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Impact of Chronic Obstructive Respiratory Disease (COPD), respiratory symptoms and oxygen saturation on the risk of incident venous thromboembolism (VTE) and VTE-related mortality in a general population

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June 2019

A dissertation for the degree of Philosophiae Doctor

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Acknowledgements

This work started out in the Hematological Research Group (HERG), Department of Clinical Medicine (IKM), Faculty of Health Sciences, The Arctic University of Norway (UiT) and Pulmonary department, Division of Internal Medicine, University Hospital of North Norway (UNN), from January 2012 to June 2014, continuing at the K. G. Jebsen Thrombosis Research and Expertise Center (TREC) from June 2014 to June 2019. My PhD-period has been funded by an independent research grant from the Northern Norway Regional Health Authority (Helse Nord). K. G. Jebsen TREC is financed by the K.G. Jebsen Foundation, the Arctic University of Norway (UiT) and the Northern Norway Regional Health Authority.

I would like to thank my main supervisor and good friend, Professor John-Bjarne Hansen. Even after watching my first horrifying attempt for a PhD-degree every day during the years 1995 – 2001, you gave me this chance to explore and hopefully to learn something about science. In every meeting where we have discussed my progress and PhD-career, you have been constructive, positive and in a good mood, I know that it must have been tough for you. Your tremendous knowledge in the field of venous thromboembolism, in all ways, is actually very impressive. Your description of my efforts and work have sometimes been hard to handle, but I am absolutely confident that this has been necessary to make me understand what is needed to complete a PhD-thesis and has come from love - platonic love, that is.

My co-supervisor professor Sigrid Kufaas Brækkan is the female version of Professor Hansen, but much, much prettier. She is the mother of endless energy, good mood, and positive attitude. Every time I have asked you if there is any chance that my work can end up as a PhD-thesis you have answered a loud “YES”, this amount of positive energy is scary to think of. You have been extremely patient when I have tried to understand medical statistics and epidemiology, and have been very constructive in revision of my work. Without you, this PhD-thesis would have ended like my former PhD-thesis - in the trash.

I would like to thank my co-authors, Vania Morelli, Line H. Evensen, Ellen Brodin, Kristin Enga, Henrik Schirmer and Hasse Melbye, for their contributions. All members of former HERG and present TREC deserve a big hug. You have, first of all, contributed to a great social environment, which I think is the corner-stone of any workplace. If you don't enjoy the people you work with and the environment they create, you should quit the job immediately. The TREC-environment has been present and dominating at Sommarøya, during Tuesdays-meetings, lunches and a million coffee breaks, and at all conferences. Thanks to Trond Isaksen, Christian Hindberg, Birgit Småbrekke, Ludvig Rinde, Esben Bjøri, Håkon S. Johnsen, Cathrine Ramberg, Robin Liang and Nadezhda Latysheva. If you ever get COPD you are free of charge when consulting me……always.

I would also like to say thank you to my former boss at the Pulmonary Department, Division of Internal Medicine Professor Ulf Aasebø, he approved my leave for three years so that this work could be realized, and further all my colleagues at the hospital who made it possible to combine research and hospital work during the same period.

I want to thank my parents, Alfon and Rigmor, who patiently have been waiting and waiting for me to finish this work, constantly reminding me, in a low-pressure way, that I had to speed up.

My brother Tore has been my greatest inspiration. He is my only brother and an actual professor with the brains, the skills and the work ethics needed to fulfill a job like this. This kinship must be genetically very skewed.

To my, despite all "arguing", best friend and wife Margrethe Tora. You did not cheer when I made my decision of entering the PhD-program, but you have kept my life outside the office very tidy throughout all these years and almost never made any comment about it. You are beautiful.

To our three amazing, pretty and talented children, Magnus, Mathias and Marthe. When a man has contributed to producing three resourceful humans like you to the world, he has done his part and can actually retire. I certainly hope to do so after this. You are the best.

Trond
Tromsø 16.06.2019

Summary

Venous thromboembolism (VTE) is a collective term for pulmonary embolism (PE) and deep vein thrombosis (DVT). Chronic Obstructive Pulmonary Disease (COPD) is described as a moderate risk factor for VTE, but the association has so far been scarcely examined. The aims of this thesis were to I) investigate the impact of COPD on the risk of incident VTE and the risk of mortality in COPD-patients with VTE; II) examine the impact of hypoxia and respiratory symptoms (cough, phlegm and dyspnea) on the risk of VTE in subjects with and without COPD; and III) investigate the impact of COPD on mortality risk in VTE patients. Study participants were recruited from the fifth and sixth surveys of the Tromsø-study conducted in 2001-02 and 2007-08, respectively. Using a cohort design, >8600 participants were followed from the date of inclusion until 2011 (paper I) or 2016 (Paper II) and all VTEs occurring during follow-up were recorded. Information on mortality was derived from the national population registry.

We found no linear increase in the risk of VTE across stages of COPD. However, there was a threshold effect, where patients with severe COPD (stage III/IV) had a 1.6 fold higher risk of overall VTE, and a 2-fold higher risk of secondary VTE, compared to subjects without COPD. VTE was also a strong predictor of all-cause mortality in all stages of COPD. Both lowered oxygen saturation and respiratory symptoms were associated with an increased risk of VTE, and the combination of COPD and respiratory impairments yielded an additive increase in the VTE risk. In patients with VTE, concomitant COPD was associated with a 2-fold higher risk of mortality, and the risk of death increased with the severity of COPD.

Our findings suggest that both severe COPD, lowered oxygen saturation and respiratory symptoms are associated with incident VTE. Moreover, our studies showed that VTE in combination with COPD is associated with substantially increased risk of mortality.

Sammendrag

Venøs tromboembolisme (VTE) er et samlebegrep for lungeemboli (LE) og dyp venetrombose (DVT). Kronisk Obstruktiv Lungesykdom (KOLS) er beskrevet som en moderat risikofaktor for VTE, men få studier har undersøkt denne sammenhengen i en prospektiv kohortdesign. Formålet med dette arbeidet var derfor å I) undersøke om KOLS påvirker risikoen for førstegangs VTE i en generell befolkning, samt undersøke mortaliteten hos KOLS-pasienter med og uten VTE; II) undersøke hvordan oksygenmetning og respirasjonssymptomer (hoste, slim og tung pust) påvirker risikoen for VTE; og III) undersøke betydningen av KOLS for risiko for død hos VTE pasienter. Studiepopulasjonen besto av deltakere fra den femte og sjette Tromsøundersøkelsen, gjennomført i henholdsvis 2001-02 og 2007-08. Deltakerne ble fulgt fra inklusjon i studien og fram til 2011 (artikkel I) eller 2016 (artikkel II), og alle VTE hendelser som oppstod i løpet av oppfølgingstiden ble registrert. Informasjon om død ble hentet fra folkeregisteret.

Vi fant ingen lineær sammenheng mellom økende stadier av KOLS og risiko for VTE. Derimot fant vi at pasienter med alvorlig KOLS (stadium III/IV) hadde 1.6 ganger økt risiko for total VTE, og 2 ganger økt risiko for sekundær VTE, sammenlignet med personer uten KOLS. VTE var assosiert med økt risiko for død i alle stadier av KOLS. Lav oksygenmetning og respirasjonssymptomer ga økt risiko for VTE, og hos KOLS-pasienter bidro disse faktorene til å øke VTE risikoen ytterligere. VTE pasienter med KOLS hadde dobbelt så høy risiko for å dø sammenlignet med VTE pasienter uten KOLS, og risikoen for død økte med alvorlighetsgraden av KOLS.

Våre funn tyder på at alvorlig KOLS, lav oksygenmetning og respirasjonssymptomer er forbundet med økt risiko for førstegangs VTE. Videre viste vi at VTE i kombinasjon med KOLS er forbundet med betydelig økt risiko for død.

List of papers

I. COPD and risk of venous thromboembolism and mortality in a general population

Børvik T, Brækkan SK, Enga K, Schirmer H, Brodin EE, Melbye H and Hansen JB.

Eur Respir J. 2016; **47**: 473-81.

II. Impact of Respiratory Symptoms and Oxygen Saturation on the Risk of Incident Venous Thromboembolism - The Tromsø Study

Børvik T, Evensen LH, Morelli VM, Melbye H, Brækkan SK, Hansen JB

Submitted manuscript

III. Chronic Obstructive Pulmonary Disease and Risk of Mortality in Patients with Venous Thromboembolism - The Tromsø Study

Børvik T, Brækkan SK, Evensen LK, Brodin EE, Morelli VM, Melbye H, Hansen JB.

Pending revision in Thromb Haemost, June 2019

Abbreviations

AF	Atrial fibrillation
AT	Antithrombin
ATS	American Thoracic Society
BMI	Body Mass Index
CI	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
CTEPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second (measured)
FEV_1- predicted	Forced expiratory volume in 1 second (calculated)
FVC	Forced vital capacity
FVL	Factor V Leiden
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Hazard ratio
HRT	Hormone Replacement Therapy
HUNT	Helseundersøkelsen I Nord-Trøndelag
ICD	International Classification of Diseases
IKM	Department of Clinical Medicine
IR	Incidence rate
LITE	Longitudinal Investigation of Thromboembolism Etiology
MI	Myocardial Infarction
O_2	Oxygen
OC	Oral contraceptives
PE	Pulmonary embolism
PEF	Peak expiratory flow
PTS	Post Thrombotic Syndrome
REV	Reversibility test
SpO_2 %	Peripheral saturation of oxygen
STATA	STATA Corp©
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TREC	Thrombosis Research and Expertise Center
UiT	The Arctic University of Norway
UNN	University Hospital of North Norway
VTE	Venous Thromboembolism
vWF	von Willebrand Factor
WHO	World Health Organization

1. Introduction

1.1 Epidemiology of venous thrombosis

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the formation of a blood clot in a deep vein, mainly in the lower limbs, causing a partly or total obstruction of the venous flow. PE might occur as a consequence to DVT, when a part of the thrombus dislodges and follows the bloodstream to the lung where it obstructs the pulmonary circulation. However, a concomitant DVT is only found in about half of all PE patients (2-4). Total embolization of the thrombus, de novo formation of the thrombus in the lung or thrombus-formation in the right atrium of the heart because of atrial fibrillation (AF), have been launched as theories to explain the occurrence of PE without a concomitant DVT. AF is associated with higher risk of PE than DVT, and explained 20% of PE events in the Tromsø study (5).

VTE is the third most common cardiovascular disease, causing significant morbidity and mortality (6). The estimated annual incidence rate is 1-2 per 1000 person-years (7-12). Several studies have suggested increased incidence of VTE over the last decades in various populations (13-15). Data from the Tromsø Study reported a 27% overall age-adjusted increase in the VTE incidence from 1996 to 2012, from 1.6 per 1000 person-years in 1996 to 2.0 per 1000 person years in 2011, mainly caused by an increased incidence of PE with and without concurrent DVT (13). The increased incidence can be explained by both increased awareness of VTE and improved diagnostic tools (16, 17).

The incident rate increases with increasing age, from one per 10 000 person-years in young adults, to one per 100 person-years in the elderly (18, 19). Women are more often affected than men through their childbearing years, and older men are more affected than older women (20). The incidence of DVT is higher (0.4-1.2 per 1000 person years) than the incidence of PE (0.3-0.8 per 1000 person years) (6, 21).

Patients with a first incident VTE have a risk of recurrence of 5-7% per year, and this risk is more than 50 times higher than for patients without a previous VTE (11, 21-23). The cumulative proportion of patients with VTE recurrence is approximately 5-12% after 1 year, 12-25 % after 5 years and 30-40% after 10 years (5, 24-26). The risk of recurrence seems to be highest the first 6-12 months (24, 27), and 30-40% of all VTE-patients experience a recurrent event within ten years (9, 26). Several factors are associated with risk of recurrence, including malignancy, increasing age, male sex, high BMI, and neurologic disease with leg paresis (13, 24). The highest recurrence risk is observed in patients with persistent provoking factors such as cancer or inherited thrombophilia (28, 29). Patients with unprovoked incident events have a moderate to high risk of recurrence (around 11% the first year after treatment). The risk of recurrence among patients with provoked incident events depends on the type of provoking factor (5, 25). Transient risk factors (e.g., recent surgery and trauma, pregnancy, oral contraceptives and hormone therapy) present at the time of the VTE event are associated with lower risk of recurrence (12) compared to more persistent provoking factors like cancer. In patients with recurrence, the recurrent event tend to occur at the same location as the first event (i.e. PE-patients develop a new PE rather than a DVT) (30). In the California Patient Discharge Data Set, 6.4% of DVT patients developed a recurrence within 6 months of hospital discharge, of which 85% developed a second DVT (31). In the same study, 70% of PE patients admitted with recurrent VTE were diagnosed with a new PE.

Post Thrombotic Syndrome (PTS) is the most common complication to DVT and develops in 25-50% of the patients. Usually, PTS appears within 1-2 years after the thrombotic event (32, 33). PTS is a condition characterized by chronic pain, edema and dermatitis, and severely affected patients may develop venous leg ulcers (34, 35). Risk factors include obesity, female sex, varicose veins, proximal DVT location and recurrent DVTs (5, 33). Cancer, surgery, plaster casts or inherited thrombophilias do not influence the risk of PTS (36, 37). PTS may considerably impair mobility and quality of life (34), which may explain the association between DVT and subsequent work-related disability (38).

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, but serious complication after acute PE. It is defined as *"precapillary pulmonary hypertension (PH) with a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg (as measured by right heart catheterization (RHC)) and mean pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg in the presence of chronic/organized flow-limiting thrombi/emboli in the elastic pulmonary arteries after at least 3 months of effective anticoagulation"* (39). The condition affects 2-4% of survivors after acute PE (17, 39). CTEPH will increase fibrotic occlusion of the pulmonary artery leading to increased pulmonary vascular resistance, progressive pulmonary hypertension, and in the end, right heart failure (11, 17). The primary treatment of CTEPH is surgical removal of the obstructive material by pulmonary thromboendarterectomy (17, 39).

VTE is strongly associated with mortality (40, 41). An overall estimate indicates around five hundred thousand VTE-related deaths per year in Europe (42). The total number of combined deaths from breast cancer, AIDS, and road traffic accidents among the inhabitants of United Kingdom, equals only 20% of the number of deaths from VTE in the same population every year (43). A recent study from Arshad *et al.* including 710 subjects with an incident VTE from 1994-2012, reported an all-cause mortality rate of 9% at 30 days and 16.6% at one year (27). These mortality rates are almost identical to those reported in a previous Norwegian study of 740 VTE patients recruited in the period 1995-2001 (44).

In two other observational studies, 5-10% of VTE-patients died within one month, and 20-30% died within 5 years (18, 27). The survival depends on the location of the thrombus (27, 44). Almost one-quarter of the PE-events present as sudden death (45), and PE is associated with more than a 3-fold increase in 30-day mortality compared to isolated DVT (42, 44, 46, 47). However, the increased mortality of PE compared to DVT only persists the first three months (12, 44, 48, 49). Of note, PE is regarded the most common avoidable cause of death among hospitalized patients (50).

The mortality of VTE is highest for patients with underlying malignancy. VTE is the second leading cause of death in patients with cancer (51). In a study from the Dutch Cancer Registry, cancer patients with VTE had a 2.2-fold increased risk of mortality compared to cancer-patients without VTE (52). A Danish registry-based population study reported a 12% one-year survival among patients with cancer associated VTE and 36% one-year survival in cancer-patients without VTE (52).

1.2 Pathophysiology of venous thrombosis

Our coagulation system is maintaining a physiological balance between bleeding and thrombosis. Venous blood clots, unlike arterial blood clots, form under low shear stress on the surface of a largely intact endothelium (53). The exact mechanism is not completely understood. A theory, presented by the German scientist Rudolph Virchow in 1856, described a model (later known as Virchow's triad), consisting of three central, interacting elements in the pathogenesis of venous thrombosis (Figure 1)(54). The elements were stasis of the blood- flow, changes in the blood composition (i.e. hypercoagulability) and endothelial damage or dysfunction. Today we know that almost all recognized risk factors for VTE can be related to one or more of these key elements.

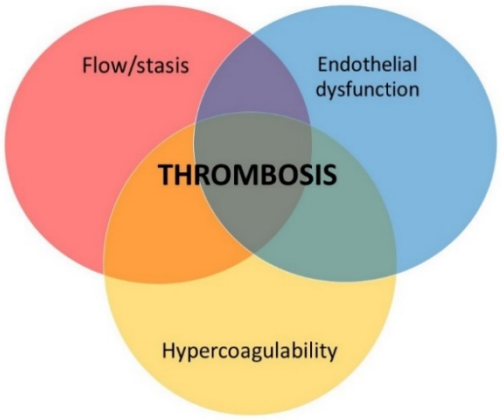


Figure 1. Virchow's triad illustrating the relation between stasis, hypercoagulability and endothelial dysfunction.

A DVT occurs most often in the large veins of the legs, more precisely in the venous valvular sinuses (55). During streamline flow and stasis in the lower limbs, a turbulent flow is created in these sinuses, leading to the formation of two counter-rotating vortices, one on top of the other. This flow-pattern leads to severe hypoxia in the region of the lower vortex (Figure 2)(56).

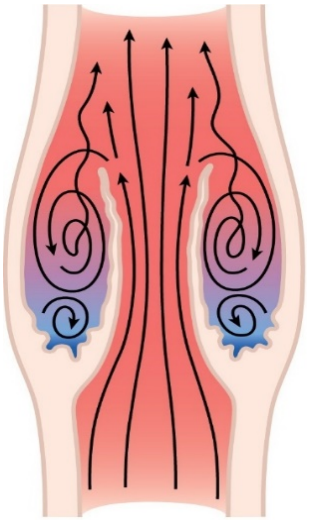


Figure 2. Schematic illustration of the blood flow observed around the venous valves of the deep veins. Oxygen tension is colour-coded with a gradient from red to blue: the darker the blue, the greater the hypoxia. The solid arrows illustrate blood flow direction with the development of vortexes in the venous valve pocket.

A normal endothelial surface presents natural anticoagulants like endothelial protein C-receptor, tissue factor pathway inhibitor (TFPI), thrombomodulin and heparin-like proteoglycans, to prevent the initiation of a clot. Endothelial dysfunction may be triggered by severe hypoxia. This results in a downregulation of the anticoagulant factors on the endothelial surface (55), promoting expression of prothrombotic factors like adhesion molecules (E-selectin, P-selectin), anti-fibrinolytic protein plasminogen activator inhibitor type 1 (PAI-1) and tissue factor (TF) (57, 58). The intra-cellular mechanism activated by hypoxia leads to high levels of hypoxia-inducible factor 1 (HIF-1) and early growth response-1 (Egr-1) pathways, which promote the described endothelial activation, and further, recruitment and activation of monocytes and platelets (53, 59). The flow-pattern in the sinuses prevent wash-out of blood, causing entrapment of blood cells, like circulating erythrocytes, leucocytes, TF-positive extracellular vesicles (EVs) and platelets, all vulnerable to the severe hypoxia (Figure 3) (59,

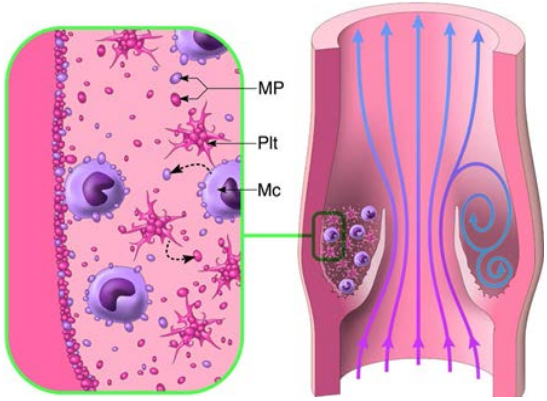


Figure 3. The venous valvular sinus as a predilection site for VTE- initiation. The vortical flow pattern at the venous valvular sinus leads to a steep decline in oxygen tension. The resultant hypoxia activates the venous endothelium on the inner-lining of the adjacent valve, leading to the recruitment and binding of monocytes (Mct), platelets (Plt) and TF-positive extracellular vesicles (EVs). TF from activated monocytes and EVs may activate the coagulation cascade and initiate thrombosis formation.

60). The activated endothelium binds leucocytes and TF-positive EVs to their surface by P- and E-selectin, causing activation of the leucocytes who responds with expression of surface-bound TF. This multifactorial process causes the environment in the venous valve sinuses to change from anti- to pro-coagulant with a local activating of the coagulation cascade as a consequence (53, 59).

1.3 Risk factors for VTE

VTE is a complex and multifactorial disease where the cause of the event remains unknown in 50% of the cases (61). All VTE-events can be classified as provoked or unprovoked based on the presence or absence of known risk factors that can be either acquired or inherited (62). An incident VTE usually requires a combination of different risk factors to occur (1). This is illustrated in the thrombosis potential model by Rosendaal (Figure 5), showing that the cumulative effect of several risk factors is needed to exceed the "Thrombosis threshold" in order to initiate a VTE.

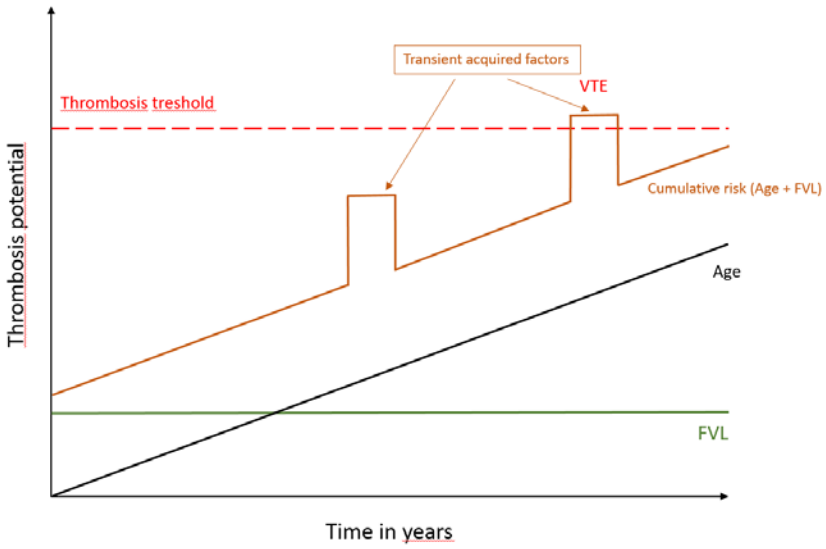


Figure 5. The thrombosis potential model adapted from Rosendaal (1). The green line illustrates inherited risk factors for VTE, here represented by factor V Leiden mutation (FVL). The black line represents the effect of increasing risk factors over time (like age). The brown line is the cumulative effect of the present, stable risk factors and transient risk factors (e.g. plaster cast or surgery) increasing the risk level above the threshold level thereby initiating an incident VTE.

1.3.1 Hereditary Risk factors

There is a strong heritability for VTE indicating that genetic factors account for more than 60% of the variation in susceptibility to thrombosis (63, 64). The known genetic factors only explain a minor proportion of the VTE heritability, and only 16 single nucleotide polymorphisms (SNP's) have been robustly associated with susceptibility to VTE. These known SNPs mainly affect factors involved in the coagulation cascade (65-67). First time overall incidence of VTE in carriers of a prothrombotic defect is 0.8%/year compared to 0.1%/year in non-carriers (68). The different types of hereditary thrombophilia show considerable differences in life- time risk of VTE (69).

There are in particular two mechanisms dominating the inherited thrombophilias: impairing natural anticoagulant pathways (*loss-of-function*) and potentiating procoagulant pathways (*gain-of-function*) (70).

Mutations causing antithrombin (AT)-, protein C- and protein S-deficiencies, are all well-known loss-of-function mechanisms (70). Antithrombin mutations, found in 0.2% of the population, are associated with a 10- to 20-fold increased risk of VTE in heterozygous carriers (45, 71, 72). Protein C is an anticoagulant that inactivates activated factor V and VIII, with protein S as a co-factor in this process (73). The prevalence of both protein C- and S-deficiency are less than 1 % in the general population, and heterozygous carriers compared to non-carriers have a 10-fold increased risk of VTE (71).

The factor V Leiden mutation is a gain-of-function mutation causing APC-resistance. It occurs in 4-7% of the Caucasian population and heterozygous carriers have a 2-5 fold increased risk of VTE (74), while homozygous carriers have a 10-80 fold increased risk of VTE (75, 76).

The Prothrombin G20210A mutation has a prevalence of 2% in the Caucasian population, and is associated with a 3-fold increase in VTE risk compared to healthy non-carriers. The risk correlates to an increase in plasma prothrombin level (45, 77, 78). A concomitant factor V Leiden and prothrombin G20210A gene mutation is associated with a 20-fold increase in VTE risk compared to individuals with no mutations (79).

The non-O blood groups are present in 60-70% of the population (80). Individuals with B and A1 blood groups are at 1.5 to 2.0-fold higher risk of VTE compared with individuals with O and A2 blood groups (45, 80). Non-O bloods groups are associated with increased vWF and FVIII, but remains significantly associated with VTE even after adjustment for both of them (45, 70). Conversely, both high plasma levels of FVIII and vWF are associated with VTE risk after adjustment for ABO blood group (45, 70).

During the last decade, a broad specter of susceptibility loci to complex diseases by GWAS studies (Genome Wide Association Studies) have been identified. In most cases, the identified risk alleles only explain a small percentage of the heritability of disease. For VTE the GWAS studies have revealed several novel single nucleotide polymorphisms (SNPs) associated with increased thrombosis risk (45), but they are only proven to have a minor effect of VTE risk with odds ratios (ORs) ranging from 1.10 to 1.35 . Besides, the clinical utility have been limited (45). Whole genome sequencing is an increasingly used approach to reveal genetic causes of VTE, and will probably be a major field in future research of VTE.

1.3.2 Non-Inherited Risk factors

Age: The incidence of VTE increases exponentially with increasing age from approximately 1 in 100 000 in childhood to nearly 1 in 100 in individuals over 85 years. The mechanism(s) for the increased risk of VTE by age is not completely understood, but could be due to age-specific factors of thrombosis (i.e. muscle strength, venous insufficiency, frailty and institutionalized living) or risk factors that increases with age (immobility, cancer, co-morbidities) (44, 81-83). In The Tromsø-study, persons above 70 years had an 11-fold higher risk of VTE than those below 50 years (84). Similar results were found in other cohort-studies such as HUNT and LITE (10, 44).

Sex: The overall incidence of first VTE is approximately equal for both sexes, but differences according to sex are observed across age groups (10, 44, 84). Middle aged and elderly men have a higher risk of VTE than women of equal age, and some of this difference might be explained by taller

body height in men (6, 84), as height is recognized as risk factor for VTE (6, 85). Women of child-bearing age have a higher risk of VTE than men of equal age (84, 86), and this is mainly attributed to pregnancy and use of contraceptives (87-89).

Obesity: Globally, the prevalence of obesity (BMI>30 kg/m^2) has nearly tripled during the last 40 years. In 2016, more than 1.9 billion adults (> 18 years) were overweight, and 650 million were obese (90). In a recent paper from The Tromsø study, 17.1% of all men and 10.9% of all women participating had a BMI > 30 kg/m^2 (91). Obesity is associated with 2-3 fold increased risk of VTE (91-93), and the risk increases with increasing BMI (91). Data from the Tromsø study reported an increase in VTE risk by 30% per 1 SD increase in BMI, and all obesity measures (waist circumference (WC), hip-circumference (HC) waist-hip ratio (WHR) and waist to height ratio (WHtR)) were related to risk of VTE (94). WC is the obesity measure that yielded the strongest risk estimate for VTE when using the established criteria for obesity measured by BMI, WC and WHR. WC also defined the highest number of persons at risk of VTE (95, 96). In addition, weight gain is associated with increased VTE-risk irrespective of the initial weight, but is particularly high in those already obese. A publication from the Tromsø study showed that further weight gain was associated with further increase in VTE-risk (97). The association between obesity and risk of VTE may be partly explained by presence of chronic low-grade inflammation (98) and higher concentrations of plasminogen activator inhibitor, TF, fibrinogen, Factor VIII and von Willebrand factor in obese people, as these are all factors shown to be associated with VTE-risk (99). Further, central obesity may increase the intra-abdominal pressure, causing an impaired venous return and thereby stasis, which is a known contributor to increased risk of VTE (100).

Body Height: A tall stature is associated with increased risk of both first and recurrent VTE (85, 101-103). A paper from the Tromsø study reported that the risk of a first-lifetime VTE increased by 34% per 10-cm increase in body height. A stature above 181 cm yielded a two-fold higher VTE risk than a stature below 173 cm (85). The combination of a tall stature and obesity showed a synergistic effect with a five-fold increased risk of an incident VTE (104). The mechanisms that explain this increased VTE-risk remain unsettled. However, a predisposition to thrombosis in people with a tall stature may

involve a greater venous surface area and thereof greater risk of damage to the vessel wall caused by higher hydrostatic pressure during standing (105).

Cancer: In 1865, the French physician Armand Trousseau observed migratory thrombophlebitis on his own extremity. He assumed this to be an early sign of cancer, as he believed the thrombophlebitis to be caused by malignancy. Unfortunately he was right, and died two months later from gastric cancer (106). This sign (unexpected and migratory thrombophlebitis) has later been extended to include chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucous endocarditis, and arterial emboli and have been named Trousseau's syndrome (107). VTE is a frequent and severe complication of cancer, and the incidence of cancer-related VTE is increasing. A study from the United Kingdom reported an increase in cancer related VTE-rates during the period 1997-2006 from 10.3 to 19 per 1000 person-years. The same increase was not found in cancer-free patients. A study from North Carolina followed hospitalized cancer-patients from 1995 to 2003 and found that the proportion of VTE increased from 3.6% to 4.6%, an increase of 28 % (108, 109). About 18-20% of all VTE events occur in patients with cancer (108, 110, 111), and subjects with cancer are at a four- to sevenfold increased risk of VTE compared to cancer-free subjects (24, 112). Clinical consequences of VTE, including recurrence, post-thrombotic syndrome and anticoagulant-related bleeding, occur more often in cancer patients (29, 113), and the risk of death following a VTE is threefold higher in cancer patients than in those without (51, 52). Several risk assessment models for VTE in cancer-patients have been developed during the years (114-118), but implementation into clinical use have so far been challenging due to the weak ability to predict incident VTE in several of the models (Khorana, Vienna, PROTECHT and CONKO)(119).

Hospitalization (surgical and medical conditions): The average annual age-and sex-adjusted incidence of in-hospital VTE is more than 100–fold compared to the general population (120). Hospitalized- / institutionalized patients account for 20-30% of all incident VTEs (8, 121), whereas recently hospitalized patients (i.e. the 3-month period after discharge) account for 20-25% of all VTEs, indicating that the risk of VTE remains elevated for a substantial period of time after discharge (110,

122-124). Hospitalized medical patients account for 70-80% of all fatal PE events (125), and in the LITE-study, surgery caused more than 40% of all provoked VTE events together with cancer (48%), hospitalization (52%) and major trauma (6%)(18). Almost 10% of all deaths in hospital are related to PE (126). Patients visiting a trauma unit have 50% increased risk of an incident DVT in the absence of prophylactic treatment (127). The VTE-risk remain high even in trauma patients receiving prophylactic anticoagulant treatment (128). As with cancer patients, several risk assessment models (RAM's) have been developed for improved VTE prevention in hospitalized medical patients, but the models are limited with regards to validation and external validity (129, 130). One study suggested that the Padua Prediction Score had the best potential to improve stratification of the thromboembolic risk in hospitalized medical patients compared with usual practice (131).

Myocardial infarction (MI): Several studies have shown an association between arterial cardiovascular diseases (MI and ischemic stroke) and the risk of incident VTE. A meta-analysis, reviewing clinical effects of anticoagulant therapy in suspected MI, showed that 4% of patients with MI had a symptomatic PE within two weeks after hospitalization (132). Two registry-based, population studies with case-control design from Denmark showed that patients with MI and other heart diseases had a transient increased risk of VTE (133, 134). In a prospective population-based cohort study, including 29506 participants, MI was associated with a 51 % increase of VTE and a 72% increased risk of PE. Further, MI was associated with a transient 4.8-fold increased (<6 months) risk of VTE with an even higher risk of PE (8.5-fold).

Ischemic stroke: Many studies have shown an increasing incidence of DVT in stroke-patients as early as two days after the stroke (135-144). Asymptomatic DVTs have been found in 30-40% of stroke-patients (139, 140, 144), while symptomatic DVT is found in 1-10% (144-147). The incidence of PE varies from 1% to 13% (148-150). Studies conducted in the general population have also revealed that stroke patients are at a high risk of VTE, particularly during the first few months after the acute event (151-153). In the Tromsø Study, the cumulative incidence of VTE was 1.5% during the first 3

months in subjects with ischemic stroke (152). Patients with ischemic stroke had an overall 3-fold higher risk of VTE compared with participants without stroke. The risk was remarkably high the first month, with a 20-fold increased risk of VTE, and declined rapidly thereafter (152). PE following stroke is associated with a higher risk of death at both 30 days and one year, and a higher risk of disability at discharge (149).

Immobilization: Even in healthy individuals, immobilization may cause venous stasis and increase the risk of VTE (154, 155). Immobilization caused by travelling (airplane, bus, train, car) increases the risk of VTE almost 3-fold, and the risk is related to the duration of the travel (156). Immobilization increases the risk of VTE both in the community and during hospitalization (157). Immobilized patients in hospital have a high risk of VTE. The risk is approximately doubled in medical bedridden patients although this risk may be influenced by the underlying disease (158). The risk is shown to be highest the first weeks of bed-rest (83). A study of patients >65 years showed that bed-rest up to 14 days was associated with a 5-6 fold increase in risk of VTE. (159). Moreover, a meta-analysis, with 43 observational studies of medical patients, reported a pooled odds ratio (OR) for VTE of more than two in immobilized patients compared to non-immobilized patients (158).

Smoking: Whether smoking is a risk factor for VTE is debated. Many prospective studies have failed to show an association between smoking and risk of VTE (6, 10, 84, 160), whereas other observational studies have demonstrated an association (101, 161, 162). Moreover, some prospective studies have reported a correlation between heavy smoking only and risk of future VTE (163-165). In an individual level random-effect meta-analysis, including 9 prospective studies with a total of 244865 participants and 4910 VTE events, current smoking was positively associated with a 19% increased risk of VTE (166). However, in stratified analyses cigarette smoking was associated with provoked (HR 1.36) but not unprovoked VTE (HR 1.08), indicating that provoking factors associated with smoking could mediate the risk. In a cause-specific analysis, Enga et al showed that the association between heavy smoking and VTE was no longer present when intermediate development of cancer and myocardial infarction was taken into account (167).

Infection: Acute infection is regarded as a risk factor for incident VTE (8). A population-based case-control study reported that infection was associated with a 4-fold increased VTE-risk regardless of health-care setting, and that hospital-related infections were associated with a 12-fold increased risk (168). A recent case-crossover study, including VTE patients derived from the Tromsø cohort (169), showed that hospitalization caused by acute infection was a strong trigger of VTE (OR 24) overall, and also in non-immobilized patients (OR 14.6). Moreover, there was a synergistic effect between infection and immobilization on the VTE risk (169).

1.4 COPD and risk of VTE

1.4.1 COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of Chronic obstructive Pulmonary Disease (COPD) states that: *"COPD is a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."* (170).

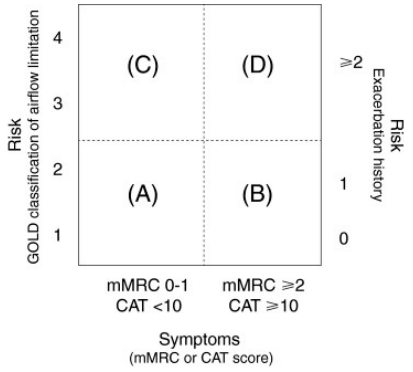
COPD is characterized by an airflow limitation (obstruction) during expiration that is not fully reversible. This airflow limitation is associated with an inflammatory process (171). The risk for COPD is related to an interaction between genetic factors and different environmental exposures. The best known genetic risk factor is a deficiency of the serine protease α1-antitrypsin. Among the clinical risk factors are tobacco smoke, occupational exposure, indoor and outdoor air pollutants and infections considered the most important (172). The pathological process results in an accumulation of inflammatory mucous exudates in the small airway lumen, infiltration of the airway walls by inflammatory cells, and deposition of connective tissue in the airway wall. The repair-process thickens the airway walls and reduces the luminal volume (173, 174). The final result is a physiological shunt and a ventilation/perfusion (V/Q) mismatch with secondary hypercapnia (high pCO_2) and hypoxemia

(low pO_2) (175). The disease is further associated with systemic inflammation and related to co-morbidities such as muscle dysfunction, secondary polycythemia, pulmonary hypertension, coronary artery disease and stroke (176-178).

1.4.2 Diagnostics and staging of COPD

FVC (Forced Vital Capacity) is the maximal volume (in liter) of air exhaled with maximally forced effort from a maximal inspiration (179). FEV_1 (Forced Expiratory Volume in 1 second) is the maximal volume of air exhaled in the first second of a forced expiration following a full inspiration (179). Once measured, this value is compared to a predicted FEV_1, calculated for a normal subject with the same age, height and weight (i.e. a patient's expiratory volume is compared to the expected expiratory volume). FEV_1% is the *fraction* of air in your lungs expired in one second (FEV1/FVC x 100%). This formula is used to determine the absence or presence of an airway-obstruction, whereas the actual FEV_1 compared to the predicted FEV_1 is used to establish the stage of COPD according to GOLD guidelines.

Until 2011, the diagnosis and staging of COPD was based on spirometry alone, according to GOLD-guidelines (180). A post-bronkodilator FEV1<80 % in combination with FEV1/FVC<70%, indicated an obstruction in airflow expiration. COPD-stages I-IV were determined according to predefined cut-offs of the FEV1-measured/FEV1-predicted fraction x 100% [Stage I >80%, Stage II 50-80%, Stage III 30-50 % and Stage IV <30 %] (180). The diagnostic criteria were revised in 2011 with an assessment and management scheme that would mirror the clinical situation better (170, 181). This



Patient category	Characteristics	Spirometric classification	Exacerbations per year	mMRC	CAT
A	Low risk: less symptoms	GOLD 1-2	≤1	0-1	<10
B	Low risk: more symptoms	GOLD 1-2	≤1	≥2	≥10
C	High risk: less symptoms	GOLD 3-4	≥2	0-1	<10
D	High risk: more symptoms	GOLD 3-4	≥2	≥2	≥10

Figure 5: *Global Strategy for Diagnosis, Management and Prevention of COPD 2013.* Spirometric classification: GOLD 1-2 = stage I and II; GOLD 3-4 = stage III and IV in the former classification system. Exacerbations per year: less or equal to 1 or more or equal to 2. Symptoms: scoring-models mMCR (modified Medical Research Council Dyspnea Scale) and CAT (COPD assessment test). Figure adapted from (182)

system, based on spirometry, number of exacerbations per year and symptoms (Figure 5) combined with assessment of potential comorbidities, reflects the complexity of COPD, and gives a better prediction of future exacerbations (170, 182). In addition to this staging, there are several diagnostic procedures for decision of COPD sub-groups (emphysema, reversibility etc.) (180).

1.4.3 Burden of COPD

COPD is one of the few chronic diseases that have shown an increase in mortality and morbidity during the recent years, and it is estimated that COPD will be the 3rd leading cause of mortality worldwide, and the 5th leading source in terms of disease burden (measured as early mortality and disability-adjusted life years), by 2020 (170). COPD is the most frequent cause of hospitalization due to disease in the respiratory organs (183).

In Norway, the prevalence of COPD is high and include a total of 200 000 persons with all stages (184). This equals 5 - 6 % of the population > 40 years. Each year, about 15 000 persons are admitted to hospital due to exacerbations, and 150 000 patients consult their GP because of COPD-related problems (184).

The mortality of chronic diseases in the lower airways during the period 2006-2014 were quite stable for both men (60-75/100 000 inhabitant) and women (40-50/100000 inhabitant) (185), and is explained by the large fraction of current- and former smokers in the population the last 40-50 years (184). Due to the decrease in prevalence of smoking in both sexes during the last 20 years, these mortality rates are expected to decrease with time (184).

1.5 COPD and VTE

1.5.1 The impact of COPD on VTE

The impact of COPD on VTE has so far been consider to be moderate (186) and mediated by concomitant risk factors such as immobilization, bronchial superinfection, right ventricular failure and venous stasis (187). The prevalence of acute PE (15–30%) in COPD patients is high, and because of the similar clinical presentation in both conditions, the possibility of clinical misinterpretation is high (187-190).

Knowledge on the association between COPD and VTE relies exclusively on results from registry-based studies reporting a two- to five-fold increased risk of VTE in COPD patients (191-196). However, in these studies, information on exposure and outcome was obtained from ICD-codes (and not further validated), and there was limited information on important confounders, such as obesity. Thus, the results from registry-based studies could be hampered by misclassification of exposure or outcomes, or confounding.

1.5.2 Risk of mortality in COPD patients with VTE

Hospitalization for acute COPD exacerbation is associated with 5–10% in-hospital mortality, increasing to >20% during the first year after hospital discharge (197, 198). In COPD patients, a concomitant VTE is associated with prolonged hospital stay and increased 1-year mortality (189). COPD patients often suffer from other comorbid conditions, which are frequently adjudicated as the primary cause of death in non-survivors (192, 199-201). Respiratory failure is considered to be the major cause of death in advanced COPD, but in mild to moderate COPD comorbidities such as cardiac disorders and malignancies are shown to be the leading cause of mortality (202). Currently, limited data exist on the prognostic impact of VTE on mortality in COPD patients recruited from a general population.

1.5.3 The impact of Hypoxemia on VTE

Hypoxia is defined as lower than normal oxygen content and pressure in the cell. The term hypoxemia refers to low oxygen content in the blood. In patients with COPD, alveolar hypoxia and subsequent hypoxemia increased with the severity of the disease (203), and may be present during exercise, rest or sleep. The prevalence of hypoxemia in COPD-patients remains somewhat uncertain, but severe hypoxemia appears to be relatively uncommon in large general COPD populations. A registry-based study of 632 COPD patients from primary care practices reported a prevalence close to 1% (204). In the UPLIFT trial, an RCT of 5993 COPD patients, 2% of the participants were prescribed supplemental oxygen (205). Conversely, more than 80% of patients with advanced emphysema, enrolled in a prospective randomized trial of lung volume reduction surgery (National Emphysema Treatment Trial, n=609), used some form of oxygen therapy during rest, exercise or sleep (206).

It has been suggested that hypoxia can lead to a hypercoagulable state. An experimental study investigating this hypothesis in 20 healthy males, found a 2- to 8-fold increase in markers of coagulation activation when the participants were exposed to an immediate hypoxic, hypobaric environment similar to an airplane cabin (207). Later, equally designed experiments could not confirm these findings (208-210). Long haul air travel has been identified as a trigger for VTE, and the risk increases with increased flight duration (211-213). However, to what extent this increased risk could be explained by concomitant immobility has not been sufficiently investigated. An observational study investigating the separate effects of immobilization and hypoxia in 59 men and women, did not find any activation of the coagulation system, assessed by F1+2, TAT and D-dimer during any of the protocols (214).

Coagulation activation secondary to short hypoxic exposure, has been examined in mountaineers with diverging conclusions (215-218). During a 3 week expedition in the Himalayas, healthy mountaineers, randomized into two groups with different acclimatization protocols (9 vs. 13 days), climbed the Muztagh Ata in China (7549 m). Extended exposure to hypobaric hypoxia induced an activation of coagulation were D-Dimer concentrations, PT and APC-resistance exhibited procoagulant changes. Increased rapidity of ascent (9 vs. 13 days), was associated with ADAMTS 13

activity and Ristocetin Cofactor activity (219). However, none of these changes were related to clinical signs of VTE. Moreover, persons living at 4000-6500 m with prolonged exposure to hypoxia are assumed to have some degree of coagulation activation, and may have increased risk of spontaneous vascular thrombosis. In support of this concept, a higher proportion of hospital admissions for thrombosis-related diseases from high-altitude areas (2.7%) than non-high altitude areas (0.1%) (OR: 30.5) was reported in a population living in Haryana India (220-222).

In a single-blind, placebo controlled study, the effect of hypoxia was examined in 20 clinically stable COPD-patients, randomized to either medical air (21% O_2) or hypoxic air (15% O_2) for 2h. A significant increase in TAT, F1+2 and IL-6 was found (223). The subjects in this study also had a high baseline of TAT and F1+2, interpreted as the pro-coagulant effect of COPD. An acute exacerbation in a COPD patient worsens the hypoxia (224) and increases the inflammatory response (225). Patients may therefore be at particularly increased risk of VTE during a COPD exacerbation. Earlier studies support this assumption by showing that pulmonary embolism frequently occurs in patients with an acute COPD exacerbation (187, 226).

Whether oxygen saturation level is associated with risk of VTE is scarcely studied. Moreover, the combined effects of COPD and hypoxia has not been assessed in previous studies.

1.5.4 The impact of Respiratory Symptoms on VTE

Common COPD symptoms include dyspnea, chronic cough, sputum production, wheezing, and chest tightness. The symptoms are heterogeneous and vary among patients and across stages of disease severity (ref GOLD). Only one previous study have prospectively explored the association between respiratory symptoms (e.g. cough, phlegm, and dyspnea) and VTE. Kubota et al. showed that any respiratory symptoms were associated with increased risk of VTE, regardless of the presence of pathological spirometry results (227). Respiratory symptoms are not considered to constitute a causal factor for VTE, but are rather markers of comorbid conditions associated with VTE risk.

1.6 COPD-related conditions and VTE

COPD is associated with many diseases and conditions that can influence the VTE risk.

A nested case-control study, including 35772 patients showed increased risk for cardiac arrhythmias, myocardial infarction and stroke in patients with COPD (191). Several studies have shown an association between MI and stroke and the risk of incident VTE (132-134, 228). Moreover, chronic heart failure is present in 20% of COPD patients (229), and studies have shown increased risk of VTE in patients with heart failure (230-232).

Cancer is strongly associated with VTE, but the risk varies by cancer site with pancreatic cancer, mesotheliomas and lung-cancer as the top three (108). Cancer is prevalent in COPD patients, and a study reported that the incidence of lung cancer in a cohort of COPD patients was 4-fold higher compared to the general population (233).

In subjects without pulmonary diseases, the frequency of lower respiratory infections are relatively low (234). In COPD patients, lower respiratory tract infections are frequent, and constitute a significant comorbidity linked to the occurrence of exacerbations (235). Acute infections are also associated with increased risk of VTE in both hospitalized and non- hospitalized patients (168, 236), and the risk of VTE is particularly increased in patients with respiratory infections (169).

A study describing obesity in COPD patients reported that 32% of the patients were overweight, while 38% were obese (237). Obesity is associated with 2-3 fold increased risk of VTE (91-93), and the risk increases with increasing BMI (91).

COPD, and particularly severe COPD, is associated with an inactive lifestyle (238, 239), and inactivity has been associated with increased risk of VTE (240, 241). Moreover, during acute exacerbation patients are generally considered to be at moderate risk for the development of VTE because of concomitant risk factors (187) such as immobilization (242, 243).

2. Aims of the thesis

- To investigate the association between stages of COPD and future risk of incident VTE in a population-based cohort.

- To assess the risk of mortality in COPD patients with and without VTE.

- To investigate whether measures of respiratory impairments, such as (i) respiratory symptoms and (ii) oxygen saturation (SpO_2), individually and combined with COPD were associated with increased risk of VTE.

- To investigate whether severity of COPD influenced mortality after a first episode of VTE when physical inactivity was taken into account.

3. Methods

3.1 Study population

The Tromsø study is a single center, population-based, cohort that has been ongoing since 1974. The primary aim of the study was to explore the high mortality and morbidity of cardiovascular disease in the male population of Northern Norway (244). With time, the study have expanded both in number of participants and in specter of diseases, and it is the most comprehensive population study in Norway during the last 40 years. Thus far, seven surveys, all following the same design, have been conducted. In total, more than 45 000 inhabitants of Tromsø have participated in one or more of the surveys. The study is managed by the Department of Community Medicine at the Arctic University of Norway, Tromsø.

The three papers included in this thesis are based on data from the 5th and 6th surveys, where a total of 30115 persons were invited. For Tromsø 5 (conducted in 2001- 02), 76 % of the men and 81% of the women participated, whereas 68 % of the men and 63 % of the women participated in Tromsø 6 (conducted in 2007-08). In both surveys, there was a second more extensive screening visit focusing on specified analysis like bone density, pain sensitivity, carotid ultrasound and spirometry. To these second visits, those who had participated in the second visit of a previous survey and a random sample of other participants were invited (refs). In Tromsø 5, 5939 persons (85% of those invited) participated in the second visit, and the corresponding number for Tromsø 6 was 7307 persons (92 % of those invited) (245).

The participants were followed from enrolment in Tromsø 5 (2001-02) or Tromsø 6 (2007-08) until end of follow-up as specified in the different papers (December 31, 2011 in paper I, and December 31, 2016 in papers II and III, respectively).

3.2 Baseline measurements

Baseline information was collected by physical examination, blood samples and self-administrated questionnaires. Blood pressure was recorded with a semi-automatic device (Dinamap Vital Signs Monitor 1846; Critikon Ink., Tampa, Fl, USA), and three measurements were performed on the right arm after two minutes at rest in a sitting position. The average of the two last readings was used in the analyses. Height and weight were measured in subjects wearing light clothes and no shoes. BMI was calculated as weight in kg divided by height in meters squared (kg/m^2). Non-fasting blood samples were collected from an antecubital vein and analyzed at the Department of Clinical Biochemistry, University Hospital of North Norway. The self-administered questionnaire provided information about education level, physical activity, alcohol consumption and smoking habits (never/former/current, number of cigarettes pr. day and duration in years). Information of co-morbidity and medication was obtained from the questionnaires (244). Cancer diagnoses prior to baseline were obtained from the Cancer Registry of Norway.

3.3 Exposure assessment

3.3.1 Identification of COPD patients

Spirometry was carried out using a SensorMedics Vmax™ Legacy 20® (VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA, USA) in Tromsø 5, and the Vmax Encore 20® (VIASYS Healthcare Respiratory Technologies) in Tromsø 6. The American Lung Association criteria for spirometry testing were followed (179) to assess the presence of COPD and to categorize stages of COPD in our population. A spirometry test was approved as acceptable in subjects who expired for more than 3 seconds. Current drug therapy was not interrupted before the spirometry test, and a reversibility test was not performed (246, 247). Predicted values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC (FEV1%) were calculated according to Langhammer et al. (248). The subjects were allocated into four groups based on lung function according to the Global Initiative of

Chronic Obstructive Lung Disease (GOLD) guidelines (249, 250). Due to few subjects with severe obstruction, participants with COPD stages III and IV (FEV1/FVC ratio <0.7 combined with a FEV1<50% normal) were merged into one category for the analyses.

The use of different spirometers in longitudinal studies may introduce bias. As the change in spirometers caused an increase in FEV1 of 2.5% and FVC of 5.2 % from Tromsø 5 to 6 survey, we adjusted the Tromsø 5 levels to accord with the Tromsø 6 levels (251).

3.3.2 Measurement of oxygen saturation (SpO2)

Pulse oximetry were measured at the second visit of Tromsø 5 and 6. SpO_2 values were measured with a digital handheld pulse oximeter (Onyx II, model 9550, Nonin Medical, Inc., Plymouth, MN, USA). The participants rested at least 15 minutes before the measurement. The highest of the three measurements was recorded. Only values between 70% and 100% were accurate to ±2 digits according to the manufacturer. Values <70% were regarded as invalid (252).

3.3.3 Assessment of respiratory symptoms

Information of respiratory symptoms were obtained from a self-administered questionnaire asking about dyspnea in various situations, daily cough for periods of the year, chronic cough (i.e. cough with continuous duration more than 3 months during the last two years), and productive cough (i.e. phlegm) for periods of the year. Categories of dyspnea were “none”, “dypsnea when walking calmly of flat, or when washing and dressing” and “dyspnea at rest”. Cough was categorized into “none”, “daily cough for periods of the year” and “chronic cough for periods of the year”. Phlegm was categorized as “none” and “productive cough for periods of the year”.

3.4 Outcome assessment

All first lifetime VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University

Hospital of North Norway. It is the only hospital in the region and withholds all relevant diagnostic patient-information concerning radiology, outpatient consultations and hospitalizations.

A VTE event was classified as either DVT or PE. When DVT and PE occurred at the same time, the event was classified as PE. The relevant discharge codes were International Classification of Diseases (ICD) 9th Revision codes 325, 415.1, 451, 452, 453, 671.3, 671.4, 671.9 from 1994 to 1998, and ICD 10th Revision codes I26, I80, I81, I82, I67.6, O22.3, O22.5, O87.1, O87.3 from 1999 to 2011.

Trained personnel from the Department of Radiology systematically reviewed the radiology procedure registry. This was done in order to identify potential cases of objectively confirmed VTE-events that may have been missed caused by coding errors in the hospital discharge diagnosis registry. All relevant diagnostic procedures performed were examined. An additional search through the autopsy diagnoses register was conducted to identify cases diagnosed with VTE that either had caused death or had contributed to death. These were recorded as outcomes when the autopsy record indicated VTE as a cause of death or as a significant condition contributing to death.

Medical records for potentially VTE cases were reviewed by trained personnel, blinded with regard to baseline variables. Events identified by the hospital discharge diagnosis registry or the radiology procedure registry were verified and recorded as a validated outcome when all four of the following criteria were met : (1) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral computed tomography (CT), perfusion-ventilation scan, pulmonary angiography or autopsy), (2) the medical record indicated that a physician had made a diagnosis of DVT or PE, (3) signs and symptoms consistent of DVT or PE were present, and (4) the patient underwent treatment with anticoagulants (warfarin, heparin or similar agents), thrombolytic or vascular surgery unless contraindications were specified in the medial record.

The VTE events were further classified as provoked or unprovoked based on the presence of provoking factors at the same time of diagnosis. An event was defined as provoked in the presence of one of the following: surgery or trauma within the previous 8 weeks, acute medical conditions (acute MI, ischemic stroke or major infectious disease), active cancer, marked immobilization (bed rest for

more than 3 days, wheelchair use or long distance air travel over 5 hours within the last 14 days prior to event). In absence of these factors, the event was classified as unprovoked.

3.5 Statistical analyses

In papers I and II, person-years of follow-up were accrued for each participant from the date of enrollment to the date a VTE was diagnosed, the date the participant died or officially moved from the municipality of Tromsø, or to the end of the study period. We used a time-varying approach, which allowed participants who were re-measured in Tromsø 6 to update their exposure status over time. In paper III, person-years of follow-up were accrued from the date of the first VTE until the date of death or end of the study period.

Statistical analyses were performed with STATA version 13.0 (Stata Corporation, College Station, TX, USA). Cox-proportional hazards regression models were used to estimate hazard ratios (HR) for different outcomes (incident VTE or all-cause mortality) with 95% confidence intervals (CI) according to the different exposures (stages of COPD, oxygen saturation or respiratory symptoms). Age was used as time-scale in all three papers. HRs were estimated in a sex-adjusted models and multivariable-adjusted models taking potential confounders such as BMI, current smoking, cancer and history of cardiovascular diseases into account. In some of the papers we also performed separate analyses for PE and DVT, as well as provoked and unprovoked VTE. Sub-distribution hazard ratios (SHR), taking competing risk of death into account according to the model described by Fine and Gray (253), were estimated in paper I. The proportional hazard assumption was tested using Schoenfeld residuals.

4. Main results

4.1 Paper I

COPD AND RISK OF VENOUS THROMBOEMBOLISM AND MORTALITY IN A GENERAL POPULATION

The association between chronic obstructive pulmonary disease (COPD) and risk of venous thromboembolism (VTE) has been scarcely studied in the general population. We aimed to investigate the association between COPD and risk of VTE and mortality in a population-based cohort. Spirometry was conducted in 8646 males and females, participating in the fifth (2001-02) and sixth (2007-08) surveys of the Tromsø Study. Incident VTE events during follow-up were registered until December 31, 2011. Cox-regression models with COPD stages and confounders as time varying covariates were used. Hazard Ratios (HR) with 95% confidence intervals for VTE and all-cause mortality were calculated. During a median follow-up of 6.2 years, 215 subjects developed VTE. Patients with COPD stage III/IV had a 1.6-fold higher risk of VTE (HR 1.61, 95% CI 0.90-2.93), two-fold higher risk of provoked VTE (HR 2.05, 95% CI 1.02-4.10), and 2.3-fold higher risk of cancer-related VTE (HR 2.28, 95% CI 0.88-5.91) compared to subjects with normal airflow. COPD patients, particularly those with stage III/IV disease and VTE, had a higher mortality compared to COPD patients without VTE (50.2% versus 5.6% per year). Our findings suggest that patients with severe COPD may have increased risk of provoked VTE, suggesting that the association was dependent on the presence of provoking factors of VTE or cancer in COPD patients. Furthermore, VTE was a strong predictor of all-cause mortality among COPD patients.

4.2 Paper II

IMPACT OF RESPIRATORY SYMPTOMS AND OXYGEN SATURATION ON THE RISK OF INCIDENT VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

Chronic obstructive pulmonary disease (COPD) is a moderate risk factor for venous thromboembolism (VTE). However, it remains to determine whether individual respiratory symptoms and lowered oxygen saturation (SpO_2), individually and in combination with COPD, affect the risk of VTE. We wanted to investigate whether measures of respiratory impairments including (i) respiratory symptoms and (ii) oxygen saturation both individually and combined with COPD were associated with an increased risk of VTE. Exposure information (spirometry, SpO_2, and self-reported respiratory symptoms) was collected in 8686 participants from the fifth (2001/02) and sixth (2007/08) surveys of the Tromsø Study. The total number of VTE-events were registered from the date of inclusion to December 31, 2016. Cox-regression models with exposures and confounders as time varying co-variates were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for VTE. During 9.1 years of median follow-up there was 330 participants with incident VTE. Subjects with SpO_2 ≤96% (lowest 20th percentile) had a 1.5-fold higher risk of VTE (adjusted HR 1.48, 95% CI: 1.13-1.93) compared with those with SpO_2 ≥98%. Severe respiratory symptoms (dyspnea, cough and phlegm) were associated with a 1.4 to 2.0-fold higher risk of VTE compared with no such symptoms. COPD, combined with respiratory symptoms or lowered SpO_2, had an additive effect on the VTE risk. We concluded that lowered oxygen saturation and severe respiratory symptoms were associated with increased VTE risk. There was an additive effect on the risk of VTE for the combination of COPD and measures of respiratory impairments. These findings suggest that particular attention with regard to preventive strategies should be considered for COPD patients with severe respiratory symptoms or lowered oxygen saturation.

4.3 Paper III

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RISK OF MORTALITY IN PATIENTS WITH VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

Previous studies have shown increased mortality in VTE patients with chronic obstructive pulmonary disease (COPD). It remains unknown whether this association increases with increasing stages of COPD or is confounded by physical inactivity. The aim of the present study was to investigate if increasing stages of COPD could influence the risk of mortality after a first episode of VTE when physical inactivity was taken into account. Patients with a first lifetime VTE (n=256) during the period 2001-2015 were recruited among individuals who participated and performed spirometry in the fifth and sixth surveys of the Tromsø Study (n=9577), a cohort derived from the general population of Tromsø, Norway. There were 123 deaths among the VTE patients during 2.9 years (range 1 day to 13.9 years) of follow-up (mortality rate 11.9, 95% CI 10.0-14.2 per 100 person-years). The risk of death was 2-fold higher in COPD patients compared to those with normal airflow (HR 2.01, 95% CI 1.30-3.08) after multivariable adjustment. We found that risk of death increased with the severity of COPD. VTE patients with COPD stage III/IV had a 5-fold increased risk of death (HR 5.20, 95% CI 2.65-10.2) compared to those without COPD, and among these patients 50% died within 3.5 months after the incident VTE event. Adjustment for physical inactivity had minor effect on the risk estimates. VTE patients with COPD, and particularly those with severe COPD, had an increased risk of death. The adverse effect of COPD on mortality in VTE patients was not explained by physical inactivity among patients with COPD. Our findings may suggest that particular attention should be drawn to prevention and management of VTE in patients with severe COPD.

5. General discussion

5.1 Methodological considerations

5.1.1 Study Design

All three papers are based on data from the Tromsø study, a prospective population-based cohort study (244). In a cohort study, a predefined population (i.e. a cohort of people) is followed from the date of inclusion in the study until an outcome of interest occurs, or until migration, death or end of the follow-up period. Compared to other designs, cohort studies have several advantages. There is a clear temporal sequence between exposure and outcome, which eliminates the risk of reverse causality. Further, compared to a retrospective study, a cohort is more likely to obtain valid and unbiased information on exposure status, and both absolute and relative risks may be provided (254-256). Our cohort comprises a large number of participants, with participation rates ranging from 66-77 % of the eligible population. This enhances the external validity and generalization of study findings to the background population. A disadvantage of the cohort design is the lack of ability to study rare diseases. A very large study population and long follow-up is required to generate results with adequate statistical power when the incidence of a disease is low (254-256).

5.1.2 Confounding

Confounding is present when a non-causal association between an exposure and an outcome is observed as a result of the influence of a third variable. A confounder is a) causally or non-causally associated with the exposure, b) causally associated with the outcome, and c) not an intermediate variable in the causal pathway between the exposure and the outcome (257). A counfounder may strengthen, weaken or even inverse the direction of the observed association (257). In a randomized controlled trial, randomization will minimize confounding, whereas in observational studies, we seek to reduce confounding through statistical modelling, such as stratification and multivariable adjustment analyses (254). However, it is impossible to rule out confounding completely in cohort

studies, as large within-strata variations, poor assessment of the confounding variable, and the presence of unmeasured or unrecognized confounders may lead to a phenomenon called residual confounding (278).

Many disease exposures and outcomes are related to age. Thus, age is often an important confounder in medical research. Different stages of COPD have been found to be associated with increasing age (258), and there is a steep increase is the incidence of VTE by increasing age (44, 84). Thus, it is likely to assume that an apparent association between COPD stages and VTE risk could be explained by age. In papers I-III, we used the subjects´ age as the time-scale in the Cox-regression model, with the baseline age as entry-time and the age at outcome or censoring event as exit time (259). Thereby, the risk of VTE is compared in subjects with the same age instead of the same follow-up time. Hence, age is taken into account without a need for modelling its effect, with a subsequent more effective adjustment for age (259).

Smoking may potentially be a confounder for the relationship between COPD and VTE. COPD is mainly caused by smoking (260), and nearly 50% of patients with stage IV disease in paper I smoked daily compared to 18% among those without COPD. Smoking has been shown to be a moderate risk factor for provoked VTE (167), indicating that the apparent association between smoking and VTE is probably due to an indirect effect on smoking-related diseases (e.g. cancer and cardiovascular diseases) with great impact on VTE (167). To ensure that smoking did not confound the relationship between COPD and VTE, we adjusted for current smoking in paper I.

As described in the introduction of this thesis, co-morbidities are often present in COPD (CVD, cancer, diabetes), and are often associated with the severity of COPD (178). Many of these co-morbidities, particularly cancer are associated with increased risk of VTE. To account for this potential confounding, we adjusted our analyses for history of CVD and cancer.

5.1.3 Bias

Bias (systematic error) refers to incorrect assessment of the association between an exposure and an effect in the target population that does not equal the true value (261). Bias leads to lack of internal validity. Bias must be distinguished from variability (random error). Variability can be diminished by increasing the study size (i.e. increases the precision), whereas this is not the case with bias.

Bias cannot be undone once your data have been collected, and attempts to avoid or reduce bias are therefore important to consider when planning a study. There are several classifications of bias, but the two most "important" ones are *selection bias* and *information bias* (261).

5.1.3.1 Selection bias

Selection bias is a systematic error that occurs when the enrollment of individuals in a study results in a biased association between the exposure and the outcome. Selection bias is generally not a big problem when measuring relative effects of exposures in cohort studies. This is because both exposed and unexposed individuals are selected to the study before the occurrence of the outcome. However, selection bias can be a problem for assessing absolute risks, particularly if those who attend the cohort are less likely to develop the outcome than those who do not respond to the invitation. To the Tromsø study surveys, participants were recruited by a written invitation and a questionnaire that had to be answered. The attendance rates ranged between 66% and 77 % in the Tromsø 4-6 surveys (245), which is considered high, and strengthens the external validity. However, there was some degree of self-selection, especially in the very young and older age groups, which could result in a non-responder bias in these age groups (261). From former health studies we know that the participants tend to be healthier and have higher education (244). However, as we mainly performed etiological studies with relative effect measures, selection bias was not considered a major problem in our study.

5.1.3.2 Regression dilution bias

All papers included in this thesis investigated modifiable risk factors, that is, risk factors which are prone to change over time. In prospective studies with long follow-up after measurements, it is likely that exposure status and risk factor profiles changes from study entry to the end of the study. Such changes over time may lead to a phenomenon called regression dilution bias, which often results in an underestimation of the true associations and type II errors (262). In this project, spirometry data and information on respiratory symptoms and covariates were collected at inclusion in Tromsø 5 (2001-02) or in Tromsø 6 (2007-08. As COPD is a progressive disease, it is assumed that some COPD patients would progress to more severe stages over time. Likewise, respiratory symptoms are expected to vary over time. To address this challenge, we used time-varying analysis which allowed for update of exposure and covariates in participants who were re-measured in Tromsø 6 (n=2752) in papers I and II.

5.1.3.3 Information bias and misclassification

The internal validity (the extent to which observed findings lead to correct inferences) of a study may be reduced by information bias. Information bias occurs when there is imperfect definition of study variables or flawed data collection procedures that result in misclassification in exposure and/or outcome status for a significant proportion of study participants (263). In all the papers included in this thesis, information on several covariates such as smoking status and physical activity was collected from self-administered questionnaires. This form of collecting data is cost-efficient and valuable in large-scale cohort studies, but is a possible source of misclassification. It is well known that study subjects over-reports behavior consistent with a "healthy" lifestyle and do the opposite with "unhealthy" activity (264). However, some studies have shown that self-reporting gave a higher degree of validity (265, 266).

The diagnosis and stages of COPD were based on airflow measures obtained from spirometry and comparison to a calculated predicted value. To differentiate between COPD (persistent airflow obstruction) and asthma (reversible airflow obstruction), it is recommended to perform a reversibility-test (repeat spirometry 15 min after administration of broncholytica) to assess the reversibility of airflow obstruction (267). The reversibility test was not performed in the Tromsø study. This would potentially result in a higher prevalence of COPD patients, diluted with some patients with asthma in the study population (COPD is much more prevalent than asthma in the population). Before a spirometry test the patient should avoid intake of the regular medicine the same morning (268, 269), as most COPD patients use some degree of medication to improve their expiratory flow. Participants performing spirometry in the Tromsø-study were not instructed to avoid medication before the test. Thereby, some COPD patients may have presented with better airflow values than their actual values. This potential misclassification of COPD patients may have contributed to an underestimation of the true association between COPD and VTE risk.

An important issue in this field is to avoid misclassification of healthy subjects as obstructive. Therefore, subjects were excluded from the analyses when peak expiratory flow (PEF) was below 3 x forced expiratory flow when 75 % of the air had been expired (PEF < (3 x FEF75)). All participants had to do the test three times after a strict instruction to adjust for miss-performances. As previously mentioned, the actual FEV_1 compared to the predicted FEV_1 was used to assess to establish the stage of disease. There are several different formulas for prediction of FEV_1 (179, 270-272). We used the method of Langhammer et al. (248), as this method yields values that are representative for a Norwegian population.

Two different spirometers were used in the Tromsø 5 and 6 surveys. SensorMedics Vmax™ Legacy 20® ; VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA, USA was used in Tromsø 5, and the Vmax Encore 20® ;VIASYS Healthcare Respiratory Technologies was used in Tromsø 6. Use of different spirometers in longitudinal studies may introduce information bias (273). The described

change in spirometers caused an increase in FEV_1 of 2.5% and FVC of 5.2 % between the Tromsø 5 and 6 surveys. Values from Tromsø 5 were therefore adjusted to correspond to the levels of Tromsø 6 (251).

Misclassification arising from measurement errors may be non-differential (unrelated to incidence or prevalence of the outcomes) or differential (probability of misclassification differs according to incidence or prevalence of the outcomes). In cohort studies, exposure variables are usually measured prior to the development of the disease, and misclassification will generally be non-differential as long as the outcome assessment is not influenced by the presence of exposure. In the Tromsø study, the personnel who identified and adjudicated the VTE events were blinded to the baseline measurements.

5.1.4 Competing Risk of Death

A particular selection bias is called "differential loss to follow". Participants who die or withdraws from a study due to various reasons during the study period, may differ from those remaining in the study. This might be a problem in cohort studies if the rate of loss to follow-up is different for exposed and unexposed subjects. Death as a competing risk factor may lead to overestimation of cumulative incidences and hazards ratios. A statistical model developed by Fine and Gray (253) has been developed to overcome this problem. In this model, death is considered a competing event to the outcome, rather than a censoring event. This kind of bias is negligible in exposures with low mortality, but for exposures with high mortality, this has a considerable influence on the cumulative incidence. In our study of 8646 participants, 914 persons died during follow-up. As a consequence of a higher mortality rate in the COPD-group, the risk of VTE could be overestimated. Therefore, we calculated sub-hazard ratios taking competing risk by death into account by using the model described by Fine and Gray (paper I).

5.2 Discussion of main results

5.2.1 COPD and risk of incident VTE.

The first aim of this thesis was to investigate the association between COPD and risk of VTE in a general population. In paper I, we found no linear increase in the risk of VTE across stages of COPD (multivariable p-value for trend=0.2), but there was a threshold effect where patients with COPD stage III/IV had a 1.6-fold higher risk of VTE compared to those with normal (i.e. non-obstructive) airflow. The risk of PE in COPD patients was driven by an increased risk of secondary VTE events (a collective term for provoked and cancer-related VTEs), and no association was found between COPD and unprovoked VTE.

Previous studies on the association between COPD and VTE risk have mainly been derived from registry-based studies. The data sources used in these studies have been characterize by low specificity of COPD diagnosis, limited information on important confounders and lack of objective outcome validation, which may limit the validity of these studies. Results from the UK General Practice Research Database (GPRD) study (191), the US healthcare database study (192), Taiwan's National Health Insurance Database (194) and the Saskatchewan database (193) showed a 2.5-fold, 2.7-fold, 3.5-fold and 5-fold higher risk of PE, respectively. Compared to these registry-based studies, our risk estimates for PE were considerably lower. The registry-based studies did not sub-divide COPD into stages, and therefore, it was not possible for them to investigate the association between degree of airflow obstruction and VTE risk. We, however, found a threshold effect at stage III/IV according to the GOLD criteria. Similar to the UK GPRD study (191), we also found an association, though not statistically significant, between severe COPD and increased risk of DVT.

Data from clinical registries have shown that PE presents more frequently than DVT in patients with COPD (274) or asthma (275). Consistently, we also observed higher risk estimates for PE than for DVT in subjects with severe COPD. A COPD exacerbation can resemble an acute PE with regard to symptoms. Often, these two conditions cannot be distinguished clinically, and this may result in either

an over- or an under-diagnosis of PE. On one hand, a PE in a COPD patient could be interpreted and treated as an acute COPD exacerbation, and thereby lead to an underestimation of the true association. On the other hand, increased awareness of a high prevalence of PE in hospitalized COPD patients (190, 276), may lower the threshold for clinicians to impose diagnostic procedures for detecting PE. The presence of detection bias would lead to an overestimation of the association between COPD and PE, and could potentially explain the higher risk estimates for non-validated PEs observed in the registry-based studies (191-194) compared to our study and clinical registries (274, 275). Detection bias could also partly explain the stronger association observed between COPD and PE rather than between COPD and DVT, as reported in most studies.

The apparent association between COPD and risk of VTE could be affected by confounders. Smoking is the leading cause of COPD (277), and smoking has been associated with VTE risk in some (101, 161), but not all (6, 167), cohort studies. After adjustment for smoking, the impact of COPD on the risk of VTE remained unchanged in our study. Furthermore, smoking is associated with both COPD and cancer, and cancer is a well-established risk factor for VTE. Since the observed association between COPD and VTE could be mediated by a higher rate of cancer in COPD patients, we also performed cause-specific analyses (Of note, the results from these analyses were not presented in the final version of the paper). In these analyses, subjects who developed cancer were censored from the date one year before the cancer diagnosis (to exclude VTEs occurring in both occult and overt cancer). The risk estimates remained essentially similar in the cause-specific analyses indicating that the observed association between COPD and VTE was not solely mediated by cancer development during follow-up. This was further supported by the analyses restricted to (non-cancer) provoked VTE as an outcome, which showed that the risk was still 1.7-fold increased.

Our finding of a relationship between the severity of COPD and risk of VTE could be overestimated due to a poorer prognosis of patients with severe COPD. When competing risk of death was taken into account, the risk estimates were slightly attenuated (from 1.6 to 1.4). We found that the association between COPD and VTE was restricted to secondary VTE (i.e. cancer-related VTEs or

VTEs occurring in the presence of other provoking factors). COPD is associated with immobilization, bronchial superinfection, right ventricular failure and repeated hospitalizations, which can act as precipitating risk factors for VTE in COPD patients. Previous registry-based studies (191-194) have not been able to differentiate between VTE occurring in the absence (unprovoked VTE) or presence (provoked VTE) of such factors. The higher risk of provoked VTE, especially PE, suggests that the risk of VTE in patients with COPD was most likely caused by concomitant provoking factors such as immobilization for acute exacerbation of COPD or infections. In a more recent population-based cohort study (the ARIC study), Kubota et al (227) confirmed that COPD was associated with risk of provoked VTE, but reported that COPD also was associated with unprovoked VTE, and revealed a linear increase in VTE risk with the severity of airflow obstruction. The reason(s) for the differential findings between the studies are unknown, but may include a larger cohort with more VTE events in the ARIC study (greater power), the slightly different age distributions of the populations, and the different definitions of COPD.

5.2.2 The impact of respiratory symptoms and oxygen saturation on the risk of incident VTE

In the second paper, we investigated the impact of individual respiratory symptoms (i.e. dyspnea, cough and phlegm) and oxygen saturation, alone and in combination with COPD, on the VTE risk. We found that subjects with $SpO_2 \leq 96\%$ (lowest 20^{th} percentile) had a 1.5-fold higher risk of VTE than subjects with $SpO_2 \geq 98\%$ (highest 40^{th} percentile). Moreover, severe manifestations of individual respiratory symptoms were associated with a 1.4 to 2.0-fold higher risk of VTE compared to those without such symptoms. COPD combined with severe respiratory symptoms or lowered SpO_2 had an additive effect on the VTE risk.

Several conditions could lead to lowered oxygen saturation, for instance obesity (251, 278), heart failure (279), COPD (203, 251), and cancers affecting the cardio-respiratory system (280). These conditions are all associated with VTE risk (227, 230, 281-283), and may therefore act as confounders

for the association between oxygen saturation and VTE risk. However, after adjustment for obesity, history of CVD and cancer, the risk estimates for VTE by categories of SpO_2 were only marginally affected. Moreover, SpO_2 was associated with increased risk of VTE in analyses restricted to subjects with non-obstructive airflow, further supporting that a skewed distribution of obesity, CVD, COPD and cancer between subjects with high and low oxygen saturation did not explain the apparent association between low oxygen saturation and VTE risk. The underlying mechanism(s) for the relationship between hypoxia or hypoxemia and VTE risk are unknown. However, several lines of evidence support a direct effect. Hypoxia induces secretion of Weibel-Palade bodies in endothelial cells (284) which leads to subsequent expression at the cell surface and release of von Willebrand factor and P-selectin (285, 286). P-selectin and vWF are factors known to be associated with VTE risk (287, 288). Furthermore, hypoxia increases platelet reactivity (289, 290), and has been shown to increase coagulation activation in some (207), but not all, studies (209). In murine models, systemic hypoxia has been shown to accelerate thromboembolic events through induction of the nucleotide binding domain, leucine-rich-containing family, pyrin domain containing 3 (NLRP3) inflammasome complex (291). Severe hypoxia is also reported to increase the incidence and size of thrombi in the inferior vena cava stenosis model in mice (292).

In COPD patients, hypoxemia is associated with a larger mean platelet volume (MPV) (293) and increased platelet reactivity (294). High MPV has been identified as a risk factor for VTE (295), and the protective effect of platelet inhibitors (e.g. aspirin) strongly suggests that platelet reactivity plays an important role in the pathogenesis of VTE (296). Finally, studies have reported a higher coagulation activation in COPD patients than their age- and sex-matched controls (297, 298), and exposure to short-term hypoxia further augments coagulation activation (223).

Using data from the ARIC study, Kubota et al. (227) reported that in subjects with normal spirometry, presence of any respiratory symptom (dyspnea, cough and phlegm) was associated with 1.4-fold higher VTE risk compared to those without respiratory symptoms. In our study, we extended this knowledge by showing that all respiratory symptoms (dyspnea, cough and phlegm) were

individually associated with VTE risk, and that the VTE risk increased with the severity of the dyspnea and cough. Although the mechanism for the association between respiratory symptoms and VTE risk is unknown, it is obvious that these respiratory symptoms merely are markers rather than causal factors for the VTE risk. Respiratory symptoms may be attributed to associated comorbidities, such as immobility, cancer, heart failure and others, which can all contribute to the increased risk of VTE. Still, the risk estimates for VTE by respiratory symptoms remained unchanged after adjustments for BMI, cancer, and CVD in our study. We did not have information on concomitant heart failure, and adjustment for CVD may not have been sufficient to capture such potential confounding. Thus, we cannot rule out the possibility of residual confounding by heart failure or other unmeasured or unrecognized confounders.

In agreement with previous cohort studies (227, 282), COPD was associated with a moderately increased risk of VTE that further increased with the severity of COPD. Moreover, we found that the combination of COPD and lowered oxygen saturation had an additive effect on the VTE risk. Thromboprophylaxis with anticoagulants reduces the risk of VTE in hospitalized medical patients by 45-66% (299, 300). Our findings may suggests that COPD patients with severe respiratory symptoms or lowered oxygen saturation should attract particular attention with regard to prevention strategies for VTE, particularly in high risk situations such as hospitalization for acute exacerbations or infections.

5.2.3 Interrelations between COPD and VTE on mortality

5.2.3.1 Impact of VTE on mortality among COPD patients

A main aim of this thesis was to explore the relationship between COPD and VTE on all-cause mortality (papers I and III). In paper I, we investigated the impact of a VTE event on the risk of mortality among COPD patients. Even though it is well-known that COPD is associated with several comorbid conditions and a poor prognosis, limited knowledge exists on to which extent these diseases influences the risk of mortality in COPD patients. A cohort of 1664 COPD patients revealed that 12 out of the 79

comorbidities registered (from oncology, pulmonology, cardiology, gastroenterology, endocrinology and psychiatry), negatively influenced survival (301). In paper I, we found that occurrence of an incident VTE was associated with higher all-cause mortality in COPD patients, particularly among those with severe COPD. Our findings suggest that a VTE event has prognostic impact on survival in COPD patients, and particularly in patients with stage III/IV COPD, as a VTE was associated with an 11-fold increased risk of mortality in these patients.

5.2.3.2 Impact of COPD on mortality among VTE patients

In paper III, we investigated whether COPD influenced the risk of all-cause mortality in VTE patients. We found that VTE patients with concomitant COPD had a 2-fold higher risk of death compared to VTE patients without COPD, and that the mortality rates and relative risks of mortality in VTE patients increased with the severity of COPD. In patients with PE, those with COPD stage III/IV had a 7.3-fold higher risk of death compared to those without COPD. In DVT patients, the risk of death was 3.8-fold higher in those with COPD stage III/IV. The overall mortality risk was high in VTE patients with COPD stage III/IV, as 50% died within the initial 3.5 months. The higher death rate in VTE patients with severe COPD could not be explained by concomitant cancer, as the results remained essentially unchanged when cancer was adjusted for. Moreover, a higher proportion of physical inactivity did not explain the increased mortality risk in COPD patients.

Our findings of a 2-fold increased mortality risk are coherent with those of previous studies. In a cohort of 399 PE patients, the presence of chronic lung disease (defined by a history of COPD, interstitial lung disease or pulmonary fibrosis on chest radiography) was associated with a 2.2-fold increased risk of death (302). Moreover, in a study of VTE patients derived from Olmstedt County residents in the period 1966-1990 (n=2218), chronic lung disease was associated with a 1.4-fold increased risk of both short- and long-term mortality after multivariable adjustments (48). Among 2488 VTE patients from the Worcester study, 19.5% had a history of COPD, and concomitant COPD was associated with a 2.0-fold increased risk of death within the first month after the VTE diagnosis (303).

In paper III, we additionally showed that the impact of COPD on mortality in VTE patients increased with the severity of COPD. VTE patients with concomitant COPD stage III/IV had a 5.3-fold higher mortality risk than those without COPD, and the mortality rate was particularly high during the first months after VTE diagnosis. Our findings indicated that approximately 60% of VTE patients with concomitant COPD stage III/IV will die during the first year after a VTE diagnosis. This proportion is of similar magnitude as the 1-year mortality in cancer-related VTE, which is reported to be around 60% (27, 44).

Several mechanisms may underlie the observed impact of COPD on VTE-related mortality. Since COPD patients often suffer from other diseases (48, 302, 303), such as arterial cardiovascular diseases and cancer, presence of comorbid conditions may confound the apparent association between COPD and VTE-related mortality. Smoking is associated with both COPD and cancer (277, 304), and active cancer is associated with increased risk of VTE (283) as well as a substantial worsening of the VTE prognosis (27, 44). Moreover, COPD is associated with arterial cardiovascular diseases (305), and arterial cardiovascular diseases are associated with a transient increased risk of VTE (152, 228) and a poor prognosis (202). When active cancer and a history of MI and stroke were included in our adjustment models the risk estimates of VTE-related mortality remained essentially unchanged, suggesting that the impact of COPD on VTE-related mortality was neither explained by concomitant cancer, nor arterial cardiovascular diseases. Moreover, although severe COPD is associated with a sedentary behavior (238, 239, 306) and frequent immobilization during hospitalization (303), the impact of COPD on VTE-related death was not explained by inactivity since adjustment for inactivity had a minor effect on the risk estimates for death in COPD patients. Unfortunately, we did not have information on heart failure, and could therefore not take this into account in our analyses. Patients with COPD and chronic right ventricular dysfunction are susceptible to cardiovascular collapse due to superimposed right ventricular failure following symptomatic and asymptomatic PE (307), and this could partly explain the increased risk of mortality in these patients.

6. Conclusions

- Patients with severe COPD (stage III/IV) had increased risk of secondary VTE, including both provoked and cancer-related VTE, a relationship mainly driven by the risk of PE.
- Patients with COPD and incident VTE had higher mortality rates than COPD-patients without VTE.
- Respiratory impairments, such as lowered oxygen saturation and severe respiratory symptoms (dyspnea, cough and phlegm), were associated with increased VTE risk.
- COPD combined with individual respiratory symptoms (dyspnea, cough and phlegm) or lowered oxygen saturation had an additive effect on the risk of VTE.
- VTE patients with COPD had an increased risk of death compared to VTE patients without COPD, and the risk was particularly high in patients with severe stages of COPD. The increased risk of death in VTE patients with COPD could not be explained by inactivity.

7. References

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Stiftelsen Kristian Gerhard Jebsen

ISBN ...-..-....-...-.

Paper I

Børvik, T., Brækkan, S.K., Enga, K., Schirmer, H., Brodin, E.E., Melbye, H. & Hansen, J.B. (2016).

COPD and risk of venous thromboembolism and mortality in a general population.

European Respiratory Journal, 47, 473-81.

COPD and Risk of Venous Thromboembolism and Mortality in a General Population

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Short title: COPD and risk of VTE and mortality

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Word count body text: 3017

Word count abstract: 198

Total number of tables: 6

Total number of references: 40

"Take home" message

Patients with severe COPD may have increased risk of VTE. VTE is associated with a worse prognosis in COPD patients.

Abstract

Background: The relationship between chronic obstructive pulmonary disease (COPD) and risk of venous thromboembolism (VTE) has been scarcely studied in the general population. We aimed to investigate the association between COPD and risk of VTE and mortality in a population-based cohort.

Methods: Spirometry was conducted in 8646 men and women, participating in the fifth (2001/02) and sixth (2007/08) surveys of the Tromsø Study. Incident VTE-events during follow-up were registered from the date of inclusion to December 31st, 2011. Cox-regression models with COPD stages and confounders as time varying co-variates were used to calculate hazard ratios (HR) with 95% confidence interval (CI) for VTE and all-cause mortality.

Results: During a median follow-up of 6.2 years, 215 subjects developed VTE. Subjects with COPD stage III/IV had a 2-fold higher risk of secondary VTE compared to subjects with normal airflow (HR 2.05, 95% CI: 1.02-4.10). COPD patients, particularly those with stage III/IV, with VTE had a higher mortality rate than COPD patients without VTE (50.2% versus 5.6% per year).

Comments: Our findings suggest that patients with severe COPD may have increased risk of secondary VTE, and that COPD patients with VTE have a higher mortality rate than COPD patients without VTE.

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) has increased dramatically in western populations during the last decades [1, 2] , and has become a major challenge to public health and health care systems due to frequent hospitalizations, severe co-morbidities, and a high mortality rate [2, 3]. Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease with complications such as the post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension (CTEPH) and death [4, 5]. COPD is considered a moderate risk factor of VTE [6]. Moreover, there is a high prevalence of acute PE (15-30%) in COPD patients interpreted as acute exacerbations [7-10]. In COPD patients, it has been assumed that the risk of VTE, and PE in particular, is mediated by concomitant risk factors such as immobilization, bronchial superinfections, right ventricular failure and venous stasis [8].

Knowledge on the impact of COPD on VTE risk in the general population relies exclusively on results from registry-based studies reporting a 2 to 5-fold increased risk of VTE in COPD patients [11-14]. In these studies the exposure (COPD) and outcome (VTE) were defined according to ICD-codes and treatment with COPD medications. Previous studies have reported low validity of COPD diagnoses obtained from administrative databases [15, 16]. Similarly, a validation of VTE diagnoses in the Danish National Patient Registry reported positive predictive values (PPV) for VTE diagnoses from emergency departments and hospitals of 44% and 67-77%, respectively [17]. Thus, it is not known whether risk ratios presented by previous registry-based studies are valid or suffer from a high degree of misclassification (i.e. false positive or false negative events) or confounding due to lack of important clinical information such as provoking factors for VTE.

Hospitalization for acute COPD-exacerbation is associated with 5-10% in-hospital mortality, increasing to more than 20% during the first year after hospital discharge [18, 19]. A

concomitant VTE-event is associated with prolonged hospital stay and higher 1-year mortality [9]. COPD patients frequently suffer from comorbidities of which often are adjudicated as the primary cause of death in non-survivors [12, 20]. Recently, some comorbidities were shown to augment the mortality rate in a cohort of 1664 COPD patients [21]. However, limited data exist on the prognostic impact of VTE on mortality in COPD patients recruited from a general population.

We therefore set out to investigate the association between stages of COPD, according to the GOLD criteria [22], and future risk of secondary (presence of one or more predisposing factors) and unprovoked VTE in a population-based cohort with well-recorded confounder information and validated VTE events. Furthermore, we aimed to assess the risk of mortality in COPD patients with and without VTE.

Methods

Study population

Study participants were recruited from the fifth (2001-02) and sixth (2007-08) surveys of the Tromsø Study [23]. To these surveys, parts of the population aged ≥30 years living in the municipality of Tromsø, Norway, were invited to participate in an extensive screening where spirometry was included. A detailed description of study participation has been published elsewhere [23]. The overall attendance rate was high with 85% (n=5918) of those invited in Tromsø 5, and 74% (n=7306) in Tromsø 6. A total of 9577 unique individuals aged 32-89 years participated in at least one of the surveys, and of these, 3647 participated in both surveys. The regional committee of medical and health research ethics approved the study, and all subjects gave their written consent to participate. Subjects who were not officially registered as inhabitants of the municipality of Tromsø at date of study enrolment (n=12], subjects with VTE before baseline (n=113], and subjects with missing values for spirometry measures (n=806) were excluded. Accordingly, 8646 subjects were included in the study, and were followed from the date of inclusion until the end of follow-up, December 31st, 2011 (Figure 1).

Baseline measurements

Data were collected by physical examination, blood samples and self-administrated questionnaires. Height and weight were measured with subjects wearing light clothes and no shoes, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Baseline information on current smoking, self-reported history of cardiovascular disease (myocardial infarction, stroke or angina) and diabetes was collected from the questionnaire. Non-fasting blood samples were collected from an antecubital vein. Serum was prepared by centrifugation after 1 h respite at room temperature,

and analysed at the Department of Clinical Chemistry, University Hospital of North Norway. Information on cancer before inclusion and during follow-up was obtained from the Norwegian Cancer Registry [24].

Calibration of the spirometer was performed every morning and on the machine demand. The subjects were sitting, using a nose clip, and were instructed to blow as long as possible and at least for 6 seconds. At least three exhalations were required. The American Lung Association criteria for spirometry testing were followed [25]. Current drug therapy was not interrupted before the test. Reversibility test was not performed. Predicted values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC (FEV1%) were calculated according to Langhammer et al. [26]. Spirometry was accepted in subjects who expired for more than 3 seconds. To avoid misclassification of healthy subjects as obstructive, those with FEV1/FVC <0.7 or predicted FEV1 <80% were excluded from the analyses if peak expiratory flow (PEF) was below 3 x forced expiratory flow when 75% of the air had been expired (PEF >3 x FEF75). Spirometry was carried out using a SensorMedics Vmax™ Legacy 20® (VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA, USA) in Tromsø 5, and the Vmax Encore 20® (VIASYS Healthcare Respiratory Technologies) in Tromsø 6. Use of different spirometers in longitudinal studies may introduce bias [27]. The change in spirometers caused an increase in FEV1 of 2.5% and FVC of 5.2 % from Tromsø 5 to 6 survey [28]. Therefore, we adjusted the Tromsø 5 levels to accord with the Tromsø 6 levels.

The subjects were allocated into four groups based on lung function according to the Global Initiative of Chronic Obstructive Lung Disease (GOLD) guidelines [22]. Due to few subjects with severe obstruction, participants with COPD stages III and IV (FEV1/FVC ratio <0.7 combined with a FEV1<50% normal) were merged into one category for the analyses.

Outcome assessment

All incident VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway as previously described [29]. The University Hospital of North Norway is the only hospital in the region, and all diagnostic radiology and hospital care is provided exclusively by this hospital. The medical record for each potential case of VTE was reviewed by trained personnel, and a VTE was considered verified and recorded when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (by compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment, as previously described in detail [29]. VTE cases derived from the autopsy registry were recorded when the death certificate indicated VTE as cause of death or a significant condition associated with death. The VTEs were classified as unprovoked or secondary depending on the presence of provoking factors at the time of diagnosis, and the secondary events were further classified into provoked and cancer-related events. Provoking factors were recent surgery or trauma within the previous 8 weeks, acute medical conditions (acute myocardial infarction, ischemic stroke or major infectious disease), immobilization (bed rest >3 days, wheelchair use or long-distance travel exceeding 4 hours within the last 14 days prior to the event) or other presumable provoking factor specifically described by a physician in the medical record (e.g. intravascular catheter). Cancer-related VTE was defined as VTE events occurring in patients with active cancer (i.e. patients with overt cancer who were under treatment or surveillance for their cancer diagnosis).

Information on date of death was obtained from the National Population Registry of Norway.

Statistical analyses

For each participant, person-years for follow-up were accrued from the date of enrollment to the date a VTE was diagnosed, the date the participant died or officially moved from the municipality of Tromsø, or to the end of the study period (December 31st, 2011). Subjects who died (n=914) or moved from Tromsø (n=318) during follow-up were censored at the date of migration or death. We used a time-varying analysis that allowed participants (n=2752) who were re-measured in Tromsø 6 to change their stage of COPD over time. Thus 8646 individuals contributed with 11398 observational periods. This is graphically illustrated in Figure 1.

Statistical analyses were performed with STATA version 13.0 (Stata corporation, College Station, TX, USA). The significance level was 0.05. Crude incidence rates (IR) with 95% confidence interval (CI) were calculated and expressed as number of events per 1000 person-years. Cox-proportional hazards regression models, with stages of COPD and potential confounders entered as time-varying co-variates were used to estimate hazard ratios (HR) with 95% CI for VTE across stages of COPD. Age was used as time-scale, and the HRs were estimated in sex-adjusted analyses, and in a multivariable model including sex, BMI, current smoking, and history of cardiovascular disease. In addition, IRs and HRs for PE and DVT, as well as provoked and unprovoked VTE, were calculated separately. The proportional hazard assumption was tested using Schoenfeld residuals, and statistical interactions between COPD and sex were tested by including cross-product terms in the proportional hazards model. No statistical interactions between COPD and sex were found.

Hypothetically, death may prevent the observation of a future VTE during the follow-up period, and consequently the cause-specific HRs may overestimate the risk of VTE in COPD patients. Since the overall risk of mortality was expected to be different across stages

of COPD, we also calculated sub-hazard ratios taking competing risk of death into account by using the model described by Fine and Gray [30].

Finally, Cox-regression models were applied to investigate the impact of COPD stages on mortality in patients without and with VTE. In these analyses, both stages of COPD and VTE status were entered as time-varying co-variates.

Results

The distribution of baseline characteristics across stages of COPD is shown in Table 1. The frequency of self-reported symptoms of dyspnoea, daily cough and chest wheezing was higher in stage IV, as were the numbers of current smokers and pack years among both current and former smokers. There were no differences in the distribution of co-morbidities (cancer, CVD and diabetes) between the different stages.

There were 215 validated VTEs during a median of 6.2 years of follow-up. In total, 50.5% presented with a clinically symptomatic PE with or without concurrent DVT, whereas 49.5% were DVTs only (Table 2). Moreover, 37.2% of the events were unprovoked. Cancer was the most frequent provoking factor and 30.9% of the VTE patients had a cancer-related VTE.

The total follow-up time was 57190 person years, and the overall crude IR was 3.76 per 1000 person-years (Table 3). There was no linear increase in the risk of VTE across stages of COPD (multivariable p for trend: 0.2). However, there was a threshold effect, and patients with COPD stage III/IV had a 1.6-fold higher risk of VTE compared to those without COPD (HR 1.61; 95% CI: 0.90-2.93). Moreover, subjects with COPD stage III/IV had a 2-fold higher risk of secondary VTE compared to subjects with normal airflow (HR 2.05, 95% CI: 1.02-4.10), and similar risk estimates were found in subgroup analyses of provoked VTE (HR 1.71; 95% CI: 0.60-4.88) and cancer-related VTE (HR 2.28; 95% CI: 0.88-5.91). The hazard ratio of PE in subjects with COPD stage III/IV versus normal airflow was 1.83 (95% CI: 0.83-4.02) (Table 3).

When competing risk of death was taken into account, the relative risk estimates were attenuated, but still, subjects with COPD stage III/IV had about 40% increased risk of VTE compared to those with normal airflow (multivariable SHR 1.39, 95% CI: 0.76-2.55) (Supplementary table 1).

The mortality rates and hazard ratios of mortality according to stages of COPD and VTE status are shown in Table 4. Overall, COPD patients with VTE had a 5-fold (HR 5.54, 95% CI 4.01-7.66) higher risk of dying than those without VTE. Moreover, within the different stages of COPD both the absolute risks and the relative risks of mortality were higher in VTE patients than in patients without VTE (Table 4 and Figure 2). Patients with COPD stage III/IV and VTE had a mortality rate of 50.2% per year and an 11-fold (10.88, 95% CI: 5.26-22.52) higher risk of death compared to those without VTE (Table 4).

Discussion

We have investigated the impact of COPD on risk of VTE, and the impact on VTE on all-cause mortality in COPD patients, in a cohort recruited from the general population with validated exposures and outcomes. Subjects with severe COPD had a 1.6-fold higher risk of VTE compared to those with normal airflow. The risk of VTE, particularly PE, by COPD was driven by secondary events, and no association was found between COPD and unprovoked VTE events. However, the confidence intervals were wide, and the risk estimates derived from the association between COPD and VTE should therefore be interpreted with caution. Additionally, we found that VTE was a strong predictor of all-cause mortality in COPD patients, particularly among those with severe COPD.

A few registry-based studies have previously investigated the relation between COPD and VTE. In general, low specificity of COPD diagnosis, limited information on important confounders, and lack of objective outcome validation may limit the validity of studies based on administrative registry data only. Our risk estimates for PE were lower than those from the UK General Practice Research Database (GPRD) study [11], the US health care database study [12], the Taiwan's National Health Insurance Database (NHIRD) [14], and the Saskatchewan database [13] which reported a 2.5-fold, 2.7-fold, 3.5-fold and 5-fold higher risk of PE, respectively. These studies treated COPD as a dichotomous variable and were therefore unable to look at the degree of airflow obstruction and risk of VTE, while we found a threshold effect at stage III/IV according to the GOLD-criteria. Similar to the UK GPRD study [11] we found that those with severe COPD had a 1.4-fold higher risk of DVT, though this association was not statistically significant.

Data from clinical registries have shown that PE presents more frequently than DVT in patients with COPD [31] or asthma [32]. Accordingly, we observed higher risk estimates of PE than DVT in subjects with severe COPD. A COPD patient with an exacerbation would

symptomatically resemble a patient with an acute PE, and in many cases the two conditions cannot be clinically distinguished. This may result in either an overdiagnosis or an underdiagnosis of PE. Awareness of a high prevalence of PE in hospitalized COPD patients among clinicians [1, 10], may entail a preponderance to impose diagnostic procedures for detecting this disease. Presence of detection bias would lead to an overestimation of the association and could potentially explain the higher risk estimates for not validated PEs observed in the registry-based studies [11-14] compared to our study and clinical registries [31,32]. Moreover, detection bias could also partly explain the strong association of COPD with PE rather than DVT found in most studies.

Any association between COPD and risk of VTE may be affected by confounders. Smoking is the leading cause of COPD [33] and also associated with risk of VTE in some [34, 35], but not all [36, 37], cohort studies. In our study, the impact of COPD on the risk of VTE remained unchanged after adjustment for smoking. Smoking is associated with both COPD and cancer, and cancer is a strong risk factor for VTE. Thus, the observed association between COPD and VTE could be confounded by a higher rate of cancer in COPD patients during follow-up. Using cause-specific analyses, we showed that the risk of VTE in severe COPD patients was not explained by cancer. Our finding of a relation between the severity of COPD and risk of VTE could be biased by poorer prognosis of patients with severe COPD. When competing risk of death was taken into account, the risk estimates were only slightly attenuated from 1.6 to 1.4.

Immobilization, bronchial superinfections, right ventricular failure, and repeated hospitalizations have been suggested as precipitating risk-factors for VTE in COPD patients. Previous registry-based studies [11-14] have not been able to differentiate between VTE occurring in the absence (unprovoked VTE) or presence (provoked VTE) of such factors. We found a higher risk of provoked VTE which suggests that the risk of VTE in patients with

COPD was most likely caused by concomitant provoking factors such as immobilization for acute exacerbation of COPD or infections.

Even though it is well known that COPD is associated with several comorbidities and poor prognosis, limited knowledge exist on how these diseases contribute to prediction of mortality in COPD patients. Recent results from a cohort of COPD patients with simultaneous registration of comorbidities revealed that some of these diseases predicted mortality in COPD patients [21]. In our study, we found that occurrence of a VTE was associated with higher all-cause mortality in COPD patients, particularly among those with severe COPD. Our findings suggest that a VTE event has prognostic impact in COPD patients.

Strengths of our study include the recruitment of subjects from the general population, long-term follow-up with repeated measurements of exposure and confounders, and thorough identification and validation of outcomes. Measuring airflow by spirometry allowed us to grade an individual's stage of COPD according to GOLD guidelines. Status on potential confounders was assessed each time spirometry was (re-)measured, and we adjusted for these in the time-dependent analyses. The cohort design ensured a clear temporal sequence between exposure and outcome, and that potential exposure misclassification would be non-differential (i.e. not related to the outcome and thereby dilute the observed effect). Some limitations merit consideration. The statistical power was low in some subgroups, resulting in wide confidence intervals. We detected a HR of 1.6 in severe COPD versus normal airflow. However, due to the low prevalence of severe COPD, the statistical power of this analysis was only 20% indicating a high chance of type II error (failure to reject a false null hypothesis). To be able to detect a hazard ratio of 1.6 with 80% power, we would have needed a cohort of around 40 000 individuals. COPD exacerbations are related to hospitalization, immobilization, infections and other conditions that may predispose for VTE. Unfortunately, we did not have

detailed information on hospital-related factors during follow-up for all individuals, and could therefore not investigate the role of these factors with regard to VTE risk in COPD patients. Finally, our spirometry measures were carried out without reversibility-test. Consequently, some subjects with asthma may have been misclassified as having COPD. This potential misclassification would be non-differential, and would most likely lead to an underestimation of the true association due to regression dilution bias.

In conclusion, severe COPD was associated with increased risk of secondary VTE, implying that the association was dependent of the presence of provoking factors of VTE or cancer in COPD patients. Although our results were obtained from a relatively large population cohort, the number of events was low in some subgroups, and the risk estimates for the association between COPD and VTE should therefore be interpreted with caution. Additionally, we found that VTE was a strong predictor of all-cause mortality among COPD patients.

Acknowledgements

K.G. Jebsen TREC is supported by an independent grant from the K.G. Jebsen Foundation. Trond Børvik receives a grant from the Northern Norway Regional Health Authority.

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Figure legends:

Figure 1. Overview of study inclusion. A total of 8646 unique individuals were included in the study. Of these, 2320 individuals participated in Tromsø 5 only, 3574 participated in Tromsø 6 only, and 2752 participated in both surveys, resulting in 11398 observational periods.

Figure 2. Age and sex-adjusted survival curves according to stages of chronic obstructive pulmonary disease (CODP) and venous thromboembolism (VTE) status

Table 1. Distribution of characteristics in 11398 observation periods (generated by 8646 unique individuals) across stages of COPD according to Gold Guidelines. The Tromsø study 2001-2011.

	Normal	**COPD Stage I**	**COPD Stage II**	**COPD Stage III/IV**
Observation periods, %	77.8 (8869)	9.2 (1051)	10.8 (1226)	2.2 (252)
Sex (male)	41.4 (3323)	48.9 (549)	49.7 (722)	57 (156)
Age (years)	63.0 ± 9.5	67.7 ± 9.2	67.8 ± 8.4	69.3 ± 7.6
FEV1 (liters)	2.7 ± 0.7	2.6 ± 0,7	1.9 ± 0.5	1.1 ± 0.3
FVC (liters)	3.6 ± 1.0	3.9 ± 1.0	3.1 ± 0.8	2.3 ± 0.7
FEV1/FVC (%)	76.6 ± 4.0	66.4 ± 3.5	62.6 ± 6.0	49.9 ± 10.1
FEV1 % normal	93.5±14.2	91.3±9.5	67.5±8.3	40.2±8.4
Dyspnea,[§] %	2.8 (146)	3.9 (31)	5.9 (61)	19.5 (38)
Cough daily, %	16.7 (917)	21.6 (183)	31.0 (342)	49.2 (102)
BMI (kg/m^2)	27.3 ± 4.1	25.5 ± 3.7	26.2 ± 4.2	26.1 ± 4.2
Current smoking, %	18.0 (1582)	29.6 (308)	41.7 (501)	47.2 (119)
Former smoking, %	42.7 (3784)	47.7 (499)	42.2 (518)	39.7 (100)
Pack years current smokers	19.7 ± 12.6	21.5 ± 12.7	23.5 ± 14.8	26.0 ± 16.1
Pack years former smokers	12.7 ± 12.6	16.6 ± 15.9	19.5 ± 15.9	27.7 ±18.3
History of Cancer, %	7.7 (616)	10.5 (118)	10.0 (145)	13.9 (38)
History of CVD, %	13.6 (1092)	16.5 (185)	24.4 (354)	28.2 (77)
Diabetes, %	5.3 (307)	3.76 (34)	5.1 (59)	6.2 (14)

Values are mean ± 1 standard deviation, or percentages with absolute numbers in parentheses. COPD stadium III and IV are combined together.
[§]Dyspnea when walking calmly.

Table 2. Characteristics of the venous thromboembolism (VTE) events (n = 215) that occurred during follow-up. The Tromsø study 2001–2011.

	% (n)
Men	47.3 (101)
Deep vein thrombosis	49.5 (106)
Pulmonary embolism	50.5 (109)
Unprovoked events	37.2 (79)
Clinical risk factors :	
Oestrogen[*†]	1.9 (4)
Pregnancy/puerperium[†]	0 (0)
Heredity[‡]	1.9 (4)
Other medical conditions[§]	17.3 (37)
Provoking factors :	
Surgery	16.4 (35)
Trauma	8.4 (18)
Acute medical conditions	17.1 (37)
Cancer	30.9 (68)
Immobility[‖]	18.4 (42)
Other[¶]	6.9 (15)

[*] Current use of oestrogens or oral contraceptives.
[†] Proportion of women.
[‡] VTE in first degree relative aged less than 60 years.
[§] Myocardial infarction, ischemic stroke, heart failure, chronic obstructive pulmonary disease, myeloproliferative disorders, inflammatory bowel disease and chronic infections within the last year.
[‖] Bed rest > 3days last 14 days, confinement to wheelchair, long time travel with car, boat, train or by air >4 hours within last 14 days, or other type of immobilization.
[¶] Other provoking factor specifically described in the medical record (e.g. intravascular catheter).

Table 3 Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for total, unprovoked and secondary venous thromboembolism (VTE) by stages of chronic obstructive pulmonary disease (COPD).

COPD stage	Person-years	VTE	IR (95% CI)*	HR (95% CI)[μ]	HR (95% CI)[§]
ALL VTE					
Normal	41744	137	3.3 (2.8-3.9)	1 (reference)	1 (reference)
Stage I	5912	26	4.4 (3.0-6.3)	0.98 (0.64-1.50)	1.02 (0.66-1.57)
Stage II	8008	40	5.0 (3.7-6.8)	1.09 (0.76-1.56)	1.12 (0.78-1.62)
Stage III/IV	1526	12	7.9 (4.5-13.8)	1.61 (0.90-2.93)	1.60 (0.88-2.92)
p for trend				*0.2*	*0.2*
UNPROVOKED VTE					
Normal	41744	55	1.3 (1.0-1.7)	1 (reference)	1 (reference)
Stages I	5912	6	1.0 (0.5-2.3)	0.55 (0.24-1.29)	0.62 (0.26-1.46)
Stage II	8008	15	1.9 (1.1-3.1)	1.00 (0.56-1.78)	1.07 (0.59-1.95)
Stage III/IV	1526	3	2.0 (0.6-6.1)	0.99 (0.31-3.25)	1.04 (0.32-3.39)
p for trend				*0.8*	*1.0*
SECONDARY VTE					
Normal	41744	82	2.0 (1.6-2.4)	1 (reference)	1 (reference)
Stage I	5912	20	3.4 (2.2-5.2)	1.28 (0.78-2.10)	1.27 (0.76-2.12)
Stage II	8008	25	3.1 (2.1-4.6)	1.16 (0.73-1.82)	1.14 (0.72-1.83)
Stage III/IV	1526	9	5.9 (3.1-11.3)	2.05 (1.02-4.10)	1.97 (0.97-3.99)
p for trend				*0.1*	*0.1*
Provoked					
Normal	41744	39	0.9 (0.7-1.3)	1 (reference)	1 (reference)
Stage I	5912	12	2.0 (1.0-3.4)	1.39 (0.71-2.74)	1.53 (0.76-3.06)
Stage II	8008	14	1.7 (1.0-3.0)	1.27 (0.68-2.35)	1.25 (0.66-2.37)
Stage III/IV	1526	4	2.6 (1.0-7.0)	1.77 (0.63-5.00)	1.71 (0.60-4.88)
p for trend				*0.2*	*0.3*
Cancer-related					
Normal	41744	43	1.0 (0.8-1.4)	1 (reference)	1 (reference)
Stage I	5912	8	1.4 (0.7-2.7)	1.05 (0.49-2.25)	1.04 (0.49-2.25)
Stage II	8008	11	1.4 (0.8-2.5)	1.03 (0.53-2.03)	1.04 (0.52-2.07)
Stage III/IV	1526	5	3.3 (1.4-7.9)	2.33 (0.91-5.95)	2.28 (0.88-5.91)
p for trend				*0.3*	*0.3*
PE					
Normal	41744	68	1.6 (1.3-2.1)	1 (reference)	1 (reference)
Stage I	5912	15	2.5 (1.5-4.2)	1.12 (0.64-1.96)	1.21 (0.68-2.14)
Stage II	8008	19	2.4 (1.5-3.7)	1.01 (0.60-1.69)	1.01 (0.60-1.72)
Stage III/IV	1526	7	4.6 (2.2-9.6)	1.83 (0.83-4.02)	1.80 (0.81-3.99)
p for trend				*0.4*	*0.4*
DVT					
Normal	41744	69	1.7 (1.3-2.1)	1 (reference)	1 (reference)
Stage I	5912	11	1.9 (1.0-3.4)	0.84 (0.44-1.60)	0.82 (0.41-1.61)
Stage II	8008	21	2.6 (1.7-4.0)	1.18 (0.72-1.93)	1.22 (0.73-2.04)
Stage III/IV	1526	5	3.3 (1.4-7.9)	1.38 (0.55-3.45)	1.39 (0.55-3.51)
p for trend				*0.5*	*0.4*

[*] Per 1000 person-years,
[μ] Age was timescale. Adjusted for sex
[§] Adjusted for age, sex, current smoking, body mass index and self-reported cardiovascular diseases (myocardial infarction, angina, stroke).

Table 4. Mortality rates (MR) per 100 person-years and hazard ratios (HR) with 95% confidence intervals (CI) of death according to stages of chronic obstructive pulmonary disease (COPD) and venous thromboembolism (VTE) status

COPD	VTE	Person-years	Deaths	MR (95% CI)	HR (95% CI)*	HR (95% CI)*
Yes	No	15654	431	2.8 (2.5-3.0)	1.00 (reference)	
Yes	Yes	194	41	21.2 (15.6-28.7)	5.54 (4.01-7.66)	
COPD-stage						
I	No	5947	118	2.0 (1.7-2.4)	1.00 (reference)	1.00 (reference)
I	Yes	70	12	17.1 (9.7-30.1)	7.02 (3.83-12.85)	7.45 (4.10-13.5)
II	No	8170	227	2.8 (2.4-3.2)	1.00 (reference)	1.37 (1.09-1.72)
II	Yes	104	19	18.3 (11.7-28.7)	4.18 (2.60-6.73)	5.57 (3.41-9.09)
III/IV	No	1537	86	5.6 (4.5-6.9)	1.00 (reference)	2.54 (1.92-3.36)
III/IV	Yes	20	10	50.2 (27.0-93.3)	10.88 (5.26-22.52)	24.60 (12.73-47.55)

*Age is timescale, adjusted for sex

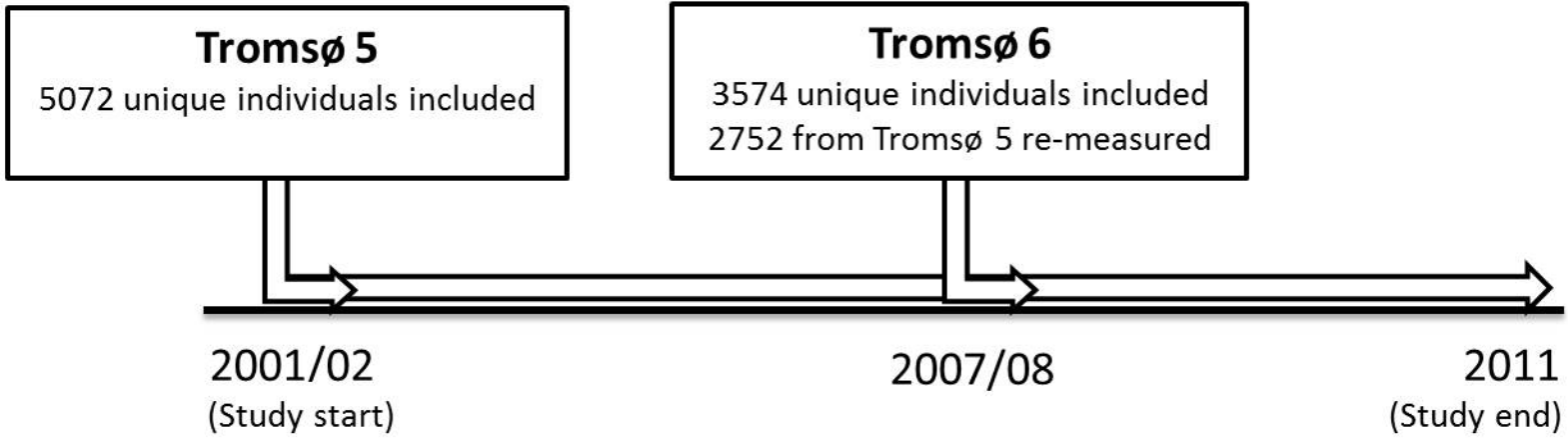
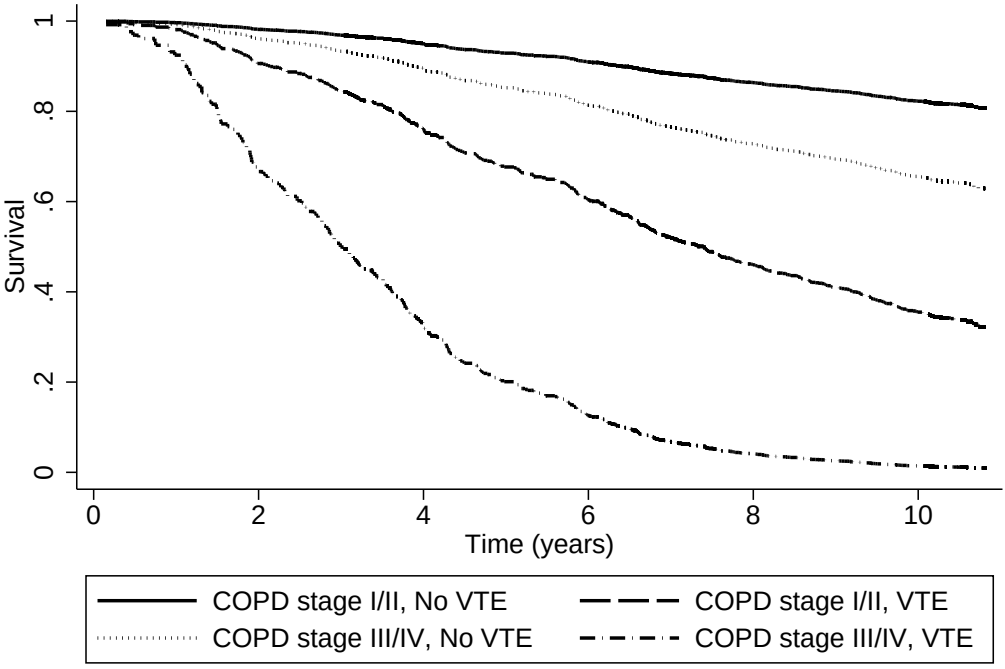

Tromsø 5
5072 unique individuals included
Tromsø 6
3574 unique individuals included
2752 from Tromsø 5 re-measured
2001/02
(Study start)
2007/08
2011
(Study end)

Figure 2


Survival
0
.2
.4
.6
.8
1
0
2
4
6
8
10
Time (years)
COPD stage I/II, No VTE
COPD stage I/II, VTE
COPD stage III/IV, No VTE
COPD stage III/IV, VTE