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Association of Work with Deep Venous Thrombosis in the legs

A literature review of the evidence

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Preface

During the recent decade increasing interest has emerged in elucidating the public health impact of blood clots in the legs also known as deep vein or deep venous thrombosis. In 2008 the United States Surgeon General published a so-called alert paper entitled 'The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis (DVT) and Pulmonary Embolism'. Link to at: (http://www.surgeongeneral.gov/topics/deepvein/calltoaction/call-to-action-on-dvt-2008.pdf).

While the authors recognized that cardiovascular mortality has generally gone down this may not be the case when it comes to mortality caused by DVT. When DVT is formed in the legs, it quite frequently travels to the lungs, where it may cause pulmonary embolism, an immediately life threatening event. The report estimated that at least 100,000 annual deaths among Americans may be related to these diseases. Assuming similar incidence rates in Denmark and a fifty times larger US population, in Denmark this would correspond to approximately 2000 deaths related to DVT and its frequent consequence pulmonary embolism.

Venous thrombus formation is a pathophysiological condition whose aetiology is ascribed to three basic mechanisms encompassed in the classical so-called Virchow's triade: 1) a decreased blood flow rate (stasis), 2) affected vessel wall integrity (vessel damage), and/or 3) increased levels of coagulation factors (hypercoagulability). Many risk factors for DVT have been identified, and are typically classified as either inborn or acquired. Whether related to travel as part of the job or not, prolonged seated immobility is a characteristic of many jobs, and may influence blood

circulation negatively – *ie* due to vein compression may cause stasis of blood flow and may induce intermittent or prolonged damage to vessel walls.

A review of the literature was undertaken following a request from the Danish National Board of Industrial Injuries. The Board wanted a literature study of the epidemiological evidence for an association between work-related exposures and development of deep venous thrombosis in the legs. This report presents the results of this quest.

The work was carried out at the Department of Occupational and Environmental Medicine, Bispebjerg Hospital, from April 1 2010 through October 15 2010. External reviews were carried out by professor Henrik Toft Sørensen and professor Christian Torp-Pedersen. Our point by point response to the reviewer remarks is provided as an addendum to this report. The work was financed by the Danish Working Environment Research Fund.

When summarizing the evidence for causality we used the score system for estimating the degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome developed by the Danish Society of Occupational and Environmental Medicine.

October 2010

The authors

Dansk resumé

Kan arbejde, *dvs* omstændigheder forbundet med menneskers arbejdsforhold, medvirke til eller være en væsentlig årsag til udvikling af blodpropper i benene? Og hvis det er tilfældet, hvad betyder det? I denne gennemgang af den videnskabeligt funderede litteratur fremlægges resultaterne af det epidemiologiske fundament for en konklusion. Hvad kan vi udlede af den viden, vi har på nuværende tidspunkt?

Det har i mange år været et etableret faktum, at især større kirurgiske indgreb og andre større fysiske traumer, f.eks. i forbindelse med trafikuheld, kan medføre komplikationer, hvor den ramte udvikler blodpropper, eksempelvis i bækkenets og underbenets dybtliggende vener, afhængigt af traumets udstrækning. Sådanne veneblodpropper udgør en stor risiko i efterforløbet af ikke mindst større operationer, og denne risiko imødegås som standardprocedure ved at patienterne underkastes antikoagulationsbehandling i umiddelbar tilknytning til operationen, ofte både medikamentel og ved brug af støttestrømper, der skal understøtte blodcirkulationen i benene.

Dybe venetromboser i benene kan udgøre en tikkende bombe, i den forstand at tilstanden enten er symptomløs, eller, når den opstår, at symptomerne ikke umiddelbart kan relateres til blodproppens placering. Klassiske kliniske tegn omfatter smerte, hævelse, og udvidede overfladevener i det ramte ben. Den mest alvorlige, og ikke sjældne, komplikation opstår, når blodproppen løsriver sig og vandrer til lungerne, hvor den kan forårsage en umiddelbart livstruende tilstand, lungemboli. Samtidig forekomst af dyb venetrombose og lungeemboli kendes som venøs tromboembolisme. Denne

tilstand er relativt hyppig, især blandt ældre mennesker, og kan ramme såvel tilsyneladende raske som hospitaliserede mennesker, dvs patienter. Venøs tromboembolisme er den tredjehyppigste kardiovaskulære dødsårsag efter akut myokardieinfarkt og apopleksi og rammer årligt mellem syv og otte tusinde personer i Danmark og kun sjældent personer under 30 år. Blandt mennesker over 85 rammes årligt op imod 500 ud af 100.000 personer. Forekomsten er sammenlignelig med tal fra USA, hvor det anslås, at minimum 350.000 rammes af venøs tromboembolisme, og at 100.000 dør årligt som følge af tilstanden. I Danmark vil det svare til ca. 2000 dødsfald som følge af venøs tromboembolisme.

Hvilke faktorer øger risikoen for dybe venetromboser og dets væsentligste, i betydningen livstruende, ledsagefænomen - lungeemboli? Mange sygdomme og sygdomstilstande bliver beskrevet som multifaktorielle. I tilfældet dybe venetromboser og venøs tromboembolisme er denne beskrivelse i sandhed passende. Ud over den førnævnte stærke sammenhæng til stigende alder bliver risikofaktorer typisk inddelt i tre hovedgrupper: 1) medfødte, *dvs* genetiske faktorer 2) erhvervede faktorer på grund af helbredsforhold, og 3) erhvervede faktorer der hænger sammen med livsstil og adfærd.

Blodpropdannelse i en vene tilskrives tre grundlæggende mekanismer, som allerede blev beskrevet i 1800-tallet af lægen, patologen, antropologen og meget andet Rudolph Virchow: 1) reduceret blodgennemstrømning 2) skade på cellevæggen i venen, og/eller 3) forhøjede niveauer af koagulationsfaktorer. Langvarigt stillesiddende arbejde forekommer i mange erhverv og kan have en negativ indflydelse på blodcirkulationen –

mao på grund af venekompression forårsage en reduceret blodgennemstrømning og inducere forbigående eller længerevarende skade på karvæggen.

Langvarig stillesidden, hvor benene holdes i en fikseret praktisk talt ubevægelig position, eksempelvis i forbindelse med længere rejser, hvad enten denne rejseaktivitet har sammenhæng med flyrejser, bilkørsel eller andre transportformer, er en integreret del af mange menneskers arbejde, og dette vil formentlig fortsætte i en stadigt mere globaliseret verden. Også arbejdsforhold der ikke rummer rejseaktivitet omfatter i dag det at sidde stille i længere perioder, f.eks. ved computerarbejde, og mange mennesker vil være utilbøjelige til at holde tilstrækkelige pauser og få bevæget ben og krop. Hvis en person en gang er blevet ramt af en dyb venetrombose, med eller uden lungeemboli, og har overlevet dette, er risikoen for at blive ramt igen stærkt forøget. Som nævnt er risikoen for dybe venetromboser og venøs tromboembolisme stærkt aldersafhængig med en langt højere risiko blandt de ældre. I lyset også af den stigende andel af ældre i Danmark og andre befolkninger, er det ydermere sandsynligt at fænomenet overordnet vil forekomme endnu hyppigere end i dag. Et forebyggende tiltag kunne være en modifikation af arbejdsforhold, *dv*s arbejdets tilrettelæggelse. Leverer den medicinske epidemiologiske litteratur et videnskabeligt grundlag for en sammenhæng mellem arbejdsforhold, hvad enten disse er relateret til rejseaktivitet eller ej, og risiko for udvikling af dybe venetromboser i benene?

Kun engelsksprogede peer-reviewede arbejder med en klar case definition, der tillige rummede originale data, blev anset relevante ved litteraturgennemgangen. Som udgangspunkt ønskede vi at identificere især arbejder, som leverede et effektestimat for

sammenhængen mellem stillesidden i forbindelse med arbejde generelt eller mellem rejseaktivitet og venøs tromboembolisme. Vi inkluderede case-kontrol studier, prospektive studier, og randomiserede kontrollerede interventionsundersøgelser, men ikke kasuistikker eller case serier.

Langt hovedparten af arbejderne vedrørte rejseaktivitet og især rejser med fly. Kun case-kontrol arbejderne rummede information om langvarig stillesidden i forbindelse med andre former for rejseaktivitet og stillesiddende arbejde uden relation til rejseaktivitet.

Syvogtredive arbejder vedrørte rejseaktivitet og venøs tromboembolisme, heraf var de 11 case-kontrol undersøgelser, 15 prospektive (eller longitudinelle) studier, og 11 randomiserede kontrollerede interventionsundersøgelser. Kun ét arbejde, et case-kontrol studie, havde undersøgt sammenhængen mellem dyb venetrombose og udsættelse for langvarigt stillesiddende arbejde ikke relateret til rejseaktivitet. Alle arbejder er publiceret inden for det seneste årti.

Case-kontrol undersøgelserne viste, at sammenhængen mellem forudgående især langvarig rejseaktivitet før en diagnosticeret venøs tromboembolisme, dvs dyb venetrombose, lungeemboli eller begge, varierede ganske stærkt undersøgelserne imellem, fra en lavere risiko, odds ratio 0,7 til en stærkt øget risiko på 6,2 i en gruppe med øget koagulationstendens; også studiernes deltagerantal varierede stærkt fra omkring 200 op til knap 4000 deltagere.

Som det er blevet observeret i et nyere oversigtsarbejde vedrørende rejseaktivitet og venøs tromboembolisme, var især et træk karakteristisk for undersøgelser der fandt en svag eller negativ sammenhæng, nemlig udvælgelsen af kontrolgruppen. Undersøgelser hvor kontrolgruppen udgjordes af patienter, der var henvist under mistanke for at de havde en dyb venetrombose i benene, men hvor de objektive undersøgelser afviste mistanken/diagnosen, tenderede mod kun at have en svag, om overhovedet nogen, sammenhæng til forudgående rejseaktivitet; ved et sådant undersøgelsesdesign er det, på grund af selve det faktum at kontrollerne var blevet henvist til en klinik for bekræftelse af eller afvisning af dyb venetrombose, langt vanskeligere at sikre sig en klar adskillelse af cases og kontroller, altså syge og ikke syge; kontroller der er udvalgt på denne måde kan være mere tilbøjelige til at besidde forskellige risikofaktorer for dybe venetromboser, og, i og med at dette i sig selv kunne medføre en øget risiko for at de ville kunne udvikle dybe venetromboser som et resultat af langvarig stillesiddende immobilitet, ville de tillige have en øget sandsynlighed for for nylig at have været udsat for rejseaktivitet; derimod var case-kontrol undersøgelser hvor kontrolgruppen ikke bestod af henviste mistænkte trombosepatienter ganske klare i deres resultater. I disse undersøgelser var sammenhængen mellem udsættelse for længerevarende rejseaktivitet forud for diagnosticeret venøs tromboembolisme statistisk klart signifikant og associeret med en odds ratio på næsten 3. Kun et arbejde der havde undersøgt sammenhængen mellem dyb venetrombose og længerevarende stillesiddende arbejde uden relation til rejseaktivitet, blev fundet ved denne litteraturgennemgang. Resultatet af dette case-kontrol studie var i overensstemmelse med ovenstående, idet forfatterne fandt en odds ratio for langvarigt stillesiddende arbejde blandt patienter med dyb venetrombose på mere end en faktor to. Blandt de 11 inkluderede case-kontrol

undersøgelser, fandtes en statistisk sikker, signifikant, sammenhæng til rejseaktivitet i seks undersøgelser, en ikke-signifikant sammenhæng i tre undersøgelser, og en ikke-signifikant lavere risiko i to undersøgelser.

Som diskuteret ovenfor er det et særligt problem ved fortolkningen af case-kontrol undersøgelser om kontrolgruppen er relevant defineret, med andre ord: kan kontrolgruppen anses for at være sammenlignelig med case-gruppen på alle andre punkter end hvad angår den undersøgte risikofaktor? Dette problem er langt mindre ved fortolkningen af resultaterne fra prospektive undersøgelser, som imidlertid kan rumme andre fortolkningsmæssige problemer. Eksempelvis er der utvivlsomt en vis helbredsmæssig selektion især ved lange rejser, fly eller ej, hvor svagelige personer formentlig vil afstå fra at begive sig på en sådan rejse. Vi har med andre ord en "healthy traveller selection", der kunne gøre det vanskeligere at påvise en eventuel sammenhæng mellem langvarig stillesidden og venøs tromboembolisme. For at etablere evidens for en kausal sammenhæng er der imidlertid generelt enighed om at eksponeringen skal forudgå udfaldet– den temporale dimension af de såkaldte Hill guidelines eller kriterier; også påvisning af en dosis-respons sammenhæng anses for at være en stærk, understøttende factor, under forudsætning af at observationerne i øvrigt giver biologisk mening. Alle de prospektive undersøgelser medtaget i denne gennemgang af litteraturen har fokuseret på flyrejser; nogle af disse giver ikke information om den relative risiko ved flyrejser; de giver imidlertid et indtryk af den overordnede risiko. Blandt de prospektive studier stammer de klareste resultater fra undersøgelser af millioner af rejsende, hvor forskerne har inddelt de rejsende i undergrupper baseret på varighed af flyrejsen. Undersøgelsernes resultater har understøttet hinanden og typisk fundet en klar dosis-respons.

Resultaterne fra observationsstudierne, hvad enten disse var af en case-kontrol eller prospektiv natur, pegede på en kausal sammenhæng mellem langvarig stillesiddende immobilitet og udvikling af dyb venetrombose eller lungeemboli; dette gjaldt uanset om den langvarige stillesiddende immobilitet var relateret til langdistance flyrejser, andre former for rejseaktivitet, eller hang sammen med andet arbejde. Selvom interventionsundersøgelserne inkluderede stort set udelukkende ikke-symptomgivende dybe venetromboser, støttede også resultaterne af disse en kausal relation. Undersøgelserne viste konsistent at anvendelse af elastiske støttestrømper reducerede risikoen for udvikling af dybe venetromboser i de undersøgelser der omfattede de længste flyrejser, og ligeledes anvendelsen medicinsk intervention med injektion af lav-molekylær heparin synes at reducere risikoen for udvikling af dybe venetromboser.

Sammenfatning

Selvom de undersøgelser der præsenteres i denne rapport har været ganske heterogene, både hvad angår design og udførelse, peger resultaterne på en to-tre gange øget risiko for dyb venetrombose og dens ledsagefænomen lungeemboli som et resultat af langvarig stillesiddende immobilitet; flertallet af undersøgelserne har fokuseret på langvarig immobilitet i forbindelse med flyvning, men også andre former for transport peger i samme retning. Bedømt på basis af resultaterne fra longitudinal studier af alle passagerer der er ankommet til en international lufthavn inden for en given periode synes den absolutte risiko at være lille; disse undersøgelser vurderede imidlertid typisk kun det mest livstruende udfald af venøs tromboembolisme, nemlig lungeemboli, og desuden skulle lungeembolien være opstået i umiddelbar forbindelse med flyvningen. Den absolutte risiko for venøs tromboembolisme vil dermed være blevet

underestimeret, også når man betænker at risikoen for udvikling af venøs tromboembolisme anses for at være forhøjet i flere uger efter længerevarende stillesiddende immobilitet.

Resultaterne af interventionsstudierne støtter ligeledes en kausal relation. Der var en vis inkonsistens i disse studier, som måske ikke er overraskende da flere af studierne kun havde relativt få deltagere – hvad der øger risikoen for en såkaldt type 2 fejl, men tendensen i disse studier viser en 2-5% risiko for at udvikle dyb venetrombose i forbindelse med langdistanceflyvning, når tilstedeværelse af tromben påvises ved hjælp af en sensitiv metode - ultrasonografi. Selvom den anvendte metode i interventionsstudierne overvejende påviste asymptomatiske tilfælde, understøtter resultaterne, at de patofysiologiske processer, som kan øge risikoen også for en klinisk manifest dyb venetrombose, er hyppigt forekommende i forbindelse med flyvning.

Man anslår at luftfartselskaber har omkring to milliarder passagerer årligt. Hvis vi antager at en fjerdedel af disse er langdistanceflyvninger, vil 500 millioner passagerer blive eksponeret for en minimum 2% risiko for dyb venetrombose, og incidensen af dyb venetrombose vil dermed løbe op i ikke færre end 10 millioner. Hvor mange af disse der rent faktisk vil udvikle sig til en klinisk relevant dyb venetrombose eller lungeemboli er på nuværende tidspunkt uafklaret, men evidensen peger på, at der er en øget risiko især blandt mennesker med andre risikofaktorer for venetrombose, eksempelvis en øget koagulationstendens. Både observationsstudier og interventionsstudier støtter relevansen af forebyggende tiltag. Især resultaterne af studierne med støttestrømper er lovende, idet disse synes på en gang både at være effektive og sikre i brug, *dvs* uden bivirkninger. Burde støttestrømper være en del af standardudstyret for mennesker, der begiver sig ud på langdistance rejser? Måske er det

en overvejelse værd og især for mennesker, der har andre erkendte risikofaktorer for dyb venetrombose.

At sidde eller at flyve?

Kun case-kontrol studierne i denne litteraturgennemgang rummede information om langvarig stillesiddende immobilitet i forbindelse med andet end flyrejser. De fleste af disse studier skelnede imidlertid ikke klart mellem flyrejser og andre former for rejseaktivitet. Stærk støtte til evidensen for at langvarig stillesiddende immobilitet ikke behøver at være relateret til flyrejser kommer fra det største af case-kontrol studierne, som rummede næsten 4000 deltagere, Cannegieter studiet. Blandt 1906 patienter med venøs tromboembolisme og 1906 kontroller, var eksponering for langvarig rejseaktivitet, minimum 4 timer, hyppigere forekommende blandt cases uanset rejseform: Odds ratio (95% sikkerhedsgrænser) for flyrejse var 1,7(1,0-3,1), busrejse, 2,2(0,8-6,3), bilrejse, 2,2(1,3-3,7), og togrejse, 3,5(0,8-16,8). Resultaterne af dette studie var dermed bemærkelsesværdigt lig resultaterne fra West-studiet, der udelukkende undersøgte ikke rejserelateret langvarig siddende immobilitet i forbindelse med arbejdet som risikofaktor for dyb venetrombose.

Konklusion

På basis af den foreliggende dokumentation, der viser stærk overensstemmelse mellem langvarig stillesiddende immobilitet i forbindelse med flyrejser og risiko for udvikling af dyb venetrombose i benene med eller uden lungeemboli, må den samlede epidemiologiske evidens for en årsagssammenhæng anses for stærk og tildeles karakteren +++: Tilstrækkelig evidens for en kausal sammenhæng.

Stillesiddende immobilitet i forbindelse med andre former for transport: bil, tog, bus, finder ligeledes nogen støtte i litteraturen, men da litteraturen er langt mindre omfangsrig tildeles en noget lavere karakter for den epidemiologiske evidens:

+: Begrænset evidens for en kausal sammenhæng.

Langvarig stillesiddende immobilitet i forbindelse med arbejdet og uden relation til transport er som beskrevet kun undersøgt i et enkelt arbejde med en sufficient epidemiologisk metode. Selv om arbejdet viser stor overensstemmelse med stillesiddende immobilitet i forbindelse med rejseaktivitet må den samlede karakter for den epidemiologiske evidens derfor primært på grund af den sparsomme litteratur ligeledes blive: 0: Utilstrækkelig evidens for en kausal sammenhæng.

Perspektiv

Relevante fremtidige studier af erhvervsgrupper

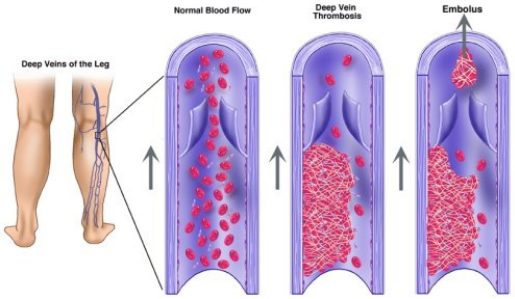
Gennemgangen af litteraturen peger på at en lang række erhverv, hvor langvarigt låst siddende arbejde er jævnligt eller ofte forekommende, kan have en øget risiko for venøs tromboembolisk sygdom. Litteraturen viser veldokumenteret evidens for øget forekomst af dyb venetrombose og fatal lungeemboli blandt flypassagerer på langdistance flyvninger. En lignende risikoøgning kunne tænkes at forekomme blandt eksempelvis langturschauffører, buschauffører og lokomotiv/elektroførere. Både nationalt og internationalt er dette indtil videre uafklaret, selv om der her foreligger et muligt helbredsproblem i en stor erhvervsgruppe – et problem der tillige kan forebygges – eksempelvis ved hyppig kortvarig fysisk aktivitet, eller, hvor dette ikke er muligt, ved anvendelse af støttestrømper.

Introduction

The aim of the present review study was to elucidate if the medical literature supports a likely relationship between work or work conditions and risk of developing deep vein thrombosis in the legs.

Deep vein thrombosis (DVT) or deep venous thrombosis describes a condition where a blood clot is formed in a deep vein.[1, 2] The most commonly affected veins in the body are those of the legs: the veins of the lower leg or calf, the large vein of the thigh, *ie* the femoral vein, and the popliteal vein located corresponding to or pertaining to the posterior surface of the knee.[3, 4] Also the deep veins of the pelvis may be affected, and even occasionally the veins of the arms. In the present review of the evidence for a likely association of working conditions with DVT, focus will be on DVT originating in the deep veins of the legs.

DVT in the legs may be an elusive condition presenting no symptoms or symptoms which cannot immediately be referred to the location of the thrombus. Classical clinical signs include pain, swelling and dilation of surface veins of the affected leg. The most serious, and not rare complication, occurs when the clot dislodges itself, and subsequently travels to the lungs causing a pulmonary embolism (PE) which is an immediately life threathening event. The simultaneous presence of DVT and PE is known as venous thromboembolism (VTE). VTE is a fairly common disorder, in particular in the elderly, which may affect apparently healthy as well as hospitalized people. The following figure illustrates the formation of the clot and embolus.



VTE is a major cause of cardiovascular mortality in Denmark and other predominantly Caucasian populations, surpassed only by acute myocardial infarction and stroke. The annual incidence of VTE is strongly age-dependent. Overall, the incidence is approximately 140 per 100,000 persons, *ie* 1.4/1,000; however, among persons under the age of 18, the incidence is only 1 per 100,000 persons (0.01/1,000), among persons under the age of 30 the incidence is approximately 5 per 100,000 persons, *ie* 0.05/1,000. At the other end of the age-scale, among persons over age 85, the incidence increases to a much higher level, approximately 450 per 100,000 persons corresponding to 4.5/1,000.[5, 6] Generally speaking, the incidence of DVT, and VTE in particular, increases after age 40 and sharply after age 50.

What causes DVT and its major complication pulmonary thromboembolism? Many diseases and disorders can be, and are often, described as multifactorial. In the case of DVT and VTE this is indeed an appropriate characterisation. In addition to increasing age, risk factors can be grouped as 1) inborn, *ie* genetic, factors, 2) acquired factors related to health conditions, and 3) acquired factors related to lifestyle and behaviour, Table 1. Adapted from Geerts et al.[7] This presentation of risk factors is pragmatic, and basically relates to the context of the present review; other overviews of risk factors include even more factors, or, for instance regarding coagulation related factors, more focus has been on e.g. specific mutations of the Factor V Leiden factor and prothrombin20210A. Also atherosclerosis

and congestive heart failure and drugs other than hormones (estrogen) have been linked to an increased risk of VTE.[8]

A community-based population-study from 2002 by *Heit et al*[9] estimated which factors appeared to have the greatest impact on risk of deep vein thrombosis among 625 Minnesota residents with a definite first lifetime deep vein thrombosis or pulmonary embolism diagnosed during the 15-year period 1976 to 1990 and 625 unaffected residents. The study participants were matched according to age and sex. The authors concluded that, factors associated with institutionalization independently account for more than 50% of all cases of venous thromboembolism in the community. Greater emphasis should be placed on prophylaxis for hospitalized medical patients. Other risk factors account for about 25% of all cases of venous thromboembolism, while the remaining 25% of cases are idiopathic.

In agreement with the above study of Heit *et al*, a recent review study states that previous studies have shown that hospitalization for medical illness confers a 6- to 11-fold increased risk for development of VTE. The authors furthermore concluded that with appropriate use of anticoagulant prophylaxis there is a 50 to 60 % reduction in the risk for symptomatic DVT or fatal and non-fatal PE.[10] In a recent paper from the Lancet, Cohen *et al* [11] describe that medical as well as surgical patients have a high risk of VTE during admission with the highest risk among surgical patients. In their concluding section they state, "VTE is a major public health issue: it is an easily preventable disease with a substantial risk of morbidity and mortality in patients hospitalised for acute medical and surgical illnesses." The present report may suggest that prophylaxis may be relevant even in non- hospital/institution settings.

Table 1. Established and suspected risk factors for Deep Vein Thrombosis
Inborn genetic factors Ethnicity Thrombophilia Hereditary venous thromboembolism
Acquired factors related to health conditions Increasing age Cancer Previous DVT Major surgery Trauma Varicose veins Pregnancy and postpartum period Hormone (estrogen) therapy Severe infection Prolonged immobility Obesity
Acquired factors related to lifestyle and behaviour Smoking Prolonged immobility associated with air travel

Among the factors presented in Table 1, in an occupational context, the primary focus pertains to seated immobility, in particular prolonged seated immobility. As described by West *et al*,[12] the history of how prolonged seated immobility became strongly suspected of being a risk factor for DVT, and, by implication, also for VTE, is fascinating, and will be shortly addressed. During the air attacks on London during World War II, known as the London Blitz, the coroner's pathologist observed a six-fold increased risk in fatal pulmonary embolism among people who sat for prolonged periods in air raid shelters. The common use of deck chairs during these air raids was thought to be a likely culprit. This hypothesis was supported by the observation that, when the deck chairs were replaced by bunks, the incidence of fatal PE dropped

dramatically. The observation was reported in the *Lancet* in 1940, shortly after the air raids.[13] It took another 14 years for the next scientific paper to appear to suggest that prolonged sitting may cause thrombosis of the deep leg veins.[14] Homans suggested that seated immobility (cramped sitting) could be a risk factor, and that specifically prolonged air travel, car trips, and even theatre attendance, might thus be causal risk factors for VTE.

These early works by Simpson[13] and Homans[14] raised strong suspicions that work conditions characterized by prolonged seated immobility might constitute a health hazard, in particular among persons with a clustering of other inherited and acquired risk factors for DVT and VTE. Despite this fact, during the next half century, very little attention has been given to sitting at work as a risk factor for DVT and VTE. Whether epidemiological studies have been of a cross-sectional, prospective, or intervention design (randomized controlled prevention trials), the majority have focused on the potentially adverse effects of air travel. Although the results of these studies point to a causal relationship between prolonged sitting, typically for at least 6 hours, and risk of VTE, the literature is not completely consistent; a number of studies have found no association, and in a review of the literature from 2003,[15] the authors suggested that for air travel to be a risk factor for VTE, travel duration apparently had to exceed 10 hours. The physiological mechanism is generally attributed to a combination of prolonged seated immobility and dehydration. As a result of the quite limited space when flying economy class, typically causing a cramped sitting position, the seated immobility circumstances may be considered comparable to the "deck chair syndrome" already described by Simpson. DVT and VTE attributed to prolonged air travel, are in common parlance often referred to as "the economy class syndrome". In a later large

case control study by Cannegieter *et al*,[16] studying travel-related venous thrombosis, the investigators found that any sort of travel was associated with an increased risk. Whether the research team looked at air travel, or travel by car, train or bus, a travel duration of four or more hours was associated with an approximately doubled risk of DVT or VTE for several weeks after the trip.

A number of factors make the potential impact of working conditions on DVT and VTE risk relevant. Prolonged seated immobility associated with travel, whether by air, car, or other means of transportation is an integrated part of many people's work conditions, and likely to become even more so in an increasingly globalized world. Also non-travel related working conditions today often encompass sitting for extended periods of time, *eg* in front of a computer, and many people will be disinclined to take sufficient breaks. If a person has once contracted DVT, with or without PE, and has survived this, risk of recurrence of the condition is highly increased. As mentioned, the risk of DVT and VTE is strongly age dependent, with a much higher risk among older people. Considering also the increased number of old people in Denmark and other populations, and the increase in the age of the working populations in the Western world, the public health impact of the condition is likely to increase. One preventive measure might be through modification of working conditions. Does the medical literature provide a scientific basis for an association between work, whether related to travel or not, and the development of DVT?

Methods

The review of relevant identified literature was based on searches in the PubMed database, and in order to locate other possibly relevant reports pertaining to the issue

under study, Google searches were performed, including a search for the Wikipedia description of deep vein thrombosis which turned out to be quite comprehensive and one of many helpful tools. The papers identified for further scrutiny should be in the English language, and should have been subjected to a peer review process in a medical journal. Only papers with original data were considered relevant for this review. A priori we intended to search for studies, which provided an effect estimate of the association between travel and VTE or between work and VTE. We included case-control studies, cohort studies, and randomized controlled trials. The years searched included the earliest available online year of indexing up to April 2010.

Regarding the association of travel, being it related to air travel or other forms of transport, with risk of either VTE outcome, the following search term was used: travel and ((deep vein thrombosis) or (deep venous thrombosis) or (venous thromboembolism) or (pulmonary embolism)). This search was exploded as: ("travel"[MeSH Terms] OR "travel"[All Fields]) AND (("venous thrombosis"[MeSH Terms] OR ("venous"[All Fields] AND "thrombosis"[All Fields]) OR "venous thrombosis"[All Fields] OR ("deep"[All Fields] AND "vein"[All Fields] AND "thrombosis"[All Fields]) OR "deep vein thrombosis"[All Fields]) OR ("venous thrombosis"[MeSH Terms] OR ("venous"[All Fields] AND "thrombosis"[All Fields]) OR "venous thrombosis"[All Fields] OR ("deep"[All Fields] AND "venous"[All Fields] AND "thrombosis"[All Fields]) OR "deep venous thrombosis"[All Fields]) OR ("venous thromboembolism"[MeSH Terms] OR ("venous"[All Fields] AND "thromboembolism"[All Fields]) OR "venous thromboembolism"[All Fields]) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields])). This search retrieved

441 papers. Following a reading of the titles and abstracts of these papers, only a small number were considered relevant for further scrutiny. To further ascertain the relevance of the search we checked and confirmed that all case-control, prospective, and randomized controlled intervention studies, included in five recent systematic reviews,[17-21] published from 2005 to 2009, were among the studies which could be identified. The total number of studies to be further addressed thus comprised 11 studies classified as case-control studies,[15, 16, 22-30] 15 studies classified as prospective,[27, 31-44] and 11 studies as randomized controlled intervention studies (trials).[32, 45-54]

A corresponding search was performed applying the search term "work" instead of "travel". This search retrieved 979 articles. No previous studies had carried out a systematic review on the association of non-travel related work and deep vein thrombosis or VTE. The total number of studies to be further addressed was very small, and comprised only 1 case-control study, 0 prospective studies, and 0 randomized controlled intervention studies.

Results

Tables 2 to 4 briefly address relevant characteristics in study design and outcomes of prolonged seated immobility during travel with risk of DVT and its related outcomes, VTE and PE (tables 2 and 3), and between seated immobility during non travel related work and risk of DVT (table 4). Following a presentation of these observational studies Table 5 shows the results of intervention trials. (All tables in Appendix 1)

Case-control studies

Table 2 presents the results of case-control studies.

After the report of Homans[14], as previously mentioned, studies on VTE and the likelihood of it being caused by air travel or other types of travel were restricted to case reports on individual cases or case series, studies not regarded relevant for the present review.

Of the 11 case-control studies included, the first case control study to be included consistently in recent reviews on the subject, was that of Ferrari[22] from 1999. In a study of 320 people, equally many cases and controls, they found a significantly increased relative risk, expressed as an odds ratio, for cases to have been exposed to prolonged travel, > 4 hours, within the preceding four weeks of a factor 4. An interesting observation in that particular study was that travel meant not only any form of travel, but that, for more than 70% of those who reported exposure to prolonged travel, this was not related to air travel, but to travel by car or train.

In another European study of almost a 1000 people, equally many cases and controls, Samana[23] et al found a significant more than twofold increased risk of exposure to prolonged travel among cases. Exposure to travel was however quite unspecific in that study, inasmuch as cases and controls only reported whether they had been exposed to long distance travel, not which type of travel they had attended or a more precise depiction of the duration of the travel; differences between the case and the control group were however quite conspicuous with 62 of 494 cases reporting long distance travel as compared with only 31 of 494 people in the control group.

In a study of 788 subjects, 186 cases and 602 controls, Kraaijenhagen et al[24] found no association to recent history of travel exposure; travel exposure included

exposure to any form of travel, *ie* travel by air, boat, car, bus, or train, and the duration of the travel should exceed only three hours.

The 2002 study by Arya[25] included a total of 568 study participants, 185 cases and 383 controls. Information on travel exposure encompassed any form of travel including air travel. Cases had been slightly but not significantly more frequently exposed to > 3 hours of travel within the preceding 4 weeks. In a subanalysis in the same study it was shown that among people with one or more concomitant DVT or VTE risk factors, the odds ratio was statistically significant: 2.7 (1.2-6.4).

The same year, 2002, Hosoi et al[26] published a study including 101 cases and 106 controls. Study participants reported on any form of travel, air, boat, train, car, or bus; relevant exposure was defined as at least 3 hours of travel within the preceding two weeks. Differences in reported prolonged travel were small and not significant between the two groups with 15 of 101 cases claiming relevant travel exposure compared to 13 of 106 among controls.

The following year, 2003, a much larger study was published by ten Wolde et al[15] including 477 cases and 1470 controls. Again it was possible for cases and controls to report on any form of travel which could mean exposure to prolonged sitting; in this study relevant exposure was defined as travel of at least 3 hours within the preceding two weeks. Despite the large number of study participants the study was negative in the sense that travel history was not more prevalent among cases than among controls. Among the cases, 32 of 477 reported to have been relevantly exposed to prolonged travel, among the controls corresponding figures were 105 of 1470; the odds ratio actually indicated a slightly lower exposure among the cases: 0.9 (0.6-1.4).

All of the above studies were European, and that is the case also for the next study by Martinelli et al[30] published in 2003. That study included 420 people, equally many cases and controls. The study addressed only air travel, and travel duration should exceed 4 hours and the travel should have taken place within the four weeks preceding the event. Using the odds ratio as an expression of relative risk those exposed to extended air travel as defined above had a significantly more than doubled risk of VTE, odds ratio 2.1 (1.1-4.0).

The next study by Cannegieter et al[16] is from 2006 and, by far, the largest of the case-control studies presented in this review. Number of cases totalled 1906 with an equally large group of controls, also 1906. The outcome was either of the elements of VTE, *ie* DVT or PE. Reporting on prolonged exposure to travel could relate to any form of travel, and should have exceeded 4 hours within the preceding 8 weeks. Among the cases 233 had been exposed to prolonged travel within the defined time period; the corresponding number of people reporting prolonged travel among controls were 182; this difference corresponded to a highly significant odds ratio of 2.1 (1.5-3.0).

The same year a New Zealand study by Parkin et al[27] was published using the hardest endpoint of VTE, fatal PE, as outcome. Exposure was restricted to air travel, and should exceed 3 hours and have occurred within the preceding 4 weeks. Cases totalled 89 subjects; in this group 5 were identified as having been exposed to relevant air travel within 4 weeks prior to the event; among 334 controls randomly selected from the electoral roll; in this group 9 had been exposed to relevant air travel; the odds ratio was 1.8 (0.5-7.1).

Within the study by Cannegieter *et al*,[16] a substudy was performed stratifying participants into low and high risk groups based on measurements of a

number of coagulation factors. Kuipers *et al*[28] showed in 2009 that compared to the odds ratio of 2.1 (1.5-3.0) presented above from the Cannegieter study, a particularly high risk was found among subjects with high levels of factor VIII, defined as belonging to the highest quintile in the study group, odds ratio 6.2 (3.6-10.5), a result at the same time supporting the overall study result, but also refining and qualifying this – meaning that, if prolonged seated immobility would increase the risk of DVT, this should theoretically be even more obvious among *a priori* vulnerable individuals.

Finally, in 2009, in another study from Europe, Schreijer[29] used a subtle approach. Based on the inherent logic that people who occupied window seats during flights would be less likely to get up and stretch their legs, the study team compared the risk of developing DVT for those with windows seats and those without. Among cases, n = 80, 33 had occupied a window seat, among controls, n = 108, the corresponding number was only 28. This difference was clearly significant and conferred an odds ratio of 2.2 (1.1-4.4).

Prospective studies (observational follow-up studies)

Table 3 presents the results of 15 studies classified as prospective. These studies show either the overall incidence of DVT or other VTE outcomes associated with travel or the incidence associated with high or low travel duration using dichotomized exposure variables, or the incidence associated with increasing travel duration using ordinal exposure variables. All studies focused on air travel and incidence rates of VTE varied considerably between studies.

In the 2001 study of a very large group of arriving air passengers, > 135 million, Lapostolle[31] subdivided the passengers into five groups according to flight

duration and used the hard VTE endpoint, *ie* PE. The absolute risk was low, however, and clearly related to flight duration. Of those flying less than 3 hours, none suffered an event despite the fact that this group comprised almost 90 million people, and among those with a flight time of 3 to 6 hours only one PE event was observed among 9 million passengers. In contrast, among the group with the longest flight duration, at least 12 hours, comprising 2.7 million, 13 people suffered a PE event corresponding to almost 5 per million.

The 2001 study by Belcaro[32] used a different approach selecting among a group of volunteers who had planned a long distance flight those who were without established risk factors for VTE and a group who had at least one risk factor; the outcome investigated was DVT. Among 355 passengers without any risk factors no events were found, among those with risk factor(s), n=389, 11 cases were found. This difference was highly significant, however, selection criteria in the study were somewhat unclear, and it was also unclear whether cases included symptomatic DVT.

In a small study of 83 participants who had arrived to join a conference in Hawaii, and to do so, had on average attended a flight lasting 9 hours, DVT during 43 weeks upon arrival was diagnosed using ultrasonography in 1 person. This study by Arfvidsson[33], in addition to being small in sample size, did also have a very low participation rate of only 30%.

A more conventional prospective study design was used by Schwarz[34] who compared the risk of DVT in a group of travellers with an equally large group of non travellers. Both groups volunteered to be included in the study, and, with respect to the travel group were examined by ultrasonography within 48 hours after return flight.

Both groups were relatively small, n = 160, and no DVT events were diagnosed in either group.

Again in 2002 a study including all arriving passengers at an international airport was performed, this time by Kline.[35] More than 1 million passengers were included to examine the incidence of PE. No cases were identified.

A 2003 study by Schwarz[36] included 964 people, volunteers planning a long distance flight. The flight duration was minimum 8 hours; 7 people developed DVT – none of these were symptomatic, but were diagnosed following objective tests including ultrasonography.

The study from 2003 by Perez-Rodriguez[37] used basically the same approach as the 2001 study by Lapostolle, except that only passengers from international flights were included. The more than 40 million passengers included were divided into three strata according to flight duration. Again the overall incidence of the hard endpoint PE was low, but clearly related to travel duration. The total number of events was 16; fifteen of these belonged to the group with the longest flight duration, > 8 hours, although this group only corresponded to less than a fourth of all arriving passengers.

The study by Hughes[38] from 2003 used a particular approach, in that, for participants to be included in the study they should have attended a minimum of two flights within a specified time period of six weeks. Study participants had been examined with objective tests prior to the study period, and were subsequently divided into two groups: those who had an accumulated travel time of less than or more than 24 hours. The outcome examined was DVT objectively diagnosed within two weeks after the flight. Cases were mainly asymptomatic. Only 123 study participants had travelled

less than 24 hours; none had developed DVT. Among 752 participants with a travel history exceeding 24 hours within the preceding 6 weeks, 9 developed DVT, a non-significant difference.

Also Kelman[39] examined records from passengers arriving from international flights. The outcomes studied were DVT or PE and covered a long period, 1981-1999, and almost 10 million passengers. The incidence per million was quite high compared to other studies, between 26 and 27. Unfortunately a more precise description of travel duration was not reported or assessed, and was described only as international.

In 2003 Jacobson[40] included 899 volunteers who had planned a long distance flight from London to Johannesburg; the flight duration exceeded 8 hours and was on average 11 hours. Following the flight 434 subjects, 48%, were examined using objective tests including ultrasonography when relevant; the outcome studied was DVT, the incidence was 0 (no events).

Also in 2003 Hertzberg[41] applied the study design used several times before, in that all passengers arriving within a given time period at an international airport, in casu Sydney, were included in the examination. Among a total of 6,580,000 arriving passengers, 2.6 per million corresponding to 17 people, came up with a manifest PE event, which the authors described as severe PE. The flight duration exceeded 9 hours.

In 2006, in a study by Gajic[42], the authors included a particular group for study, namely subjects who were to undergo elective surgery. The authors divided the study population into two groups, those having recently been on an air flight of at least 4 hours and non-travellers. The two groups were been exposed to the same spectrum of elective surgery. The outcome studied was DVT occurring with a 4-week period

following surgery. The group of travellers comprised 223 people, the group of non-travelling controls amounted to 8,637 people. Among travellers DVT was diagnosed in 11 subjects, 4.9%, among the much larger control group DVT was diagnosed in 13 subjects, corresponding to 0.2%.

The study by Parkin[27] from the same year included all passengers, this time all passengers arriving at New Zealand. The total number of subjects was close to 70 million. Flight duration should exceed 3 hours and again, as in similar studies, the endpoint included was severe PE; in the Parkin study fatal PE. The incidence was approximately 0.5 per million - whether the groups studied were New Zealand residents or visitors to the country. A perhaps serious limitation, considering the established strong association between age and various outcomes of VTE, was that the study was limited to the age range 15 to 59.

The 2007 study by Kuipers[43] again basically using a more conventional prospective design compared risk among travellers with risk among non-travellers. However, instead of subdivision into strata of flight duration, that study used a form of cumulative exposure, namely person years at risk. Among travellers symptomatic venous thrombosis was identified in 3.2 per 1000 person years, compared to only 1 per 1000 person years among non travellers.

The recent study by Lapostolle[44], 2009, included all passengers who had arrived at the Charles-de-Gaulle airport during a 13-year period, close to 300 million people. The study focused on two issues related to travel related incidence of PE: gender differences and a proxy for flight duration, *ie* flights below or above 10,000 km. Overall the incidence was low and comparable to previous studies of a similar design, 0.6 per million among females, and 0.2 per million among males; thus the incidence

was three times higher among women. The incidence rates were much higher among those having attended long flights, > 10,000 km, 7.2 per million among women and 2.4 per million among men, that is also in this group the incidence rate was three times higher in women.

Association of work or working conditions not related to travel with DVT

As mentioned only one methodologically sufficient study could be identified relating non-travel related prolonged seated immobility with DVT. In a case-control study by West[12], the authors included 97 cases, *ie* subjects with a discharge diagnosis of either DVT or PE, and subjects from the same coronary clinic with no such diagnoses. The period consisting of a prolonged period of seated immobility should have occurred within 4 weeks prior to the event, and the duration of prolonged seated immobility was based on three descriptions as shown in the table. Exposure to prolonged seated immobility was defined as reporting positively to at least one of these categories. Although the sample size of the study was quite limited, cases had significantly more often been exposed to prolonged seated immobility compared to controls; the odds ratio (95% CI) was 2.2 (1.0-5.0).

The intervention studies

Table 5 shows the results of 11 randomized controlled intervention studies or trials. All studies had as main outcome development of DVT, and all occurrences were objectively diagnosed by use of ultrasonography. Furthermore all of the studies investigated the effectiveness of intervention related to long duration air flights. The first paper by Scurr[45] was published in the *Lancet* in 2001 and included 100 subjects in the intervention group and 100 in the control group. The intervention was use of

compression stockings put on before the start of travel, and the average flight duration was 16.5 hours accumulated over a period of a few weeks. In the control group, 12 people had developed DVT which could be diagnosed by ultrasonography, in the intervention group 0 (none) had DVT by ultrasonography, a highly significant difference.

The following 10 studies presented in the table were performed by research teams which included Belcaro or Cesarone or both. The study of Belcaro[32] from 2001 was comparable in its approach to the above study by Scurr. The study group was however much larger with 411 subjects in the intervention group and 422 in the control group. The intervention group used graduated compression stockings applied long before the flight, 6 to 10 hours. Differences between the intervention and the control group in the development of DVT were conspicuous with only 1 (one) DVT case in the intervention group as compared with 19 cases in the almost equally large control group. This difference was obviously highly significant.

Also the next study by Belcaro[46] from 2002 supported a strong preventive effect of compression stockings. The group studied comprised 629 subjects, 315 in the intervention and 314 in the control group. The compression stockings were applied closer to take off than in the study from 2001, 2 to 3 hours prior to the flight. Of 315 intervention subjects, 0 (none) developed DVT, of the 314 in the control group, 7 developed DVT. The difference was clearly statistically significant, and the result in agreement with the findings of the 2001 study.

Also in 2002, Cesarone[47] first-authored an intervention study using medical intervention. One intervention group received a relatively low dose of acetyl salicylic acid (ASA), 400 mg daily, for three days prior to the flight, another received a

low molecular weight heparin product, Enoxaparin, a drug used in the prevention or treatment of DVT and PE, injected approximately two and a half hours before the flight; the control group received neither. Following the flight DVT was diagnosed by ultrasonography in 3 of 84 subjects who had taken ASA, a similar incidence was observed among controls with 4 DVT cases diagnosed in a group of 82; only the heparin group differed from the two other groups in that 0 (none) of 82 developed DVT; compared with controls this difference was not statistically significant using a 2-sided Fisher exact test, $p = 0.12$.

In a 2003 study Belcaro[48] included only passengers with varicose veins. One group, the intervention group, was given Venoruton, an anti-oedema drug. No differences were observed between the intervention and the control group. No DVT cases were found among 78 allocated to intervention, and no cases among 73 controls.

In 2003, Belcaro[49] repeated the compression stockings design, this time using a somewhat lower pressure to the lower leg and calf. Again those in the compression stockings group were less likely to develop DVT, with 1 (one) case in 103 in the intervention group and 6 DVT cases in 102 controls. Using a 2-sided Fisher exact test this difference corresponded to $p = 0.06$.

Another four studies from 2003 had Cesarone as first author. Two of these used compression stockings as intervention strategy,[50, 52] and one study investigated the possibly protective effect of Venoruton.[51] Few DVT cases were observed in these studies, and the results were basically negative. Also from 2003 was the study using Flite-tabs, an extract from the French maritime pine assumed to have anti-coagulation properties, as a means of intervention; the control group received placebo capsules. The study included 94 in the intervention group and 92 in the control group. There were no

DVT cases in the intervention group but 5 DVT cases in the control group, a statistically significant difference.

Finally, in a study by Belcaro[54] from 2004, 101 subjects received Pycnogenol, 97 subjects acted as controls. One DVT case was found in the control group, none in the intervention group, a non significant difference.

Discussion

Characteristics of positive and negative observational and intervention studies

Ad case-control studies

As shown in table 2 an association between history of travel prior to the development of VTE, DVT or PE or both, varied quite strongly between the studies ranging from a non significantly lower risk, OR = 0.7 to a highly significantly increased risk of 6.2; also the sample size of studies varied substantially from about two hundred to about 4,000 study participants. Of the 11 studies included, a significant association to travel history was found in six studies,[16, 22, 23, 28-30] a non significant association in three studies,[25-27] and a non significant lower risk in two studies.[15, 24] As reported in a previous review, one study feature in particular characterized studies finding weak or negative associations between VTE and travel history, namely the selection of the control group. Studies in which controls were patients referred under suspicion of lower extremity deep vein thrombosis, but had negative objective test results, tended to be only weakly, if at all, associated with long duration travel; in such studies, due to the very fact that controls had been referred to a clinic for confirmation or rejection of DVT, a clear distinction between cases and controls is much more difficult to make; controls selected in this way may be more likely to cluster various risk factors for DVT, and, since this would per se

increase their risk of developing DVT as the result of prolonged seated immobility, they would even have an increased probability of having been recently exposed to travel; in contrast, in studies using so-called non-referred controls, the association of VTE with travel exposure was clearly significant and associated with an odds ratio of almost a factor 3. The result of the only eligible non-travel related study of work and DVT by West *et al*, is in agreement with the above result, showing a more than two-fold increased risk of developing DVT among subjects with a recent history of prolonged seated immobility associated with the work situation.

Ad prospective studies

Generally speaking, clinically manifest VTE associated with travel, whether related to air or land based travel, is quite rare, and to obtain a large number of cases a case-control design is a methodologically sound approach. However, as discussed, a particular problem when interpreting the results of case-control studies, is how to deal with the control group, in other words is the control group relevant and different from the case group only with respect to the risk factor under study? That problem is much less likely to interfere with inferences drawn from prospective studies. In establishing evidence for a causal relationship there is general consensus that the exposure must precede the outcome – the temporality dimension of the so-called Hill guidelines or criteria;[55] also the demonstration of a dose-response relationship is considered a strong supporting factor provided the observations make biological sense. Some of the prospective studies, all of which have focused on air travel, give no clues about relative risk associated with either long or short travel duration. They do however give an idea about the overall risk. Among the prospective studies, the clearest results stem from studies including millions of travellers, where the study teams have subdivided

travellers into groups based on flight duration. The results have been mutually supportive with Lapostolle[31] finding a clear dose-response; also, of 56 cases of the life-threatening condition pulmonary embolism, 55 occurred in passengers attending flights of at least 6 hours, and only one case among those with a shorter flight duration. A corresponding pattern was found by Perez-Rodrigues showing a clear dose-response for PE, and no cases in a very large group of 28 million flying less than 6 hours. Two of the studies compared travellers to non travellers. Gajic found that among subjects exposed to surgery those shortly after attending an air flight had a much higher risk of developing DVT than those staying home; a similar result was found by Kuipers in a study which had no a priori selection criteria other than being exposed to air travel or not.

The intervention studies

The results of the observational studies, whether of a case-control or prospective nature, pointed to a causal relationship between prolonged seated immobility and development of DVT or PE, whether related to long distance air travel, other forms of travel, or prolonged seated immobility associated with non-travel related work. Despite using mainly asymptomatic DVT outcomes, the results of the intervention trials supported a genuine relationship. Use of graduated compression stockings was consistently associated with a reduced risk of DVT in the studies including the longest flight durations, and also the use of medical intervention by injection of a low molecular weight heparin drug seemed to reduce the risk of developing DVT.

Although studies have been quite heterogenous in their design and execution, the results of observational studies point to a two- to threefold increased risk of DVT and its

frequent concomitant outcome PE associated with prolonged seated immobility; the majority of the studies have focused on prolonged immobility associated with flying, but also other means of transportation point in the same direction. Judged on the basis of the results from longitudinal studies of all passengers arriving at international airports the absolute risk appears to be quite small; these studies did however typically assess only the hardest (and rarest) outcome of VTE, *ie* PE, and furthermore these events should have occurred in immediate connection to the flight. The risk of VTE in these studies will thus have underestimated the absolute risk also considering that it is well established that the risk following prolonged seated immobility seems to be increased for at least several weeks.

Also the results of the intervention studies support a causal relationship. Although some inconsistencies were found in these studies, perhaps not surprising considering the relatively low sample size in some of these studies - which would increase the risk of a type 2 error, the tendency of the studies suggest a 2-5 % risk of developing DVT during a long distance flight when assessed by an objective sensitive method. Although the method used in the intervention studies mainly identified asymptomatic cases, they show that pathophysiological processes which may increase the risk also of clinically manifest DVT are quite frequent phenomena related to flying.

It is estimated that air companies have about 2 billion passengers per year. Assuming that one fourth of these are long distance flights, 500 million passengers would be exposed to a 2% risk of DVT, and the incidence of DVT would amount to no less than 10 million. How many of these develop clinically relevant DVT or PE is uncertain at the present time, but the evidence points to an increased risk in particular among individuals who cluster other risk factors, *eg* an increased clotting tendency.

Observational as well as intervention studies support the relevance of preventive measures. In particular the results of the compression stockings studies are promising, in that these appear to be at the same time very efficient and safe to use. Should compression stockings be standard equipment for people going on long distance air flights or people exposed to long-term (cramped) sitting during their work? Perhaps this would be relevant and in particular when other risk factors for DVT are recognized.

Sitting or flying?

As shown in the tables, only the case-control studies included in this literature study had information about prolonged seated immobility related to travel other than air travel. Most of these studies did however not clearly distinguish between air travel and other forms of travel. Strong support that prolonged seated immobility did not have to be air related comes from the largest of the case-control studies including almost 4000 participants, the Cannegieter study. Among 1906 VTE cases and 1906 controls, exposure to prolonged travel, for a minimum 4 hours, was more prevalent among cases irrespective of travel type: Odds ratio (95%CI) for air travel was 1.7(1.0-3.1), travel by bus, 2.2(0.8-6.3), travel by car, 2.2(1.3-3.7), and travel by train, 3.5(0.8-16.8). The results of that study were thus remarkably similar to the results of the West study examining only non travel related prolonged sitting as a risk factor for DVT.

Broader occupational implications

This review of the literature suggests that prolonged seated immobility may be a genuine problem also in the work environment. Many forms of work encompass prolonged seated immobility in a travel situation, *eg* the work of long-haul truck drivers and engine drivers, and studies on the risk of developing DVT as a result of their working conditions for these groups, do not exist.

Conclusion

The principles for categorisation by degree of evidence of causality are described in detail in Appendix 2.

On the basis of the presently available documentation, the overall epidemiological evidence for a causal relationship between prolonged seated immobility in connection with air travel and risk of developing DVT with or without PE is strong and must be given the Grade +++: Sufficient evidence of a causal association.

Prolonged seated immobility as a risk factor for DVT in connection with other means of transportation, car, train, bus, is also to some extent supported by the literature, but, considering a much less comprehensive literature, the epidemiological evidence for a causal relationship must be rated somewhat lower and given the grade +: Limited evidence of a causal association.

Prolonged seated immobility in connection to people's work and without relation to transport has been examined only in one study using an epidemiologically sufficient method. Although the results of that study were basically in agreement with studies on travel related prolonged seated immobility, on balance the epidemiological evidence for a causal relationship must be rated as fairly low: 0: Insufficient evidence of a causal association.

Appendix 1

Tables

Table 2. Case-control studies. Association of travel with venous thromboembolism. Relevant studies are presented in chronological order.

Year of publication	First author	Location of study	Case characteristics	Controls	Type of travel	Travel duration	Exposure rate		Odds ratio (95%CI)
							Cases	Controls	
1999[22]	Ferrari	Europe	Patients hospitalized for either DVT or PE confirmed by ultrasonography	Patients hospitalized at same department for other reasons	Any form	Min 4 h preceding 4 weeks	39/160	12/160	3.98 (1.9-8.4)
2000[23]	Samama	Europe	Patients diagnosed with DVT by objective tests at their general practitioner: venography, ultrasonography, and/or impedance plethysmography	Patients arriving at the same clinic with influenza-like symptoms	Not reported	Reported only as "long distance travel"	62/494	31/494	2.35 (1.45-3.80)
2000[24]	Kraaijenhagen	Europe	Patients referred with clinically suspected lower extremity DVT which was confirmed by objective tests: ultrasonography + D-dimer assay	Patients referred with clinically suspected lower extremity DVT which was ***not*** confirmed by objective tests	Any form	Min 3 h preceding 4 weeks	9/186	43/602	0.7 (0.3-1.4)
2002[25]	Arya	Europe	Patients referred with clinically suspected DVT which was confirmed by duplex ultrasound	Patients referred with clinically suspected DVT who had a negative duplex ultrasound	Any form	Min 3 h preceding 4 weeks	20/185	31/383	1.3 (0.6-2.8)
2002[26]	Hosoi	Europe	Patients referred with clinically suspected DVT which was confirmed by duplex ultrasound	Patients referred with clinically suspected DVT who had a negative duplex ultrasound	Any form	Min 3 h preceding 2 weeks	15/101	13/106	1.3 (0.6-2.8)
2003[15]	ten Wolde	Europe	Patients referred with clinically suspected lower extremity DVT which was confirmed by objective tests including ultrasonography and D-dimer assay	Patients referred with clinically suspected lower extremity DVT which was ***not*** confirmed by objective tests	Any form	Min 3 h preceding 2 weeks	32/477	105/1470	0.9 (0.6-1.4)

Table 2 continued

Year of publication	First author	Location of study	Case characteristics	Controls	Type of travel	Travel duration	Exposure rate Cases	Exposure rate Controls	Odds ratio (95%CI)
2003[30]	Martinelli	Europe	Consecutive patients at thrombosis center with VTE preceding 12 months confirmed by objective tests: DVT by ultrasound or venography PE by perfusion lung scan, computed tomography, or angiography	Sex- age, and education matched controls (partners and friends) without any history of VTE	Air travel	Travel vs no travel in the month prior to the event	31/210	16/210	2.1 (1.1-4.0)
2006[16]	Cannegieter	Europe	VTE (DVT and PE) registered at anticoagulation clinic Objective tests included ultrasonography, D-dimer assay, and perfusion and ventilation scintigraphy	Partners of cases	Any form	Min 4 h preceding 8 weeks	233/1906	182/1906	2.1 (1.5-3.0)
2006[27]	Parkin	New Zealand	PE (fatal events) Diagnosis confirmed by necropsy findings	Selected randomly from the electoral roll	Air travel	Min 3 h preceding 4 weeks	5/89	9/334	1.8 (0.5-7.1)
2009[28]	Kuipers	Europe	VTE (DVT and PE) registered at anticoagulation clinic; See Cannegieter 2006 above	Partners of cases	Any form	Min 4 h preceding 8 weeks	N/A. Subgroup from Cannegieter study 2006. High factor II (prothrombin): High factor VIII:		2.2 (1.3-3.7) 6.2 (3.6-10.5)
2009[29]	Schreijer	Europe	Consecutive DVT patients from six anticoagulation clinics	Partners of patients	Air travel	Min 4 h preceding 8 weeks Windows seated vs not	33/80	28/108	2.2 (1.1-4.4)

Abbreviations: DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; 95%CI: 95% confidence interval; N/A: not applicable

Table 3. Prospective studies. Association of air travel with venous thromboembolism. Relevant studies are presented in chronological order.

Year of publication	First author	Study population	Main outcome	Travel duration	Incidence/total	Incidence (95%CI) Per mio. or %
2001[31]	Lapostolle	All arriving air passengers at Charles de Gaulle airport 1993-2000	Pulmonary embolism in immediate connection to the flight	< 3 h ≥ 3 to < 6 h ≥ 6 to < 9 h ≥ 9 to < 12 h ≥ 12 h	0/88.490.000 1/9.180.000 9/22.530.000 33/12.370.000 13/2.720.000	0.0 (0.0-0.04) 0.11 (0.01-0.71) 0.40 (0.19-0.79) 2.66 (1.83-3.79) 4.77 (2.66-8.41)
2001[32]	Belcaro	Volunteers planning long-distance travel	Mainly or exclusively asymptomatic DVT diagnosed by ultrasonography	10-15 h	Low risk group without DVT risk factors: 0/355 High risk group with one or more DVT risk factors: 11/389	 0% (0.0-1.0) 2.8% (1.4-5.0)
2001[33]	Arfvidsson	83 conference participants in Hawaii	DVT asymptomatic diagnosed by duplex scan	Mean: 9 h	4-week incidence: 1/83	 1.2% (0-3.6)
2002[34]	Schwarz	Volunteers planning long-distance travel Controls: non travelling persons matched according to age and gender	DVT by compression ultrasound	> 8 h	Volunteers: 0/160 Controls: 0/160	0.0% (0-2.3%) 0.0% (0-2.3%)
2002[35]	Kline	All passengers arriving at Charlotte-Douglas International Airport following an international flight (1.1 mio people)	Fatal pulmonary embolism immediately after the flight	Not specified, denoted as International	0/1.100.000	0.0%
2003[36]	Schwarz	Volunteers planning long-distance travel	DVT diagnosed by ultrasonography	> 8 h	7/964	0.7% (0.3-1.5) (relative risk compared to non travelling control group: 4.4 (1.04-18.62)
2003[37]	Perez-Rodriguez	All passengers arriving from international flights at Madrid-Barajas Airport 1995-2000	Pulmonary embolism in immediate connection to the flight	< 6 h 6-8 h > 8 h	0/28.038.726 1/3.926.208 15/9.070.398	0 0.25 (0.00-0.75) 1.65 (0.81-2.49)
2003[38]	Hughes	Volunteers planning long-distance travel	VTE D-dimer assay and ultrasound	< 24 h > 24 h (mean 39.4 h)	0/123 9/752	0% 1.2%(0.6-2.3)

Table 3 continued

Year of publication	First author	Study population	Main outcome	Travel duration	Incidence/total	Incidence (95%CI) Per mio. or %
2003[39]	Kelman	All passengers arriving to Australia from international flights 1981-1999	VTE Hospital admission for within 14 days of arrival from an international flight	Not specified, denoted as International	246/9.257.842	26.6 (23-30)
2003[40]	Jacobson	Volunteers planning long-distance travel	DVT	Mean: 11 h	0/434	0.0%(0.0-0.9)
2003[41]	Hertzberg	All passengers arriving at Sydney airport (6.58 mio)	PE defined as severe	Minimum 9 h	17/6.580.000 (author's estimate)	2.6
2005[42]	Gajic	223 travellers undergoing surgery 8637 non travellers undergoing same kind of surgery	DVT (within 28 days)	> 4 h	Travellers: 11/223 Non Travellers: 13/8637 (author's estimate)	4.9% (2.5-8.7) 0.15% (0.08-0.3)
2006[27]	Parkin	Passengers arriving at New Zealand Residents of New Zealand (55.8 mio) Overseas visitors (11.2 mio)	Fatal PE	> 3 h	N/A (study population limited to age range 15-59)	Residents: 0.6/mio Visitors: 0.5/mio
2007[43]	Kuipers	8755 employees of large international companies and organisations	Symptomatic venous thrombosis	Exposed to air travel or not	N/A	Travel: 3.2(2.0-4.7)/1000 PY No travel: 1.0(0.7-1.5)/1000 PY
2009[44]	Lapostolle	All passengers who landed at the Charles-de-Gaulle airport during a 13-year period (287.6 mio.)	PE after landing	Long distance	N/A	***Overall:*** Females: 0.61(0.61-0.61)/mio Males: 0.2 (0.20-0.20)/mio ***Travel > 10,000 km:*** Females: 7.24 (7.17-7.37)/mio Males: 2.35 (2.33-2.38)/mio

Abbreviations: DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; 95%CI: 95% confidence interval; N/A: not applicable

Table 4. Association of work or working conditions not related to travel with venous thromboembolism.

Year of publication	First author	Location of study	Case characteristics	Controls	Immobility at work	Immobility at work, duration	Exposure rate		Odds ratio (95%CI)
							Cases	Controls	
2008[12]	West	New Zealand	Patients < 65 years old attending the Wellington Hospital Outpatient VTE Clinic following hospital discharge for DVT and/or PE	Patients < 65 years old admitted to the Coronary Care Unit at Wellington Hospital	Prolonged seated immobility at work in the 4 weeks preceding the event	Seated at least 8 hours in a 24-hour period and at least 3 hours at a time without getting up Seated at least 10 hours in a 24-hour period and at least 2 hours at a time without getting up Seated at least 12 hours in a 24-hour period and at least 1 hour at a time without getting up	20/97	11/106	2.2(1.0-5.0) Adjusted for potential confounders: Family history of VTE, medical risk factors, personal history of VTE, prolonged travel: 1.8(0.7-4.8)

Abbreviations: DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; 95%CI: 95% confidence interval

Table 5 Randomized controlled studies. Relevant studies are presented in chronological order.

Year of publication	First author	Type of Intervention	Total no. of subjects	Main outcome	Travel duration, mean	DVT incidence Intervention group Control group	P-value of Fisher exact test
2001[45]	Scurr	Graduated compression stockings 20-30 mmHg at ankle	200	DVT diagnosed by ultrasonography	16.5 h over a period of 13 to 32 days	0/100 12/100	< 0.001
2001[32]	Belcaro	Graduated compression stockings 25-30 mmHg at ankle applied 6-10 h before flight	833	DVT diagnosed by ultrasonography	12.4 h	1/411 19/422	< 0.001
2002[46]	Belcaro	Graduated compression stockings 20-30 mmHg at ankle applied 2-3 h before flight	629	DVT diagnosed by ultrasonography	Composed of two groups: 7-8 h and 11-12 h	0/315 7/314	< 0.01
2002[47]	Cesarone	400 mg ASA daily for 3 d, starting 12 h before flight or Enoxaparin 1 mg/kg injected 2.4 h before flight	249	DVT diagnosed by ultrasonography	Not specified, Duration defined as "Long haul"	3/84 (first intervent.) 0/82 (sec. intervent) 4/82	NS
2003[48]	Belcaro	Passengers with varicose veins Intervention: Venoruton®	151	DVT diagnosed by ultrasonography	8 h	0/78 0/73	NS
2003[49]	Belcaro	Graduated compression stockings 14-17 mmHg at ankle applied 3-4 h before flight	205	DVT diagnosed by ultrasonography	11.8 h	1/103 6/102	(0.065)

Table 5 continued

Year of publication	First author	Type of Intervention	Total no. of subjects	Main outcome	Travel duration, mean	DVT incidence Intervention group Control group	P-value of Fisher exact test
2003[50]	Cesarone	Compression stockings (Sigvaris Traveno elastic stockings producing 12-18 mm Hg of pressure at the ankle)	341	DVT diagnosed by ultrasonography	7-12 h	0/172 0/169	NS
2003[51]	Cesarone	Intervention: Venoruton®	148	DVT diagnosed by ultrasonography	7-8 h	0/69 0/79	NS
2003[52]	Cesarone	Compression stockings 20-30 mm Hg pressure at ankle	274	DVT diagnosed by ultrasonography	7-12 h	0/136 2/138	NS
2003[53]	Cesarone	Intervention: Flite Tabs®	186	DVT diagnosed by ultrasonography	7.7 h	0/94 5/92	<0.05
2004[54]	Belcaro	Intervention: Pycnogenol®	198	DVT diagnosed by ultrasonography	8.25 h	0/101 1/97	NS

Abbreviations: DVT: deep vein thrombosis; ASA: acetyl salicylic acid

Appendix 2

Evidence score

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome. The score system has been developed by the Scientific Committee of the Danish Society of Occupational and Environmental Medicine.

The following categories are used.

+++	strong evidence of a causal association
++	moderate evidence of a causal association
+	limited evidence of a causal association
0	insufficient evidence of a causal association
-	evidence suggesting lack of a causal association

Description of categories:

Strong evidence of a causal association (+++):

A causal relationship is *very likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with *reasonable* confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):

A causal relationship is *likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+):

A causal relationship is *possible*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):

Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments:

The classification does not include a category for which a causal relation is considered as established beyond any doubt.

The key criterion is the epidemiological evidence.

The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of a causal association.

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