same time (20). CUS has a high diagnostic value in patients with symptoms of proximal DVT with a sensitivity of about 95% and specificity of about 96%. Consequently, anticoagulation therapy can already be started in case of a positive test result, or it can be delayed in case of a negative result. In asymptomatic patients, however, the sensitivity of CUS is much lower and therefore cannot be used alone as the basis for a treatment decision (25). Sensitivity of proximal lower limb CUS in patients with suspected PE was also low with about 41% and therefore is not suitable for ruling out PE. However, it is suitable to indirectly indicate PE due to its high specificity of 96%. This may be helpful in patients for whom a CT scan is contraindicated (26).

1.1.8.2 Contrast venography

Contrast venography (CV) has long been the gold standard for diagnosis in suspected DVT. However, due to its invasiveness, expense, and the potential side effects from contrast media administration, this method is slowly being superseded by CUS. CV may nevertheless be used as a backup in case of doubt (27).

1.1.8.3 Computed tomographic pulmonary angiography (CTPA)

CTPA is the method of choice for the detection of emboli in patients with suspected PE. It is capable of imaging the pulmonary arteries down to the subsegmental branches and allows simultaneous examination of the heart (20). The Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) II study (28) aimed to determine the accuracy of CTPA for the diagnosis of PE and

observed a sensitivity of 83% and specificity of 96%. Because normal CTPA has a high negative predictive value in patients with low or intermediate pre-test probability, it is sufficient to rule out PE in these cases. The reverse is also true, a positive CTPA at intermediate or high pre-test probability is sufficient to confirm the diagnosis. However, if CTPA is normal at high pre-test probability or positive at low pre-test probability, it is recommended to consider further investigation (28).

1.1.8.4 Ventilation-perfusion lung scintigraphy

Perfusion scintigraphy is based on the injection of gamma-emitting albumin particles, whose distribution in the lungs reflects the blood flow there. Detection of the radiation allows detection of perfusion defects in the pulmonary arteries, which might be due to blood clots. However, perfusion scintigraphy may appear abnormal due to several different causes, leading to a rather low specificity. To increase specificity, ventilation scintigraphy can additionally be performed, in which radiolabeled gas such as xenon or krypton is inhaled. Areas with low perfusion but normal ventilation (V/Q mismatch) then indicate the presence of PE. Yet, lung scintigraphy is now largely used only as a back-up procedure as both sensitivity and specificity of CTPA are superior. Lung scintigraphy, however, is helpful in patients with contrast intolerance and in young people and/or pregnant women, in whom radiation exposure should be kept low (20,29).

1.1.8.5 Magnetic resonance angiography (MRA)

MRA to visualize the pulmonary arteries in suspected PE is less suitable than CTPA because the sensitivity is lower. Smaller segmental or subsegmental PEs cannot be detected reliably enough (20). Also, the poor availability of MRA scans in emergency settings is another disadvantage (22). Nevertheless, an MRA is a useful method to detect DVTs in case of an inconclusive ultrasound finding (20).

1.1.8.6 Echocardiography

Echocardiography rarely allows direct visualization of an embolus and is therefore not reliable for direct detection of PE. It, however, allows to exclude other pathologies with similar symptoms. In addition, it is useful for visualising possible effects of PE such as RV overload or dysfunction and thus may indirectly indicate PE. Dilation of the right ventricle or hypokinesia of its free wall (McConnell's sign) are typical findings. Echocardiography is therefore particularly suitable for risk

stratification and is a recommended diagnostic tool in patients with haemodynamic instability in suspected high-risk PE (20,22).

1.1.8.7 Chest X-ray

Often, no signs of pulmonary embolism can be found on chest x-ray. Therefore, this examination is mainly suitable for the exclusion of other thoracic diseases. And if, these signs tend to be nonspecific, such as an enlarged pulmonary artery, focal vascular hyperlucency (Westermark sign), peripheral consolidation in pulmonary infarction (Hampton's hump), pleural effusion and atelectasis (19,20).

1.1.9 Assessment of pulmonary embolism severity and risk of early death

The severity of PE is determinant for the further therapeutic approach. This includes which therapy methods are used, e.g. anticoagulation or reperfusion therapy, and whether treatment should take place on an inpatient or outpatient basis (19). Therefore, a reliable and accurate method for risk stratification is required. A validated tool for this purpose is the Pulmonary Embolism Severity Index (PESI) (30). The PESI assigns points for 11 different criteria regarding the medical history and condition of a patient suffering from PE and thus allows an estimation of the 30-day mortality risk. Depending on the total score, the mortality is divided into 5 classes of increasing risk (31). The PESI is also available in a shortened version, the simplified Pulmonary Embolism Severity Index (sPESI). It contains only 6 of the 11 criteria of the original PESI and divides the mortality risk into 2 classes (32). Both versions of the PESI are shown in **Table 3**.

Table 3: PESI/ sPESI for the assessment of mortality risk in PE.

Criteria	**Score**	
	PESI	**sPESI**
Age	Age in years	1 for >80
History of cancer	30	1
Systolic blood pressure <100 mmHg	30	1
Heart rate ≥ 110/min	20	1

O2 saturation <90%	20		1	
History of heart failure	10		1 (maximum of 1 point even if both apply)	
History of chronic lung disease	10			
Altered mental status	60		Not included	
Body temperature <36°C	20			
Respiratory rate ≥ 30/min	20			
Male sex	10			
	Total score	30-day mortality risk	Total score	30-day mortality risk
	≤65 (I)	0-1.6%	0	0.0-2.1%
	66-85 (II)	1.7-3.5%		
	86-105 (III)	3.2-7.1%	≥1	8.5-13.2%
	106-125 (IV)	4.0-11.4%		
	>125 (V)	10.0-24.5%		

Abbreviations: mmHg, millimeter mercury; min, minute; O2, oxygen; °C, degrees Celsius; (s)PESI, (simplified) Pulmonary Embolism Severity Index. Roman numerals in brackets represent risk classes. Own table based on Konstantinides et al. (22).

The PESI has an excellent negative predictive value of 99% for predicting mortality, making it highly suitable for distinguishing patients at low risk of early death from those at high risk. This allows and facilitates physicians to make reliable therapy decisions (30,33).

The European Society of Cardiology incorporates the PESI into their recommended prognostic assessment strategy in their 2019 Guidelines on Acute Pulmonary Embolism as shown in **Table 4** (22). This strategy combines four different criteria to assess the PE severity. These include the presentation with haemodynamic instability, the PESI score, the detection of RV dysfunction and the cardiac troponin level (22).

Table 4: Risk stratification of pulmonary embolism and the risk of early death.

Risk of early death	Indicators of risk			
	Haemodynamic instability (cardiac arrest, shock, or persistent hypotension)	PESI class III-V or sPESI ≥1	RV dysfunction on echocardiography or CTPA	Elevated cardiac troponin levels
High	+	(+)	+	(+)
Intermediate-high	–	+	Both criteria positive	
Intermediate-low	–	+	One or no criterion positive	
Low	–	–	–	– (Assessment optional)

Abbreviations: PE, pulmonary embolism; (s)PESI, (simplified) Pulmonary Embolism Severity Index; RV, right ventricle; CTPA, computed tomographic pulmonary angiography. Own table based on Konstantinides et al. (22).

According to the mentioned guidelines, patients with haemodynamic instability and evidence of PE by CTPA and/or evidence of RV dysfunction by CTPA or TTE can be assigned to the high-risk PE group. In such cases, no measurement of biomarkers, as well as calculation of PESI, is necessary for immediate therapeutic intervention. If the patient presents without haemodynamic instability, it is recommended to continue risk stratification with the remaining criteria. The PESI is a suitable tool to then distinguish low-risk and intermediate-risk PEs. Given its high negative predictive value, a PESI of class I - II or a sPESI of 0 is sufficient to classify a PE as low-risk. A higher score indicates intermediate-risk PE. Patients in the intermediate-risk group who have both RV dysfunction and elevated troponin levels are assigned to the intermediate-high-risk group. If only one or neither of these two criteria apply, the PE is classified as intermediate-low-risk (22).

1.1.10 Anticoagulation

Available anticoagulant agents

Available medications for the treatment of VTE include parenteral anticoagulants such as

- low molecular weight heparin (LMWH),
- fondaparinux and
- unfractionated heparin (UFH),

and oral anticoagulants like

- vitamin K antagonists and
- non-vitamin K antagonist oral anticoagulants (NOACs) / direct oral anticoagulants (DOACs).

Table 5: Comparison of oral anticoagulants.

	NOACs				VKAs
	Apixaban	**Edoxaban**	**Rivaroxaban**	**Dabigatran**	**Warfarin**
Target	Factor Xa	Factor Xa	Factor Xa	Factor IIa (Thrombin)	Vitamin K epoxide reductase
Half-life	10-14h	9-11h	5-9h	12-14h	20-60h
Bridging	Not required				Necessary (with LMWH)
Necessity of monitoring	Not required				Necessary (International normalized ratio (INR))
Reversibility	Andexanet alfa	–	Andexanet alfa	Idarucizumab	Vitamin K

Abbreviations: NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; LMWH, low molecular weight heparin; INR, international normalized ratio. Own table. Data obtained from (34,35).

Initial anticoagulation treatment

The initial therapy for VTE usually involves parenteral anticoagulation and should be initiated immediately after diagnosis or already before, in case the clinical probability for VTE is high. LMWH and fondaparinux are usually preferred over UFH in this regard as they are associated with a lower risk of bleeding and heparin-induced thrombocytopenia (HIT). Moreover, their use does not require monitoring in contrast to the use of UFH, where monitoring of the activated partial thromboplastin time (aPTT) is necessary (36,37). However, since UFH comes with a short half-life and may be antagonized using protamine sulfate, it is preferably used in cases where thrombolysis is being considered. Another indication for the use of UFH instead of the other parenteral anticoagulants is in patients with known renal failure, due to its non-renal excretion (2,38).

Administration of NOACs alone can achieve an anticoagulant effect as rapid as that with parenteral anticoagulants, with a similarly low risk of bleeding, studies showed when investigating the effect of rivaroxaban and apixaban. Therefore, they are also a considerable alternative for the initial treatment (39,40).

Long-term anticoagulation treatment

It is carried out for at least 3 months either with the same anticoagulant as in the initial therapy at a lower dose or with a different anticoagulant (2). Until now, the conventional treatment has been the administration of VKAs after initial therapy with parenteral anticoagulants. The aim here is to achieve an international normalized ratio (INR) of 2.0 to 3.0. NOACs, however, show noninferiority to VKAs and come with a lower risk of bleeding and HIT. In addition, they offer other advantages such as administration as oral monotherapy and lack of need for laboratory monitoring and individual dose adjustment (2). In cancer patients, LMWHs are still used as standard long-term therapy, as long as the use of NOACs for these patients has not been sufficiently investigated (2).

1.1.11 Risk-adjusted acute phase treatment

Specific objectives are defined for the treatment of DVT and PE, respectively. The therapeutic aims for DVT include prevention of pulmonary embolism, thrombus

growth and recurrent DVT, and promotion of endogenous fibrinolysis to mitigate post-thrombotic syndrome (41). One aim of PE therapy is to reduce mortality through risk-stratified treatment. The second aim is to prevent embolic recurrence. This is particularly important because the risk of recurrence is high, and many lethal PEs tend to occur in episodes (19).

1.1.11.1 Acute phase treatment of high-risk pulmonary embolism

Anticoagulation

In patients with high-risk PE, it is recommended to initiate parenteral anticoagulation with UFH (22).

Haemodynamic and respiratory support

In high-risk pulmonary emboli, usually large areas of the lungs are no longer perfused, making the occurrence of hypoxemia very likely. If oxygen saturation falls below 90% in these patients, they should be administered oxygen. In more severe cases, mechanical ventilation may be necessary. Since RV failure is the major cause of fatal outcome in PE, it is also important to improve cardiac output. Strategies for this purpose include cautious fluid loading, pharmacological increase of right ventricular inotropy and systemic blood pressure, and performing temporary extracorporeal life support, if necessary (22,42). However, it is important to be aware that even the short-term use of extracorporeal membrane oxygenation (ECMO) is associated with a high rate of complications and requires an experienced team. It should therefore only be utilized thoughtfully. In the event of cardiac arrest, advanced life support guidelines should be followed (22).

Reperfusion

Reperfusion treatment is primarily required in cases of severe VTE, i.e. proximal DVTs or high-risk PEs (43). Several procedures are available in this regard: systemic thrombolysis, catheter-directed intervention, and surgical embolectomy (22). Systemic thrombolysis with streptokinase, urokinase, or recombinant tissue-type plasminogen activator (rtPA), is the treatment of choice for reperfusion in high-risk PE. However, if such medication is contraindicated for the patient, one of the other mentioned procedures may be performed as an alternative. Once the

patient has regained haemodynamic stability through successful reperfusion, parenteral can be switched to oral anticoagulation treatment (22).

1.1.11.2 Treatment of intermediate- and low-risk pulmonary embolism

General management

Management of patients with intermediate-risk PE involves hospitalization and anticoagulation treatment, which is usually sufficient. However, patients with intermediate-high-risk PE require additional monitoring as reperfusion treatment may become necessary, in the event that signs of haemodynamic instability develop (22).

Early discharge home may be considered for patients with low-risk PE, provided there are no other reasons for hospitalization. In addition, it must be ensured that the patient is able to continue anticoagulation therapy adequately at home given his or her condition and has access to medical facilities and social support (22).

Anticoagulation

For both, patients with intermediate-risk and low-risk PE, initiation of anticoagulation treatment is indicated as soon as there is a high or intermediate clinical probability. For parenteral anticoagulation, LMWH or fondaparinux is recommended over UFH unless contraindications exist. If oral anticoagulation is chosen, the administration of NOACs is recommended over VKAs. However, if VKAs are opted for instead, bridging treatment with parenteral anticoagulation should be provided until an INR of 2.0 - 3.0 is achieved (22).

Reperfusion

Routine systemic thrombolysis is not recommended for these patients unless their haemodynamic condition worsens with anticoagulation therapy already in place (22).

1.1.12 Long-term treatment and prevention of recurrence

The aim of continuing anticoagulation therapy after acute PE is firstly to complete the purpose of the initial therapy and secondly to prevent recurrence of VTE.

According to the 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism, anticoagulation for at least 3 months is recommended for all patients presenting with PE. In deciding whether to continue therapy beyond 3 months, the risk of VTE recurrence must be weighed against the risk of bleeding. Thus, it depends on whether risk factors are still present, whether they are transient or persistent, and to what extent they provoke VTE (22).

Consequently, anticoagulation treatment can be discontinued after 3 months in patients with first-ever VTE associated with a strong transient risk factor (e.g., major surgery). However, in patients with recurrent VTE in the absence of a strong transient risk factor or in patients suffering from hereditary prothrombotic disease such as antiphospholipid antibody syndrome, extension of anticoagulation treatment for an indefinite duration is recommended. In cases of first-time PE and unidentifiable risk factor, weak transient risk factor, or persistent risk factor, extension beyond 3 months should be considered (22).

Since the balance between sufficient anticoagulation and low bleeding risk is often difficult to achieve, new pharmacological approaches are being explored to achieve this balance. Factor XI (FXI) from the coagulation cascade is of particular interest in this regard, as there is evidence that there is a correlation between FXI levels and VTE risk. Reduced FXI levels appear to be protective without increasing the risk of bleeding (44,45). In a phase 2 study, the FXI-specific antibody abelacimab at 3 different doses (30 mg, 75 mg, and 150 mg) was compared with 40 mg enoxaparin administration for the prevention of postoperative VTEs after knee arthroplasty. This found the 30 mg dose of abelacimab to be noninferior and 75 mg and 150 mg doses to be superior to enoxaparin in preventing VTE development with similar low risk of bleeding (46).

1.1.13 General measures

After diagnosis of DVT, treatment with compression stockings may be started immediately (19). The benefit of this treatment is controversially discussed. Some studies observed a reduction in the risk of PTS, others observed no benefit, and most meta-analyses found only low evidence in this regard. The decision for this treatment should hence be made on an individual patient basis (47). Along with

compression therapy, early mobilization, range-of-motion exercises, instruction in self-exercise and adequate fluid intake can help reduce the incidence and severity of PTS. Thrombosis-promoting drugs should also be discontinued when possible (48,49).

1.2 Lipoprotein(a) overview

1.2.1 Structure

Lipoprotein(a) [Lp(a)] is produced almost exclusively in the liver and is composed of two subunits (50). One subunit is similar in structure to a low density lipoprotein (LDL) particle. It is made of apolipoprotein B-100 (apoB) and a high proportion of cholesterol. The second subunit is a glycoprotein called apolipoprotein(a) [apo(a)], which is linked to apoB by disulfide bridges (51,52). The structure of apo(a) contains so-called kringle domains, which also occur in the structure of plasminogen. Hence, apo(a) and plasminogen show structural similarity (53,54).

1.2.2 Physiological function and pathophysiology of Lp(a)

The physiological function of Lp(a) has not been adequately resolved to date. However, due to its structure and properties, and several observations, there are some hypotheses in this regard. Moreover, the physiological mechanisms of Lp(a) may be concomitantly the basis for its pathogenicity in elevated concentrations.

One hypothesis is that Lp(a), given its LDL-like and plasminogen-like structure, is a linking component between cholesterol transport and the fibrinolytic system and thus plays a role in the balance between coagulation and fibrinolysis (55). Due to its similarity to plasminogen, it competes with it for binding sites on endothelial cells and fibrin, thereby preventing the conversion to plasmin and thus inhibiting fibrinolysis (56). Lp(a) further prevents the activation of plasminogen by tissue-type plasminogen activator (t-PA) and streptokinase, which likewise impairs fibrinolysis and therefore promotes thrombosis (57,58).

Another hypothesis is that Lp(a) contributes to wound healing. This is supported by the fact that Lp(a) accumulates in endothelial injuries and interacts with various cells involved in wound healing, such as macrophages, endothelial cells,

fibroblasts, smooth muscle cells and platelets (59,60). More precisely Lp(a) promotes several cascades through these interactions, such as the differentiation of proinflammatory monocytes, and proliferation and migration of endothelial and smooth muscle cells. These mechanisms promote tissue remodeling and thus wound healing, but also the development of atherosclerotic plaques (60). Because Lp(a) is transported to wounds by binding to fibrin and inhibiting fibrinolysis there, it can be speculated that higher Lp(a) concentrations may also have resulted in more rapid haemostasis and thus less blood loss, providing an evolutionary advantage (61).

Studies also show that Lp(a) serves as the main carrier for oxidized phospholipids (OxPL), which possess a proinflammatory and proatherogenic property. It is speculated that Lp(a) may have physiological anti-inflammatory properties at low plasma concentrations by binding OxPLs (62). However, increased plasma levels of Lp(a) are strongly associated with increased incidence of myocardial infarction, ischemic stroke, atherosclerotic stenosis and aortic valve stenosis, which is why Lp(a) is considered an independent risk factor for ASCVD (63–66).

1.2.3 Lp(a) levels and influencing factors

Lp(a) plasma concentration varies widely within and between populations (67). There are differences between different ethnicities, with African Americans having higher Lp(a) levels on average than Caucasians or Asians (68,69). Also, sex, age, fasting state, body mass index (BMI) and diet do not appear to influence Lp(a) levels (70). The reason for this is that Lp(a) production is predominantly genetically determined by the LPA gene, which also explains the stability of Lp(a) concentrations throughout life (67).

Several studies found that the risk of ASCVD increases with increasing Lp(a)-levels, particularly starting at a threshold value of 30 mg/dL. Therefore, concentrations of >30 mg/dL are considered pathologically elevated (64,71–73).

1.2.4 Therapeutic options for reducing Lp(a) levels

At the time of writing this thesis, there are no approved drugs that specifically and effectively reduce Lp(a) levels. So far, the effect on Lp(a) levels of other lipid lowering therapies, which are already in use, has been studied. However, these primarily affect LDL-C and do neither specifically nor effectively decrease Lp(a) levels (74).

1.2.4.1 Effect of lipid-lowering drugs on Lp(a)

A systemic literature review of several studies that assessed the effect of statins (atorvastating, pitavastatin, pravastatin and rosuvastatin) on Lp(a) levels shows that statins not only do not lower Lp(a) levels but may actually increase them. Statin monotherapy accordingly increased Lp(a) by a mean of about 11% along with an ~24% increase in OxPL-apoB (75).

Ezetimibe is also used in lipid-lowering therapy and has been studied for its effect on Lp(a). A meta-analysis of 7 randomized controlled trials (RCT) found a significant yet only slight reduction in Lp(a) levels of about 7%, which alone is not considered clinically relevant (76).

A different meta-analysis including 14 RCTs was conducted to determine the efficacy of extended-release nicotinic acid (ER niacin) in decreasing Lp(a). The analysis found a significant mean reduction in Lp(a) levels of roughly 21-24% (77). For niacin, however, no beneficial effect on cardiovascular disease risk and mortality was found. Instead, niacin raises the number of adverse effects such as skin flushing, pruritus, rash, headache, and gastrointestinal symptoms. It is therefore not suitable as a therapeutic option (78).

The proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors evolocumab and alirocumab were also studied for their benefit in reducing Lp(a). The FOURIER study found a significant median reduction of 26.9% after 48 weeks of treatment with evolocumab (79). Concordantly, alirocumab achieved a significant reduction in Lp(a) of 23.3% to 29.1% after 24 weeks of treatment in the phase III ODYSSEY program (80).

1.2.4.2 Antisense oligonucleotides for reduction of Lp(a)

Lp(a) offers only few points of attack due to its genetic basis, however, this very fact also provides a therapeutic target which is utilized in antisense oligonucleotide

(ASO) therapy. Mipomersen (trade name: Kynamro) is an ASO developed to inhibit the synthesis of apoB, leading to a reduction in atherogenic apoB-containing lipoproteins such as LDL-C and Lp(a). The meta-analysis by Fogacci et al. found a significant mean reduction in Lp(a) of 22.7%. However, treatment with mipomersen was poorly tolerated overall due to adverse effects such as flu-like symptoms, injection site reactions, hepatic steatosis, and liver enzyme elevation, resulting in approximately 42% of participants discontinuing treatment versus 20% in the placebo group (81). Consequently, mipomersen was refused marketing authorisation in the European Union by the European Medicines Agency (EMA) due to safety concerns (82). In the U.S., mipomersen is approved by the U.S. Food and Drug Administration (FDA), however, only for patients with homozygous familial hypercholesterolemia (HoFH).

Another ASO is currently being developed to specifically inhibit the synthesis of apo(a) and hence Lp(a): Pelacarsen. It has already shown promising results in phase 1 and phase 2 trials and is currently being studied in a phase 3 trial. Pelacarsen, also known as IONIS-APO(a)$_{Rx}$ or IONIS-APO(a)-L$_{Rx}$, respectively, specifically reduces plasma Lp(a) levels through binding directly to the apo(a) mRNA in hepatocytes, thereby hindering the formation of apo(a) and consequently Lp(a). In the phase 2 trial of IONIS-APO(a)$_{Rx}$, a significant reduction in mean Lp(a) of 66.8% to 71.6% could be observed, depending on baseline. Furthermore, a significant decrease in LDL-C, apoB, OxPL-apoB and OxPL-apo(a) was achieved (83). A second RCT was then conducted to determine the efficacy of IONIS-APO(a)-L$_{Rx}$, which is an IONIS-APO(a)$_{Rx}$ molecule conjugated to triantennary *N*-acetyl galactosamine (GalNAc3). GalNAc3 is a ligand for hepatocyte-specific asialoglycoprotein receptors. Its function is to enhance the distribution of IONIS-APO(a)$_{Rx}$ to the liver and to facilitate its uptake into hepatocytes, which leads to an increase in potency (83,84). In fact, treatment with IONIS-APO(a)-L$_{Rx}$ resulted in a dose-dependent mean Lp(a) reduction of 59.4% to 82.4% versus placebo at a lower dose than IONIS-APO(a)$_{Rx}$, resulting in a more than 30-fold greater potency. Additionally, all participants completed the study as no treatment-related adverse events occurred with IONIS-APO(a)-L$_{Rx}$ (83).

1.2.4.3 Apheresis

So far lipoprotein apheresis (LA) is the only available and approved method to effectively lower Lp(a) levels. To evaluate the effect of LA on Lp(a), 3 retrospective and prospective studies, respectively, measured Lp(a) levels in patients with elevated Lp(a) before and after LA treatment. They observed a mean Lp(a) reduction between 68% and 72%. There are also drawbacks, however, as LA treatment is expensive and invasive and must be repeated weekly to ensure a consistent reduction in Lp(a). For this reason, it has so far been used mainly in patients for whom a reduction of lipoproteins is not feasible with medication (85–87).

2 MATERIAL AND METHODS

2.1 Study design

The findings presented in this thesis result from a retrospective data analysis. All patients who were treated for pulmonary embolism at the Department of Internal Medicine of the University Hospital Graz in the period of January 1, 2002 to August 1, 2020 with an available Lp(a) concentration were included.

Patients were categorized into four groups based on the severity of pulmonary embolism in accordance with the 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism: Low risk (LR), intermediate low risk (IML), intermediate high risk (IMH), and high risk (HR). These guidelines classify PE events based on early mortality risk. For risk assessment, 4 different determinants are considered (**Table 4**): Haemodynamic instability, (Simplified) Pulmonary Embolism Severity Index [(s)PESI] (**Table 3**), signs of right ventricular (RV) dysfunction, and elevated troponin levels. Patients with haemodynamic instability are classified in the high risk PE category. Patients without haemodynamic instability but positive sPESI or PESI score are classified as intermediate-high risk (signs of RV dysfunction and elevated troponin) or intermediate-low risk (signs of RV dysfunction or elevated troponin or neither). Patients with proven PE but neither haemodynamic instability nor positive sPESI or PESI score are classified as low risk. The sPESI score was assessed by age, sex, malignant or cardiopulmonary comorbidities, heart rate, systolic blood

pressure, and blood oxygen saturation. RV dysfunction was assessed by computed tomography (CT) or echocardiography (88).

The study protocol was approved by the Ethics Committee (EK 32-646 ex 19/20) of the Medical University of Graz.

2.2 Data collection and statistical analysis

The data was obtained using the electronic medical records and outpatient records of the Department of Internal Medicine of the University Hospital Graz, Austria.

All statistical analyses were performed with Stata (Windows Version 17.0, Stata Corp., Houston, TX, USA). Continuous variables were summarized as medians [25th-75th percentile], and count data as absolute frequencies (%). Correlations between two continuous variables were evaluated with Spearman's rank-based correlation coefficient. The primary analysis quantity was the association between PE severity as indicated by the ESC PE risk stratification (4-level ordinal variable defined above) and the Lp(a) levels, both as a continuous variable and as a binary variable dichotomized at a pre-defined cut-off at 30 mg/dL. For these analyses, we employed Kruskal-Wallis tests, simple and multiple linear regression models (multiple linear regression adjusted for age and sex), F-tests for linear trend, box plots, $\chi 2$-tests, and Fisher's exact tests, as appropriate. We performed a sensitivity analysis restricting our analysis population to patients who had their Lp(a) measurement taken within one year before to one year after PE diagnosis. In a second pre-specified sensitivity analysis, we examined whether extremely high levels of Lp(a), defined by three Lp(a) cut-offs >60 mg/dL, >80 mg/dL, and >100 mg/dL, were associated with high-risk PE.

3 RESULTS

Cohort description

We analyzed 1,171 patients with PE, of whom 450 (38%) had low-risk PE, 508 (43%) had intermediate-low-risk PE, 104 (9%) had intermediate-high-risk PE, and 109 (9%) had high-risk PE, respectively (**Table 6**). Median Lp(a) concentration

was 15 mg/dL [25th-75th percentile: 10-35, range: 0.3 – 254]. Higher Lp(a) did not correlate with age (Spearman's ρ=0.01, p=0.640), and was comparable between males and females (median Lp(a). 14 vs. 15, p=0.253).

Table 6: Baseline characteristics of the study population (n=1,171).

Variables	Overall (n=1,171)	Lp(a) ≤ 30mg/dL (n=847)	Lp(a) > 30mg/dL (n=324)	p
Age at PE diagnosis (years)	70 [56-80]	70 [55-80]	69 [58-81]	0.802
Female sex	595 (51%)	418 (49%)	177 (55%)	0.106
PE risk stratification	/	/	/	0.057
---Low-risk	450 (38%)	327 (39%)	450 (38%)	/
---Intermediate-Low-risk	508 (43%)	372 (44%)	136 (42%)	/
---Intermediate-High-risk	104 (9%)	64 (8%)	40 (12%)	/
---High-risk	109 (9%)	84 (10%)	25 (8%)	/

Distribution overall and by Lipoprotein(a) status. We used an Lp(a) cut-off at 30 mg/dL according to the established reference range of this parameter. Reported data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. P-values are from rank-sum tests and χ^2-tests, as appropriate. Abbreviations: Lp(a) – Lipoprotein(a), PE – Pulmonary embolism. Derived from Gressenberger et al. (88) under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/); In the published manuscript other cut off values were used. Furthermore only patients with a latency between PE diagnosis and Lipoprotein(a) measurement with a maximum of one year were included in the published paper, resulting in a different sample size (n =1171 vs. n= 811).

Lp(a) concentration by PE severity

We did not observe an association between PE severity and Lp(a) concentrations. In detail, median Lp(a) concentrations were 15 mg/dL [25th-75th percentile: 10-34] in low-risk PE patients, 15 mg/dL [10-33] in intermediate-low-risk PE patients, 13 mg/dL [10-41] in intermediate-high-risk PE patients, and 13 mg/dL [10-29] in high-risk PE patients, respectively (Kruskal-Wallis p=0.943, p for linear trend=0.640, **Figure 3**).

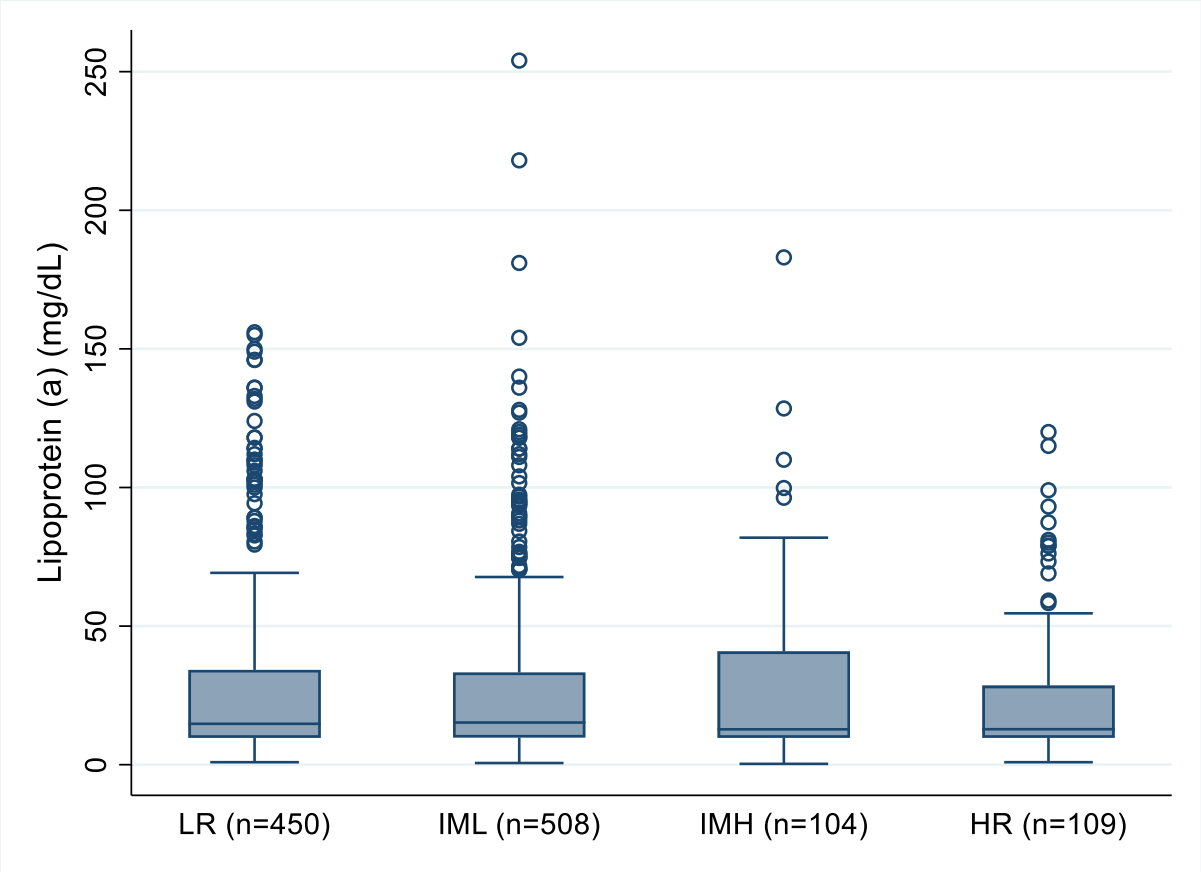

Figure 3: Boxplots of Lipoprotein(a) levels according to PE severity (n=1,171).
Abbreviations: PE – Pulmonary embolism, LR – Low-risk PE, IML – Intermediate-Low-risk PE, IMH – Intermediate-High-risk PE, HR – High-risk PE. Derived from Gressenberger et al. (88) under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/); In the published manuscript only patients with a latency between PE diagnosis and Lipoprotein(a) measurement with a maximum of one year were included, resulting in a different sample size (n =1171 vs. n= 811).

This result prevailed also after multivariable adjustment for age and sex (Adjusted p for association between Lp(a) and PE severity=0.777, **Table 7**).

Table 7: A multiple linear regression model of Lipoprotein(a).

Variable	β coefficient	95%CI	p
Age at PE diagnosis (per 5 years increase)	0.13	-0.4-0.7	0.648
Female sex	2.86	-0.63-6.35	0.108
PE risk stratification	/	/	/
---Low-risk	Ref.	Ref.	Ref.
---Intermediate-Low-risk	-0.74	-5.02-3.53	0.733

---Intermediate-High-risk	0.71	-5.98-7.41	0.834
---High-risk	-3.08	-9.49-3.34	0.347
Constant	25.23	1.18-23.27	<0.0001

The β coefficient represents the change in Lp(a) per one unit change in the respective variable. Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, PE – Pulmonary embolism, Ref. – Reference category.

Sensitivity analysis – Latency between PE and Lp(a) measurement

Median time between PE and Lp(a) determination was 1 day, but a considerable proportion of patients had some latency between PE and Lp(a) determination [25th-75th percentile: -176 days – 1 days, range: -6584 days – 4868 days (with negative numbers indicating days before PE and positive numbers indicating days after PE, **Figure 4**).

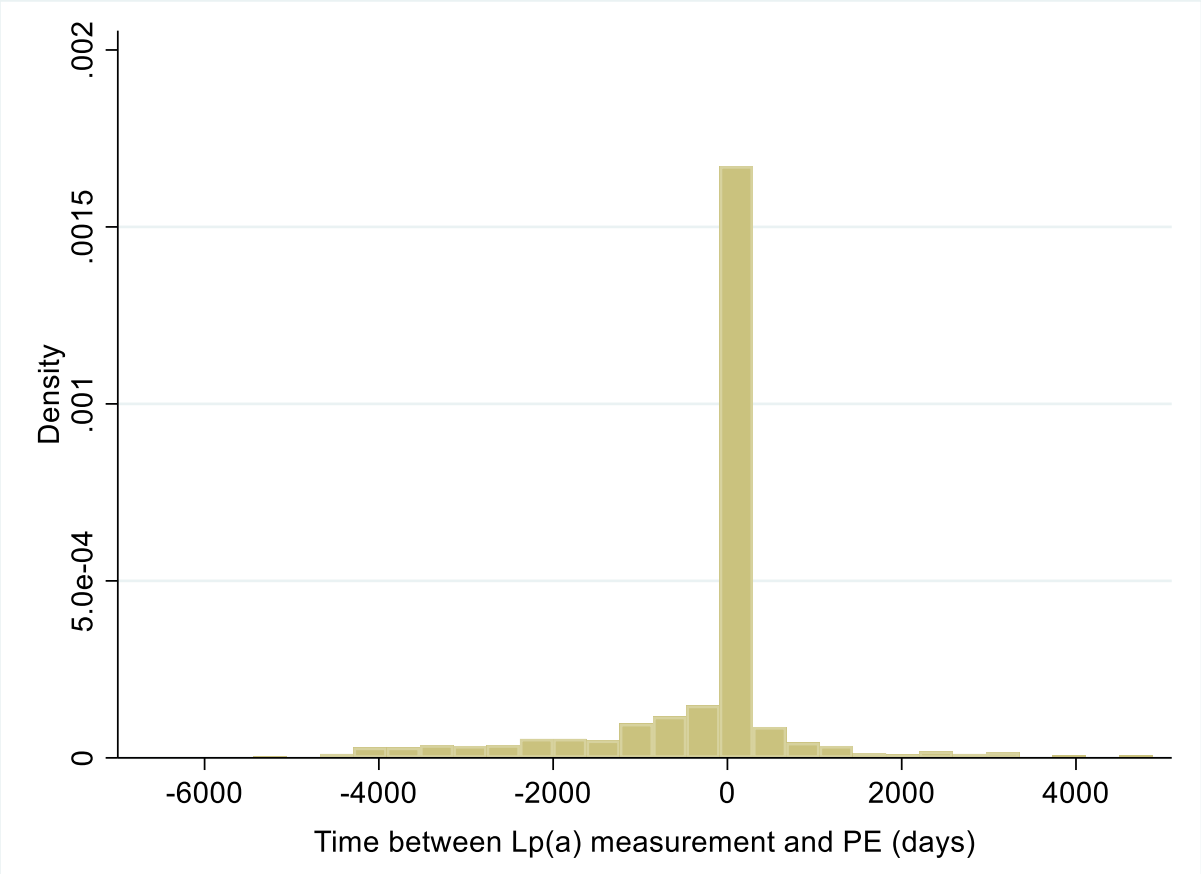

Figure 4: Histogram of the latency between PE diagnosis and Lipoprotein(a) measurement. *Latency is measured in days. Negative values represent Lp(a) measurements*

prior PE, and positive values Lp(a) measurements after PE, respectively. Abbreviations: Lp(a) – Lipoprotein(a), PE – Pulmonary embolism.

Although Lp(a) is thought to be relatively stable within patients over time, and we did not observe a correlation between Lp(a) levels and latency between PE and Lp(a) determination (Spearman's ρ=-0.04, p=0.179), we performed a sensitivity analysis restricting our analysis population to patients who had their Lp(a) measurement taken within one year before to one year after PE diagnosis (n=811). In comparison to the full cohort, this subcohort had slightly lower Lp(a) levels and was slightly older but had comparable PE risk category distribution (**Table 8**).

Table 8: Baseline characteristics of the study population according to elapsed time between PE diagnosis and Lipoprotein(a) determination (n=1,171).

Variables	Time between PE and Lp(a): 1 year prior until 1 year after PE (n=811)	Time between PE and Lp(a): > 1 year prior or > l 1 year after PE (n=360)	p
Lp(a) (mg/dL)	15 [10-35]	12 [10-33]	0.091
Age (years)	69 [54-80]	72 [60-81]	0.006
Female sex	417 (51%)	178 (49%)	0.533
PE risk stratification	/	/	0.099
---Low-risk	323 (40%)	127 (35%)	/
---Intermediate-Low-risk	343 (42%)	165 (46%)	/
---Intermediate-High-risk	64 (8%)	40 (11%	/
---High-risk	81 (10%)	28 (8%)	/

We used a cut-off of 1 year prior or after PE diagnosis. Reported data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. P-values are from rank-sum tests and χ2-tests, as appropriate. Abbreviations: Lp(a) – Lipoprotein(a), PE – Pulmonary embolism. Derived from Gressenberger et al. (88) under CC BY 4.0

(https://creativecommons.org/licenses/by/4.0/); In the published manuscript analysis only included patients with a latency between PE diagnosis and Lipoprotein(a) measurement with a maximum of one year (n =811).

Also, in this subcohort of patients with a latency between PE and Lp(a) determination of a maximum of 1 year, we did not observe a consistent association between Lp(a) and PE risk category. In detail, median Lp(a) concentrations were 17 mg/dL [25th-75th percentile: 10-37] in low-risk PE patients, 16 mg/dL [10-33] in intermediate-low-risk PE patients, 15 mg/dL [10-48] in intermediate-high-risk PE patients, and 13 mg/dL [10-27] in high-risk PE patients, respectively (Kruskal-Wallis p=0.60, p for linear trend=0.358, **Figure 5**). Again, this result prevailed also after multivariable adjustment for age and sex (Adjusted p for association between Lp(a) and PE severity=0.197, full model not shown).

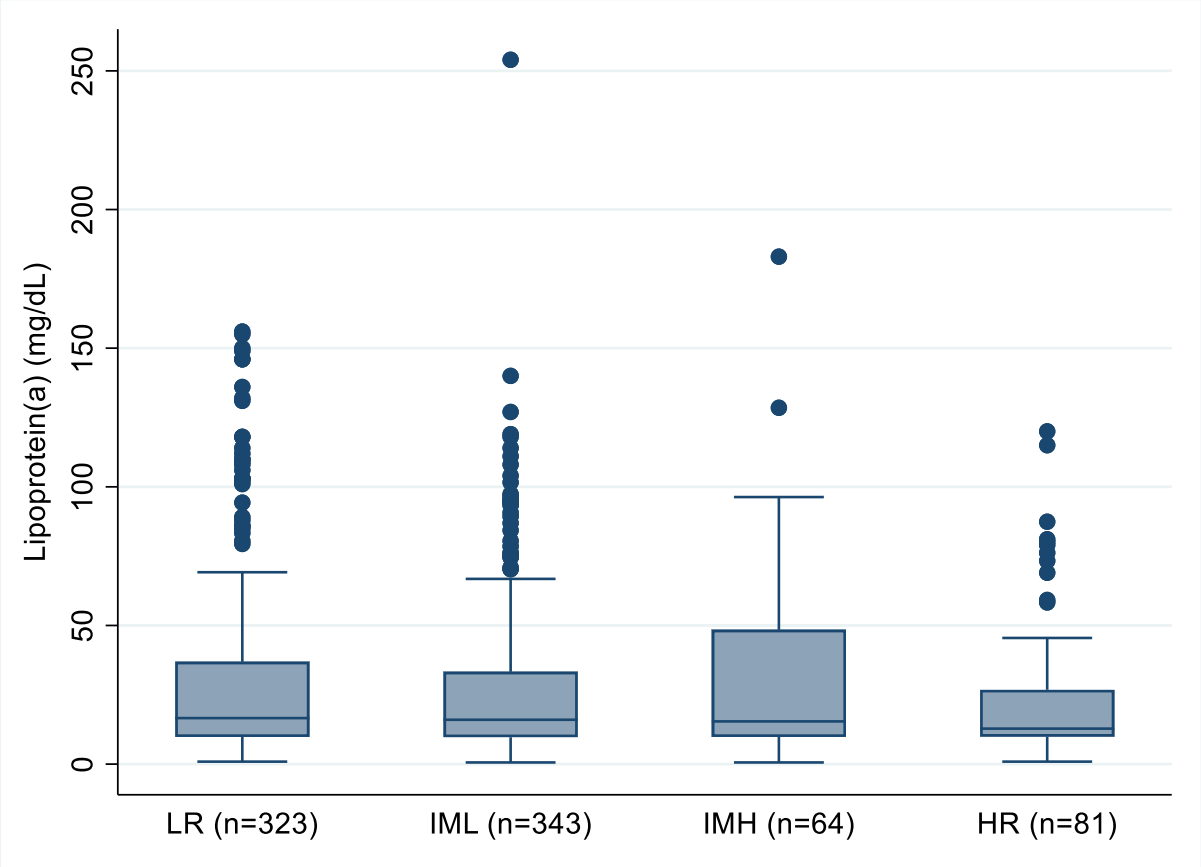

Figure 5: Boxplots of Lipoprotein(a) levels according to PE severity in the subgroup of patients with a latency between PE and Lipoprotein(a) measurement of a

maximum of 1 year (n=811). Abbreviations: PE – Pulmonary embolism, LR – Low-risk PE, IML – Intermediate-Low-risk PE, IMH – Intermediate-High-risk PE, HR – High-risk PE. Created using data published in Gressenberger et al. (88) under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/);

Sensitivity analysis – Very high levels of Lp(a)

In this sensitivity analysis, we examined whether extremely high levels of Lp(a), defined by three Lp(a) cut-offs >60 mg/dL, >80 mg/dL, and >100 mg/dL, are associated with high-risk PE, which was not the case (**Table 9**).

Table 9: Exploratory analysis of extremely high Lp(a) levels and high-risk PE according to three ascending cut-offs.

Cut-off	Group	No high-risk PE (n=1,062)	High-risk PE (n=109)	p
60 mg/dL	Lp(a) ≤60 mg/dL (n=1,036)	939 (88%)	97 (89%)	0.858
	Lp(a) >60 mg/dL (n=135)	123 (12%)	12 (11%)	
80 mg/dL	Lp(a) ≤80 mg/dL (n=1,083)	981 (93%)	102 (94%)	0.649
	Lp(a) >80 mg/dL (n=88)	81 (8%)	7 (6%)	
100mg/dL	Lp(a) ≤ 100mg/dL (n=1,119)	1,012 (95%)	107 (98%)	0.166
	Lp(a) > 100mg/dL (n=52)	50 (5%)	2 (2%)	

Abbreviations: PE – Pulmonary embolism, p – p-value from $\chi 2$-tests or Fisher's exact test, as appropriate, Lp(a) – Lipoprotein(a). Derived from Gressenberger et al. (88) under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/); In the published manuscript other cut off values were used. Furthermore, only patients with a latency between PE diagnosis and Lipoprotein(a) measurement with a maximum of one year were included in the analysis, resulting in a different sample size (n =1171 vs. n= 811).

4 DISCUSSION

Lipoprotein(a) (Lp(a)) is a relatively stable genetically determined lipoprotein (67). While several studies have shown that elevated Lp(a) levels are a strong risk factor for the development of atherosclerotic cardiovascular diseases (ASCVD) such as peripheral artery disease or coronary heart disease, the role of Lp(a) as risk factor for venous thrombotic events such as pulmonary embolism remains unclear (54,64,65,72,89). Potential pathogenic mechanisms of Lp(a) include proatherogenic inflammatory activities and similarities of Lp(a) to plasminogen leading to a decrease of plasmin synthesis and inhibition of fibrinolysis (56,90). However, this antifibrinolytic effect has only been observed in in-vitro studies, thus it remains elusive if this effect plays a relevant role in real life.

To identify a possible association between elevated Lp(a) levels and clinical PE severity, we performed a retrospective data analysis. Therefore, we categorized patient data by pulmonary embolism severity, according to the 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism and at a pre-defined cut-off at 30 mg/dL. After statistical analysis of the data, we could not find a correlation between elevated Lp(a) concentrations and pulmonary embolism severity.

A study from Nordestgaard and Langsted (61) also looked at higher Lp(a) concentrations and found a significant association between VTE risk and Lp(a) concentrations above the 95th percentile, which in their study equals a median of 124 mg/dL. We also examined our data for a possible association between extremely high Lp(a) concentrations and high-risk PE defined by 3 different ascending cut-offs: >60 mg/dL, >80 mg/dL and >100 mg/dL. However, in this sensitivity analysis, we did not find an association between PE severity and extremely high Lp(a) concentrations.

As the diagnosis of PE and the determination of Lp(a) concentration were sometimes several years apart, we performed a subgroup analysis in which we only included patients with a latency between PE diagnosis and Lipoprotein(a) measurement with a maximum of one year. The PE risk distribution in this subcohort was similar to that in the full cohort and did not show any association.

Several studies and laboratory experiments have been conducted to determine whether the aforementioned antifibrinolytic effect is based on the plasminogen-like structure. J. Knapp and W. Herrmann (91) investigated the formation rate of plasmin in relation to the Lp(a) concentration and measured a reduction of the formation rate with increasing Lp(a) concentration. Sangrar et al. (92) observed in their study an inhibitory effect of apo(a) on the activation of plasminogen and on the degradation of fibrin by plasmin. In another study by Loscalzo et al. (93), Lp(a) was shown to compete with plasminogen and t-PA for fibrin binding. In this way, it hinders clot lysis induced by t-PA. The findings of these studies, however, were observed exclusively in-vitro, therefore it remains uncertain whether the noted antifibrinolytic effect has clinical relevance.

Other studies attempted to find an association on a clinical basis rather than in laboratory setting. They therefore investigated whether there was an association between elevated Lp(a) levels and the risk of VTE and obtained different results. While Vormittag et al. (94) did not observe an association between elevated Lp(a) levels and VTE risk, von Depka et al. (95) as well as Marcucci et al. (96) did find a strong correlation for Lp(a) levels above 30 mg/dL. Due to the disparity of observations and lack of data regarding the association between elevated Lp(a) levels and VTE, a systematic review and meta-analysis by Dentali et al. (97) was conducted on this issue, which included almost 14, 000 patients. This study observed only a slightly significant correlation, indicating that Lp(a) is at most a weak risk factor for the development of VTEs.

A recent pilot study by Nurmohamed et al. (98) also addressed a potential association of Lp(a) and VTE risk, but in the setting of Covid-19 infection. They particulary looked on Lp(a), C-reactive protein (CRP), and interleukin-6 (IL-6) levels and observed that Lp(a) levels in Covid-19 patients increased significantly in the first 3 weeks after admission. Interestingly, patients in the highest tertile of Lp(a) increase experienced VTE in 56%, whereas patients in the lowest tertile experienced VTE in only 18%. Lp(a) increase was significantly associated with VTE, whereas increases in CRP or IL-6 were not. However, caution is given when drawing conclusion from this study, as patient admission occurred after infection with Covid-19 and, accordingly, no comparative laboratory measurements of study participants in a healthy state pre- or post-admission are available. Larger studies

will be needed in the future to explore whether the change in LP(a) concentration is relevant with regard to VTE development (98).

In 2017, Langsted et al. (99) sought to gain a better understanding of the physiological role of Lp(a) and addressed the hypothesis that it serves a haemostasis-promoting function. They analyzed data from nearly 60,000 individuals from the Copenhagen City Heart Study and the Copenhagen General Population study and found that high Lp(a) concentrations (especially >80 mg/dL) were associated with a lower risk of major bleeding in the brain and airways. Another study by Ishikawa et al. (100) with 10,494 participants from the general Japanese population supports these findings. In this one, Lp(a) was observed to be significantly and inversely associated with the incidence of cerebral haemorrhage. The highest versus lowest tertile of Lp(a) levels was associated with a risk ratio of 0.34 in men and 0.44 in women for the risk of cerebral haemorrhage (100).

Several limitations of our study should be mentioned as it was based on a retrospective data analysis, and it was conducted only at a single center. Perhaps the evaluation of a larger study population could have led to different statistical results. Furthermore, in a larger study population with more participants, a higher rate of high-risk PEs could have been observed.

In conclusion, we did not find an association between PE severity and Lp(a) levels. The antifibrinolytic effect of Lp(a) seems to play no significant role in clinical PE severity. Nevertheless, our study should encourage other researchers to investigate a possible association between Lp(a) and PE severity in further studies.

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