ACUTE PULMONARY EMBOLISM

Not just an acute condition after all

Therese Andersson
“Why can’t people just sit and read books and be nice to each other?”

David Baldacci – The Camel Club
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Abstract

Background

Acute pulmonary embolism (PE) is the third most common cardiovascular disease following myocardial infarction and stroke. In the general population, estimates of the incidence of PE have varied from 0.2 to 1.2 per 1000 person-years. The methods for diagnosis have improved in recent decades with better and more accessible computed tomography pulmonary angiography (CTPA) and the widespread use of D-dimer testing. Despite these improvements, the diagnosis of PE is still associated with many difficulties, and the physician must remain vigilant because the symptoms of acute PE are nonspecific and can imitate many other pulmonary and cardiovascular disorders.

Previous estimates of mortality rates with acute PE have varied from 17% to 48% at 30 days, but less attention has been given to long-term mortality. Some studies have indicated that the increased mortality risk persists for several years after the PE event. In addition to survival, the clinical course following an acute PE may be accompanied by additional serious events. One of the most feared complications is chronic thromboembolic pulmonary hypertension (CTEPH), a progressive pulmonary vasculopathy associated with substantially high morbidity and mortality. The exact incidence of CTEPH following a PE event is unclear, but previous studies have revealed a cumulative incidence in the range of 0.6%–4.8%. In contrast to the minority that develops CTEPH, increasing evidence points to a larger proportion of patients who report persistent functional impairment several years after an acute PE. These symptoms may be accompanied by incomplete thrombus resolution, persistent right ventricular dysfunction, altered gas exchange, and/or exercise-induced pulmonary hypertension. In the last couple of years, it has been suggested that this condition should be called chronic thromboembolic disease (CTED), which is a form of exercise-induced CTEPH, or post-PE syndrome (PPES), which is a more general term that includes all forms of physical impairments following an acute PE. In a newly published consensus statement from the European Respiratory Society in collaboration with the International CTEPH Association and the European Reference Network–Lung in the pulmonary hypertension domain, the authors propose using the term “chronic thromboembolic pulmonary disease” (CTEPD) in all patients for whom symptoms can be attributed to post-thrombotic deposits within the pulmonary arteries.
Patient registers may represent valuable resources for large-scale epidemiological studies because they enable cost-effective compilation of large quantities of health-related data. The Swedish National Patient Register (NPR) contains data regarding diagnoses according to the International Classification of Diseases (ICD), and it has national coverage >99%, making it an excellent source of data for researchers. However, assessing the accuracy of the register requires validation of the ICD diagnoses versus medical records.

Methods

The NPR was used to identify all hospitalized patients with an acute PE diagnosis in Sweden during 2005, based on the ICD codes I26.0 and I26.9. An age-, gender-, and residence-matched control group was created by the Swedish agency of statistics. In the first paper, the incidence of PE in Sweden was calculated, the regional differences were analyzed, and survival analysis according to the Kaplan–Meier method was performed. In addition, the most common comorbidities registered for each gender and age group were presented.

The second paper used information for the PE population identified in paper I, and all patients who were alive in 2007 were invited to answer a questionnaire regarding dyspnea and related comorbidities. A control group was developed from the northern Sweden MONICA survey conducted in 2004 with identical questions regarding dyspnea, and the prevalence and predictors of dyspnea among the post-PE population compared with the control group were investigated using multivariable logistic regression and propensity score matching.

In the third paper, PE patients from the Swedish counties of Västerbotten and Västra Götaland, which together represented approximately 10% of the above-mentioned national cohort, were selected. A manual review of each patient’s medical record was performed to validate the PE diagnosis and gather information about diagnostic procedures, treatment, and follow-up strategies.

In the fourth paper, post-PE patients with dyspnea and/or previously known risk factors for CTEPH development, as conveyed in the questionnaire for paper II, were invited to donate a blood sample for N-terminal (NT)-prohormone (pro) brain-type natriuretic peptide (BNP) analysis. All remaining patients with dyspnea and those with risk factors and NT-pro-BNP levels above 100 ng/L were referred to their local
hospital for a V/Q scan. If the V/Q scan demonstrated perfusion defects, a new referral for echocardiography was sent to allow for assessment of signs of pulmonary hypertension. Finally, if there was a suspicion of CTEPH, a referral was provided to the nearest pulmonary arterial hypertension center for a right heart catheterization. The prevalence and cumulative incidence of CTEPH were calculated. In addition, real-life data regarding symptoms, NT-pro-BNP levels, and investigational findings of a national cohort of PE patients were presented.

Results

There were 5793 patients identified with acute PE in Sweden in 2005, demonstrating an incidence of 0.6/1000 person-years. The age range was 1–103 years with a mean age of 72.1 years for males and 68.7 years for females. There were minor differences between regions but no clear difference between the northern vs. the southern parts of Sweden, or between counties with low vs. high population densities. The most common comorbidity registered was cardiovascular disease, followed by infectious and gastrointestinal disease, injuries, and malignancies. Furthermore, during a 4-year follow-up, mortality was more than doubled in the post-PE population compared with the matched control group (49.1% vs. 21.9%). This increase in mortality persisted after exclusion of deaths occurring within the first years after the PE event, and even after exclusion of patients with known malignant disease (cancer) from the post-PE-group.

In the second paper, a substantially higher prevalence of both exertional dyspnea (53.0% vs. 17.3%) and wake-up dyspnea (12% vs. 1.7%) was found in patients with a previous PE compared with the control group, and the difference was most pronounced in the younger age groups. In addition, PE was independently associated with dyspnea in both logistic regression and propensity score matching.

In the third paper, a positive predictive value of 79% was found for a PE diagnosis in the NPR. PE diagnosis was established on clinical grounds in 11%. These diagnoses may be correct but were not possible to confirm as the treating physician refrained from imaging. Furthermore, a low proportion of follow-up visits (47%) was identified, and among those who had a follow-up visit, there was a high proportion (29%) of symptoms (dyspnea and/or decreased physical performance) in need of further attention.
In the fourth paper, 944 individuals were identified with symptoms of dyspnea or with risk factors for CTEPH and NT-pro-BNP levels above 100 ng/L. In this group, 544 V/Q scans were performed, and approximately 45% had perfusion defects. There were 331 echocardiographies performed within the study protocol, and signs of pulmonary hypertension were found in 88 individuals (27%). In total, 24 cases of CTEPH were identified, resulting in a prevalence of 0.4% (95% confidence interval 0.2%–0.6%). Additionally, all patients with CTEPH were symptomatic, and most (89%) had signs of pulmonary hypertension on echocardiography.

Conclusion

The incidence of PE in Sweden is in line with previous studies, and there are no obvious differences in PE incidence among regions within the country. Acute PE is associated with multiple comorbidities and with cardiovascular disease in particular. There are proposed links between venous thromboembolism and arterial cardiac disease. This association is not fully understood, although PE and arterial cardiovascular disease share several risk factors. The increased mortality rate, especially in the long term, highlights the need for a proper follow-up strategy following a PE diagnosis.

More than half of the PE survivors had complaints of dyspnea to some degree that could not be explained simply by comorbidities. These findings of dyspnea prevalence may support the previously suggested concept of post-PE syndrome (PPES). However, the incidence of possible CTED in this group is uncertain, and no available data address the incidence of CTED after a PE event in any published cohort. This information would be of great interest for further investigation given increasing evidence that CTED patients may benefit from the same treatment as CTEPH patients (anticoagulation, specific medical treatment, and invasive treatment such as pulmonary endarterectomy and balloon pulmonary angioplasty).

The fact that 79% of the PE diagnoses from the NPR were validated by imaging or autopsy highlights the NPR as a reliable source of data for register-based research regarding PE. It is reasonable that under some circumstances, PE diagnoses may be made on clinical grounds, even though doing so is not supported in the guidelines. The low proportion of follow-up visits was unsatisfactory, and it would be of great interest to repeat this study. We hypothesize that this proportion has increased after
publication of the latest guidelines, which highlight the need for proper follow-up.

The overall prevalence of CTEPH presented in paper IV is in line with a recently published meta-analysis. However, some reports suggest a considerably higher prevalence, but those studies have usually been smaller and used multiple inclusion and exclusion criteria, which may have influenced prevalence, making the findings less useful in daily clinical practice. The high proportion of pathological V/Q scans and echocardiography detected in the current study supports previous findings in the post-PE population, but further studies are needed to confirm these findings and the prevalences of PPES, CTED, and CTEPD.

Based on all four papers constituting this thesis, acute PE is a serious event, associated with decreased survival, multiple comorbidities, and high proportions of dyspnea and pathological investigational findings. Although the designation for this group of patients remains unclear, the term CTEPD seems reasonable because it captures that this condition is a disease of the pulmonary vessels and it includes patients who may experience improvements with the same treatment as CTEPH. Regardless, proper follow-up after acute PE is essential for timely identification of these patients and to provide them with appropriate care.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
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<tr>
<td>APS</td>
<td>Antiphospholipid Syndrome</td>
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<td>BPA</td>
<td>Balloon Pulmonary Angioplasty</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CO</td>
<td>Cardiac Output</td>
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<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>CTED</td>
<td>Chronic Thromboembolic Disease</td>
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<td>CTEPD</td>
<td>Chronic Thromboembolic Pulmonary Disease</td>
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<td>CTEPH</td>
<td>Chronic Thromboembolic Pulmonary Hypertension</td>
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<tr>
<td>CTPA</td>
<td>Computed Tomography Pulmonary Angiogram</td>
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<tr>
<td>DOAC</td>
<td>Direct-acting Oral Anticoagulants</td>
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<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>ERA</td>
<td>Endothelin Receptor Antagonist</td>
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<td>ERS</td>
<td>European Respiratory Society</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>IQR</td>
<td>Interquartile Range</td>
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<td>IVC</td>
<td>Inferior Vena Cava</td>
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<td>MONICA</td>
<td>Monitoring Trends and Determinants in Cardiovascular Disease</td>
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<td>LMWH</td>
<td>Low-molecular-weight Heparin</td>
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<td>NO</td>
<td>Nitric Oxide</td>
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<td>NPR</td>
<td>National Patient Registry</td>
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<tr>
<td>(NT-pro)-BNP</td>
<td>(N-terminal prohormone of) Brain-type Natriuretic Peptide</td>
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<td>NUTS</td>
<td>Nomenclature of Territorial Units for Statistics</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PA</td>
<td>Pulmonary Artery</td>
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<td>PAI-1</td>
<td>Plasminogen Activator Inhibitor-1</td>
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<tr>
<td>PAH</td>
<td>Pulmonary Arterial Hypertension</td>
</tr>
<tr>
<td>(m)PAP</td>
<td>(mean) Pulmonary Artery Pressure</td>
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<tr>
<td>PAWP</td>
<td>Pulmonary Arterial Wedge Pressure</td>
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<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PEA</td>
<td>Pulmonary Endarterectomy</td>
</tr>
<tr>
<td>(s)PESI</td>
<td>(simplified) Pulmonary Embolism Severity Index</td>
</tr>
<tr>
<td>PH</td>
<td>Pulmonary Hypertension</td>
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<tr>
<td>PK-INR</td>
<td>Prothrombin Complex – International Normalized Ratio</td>
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<td>PPES</td>
<td>Post-PE Syndrome</td>
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<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>PVR</td>
<td>Pulmonary Vascular Resistance</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>RAP</td>
<td>Right Arterial Pressure</td>
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<td>RHC</td>
<td>Right Heart Catheterization</td>
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<tr>
<td>RV</td>
<td>Right Ventricle</td>
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<tr>
<td>SCB</td>
<td>Swedish Board of Statistics</td>
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<tr>
<td>SCD</td>
<td>Sudden Cardiac Death</td>
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<tr>
<td>SPECT</td>
<td>Single-photon Emission Computed Tomography</td>
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<tr>
<td>S\textsubscript{v}O\textsubscript{2}</td>
<td>Mixed Venous Oxygen Saturation</td>
</tr>
<tr>
<td>VKA</td>
<td>Vitamin K Antagonist</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>Ventilation/Perfusion Scintigraphy</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Enkel sammanfattning på svenska

Bakgrund

Akut lungemboli, eller blodpropp i lungan, uppstår när en blodpropp i ett kärl lossnar och transporteras genom vensystemet, och vidare genom höger sida av hjärtat, och ut i en lungartär. När den fastnar i lungartären blockeras blodflödet vilket kan ge upphov till symtom i form av andfåddhet och bröstsmärta men även påverkan på hemodynamiska parametrar såsom puls och blodtryck. Efter hjärtinfarkt och stroke är akut lungemboli den tredje vanligaste kardiovaskulära sjukdomen i världen med en incidens på 0,2–1,2/1000 person-år.

Metoderna för att diagnostisera en lungemboli har förbättrats under de senaste årtiondena, men trots dessa förbättringar är diagnosen fortfarande associerad med ett flertal svårigheter. Detta beror främst på att symtomen är ospecifika, vilket innebär att den kan härma flertalet andra hjärt- och lungsjukdomar.

Enligt tidigare studier är dödligheten vid akut lungemboli 17–48 % inom 30 dagar från diagnos. Långtids-dödligheten är mindre välstuderad men studier har indikerat att den ökade dödligheten kvarstår många år efter diagnos. Förutom ökad dödlighet, kan akut lungemboli följas av olika komplikationer och följdsjukdomar. En av de mest fruktade följdsjukdomarna kallas kronisk tromboembolisk pulmonell hypertension eller CTEPH. CTEPH tros uppstå när icke-upplösta blodproppar bäddas in i lungkärlen och ökar deras motstånd, vilket i sin tur leder till pulmonell hypertension, vilket betyder högt blodtryck i lilla kretsloppet. Hur vanligt det är med CTEPH efter lungemboli är fortfarande oklart, men tidigare studier har förslagit att förekomsten ligger mellan 0,6–4,8 %.

Även om en minoritet utvecklar CTEPH efter en akut lungemboli, så har det på senare år visat sig vara en förhållandevis stor andel patienter som har kvar symtom i form andfåddhet eller nedsatt ork. Tillsammans med dessa symtom har man i vissa fall hittat tecken på att icke-upplösta blodpropprester, kvarvarande påverkan på hjärtats höger kammare, påverkat syrgas-utbytet och ibland även ansträngningsutlöst pulmonell hypertension. Detta tillstånd har fått flera benämningar såsom kronisk tromboembolisk sjukdom (CTED), post-PE-syndrom (PPES) och kronisk tromboembolisk lungsjukdom (CTEPD).
Metod


För att validera diagnosen akut lungemboli valde vi att granska sjukhusjurnalerna från insjuknandet 2005 för patienter från Västerbotten och Västra Götaland ut, vilka utgjorde cirka 10% av samtliga patienter. Syftet var att bedöma tillförlitligheten av slutenvårdsregistret. Information om vilken metod som användes för diagnos, vilken behandling som gavs och vilken uppföljning som erbjöds registrerades.

Samtliga överlevande lungembolipatienter med andfåddhet eller tydliga riskfaktorer för CTEPH ombads att uppsöka närmaste vårdcentral för blodprovstagnation och en hjärtsviktsmarkören NT-pro-BNP analyserades. Därefter remitterades patienterna till närmaste sjukhus för vidare utredning. Vi föreslog att lungscintigrafi (V/Q scan) skulle utföras eftersom en normal lungscintigrafi utesluter förekomst av CTEPH. Om undersökning inte kunde utesluta CTEPH, remitterade vi patienten för uppföljning med ultraljudsundersökning av hjärtat. Om misstanke om CTEPH kvarstod efter dessa undersökningar föreslog vi en remiss till närmaste specialist-centrum för pulmonell hypertoni för utredning med högersidig hjärtkateterisering, vilket är den undersökning som kan bekräfta diagnosen CTEPH.
Resultat

Totalt 5793 patients identifierades med diagnosen akut lungemboli under 2005, vilket gav en incidens på 0,6/1000/person-år. Det var endast mindre skillnader i incidens mellan de olika länen. Den vanligast samsjukligheten var kardiovaskulär sjukdom, följt av infektioner, gastrointestinal sjukdom, skador och malignitet. Dödligheten var dubblerad (49,1 % vs. 21,9 %) i lungemboli-gruppen jämfört med kontrollgruppen och detta kvarstod upp till 4 år efter diagnos. Den ökade dödligheten kvarstod även efter att patienter med känd malignitet excluderades.

Personer med tidigare lungemboli hade en högre förekomst av både ansträngningsutlöst andfåddhet (53,0 % vs. 17,3 %) och andfåddhet i vila (12,0% vs. 1,7%) jämfört med kontrollgruppen. Skillnaden kvarstod efter statistisk justering för ålder och övriga sjukdomar.

Majoriteten av lungembolidiagnoserna kunde verifieras, baserat på bildavgivande undersökning eller obduktion. I 11 % baserades diagnosen på kliniska grunder, utan bildavgivande undersökning. Dessa 11 % kan mycket väl vara korrekt men kan formellt inte verifieras eftersom ingen bildavgivande undersökning utfördes. De kvarvarande 10 % var felaktigt registrerade. Få patienter (47 %) hade ett uppföljningsbesök, och hos de som följes upp noterades en hög förekomst (29%) av kvarvarande symtom.

Niohundra fyrtiofyra patienter med andfåddhet eller med kända riskfaktorer för CTEPH och förhöjd nivå av NT-pro-BNP identifierades. I denna grupp utfördes 544 lungscintigrafier, där 45 % ingav misstanke om kvarvarande blodpropprester. Det utfördes 331 ekokardiografier där 88 (27 %) visade indirekta tecken på pulmonell hypertension. Totalt identifierades 24 patienter med CTEPH vilket motsvarar en förekomst på 0,4 %.

Slutsats

Förekomsten av akut lungemboli i Sverige är i linje med tidigare studier. Sjukdomen är associerade med multipla andra sjukdomar, främst kardiovaskulär sjukdom. Kopplingen mellan kardiovaskulär sjukdom och akut lungemboli har även noterats tidigare, även om orsaken till denna koppling fortfarande är oklar. Kardiovaskulär sjukdom och akut
lungemboli delar dock flera riskfaktorer såsom övervikt, rökning, diabetes m.fl. Den ökade dödligheten, framför allt på lång sikt, tydliggör hur viktigt med är med en adekvat uppföljning efter en akut lungemboli


Att 79 % av lungemboli-diagnoiserna enligt slutenvårdsregistret kunde verifieras stödjer att detta register är en tillförlitlig källa för registerbaserad forskning gällande akut lungemboli. Att diagnosen i visa fall ställdes på kliniska grunder bedöms rimligt då den behandlande läkaren alltid måste avgöra om en undersökning är till vinst för patienten eller inte. Den låga förekomsten av uppföljningsbesök är dock en källa för förbättring och det skulle vara av intresse att upprepa denna studie efter dom senaste europeiska riktlinjerna om lungemboli publicerades 2019, där man tydligt poängterar vikten av återbesök.

Förekomsten av CTEPH är i linje med tidigare studier, även om i den lägre delen av skalan. Detta beror sannolikt på att vi inte exkluderade någon patient på grund av ålder eller annan sjukdom, vilket resulterar i en äldre och sjukligare grupp jämfört med tidigare studier. Detta medför också att våra resultat är mer generalisbara och mer anpassade till verkligheten.

Den höga andelen patologiska lungscintigrafier och ekokardiografier, tillsammans med den höga andelen patienter med andfåddhet, stödjer förekomst av det föreslagna post-PE-syndromet (PPES) men detta område är fortfarande förhållandevis oforskat, och kommer sannolikt ligga till grund för flertalet framtida studier.

Sammanfattningsvis, akut lungemboli är ett allvarligt tillstånd med ökad dödlighet akut och på lång sikt. Tillståndet samvarierar med andra sjukdomar och är associerad med hög förekomst av både andfåddhet och patologiska undersökningarna. En adekvat uppföljning är viktig för att hitta de patienter som är i behov av ytterligare utredningar och för att kunna erbjuda patienter rätt vård i tid.
Introduction

In 1856, Rudolf Virchow postulated a triad of endothelial injury, hypercoagulability, and stasis associated with the formation of a venous thrombus. One of the most common forms of venous thromboembolism (VTE) is acute pulmonary embolism (PE). PE occurs when a thrombus detaches from a vein, usually from the deep venous system in the leg, and travels through the venous system through the right side of the heart and to the pulmonary arterial bed. In rare cases, a pulmonary embolus may also originate from the pelvic, renal, or upper extremity vein or from the right side of the heart. In the pulmonary artery (PA), the embolus obstructs blood flow and gives rise to hemodynamic abnormalities, where the impact on and the response of the right ventricle (RV) are the main drivers of its effects [1].

The pulmonary circulation is a closed circuit of blood vessels connecting the heart and lung. It begins where deoxygenated blood from the body enters the right side of the heart where the RV pumps blood through the PA. From the PA, the blood enters smaller and smaller arteries and then the capillaries surrounding the pulmonary alveoli. In the capillaries, oxygen from inhaled air in the alveoli diffuses into the blood, and the oxygenated blood returns through the pulmonary veins to the left side of the heart, where it enters the systemic circulation. Compared with the systemic circulation, the pulmonary circulation is low pressure and low resistance, as reflected by the relatively thin-walled structure of the RV. Under normal circumstances, the mean PA pressure (mPAP) is 15 mmHg, compared with 90 mmHg in the systemic circulation [1, 2].

![Figure 1. Schematic drawing of the pulmonary and systemic circulations. Tomás Kebert & umimeto.org License: CC-BY-SA 4.0.](image-url)
Globally, PE is the third most frequent acute cardiovascular disease after myocardial infarction and stroke [3]. Estimates of the incidence of PE in the general population range from 0.2 to 1.1 per 1000 person-years, and incidence seems to have increased following the introduction of D-dimer testing and computed tomography (CT) pulmonary angiography (CTPA) in the 1990s [4-10]. In Sweden, the incidence of PE has been reported at 0.8/1000 person-years, based on a single-center study in which the PE diagnosis was validated through medical record reviews [11]. A prospective longitudinal study of Swedish men followed from ages 50 to 80 years showed a PE incidence of 0.2 /1000 person-years [12].

Figure 2. An embolus located in the pulmonary artery. www.scientificanimations.com License: CC BY-SA 4.0.

The incidence of PE increases with age and is almost five times higher in individuals over age 80 years compared with those ages 50 to 59 years [13]. In addition to age, the several well-known risk factors for thrombosis for PE are traditionally divided into hereditary (genetic) or acquired. Acquired risk factors can be further subclassified as unprovoked or provoked, and provoked risk factors can be categorized as transient or persistent [14]. For healthcare professionals, it is essential to identify especially strong risk factors (with odds ratios [ORs] >10) because these conditions imply an indication for PE prophylaxis. Risk factors with ORs >10 include hip or leg fractures, hip or knee replacement surgery, major general surgery, major trauma, and spinal cord injury [1, 15].
### Table 1. Risk factors for pulmonary embolism.

<table>
<thead>
<tr>
<th>Risk factors for pulmonary embolism</th>
<th>Strong risk factors (odds ratio &gt;10)</th>
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<tbody>
<tr>
<td>Advancing age</td>
<td>Hip or leg fracture</td>
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<tr>
<td>Arterial Disease</td>
<td>Hip or knee replacement</td>
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<tr>
<td>Family history of VTE</td>
<td>Major general surgery</td>
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<tr>
<td>Recent surgery, trauma or immobility</td>
<td>Major trauma</td>
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<tr>
<td>Congestive heart failure</td>
<td>Spinal cord injury</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Acute infection</td>
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<tr>
<td>Long-haul air travel</td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Oral hormone replacement therapy</td>
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<tr>
<td>Pacemaker/ICD or central venous line</td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Metabolic syndrome</td>
<td></td>
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<tr>
<td>Cigarette smoking</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Abnormal lipid profile</td>
<td></td>
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<tr>
<td>Malignancy</td>
<td></td>
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<tr>
<td>Renal disease</td>
<td></td>
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<tr>
<td>Liver disease</td>
<td></td>
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<tr>
<td>Inflammatory bowel disease</td>
<td></td>
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</tbody>
</table>

All patients with a first-time PE should be clinically evaluated for acquired risk factors. If no apparent risk factor can be identified, inherited thrombophilia might be suspected. The presence of inherited thrombophilia is generally considered only in younger patients because advancing age is a risk factor by itself. According to the current ESC guidelines, testing for inherited thrombophilia can be considered in those who experience PE before age 50 years, in the absence of otherwise identifiable risk factors, and especially in those with a strong family history of VTE [16].

The most common inherited thrombophilia is a variant of human factor V known as factor V Leiden, found in 2%–5% of the general population. The presence of factor V Leiden is considered to be a mild-moderate risk factor for VTE, and for heterozygote carriers, a 2013 meta-analysis reported an OR of 4.22 (95% confidence interval [CI] 3.35–5.32) [17-20]. Other inherited thrombophilias considered to represented mild-moderate risk factors for VTE are protein C deficiency, protein S deficiency, and prothrombin gene mutation [21, 22].

Antithrombin deficiency is an uncommon inherited thrombophilia that poses a significantly increased risk of VTE (OR 16.3; 95% CI 9.9–26.7), as demonstrated in a meta-analysis [21]. However, this condition is uncommon, and the estimated prevalence in the general population is thought to be in the range of 0.02%–0.2% [21, 23].
Antiphospholipid syndrome (APS) is an autoimmune state with hypercoagulability caused by antiphospholipid antibodies. The condition can be either primary or secondary, in the latter cases occurring with other autoimmune diseases, most commonly systemic lupus erythematosus. When testing for inherited thrombophilia, antiphospholipid antibodies and lupus anticoagulant should be included, as APS is an essential differential diagnosis [16, 24, 25].

Diagnosis of Pulmonary Embolism

The diagnosis of PE is challenging even for the most experienced physician. One reason is that the clinical presentation is highly variable, with a broad spectrum in symptom severity, from asymptomatic presentation to cardiogenic shock (from right heart failure) and death [1, 16, 24]. Furthermore, the PE diagnosis is difficult because the symptoms are nonspecific and can mimic several other acute medical conditions. The most commonly reported symptoms are dyspnea (73%), chest pain (66%), and cough (37%) [26]. Hemothysis and syncope also can be a part of the initial presentation of PE. In about 10% of PE patients, small thrombi lodge distally in the segmental and subsegmental pulmonary arteries, resulting in pulmonary infarction. These patients are more likely to have pleuritic chest pain and hemothysis because of an intense inflammatory response in the lung and adjacent visceral and parietal pleura [27].

The physical examination may reveal findings of tachycardia, tachypnea, hypoxia, low-grade fever, elevated jugular venous pressure, RV heave, and prominent P2 or hypotension, which may contribute to the suspicion of PE. The most important hemodynamic factors with PE are the impact on and response of the RV. In the setting of PE, RV afterload can be acutely increased by mechanical obstruction and hypoxic vasoconstriction of the pulmonary arteries. Vasoconstriction can be even further increased by the release of inflammatory mediators in response to the emboli. As an example, when the obstruction of the pulmonary vascular bed approaches 75%, the RV must generate a systolic pressure in excess of 50 mmHg to preserve adequate PA flow. When the clot burden reaches a critical threshold, the RV cannot adapt to the increased pulmonary vascular resistance (PVR) and will fail to generate enough force to achieve cardiac output (CO), so that cardiogenic shock or even cardiac death may occur. RV pressure overload also can lead to ischemia from compromised left ventricular filling, increased wall stress, and limited myocardial oxygen
supply. Furthermore, significant pulmonary vascular obstruction leads to increased dead space, hypoxemia, and hypocapnia. These events translate into clinical findings that can offer clues to the diagnosis of PE [1, 28-34].

Figure 3. The anatomy of the human heart and major vessels. ZooFari. License: CC BY-SA 3.0.

The nonspecific clinical presentation of PE has led to the development of several clinical scores to aid the treating physician when PE may be suspected. In Sweden, the most commonly used clinical score is the “Wells score,” which includes clinical symptoms of deep vein thrombosis (DVT), heart rate >100 bpm, hemoptyisis, and the presence of immobilization, malignancy, or previous venous thrombosis in the patient’s medical history [35].
One useful diagnostic tool is the D-dimer blood test, which measures one of the major fibrin degradation products. It is used as a surrogate marker of fibrinolysis and is expected to be elevated during a thrombotic event. D-dimer has demonstrated a high diagnostic sensitivity of 99.5% for PE. However, D-dimer can be elevated in various conditions, and the specificity of the test is only 41% (even lower among elderly patients). For this reason, in most clinical scenarios, D-dimer should be used only to rule out PE in patients with a low or intermediate pre-test probability of it [27, 36].

Elevated cardiac troponin suggests myocardial injury and might be present in PE as a sign of this injury. Elevated brain natriuretic peptide (BNP) is also possible, indicating a tension of the ventricular wall. In addition to their role in differential diagnostics, troponin and BNP represent important components in risk stratification in the acute phase of PE [27].

PE-related findings on electrocardiogram (ECG) and chest radiography are nonspecific. However, like troponin and BNP, both ECG and chest radiography are generally part of the initial work-up in the emergency department when a patient has complaints of chest pain and/or dyspnea. ECG findings that increase the probability of PE include sinus

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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Previous pulmonary embolism or deep vein thrombosis</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats/minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>1.5</td>
</tr>
<tr>
<td>Clinical signs of deep vein thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
</tbody>
</table>

**Interpretation:**
- Low probability: 0-1 points
- Intermediate probability: 2-6 points
- High probability: ≥ 7 points

*Figure 4. Wells score of PE probability.*
tachycardia, S1Q3T3 pattern, right bundle branch block atrial fibrillation, P pulmonale, right axis deviation, clockwise rotation, and ST-segment elevation/depression [37, 38].

Imaging

Chest radiography may be performed for differential diagnostics, and when an acute PE is present, chest radiography may demonstrate nonspecific signs such as atelectasis and pleural effusion [39]. Echocardiography in the acute setting may be performed for differential diagnostics and can provide indirect signs of PE in the form of RV dysfunction or in rare cases even demonstrate an emboli in-transit in the right atrium or ventricle. However, the role of echocardiography in the setting of acute PE is mostly related to risk stratification [33].

CTPA is the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It has a high sensitivity of 83% and specificity of 96% for PE diagnosis (with an even higher sensitivity when combined with a clinical assessment score) [24, 40]. This method is relatively quick, easily performed, and available in most hospitals and can provide additional information regarding other causes of dyspnea and chest pain, such as a wide range of pulmonary diseases, pneumonia, effusion, and aortic aneurysm dissection. CTPA also can provide additional data for prognostication and risk stratification if a PE diagnosis is confirmed. Septum position, right ventricular/left ventricular ratio, and reflux in the inferior vena cava (IVC) provide information regarding RV dysfunction, which is a main component of the risk stratification in PE. However, because CTPA carries a risk of contrast-induced nephropathy (especially in patients with renal failure), allergic reactions, and exposure to radiation, the procedure is not always feasible [27].
An alternative imaging method for diagnosing acute PE is ventilation/perfusion scintigraphy (V/Q scan). This method may be chosen if CTPA is unavailable or contraindicated. A planar V/Q scan has a sensitivity of 77% if the scan demonstrates a high probability for PE. The specificity of a normal scan or a scan demonstrating very low probability for PE is 98%. However, the crucial disadvantage of the V/Q scan is the significant frequency of nondiagnostic readings (intermediate probability of PE) [41]. In addition, V/Q scans are not as available as CTPA, and the method is more time-consuming.

In addition to imaging techniques, confirmation of the PE diagnosis is sometimes made by autopsy. Because the first presentation of acute PE might be sudden cardiac death (SCD), autopsy may be the only diagnostic tool possible [42].

For establishing the PE diagnosis, an imaging procedure (or autopsy) is mandatory for verifying the thrombus. In reality, there are some cases where the treating physician may refrain from radiological examinations because of a lack of benefit or a risk for harm to the patient. For example, if a patient is hemodynamically unstable, there might not be time for imaging, and the clinician may need to act on clinical grounds only. In other cases, a patient might have other concomitant diseases that guide the decision to forgo imaging that will not benefit the patient. In these cases, PE diagnosis may be established on clinical grounds, even though
doing so is not recommended according to current guidelines [24]. A clinical PE diagnosis can sometimes be strengthened by indirect signs of RV pressure overload on echocardiography and/or by duplex ultrasonography, which may reveal a DVT in the leg.

Treatment

After initial resuscitative therapy in unstable patients, anticoagulation is the mainstay of treatment for PE patients. Additional treatments can include thrombolysis, IVC filters, and surgical embolectomy. Thrombolysis of acute PE is reserved only for PE patients who are hemodynamically unstable. This narrow indication for thrombolysis in PE patients is based on a risk of potentially fatal bleeding complications that exceeds the potential benefits of the treatment in hemodynamically stable patients [43]. Embolectomy is an alternative in unstable patients in whom thrombolysis is contraindicated. Because IVC filters are associated with considerable complications, this approach is recommended only if anticoagulation is contraindicated or if there are recurrent PE episodes despite adequate anticoagulation treatment [24, 44].

Most PE patients are hemodynamically stable at presentation, and parenteral or oral anticoagulation can be initiated. Traditionally, PE patients first receive low-molecular-weight heparin (LMWH) and a vitamin K antagonist (VKA) and then are switched to VKA monotherapy when the prothrombin complex–international normalized ratio (PK-INR) is in the therapeutic range. In the last decades, the advent of direct-acting oral anticoagulants (DOACs) has resulted in a switch in treatment strategy, and the anticoagulants most often prescribed for PE patients are DOACs. The duration of anticoagulation therapy can range from a minimum of 3 months to indefinite treatment, based on the presence of risk factors for VTE recurrence in combination with the risk of bleeding [24].

Prognosis

In Europe alone, PE accounts for approximately 300,000 deaths annually [45, 46], but the prognostic spectrum of acute PE is wide, ranging from
sudden death within minutes of a thromboembolic episode to a benign treatable condition associated with a stable clinical course and without long-term complications or sequelae.

Accurate mortality rates for acute PE can be difficult to determine because an unknown number cases present as SCD. However, data from the first published multinational report on short-term prognosis indicated a 3-month mortality rate of 17.4% [47], and more recent studies suggest that mortality rates for acute PE may be decreasing [4-7, 48, 49]. For determining the short-term prognosis of PE, patients can be classified into three categories based on their clinical presentation: low-risk, sub-massive, or massive PE.

Massive PE accounts for 3%-5% of PE cases and is defined as acute PE with hypotension, need for vasopressor support, or cardiac arrest. Massive PE has a short-term mortality rate of 52% [47, 50].

Sub-massive or intermediate-risk PE accounts for approximately 20%-40% of acute PE and is defined as acute PE with RV enlargement on imaging and/or positive biomarkers. Sub-massive PE has a short-term mortality rate of 5%-21% [47, 50].

Low-risk PE constitutes the majority of PE patients. The estimated short-term mortality in this group is approximately 1% [47, 50].

For predicting short-term mortality, different prognostic models incorporate clinical findings with or without laboratory findings. Of these models, the Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) are the most well known [51-55]. These risk scores are only tools for assessing the short-term risk of mortality, and in the clinical setting, they are used mostly in emergency departments for determining whether a patient needs hospitalization.
Figure 7. The PESI and sPESI risk scores (p=point) for assessment of short-term mortality in PE patients. Modified from [55] and [51].

Although much attention has focused on short-term risk stratification, less attention has gone to long-term prognosis after acute PE. A retrospective study enrolling 1112 patients during 2000–2007 demonstrated a 5-year cumulative mortality rate of 31.6% [56]. Another study in a Dutch cohort of 938 patients reported 30% all-cause mortality after a median of 3.3 years [57]. This rate was in line with results from a previous study in 1991 [58]. In 2012, Flinterman and colleagues published data from a large cohort of 4797 patients with a first-time nonfatal venous thrombosis (PE included) and reported an increased mortality rate up to 8 years after the event. Additionally, these authors demonstrated that an increased risk of death remained after exclusion of patients with malignancies [59]. Whether malignancies are responsible for the increased mortality in the long-term setting is unclear because of discrepancies among study results [59-61].
Short-term complications

Patients surviving acute PE face increased risk for several short-term and long-term complications. During the first 1-2 weeks following a diagnosis, patients may deteriorate and develop right-sided heart failure, respiratory failure, or hypotension. Furthermore, the occurrence of pleuric pain and/or fever may be a sign of evolving lung infarction or pneumonia.

The risk of recurrent PE is greatest in the first 2 weeks and declines thereafter. The cumulative proportion of recurrence is approximately 6% at 3 months, with higher rates in patients with malignancies or in those who do not receive adequate anticoagulation [62-64]. In addition, risk for stroke is significantly increased, especially in PE patients with a patent foramen ovale [65-69].

The first months of anticoagulant treatment involve a 2-fold higher incidence of bleeding complications than during long-term treatment. Thus, it is essential to focus on identifying and targeting modifiable risk factors for bleeding such as hypertension, nonsteroid anti-inflammatory drug therapy, alcohol abuse, and reversible renal insufficiency. Bleeding risk is especially high in patients who received thrombolytic therapy, with an incidence of major bleeding of 9.9% [70].

Long-term complications

For patients with PE, bleeding risk is relevant throughout the course of treatment, and major bleeding rates are as high as 7.2 per 100 patient-years [70]. Bleeding-related complications have been reduced since the introduction of DOACs, which is why DOACs are the first treatment of choice, even though LMWH and VKAs remain in use if a DOAC is contraindicated or poorly tolerated [16].

The risk of PE recurrence increases with time, and the cumulative rate has been reported to be 8% at 6 months, 13% at 12 months, and 23% at 5 years [62-64]. Additionally, several studies have demonstrate an increased risk of cardiovascular events following an acute PE event [71-73]. Why this relationship exists is not clear, although PE and arterial cardiovascular disease have some risk factors in common, such as obesity, hypertension, smoking, and diabetes [1]. A large-scale population-based cohort study from 2007 showed a 20%-40% increased risk of an arterial
Similarly, a population-based cohort study from 2012 showed increased risk for a cardiovascular event with an adjusted hazard ratio of 1.4 [73]. However, the most feared long-term complication after PE is the potentially life-threatening obstructing vasculopathy known as chronic thromboembolic pulmonary hypertension (CTEPH). To understand CTEPH, however, requires recapturing the features of the low-pressure/low-resistance pulmonary circulation, which is in contrast to the systemic circulation.

Pulmonary Hypertension

Multiple clinical conditions can interfere with the normal pulmonary circulation. Regardless of the cause, elevated blood pressure in the pulmonary circulation is called pulmonary hypertension (PH). PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, assessed by an invasive hemodynamic procedure called right heart catheterization (RHC). In the Sixth World Symposium on Pulmonary Hypertension in 2018, it was proposed that the mPAP limit should be decreased to ≥20 mmHg, although this statement has not yet been incorporated into the latest guidelines [74, 75]. PH can be further divided into post-capillary PH and pre-capillary PH by assessment of the pulmonary arterial wedge pressure (mPAWP, an estimation of the left arterial pressure) and the PVR. Pre-capillary PH is defined as mPAP ≥25 mmHg, PAWP <15 mmHg, and PVR >3 Wood units, whereas post-capillary PH is defined as mPAP ≥25 mmHg, PAWP >15 mmHg, and PVR >3 Wood units.

To categorize the different clinical conditions according to their pathological findings, hemodynamic characteristics, and treatment strategies, the World Health Organization (WHO) has organized PH into five classes [75, 76].
Classification of pulmonary hypertension (PH) defined by WHO

1. Pulmonary arterial hypertension
2. PH because of left-sided heart disease
3. PH because of chronic pulmonary disease
4. Chronic thromboembolic PH
5. PH associated with unclear or multifactorial mechanisms

The first class is pulmonary arterial hypertension (PAH), a disease of the pulmonary arteries characterized by vasoconstriction, cell proliferation, fibrosis, and micro-thrombosis. The increase in pulmonary pressures seen in PAH patients is mainly the result of increased PVR caused by the affected pulmonary vessels. The second class, left-sided heart disease, represents the most common cause of PH [77]. Increased pulmonary pressure in this group is the result of increased left-sided filling pressures resulting in post-capillary PH. Hypoxic vasoconstriction and remodeling are the main causes of PH in the third group, which consists of PH resulting from chronic pulmonary disease and/or hypoxia. PH from CTEPH constitutes the fourth group, and the fifth group consists of PH associated with unclear or multifactorial mechanisms [74].

The diagnosis of PH (CTEPH included) is difficult, mainly because of the nonspecific nature of the symptoms. A patient usually presents with dyspnea and/or exercise intolerance, which can be misinterpreted as a number of more common pulmonary or cardiac diseases. Patients may also experience chest discomfort, syncope, hemoptysis, light-headedness, and peripheral edema, which are all signs of advanced disease with RV failure [74, 78]. A baseline diagnostic approach including ECG, blood
panels that include natriuretic peptides, spirometry, and echocardiography should be performed to rule out anemia, hypothyroidism, arrhythmias, heart failure, valvular disease, asthma, chronic obstructive pulmonary disease (COPD), and other more common conditions that may present with dyspnea. Echocardiography is a cornerstone of the initial investigation of suspected PH because it allows for an estimation of RV systolic pressure. Additionally, there can be indirect signs of PH, such as right atrial, RV, and PA dilatation, reduced RV contractility, shortened right pulmonary acceleration time, and dilated IVC [74, 79, 80]. If the baseline investigations (including echocardiography) suggest PH, the current European Society of Cardiology (ESC) PH guidelines propose first considering left-sided heart disease and lung disease (PH group 2 and 3). If there are no signs of lung or left-sided heart disease, or if there is confirmed lung or left-sided heart disease but with severe RV dysfunction, the next step in the diagnostic algorithm for PH is to perform a V/Q scan [74].

The V/Q scan is the main first-line imaging modality for CTEPH, with a 96%–97% sensitivity and a 90%–95% specificity for the diagnosis [81]. However, the V/Q scan is part of the standard PH investigation workup and is not reserved only for cases involving previous PE. This approach is based on the knowledge that only 50%–75% of patients diagnosed with CTEPH have a known PE in their medical history [82].

CTPA is performed mainly to identify complications of the disease such as PA dilatation (which can compress the left main coronary artery) or hypertrophied bronchial arterial collaterals, which can lead to hemoptysis, and to assess operability in case of CTEPH. Even though CTPA is the gold standard for diagnosing acute PE, a normal CTPA does not rule out CTEPH. Furthermore, CTPA can provide clues to the other causes of PH, such as lung disease, esophageal dilatation (as a sign of systemic sclerosis), or congenital cardiac defects [74].

Right heart catheterization (RHC) is the diagnostic gold standard for PH, including CTEPH. This invasive hemodynamic procedure allows direct measurements of CO, mixed venous oxygen saturation ($S_vO_2$), pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), and RV end-diastolic pressure. From these measurements, the transpulmonary pressure gradient, diastolic pressure gradient, PVR, systemic vascular resistance, and cardiac index can be calculated. RHC is usually performed by accessing the common femoral vein, internal jugular vein, or antecubital vein in the arm. After venous access is gained, a PA catheter (i.e., a Swan-Ganz catheter) is advanced to
the right atrium of the heart. When the catheter reaches the right atrium, a pulsatile right atrial pressure waveform will be observed. Thereafter, the catheter is manipulated to the RV, where RV pressure is obtained. Following this, the catheter is usually advanced to a wedge position to measure the pulmonary capillary wedge pressure, which is obtained by inflating a balloon at the tip of the catheter. After this step, the balloon can be deflated and brought back a few centimeters into the PA to record the PA pressure. CO can be measured by thermodilution, with injection of cold saline into the right side of the heart, where it mixes with blood and the temperature difference is detected by the thermistor at the tip of the catheter. Another way to measure CO is by the Ficks’ method, in which CO is measured by dividing oxygen uptake with the difference in oxygen saturation between a systemic (femoral) artery and the pulmonary artery (S,O₂) [2, 83].

Figure 8. Anatomy of right heart catheterization (Swan-Ganz catheter).

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In the investigation of CTEPH, the final step in the diagnostic pathway is selective pulmonary angiography, on which typical CTEPH findings
include ring-like stenosis, webs (‘slits’), pouches, wall irregularities, complete vascular obstructions, and bronchial collaterals. The diagnosis of CTEPH can be obtained only after at least 3 months of effective anticoagulation in order to discriminate this condition from ‘subacute’ PE [74].

**Table 2. Diagnostic criteria for CTEPH according to 2015 ESC/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension.**

**CTEPH**

Estimates of CTEPH prevalence following an acute PE vary from 0.1% to 5% [84-88], and whether to screen for CTEPH after PE has been controversial. The relatively low prevalence of CTEPH, in combination with its non-specific symptoms, contributes to the median diagnostic delay of 14 months identified in the European CTEPH registry [82]. This delay is less than optimal because longer diagnostic delay is associated with less favorable hemodynamic profiles and shorter survival, and there is ongoing concern about how to diagnose CTEPH at an earlier stage [89].

The pathogenesis of CTEPH is largely unknown, but the theory is that unresolved thromboses in the pulmonary arteries become persistent and organized, with a vascular remodeling process that leads to increased PVR. Little is known about the mechanisms underlying the development of vascular remodeling, but current evidence implies remodeling arising from redistribution of pulmonary flow that is caused by occluded vessels, leading to high pulmonary pressure and shear stress to the endothelium.

Furthermore, there can be openings of preexisting anastomosis between the bronchial arteries and the pulmonary circulation downstream from the obstructed vessels. This opening results in a pressure gradient that can revascularize inadequately perfused territories, resulting in exposure of
the systemic blood pressure to the pulmonary circulation and following remodeling. Additionally, a reduction in nitric oxide (NO) because of platelet dysfunction may contribute to the remodeling, as NO released by the lung vessel endothelium inhibits platelet aggregation and growth of perivascular smooth muscle [90, 91].

Risk factors for CTEPH development

Why some patients develop CTEPH after an episode of acute PE and some do not is unclear, even though numerous risk factors for CTEPH development have been recognized. First, larger perfusion defects at the initial PE presentation, unprovoked PE, and recurrent PE are associated with increased risk for CTEPH. Hemostatic risk factors include elevated phospholipid antibodies, factor VIII, and von Willebrand factor antigen and abnormalities in fibrinogen. Increased expression of type 1 plasminogen activator inhibitor (PAI-1) has been reported in situ within CTEPH thrombotic material, but not when PAI-1 levels are analyzed in plasma. Non–O-blood group and elevated lipoprotein (a) are also associated with increased risk. A previous splenectomy significantly increases the risk for CTEPH. Additional risk factors include the presence of ventriculo-atrial shunts, infected pacemakers, and chronic inflammatory diseases such as inflammatory bowel disease and osteomyelitis. Approximately 20% of CTEPH patients are treated for hypothyroidism compared with 3.5% of patients with non-thromboembolic PH. However, because levothyroxine is associated with an increase in von Willebrand factor, it is unclear whether the treatment for hypothyroidism or the disease itself is the true risk factor. Malignancy has also been associated with increased risk for CTEPH development [92].

CTEPH treatment

In the 1980s, the 3- and 5-year survival rates for CTEPH were 50% and 10%, respectively [93]. Since then, many therapeutic options have become available. Oxygen therapy and/or diuretics are adjusted according to the patient’s individual needs. Lifelong anticoagulation therapy in the form of VKAs is given to all patients with CTEPH, despite the lack of relevant controlled studies. The use DOACs in CTEPH is an ongoing debate with
no consensus reached. Because the aim with anticoagulants in CTEPH is to reduce risk for recurrent PE, it is logical to think that DOACs should be sufficient. However, there is a high proportion of antiphospholipid antibodies among CTEPH patients, calling into question the use of DOACs [94].

Pulmonary endarterectomy (PEA) is the preferred treatment for CTEPH, and long-term data indicate 10-year post-surgical survival rates of 72%. In addition to survival, PEA is associated with improvements in WHO function class, hemodynamics, and quality of life (QoL). PEA has been described as a potentially curative treatment for CTEPH, but a recent statement from the European Reference Network for rare lung disease claims that CTEPH is unlikely to be completely cured even if hemodynamic parameters are normalized [95-97]. PEA is a complex, high-risk surgical procedure, performed under deep hypothermia and circulatory arrest, in which the intraluminal scar tissue is “peeled away” from the vascular walls. In-hospital post-procedural mortality rates have improved and are now reported to be below 5%. Of note, one factor in these improvements is the centralization of the interventions. Although PEA should be considered for all CTEPH patients, as it offers the best long-term outcomes, it is associated with certain risks. Approximately 50% of CTEPH patients are not suitable candidates because they have a predominantly peripheral disease, concomitant diseases, and/or advanced age, factors that make operative risk too high [98].
Balloon pulmonary angioplasty (BPA) is a relatively new treatment option in Europe for inoperable CTEPH. It is a transcutaneous procedure in which a guide wire is inserted through the femoral or jugular vein, placing a balloon at the site of the lesion. Inflated of the balloon breaks the intraluminal webs and band and widens the obstructed vessels. BPA improves hemodynamics, symptoms, and physical capacity, and 4-year survival rates are reported to be 85%. BPA is not without risks, however, including vessel perforation, reperfusion injury with pulmonary edema, and hemoptysis. As with PEA, complication rates have been declining as the procedure has become more established [98].
In non-operable CTEPH, PH-specific treatment such as parenteral prostanoids, soluble guanylate cyclase stimulants, an endothelin receptor antagonist (ERA), phosphodiesterase-5 inhibitors, and oral prostanoid agonists may be considered, even though the scientific support is difficult to interpret. For example, the ERA bosentan yields a significant improvement in hemodynamics but none in exercise capacity [100]. The oral soluble guanylyl cyclase stimulant riociguat yields a significant increase in 6-meter walk distance and a significant decrease in PVR. It is the only PH-specific drug with a class I recommendation in the latest ESC/ERS guidelines, whereas the other PH-specific drugs have IIb recommendations [74, 101]. Medical therapies are also used as a bridge to surgery/BPA, and in persistent or recurrent PH after surgery/BPA, even though there are no recommendations in the guidelines that support this approach [74]. With the treatment options available today, the 3-year survival rate has increased to 70% for inoperable CTEPH and to 89% for operable CTEPH [96, 102].

**Figure 10. Management options for chronic thromboembolic pulmonary hypertension (CTEPH) target different pathogenic manifestations in different parts of the pulmonary vascular bed. Republished from [98] under the terms of CC BY-NC License 4.0.**

**Chronic Thromboembolic Disease**

The rarity of CTEPH is in contrast to the large number of patients who report persistent functional impairment several months to years after acute PE. A couple of years ago, a classification designated as chronic thromboembolic disease (CTED) was developed [80, 103-106]. CTED is
characterized as dyspnea and/or exercise intolerance, with imaging showing remaining vascular obstruction after at least 3 months of anticoagulants. However, CTED does not meet the hemodynamic criteria of PH at rest. CTEPH and CTED share many similarities beyond features on imaging. During cardiopulmonary exercise testing, in both CTEPH and CTED, elevated minute ventilation/carbon dioxide production slopes can be found as a sign of pulmonary vascular disease, along with markedly decreased end-tidal partial pressure of carbon dioxide [106].

Even though it is a relatively new concept, CTED is now considered to be included as a subgroup in class 4 of PH, as stated at the 6th World Symposium of Pulmonary Hypertension 2018 [107]. The surgical treatment options (PEA and BPA) for CTEPH seem to be beneficial even for CTED, and lifelong anticoagulation is recommended [108].

Recently, a consensus statement from the European Respiratory Society in collaboration with the International CTEPH Association and the European Reference Network–Lung in the pulmonary hypertension domain was published, where the authors propose using the term “chronic thromboembolic pulmonary disease” (CTEPD) in all patients for whom symptoms can be attributed to post-thrombotic deposits within the pulmonary arteries [95].

**Post-PE syndrome**

Previous long-term studies have consistently demonstrated that approximately half of the post-PE population reports some degree of dyspnea, functional limitation, or decreased QoL several years after the PE. Incomplete thrombus resolution occurs in one-fourth of patients, PAP and RV function remain abnormal in up to one-third of patients, and altered gas exchange has been demonstrated in the post-PE population without CTEPH [109].

CTEPH and even CTED seem to be responsible for only a minority of these patients. In 2014, Klok et al. proposed a condition called “post-PE syndrome” or PPES, which in simple terms can be described as any kind of dyspnea or functional impairment following acute PE. They describe PPES as a parallel to post-thrombotic syndrome (PTS), which is a well-established complication of DVT in the leg. Even though the concept of PPES is not yet established, there has been an increased awareness of
symptoms and abnormal investigational findings in the post-PE population that has gained more interest in the last couple of years [109, 110].
Aims

The overall aim of this thesis was as follows:

- To perform follow-up in a large-scale national cohort of Swedish patients diagnosed with acute PE in order to investigate long-term complications related to their PE event and to describe the clinical course following an acute PE.

Specific aims were as follows:

- To determine the incidence of PE in Sweden, including analyses of regional differences of PE incidence between counties;

- To analyze short- and long-term survival following an acute PE and to analyze associated comorbidities;

- To validate the diagnosis of PE in the National Patient Registry (NPR) (I26.0, I26.9);

- To determine the prevalence of dyspnea following an acute PE, compared with a matched control group; and

- To determine the prevalence of CTEPH in a national post-PE cohort, including analyses regarding long-term symptoms and investigational findings following an acute PE.
Materials and Methods

Swedish National Patient Registry

The Swedish NPR is a nationwide population-based registry, containing records of healthcare visits in Sweden with diagnoses registered by the International Classification of Diseases (ICD) codes. The registry is hosted by the Swedish National Board of Health and Welfare and has a national coverage >99% because reporting is mandatory by law. The Inpatient Registry, also called the Hospital Discharge Register, is part of the NPR and contains data from all in-hospital medical records.

The NPR includes data of over 40 million registered in-hospital care episodes including information related to each patient’s unique identification number, such as age, gender, location of the treating hospital, dates of admission and discharge, and all main and subsidiary diagnoses according to the ICD coding system. The overall positive predictive value (PPV) of the diagnoses in the register has been reported to be 85%–95% [111].

The main patient cohort (papers I–IV) originated from the Swedish NPR, where the Swedish modification of the 10th revision of the ICD (ICD-10-SE) was used to identify patients with PE (Figure 11). The cohort included all patients in Sweden with acute PE as a main or subsidiary diagnosis (ICD codes 126.0 and 126.9) admitted to any Swedish hospital during 2005. In addition, data were collected related to all in-hospital care episodes, including comorbidities (e.g., cancer, congestive heart failure, atrial fibrillation, ischemic heart disease, and cerebrovascular disease) that were registered in the NPR 8 years prior to the PE diagnosis. In total, our main patient cohort consisted of 5793 patients, with 30,061 registered in-hospital care episodes, each with one main diagnosis and up to eight subsidiary diagnoses.

For paper I, a control population was created by the Swedish Agency of Statistics (SCB), and each unique person with PE was matched with a control person on the basis of date of birth, gender, and residency (Figure 11). This matching was successful for all but five cases. For survival analysis, the combined cohort of patients with PE and their matched
controls were followed until April 23, 2010. Data regarding date of death or date of emigration were obtained from SCB.

![Flowchart of the participants included in the different studies represented by the papers.](image)

**Figure 11. Flowchart of the participants included in the different studies represented by the papers.**

### Nomenclature of Territorial Units for Statistics

For analysis of regional differences in PE incidence (paper I), a geocode was used, designated as the Nomenclature of Territorial Units for Statistics (NUTS) and developed by the European Union for statistical purposes. It contains a three-level hierarchy of within-country subdivisions. In our analysis, we used the third NUTS level, where Sweden is divided by counties.
Validation

From our main patient cohort, all patients who received in-patient care at three hospitals located in Västerbotten County \((n = 195)\) and at three hospitals located in the Västra Götaland Region \((n = 364)\) were identified \((Figure 11)\). This cohort constituted approximately 10\% (paper III) of the national PE cohort (main cohort). Thereafter, a thorough manual review of all corresponding hospital records was conducted to validate the PE diagnosis. A standardized form was used to gather data regarding symptoms and clinical signs, investigational findings, treatment, and follow-up procedures. Acute PE was considered validated when the diagnosis was based on imaging (CTPA, V/Q scan) or autopsy. In cases of clinically diagnosed PE, an analysis of all other ICD-10 codes registered for those patients was performed to gain a better understanding of why the treating physician refrained from imaging.

MONICA

The WHO initiated a project in the early 1980s with the aim of continuously registering the prevalence of cardiovascular diseases (ischemic heart disease and stroke) and its risk factors, and changes in mortality and morbidity rates over time. In Sweden, the counties of Norrbotten and Västerbotten joined the MONICA (MOntoring trends and determinants in CArdiovascular disease) study in 1986 \([112, 113]\). The WHO part of the MONICA study ended in 1995, but the Northern Sweden MONICA study has continued to register and validate events and to perform surveys. Seven population-based surveys were performed between 1986 and 2014, and inhabitants in Västerbotten and Norrbotten who were ages 25–74 years were randomly selected. At the end of December 2014, a total of 12,368 unique individuals had participated, and the overall participation rate was 74\%. For paper II, a control group was recruited from the Northern Sweden MONICA survey conducted in 2004 \((Figure 11)\).
Questionnaire

A two-part questionnaire was sent to patients in the post-PE group who were still alive in 2007 (2 years after the index event). The first part included questions identical to those used in the questionnaire from the Northern Sweden MONICA survey in 2004. This part included questions regarding dyspnea, lifestyle (previous and present smoking), and selected comorbidities (e.g., angina pectoris, myocardial infarction, coronary intervention, COPD). The questions related to dyspnea were as follows:

1. “Do you experience shortness of breath when climbing two stairs, or the equivalent, at the same pace as people of the same age? Yes/No”

2. “Do you wake up because of shortness of breath? Yes, often/Yes, sometimes/No”

The patients in the post-PE group were sent a second part of the questionnaire that was specifically designed to identify risk factors for CTEPH development and changes in health after the PE diagnosis (Figure 12; see the appendix for the questionnaire).

Cardiac biomarkers

All patients from the post-PE group who reported dyspnea to some degree and/or known risk factors for CTEPH development were asked to send a blood sample for analysis of N-terminal prohormone of BNP (NT-pro-BNP). Pro-BNP is synthesized in response to increased wall stress in the cardiac ventricles and is used clinically as a marker of heart failure. NT-pro-BNP is an inactive amino-terminal fragment that arises when pro-BNP undergoes cleavage to form active BNP, which is a potent natriuretic, diuretic, and vasorelaxant peptide. NT-pro-BNP and its active form BNP can be analyzed with comparable results, but NT-pro-BNP has a longer half-life (1-2 hours) than BNP (20 minutes), resulting in less fluctuation [114].

The NT-pro-BNP values reported in paper IV were analyzed from blood sampled in sodium heparin tubes. The analysis was performed at the
clinical chemistry laboratory at Skellefteå Hospital according to standard clinical practice using an Immulite machine and the reagent IMMULITE® from Diagnostic Products Corporation, USA (Figure 12).

Figure 12. Flowchart for the participants included in papers II and IV. For questionnaire, consent form and letter of information, see appendix.
Ventilation/perfusion (V/Q) scan

The V/Q scan is an imaging technique that relies on scintigraphy and medical isotopes to assess air and blood circulation in the lungs. The perfusion phase involves intravenous injection of a radioisotope into the blood stream, and ventilation is assessed by using a gaseous radioisotope inhaled through a mouthpiece or mask covering the mouth and nose. The agents used in the V/Q scans presented in paper IV were radioactive technetium macro aggregated albumin for the perfusion phase and \(^{99m}\text{Tc}\)-labeled aerosol of diethylenetriaminepentaacetate, \(^{99m}\text{Tc}\)-labeled carbon microparticles (Technegas), or \(^{133}\text{Xe}\) gas for the ventilation phase, depending on the routines at each local hospital.

A gamma camera, providing a planar image of the isotope distribution, acquires images for both the ventilation and perfusion parts of the scan. Single-photon emission computed tomography (SPECT) acquisition is similar to planar gamma camera imaging but with a rotating gamma camera, which can provide 3D images. The majority of V/Q scans presented in paper IV were performed at hospitals using planar imaging. The recommendation is to obtain eight standard projections, with a pixel size \(\leq 5\) mm. For those using SPECT, the recommendation was to collect 60–64 projections over 360° with a pixel size \(\leq 5\) mm.

Typically, at least one segmental perfusion defect with adequate ventilation, or adjacent subsegmental perfusion defects (of segmental equivalent size) with adequate ventilation are considered indicative of pulmonary embolism (acute or chronic). The V/Q scan interpretations issued at the time of the procedures, performed by each unit responsible for the investigations, were used for the analysis. In addition, a sample of 86 V/Q scans (16%) from different centers was obtained and double-checked by two experienced investigators for agreement purposes [81, 115-118].

Statistics

For all papers included in this thesis, categorical variables are expressed as frequencies and percentages, and continuous variables as means with 95% CIs or as medians with interquartile ranges (IQRs) when appropriate.
In paper II, Q-Q plots, histograms, and the Kolmogorov–Smirnov test were used to check continuous variables for normality. Variables with a normal distribution were expressed as the mean ± standard deviation, and variables with a non-normal distribution were expressed as the median and IQR. Differences between groups were tested with independent-samples Student t-tests, when appropriate.

All statistical data were analyzed with IBM SPSS statistics software versions 21, 25, 27, and 28 and R version 4.0.3. For the propensity score matching, the function matchit from the R package MatchIt was used.

Survival analysis

In medical research, it is often of interest to analyze not only whether an event occurred but also time-to-event. The statistical analysis used is called survival analysis, even if the event of interest is not necessarily death. Survival analysis is a unique statistical method because it includes a combination of a binary outcome (if the event occurred or not) and continuous outcome (time). One important feature of survival analysis is that it can handle right-censoring, which occurs when a participant either dropped out before the event occurred or did not experience the event before the end of the study. For the survival analysis in paper I, the non-parametric Kaplan–Meier estimation was used, and the differences between the groups were tested with the log-rank test.

Logistic regression

Regression techniques are important to medical research because they can measure associations, predict outcomes, and control for confounding variables. Logistic regression is an efficient method used when the outcome is binary, such as dyspnea, yes/no. Logistic regression models can include one or multiple independent variables, and multiple variable regression is generally more informative because it includes the unique contribution of each variable after adjustment for the others. In the second paper, the covariates were collected from self-reported data from the questionnaire (dyspnea, angina pectoris, hypertension, COPD, and smoking habits) as well as diagnoses from the NPR (heart failure,
malignancy, ischemic heart disease, cerebrovascular disease, atrial fibrillation, and recurrent PE). Ensuring that logistic regression produces an accurate model requires careful selection of independent variables. This selection can be performed by analyzing differences between groups using univariable statistics. The sequential or hierarchical approach used in paper II is a regression-building model in which the variables were added sequentially to see if they further improved the model based on their predetermined order of priority. Finally, after a logistic regression model is created, it is crucial to evaluate the goodness of fit to determine if the model fits the data [119].

Propensity score

Propensity score methods have been increasingly used in cardiovascular research to reduce bias and the likelihood of confounding in non-randomized, observational data. The propensity score is the probability that a participant would belong to the study group or to the control group, based on the characteristics of the patient. The most common way to use this approach is propensity score matching, which involves assembling two groups with matching individuals with similar or identical propensity scores [120]. The propensity scores used in paper II were conditioned on sex, age, COPD, heart valve surgery, hypertension, present smoking, previous smoking, chronic heart failure, atrial fibrillation, and cerebrovascular disease.

Ethical considerations

The studies underlying this thesis were conducted in compliance with the Declaration of Helsinki, and the study protocol for papers I–IV was approved by the Regional Ethical Review Board in Umeå (Dnr. 07-074). The Ethics Board at the Swedish National Board of Health and Welfare reviewed and approved the extraction of data from the Swedish NPR.

Written consent was obtained from all participants from the main cohort who were alive when the study started in 2007, and from the participants in the MONICA survey in 2004 (papers I, II, and IV). Department heads granted access to local hospital records for the validation study (paper
III). Written approval for continued care of any individual who would be in need of further investigations and follow-up was obtained from all heads of department at the local hospitals (paper IV) *(Consent form, questionnaire and letter of information can be found in the appendix).*

The ability to crosslink data from different national registers, based on the unique Swedish personal identification number, constitutes a valuable source of data for epidemiological research. However, it entails a great demand for handling data to preserve the participant's privacy. To protect the privacy of participants included in papers I–IV, personal identification numbers were replaced with serial numbers before the dataset for the different papers was created.

The participants in paper IV, who reported dyspnea or known risk factors for CTEPH development and had NT-pro-BNP levels above 100 ng/L, were referred to their local hospitals for follow-up. At this stage, they were considered to be patients. According to the written approval for continued care obtained from the department heads, their continuous follow-up strategy was to be managed from their local hospitals (with support from the authors). In some cases, the local hospitals refrained from follow-up, with no reason declared. Related ethical considerations were handled through a second referral of these patients to the nearest primary healthcare physician to establish an alternative follow-up strategy. However, there is a risk that these patients did not receive appropriate follow-up because patients with previous PE presenting with dyspnea should undergo investigations that usually are performed in hospitals *(e.g.,* echocardiography, V/Q scan).*

The risks for most participants in our main cohort were minor but included possible discomfort and pain when taking the blood test and possible anxiety regarding symptoms and findings identified throughout the study. For those who were referred for a V/Q scan, there was a minor risk of allergic reaction to the tracer, in addition to possible anxiety and discomfort during the procedure. Finally, for the minority of patients referred for RHC, there was a procedure-related risk of bleeding and malignant cardiac arrhythmias. However, all invasive procedures (V/Q scan and RHC) performed during our study are included in the regular follow-up after PE according to the ESC guidelines [24, 74], and as noted above, the study participants were considered to be patients in need of further investigations to provide them with adequate treatment for their symptoms. The risks for the participants in our study were justified by the potential benefits, including the possibility of finding a treatable explanation (not only CTEPH, but also left-sided heart failure, valvular
disease, cardiomyopathies, etc.) for their symptoms. In the larger perspective, gaining more knowledge about the clinical impacts of a PE event may benefit a large proportion of PE patients in the future.
Results

Paper I

There were 5793 patients identified with a main or subsidiary diagnosis of acute PE in Sweden in 2005, for a national incidence of 0.6/1000 person-years. Fifty-two percent of the cohort was female. The age range was 1–103 years, with a mean age of 72.1 years for males and 68.7 years for females.

Stratified by county, the age-adjusted distribution of PE incidence demonstrated minor differences with no clear polarity between the northern vs. the southern parts of Sweden, or between counties with low vs. high population densities.

In total, the most common comorbidity registered was cardiovascular disease, followed by infectious and gastrointestinal diseases, injuries, and malignancies. There were no major differences regarding comorbidities between males and females.

Mortality was more than doubled in the post-PE population compared with the matched control group (49.1% vs. 21.9%). The highest mortality was seen in the first 3 months following the PE event. After exclusion of these early deaths, the survival analysis demonstrated a remaining increased mortality in post-PE patients compared with the control group (p < 0.001). This analysis was repeated after 1, 2, and 3 years, with the same results. Finally, the excess mortality remained after excluding all post-PE patients with known malignant disease (Figure 13). Altogether, there were 2841 deaths in the post-PE group and 1461 deaths in the control group.
Figure 13. Kaplan–Meier curve (left) demonstrating survival after PE compared with the matched control group; log-rank test: $p < 0.001$. Survival after acute PE of patients with or without a previous history of malignancy compared with the matched control group (right); log-rank test: $p < 0.001$.

Paper II

There were 2105 (65%) responders to the questionnaire from the post-PE population and 1905 (76%) responders from the control group recruited from the 2014 MONICA health survey. The post-PE population demonstrated a significantly higher prevalence of both exertion (53% vs. 17%, $p < 0.001$) and wake-up dyspnea (12% vs. 2%, $p < 0.001$) compared with the control population.

Multivariable logistic regression was then performed to control for comorbidities. In this regression, a significant interaction was found between age and study cohort. Because of this interaction, ORs could not be interpreted as average effects, and to quantify and visualize this interaction, a stratification into 10-year groups was performed. The differences in the risk of dyspnea were most pronounced in the younger age groups (Figure 14).
Figure 14. Fully adjusted risk of exertional dyspnea (a) and wake-up dyspnea (b) in the post-PE group compared with the control group, stratified by age. Presented as odds ratios (ORs) with 95% confidence intervals (CIs).

To confirm these findings, a propensity score matching was performed with 1425 matched pairs. The ORs for exertional dyspnea were 4.1 (95% CI 3.1–5.4) in the post-PE group and 3.4 (95% CI 2.0–6.1) in the wake-up dyspnea group (Figure 15).
Figure 15. Odds ratio for (a) exertional dyspnea and (b) wake-up dyspnea comparing the post-PE group and MONICA control group, conditioned on age and adjusted for propensity scores. The gray band represents the 95% confidence intervals.
Paper III

There were 559 patients identified in the NPR with an acute PE diagnosis (ICD–10 code I26.0 or I26.9) from the selected regions, representing approximately 10% of the national PE cohort. Fifty-four percent (of the confirmed cases) were women, with a median age of 77 (IQR 17) years; the median age for men was 69 (IQR 19) years. A total of 44 patients died during the hospital stay.

The diagnosis was confirmed by imaging in 435 patients and by autopsy in 6 patients, resulting in a PPV of 79% for the PE diagnosis in the NPR. In 11 patients, the PE diagnosis was incorrect, and in 47 patients, the PE diagnosis was related to a previous admission and therefore regarded as incorrectly registered.

<table>
<thead>
<tr>
<th>Validation of acute PE diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis confirmed by imaging</td>
<td>435 (78)</td>
</tr>
<tr>
<td>CT angiography</td>
<td>387 (69)</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>36 (6)</td>
</tr>
<tr>
<td>Both CT angiography and V/Q scan</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Diagnosis confirmed by autopsy</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Clinical diagnosis without imaging</td>
<td>60 (11)</td>
</tr>
<tr>
<td>Previous PE diagnosis</td>
<td>47 (8)</td>
</tr>
<tr>
<td>Incorrect diagnosis</td>
<td>11 (2)</td>
</tr>
</tbody>
</table>

*Table 3. Validation of acute PE diagnosis*

In 60 patients, the PE diagnosis was based on clinical grounds without radiological confirmation. Additional diagnoses that may have influenced the decision to refrain from imaging in these cases were documented cognitive failure in six patients, significant renal failure in 13, cancer in 16 patients, and another indication for anticoagulant treatment (mainly DVT and atrial fibrillation) in 25 patients. Furthermore, six (10%) patients in this subgroup received thrombolytic therapy compared with 22 (5%) of those with a diagnosis verified by imaging.

Of the surviving patients with a PE diagnosis confirmed by imaging, 214 (49%) were offered a follow-up visit within 6 months after the PE event. At follow-up, 51 patients were still dyspnoic or had reduced physical capacity, and 8 patients reported worsening dyspnea compared with the time of diagnosis.
Of the 2105 questionnaire responders from paper II, 673 had no dyspnea and no self-reported risk factors for CTEPH development. Of the remaining 1432 post-PE patients, 1029 had NT-pro-BNP analysis performed. Finally, 944 remaining post-PE patients from the main cohort had reported symptoms of dyspnea or known risk factors for CTEPH development and NT-pro-BNP levels above 100 ng/L (Figure 12).

In this last group of 944 patients, 544 V/Q scans were performed, and 244 (44.9%) showed signs of perfusion defects. Among 331 echocardiographies performed, 88 patients had signs of PH (27%).

In all cases where the patient or treating doctor stated that the patient already had been diagnosed with CTEPH, a thorough review of the medical record (including the RHC protocol if available) was performed. After this review, 10 patients had a confirmed diagnosis of CTEPH before

Figure 16. Flowchart demonstrating results and investigational findings after referral for a V/Q scan.
2005, and 8 patients were diagnosed with CTEPH after 2005 but outside this study.

In total, 24 cases of CTEPH were identified, resulting in an overall prevalence of 0.4% (95% CI 0.2%–0.6%). Among the surviving symptomatic patients who underwent a V/Q scan within the study protocol, the cumulative CTEPH incidence was 1.1% (95% CI 0.2%–2.0%). Additionally, all patients in the CTEPH group were symptomatic, and almost all (89%) had signs of PH on their echocardiography. The median NT-pro-BNP was 504 (IQR 591) in the CTEPH group, compared with 177 (IQR 344) in the non-CTEPH group.
Discussion

Methodological considerations

In every clinical study, it is essential to identify biases and assess their potential impact. First, the nationwide PE cohort included all hospitalized patients with a PE diagnosis in 2005. When using no exclusion criteria, the risk for selection bias decreases substantially. In addition, an age-, sex-, and residence-matched control group was obtained, and only 5 of 5793 patients remained unmatched as no controls could be found. Because no information regarding comorbidities in the control group was available, no statistical analyses regarding the individuals’ registered comorbidities could be performed. When excluding patients with malignancies from the study group, the corresponding exclusion from the control group could not be made. This means that individuals with malignancies probably were still included in the control group, resulting in an unhealthier control group and a potential underestimation of the survival difference. However, this possibility does not affect the conclusion of the increased mortality rate among post-PE patients.

When approximately 10% of the cohort was selected for validation, the selection bias was considered to be random. There were six hospitals (both university and minor local hospitals) included from regions with both densely and sparsely populated areas. There are no major differences in diagnostic approaches to acute PE among hospitals in Sweden, even though V/Q scans are not always available.

The questionnaires were sent out approximately 3 years after the PE event, and almost half of the cohort was then deceased; the survivors were probably younger and healthier. When taking into account the high mortality rates with CTEPH, there is a risk of having cases of undiagnosed CTEPH included among the deceased. In addition, there might have been cases with CTEPH misclassified as acute PE, which means that there can be patients in the post-PE cohort with pre-existing CTEPH.

There is generally a risk of bias in all health surveys, with responders who are healthier than the general population, and participants are more likely to be women and with better economic status. To minimize this risk, our research nurse attempted to contact non-responders by telephone, with a relatively high success rate, making the responses more reliable. The same approach was used in the MONICA study, where an analysis of non-
participants demonstrated that the responders were representative for the population [121]. In addition, there is always a risk of recall bias when self-reported data are used. Dyspnea and exertional dyspnea in particular are nonspecific and involve a risk of being both overreported and underreported. To address this risk, a thorough letter of information regarding the purpose of the questionnaire, along with well-formulated questions, is essential.

During the course of the follow-up from acute PE to a potential CTEPH diagnosis, some individuals were lost to follow-up, increasing the risk of selection bias. To determine if this loss was random, the reasons for ending the study were gathered and are presented in the flowchart (paper IV). The time-point where the highest risk of selection bias occurred was considered to be at the stage of V/Q scans. At this stage, there were 120 cases for which the treating hospital refrained from referral for a V/Q scan, with no reason declared. Because of this important risk of selection bias, an underestimation may be present, and the prevalence and cumulative incidence are reported as minimum frequencies.

**General discussion of the main findings**

**Papers I and III**

The incidence of acute PE in Sweden identified in this work does not seem to differ from that reported in previous studies, and there were no clear differences in PE incidence between the counties. The increased mortality rate, which remained after early deaths and malignancies were excluded, was noteworthy, and the reason for this increase is not clear. It is not likely that CTEPH, a rare condition, is responsible for this increase. However, acute PE is associated with many comorbidities, and unfortunately, we are missing data for comorbidities in the control group, precluding comparison of comorbidities between the groups. There was an especially high proportion of cardiovascular disease in the PE cohort. Links have been proposed between venous thromboembolism and arterial cardiac disease, and it is logical that an acute cardiac event, such as myocardial infarction, increases PE risk, but why PE increases risk for a following cardiac event is unclear. However, these conditions share many risk factors, including obesity, smoking, and diabetes mellitus, which may contribute to the association between them.
The PPV of 79% for a PE diagnosis in the NPR supports that the NPR is a reliable source of data that can be used for register-based research regarding PE. The additional 11% of PE diagnoses based on clinical grounds is considered to be reasonable because there always are occasions and clinical conditions in which guidelines cannot be strictly followed. In analyses of clinically based diagnoses, there was a high proportion of patients with another indication for anticoagulant treatment, such as atrial fibrillation. Such comorbidities may have influenced the decision to avoid imaging to confirm the PE diagnosis, as the results would not have changed the treatment strategy. There were also cases with DVT, which is another indication for anticoagulant treatment. The presence of DVT together with an echocardiography demonstrating signs of RV pressure overload increases the probability of an acute PE and may, under some circumstances, be an alternative clinical approach. Furthermore, six patients in this subgroup received thrombolytic therapy, which may indicate that they were hemodynamically unstable and that there might not have been time for image confirmation. The low proportion of follow-up visits was unsatisfactory, but we hypothesize that this proportion increased after publication of the latest guidelines that highlight the need for proper follow-up. However, if this study were repeated today, a different approach in finding patients with a PE diagnosis would need to be considered because, in contrast to 2005, not all patients with a confirmed PE diagnosis are hospitalized and therefore would not be included in the NPR to the same extent.

Papers II and IV

The post-PE groups had higher proportions of dyspnea compared with the control group, which could support the previously proposed term PPES. The statistical analysis results clearly demonstrate that PE is independently associated with dyspnea, even though the pathophysiological explanation is not clear. It is unlikely that CTEPH is the main component of this proportion, based on the same arguments given for the survival analysis findings. The incidence of possible CTED remains unclear, and no available data address the incidence of CTED in any published cohort. In addition, the suggestion to decrease the mPAP and PVR cut-offs for a CTEPH diagnosis, would imply a transition from CTED to CTEPH in an unknown number of cases. The increasing evidence that CTED patients may benefit from the same treatment as CTEPH patients – such as anticoagulation, BPA, PEA and perhaps even PAH-
specific medication, – indicates that we probably should pay more attention to this condition.

The high proportion of pathological V/Q scans and echocardiography findings supports previously published results. However, in similarity to the high proportion of dyspnea, further studies are needed regarding these findings and the prevalence of CTED within this group. In recent decades, increasing knowledge of the high prevalence of dyspnea, physical impairments, incomplete thrombus resolution, RV dysfunction, and even altered gas exchange has led to the proposal of PPES and CTED as clinical terms. PPES is more general and includes complaints that might not be attributed to the PE event, whereas the term CTED does not clearly indicate that this is a disease of the lung and pulmonary vessels. Lately, chronic thromboembolic pulmonary disease (CTEPD) has been proposed as an alternative, which seems reasonable.

![Figure 17. An illustrative interpretation of the relationship among PPES, CTEPD, and CTEPH.](image)

Previous data regarding the frequency of CTEPH are often a mixture of both prevalence and incidence, which contributes to the difficulty in determining the actual risk of CTEPH following an acute PE. This difficulty is mainly the result of the complexity of differentiating acute PE from pre-existing CTEPH. Estimated right systolic ventricular pressure >60 mmHg on echocardiography is one sign that may indicate pre-existing CTEPH. Additionally, typical CTPA features of CTEPH could be present, but differentiating CTEPH from acute PE on CTPA requires a highly experienced radiologist with knowledge of CTEPH [80, 84, 92]. The overall prevalence of CTEPH presented in our study is in line with previous data, and the cumulative incidence is on the lower end of the scale compared with earlier reports. The prevalence and cumulative incidence in our study should be regarded as a minimum but could still be considered as representative for the general post-PE population. Because
acute PE incidence increases substantially with age and we used no exclusion criteria when constructing the national post-PE cohort, the resulting cohort was elderly and had multiple comorbidities. Thus, it is considered to be both natural and expected that some patients abstained from further participation because of other medical conditions or death.

Future perspective and personal reflections

To screen or not to screen for CTEPH

Through early detection, screening programs have the potential to reduce morbidity and mortality by identifying people who could benefit from early treatment or intervention. Medical screening programs have been increasingly implemented and are now considered among the success stories of modern medicine. Many countries already have active screening programs for PH in certain high-risk populations, such as patients with systemic sclerosis. Pengo et al. published their paper proposing a 4% CTEPH incidence following an acute PE and set off an intensive debate about whether to screen for CTEPH [85]. The method of screening, target population, and best time point for screening have been major components in the screening debate.

The CTEPH diagnosis is confirmed using RHC, but RHC is unsuitable as a first-line screening method given its invasive nature. Similarly, V/Q scans are not suitable for first-line screening because of suboptimal specificity and radiation exposure. Echocardiography is a readily available, non-invasive screening method without risks for patients except for possible anxiety. But echocardiography can provide only an estimation rather than a measurement of pulmonary artery pressure and yields a high number of false-positive results. Studies have evaluated clinical prediction scores for selecting patients for echocardiography [87, 122, 123]. The proposed scores include parameters focusing on symptoms and risk factors for CTEPH development, and an ongoing trial is evaluating one of these algorithms in a prospective multicenter outcome study (NCT02555137).

Screening echocardiography in all PE survivors is not considered to be necessary or cost-effective because of low diagnostic yield [122, 124, 125]. For the first time, the 2019 ESC/ERS guidelines proposed a follow-up strategy in which echocardiography is recommended for all PE survivors
with persistent or new-onset dyspnea and to consider echocardiography in those with risk factors for CTEPH development [24]. The benefits of this approach include screening that may be organized in an already existing infrastructure for follow-up. Disadvantages include a probable higher proportion of echocardiography performed compared with using prediction scores.

Early detection of CTEPH remains a challenge, with a median diagnostic delay exceeding one year and approximately 80% of patients in New York Heart Association (NYHA) class III-IV at diagnosis [82, 102, 126]. The main reason for this delay is thought to be the nonspecific and insidious clinical presentation in combination with a lack of knowledge of CTEPH. Diagnostic delay is associated with a worse hemodynamic profile and less favorable survival, and the optimal timing for screening is an ongoing debate [89]. A complicating factor is the typically asymptomatic “honeymoon” period following the acute PE, making the optimal timing difficult to determine [127, 128].

It is noteworthy that most CTEPH patients in our study (paper IV) were diagnosed outside of the study protocol. To assess the possible impact of a screening program, it would have been interesting to know how many patients would have been diagnosed with CTEPH during the same time frame had they not been invited to participate in the study. One could speculate that patients may have sought help for their symptoms to a greater extent if they were not a part of the study, and it is not certain that our study had any actual impact on the CTEPH incidence rate.

Are we even on the right track?

A high proportion of patients with CTEPH following an acute PE have signs of CTEPH on CTPA performed at the PE event. This understanding triggers the idea that CTEPH may not be a complication of PE after all [84, 129].

Although many risk factors for CTEPH development have been identified, the pathophysiology behind CTEPH remains a mystery. The unresolved thrombus theory cannot explain why only a minority of patients with incomplete thrombus resolution develop CTEPH. It has been proposed that biological abnormalities causing a hypercoagulability state may be
responsible. However, many classical inherited thrombotic risk factors are no more frequent in patients with CTEPH than in controls [128].

A main reason CTEPH is considered to be a complication of acute PE is that 50%–75% of CTEPH patients have a history of acute PE. It is thought that the remaining 25% must have had a “silent” previous PE. Of interest, compared with data from the European registers, the proportion of prior PE in the Japanese CTEPH population is reportedly as low as 15% [95, 130].

The increasing recognition of misclassification of CTEPH as acute PE in combination with patients without a verified acute PE in their medical history may challenge the link between acute PE and CTEPH.

Acute PE follow-up

Even if data available today do not support the need to screen all surviving PE patients for CTEPH, the current ESC guidelines clearly state the need for a follow-up visit [16]. This recommendation seems more than reasonable because it is important to consider the risk of bleeding and recurrent PE in all patients. In addition, there may be a need to screen for unknown thrombophilia and for selection of patients to screen for malignancies. If the patient has complaints of dyspnea, a referral for echocardiography is a proper first-line investigation. One problem that might emerge is that CTEPH may have a latent phase longer than the interval to the follow-up visit, leaving a risk of missing those patients. A second follow-up visit does not seem practical, but with thorough information provided to all patients regarding which symptoms require attention and whom to contact if those symptoms emerge might be an alternative.

Because the follow-up is essential, additional studies need to investigate the frequency of follow-up visits after the new guidelines were published in 2019. If the proportion of follow-up visits remains similar to what we report in paper III, the reason needs to be investigated. In that scenario, physicians and individuals in charge likely need to be educated regarding the importance and purpose of follow-up. In addition, more resources or a change in priorities might be required to provide this group of patients with the attention they deserve.
Physical exercise therapy

The high proportion of patients with complaints of dyspnea and physical impairment following an acute PE and who do not have CTEPD probably includes a mixture of dyspnea related to deconditioning and dyspnea from other cardiac or pulmonary diseases. Well-established exercise training programs can improve symptoms and physical capacity in patients with myocardial infarction, COPD, heart failure, and other conditions, but little is known regarding exercise therapy post-PE. In a small prospective intervention study from 2020, a 3-month exercise program of low-moderate intensity was offered to 23 patients [131]. The exercise therapy was safe and effective, with significant improvements in peak VO$_2$ and QoL. The hope is that larger studies will follow, preferably with a randomized controlled approach. Studies also are needed to assess the efficacy and safety in a larger population and to determine if an exercise program may reduce the proportion of patients with post-PE symptoms.
Conclusions in summary

- The acute PE incidence in Sweden during 2005 was 0.6/1000 person-years, which is in line with previous data.

- Acute PE is associated with multiple comorbidities, especially cardiovascular disease, and there is increased short- and long-term mortality, even after exclusion of patients with known malignancies.

- There was a high prevalence (53%) of self-reported dyspnea at 2 years following a PE event, which is consistent with previously published data.

- Patients who have experienced an acute PE have a significantly higher prevalence of both exertional and wake-up dyspnea compared with controls. The post-PE group also has a higher prevalence of self-reported comorbidities compared with controls, but these comorbidities could not fully explain differences in dyspnea prevalence.

- The PPV of 79% for the PE diagnosis in the NPR supports the NPR as a reliable source of data that can be used for register-based research regarding acute PE.

- There was a notably low frequency of follow-up visits after an acute PE in Sweden in 2005.

- Anamnestic and echocardiography are appropriate first-line screening methods for CTEPH because all CTEPH patients were symptomatic and all but one demonstrated indirect signs of PH on echocardiography.
- A high proportion of V/Q scans show perfusion defects, and a high proportion of echocardiography studies show signs of PH, which together with the high prevalence of dyspnea may support the presence of the previously described post-PE syndrome, or PPES.

- The overall CTEPH prevalence was 0.4%, and among survivors who were symptomatic, the cumulative CTEPH incidence was 1.1%.
Strengths and Limitations

Paper I

The strength of this study is mainly its size and completeness, as no patients were excluded because of age or comorbidity. In addition, this study is to our knowledge the only investigation of regional differences in PE incidence in Sweden. However, the PE incidence was based on hospital records only. There might have been patients with a PE diagnosis who were not admitted, and there are probably some patients with PE who presented as SCD and who were not included. An important limitation is the lack of available data regarding comorbidities in the control group and that the data were from 2005.

Paper II

The major strength of this study is the size of the cohort and the additional data regarding comorbidities. Thus, in contrast to previous studies, this paper demonstrated that the PE event was independently associated with dyspnea. However, the prevalence of dyspnea was based on self-reported data, and no objective measurement of dyspnea was available. In addition, data regarding all diagnoses that can be dyspnea-related, such as anemia, obesity, and obstructive sleep apnea, were not available.

Paper III

One strength of this paper is that no patients were excluded based on age or comorbidities. In addition, we added an analysis regarding treatment and follow-up routines, which to our knowledge has not been demonstrated before. Another strength of this study is its size because we validated approximately 10% of all cases of acute PE in Sweden in 2005. The major limitation is that this paper is based on data from 2005, and even if the diagnostic approach to PE has not changed in Sweden since then, there has probably been a shift in the choice of treatment following the advent of DOACs, along with a possible change in follow-up routines since the new ESC guidelines on PE were published in 2019.
Paper IV

This study is unique in its design because it follows a complete national cohort of PE patients up to 12 years after their PE event, which provides real-life data on the clinical course after acute PE.

Because there were no exclusion criteria at the beginning of the study, the cohort was elderly with multiple comorbidities. Following such a cohort for 12 years may be complicated by a high risk of non–PE-related deaths and other medical events that may have meant that some patients were unable to proceed with CTEPH investigations.

Furthermore, in phase 2, the authors had less influence over the investigations, which may have affected the prevalence and cumulative incidence of CTEPH. There is also a risk of selection bias because the different local hospitals had different approaches regarding selection for V/Q scan referral. However, the authors took full responsibility for all patients, and when the local hospitals refrained from follow-up, an alternative follow-up at the patient’s primary healthcare center was established.

In this study, as in most studies regarding CTEPH following an acute PE, there might have been cases in which CTEPH was misclassified initially as acute PE. This possibility contributes to the difficulties in assessing the actual risk for CTEPH development following an acute PE.
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Appendix