Air travel and venous thrombosis : results of the WRIGHT study : Part I: Epidemiology

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Air travel and venous thrombosis

Results of the WRIGHT study

Part I: Epidemiology

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Air travel and venous thrombosis

Results of the WRIGHT study
Part I: Epidemiology

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Chapter 1

Introduction

Introduction

In venous thrombosis, blood clot formation occurs at an inappropriate site in one of the veins, causing obstruction. This usually causes swelling, redness and pain at the affected site. Most often the deep veins of the legs are involved, but it may also occur in other sites, such as the upper extremity, cerebral sinus, liver or retina. Sometimes, parts of a blood clot dislodge and travel through the bloodstream. These so-called emboli usually end up in the lungs, where they reduce the blood flow, causing a potentially fatal condition called pulmonary embolism.

Venous thrombosis occurs at an incidence rate of approximately 1-2 per 1000 persons per year[1,2,3], with an estimated mortality of approximately 5% in patients with deep vein thrombosis of the leg and even 10% in those with pulmonary embolism[2]. A serious complication is the disabling post-thrombotic syndrome, occurring in up to 50% of patients with deep vein thrombosis of the leg[4]. Treatment consists of anticoagulant therapy, which is highly effective, but has the serious side-effect of bleeding. The annual risk of any bleeding in patients using oral anticoagulants is approximately 15% and that of a major hemorrhage (intracranial or life-threatening bleeding at other sites) approximately 3%[5].

Venous thrombosis is a multicausal disease, in which genes and environment interact[6]. The strongest risk factor for venous thrombosis is older age, since the risk increases exponentially with age[2]. The most prevalent genetic risk factors for venous thrombosis are factor V Leiden mutation[7] and prothrombin G20210A mutation[8], each present in several percent of the population. Environmental factors that increase the risk of venous thrombosis include oral contraceptive use, hormone replacement therapy, pregnancy, recent delivery, recent surgery, major trauma, plaster cast, immobilization and malignant diseases[6-9]. In the past decades, long distance travel, especially by air, has been identified as a risk factor for venous thrombosis as well.

The first cases of travel-related venous thrombosis were reported by Jacques Louvell in 1951[10]. Since then, many case reports and case-series on venous thrombosis associated with long distance travel have been published. After a young woman died of pulmonary embolism at Heathrow airport, after a flight from Australia to the United Kingdom, the UK government and the European Union decided to fund a large international research program on the association between air travel and venous thrombosis. This research program was called the WRIGHT project (World Health Organisation Research Into Global Hazards of Travel). This project was carried out, under auspices of the World Health Organisation, by researchers from the Netherlands (at the department of Clinical Epidemiology at the Leiden University Medical Center and the department of Vascular Medicine at the Academic Medical Center in Amsterdam) and the United Kingdom (at the department for Cardiovascular Sciences at the University of Leicester). Several studies were conducted at the same time, to study both epidemiologic and pathophysiological aspects of the association between venous thrombosis and air travel.

Thesis outline

This thesis focuses on epidemiological aspects of the association between long distance travel and venous thrombosis.

Chapter 2 summarizes all literature available on the association between venous thrombosis and travel so far. Both epidemiological studies and studies on the possible mechanisms responsible for the increased risk of venous thrombosis after travel are discussed.

In Chapter 3, a study on the use of prophylactic measures to prevent travel-related thrombosis amongst visitors of three international conferences is reported.

In Chapter 4, we present an estimate of the absolute risk of developing venous thrombosis shortly after air travel. Furthermore, the effect of exposure to several flights at the same time, duration of flights and time after a long haul flight was studied.

In Chapter 5, a study on the effect of elevated coagulation factors and combinations with other known risk factors for venous thrombosis (Factor V Leiden mutation, prothrombin 20210A mutation, increased body mass index and oral contraceptive use) on the risk of venous thrombosis within travellers is presented.

In Chapter 6, we present a study on the effect of transient risk factors for venous thrombosis (recent surgery, malignant diseases, plaster cast, oral contraceptive use, hormone replacement therapy, pregnancy or recent delivery) on the risk of travel-related venous thrombosis.

Finally, in Chapter 7, a study on the occurrence of symptomatic venous thrombosis in commercial airline pilots in the Netherlands is described.

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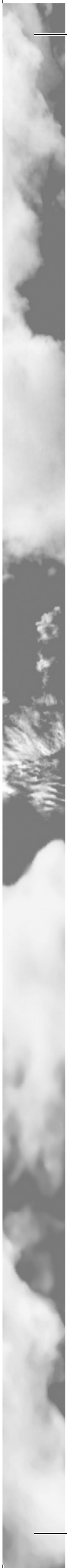

Chapter 2

Travel and venous thrombosis: a systematic review

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Abstract

In the past decade, numerous publications on the association between venous thrombosis (VT) and travel have been published. Relative and absolute risks of VT after travel, and particularly after travel by air, have been studied in case-control and observational follow-up studies, whereas the effect of prophylaxis has been studied through intervention trials of asymptomatic clots. The mechanism responsible for the association between travel and VT was addressed in pathophysiologic studies. Here, we systematically reviewed the epidemiologic and pathophysiologic studies about the association between travel and VT.

We conclude that long distance travel increases the risk of VT approximately 2-4 fold. The absolute risk of a symptomatic event within 4 weeks of flights longer than 4 hours is 1/4600 flights. The risk of severe pulmonary embolism occurring immediately after air travel increases with duration of travel, up to 4.8 per million in flights longer than 12 hours. The mechanism responsible for the increased risk of VT after (air) travel has insufficiently been studied to draw solid conclusions, but one controlled study showed evidence for an additional mechanism to immobilization that could lead to coagulation activation after air travel.

Introduction

Venous thrombosis is a serious disease that affects approximately 2-3 per 1000 persons per year (1;2). Both genetic and environmental factors are known to increase the risk of venous thrombosis and these are mainly associated with procoagulant changes of the blood or immobilization. Prevalent genetic risk factors for venous thrombosis are the factor V Leiden mutation (3) and the prothrombin G20210A mutation (4), each present in several percent of the population. Environmental factors that increase the risk of venous thrombosis include oral contraceptive use, pregnancy, recent surgery, major trauma, immobilization and malignant diseases (5). In the last decade, it has become clear that long distance travel increases the risk of venous thrombosis as well.

The first four cases of venous thrombosis associated with air travel were described in 1951 (6). Since then, many case-reports and case-series have been published on venous thrombosis associated with not only air travel, but also travel by train, bus or car and even tractor driving (7). The term economy class syndrome was coined in 1977 (8) and the first controlled study was published in 1986. Sarvesvaran and colleagues studied causes of death occurring at a large international airport and concluded that pulmonary embolism occurred more often in the arrival hall than in the departure hall (9). More controlled studies were not conducted until a young woman died of pulmonary embolism at Heathrow airport in 2000. Since then, numerous reports have published results of case-control, follow-up and intervention studies on the association between air travel and venous thrombosis. Furthermore, several studies have looked into the mechanism responsible for venous thrombosis after air travel. A number of investigators have studied the effect of prolonged immobilization with or without the combination with flight-related factors, such as hypobaric hypoxia or dehydration.

The objective of this systematic review is to quantify the risk of venous thrombosis after long distance travel, when possible to assess the effect of various prophylactic measures on this risk and to summarize the available literature about potential mechanisms of the association between air travel and venous thrombosis.

Methods

A systematic literature search was performed to identify all studies that included data on long distance travel and venous thrombosis. Studies that included epidemiological data on absolute and relative risks of venous thrombosis after any kind of travel, randomized controlled trials that assessed the effect of prophylactic measures and publications that described pathophysiological studies were included.

Search strategy

Publications were identified through an extensive search, using PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials. We did not apply a language restriction and searched all databases until January 1st 2007. Two reviewers independently screened the titles of all retrieved records for obvious exclusions. The same two reviewers read all remaining abstracts to identify eligible studies. Differences were solved by discussion.

Exposures of interest and outcomes

The main exposure of interest was travel, irrespective of mode of transportation and duration of travel. Studies that assessed the effect of prolonged immobilization and hypobaric hypoxia were evaluated as well. The main outcome of interest was symptomatic deep vein thrombosis and pulmonary embolism, diagnosed by objective methods (ultrasound, venography, ventilation-perfusion scanning, spiral ct-scanning, angiography or at autopsy). We also considered asymptomatic venous thrombosis (diagnosed by objective methods), although of unclear clinical significance, and the effect of prophylactic interventions. The effect of any of the exposures of interest on coagulation parameters was the main outcome in the pathophysiological studies.

Quality assessment

All studies were judged on both internal and external validity by 2 reviewers independently, according to guidelines of the Cochrane Collaboration Handbook (10). Disagreement was solved by discussion and when no consensus could be reached a third reviewer was consulted.

We considered case-control studies to have a low risk of bias (i.e. to have a good internal validity) when selection-bias of cases and controls was unlikely (when they came from the same population and travel frequency did not influence the likelihood of inclusion in the study), when travel frequency was assessed in the same way in cases and controls, when recall bias was minimized, when venous thrombosis was diagnosed by objective means and when cases were consecutive, unselected patients with a first thrombotic event.

Follow-up studies that assessed the risk of venous thrombosis in groups of travellers were considered to have a low risk of bias when loss to follow-up was less than 10%, when details of the exposure of interest were mentioned (mode of transportation, duration of travel, number of flights) and when the outcome of interest was assessed in the same way in all study participants. Symptomatic venous thrombosis had to be diagnosed by objective methods as described above.

Intervention studies were included when they assessed the effect of prophylactic measures on the risk of venous thrombosis (both symptomatic and asymptomatic). They were considered to have a low risk of bias when randomization procedure and allocation concealment were adequate, when outcome assessors were blinded for the exposure status of the participants and when loss to follow-up was described and less than 10%. Ideally, study participants were blinded as well.

We included pathophysiological publications when they contained original data on studies on the effect of either travel, or one of its specific factors (such as immobilization or hypobaric hypoxia), on thrombin generation or fibrinolysis in humans. Ideally, pathophysiological studies assessed the effect of an exposure of interest as compared to a control situation that would be exactly the same as the exposure situation except for the exposure itself. This would rule out other effects, such as circadian rhythm.

Data extraction:

For epidemiological studies, we used standardized forms for extraction of the following data:

- Case-control studies: source population of cases and controls, number of cases and controls, methods of diagnosis, disease characteristics (types of thrombotic events that were included), general characteristics of cases and controls (age, sex, prevalence of risk factors for venous thrombosis), frequency of travel in both study groups and when possible mode of transportation, duration of travel and time interval between travel and event or index date.
- Follow-up studies: method of selection and inclusion of the study participants, numbers of participants (when applicable per subgroup), presence of a non-travelling control population, general characteristics (age, sex, prevalence of other risk factors for venous thrombosis), outcome assessment, frequency of all relevant outcomes (symptomatic venous thrombosis and asymptomatic thrombi), numbers lost to follow-up.
- Prophylactic intervention studies: method of recruitment of participants, details of the treatment (type of stockings, dosage and frequency of any pharmacological treatment), use of placebo, method of randomization, concealment of allocation, method of outcome assessment, frequency of all relevant outcomes per treatment group, occurrence of adverse

outcomes per treatment group (such as hemorrhagic complications when antithrombotics were studied), numbers lost to follow-up.

- Pathophysiological studies: general characteristics, presence of a control population, intervention (immobilization, hypobaric hypoxia or travel), outcomes, assessment of outcome of interest (methods and timing), main results.

Statistical analysis

All reported odds ratios from case-control studies were extracted. When possible, we pooled odds ratios to estimate relative risks for both air travel and travel by other modes of transportation. Pooling was performed using the inverse-variance-weighted average of the log odds ratios from the individual studies.

From follow-up studies, we calculated the absolute risk of symptomatic venous thrombosis per flight. We also calculated the risk of asymptomatic thrombi per flight. When possible, we calculated incidence rates of venous thrombosis within a few weeks after a long haul flight. When data on different modes of transportation and duration of travel were available, we calculated risks per flight and incidence rates for each mode of transportation and duration of travel separately. We did not attempt to pool the data from follow-up studies, because of anticipated differences in study design and participants.

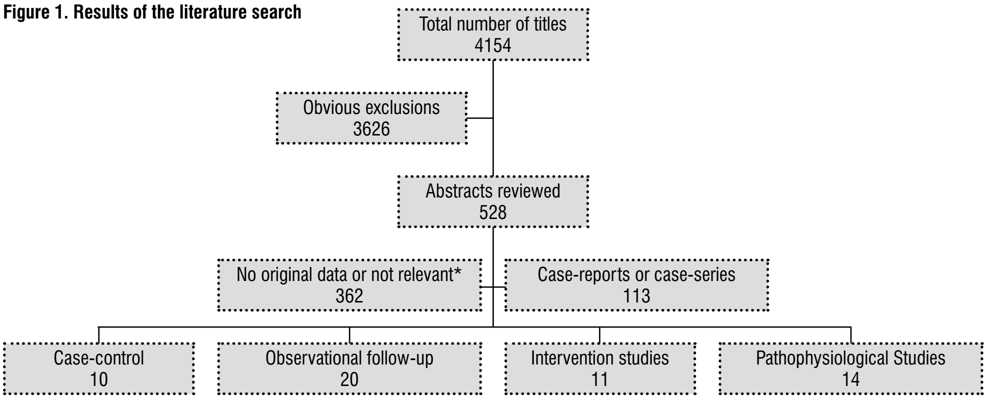
From prophylactic intervention studies, we calculated absolute risks of thrombotic events per flight per intervention group. Furthermore, relative risks of the treated groups versus the control groups were calculated and, when possible, data were pooled. To assess heterogeneity, we calculated the I^2-statistic. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. We considered heterogeneity present when I^2 was greater than 50%.

Due to the diversity of the study designs, no attempt to pool data for pathophysiological studies was made.

Results

At the first search we found a total of 4154 titles. Based on the title, 3626 papers were excluded. We screened the abstracts of 528 publications, after which 10 publications with case-control data, 20 papers describing observational follow-up studies, 11 reports on intervention studies, 113 with case-reports or small case-series and 14 describing studies on the possible mechanism causing venous thrombosis after long distance travel were identified (Figure 1). The remaining publications were comments, reviews, letters or editorials or did not concern venous thrombosis and long distance travel.

Figure 1. Results of the literature search



* *These publications were editorials, reviews or comments or did not concern travel-related thrombosis.*

Case-control studies – estimate of relative risks

We identified ten publications in which travel frequency of cases with symptomatic venous thrombosis was compared to a control population without venous thrombosis (Table 1) (11-20). One publication was excluded because the data were also used in a subsequent more extensive publication (16). There were 4 studies with an increased potential of bias. In one study, cases were self-reported, without verification of the diagnosis and both cases and controls were selected frequent travellers (13). In 3 studies, individuals with suspected venous thrombosis in whom the diagnosis was ruled out were used as control persons (11;15;20), which may have caused overrepresentation of travel exposure in the controls and thus underestimation of the effect of travel. In these studies with a potential of bias, the odds ratios for any travel ranged from 0.5 to 1.3, whereas in the other studies, the odds ratios ranged from 1.8 to 4.0 (12;14;17-19). The pooled odds ratio of all studies together was 1.7 (CI95 1.4-2.1). After exclusion of the 4 studies with a high potential bias, this increased to 2.3 (CI95 1.8-2.9). Six studies contained data on air travel only or separately for air travel and other modes of travel (11;12;15;17;18;20). The pooled odds ratio for air travel of any duration of all studies was 1.4 (CI95 0.9-2.0). After exclusion of three studies with a potential bias (11;15;20), the pooled odds ratio of the remaining studies (12;17;18) was 1.9 (CI95 1.2-2.8). Three publications showed data on long distance air travel (17;18;20), defined as flights longer than 8 hours, with odds ratios ranging from 1.3 to 7.9 and a pooled odds ratio of 1.9 (1.1-3.6). After exclusion of one study with a high potential bias (20), this pooled odds ratio increased to 3.9 (CI95 1.4-10.7).

Table 1: Case-control studies

First author + year of publication [reference]	Cases	Controls	Travel data	Potential biases	N cases/ controls	Travel Cases/ Controls	OR (CI95)
Ferrari 1999[14]	Hospitalized at cardiology department for VTE	Hospitalized for the first time at same department for other reasons	Any travel > 4 hours <4 weeks	Selection of cases and controls (severe cases are hospitalized and patients hospitalized for other reasons may have traveled less)→ possibly overestimation of the effect	160/160	39/12	3.98 (1.9 - 8.4)
Samama 2000[19]	Consecutive DVT	Patients of GP with flu-like symptoms	Not specified	Selection of controls: those visiting GP may have lower travel frequency → possibly small bias to greater effect	636/636	62/31	2.4 (1.5-3.8)
Dimberg 2001[13]	Self-reported or insurance-claim	Random from insurance records	'Corporate air travel' < 30 days	Cases not objectively confirmed (self reported), selection of frequent travellers → bias in any direction	30/891	3/163	0.5 (0.1-1.6)
Arya 2002[11]	Consecutive DVT	Suspected DVT	Any travel >3 hours < 4 weeks	Selection of controls: travel creates symptoms similar to those in VT (edema) → overrepresentation of travel in control population → bias to smaller effect	185/383	20/31	1.3 (0.6-2.8)
Hosoi 2002[15]	Consecutive DVT	Suspected DVT	Any travel < 2 weeks		101/106	15/12	1.2 (0.6-2.8)
Ten Wolde* 2003[20]	Consecutive, DVT and PE	Suspected DVT/PE	Any travel >3 hours < 4 weeks		477/1470	32/105	0.9 (0.6-1.4)
Martinelli 2003[17]	PE and DVT, visiting thrombosis center for thrombophilia screen	Partners and friends	Air travel > 4 hours < 4 weeks	Selection of cases who underwent thrombophilia screen. Selection of controls: partners / friends often travel together, no matched analysis performed → bias to smaller effect	210/210	31/16	2.1 (1.1-4.0)
Parkin 2006[18]	Fatal PE	Randomly from electoral roll	Air travel >3 hours < 4 weeks	Selection of only fatal cases → recall bias → bias to greater effect	89/334	5/9	1.8 (0.5-7.1)
Cannegieter 2006[12]	Consecutive DVT and PE registered at anticoagulation clinic	Partners of cases	Any travel > 4 hours < 3 months	Selection of controls: partners often travel together, but a matched analysis was performed.	1906/1096	233/182	2.1 (1.5-3.0)**

* *The study of Ten Wolde includes data from a previous publication by Kraaijenhagen and colleagues (16).*

** *Cannegieter and colleagues performed a matched analysis.*

Observational follow-up studies – estimates of absolute risks

Twenty publications reported data on observational follow-up studies (13;18;21-38). Two publications (22;34) contained data that were also used in another publication (27;33). From three studies, no absolute risks could be calculated, because either the number of events or the number of flights was not provided (13;28;36). Of one paper (24), no full text version could be retrieved. The remaining 14 publications are listed in Table 2.

Six publications concerned studies in which passengers were systematically screened for the presence of asymptomatic venous thrombosis after a long haul flight (21;23;27;29;37;38). In one study, the methods were inadequately described (23) and in another, the follow-up was incomplete (29). The risk of mainly asymptomatic thrombosis in air travellers as found by screening ranged from 0% (no events in 160 passengers) to 1.5% (11 events in 744 passengers). Only two studies included a non-travelling control population (37;38). In the first study, none of the 160 control persons developed a thrombus and in the second study, 2 out of 1213 (0.2%) non-travelling participants developed deep vein thrombosis.

The absolute risk of symptomatic venous thrombosis was assessed in a study of approximately 9000 employees of international companies and organizations (32). A total of 22 events occurred within 8 weeks of flights longer than 8 hours, yielding an absolute risk of symptomatic venous thrombosis of 215 per million travellers (CI95 133-316 per million) after flights longer than 4 hours. This was equivalent to a risk of 1/4600 flights. The risk increased with travel duration, up to 793 (CI95 198-1784) per million travellers after flights longer than 16 hours. The results of this study may not be generalisable to all travellers, since the study was conducted in a healthy, working population.

One retrospective follow-up study (25) assessed the frequency of deep vein thrombosis in high risk surgical patients that had to travel long distances prior to their operation and found a risk of 4.9% (CI95 2.1-7.8) within 2 weeks of the operation, as compared to 0.2% (CI95 0.1-0.2%) in patients undergoing the same types of high-risk surgery without prior air travel. In this study, the use of prophylaxis for thrombosis was unclear and travelling and non-travelling study participants came from different source populations, because the non-travellers were all US citizens, whereas all travellers were non-US citizens visiting the country for the surgical procedure.

Table 2: Observational follow-up studies

First author, year of pub [reference]	Study population	Examinations	Flight duration	Limitations	Outcome	Time window and absolute risk (CI95)
Outcome: asymptomatic DVT						
Arfvidsson 2001[70]	83 Visitors of conference in Hawai, voluntary participation	US* in all passengers	Mean 9 hours	Response 30%, incomplete follow up, only asymptomatic thromboses	DVT**	4 Weeks 1.2% (0-3.6)
Belcaro 2001[23]	355 Passengers at low risk for VT and 389 passengers at higher risk. Method of recruitment unclear	US of all passengers	10-15 hours	Selection of participants unclear, overlapping in- and exclusion criteria, unclear whether any event was symptomatic	DVT**	24 Hours 1.5%
Schwarz 2002[37]	160 Passengers making ≥ 2 flights and 160 controls, recruitment through advertisements No use of stockings or anticoagulants	US in all travellers and controls	≥ 8 hours	Only asymptomatic thromboses	DVT ** travellers non-travellers	48 Hours after return flight 0% 0%
Hughes 2003[27]	878 Individuals making ≥ 2 long distance flights in 6 weeks, recruited through media, no severe risk factors, no increased d-dimers at baseline	D-dimer and clinical probability US when either high, FU by telephone after 3 months	> 4 hours	Mainly asymptomatic cases	DVT**	2 Weeks after return flight 1% (0.4-1.7)
Schwarz 2003[38]	964 Passengers making ≥ 2 flights and 1213 non-travelling controls, recruitment through advertisements No use of stockings or anticoagulants, no thrombus at baseline examination	Thrombophilia screen, d-dimers and US	≥ 8 hours	Only asymptomatic cases	DVT** travellers non-travellers	48 Hours 0.7% 0.2%
Jacobsen 2003[29]	Passengers flying London-Johannes-burg, recruited at check-in, 180 business and 719 economy class	Guestionnaire, d-dimers, thrombophilia screen and optional US. Follow up after 6 months	> 8 hours	Incomplete follow-up in 52%, time window unclear	DVT**	Time window unclear 0%
Outcome: Symptomatic DVT/PE						
Kuipers 2005[32]	8 755 Frequently travelling employees of international companies and organizations	Questionnaire and confirmation through medical chart review	> 4 hours	Only healthy, working population	Symptomatic DVT and PE	8 Weeks 215/million
Gajic 2005[25]	223 Travellers undergoing surgery and 8637 non-travelling controls with the same type of surgery	Medical chart review	> 4 hours	Method of prophylaxis unclear, unclear how complete the FU was, incomparability of travellers and non-travellers	DVT travellers non-travellers	28 Days 4.9% 0.15%

Outcome: severe PE						
Kelman 2003[30]	4.8 Million Australians and 4.6 million non-Australians arriving after intercontinental flights in Western Australia	Records of all patients admitted with DVT or PE in Western Australia in 1981-1999	'International'	Fatal or ambulatory treated cases were missed	Hospitalized for VT - Australians - Visitors	28 Days 9.6/million 43.5/million
Lapostolle 2001[33]	All 134.29 million passengers arriving at Charles de Gaulle airport 1993-2000	Review of all records of patients requiring medical help for PE immediately after arrival at the airport	 <3 hours 3-6 hours 6-9 hours 9-12 hours >12 hours	Very short time window: only cases that seeked help within a few hours after landing were included	Severe PE	Few hours 0 0.1/million 0.4/million 2.7/million 4.8/million
Hertzberg 2003[26]	All 6.58 million passengers arriving at Sydney Airport	Review of all records of patients admitted with PE at 2 hospitals	>9 hours	Cases who went to other hospitals than the study hospital were missed	Severe PE	Few hours 2.6/million
Perez-Rodriguez 2003[35]	All 4.1 million passengers arriving at Madrid Barajas Airport	All patients admitted to 1 hospital with PE coming directly from the airport	 <6 hours 6-8 hours >8 hours	Very short time window: only cases that seeked help within a few hours after landing were included	Severe PE	Few hours 0 0.3/million 1.7/million
Outcome: Fatal PE						
Parkin 2006[18]	All passengers arriving at New Zealand, 55.8 million residents of New Zealand and 11.2 million overseas visitors	Review of death records and interviews with relatives to identify fatal cases of PE with international air travel within 4 weeks	> 3 hours	Only fatal cases of PE and age-limit 15-59	Fatal PE Residents Visitors	Few hours 0.6/million 0.5/million
Kline 2002[31]	All 1.1 million passengers arriving after international flights at Charlotte-Douglas international airport	Review of records of all passengers with cardiac arrest or unstable patients at the airport.	'International'	Only fatal cases that caused severe symptoms immediately after the flight were included	Fatal PE	Immediately after the flight 0%

* *US = Ultrasonography*

** *DVT and STF were mainly asymptomatic, detected by ultrasound.*

Three studies assessed the risk of pulmonary embolism, requiring medical care immediately after long distance air travel (26-28;33;35;38). Two studies found a dose-response relationship between the frequency of pulmonary embolism and duration of travel (33;35). In one study, the risk ranged from no events in 74.2 million flights shorter than 3 hours to 13 in 2.7 million flights (4.8 per million, CI95 2.2-7.4 per million) in flights longer than 12 hours (33). In a similar Spanish study, no PE was seen after 28.0 million flights shorter than 6 hours and in 9.1 million flights longer than 8 hours, 15 cases of severe pulmonary embolism occurred (absolute risk 1.7 per million, CI95 0.8-2.5) (35). In another study using a similar design, the risk of PE immediately after a flight longer than 9 hours was 2.6 per million (CI95 1.4-3.8 per million) (26). In all three studies, the time window in which a traveller could become a case was extremely small, since only persons that developed severe symptoms immediately after arrival were included.

One study assessed the risk of hospital admission for pulmonary embolism within 2 weeks of international flights to Australia, which was found to be 9.6 per million (CI95 7.0-12.6 per million) for 4.9 million passengers who were residents of Australia and 43.5 per million (CI95 37.5-49.8 per million) for 4.6 million passengers who were visiting Australia (30). In this study, travellers who died before reaching the hospital or patients who were treated ambulatory were not included, which may partly explain the difference between residents and non-residents of Australia.

The risk of fatal pulmonary embolism after air travel was assessed in 2 studies (18;31). One study found no fatal PE's in 1.1 million passengers arriving after international flights to Charlotte-Douglas airport, Charlotte, NC in the US, whereas another study found 11 cases of fatal PE within 4 weeks of 19.3 million flights longer than 3 hours, yielding an absolute risk of 0.6 per million passengers (CI95 0.2-0.9 per million). In both studies, patients who were not sent to the study hospital were missed.

Randomized controlled trials – estimate of the effect of interventions

A total of 11 randomized trials were conducted to assess the effect of various prophylactic measures on the risk of venous thrombosis after air travel (23;39-48). The main results of these trials are shown in Table 3. All studies had a similar design: a number of air travellers, varying from 148 to 833, making long haul flights (>7 hours) were randomized to either a control group or an intervention group that received elastic compression stockings, aspirin, heparin, venoruton (hydroxyethylrutosides), pycnogenol (pine tree extract containing procyanidins, bioflavonoids and organic acids) or FLITE tabs (containing pycnogenol and nattokinase, a soy bean extract). All passengers were routinely screened for venous thrombosis by ultrasound after their flight (within a maximum of 48 hours). All but one of these studies were conducted by the same research group. In these publications, the methods of the study were inadequately described or even contradictory. Most striking was that in- and exclusion criteria were frequently overlapping. Furthermore, the method of recruitment of participants and whether study participants and outcome-assessors were blinded for the treatment group was unclear. The majority of the thrombotic events in all trials were asymptomatic, which may partly explain the high prevalence in the control population. The number of symptomatic events was not clearly described, but is likely to be much lower. These drawbacks, as well as a report from the Medical research Counsil's Fitness to Practice Panel (49), judging it proved that these papers named co-authors who had not approved the papers, hamper the credibility of these trials. We therefore will not discuss the results of these trials in this systematic review. In the only remaining trial (48), the effect of elastic compression stockings was assessed in 231 airline passengers travelling at least 8 hours. None of the 100 passengers who were randomized to the elastic compression stockings group developed venous thrombosis, whereas 12 of the 100 control passengers did, yielding a relative risk of 0.04 (CI95 0-0.6). However, 4 passengers wearing elastic compression stockings developed superficial thrombophlebitis, whereas none of the control passengers did.

Mechanism of travel related thrombosis

There are several explanations for the increased risk of venous thrombosis after air travel. Apart from immobilization, flight specific factors, such as hypobaric hypoxia may affect the coagulation system. Various investigators have examined the effect of air travel, or one of its specific aspects (e.g. immobilization and hypobaric hypoxia) on thrombin generation and fibrinolysis.

The studies differed much in participant characteristics, duration of exposure, type of exposure and statistical analyses. Most studies determined changes in various parameters before and after specific exposures in volunteers. Table 4 summarizes the relevant aspects of the studies and the direction of the changes in the most commonly used coagulations parameters during thedifferent exposures.

Table 3 Randomized controlled trials

First author + year of pub [reference]	Participants	Intervention	Examinations#	Potential biases	Outcomes	Frequency outcomes (%)*	Relative risk** (CI95)
Scurr 2001[48]	200 Unselected travellers flying making at least 2 flights >8 hours	100 Stockings 100 No intervention	US all passengers <48 hours of the return flight	Only asymptomatic thromboses	DVT No intervention Stockings	12 (12) 0 (0)	0.04 (0-0.6)
Belcaro 2001[23]	833 Passengers at increased risk for VT making 1 flight 10-15 hours	422 No intervention 411 Stockings	US all passengers <24 hours	***	DVT No intervention Stockings	19 (4.5) 1 (0.2)	0.05 (0-0.4)
Belcaro 2002[39]	629 Travellers at low risk making 2 flight 7-12 hours	314Nno intervention 315 Stockings	US all travellers before and after flight	***	DVT No intervention Stockings	7 (2.2) 0 (0)	0.07 (0-1.2)
Cesarone 2002[43]	249 Passengers at increased risk making one flight 7-8 hours	83 No Intervention 84 Aspirin 400mg 3d 82 lmwh therapeutic dose once pre-flight	US all travellers within a few hours of the flight	***	DVT No intervention Aspirin Heparin	4 (4.8) 3 (3.6) 0 (0)	0.7 (0.2-3.4) 0.1 (0.01-2.0)
Belcaro 2003[41]	151 Passengers with varicose veins making 1 flight 8 hours	73 No intervention 78 Venoruton	US all travellers within a few hours of the flight	***	DVT No intervention Venoruton	0 (0) 0 (0)	
Belcaro 2003[40]	205 Passengers at increased risk making 1 flight 11.5-12 hours	102 No intervention 103 Stockings	US all travellers < 90 minutes of the flight	***	DVT No intervention Stockings	6 (6) 0 (0)	0.07 (0-1.3)
Cesarone 2003[44]	341 Passengers at low-medium risk making 1 flight 7-12 hours	169 No intervention 172 Stockings	US all travellers within a few hours of the flight	***	DVT No intervention Stockings	0 (0) 0 (0)	-
Cesarone 2003[45]	148 Passengers with varicose veins making 1 flight 7-8 hours	79 No intervention 69 Venoruton 3 days	US all travellers within a few hours after the flight	***	DVT No intervention Venoruton	0 (0) 0 (0)	-
Cesarone 2003[47]	274 Passengers at low-medium risk making 1 flight 7-12 hours	138 No intervention 136 Stockings	US all travellers within a few hours of the flight	***	DVT No intervention Stockings	2 (1.4) 0	0.2 (0.01-4.2)

Cesarone 2003[46]	186 Passengers at increased risk making 1 flight 7-8 hours	92 No intervention 94 FLITE tabs	US all travellers within a few hours of the flight	***	DVT No intervention FLITE tabs	 5 (5.4) 0 (0)	0.08 (0-1.5)
Belcaro 2004[42]	198 Passengers at increased risk making 1 flight 8 hours	97 No intervention 101 Pycnogenol	US all travellers < 2 hours of the flight	***	DVT No intervention Pycnogenol	 1 (1) 0 (0)	0.3 (0.01-7.9)

In all studies, most DVTs were asymptomatic

* *Number of passengers with the outcome of interest (%)*

** *Relative risk of the intervention group as compared to the control passengers*

*** *In these studies, all by the same research group, only asymptomatic events were assessed, the method of selection of participants were unclear and in- and exclusion criteria were frequently overlapping. Furthermore, the credibility of the authors of these trials was seriously questioned by the Medical research Counsil's Fitness to Practice Panel.*

\# *US= Ultrasound*

Table 4: Pathophysiological studies

				Markers of thrombin generation*		Markers of fibrinolysis*		
Mechanism	**First author / Year of publication [ref]**	**Volunteers (number of women)**	**Methods**	**TAT**	**F1+2**	**D-dimer**	**PAI**	**tPA**
Immobilization	Tardy I 1996[64]	31 (28) Elderly with varicose veins 9 (7) Non travelling controls	8-Hr bus trip, freedom of walking during bus trip	Travellers vs controls no difference	Travellers vs controls no difference	Travellers vs controls no difference		
	Tardy II 1996[64]	23 (20) Elderly with varicose veins	16-Hr bus trip, freedom of walking during bus trip	After vs before: increase	After vs before: no change	After vs before: no change	After vs before: no change	After vs before: no change
	Stricker 2003[61]	40 (20) Healthy	6 Hrs of immobilization		After vs before: decrease	After vs before: no change		
	Schobersberger 2004[58]	19 (11) Healthy	Return bus trip Innsbruck to Rome, 10 hr per trip, 2 nights stop over in Rome	After vs before: no change	After vs before: increase	After vs before: no change	After vs before: decrease	After vs before: decrease
	Ansari 2006[52]	10 (0) Healthy	8 Hrs of immobilization	After vs before: no change	After vs before: no change	After vs before: no change	After vs before: decrease	After vs before: no change
	Stricker 2006[62]	20 (9) Healthy	6 Hrs of immobilization		After vs before: decrease	After vs before: no change		
Hypoxia	Bendz 2000[53]	20 (0) Healthy	8 Hrs of hypobaric hypoxia ~2400 m	After vs before: increase	After vs before: increase	After vs before: no change		
	Crosby 2003[55]	8 (?) Healthy	Cross over study 8 hrs of socapnic hypoxia ~3600 m and 8 hrs of normobaric normoxia	Hypoxia vs control: no difference	Hypoxia vs control: no difference	Hypoxia vs control: no difference		
	Hodkinson 2003[56]	6 (0) Healthy	Cross over study 3 hrs of normobaric hypoxia ~3660 m and 3 hrs of normobaric normoxia		Hypoxia vs control: no difference		Hypoxia vs control: no difference	
	Schobersberger 2006[59]	12 (3) Healthy	10 Hrs of normobaric hypoxia ~2400 m	After vs before: no change	After vs before: no change	After vs before: no change	After vs before: no change	After vs before: decrease
	Toff 2006[65]	49 (22) No risk factors 24 (20) With risk factors (OC or age >50)	Cross over study 8 hrs of hypobaric hypoxia ~ 2438 m and 8 hrs of normobaric normoxia	Hypoxia vs control: no difference	Hypoxia vs control: no difference	Hypoxia vs control: no difference	Hypoxia vs control: no difference	Hypoxia vs control: no difference

Air travel	Schobersberger 2002[57]	10 (5) Healthy 10 (6) With risk factors (>40 yrs, OC, obesity, venous insufficiency)	Return flight Innsbruck to Washington with 2 hr stop-over in Vienna Flight time one way: 8 h 20 min (Vienna-Washington) 2 night stays in Washington	After vs before: no change		After vs before: no change	After vs before: increase	After vs before: decrease
	Boccalon 2005[54]	30 (0) Healthy	11 Hr flight	After vs before: decrease	After vs before: decrease	After vs before: no change		After vs before: no change
	Schreijer 2006[60]	30 (15) No risk factors 41 (41) With risk factors (OC, FVL or both)	Cross over study 8 hr flight 8 hr movie marathon 8 hrs of daily activities	All 3 parameters increased in more participants during the flight than during the immobilized or ambulant situation				

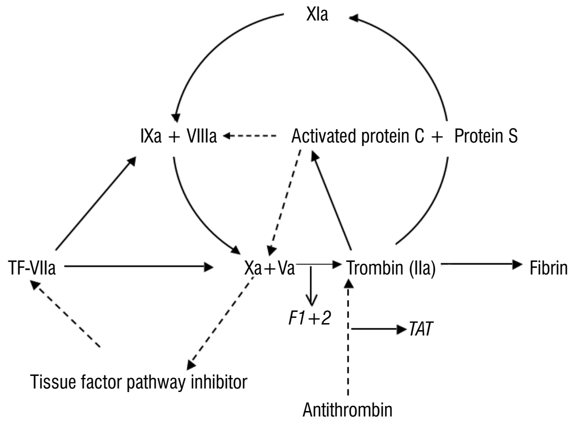
* *This table roughly indicates the changes in the most commonly used markers of coagulation activation and fibrinolyis during the several exposures. VT= venous thrombosis, FVL = Factor V Leiden mutation, OC=oral contraceptive/hormone use. When studies took blood from both arm and leg veins results from arm veins are shown.*

Parameters of thrombin generation and fibrinolysis

Thrombin generation and fibrinolysis are regulated by its activators and inhibitors (Figures 1 and 2). The amount of thrombin generated is often assessed by levels of activation peptide prothrombin fragment 1+2 (F1+2), and its inhibitor complex thrombin-antithrombin (TAT). Activation of the fibrinolytic system is reflected by increased levels of D-dimers (fibrin degradation products), which by definition also points to thrombin generation and hence may be its simple consequence (50).

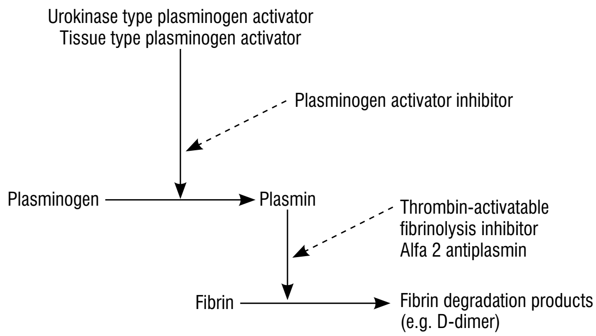
Increased levels of activated coagulation factors (such as FVIIa and FVIIIa) are also known to increase thrombin generation (50;51).

Figure 2. Thrombin generation*



* *Dashed lines reflect inhibition, solid lines reflect activation, and substances in italic are products of the process.*

Figure 3. Fibrinolysis*



* *Dashed lines reflect inhibition, solid lines reflect activation.*

Immobilization

The most obvious explanation for air travel related thrombosis is immobilization. Passengers are restricted to limited space, resulting in a cramped position during long haul flights and are even more immobilized when they are asleep.

Several studies investigated the effect of prolonged immobilization on thrombin generation, but conflicting results were shown (52-65) (Table 4). Stricker et al. found a decrease in markers of thrombin generation during 6-hours of immobilization in 40 volunteers, whereas they found no change in 18 participants during the ambulant situation (61). In a subsequent study with a similar design, the investigators found similar results in 20 volunteers and also found evidence for down-regulation of the protein C system, one of the inhibitors of the coagulation system (62). Others found evidence for thrombin activation during a 10-hour bus journey in a group of 19 healthy volunteers (58). In a similar study, but with 23 elderly with varicose veins, TAT increased after a 16-hour bus trip (especially in two high responders), indicating thrombin generation. However, F1+2 remained unchanged after the bus trip and FVIIa decreased (64). The same study group found no difference in a comparable study in markers of thrombin generation between 31 bus travellers and a non travelling control group (n=9). More recently, Ansari et al. found no change in markers of thrombin generation in 10 healthy volunteers after 8 hours of prolonged sitting, although F1+2 levels showed a tendency to decrease (52). In an artificial model of immobilization, with 30 min of blood stasis provoked by a pressure cuff around the thigh, F1+2 decreased (66).

The effect of immobilization on the fibrinolytic system was also contradictory (Table 4). In some studies, markers of fibrin generation and fibrinolysis remained unchanged (61;62;64;66). Others found a decrease in levels of tPA (an activator of the fibrinolytic system) and PAI (an inhibitor of the fibrinolytic system). D-dimers remained unchanged in this study, with the exception of two subjects in whom D-dimers increased (>0,5 mg/l) (58). In a more recent study, PAI decreased after 8 hours of immobilization, whereas D-dimer and tPA levels did not clearly differ from baseline, although both parameters had a tendency to decrease (52).

In the majority of the studies, no control population was used to assess whether any observed effect was the result of immobilization or other factors, such as circadian rhythm. Only in one study, coagulation parameters in passengers after an 8-hour bus trip were compared to those in a non-travelling control population (64). No differences in TAT, D-dimers or F1+2 were observed between the two groups.

Hypoxia during simulated air travel

During air travel, cabin pressure drops to 75.8 kPA, which is equivalent to an altitude of 2400 meters above sea level. Consequently, oxygen saturation can drop as low as 90-93% and even to 80% in passengers who are asleep (67;68). To separate the effect of sole hypoxia from hypobaric hypoxia, both the effects of hypobaric as well as normobaric hypoxia on human coagulation have been investigated.

Already in 1976, Maher et al. studied the effect of acute hypobaric hypoxia (corresponding to an altitude of 4400 meters above sea level) on human coagulation (69). He found a shortening of the partial thromboplastin time (aPTT) after 1 hour and 24 hours in a hypobaric chamber whereas fibrinogen and FVIII levels returned to baseline at 24 hours after an abrupt decrease after 1 hour. Fibrin degeneration products (e.g. D-dimers) were transiently increased in three subjects.

Years later, when more laboratory assays became available, the effect of hypoxia on both thrombin generation and fibrinolysis was further investigated (Table 4). Bendz et al. exposed 20 volunteers to 8 hours of hypobaric hypoxia (76 kPa) by natural elevation and found an increase in thrombin generation (reflected by TAT and F1+2), with a maximum increase after 2 hours of hypobaric hypoxia (53). These changes were accompanied by an increase in FVIIa (measured as FVIIa-tissue factor complex), while FVII antigen and TFPI (antigen and activity) decreased. However, in a controlled experiment with eight participants, Crosby et al. found no evidence for thrombin generation during exposure to 8 hours of isocapnic hypoxia compared to 8 hours of normobaric normoxia (55). Also short term exposure to normobaric hypoxia did not seem to affect markers of thrombin generation in a cross over study (56). In a much larger study, Toff and colleagues exposed 73 volunteers alternately to hypobaric hypoxia and normobaric normoxia. They found no difference between the changes in markers of thrombin generation during hypobaric or normobaric exposures (65). These findings were confirmed by Schobersberger and colleagues (59).

Markers of fibrinolysis mainly remained unchanged during hypoxia in most studies (53;55;56;65), although Schobersberger found a decrease in t-PA after 10 hours of hypoxia (59).

Air travel

Only few studies have investigated the effect of actual air travel on the coagulation system (Table 4). No evidence for increased thrombin generation was found in a study with 20 volunteers (including 10 volunteers who were obese, aged >40 years, used oral contraceptives or had venous insufficiency) after a return flight from Vienna to Washington (57). In a similar study, Boccalon et al. found a reduction in thrombin generation after an 11-h return flight with 30 healthy male volunteers (54). In a tightly controlled crossover study with 71 volunteers (including 41 women with risk factors for venous thrombosis, i.e. factor V Leiden mutation, oral contraceptive use or both) evidence was found for thrombin generation in 17% of individuals during an 8-h flight, whereas this was found in only 3% during an 8-h movie marathon and in 1% during the ambulant situation. The effect was most evident in women with FVL who use oral contraceptives (60).

Schobersberger et al. found evidence for suppressed fibrinolysis during air travel (57), whereas markers of fibrinolysis remained unchanged in the study by Boccalon et al (54). In the crossover study, the fibrinolytic system was activated in more participants during the flight then during the immobilized or ambulant situation (60).

Drawbacks of the studies

Thus, the results in all three settings (immobilization, hypoxia and air travel) were conflicting. There are several possible explanations for these discrepancies. Firstly, since it is plausible that only some individuals are susceptible to coagulation activation during air travel, people with risk factors for venous thrombosis may react differently than those without. In order to control for the large inter-individual normal range of coagulation parameters, data are best analyzed on an individual level in a crossover design. Most studies that have been conducted so far included few participants (mostly without risk factors for venous thrombosis) and presented data on group level only. Secondly, when only pre- and post exposure data are compared, effects of circadian rhythm are not accounted for. Only four studies compared changes in coagulation parameters during air travel or hypobaric hypoxia to a control situation and may be considered to have yielded valid data (55;56;60;65).

Discussion

Long distance travel increases the risk of venous thrombosis 2-4 fold. Only one study assessed the risk of symptomatic venous thrombosis in a frequently travelling working population and found a risk of 1/4600 travellers within 4 weeks of flights longer than 4 hours. The risk of pulmonary embolism occurring immediately after air travel increases with duration of travel, from 0 in flights shorter than 3 hours up to 4.8 per million in flights longer than 12 hours. The risk of fatal PE immediately after arrival, which was assessed in two studies, is estimated at less than 0.6 per million passengers in flights longer than 3 hours. The risk of venous thrombosis is not increased after travel shorter than 3-4 hours. The risk of asymptomatic venous thrombosis after long haul flights ranged up to 12%.

In one randomized controlled trial comparing the prevalence of asymptomatic venous thrombosis in control travellers to that in travellers assigned to wear stockings, stocking effectively prevented the development of asymptomatic thrombi. The effect of stockings, low molecular weight heparin and aspirin has been studied in a series of trials by the same research group. These studies had serious methodological flaws and the scientific integrity of the authors was questioned by the Medical Research Councils Fitness to Practice Panel (49-51).

Although several studies have addressed the mechanism responsible for the association between venous thrombosis and long distance travel, differences in design, analysis and interventions do not allow us to draw solid conclusions. One controlled study that included volunteers with risk factors for venous thrombosis showed evidence for an additional mechanism to immobilization that could lead to coagulation activation after air travel, especially in susceptible individuals.

Future research should focus on the mechanism responsible for coagulation activation due to (air) travel, identification of individuals at high risk, and prophylactic measures that prevent symptomatic venous thrombosis and outweigh its potential harms. Based on the currently available evidence, we conclude that the absolute risk of symptomatic venous thrombosis in the general travelling population is not high enough to justify the widespread use of prophylaxis, in particular of prophylaxis that may cause side effects. There may be a rationale for preventive measures in individuals at high risk, but it is currently not known which prophylactic measures have a positive balance of effect and risk.

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Chapter 3

Use of preventive measures for air travel-related venous thrombosis in professionals who attend medical conferences

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Abstract

Background: Clear guidelines for the use of prophylaxis for air travel-related venous thrombosis are not available.

Objectives: To assess the use of preventive measures for air travel-related venous thrombosis in professionals employed in the field of thrombosis and haemostasis and in other fields.

Methods: We performed a survey amongst delegates of the XXth ISTH Congress, the 15th ISDB Congress and the 13th Cochrane Colloquium, which all took place in Australia 2005. All delegates received a questionnaire with questions on personal and travel details, risk factors for thrombosis and preventive measures taken.

Results: 2089 questionnaires were completed (response 53%). Overall, 80% of the respondents used preventive measures. Low molecular weight heparin and vitamin K antagonists were mostly used by ISTH delegates (10%, as compared to 1% by delegates of the other conferences). Aspirin was used by 20% of the ISTH delegates and by 21% of the other delegates. Medical doctors used more pharmacological prophylaxis (31%) than research fellows (11%) and non-clinical scientists (22%). Dutch (64%) and Asian respondents (67%) least used any form of prevention, whereas Israeli used most (94%). Subjects with risk factors for venous thrombosis more often used prophylaxis (90%) as compared to those without (77%). In a multivariate analysis, the conference attended, nationality, age, the presence of risk factors and professional background were determinants of prophylaxis use, while seating class was not.

Conclusion: The use of prophylaxis for air travel-related venous thrombosis varied between conferences, professional backgrounds and countries. These differences stress the need for clear guidelines on prevention of air travel-related venous thrombosis.

Introduction

Travel- related venous thrombosis (VT) has received major media-attention since a young woman died of pulmonary embolism at Heathrow airport after a flight from Australia in 2000. Several controlled studies on air travel-related thrombosis showed a 2- to 4-fold increased risk of thrombosis after air travel[1-6] and an increasing incidence of venous thrombosis with the distance travelled[7-8]. For advice to travellers, the absolute risk is relevant, but only limited information is available so far. The risk of severe pulmonary embolism was found to be 4.7 per million passengers after flights longer than 10.000 km[7]. Another study showed a risk of fatal pulmonary embolism of 1.3 per million passengers travelling for at least eight hours[9]. In 3 follow up studies, the risk of mainly asymptomatic venous thrombosis was found to be several percent[10-12]. The absolute risk of symptomatic venous thrombosis after air travel must lie somewhere between the extremes of asymptomatic venous thrombosis and severe pulmonary embolism. In a large follow up study amongst 9000 employees of international companies and organizations, we found the absolute risk of VT within 4 weeks of flights longer than 4 hours to be 1/6000 flights[13]. Large randomized trials on preventive measures for symptomatic air travel-related VT have not been conducted and therefore clear guidelines are not available. A media-hype combined with lack of knowledge of the actual risk of developing VT after air travel may lead to excessive use of potentially dangerous precautions, such as anticoagulant therapy.

The objective of this study was to assess the use of preventive measures for air travel-related thrombosis in professionals, either working in the field of haemostasis and thrombosis or in other areas.

Methods

To assess the use of preventive measures for air travel-related venous thrombosis we sent questionnaires to all delegates of the XXth Congress of the International Society on Thrombosis and Haemostasis (ISTH), held in Sydney in August 2005, to those of the 15th International Society of Developmental Biology (ISDB) Congress, held in Sydney in September 2005, and to those of the 13th Cochrane Colloquium (on the production, dissemination and use of systematic reviews), which took place in Melbourne in October 2005.

Questionnaire

All delegates of the three congresses for whom a correct e-mail address was available received an e-mail with an explanation about the study and a link to a short on-line questionnaire.

In the questionnaire, we asked questions about 1) general demographic data (age, sex, professional background and country of residence), 2) the flight to the conference (mode of travel, total duration and duration of longest uninterrupted leg, class of travel), 3) risk factors for thrombosis (personal history, presence of thrombophilia, active cancer, recent surgery, varicose veins, estrogen use and pregnancy or puerperium), 4) in-flight behavior (sleeping, use of sleeping medication, alcohol-use and non-alcoholic consumptions) and 5) preventive measures for air travel-related thrombosis (walking at least once every 2 hours, exercises as suggested in in-flight magazines or videos, elastic compression stockings, aspirin, low molecular weight heparin (LMWH) or vitamin K antagonists (VKA)). The questions in the questionnaire only covered travel to Australia, not the return-flight. About 2-3 weeks after the initial e-mail, a first reminder was sent, followed by a second after 5-6 weeks.

Statistical analysis

For each type of preventive measure, percentages of use were calculated. Ninety-five percent confidence intervals for differences of proportions were based on binomial distributions. Subgroups were defined based on the conference that was attended, professional background, nationality, risk factors for venous thrombosis and class of travel. Delegates of the conference on thrombosis and haemostasis were compared to delegates of the other 2 conferences. Medical doctors were compared to non-clinical scientists (mainly biologists and biochemists), research fellows (post-graduate students and PhD students) and individuals with a different professional background (such as employees of pharmaceutical companies and policy makers). Medical doctors who were also doing PhD research project were only counted as medical doctors. To assess differences between nationalities, countries with a high number of respondents were analyzed as such (USA, Canada, UK, Netherlands, Germany, France, Italy and Israel). Inhabitants of Scandinavian countries (Denmark, Sweden, Norway and Finland) were analyzed together, because there were no major differences in in-flight behavior and use of preventive measures between these countries. Citizens from Asian countries were grouped as well, because of the small numbers per country. Inhabitants of Australia and New Zealand were excluded from the analyses because their duration of travel was unlikely to be extreme. To study the effect of risk factors, all risk factors mentioned in the questionnaire were analyzed separately. Furthermore, individuals with any risk factor (personal history of venous thrombosis, presence of thrombophilia, active cancer, recent surgery, varicose veins, pregnancy and puerperium) were compared to individuals with none of the risk factors, which latter group included those using estrogens.

Because many variables were associated, such as age, profession and class, we performed a logistic regression analysis to determine which factors were the strongest determinants of prophylaxis. Whether or not pharmacological prophylaxis was taken (both in- and excluding aspirin) was used as outcome measure. Age (split in 5 categories), sex, country, professional background, presence of risk factors and class of travel were entered as independent variables in the regression model.

Results

2941 delegates of the XXth ISTH conference, 672 of the ISDB congress and 445 of the Cochrane Colloquium received the invitational e-mail with a link to the questionnaire. After exclusion of inhabitants of Australia and New Zealand, a total of 3939 eligible delegates remained. The responses were 63% (ISTH, n=1638), 26% (ISDB, n=170) and 69% (Cochrane, n=281). The overall response was 57%. General characteristics of the responders are shown in Table 1. Overall, 59% of the respondents were men (n=1198). Almost half of the delegates of the ISTH conference were medical doctors (43%, n=703), as compared to 5% (n=9) at the ISDB conference and 26% (n=74) at the Cochrane Colloquium. Almost all respondents (99%, n=2049) had travelled by air to the conference. Most delegates (70%, n= 1442) of the delegates had travelled for 20 hours or more and 1627 (79%) respondents had at least one flight longer than 10 hours. The mean duration of travel did not differ between delegates of the three conferences. Delegates of the ISTH conference travelled more frequently in business or first class than delegates of the other two conferences (29% vs 9%). The respondents came from 69 different countries with most delegates at all three conferences coming from the United States (n=405) and the UK (n=306). The distribution over the represented continents was approximately equal in the ISTH compared to the other two conferences.

Table 1 General Characteristics of the respondents of the three conferences

Characteristic	ISTH (1638)		ISDB (170)		Cochrane (281)		Total (2089)	
	N	%	N	%	N	%	N	%
Age distribution:								
- < 35 yrs	369	23	88	52	72	26	529	26
- 36-45 yrs	489	31	48	28	98	35	635	31
- 46-55 yrs	457	29	25	15	71	25	553	27
- 56-65 yrs	228	14	6	4	33	12	267	13
- >65 yrs	52	3	2	1	5	2	59	3
Sex:								
- Male	987	62	95	56	116	42	1198	59
- Female	608	38	74	44	163	58	845	41
Professional background								
- Medical doctor	703	43	9	5	74	26	786	38
- Non-clinical scientist	493	30	105	62	108	38	706	34
- Research Fellow	116	7	49	29	17	6	182	9
- Other	326	20	7	4	82	29	415	20
Class								
- Economy class	1159	71	160	94	249	89	1568	75
- Business/first class	479	29	10	6	32	11	521	25
Countries								
- USA	345	21	29	17	31	11	405	19
- Canada	81	5	6	4	29	10	116	6
- UK	170	10	34	20	102	36	306	15
- Netherlands	137	8	5	3	15	5	157	8
- Germany	136	8	10	6	10	4	156	8
- France	79	5	7	4	2	1	88	4
- Italy	64	4	1	1	14	5	79	4
- Scandinavia	132	8	13	8	32	11	177	9
- Europe other*	208	13	6	4	11	4	225	11
- Israel	20	1	0	0	0	0	20	1
- Asia**	185	11	56	33	18	6	259	12
- Other	81	5	3	2	17	6	101	5
Risk groups								
- History	48	3	2	1	4	1	54	3
- Thrombophilia	54	3	5	3	7	3	66	3
- Varicose veins	150	9	12	7	35	13	197	9
- Recent surgery	12	1	1	1	3	1	4	0.2
- Active Cancer	2	0.2	0	0	1	0.4	16	1
- Estrogen use	148	9	22	13	35	13	205	10
- Pregnant/postpartum	9	1	1	1	5	1	15	2
- Any risk factor	249	15	16	9	46	16	311	15

* *Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Luxemburg, Poland, Portugal, Romania, Russia, Slovak Republic, Slovenia, Spain, Switzerland, Turkey and Ukraine.*

** *Cambodia, China, India, Indonesia, Japan, South-Korea, Malaysia, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand and Vietnam*

Overall use of preventive measures

The overall use of preventive measures is shown in Table 2. 1577 delegates (80%, CI95 78-81%) used some kind of preventive measure, of whom 509 (26%, CI95 24-28%) delegates used medication to prevent air travel-related thrombosis (aspirin, LMWH or VKA). Stockings were used by 344 respondents (17%, CI95 16-19%). 1466 delegates (74% CI95 72-76%) did exercises or walked around at least once every 2 hours.

Use of preventive measures per conference

The use of preventive measures varied considerably per conference. Delegates of the ISDB conference least used any type of preventive measure. Anticoagulants (LMWH, VKA or aspirin) were used by 27% (n=413) of the professionals in the field of thrombosis and haemostasis, compared to 21% (n=96) at the other 2 conferences (difference 6%, CI95 1-10%). LMWH and VKA were used almost exclusively by delegates of the ISTH conference (10%, n=121), while this was 1% at the other 2 conferences combined (difference 9%; CI95 7-11%). Aspirin was used mostly by delegates of the Cochrane Colloquium (29%, n=80) as compared to delegates of the ISTH conference (20%, n=313, difference 9%, CI95 3-14%). Stockings were also most worn by delegates of the Cochrane colloquium (27%, n=75) as compared to the ISTH conference (17%, n=255, difference 10%, CI95 5-16%) and the ISDB conference (8%, n=14, difference 19%, CI95 12-25%). Regular exercises and walking were practiced mainly by delegates of the Cochrane colloquium as well.

Use of preventive measures by professional background

Use of preventive measures per occupation is shown in Table 2. Research fellows least used any kind of preventive measure (74%, n=134). It should be noted that research fellows were younger and had less risk factors for venous thrombosis than medical doctors, non-clinical scientists and those with other professional backgrounds Pharmacological prophylaxis was used most by medical doctors (31%, n=233) and individuals with a professional background other than medical doctor, research fellow or non-clinical scientist (31%, n=111). LMWH and VKA were used predominantly by medical doctors (14%, n=86). Aspirin was taken most by the delegates with other professional backgrounds (28%, n=99). Stockings were used by approximately 20% of the medical doctors (n=150) and delegates with other professional backgrounds (n=76). Twelve percent (n=22) of the research fellows and 14% (n=96) of the non-clinical scientists wore elastic compression stockings. The percentages of individuals doing exercises or walking did not vary much between professional backgrounds.

Use of preventive measures by country

The use of preventive measures varied remarkably per country, which is shown in Table 2. Inhabitants of the Netherlands (64%, n=93) and people originating from Asia (67%, n=167) least frequently used any measures to prevent air travel-related thrombosis, whereas the inhabitants of Israel used most (94%, n=19). Pharmacological prophylaxis (aspirin, LMWH or VKA) was used most by inhabitants of Germany (35%, n=52), the USA (33%, n=129) and the UK (33%, n=97). LMWH or VKA was used mainly by inhabitants of Israel (22%, n=4) and Germany (16%, n=24). Aspirin was used by 32% (n=92) of the respondents from the UK, by 31% (n=119) of those from the USA and by 22% (n=25) of those from Canada. Stockings were mostly used by delegates from France (42%, n=33), Scandinavia (38%, n=63) and the UK (35%, n=102).

Use of preventive measures by risk groups

Individuals with a known risk factor for thrombosis more often used preventive measures (90%, n=280) than those without known risk factors (77%, n=1384). Pharmacological prophylaxis was used by 44% (n=130) of the individuals with a known risk factor for venous thrombosis and by 23% of the individuals without risk factors (n=379, difference 22%, CI95 16-28%). 27% (n=62) of the respondents with a risk factor used either LMWH or VKA during their flight, compared to 5% (n=61, difference 23%, CI95 17-29%) of those without a risk factor. LMWH was most frequently used by individuals with a history of venous thrombosis (33%, n=17) and known thrombophilia without a personal history of venous thrombosis (34%, n=21). VKA was used most by respondents with a positive history (16%, n=8). Aspirin was taken by 27% (n=79) of the individuals with a risk factor, compared to 19% (n=291) of those without a risk factor (difference 7%, CI95 2-13%). Of the delegates with a risk factor, 37% (n=110) wore elastic compression stockings and of the individuals without a risk factor 14% (n=234) used stockings (difference 23%, CI95 17-29%). Stockings were most used by women who were pregnant or had given birth in the 3 months prior to the conference (79%, n=9).

Use of preventive measures per class of travel

Delegates who travelled in business class used as much preventive measures (81%, n=399) as those in economy class (79%, n=1178). Only aspirin was used more by individuals in business class (27%, n=133) than by those in economy class (18%, n=274, difference 9% CI95 4-13%).

Table 2: Use of preventive measures overall and per conference, occupation, country, risk-group and class of travel

	Walking / Exercises* %	Stockings %	Aspirin %	LMWH %	VKA %	Any** %
Overall (2089)	74	17	21	5	1	80
Conference (n)						
- ISTH (1638)	74	17	20	7	1	80
- ISDB (170)	68	8	8	0	0	71
- Cochrane (281)	79	27	29	0.4	0.4	85
Professional background (n)						
- Medical doctor (786)	75	20	21	11	1	83
- Non-clinical scientist (706)	72	14	19	2	1	77
- Research fellows (182)	73	12	9	1	0	74
- Other (415)	76	21	28	3	1	82
Country (n)						
- USA (405)	77	9	31	3	2	82
- Canada (116)	72	10	22	1	4	78
- UK (306)	79	35	32	2	0	86
- Netherlands (157)	63	5	3	0	1	64
- Germany (156)	63	19	20	16	0	77
- France (88)	74	42	22	6	4	89
- Italy (79)	73	11	12	8	0	78
- Scandinavia (177)	80	38	19	4	1	84
- Other Europe (225)	82	12	21	15	1	86
- Israel (20)	89	6	6	22	0	94
- Asia (259)	66	4	6	0	0	67
- Other (101)	77	21	21	15	0	84
Class of travel						
- Economy class	75	17	18	5	1	79
- Business/first class	71	18	27	7	1	81
Risk groups (n)						
- History (54)	90	53	35	33	16	96
- Thrombophilia(66)	86	31	13	21	0	94
- Varicose veins (197)	81	36	27	12	3	88
- Recent surgery (16)	93	43	36	21	7	100
- Active Cancer (4)	100	50	50	25	25	100
- Estrogen use (204)	77	32	25	4	1	85
- Pregnancy /postpartum (15)	86	64	14	7	0	86
- Any risk factor (311)***	83	37	27	19	3	90
- No risk factor (1778)	73	14	20	3	1	78

* *Walking around the airplane at least once every 2 hours or exercises as suggested in in-flight magazines or videos*
** *Walking, exercises, stockings, aspirin, LMWH or VKA*
*** *Personal history of venous thrombosis, known thrombophilia, varicose veins, recent surgery, active cancer, pregnancy or postpartum.*

Multivariate analysis

Several variables in this study were strongly linked. Medical doctors for example were older and more often male than individuals from other professions. They often travelled in business class and constituted a large part of the ISTH conference. Research fellows were the youngest and usually travelled economy class. They were more often female and more often attended the ISDB conference than individuals with other professions. The odds ratios from the logistic regression analysis, each adjusted for all other variables in the regression model, are shown in table 3. Odds ratios (OR) are shown for the use of all pharmacological prophylaxis (aspirin, LMWH and VKA) and the use of only LMWH or VKA. The strongest independent determinants for the use of LMWH or VKA were presence of risk factors (OR for any risk factor vs none 6.1, CI95 3.8-9.6), professional background (OR for MDs vs other professional backgrounds 2.8, CI95 1.8-4.5), German nationality (OR vs Dutch 25.5, CI95 3.2-202.5) and Israelian nationality (OR vs Dutch 15.8, 95CI 1.5-169.7). There were no major differences for the use of pharmacological prophylaxis between sexes and class of travel.

Table 3: Odds ratios for use of any anticoagulants (aspirin, LMWH or VKA) and for the use of only LMWH or VKA, per subgroup. Each variable was adjusted for the others by logistic regression analysis

Characteristic	OR all anticoagulation (CI95)		OR LMWH/VKA (CI95)	
Conference (n)				
- ISTH (ref)	1		1	
- ISDB	0.4	(0.2-0.8)	0	
- Cochrane	1.0	(0.8-1.4)	0.1	(0.03-0.6)
Sex				
- Male (ref)	1			1
- Female	1.1	(0.9-1.4)	1.5	(0.9-2.3)
Age category				
- < 35 yrs	1		1	
- 36-45 yrs	0.7	(0.9-1.7)	1.2	(0.6-2.5)
- 46-55 yrs	0.6	(1.1-2.2)	1.6	(0.8-3.2)
- 56-65 yrs	1.1	(1.5-3.3)	1.6	(0.7-3.8)
- >65 yrs	4.9	(2.6-9.3)	4.9	(1.7-14.6)
Professional background				
- MD (ref)	1		1	
- Non-clinical scientist	0.7	(0.5-0.9)	0.3	(0.1-0.5)
- Research fellow	0.6	(0.3-1.1)	0.3	(0.1-1.4)
- Other	1.1	(0.8-1.5)	0.6	(0.3-1.2)
Class of travel				
- Economy class (ref)	1			1
- Business class	1.2	(0.9-1.5)	0.8	(0.5-1.4)
Risk groups				
- No risk factor (ref)	1			1
- Any risk factor	2.2	(1.7-2.9)	6.1	(3.8-9.6)
Country				
- Netherlands (ref)	1		1	
- USA	9.7	(3.8-24.6)	4.6	(0.6-37.2)
- Canada	6.6	(2.4-17.9)	6.5	(0.7-57.7)
- UK	13.0	(5.1-33.3)	3.2	(0.3-30.3)
- Germany	12.2	(4.6-32.4)	25.5	(3.2-202.5)
- France	6.6	(2.3-19.0)	7.3	(0.8-65.7)
- Italy	4.8	(1.6-14.0)	8.1	(0.9-72.6)
- Scandinavia	6.4	(2.4-17.0)	3.8	(0.4-33.6)
- Other Europe	10.7	(4.1-27.6)	16.6	(2.2-128.3)
- Israel	6.4	(1.6-26.0)	15.8	(1.5-169.7)
- Asia	1.4	(0.4-4.4)	0	0
- Other	9.2	(3.3-25.4)	10.4	(1.2-87.3)

Ref: reference category. The odds ratio indicates the ratio between odds in the category of interest and the reference category

In-flight behavior

In-flight behavior per subgroup is shown in Table 4. In-flight behavior also varied considerably per country. Almost 90% of all respondents took at least 3 non-alcoholic beverages and almost half of the delegates (48%, n=978) took at least 6 non-alcoholic consumptions. Overall, alcohol was consumed by 65% of all participants. Individuals from Scandinavia, Germany, the UK and the Netherlands consumed the highest number of alcoholic beverages. Sleeping medication was mainly used by the French (27%), Israeli (25%) and Americans (23%).

Table 4: In-flight behavior per subgroup (%)

	≥6 non-alcoholic consumptions %	Any alcohol %	≥3 alcoholic consumptions %	Sleep-medication %
Overall	48	64	22	14
Per conference:				
- ISTH	47	65	23	15
- ISDB	40	53	11	9
- Cochrane	55	67	20	9
Professional background				
- Medical doctor	45	66	21	19
- Non-clinical scientist	47	65	22	11
- Research fellow	54	48	12	5
- Other	51	66	22	11
Country				
- USA	35	57	9	23
- Canada	56	56	20	17
- UK	54	74	29	7
-Netherlands	63	62	26	10
-Germany	68	78	31	11
- France	54	66	24	26
- Italy	56	52	13	10
- Scandinavia	57	81	40	6
- Europe other	62	69	26	16
- Israel	50	30	0	25
- Asia	14	59	17	8
- Other	39	42	10	18
Class of travel				
- Economy class	46	58	16	12
- Business/first class	52	83	39	19
Risk groups				
- History	46	65	28	26
- Thrombophilia	61	57	14	14
- Varicose veins	51	58	18	16
- Recent surgery	38	77	29	18
- Active Cancer	50	75	25	0
- Estrogen us	63	51	11	14
- Pregnancy /postpartum	60	30	0	0
- Any risk factor	53	62	21	18
- No risk factor	47	65	22	13

Discussion

In this study amongst delegates of three international conferences in Australia, we showed that a considerable number used some kind of preventive measure for air travel-related thrombosis. Overall, 80% of the participants in this survey used one or more measures to prevent air travel-related thrombosis. The use of preventive measures varied between conference content, professional background, risk groups and nationality.

Delegates of the haemostasis and thrombosis conference used more aggressive preventive measures than delegates of the conferences that did not concern thrombosis. This is likely to be a consequence of greater concern about the association between air travel and thrombosis amongst professionals working in the field of thrombosis and haemostasis.

Compared to people with other occupations, medical doctors more often used pharmacological prophylaxis (aspirin, LMWH and VKA). This may again reflect concern about a disease they are well-acquainted with, and also, particularly for LMWH and VKA, that they have more easy access to drugs. Still, it is of interest to note that medical doctors used more potentially harmful preventive measures than their non-clinical colleagues, while there is no evidence available that supports the use of LMWH or VKA, especially in individuals that have no known risk factors for venous thrombosis.

Individuals with known risk factors for venous thrombosis more often used preventive measures than those without risk factors. However, even some people who had no known risk factor for venous thrombosis used anticoagulant therapy (3% LMWH and 1% VKA) during their flight to Australia.

The large variation between countries may reflect cultural differences and possibly the effect of disparate views among medical opinion leaders.

Since we expected that many variables were linked this way, we performed a multivariate analysis. However, from this analysis it appeared that the determinants found in the univariate analysis were still all predictors for the use of preventive measures. The type of conference attended still was an important determinant, as well as professional background, the presence of risk factors and nationality. So the higher proportions of use of anticoagulants by delegates from the ISTH could not be explained by the higher number of medical doctors attending, but is probably indeed related to the greater concern about air travel-related thrombosis in professionals working in this field.

The limited guidelines on preventive measures for air travel-related venous thrombosis that are available generally promote drinking large amounts of non-alcoholic beverages and avoiding alcoholic consumptions. Only half of the respondents in this survey followed the advice regarding non-alcoholic beverages, as 52% took less than 6 non-alcoholic consumptions, which is not much, considering that most respondents had been travelling for at least 20 hours. Few people seemed worried about the dehydrating effect of alcohol, as more than half of the respondents consumed at least one alcoholic beverage and 22% of all respondents consumed 3 or more alcoholic beverages.

One previous study investigated the use of preventive measures for air travel-related venous thrombosis amongst passengers arriving at Heathrow and Gatwick airport in the UK[14]. In that study, passengers with a personal history of thrombosis, a known 'clotting tendency', recent surgery and ongoing chemotherapy, as well as passengers on daily aspirin for other reasons were excluded. 18% of these passengers bought elastic compression stockings, 30% did exercises or moved around during their flight and 16% intended to take aspirin for prevention of flight-related thrombosis. If only inhabitants from the UK without the above mentioned risk factors were taken into account in our study, 295 respondents remained of whom 32% used aspirin, 65% did exercises and 35% used elastic compression stockings. The higher percentages in our study are likely to reflect the greater concern about the association between air travel and venous thrombosis among individuals who are employed in the field of thrombosis and haemostasis.

A limitation of our study is that in the questionnaire, daily medication use could not be distinguished from occasional use for prophylaxis of air travel-related thrombosis. In particular, in North-America daily aspirin use is quite common, as an observational study showed that 29% of the American citizens aged 34-64 used aspirin daily[15]. This may have contributed to the high prevalence of aspirin use in the USA and Canada and therefore it is not possible to say what proportion of the respondents in our study used aspirin only for prevention of air travel-related thrombosis. Another limitation in this study is the low response of 29% in delegates of the ISDB conference. Individuals who are concerned about thrombosis may have preferentially completed our survey, leading to an overestimate of the use of preventive measures. However, these limitations would not explain differences between subgroups.

Convincing evidence on who is most at risk for developing thrombosis after air travel and which preventive measures would be most beneficial is not available at this time. In other circumstances, pharmacological prophylaxis is accepted in individuals at high risk, when there is a positive efficacy/safety ratio, such as in post-operative patients. However, as the risk for thrombosis decreases, this ratio decreases and the use of pharmacological prophylaxis becomes potentially unsafe. Large epidemiological studies are required to assess the absolute risk for developing symptomatic thrombosis after air travel and to identify individuals who are most at risk and who would therefore benefit most from preventive measures. Furthermore, large randomized trials are necessary to assess which preventive measure is most beneficial, if at all, and to assess the optimal dose and duration of pharmacological prophylaxis.

From this study we conclude that medical and non-medical preventive measures for air travel-related thrombosis are widely used and their use varies considerably between nationalities and professional backgrounds. The potential harm associated with anticoagulant prophylaxis stresses the need to gather evidence that should lead to clear guidelines.

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Chapter 4

The absolute risk of venous thrombosis after air travel:

a study of 8 755 employees of international organisations

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Plos Medicine 2007; 4: e290

Abstract

Background: The risk of venous thrombosis is approximately 2-4 fold increased after air travel, but the absolute risk is unknown. The objective of this study was to assess the absolute risk of venous thrombosis after air travel.

Methodology and principle findings: We conducted a cohort study among employees of large international companies and organisations, who were followed between January 1st 2000 and December 31st 2005. The occurrence of symptomatic venous thrombosis was linked to exposure to air travel, as assessed by travel-records provided by the companies and organisations. A long-haul flight was defined as a flight of at least 4 hours and subjects were considered exposed for a post-flight period of 8 weeks. A total of 8 755 employees were followed during a total follow-up time of 38 910 person-years. The total time employees were exposed to a long-haul flight was 6 872 person-years. In the follow-up period, 53 thromboses occurred, 22 of which within 8 weeks of a long-haul flight, yielding an incidence rate of 3.2/1000 person-years, as compared to 1.0/1000 person-years in individuals not exposed to air travel (incidence rate ratio 3.2, CI95 1.8-5.6). This was equivalent to a risk of 1 event per 4 656 long-haul flights. The risk increased with exposure to more flights within a short time frame and with increasing duration of flights. The incidence was highest in the first two weeks after travel and gradually decreased to baseline after 8 weeks. The risk was particularly high in employees under 30, women who used oral contraceptives, individuals who were particularly short, tall or overweight.

Conclusions/significance: The risk of symptomatic venous thrombosis after air travel is moderately increased on average, and rises with increasing exposure and in high-risk groups.

Introduction

In 1951, Jacques Louvel reported four cases of venous thrombosis following air travel[1]. More recently, several investigators have shown an association between air travel and venous thrombosis, with a 2-4 fold increased risk in most studies[2-8]. Two follow-up studies demonstrated a dose-response relationship between the occurrence of pulmonary embolism shortly after arrival at the airport and the distance travelled[9,10]. Still, the most relevant element, i.e. the absolute risk of symptomatic venous thrombosis after long distance air travel, remains unknown. One follow-up study demonstrated an absolute risk of severe pulmonary embolism occurring shortly after arrival of 1 per 200 000 passengers[9], whereas another study showed a risk of fatal pulmonary embolism of 1.3 per million passengers[11]. Asymptomatic clots have been found in 1 to 10% of air travellers[12-14]. Hence, the absolute risk of symptomatic venous thrombosis after long-haul travel must lie between these extremes.

Knowledge of the absolute risk of symptomatic thrombosis after air travel is needed to provide travellers with solid advice regarding their actual risk and to evaluate the utility of prophylactic measures. Since there are two billion passengers annually[15], even a small increase in risk will have a major impact on the number of events. Overestimation of the risk may lead to inappropriate use of potentially dangerous antithrombotic drugs[16,17].

In addition to estimating the absolute risk of symptomatic deep vein thrombosis or pulmonary embolism after long haul air travel, we assessed the effect of exposure to several flights within a short time frame, duration of travel and the occurrence of venous thrombosis in relation to the time passed after air travel. Finally, we determined the effect of air-travel within high-risk groups.

Methods

Study design

We performed a cohort study among employees of large international companies and organisations. During the follow-up period, thrombotic events were linked to exposure to air travel.

Participating companies and organisations

Participating companies and organisations were Nestlé (Vévey, Switzerland), General Mills (Minneapolis; Minnesota, USA), the Centers for Disease Control and Prevention (Atlanta; Georgia, USA), the World Bank and the International Monetary Fund (Washington; DC, USA), Shell Companies based in The Hague

(The Netherlands) and London (UK), Shell Exploration and Production (SIEP) based in Rijswijk (The Netherlands) and Sakhalin Energy Investment Company Ltd (SEIC) based in Sakhalin (Russia) and TNT NV (Thomas Nationwide Transport, Hoofddorp; the Netherlands). All organisations and companies had a central database with records of employees' business travel. Start of follow-up varied per company, between January 1st 1998 to January 1st 2001 or at start of the employment if later. Follow-up ended between December 1st 2002 and January 1st 2006, when venous thrombosis was diagnosed or at the end of employment, whichever occurred first, with approximately 5 years of follow-up per company.

Questionnaires and flight data

We developed web-based questionnaires, using Apian Survey Pro 3.0 (Seattle; Washington, USA). These contained questions about venous thrombosis occurrence (at any time point in the follow up period) and risk factors for venous thrombosis. Employees were invited to take part by a personal e-mail, containing a link to the questionnaire and a unique password, which ensured that each individual could enter only once. With intervals of a few weeks, non-responding employees received 2-3 reminders.

Date of travel and duration of travel (not including stop-over time) was taken from the organisations' travel database.

Outcomes

Participants who reported venous thrombosis were asked to fill in a consent form for medical chart review. Only symptomatic first venous thrombotic events that were diagnosed with objective methods were considered. Deep vein thrombosis had to be diagnosed by compression ultrasonography or venography. Pulmonary embolism had to be diagnosed by spiral-CT scanning, high probability ventilation-perfusion scanning or angiography. Superficial thrombophlebitis was not included.

Statistical analysis

For the analysis of the overall effect of flying, exposure time was defined as a time-window of 8 weeks after a long haul flight (flights of at least 4 hours). For each individual, the total time exposed and not exposed was calculated. The incidence rate of venous thrombosis within 8 weeks of a long haul flight was calculated by dividing the number of cases that occurred in this exposure window by the number of exposed person-years. The incidence rate of venous thrombosis without exposure was calculated in the same way (events over person-time outside exposure windows). The incidence rate ratio adjusted for age and sex was calculated using Poisson regression analysis. The overall effect of flying was assessed for the whole group of employees and separately for subgroups based on sex, age, oral contraceptive use, body mass index (BMI) and height., The number of person-years exposed and unexposed to oral contraceptive use was calculated for women younger than 50 years.

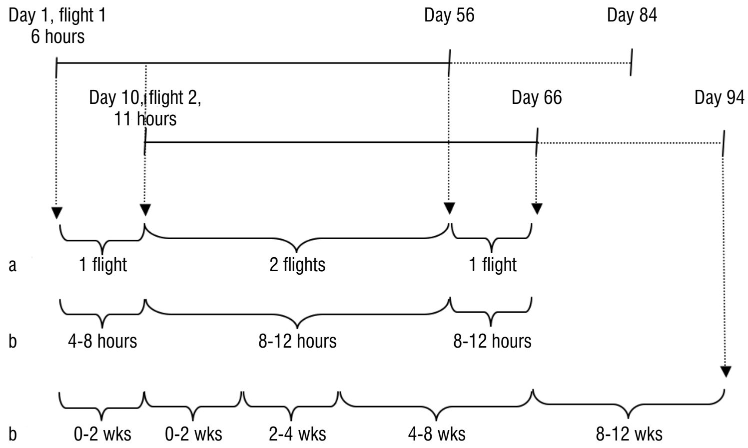
In addition, we calculated the absolute risk of venous thrombosis per flight, by dividing the number of cases that occurred within 8 weeks of a long haul flight by the total number of flights longer than 4 hours made by all responding employees.

Employees were often exposed to more than one flight in the eight weeks exposure windows, so time-windows were frequently overlapping. To assess the effect of number of flights, the total time employees were exposed to 1 to 5 flights or more was calculated. Thus, incidence rates and rate ratios for exposure to 1-2, 3-4 and 5 or more flights could be calculated (Figure 1a). Furthermore, we calculated the increase in risk for each extra flight using Poisson regression.

To assess the effect of duration of travel, we calculated incidence rates and rate ratios within 8 weeks of flights of varying duration, i.e. 0-4 hours, 4-8 hours, 8-12 hours, 12-16 and longer than 16 hours. If time windows were overlapping, only the duration of the longest flight was considered for this analysis (Figure 1b). The absolute risk per flight for each category of duration was calculated by dividing the number of cases that occurred within 8 weeks of a flight by the total number of flights in the corresponding category. Furthermore, we calculated the increase in risk for each extra hour of duration of a flight using Poisson regression.

The occurrence of venous thrombosis in relation to the period of time that had passed after travelling was assessed by calculating incidence rates and rate ratios for periods of 0-2, 2-4, 4-8 and 8-12 weeks after a flight of at least 4 hours. The period of 12 weeks after a flight was split into these 4 time windows, creating mutually exclusive exposure windows. If a person was exposed to several flights and hence to more than 1 time-window, the overlapping time was counted only in the time window closest to the flight (Figure 1c).

Figure 1: Example of the calculation of person-years of exposure in 3 different ways.



An employee makes one flight of 6 hours on day 1 and another flight of 11 hours on day 10.

a) Per number of flights: from day 1 to 10, this employee is exposed to only 1 flight. From day 10 to 56, he is exposed to 2 flights and from day 56 to 66 he is again exposed to 1 flight.
b) Per category of duration: from day 1-10 the employee is exposed to one flight of 6 hours (so 10 days in the category of 4-8 hours). From day 10 to 56, he is exposed to 2 of which the longest is 11 hours (so 46 days in the category of 8-12 hours). From day 56 to 66 he is exposed to one flight of 11 hours (so again 10 days in the category of 8-12 hours).
c) Per time window: from day 1 to 10, the employee is exposed to the time window of 0-2 weeks due to the first flight. At day 10, the time is 'reset', so from day 10 to 24, the employee is exposed to the time window of 0-2 weeks again. From day 24 to 38, he is exposed to the time window of 2-4 weeks, from day 38 to 66 he is exposed to the time window of 4-8 weeks and finally, from day 66 to 94 the time window is 8-12 weeks.

Results

A total of 27 496 employees were invited to participate. 8755 questionnaires were completed, yielding an overall response of 32% (range per organisation: 15-80%). General characteristics of the study population are shown in Table 1. More than half of the responders (n=4915, 56%) were men and the mean age was 40 years. The total follow-up time of participating employees was 38 910 person-years, with a mean follow-up per participant of 4.4 years.

Table 1: General characteristics of the study population and flight data

Characteristic		
Age, mean (range)		39.9 (18-71)
Sex, % male		56
Oral contraceptive use (% in women <50)	No OC use entire FU period OC use during part of the FU period OC use during the complete FU period	56.5 26.1 17.3
Height: (n, %)	< 165 cm 165-180 cm >180 cm	2046 (23.5) 5445 (62.6) 1202 (13.8)
BMI: (n, %)	< 25 > 25	4741 (54.7) 3934 (45.3)
Flight data:	Total number of flights Flights 0-4 hours Flights 4-8 hours Flights 8-12 hours Flights 12-16 hours Flights >16 hours Median number of flights per year (range) Median number of flights > 4 hours per year (range) Mean duration per flight	315 762 213 333 46 272 37 904 13 208 5 045 3.5 (0-143) 0.8 (0-48) 3.9 hours (0-24 hours)

**BMI = body mass index in kg/m²*

Flight data

Flight data are shown in Table 1. The 8 755 responders had made 315 762 flights during follow-up, and 6440 individuals had travelled by air at least once. Approximately one third of all flights were long haul flights (at least 4 hours, n=100 208). The mean number of long haul flights per person per year was 2.6 (range: 0-48, median: 3.5).

Thrombotic events

Seventy-six employees reported that they had suffered from venous thrombosis in the follow-up period. Of these 76 possible cases 23 were not validated: 4 employees did not give permission for medical chart review, 2 doctors could not be traced, 6 appeared to have suffered from an arterial event and 11 had been diagnosed with superficial thrombophlebitis. The remaining 53 employees all had an objectively confirmed venous thrombotic event. Deep vein thrombosis of the leg was diagnosed in 34, pulmonary embolism in nine, a combination in eight and deep vein thrombosis of the arm in two.

Absolute risks and incidence rate ratios

The overall incidence rate of venous thrombosis was 1.4 per 1000 person-years (95% confidence interval (CI95) 1.0-1.8/1000 person-years). The total time employees were exposed to a post-flight period of 8 weeks added up to 6872 person-years when only flights longer than 4 hours were considered. Twenty-two events occurred within eight weeks of a long haul flight, yielding an incidence rate of 3.2 per 1000 person-years (CI95 2.0-4.7/1000 person-years). The time the employees were not exposed to any flight (long- or short haul) was 27 772 person-years, during which 29 cases occurred, yielding an incidence rate of 1.0 per 1000 person-years (CI95 0.7-1.5/1000 person-years). Thus, the incidence rate ratio (IRR) was 3.2 (CI95 1.8-5.6). The total number of long haul flights made by the employees was 102429, hence the absolute risk of venous thrombosis was 21.5/100 000 flights, or 1 per 4656 flights.

Table 2: Incidence rates, absolute risks and incidence rate ratios within 8 weeks of long haul flights, for the whole study population as well as stratified on sex, age category, oral contraceptive use, height and bmi.

Category	air travel	Cases	Py#	IR (CI95)**	IRR (CI95)##	Flights	Risk/ flight ***	Case/ number of flights ###
All (8 755)	No	29	27 772	1.0 (0.7-1.5)	1$			
	Yes	22	6 872	3.2 (2.0-4.7)	3.2 (1.8-5.6)	102 429	21.5	1/4 656
Men (4 915)	No	12	14 728	0.8 (0.4-1.4)	1$			
	Yes	13	4810	2.7 (1.4-4.4)	2.7 (1.2-6.0)	76 461	17.0	1/5 882
Women (3 819)	No	17	12 968	1.3 (0.8-2.0)	1$			
	Yes	9	2050	4.4 (2.0-7.8)	3.3 (1.5-7.5)	25 780	34.9	1/2 864
<30 Yrs (1 392)	No	3	4132	0.7 (0.1-1.8)	1$			
	Yes	3	616	4.9 (0.9-12.1)	7.7 (1.6-38.4)	8 014	37.4	1/2671
30-50 Yrs (6017)	No	17	19576	0.9 (0.5-1.3)	1$			
	Yes	15	4879	3.1 (1.7-4.9)	3.7 (1.8-7.5)	73 624	20.4	1/4908
>50 Yrs (1 345)	No	9	4063	2.2 (1.0-3.9)	1$			
	Yes	4	1376	2.9 (0.7-6.5)	1.4 (0.4-4.6)	20 791	19.2	1/5198
OC$$ No	No	9	10193	1.0 (0.5-1.8)	1$			
	Yes	3	1533	2.3 (0.4-5.6)	2.2 (0.6-8.1)	18 085	20.3	1/4938
OC$$ Yes	No	5	2367	1.9 (0.6-3.9)	1$			
	Yes	3	436	6.6 (1.2-16.4)	3.6 (0.8-14.9)	7 695	55.3	1/1808
<165 cm	No	5	7284	0.7 (0.2-1.5)	1$			
	Yes	7	1108	6.3 (2.4-12.0)	9.8 (3.1-30.9)	14250	49.1	1/2036
165-185 cm	No	21	16759	1.3 (0.8-1.9)	1$			
	Yes	11	4602	2.4 (1.2-4.0)	1.9 (0.9-3.9)	69095	15.9	1/6281
>185 cm	No	3	3493	0.9 (0.2-2.1)	1$			
	Yes	4	1115	3.6 (0.9-8.1)	3.7 (0.8-16.9)	18242	21.9	1/4561
BMI <25	No	16	14919	1.1 (0.6-1.7)	1$	51958	13.5	1/7423
	Yes	7	3617	1.9 (0.7-3.7)	1.9 (0.8-4.7)			
BMI >25	No	13	12546	1.0 (0.5-1.7)	1$	49509	30.3	1/3301
	Yes	15	3198	4.7 (2.6-7.4)	4.9 (2.3-10.6)			

* *Travel: No=no exposure to air travel within 8 weeks, Yes=exposure to a flight of at least 4 hours*
\# *PY: Person-years*
** *IR: Incidence rate per 1000 person-years, CI95: CI95*
\#\# *IRR: Incidence rate ratio adjusted for age and sex*
$: *Reference category*
$$: *Oral contraceptive use amongst women <50 years*
*** *Risk per flight: risk per 100 000 flights*
\#\#\#: *number of flights needed to cause one case*

Both the unexposed incidence rate and the incidence rate in the exposed were higher in women (1.3/1000 person-years and 4.4/1000 person-years) than in men (0.8/1000 person-years and 2.7/1000 person-years), so their rate ratios were approximately the same (Table 2). Although the unexposed incidence rate of venous thrombosis increased with age, the incidence rate in the subjects exposed to air travel was highest in the youngest age category (4.9/1000 person-years, CI95 0.9-12.1/1000 person-years) and lowest in the oldest (2.9/1000 person-years, CI95 0.7-6.5/1000 person-years), and hence the rate ratio decreased with age, with an IRR of 7.7 (CI95 1.6-38.4) for those under 30 (Table 2). Women using oral contraceptives had an increased risk of venous thrombosis, both at baseline (IR 1.9, CI95 0.6-3.9) and after long distance flights (IR 6.6, CI95 1.2-16.4). Thus, the incidence rate ratio of exposure to air travel was higher in women using oral contraceptives (3.6, CI95 0.8-14.9) than in women not using hormone therapy (2.2, CI95 0.6-8.1). The baseline incidence rate of venous thrombosis did not differ much between subgroups based on height. The incidence rate after air travel was highest in individuals shorter than 165 cm (IR 6.3/1000 person years, CI95 2.4-12.0/1000 person years) and lowest in those between 165 and 185 cm (IR 2.4/1000 person years, CI95 1.2-4.0/1000 person years). In employees taller than 185 cm, the incidence rate after air travel was 3.6/1000 person years (CI95 0.9-8.1/1000 person years). Hence, the rate ratio was highest in the shortest employees (IRR 9.8, CI95 3.1-30.9). BMI did not affect the baseline thrombosis risk, but the incidence rate after air travel was higher in employees with a BMI over 25 kg/m^2 (IR 4.7/1000 person years, CI95 2.6-7.4/1000 person years) as compared to those with a BMI lower than 25 kg/m^2 (IR 1.9/1000 person years, CI95 0.7-3.7/1000 person years).

The risk of venous thrombosis increased with the number of flights per employee, as shown in Table 3. When someone was exposed to only one or two long haul flights, the incidence rate was 2.6 (CI95 1.4-3.2) per 1000 person-years, which tripled after exposure to 5 or more long haul flights. With each extra flight the employees were exposed to, the risk increased 1.4-fold (CI95 1.2-1.6).

Table 3: Incidence rates and incidence rate ratios for exposure to an increasing number of flights. Only flights longer than 4 hours were taken into account.

Number of flights	Cases	PY*	IR (95%CI)**	IRR (95%CI)#
0	29	27 772	1.0 (0.7-1.5)	1$
1-2	13	5 052	2.6 (1.4-3.2)	2.5 (1.2-4.9)
3-4	6	1 494	4.4 (1.5-8.7)	4.2 (1.4-10.3)
5 or more	3	547	7.2 (1.3-18.0)	6.9 (1.3-22.3)

$ *The reference category for calculation of incidence rate ratios was no flight longer than 4 hours in the preceding 8 weeks.*
* *PY= Person-years*
** *Incidence rate per 1000 person-years and 95% CIs*
# *Incidence rate ratio adjusted for age and sex and 95% CIs*

The effect of duration of travel is shown in Table 4. The incidence rate increased from 0.5/1000 person-years (CI95 0-1.4/1000 person-years) when employees had travelled for less than 4 hours, to 5.9/1000 person-years (CI95 1.5-13.4/1000 person-years) when they had travelled for more than 16 hours. For each extra hour duration of the flight, the incidence rate ratio increased 1.1 fold (CI95 1.1-1.2). Expressed as risk per number of flights, the risk increased from 1/106 667 flights for flights shorter than 4 hours up to 1/1264 for flights longer than 16 hours.

Table 4: Incidence rates and incidence rate ratios after flights of increasing duration.

Duration	Cases	PY*	IR(CI95)**	IRR(CI95)#	Flights	Risk/ flight***	Case/ number of flights###
No flight	29	27 772	1.0 (0.7-1.5)	1$	213 333	0.9	1/106 667
0-4 hrs	2	4 267	0.5 (0-1.4)	0.4 (0.1-1.9)	46 272	10.8	1/9 254
4-8 hrs	5	2 180	2.3 (0.7-4.8)	2.3 (0.9-5.9)	37 903	15.8	1/6 317
8-12 hrs	6	2 676	2.2 (0.8-4.4)	2.2 (0.9-5.4)	13 209	53.0	1/1 887
12-16 hrs	7	1 344	5.2 (2.0-9.9)	5.3 (2.3-12.4)	5 045	79.3	1/1 264
>16 hrs	4	672	5.9 (1.5-13.4)	5.7 (2.0-16.5)			

$ *The reference category for calculation of incidence rate ratios was no flight in a time-window of 8 weeks*
* *PY: Person-years*
** *IR: Incidence rate per 1000 person-years with CI95s*
\# *IRR: Incidence rate ratio adjusted for age and sex with CI95s*
*** *Risk per flight: risk per 100 000 flights*
\### *Number of flights needed to cause one venous thrombosis*

In Table 5, the incidence rates and rate ratios are shown in relation to the time that had passed after travelling. In the first two weeks after a long haul flight, the risk of venous thrombosis was highest, with an incidence rate of 4.7 per 1000 person-years (CI95 2.4-7.7/1000 person-years). The risk gradually decreased with time and returned to the baseline risk after 8 weeks.

Table 5: Incidence rates and incidence rate ratios in varying time windows after long haul flights. Only long haul flights (>4 hours) were taken into account

Time window	Cases	PY*	IR (95%CI)**	IRR (95%CI)#
No flight <12 wks	29	30 173	1.0 (0.6-1.4)	1$
0-2 weeks	12	2 579	4.7 (2.4-7.7)	4.9 (2.5-9.9)
2-4 weeks	5	1 713	2.9 (0.9-6.1)	3.1 (1.2-8.2)
4-8 weeks	5	2 548	2.0 (0.6-4.1)	2.2 (0.8-5.7)
8-12 weeks	2	1 897	1.1 (0.1-3.1)	1.2 (0.3-4.9)

* *Person-years*
** *Incidence rate per 1000 person-years and CI95s*
\# *Incidence rate ratio adjusted for age and sex and CI95s*
$ *Reference category*

Discussion

In this follow-up study, we found an overall absolute risk of symptomatic venous thrombosis of 1 per 4656 passengers within 8 weeks after flights longer than 4 hours. This is equivalent to an incidence rate of 3.2 per 1000 person-years. The risk was 3.2-fold increased compared to those who did not travel by air. The risk of venous thrombosis increased with exposure to several flights and longer duration of travel and it decreased with time after a flight. It was particularly high in younger travellers, women - especially those taking oral contraceptives - individuals who were particularly short or tall and those with a BMI over 25 kg/m^2, although due to the small number of cases, some confidence intervals were wide, indicating considerable uncertainty for the effect estimates.

The observed rate ratio of 3.2 for flights longer than 4 hours is similar to the odds ratios found in most case-control studies[3,4,7,8]. Only two studies have previously described absolute risks of venous thrombosis after air travel, but only for severe pulmonary embolism occurring immediately after flying[9,10]. In our study, the risk of venous thrombosis was highest in the first 2 weeks after air travel, which was also demonstrated by Kelman in a record-linkage study[5].

Previous studies showed a dose-response relationship between the distance travelled and the risk of venous thrombosis[9,10]. In our study we observed three dose-response relationships. The risk of venous thrombosis increased with duration of air travel and number of flights and decreased with time after the flight. These dose-response relationships are in line with a causal association between air travel and deep vein thrombosis.

The effect of air travel was pronounced in women using oral contraceptives. This was also demonstrated in a previous case-control study[7]. Travellers who were particularly short or tall also had a higher risk of venous thrombosis after air travel than those with a height between 165 and 185 cm. In the tall travellers, this may be explained by an extremely cramped position due to insufficient leg-space. In travellers who are shorter than 165 cm, the increased risk may be explained by pressure on the poplitial vein by the airplane seat, when their feet do not touch the floor. This higher risk in both tall and short travellers was previously found in a large population-based case-control study[3]. This is an important finding that has now been demonstrated in two different populations, indicating a need for adjustable seating in the aircraft.

A remarkable finding in our study was that the incidence rate of venous thrombosis after exposure to flights shorter than 4 hours seemed lower (0.5/1000 person-years) than the unexposed incidence rate (1.0/1000 person-years). Although the confidence intervals overlap and a difference by chance cannot be ruled out, we think that it may be explained by a so-called healthy traveller effect, which has also been proposed by Kelman and colleagues[5]. This implies that the incidence rate in the absence of travel is lower in a travelling population than in the general population, since the former is generally healthier. To assess whether this was the case in our study, we separately calculated the baseline (unexposed) incidence rates for employees who travelled at least once a year and for those who travelled less than once a year. We found that the baseline incidence rate was indeed lower in employees who travelled more frequently (incidence rates

0.5/1000 person-years vs 1.2/1000 person-years for those who travelled hardly). One could therefore argue to use only employees who made at least one long haul flight per year as a reference group, which would have resulted in higher rate ratios (which can be inferred from the tables). However, the absolute risks would have remained the same.

Another remarkable finding in this study was the high risk in young travellers. This may be due to a phenomenon called attrition of susceptibles, meaning that susceptible individuals are likely to develop a disease shortly after start of exposure to a risk factor, such as haemorrhage shortly after start of anticoagulant therapy[18]. Most employees in our cohort had been frequent travellers long before our observation period started. Since the youngest employees are most likely to be 'new frequent travellers', this may explain the high absolute risk of thrombosis after air travel in the youngest age category. We assessed whether this was the case as follows: If attrition of susceptibles is present, the baseline incidence rate (i.e. the incidence rate of venous thrombosis without exposure to air travel) in employees who hardly travel (less than once a year) would increase with age. The baseline incidence in employees who do fly frequently (> once a year) would not increase as much with age, since in this group, susceptible individuals would already have suffered from VT at a younger age, soon after they became frequent traveller, and hence be excluded from our study population. We found that in our study, the baseline incidence in individuals with a low travel-frequency (less than once a year) indeed rose from 0.7/1000 person years in the youngest age category (<30 years), to 3.2/1000 person years in the oldest age category (>50 years). In contrast, in individuals with a higher travel frequency, the baseline incidence rate in both the youngest age category and those between 30 and 50 was 0.8 per 1000 person years, whereas no VT occurred in 1521 person-years in the oldest age category. Furthermore, in the individuals with a low travel-frequency (< once per year), the incidences in all age-groups were very high in case they did travel (24/1000 person years for those under 30, 7/1000 person years for those between 30-50 and 40/1000 person years for those over 50). So, in these subjects, who do not travel on a regular basis, the thrombosis risk is high when they occasionally do. These results all suggest that the risk of air-travel related VT is highest in susceptible subjects soon after they first start travelling by air, i.e. that attrition of susceptibles is present.

A possible limitation of this study is the response of 32%. Employees who suffered from venous thrombosis may be more likely to complete the questionnaire than employees who did not. This would only create bias if employees who suffered from VT directly after air travel responded more frequently than those who suffered from thrombosis without air travel. The response varied considerably per organisation between 15% and 80%. To assess the effect of the response, we analyzed organisations with a low response (<60%) and those with a high response (>60%) separately. The outcomes did not differ substantially between these two groups of employees, indicating that the low response did not bias our findings. Furthermore, we may have missed employees who died or stopped working due to disability resulting from a venous thrombosis. Although this is unlikely to have occurred often, it may have led to an underestimation of the number of cases.

Another limitation is that these results cannot be generalized to an older, less healthy population. This study has been performed in a working population with a mean age of 40. We do not have any data on people older than 70, nor on individuals who are not fit enough to be employed. Considering this, the absolute risk of venous thrombosis in the general population is likely to be higher than the risk we found. Furthermore, the results cannot be generalized to individuals that have a history of venous thrombosis, as we only considered first events.

From this cohort study among employees of international organisations and companies, we conclude that the absolute risk of symptomatic venous thrombosis within 8 weeks of a flight of at least 4 hours is approximately 1 per 4500 flights. Furthermore, we found 3 dose-response relationships: the risk of venous thrombosis increased with duration of travel and number of flights a person was exposed to and decreased with time after a long haul flight. The results of our study do not justify the use of potentially dangerous prophylaxis such as anticoagulant therapy for all long haul air travellers, since this may do more harm than good[17]. However, for some subgroups of people with a highly increased risk, the risk-benefit ratio may favour the use of prophylactic measures. Large randomized trials are required to assess who would benefit most from which prophylactic measure.

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Chapter 5

The Risk of Venous Thrombosis after Air Travel: the contribution of clinical risk factors

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Abstract

Air travel increases the risk of venous thrombosis (VT), but not to an extent that necessitates the widespread use of prophylaxis. However, prophylaxis may be indicated in certain subgroups of travellers that are at increased risk. The aim of this study was to assess the effect of transient clinical risk factors for VT (such as recent surgery or pregnancy) on the risk of air travel-related VT.

Methods: A nested case-control study in a cohort of employees of international companies and organisations. Through questionnaires we assessed the occurrence of VT and prevalence of its risk factors. Exposure to air travel was assessed using flight data provided by the companies. Odds ratios were calculated for each risk factor separately and for the combination of these risk factors with air travel.

Results: Transient risk factors that showed most interaction with air travel were surgery (OR of surgery combined with air travel 19.8 (CI95 5.6-70.1)), malignant diseases (OR 18.0, CI95 2.2-148.7) and pregnancy (OR 14.3, CI95 1.7-121.0). Conclusions: The risk of travel-related VT is highest in pregnant travellers, those who have recently undergone surgery and those with a malignant disease.

Introduction

Since the first 4 cases of venous thrombosis related to air travel were published by Jacques Louvell in 1951[1], many authors have described case-reports of travel-related venous thrombosis. Only after a young woman died of pulmonary embolism at Heathrow Airport shortly after an intercontinental flight, more controlled studies on the association between long distance travel and venous thrombosis have been performed.

First, case-control studies demonstrated that the risk of symptomatic venous thrombotic events within a few weeks after a long haul flight is approximately 2-4 fold increased [2-8]. We recently described the same relative risk in a cohort-study among frequently travelling employees of international companies and organisations[9]. In this study, the absolute risk of developing symptomatic venous thrombosis within 8 weeks of flights longer than 4 hours was 1 in 4500 flights. This risk increased with flight-duration and the number of flights a person was exposed to and decreased with time after a long haul flight. These three dose-response relationships strongly indicate a causal association between air travel and venous thrombosis.

The absolute risk of 1 in 4500 passengers in the general travelling population is not high enough to promote the widespread use of potentially harmful preventive measures, such as anticoagulant therapy. However, for some subgroups of travellers at highly increased risk, the risk-benefit ratio may favour the use of prophylactic measures. It is therefore important to identify individuals that are most at risk for developing travel-related venous thrombosis. In previous studies, the risk was found to be increased in individuals using oral contraceptives, in those who were particularly short, tall or obese and in travellers with factor V Leiden mutation[3-7]. The effect of other risk factors, such as recent surgery, pregnancy or a plaster cast, on the risk of venous thrombosis in air-travellers has not been studied before.

The objective of the current nested case-control study among frequently flying employees of international companies and organisations was to assess the effect of transient classical risk factors for venous thrombosis on the occurrence of air travel-related venous thrombosis.

Methods

Study design

We performed a cohort study of frequently travelling employees of large international companies and organisations. The occurrence of venous thrombosis was related to exposure to air travel. The design of the study has been described in detail in a previous publication[9]. To assess the effect of transient risk factors for VT, we performed a case-control analysis within this cohort.

Data collection and questionnaires

The cohort in this study consisted of employees of large international companies and organisations in which air travel was frequent. The employees were followed for a period of approximately 5 years. Start of follow up varied per company, between January 1st 1998 to January 1st 2001 or at start of the employment if later. Follow-up ended at a fixed date per company, between December 1st 2002 and January 1st 2006, or when venous thrombosis was diagnosed or at the end of employment, whichever occurred first.

All participating employees received a web-based questionnaire to assess the occurrence of venous thrombosis during the follow up period. Furthermore, we asked questions on presence of transient risk factors for venous thrombosis in a three-month period. Individuals who suffered from venous thrombosis were asked to answer these questions for the three months preceding their diagnosis. Individuals who had not suffered from venous thrombosis were asked to answer these questions for a randomly picked period of 3 months. Thus, we assessed the prevalence of surgery, plaster-cast, pregnancy, delivery, hormone replacement therapy and malignancies (active malignant disease) in the 3-month period that we were interested in. We did not specify the type of surgery. Flight data (date and duration of each individual flight) were provided by the participating companies. Using these data, we assessed who had been exposed to at least one long haul flight (a flight of at least 4 hours duration) in the three month period that we were interested in.

The first part of our study, performed in one company (Nestlé, Vevey, Switzerland), was a pilot study. Employees from this company (n= 1163) had to be excluded from the current analysis, since the questions regarding transient risk factors for venous thrombosis were added after this pilot study.

Outcomes

Participants who reported venous thrombosis were asked to sign a consent form for medical chart review. Only symptomatic first episodes of venous thrombosis, diagnosed with objective methods, were considered. Deep vein thrombosis had to be diagnosed by compression ultrasonography or venography. Pulmonary embolism had to be diagnosed by spiral-CT scanning, high probability ventilation-perfusion scanning or angiography. Superficial thrombophlebitis was not included.

Statistical analysis

To assess the effect of transient risk factors for venous thrombosis, we used a nested case-control design and determined odds ratios. We assessed how many employees were exposed to neither air travel nor the other risk factor (for example surgery), only air travel, only the other risk factor and both air travel and the other risk factor. Odds ratios and corresponding 95% confidence intervals were calculated for these exposure categories, with individuals exposed to neither air travel nor the other risk factor as a reference category. All odds ratios were adjusted for age and sex using logistic regression.

For all statistical analyses we used SPSS version 12.0 (SPSS Inc., Chicago, Ill) and Stata statistical software (Stata Corp LP, College Station, TX).

Results

Participants and thrombotic events

A total of 8 755 employees of 8 different companies or organisations participated in our study. General characteristics of all participants have been described in a previous publication[9]. More than half of the responders (n=4915, 56%) were men and the mean age was 40 years. Of these 8 755 employees, 1 163 participated in the pilot study, and were excluded from the current analysis. The remaining 7 592 employees were followed up for a total of 33 279 person years (py), with an average follow up per person of 4.4 years. The total time the employees were exposed to air travel added up to 5 916 py. In the follow up period, 44 employees were diagnosed with venous thrombosis. Twenty-seven were diagnosed with deep vein thrombosis of the leg, 8 with pulmonary embolism, 7 with both deep vein thrombosis of the leg and pulmonary embolism and 2 with deep vein thrombosis of the arm. Out of the 44 thrombotic events, 18 occurred within 3 months of a long haul flight.

Effect of transient risk factors

To assess the effect of transient risk factors for VT, we asked questions about the presence of such risk factors in a three-month period: the three months before the diagnosis for the cases and a randomly picked three month period for the non-cases. We calculated odds ratios for presence of only the risk factor, only air travel or both, as compared to employees who had not travelled by air without the risk factor of interest. All odds ratios were adjusted for age and sex and are shown in Table 1.

As compared to non-travellers who had not recently undergone surgery, individuals who had undergone surgery had an odds ratio of 9.1 (CI95 3.6-23.1). For individuals who had travelled and undergone surgery it was 19.8 (CI95 5.6-70.1).

For presence of a malignant disease (diagnosed in the follow-up period or within 5 years before start of the follow up period), the OR without air-travel was 8.8 (CI95 2.0-39.4). There was only one patient who suffered from cancer and had travelled by air in the three months before the diagnosis of VT (OR 18.0, CI95 2.2-148.7).

Out of the 44 cases, 4 had had a plaster cast in the three months preceding their diagnosis, of which one had also travelled by air. The odds ratio for plaster cast only was 23.9 (CI95 6.7-85.9), whereas it was 24.4 (CI95 2.9-207.1) for both plaster cast and air travel.

For the analysis of the effect of oral contraceptives, hormone replacement therapy (HRT), pregnancy or delivery, only female cases and controls were included. There were 26 female cases, 10 of whom had taken oral contraceptives. The odds ratio for women only taking oral contraceptives was 3.2 (CI95 1.0-9.7), whereas it was 8.2 (CI95 2.3-27.7) for women who took oral contraceptives and travelled by air. The odds ratio was 6.8 (CI95 1.5-32.8) for women who travelled and took HRT.

Three women with thrombosis were pregnant in the 3 months before their diagnosis of VT. The odds ratio for both pregnancy and air travel was 14.3 (CI95 1.7-121.0), whereas it was 4.3 (CI95 0.9-19.8) for women who had been pregnant but had not travelled.

Discussion

In this nested case-control study in a cohort of frequently flying employees, we studied the effect of other risk factors for VT on the risk of VT after air-travel. Most of the transient risk factors we studied (recent surgery, plaster cast, malignant diseases, oral contraceptive use, pregnancy and recent delivery) also increased the risk of VT in our study population. For each of these risk factors, the risk was clearly higher in combination with air travel. This effect was strongest for recent surgery, malignant diseases and pregnancy.

Interaction of air travel with transient risk factors for venous thrombosis (recent surgery, malignant diseases, plaster cast, oral contraceptive use, pregnancy and recent delivery) has not been studied extensively before. Two previous studies found a synergistically increased risk for the combination of oral

Table 1. Odds ratios for transient risk factors for venous thrombosis combined with air travel.

	Air travel	Other factor	Cases	Controls	OR*	95%CI
Surgery	-	-	20	5062	1	
	-	+	6	148	9.1	3.6-23.1
	+	-	15	2045	2.1	1.0-4.1
	+	+	3	35	19.8	5.6-70.1
Malignancy	-	-	24	5174	1	
	-	+	2	36	8.8	2.0-39.4
	+	-	17	2070	2.0	1.1-3.8
	+	+	1	10	18.0	2.2-148.7
Plaster cast	-	-	23	5184	1	
	-	+	3	26	23.9	6.7-85.9
	+	-	17	2070	2.1	1.1-4.0
	+	+	1	10	24.4	2.9-207.1
Oral contraceptives	-	-	10	2129	1	
	-	+	6	526	3.2	1.0-9.7
	+	-	6	522	2.5	0.9-7.0
	+	+	4	133	8.2	2.3-28.7
HRT	-	-	15	2479	1	
	-	+	1	181	1.0	0.1-7.9
	+	-	8	600	2.2	0.9-5.2
	+	+	2	52	6.8	1.4-32.8
Pregnancy	-	-	14	2566	1	
	-	+	2	92	4.3	0.9-19.8
	+	-	9	640	2.6	1.1-6.0
	+	+	1	14	14.3	1.7-121.0
Delivery	-	-	14	2620	1	
	-	+	2	38	10.2	2.2-46.9
	+	-	10	649	2.9	1.3-6.6
	+	+	0	2	-	

* *OR: Odds ratio, adjusted for age and sex*

contraceptive use and long distance travel[3,7-9]. In our population, the odds ratio of oral contraceptives without air travel was 3.2 (CI95 1.6-17.1), whereas it was 8.2 (CI95 2.3-28.7) when air travel was present as well, confirming this synergistic effect between oral contraceptive use and long distance travel. This is also supported by a study in which women using oral contraceptives were found to have more coagulation activation during a long haul flight[10].

There is only one previous publication that mentioned the occurrence of venous thrombosis after air travel in post-surgical patients[11], but it was not possible to assess the effect of combination of air travel and surgery on the risk of venous thrombosis in this study. In our study, the risk was already much increased in individuals with recent surgery (OR 9.1, CI95 3.6-23.1), but it was even higher in those who had also travelled by air (OR 19.8, CI95 5.6-70.1).

Similar odds ratios were found for the combination of malignant disease and recent air travel, although there was only one case with a malignancy who had also travelled by air in the 3 months preceding the diagnosis. We observed no increased risk for the combination of air travel and plaster cast, but again, there was only one case who had a plaster cast and also travelled by air before the thrombotic event.

The effect of the combination of a recent delivery and air travel could not be assessed, since there were no women who had had venous thrombosis and both given birth and travelled by air in the 3 months before their diagnosis. Since air travel is usually discouraged in women over 32 weeks pregnant, it is likely that women about to give birth rarely travel by air. There was only one case who had travelled by air and been pregnant in the 3 months before the diagnosis. Therefore, the confidence interval of the odds ratio for the combination of the 2 risk factors is wide (OR 14.3, CI95 1.7-121.0).

The same problem was encountered with hormone replacement therapy, since there were only relatively few women using HRT with only 3 cases, of whom 2 had also travelled by air.

A possible limitation of our study is the relatively small number of cases with a combination of air travel and the risk factor of interest. Therefore, the confidence intervals were wide. Nevertheless, we found consistently increased risks for almost all classical risk factors for venous thrombosis which appeared to double in combination with air travel. Furthermore, it may be possible that only the least sick employees who had a malignant disease or plaster cast travelled by air and that the sickest persons with these risk factors did not travel. This may have lead to an underestimation of the risk associated with these risk factors.

From this nested-case control study, we conclude that the risk of travel-related venous thrombosis is most increased in travellers who have recently undergone surgery, those taking oral contraceptives and pregnant women. The risk groups that we have identified in this study should be aware of their increased risk. In these populations, the risk-benefit ratio of prophylaxis may favour the use of prophylaxis. Therefore, large randomised controlled studies in travellers at increased risk are needed to assess which preventive measure is most effective and least harmful.

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Chapter 6

The effect of elevated levels of coagulation factors on the risk of venous thrombosis in long distance travellers

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Abstract

The risk of venous thrombosis is increased after long distance travel. Identifying high-risk groups may provide a basis for targeted prevention. We assessed the effect of increased levels of coagulation factors and combinations of risk factors on the risk of venous thrombosis in travellers in a large case-control study.

We calculated odds ratios for 334 travellers (200 cases and 134 controls) with coagulation factors II (prothrombin, FII), VII (FVII), VIII (FVIII) and IX (FIX), fibrinogen and vWF above the 80th percentile, for increasing numbers of risk factors and for specific combinations of risk factors. The risk was increased in travellers with a high FII (OR 2.2, CI95 1.3-3.7) and FVIII (OR 6.2, CI95 3.6-10.5) as compared to travellers with normal levels. High FIX and fibrinogen levels increased the risk in air travellers (OR FIX 3.2, CI95 0.9-11.0; OR fibrinogen 2.0, CI95 0.7-5.5), but not in other travellers. The odds ratios increased with the number of risk factors and the risk was increased the most in women with the combination of oral contraceptives and high FVIII levels (OR 51.7, CI95 5.4-498).

From this case-control study in travellers, we conclude that increased levels of factors II and VIII increase the risk of venous thrombosis. Furthermore, the risk is greatly increased if other risk factors are present as well.

Introduction

Several studies have shown an association between long distance travel and the risk of venous thrombosis. Most case-control[1-6] and follow up studies showed a 2-4 fold increased risk[7-9]. A dose-response relationship between the distance travelled and the incidence of venous thrombosis has been demonstrated in three studies[10-12] and the overall risk of venous thrombosis after air travel has been found to be 1 per 4500 flights in a frequently travelling population[12].

Even though the risk of venous thrombosis is increased after long distance travel, it is not sufficiently elevated to justify the use of prophylaxis in all long distance travellers, since most prophylactic measures, such as anticoagulant therapy, are potentially harmful[13]. Only in individuals at particularly increased risk the risk-benefit ratio may favour the use of such prophylactic measures. However, knowledge on who is most at risk among long distance travellers is limited. As a result, the use of prophylactic measures varies widel [14]. Previous reports showed excess risks for travellers carrying the factor V Leiden mutation (FVL) or the prothrombin mutation (PT20210A), women using oral contraceptives and travellers who are obese or particularly tall or short[5,6,12]. The joint effect of long distance travel, either by air or by other modes of transport, and elevated levels of pro-coagulant factors has not been previously investigated

The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study is a large population-based case-control study aimed at assessing the combined effect of genetic and environmental risk factors for venous thrombosis. The aim of the current analysis was to assess the effect of elevated levels of coagulation factors and combinations with other known risk factors (FVL mutation, prothrombin mutation, increased body mass index, oral contraceptive use and a positive family history of venous thrombosis) on the risk of venous thrombosis in long distance travellers, both by air and by other means of transport.

Materials and methods

Patients and control subjects

The MEGA study is a population-based case-control study on genetic and environmental risk factors for venous thrombosis. Cases were consecutive patients with a first episode of deep vein thrombosis or pulmonary embolism recruited at six anticoagulant clinics in the Netherlands. Patients who were unable to complete a questionnaire (due to language or severe psychiatric problems) and patients who died soon after the diagnosis were not included, nor were patients without a partner. Partners of patients were invited as control subjects. Patients and their control subjects were recruited between March 1st 1999 and August 31st 2004. Details have been described previously [6]. From these patients and control subjects, we selected individuals who had travelled by air, bus, train or car in the 8 weeks prior to the index-date (date of the thrombotic event for each case-control pair). Each patient or control had made at least one journey of at least 4 hours. We used 4 hours and 8 weeks as cut off values for travel, because previous studies have found that the risk of venous thrombosis is increased in the first 8 weeks after journeys longer than 4 hours[12].

Questionnaire

All participants were asked to fill in a questionnaire, which contained questions regarding long distance travel by air, train, bus or car in the 8 weeks prior to the index date as well as questions on other (possible) risk factors for venous thrombosis, such as height, weight and oral contraceptive use. These questionnaires were sent to eligible patients and their partners shortly after the index date.

Laboratory assays

Approximately three months after discontinuation of oral anticoagulant therapy, patients and their partners were invited for collection of a blood sample. In patients who were still on anticoagulant therapy one year after their event, blood was drawn during anticoagulant therapy. All assays were performed in an automated machine by laboratory technicians who were unaware of the case-control status of the samples. Plasma samples were available for 200 out of 233 cases and 134 out of 181 control subjects. The remaining patients and control subjects either refused or were unable to visit the research centre for a blood draw.

Prothrombin activity (FII), Factor VII activity (FVII) and Factor VIII activity (FVIII) were measured with a mechanical clot detection method on a STA-R coagulation analyzer following the instructions of the manufacturer (Diagnostica Stago, Asnieres, France). Levels of factor IX antigen (FIX) were determined by enzyme-linked immunosorbent assay (ELISA). Fibrinogen activity was measured on the Sta-R analyzer according to methods of Clauss. In the presence of excess thrombin, the coagulation time of a diluted plasma sample was measured. Von Willebrand factor antigen (vWF) was measured with the immuno-turbidimetric method, using the STA liatest kit (rabbit anti-human vWF antibodies), following the instructions of the manufacturer.

Statistical analysis
The overall relative risk of travel in this study population has been previously described and was 2.1 (CI95 1.5-3.0)[6]. In the current analysis, we assessed the effect of elevated levels and activity of coagulation factors among travellers, as well as the effect of several combinations of risk factors. Hence, all relative risks are to be superimposed on the risk of travel itself when a comparison to non-travellers is made.

Odds ratios were adjusted for age and sex for elevated levels of all coagulation factors and their 95% confidence levels using logistic regression. Cut-off points were antigen or activity levels at the 80th and 90th percentile in the control population. Individuals who were using anticoagulant therapy at the time of blood collection were excluded from the analysis of the effect of vitamin K dependent coagulation factors (FII, FVII and FIX). Odds ratios were calculated separately for individuals who had travelled by air and those who had travelled by other means of transport.

In an effort to identify those at particularly high risk, we calculated risks for combinations of risk factors and determined the number of coagulation abnormalities present in each individual. Both high levels of coagulation factors that increased the risk of venous thrombosis in our population and well established prothrombotic risk factors[15-17] were taken into account, i.e. FII, FVIII, FVL mutation and the prothrombin mutation (PT20210A mutation). Odds ratios were calculated for the presence of 1 and 2 or more prothrombotic factors, with travellers in whom all of these factors were absent as the reference category. The same analysis was performed including also environmental risk factors. For this analysis, only risk factors that have previously been described in the literature and that were sufficiently prevalent in our population to allow such analyses were considered[6;18-20]. These were a high body mass index (BMI in the third tertile as compared to the first, i.e. higher than 26.9 kg/m^2 as compared to lower than 23.7 kg/m^2), oral contraceptive use and a positive family history for venous thrombosis (at least one thrombotic event in a parent, brother or sister).

For all analyses, one could discuss whether a conditional ('matched') analysis would be necessary, since partners of patients were used as a control population. As they were usually of the opposite sex, and generally in a similar age range, the controls were not a random sample of the population. Generally, whether or not this is relevant depends on the exposure in question. The exposure of interest here was the effect of coagulation abnormalities on travel-related thrombosis in addition to the actual travel itself. There is no reason to assume that high levels of clotting factors are more common among partners of patients than in the general population and an unconditional analysis suffices.

Therefore we performed unconditional analyses and adjusted for the potential confounders age and sex.

For all statistical analyses we used SPSS version 12.0 (SPSS, Chicago, Ill, United States).

Results

Patients and control subjects

Of the 1906 consecutive patients with venous thrombosis, 233 had travelled by air, bus, train or car in the 8 weeks prior to their thrombotic event. Of the 1906 control subjects, 182 had travelled before the index date. Plasma was available in 200 out of 233 patients (86%) and 134 of 182 control subjects (72%). Table 1 shows the general characteristics of cases and controls.

Table 1: General characteristics of patients with venous thrombosis and control subjects who travelled by air and those who travelled by other modes of transportation.

Characteristic		Air travellers		Other travellers	
		Cases (76)	Controls (52)	Cases (124)	Controls (82)
Age (yr)	Mean (range)	46.9 (22-65)	48.5 (23-68)	48.0 (21-69)	50.2 (21-68)
Sex	Men, n (%)	32 (42.1)	35 (67.3)	66 (53.2)	48 (58.5)
	Women, n(%)	44 (57.9)	17 (32.7)	58 (46.8)	34 (41.5)
BMI (kg/m^2)*	Mean (range)	26.5 (19-38)	25.7 (20-37)	27.2 (20-45)	25.6 (18-40)
OC use*	N (%**)	23 (88.5)	2 (40)	29 (82.9)	7 (43.8)
Malignancy	N (%)	0	1 (1.9)	2 (1.6)	2 (2.4)

* *BMI = body mass index, OC = oral contraceptives*

** *Percentage of pre-menopausal women.*

Coagulation factors

Mean FII, FVII, FVIII, FIX, fibrinogen and vWF levels are shown in table 2, as well as their cut-off levels for the 80th and 90th percentile in the control population. Odds ratios in travellers for elevated levels of these coagulation factors for both cut-off levels are shown in table 3. This table also shows the odds ratios separately for air travellers and other travellers, with the 80th percentile as cut-off level, all compared to travellers with normal levels.

Table 2: Levels and activity of coagulation factors in patients with venous thrombosis and control subjects and cut-off values for the 80th and 90th percentile in control subjects.

Coagulation factor	Mean (range) Cases	Mean (range) Controls	P80 Controls	P90 Controls
FII activity*, IU/ml	112 (65-150)	108 (75-150)	117	127
FVII activity, IU/ml	113 (58-250)	110 (47-170)	132	149
FVIII activity, IU/dl	140 (61-263)	106 (37-193)	130	144
FIX, IU/dl	106 (63-159)	105 (66-163)	118	128
Fibrinogen activity, g/l	3.3 (2.0-6.2)	3.2 (2.0-4.6)	3.6	3.9
vWF, g/l	147 (67-567)	109 (21-273)	134	154

* *Cases and controls that were using anticoagulant therapy at the time of the blood draw were excluded for calculation of means of vitamin-K dependent coagulation factors.*

High FII levels increased the risk of venous thrombosis among travellers. The odds ratio was similar for cut-off levels at the 80th (OR 2.2, CI95 1.3-3.7) and 90th percentile (OR 1.7, CI95 0.9-3.4). This association was somewhat stronger in air travellers (OR 3.0, CI95 1.2-7.7) than in other travellers (OR 1.9, CI95 1.0-3.7). Adjustment for presence of the PT20210A mutation did not affect our results. High FVII levels did not show an association with venous thrombosis in travellers, neither when we used the 80th percentile (OR 1.1, CI95 0.7-2.0) nor the 90th percentile (OR 0.6, CI95 0.3-1.3).

High levels of FVIII had the most pronounced effect on the risk of venous thrombosis among travellers. The odds ratio was 6.2 (CI95 3.6-10.5) when the 80th percentile was used and 7.5 (CI95 3.9-14.5) when the 90th percentile was used as cut-off level. After adjustment for vWF levels, the risk was attenuated but remained increased (OR 4.1, CI95 2.2-7.6 for FVIII above the 80th percentile). Neither FIX nor fibrinogen levels increased the risk of venous thrombosis when the 80th percentile was used. Using the 90th percentile, the odds ratio was 1.5 (CI95 0.7-3.2) for high levels of FIX and 1.5 (CI95 0.8-3.1) for high fibrinogen levels. FIX levels above the 80th percentile increased the risk of venous thrombosis in air travellers (OR 3.2, CI95 0.9-11.0), but not in other travellers (OR 0.9, CI95 0.5-1.7). For fibrinogen concentrations above the 80th percentile, we again found an effect in air travellers only (2.0 (CI95 0.7-5.5) vs 1.1 (CI95 0.6-2.0)).

Elevated levels of vWF increased the risk of venous thrombosis (OR 4.6, CI95 2.7-7.7) for all travellers, with no major differences between air travellers and other travellers. However, the effect disappeared after adjusting for FVIII.

Adjustment for oral contraceptive use did not affect any of the odds ratios mentioned above. We also calculated odds ratios separately for pulmonary embolism and deep vein thrombosis of the leg. There were no major differences between these 2 groups, although most odds ratios were slightly higher in the DVT group than in the PE group.

To assess whether duration of travel affected our results, we also calculated odds ratios including only individuals who had made at least 1 journey longer than 8 hours in the 8 weeks prior to the event or index-date. Again, this did not affect any of the results.

Table 3: Odds ratios for venous thrombosis for elevated coagulation factors in 334 travellers.

Coagulation Factor	P80[$] OR* (CI95)	P90[$$] OR* (CI95)	P80air** OR* (CI95)	P80other** OR* (CI95)
FII	2.2 (1.3-3.7)	1.7 (0.9-3.4)	3.0 (1.2-7.7)	1.9 (1.0-3.7)
FVII	1.1 (0.7-2.0)	0.6 (0.3-1.3)	1.3 (0.5-3.3)	1.2 (0.6-2.3)
FVIII	6.2 (3.6-10.5)	7.5 (3.9-14.5)	5.4 (2.3-13.0)	6.9 (3.4-13.8)
FIX	1.2 (0.7-2.1)	1.5 (0.7-3.2)	3.2 (0.9-11.0)	0.9 (0.5-1.7)
Fibrinogen	1.3 (0.8-2.2)	1.5 (0.8-3.1)	2.0 (0.7-5.5)	1.1 (0.6-2.0)
vWF	4.6 (2.7-7.7)	5.0 (2.6-9.3)	4.1 (1.7-9.9)	4.9 (2.5-9.5)

* *Odds ratios are adjusted for age and sex*

** *Air= Odds ratios for individuals who had travelled by air. Other= Odds ratios for individuals who had travelled by bus, train or car*

$: *Odds ratios elevated levels of all coagulation factors with the P80 in the control population used as cut off levels (cut off levels are mentioned in Table 1)*

$$: *Odds ratio for elevated levels of all coagulation factors using the P90 in the control population as cut off levels (again, cut off levels are mentioned in Table 1)*

Combinations of risk factors

Odds ratios for the number of coagulation abnormalities present per individual (FII, FVIII, FVL mutation and prothrombin mutation) are shown in Table 4. When one abnormality was present, the odds ratio was 4.3 (CI95 2.6-7.2) as compared to travellers in whom all factors were normal. This increased to an odds ratio of 10.0 (CI95 4.7-217) when 2 or more clotting abnormalities were present. The increase in odds ratios was more pronounced in air travellers than in other travellers.

Table 4: Odds ratios for venous thrombosis (adjusted for age and sex) for total number of risk factors present per individual.

	Cases n	Control n	All OR (CI95)	Air travellers OR (CI95)	Other travellers OR (CI95)
Number of laboratory risk factors*					
0	45	82	1#	1#	1#
1	99	42	4.3 (2.6-7.2)	3.1 (1.4-7.1)	5.4 (2.7-10.8)
≥ 2	56	10	10.0 (4.7-21.7)	36.4 (4.4-298)	7.3 (3.0-17.6)
Total number of risk factors**					
0	12	48	1#	1#	1#
1	54	48	4.4 (2.1-9.2)	2.9 (0.9-9.6)	5.8 (2.2-15.4)
2	54	28	7.4 (3.4-16.3)	7.5 (2.2-25.9)	8.0 (2.9-22.4)
3	60	7	32.1 (11.7-88.2)	-	22.9 (7.2-73.3)
4-7	20	3	23.9 (6.0-95.0)	-	16.8 (3.7-77.1)

* *High (>P80) FII, FVIII, FVL mutation and/or prothrombin mutation*

** *Any of the prothrombotic factors mentioned above, as well as oral contraceptives, positive family history (at least 1 thrombotic event in a parent, brother or sister) and BMI (3rd tertile as compared to 1st). The cut off values for tertiles of BMI were 23.7 and 26.9.*

\# *Reference category, travelling individuals in whom all coagulation factors are normal and in whom the clinical factors were absent*

The odds ratio also increased with the total number of risk factors (coagulation abnormalities and environmental risk factors combined) present per subject. When only one out of 7 possible risk factors (FII, FVIII, FVL mutation, prothrombin mutation, a high BMI, oral contraceptive use and a positive family history) was present, the odds ratio was 4.4 (CI95 2.1-9.2) as compared to travellers with none.

This increased to 23.9 (CI95 6.0-95.0) when a traveller had 4 or more risk factors. The risk again increased slightly more in air travellers than in other travellers.

Odds ratios for all combinations of risk factors are shown in Table 5. The risk was high for most combinations with FVL. Individuals with FVL combined with high FII had an odds ratio of 17.5 (CI95 2.3-135), combined with FVIII it was 24.7 (CI95 4.4-139) and combined with a high BMI it was 20.5 (CI95 2.5-170).

Women using oral contraceptives who also had FVL had an odds ratio of 18.3 (CI95 2.0-171). Having a positive family history did not add to the risk of FVL alone (OR 4.7, CI95 1.7-16.5). Women using oral contraceptives with a high FVIII had an odds ratio of 51.7 (CI95 5.4-498) and in those with a high body mass index the risk was 31.4 fold increased (CI95 3.0-334) as compared to women who did not use oral contraceptives with a low body mass index. In women using oral contraceptives, having a positive family history doubled the risk (OR of the combination 10.7, CI95 1.5-75.6). The number of cases and control subjects with specific combinations was too small to calculate odds ratios for air travellers and travellers by other means of transport separately.

Table 5 Odds ratios for venous thrombosis for combinations of risk factors.

	FII	FVIII	FVL*	OC*	BMI*	Fam**
FII	2.2 (1.3-3.7)					
FVIII	7.9 (3.4-18.3)	6.2 (3.6-10.5)				
FVL	17.5 (2.3-135)	24.7 (4.4-139)	4.5 (1.9-10.4)			
OC	4.6 (1.1-19.8)	51.7 (5.4-498)	18.3 (2.0-171)	5.0 (2.1-12.1)		
BMI	9.5 (3.6-25.1)	18.6 (7.0-49.9)	20.5 (2.5-170)	31.4 (3.0-334)	1.9 (1.4-2.7)	
Fam**	2.4 (0.9-6.1)	8.7 (3.5-21.7)	4.7 (1.7-16.5)	10.7 (1.5-75.6)	2.4 (1.0-5.8)	1.7 (1.0-2.9)

* *FVL = factor V Leiden mutation, OC= Oral Contraceptive use, BMI= body mass index > 26.9 kg/m^2 as compared to a BMI of <23.7 kg/m^2 . For each combination, the odds ratio for presence of both risk factors compared to absence of both factors is presented. In the boxes where the risk factor in the column is the same as in the row, the odds ratio for presence of only that risk factor is given.*
Fam: a positive family history, meaning at least one thrombotic event in a brother, sister or parent

Discussion

In this case-control study amongst 334 long distance travellers, we demonstrated an increased risk of venous thrombosis in individuals with high levels of coagulation factors II and VIII. The relative risk increased with the number of coagulation abnormalities (factor II, VIII, prothrombin mutation and factor V Leiden mutation) and with the overall number of risk factors present per individual (coagulation factors, high body mass index, a positive family history and oral contraceptive use). The relative risk was highest in female travellers using oral contraceptives who also had high levels of FVIII (odds ratio 51.7, CI95 5.4-498). Combinations with the factor V Leiden mutation were associated with a particularly high relative risk as well. All these effects were superimposed on the relative risk of travel itself, which is about two in this population[6].

Previous studies have also demonstrated a synergistic effect between long distance travel and other risk factors for venous thrombosis. Individuals with obesity, thrombophilia (factor V Leiden or the prothrombin 20210A mutation) and women taking oral contraceptives were shown to have an additionally increased risk when they travelled long distances [5,6]. The effect of increased levels of coagulation factors and of combinations of other risk factors for venous thrombosis has not been studied in a travelling population before. In the general population, FVIII levels higher than 150% are associated with an approximately 5-fold increased risk of venous thrombosis [16,17] and high FII increases the risk approximately two-fold [18]. We observed similar odds ratios in our travelling population. However, levels of fibrinogen and FIX are also known to increase the risk of venous thrombosis [16,19] in the general population, while in our travelling population these factors were only associated with a mildly increased risk in individuals who travelled by air.

For most coagulation abnormalities and their joint effect with environmental risk factors we observed a more pronounced excess risk for travellers by air than for travellers by other modes of transport. This may be explained either by a difference in baseline thrombosis-risk or by a different underlying mechanism (air travel compared to other modes of transport). In general, individuals who travel by air may have a lower baseline risk, because they have less other risk factors for venous thrombosis, such as malignant disease or severe obesity. This would lead to higher relative risks in those who travel by air, when the absolute excess risk due to an increased coagulation factor is equal for both modes of travel. However, when the baseline risk is similar in all travellers, a higher odds ratio for high levels of coagulation factors after air travel than after travel by other means, would indicate a different underlying pathophysiology. In our population, there were no major differences in baseline characteristics between those who travelled by air and those who travelled by other modes of transportation (Table 1). This indicates that the mechanism of venous thrombosis related to air travel may be different from that related to other modes of travel. In a previous study, coagulation parameters were measured both after air travel and after immobilisation only. Only after air travel, hypercoagulability was observed in a small subgroup of the participants, indicating that not only immobilisation plays a role in the pathogenesis of air-travel related venous thrombosis[20]. However, the numbers in our study were too small to draw solid conclusions regarding the difference between thrombosis after air-travel and that after travel by other means.

A limitation of this study is that the blood sample was collected after the thrombotic event. Therefore, we cannot exclude the possibility that differences in plasma levels of the coagulation factors between cases and control subjects were the result of the thrombotic event itself. However, the blood draw was performed at least 3 months after the thrombotic event and it is unlikely that the thrombotic event itself caused persistent abnormalities in coagulation factor levels. Furthermore, in a previous case-control study, no differences in coagulation factors were observed between patients in whom blood was drawn shortly after their thrombotic event as compared to those in whom the blood draw took place much later, sometimes even years after their diagnosis[16,19]. Anticoagulant therapy did not affect our results, since individuals who were still on anticoagulant therapy were excluded from analyses in which vitamin-K dependent coagulation factors were involved.

Another limitation is that we did not have plasma samples available of 14% of the cases and 26% of the control subjects. The reason for unavailability of a plasma sample may have been different in cases and control subjects. In cases, a reason for not visiting the research unit for a blood draw may have been severe illness, whereas in control subjects lack of motivation to visit the research centre for a blood draw may have been a reason for unavailability of a plasma sample. Cases who did not show up for a blood draw had more often suffered from pulmonary embolism than those in whom plasma was available, indicating that the former may have been more disabled after the thrombotic event. This would only have led to an underestimation of the effect of increased coagulation levels if pulmonary embolism is associated with higher levels of coagulation factors than other thrombotic events, which is unlikely. Only few studies have investigated this and the results are contradictory [21,22]. Furthermore, as we analyzed data in long distance travellers only, we do not expect that severe illness, such as advanced cancer, was a cause of unavailability of a plasma sample, as long distance travel requires some degree of healthiness.

One of the reasons for performing this study was to find out whether risk groups can be identified that could be specifically targeted for prevention. We therefore questioned whether the risk of venous thrombosis in individuals with any of the risk factors we studied would be high enough for cost-effective screening in all travellers. The absolute risk of venous thrombosis is estimated as 1 in 4500 flights of more than 4 hours [12]. This is the risk in the general travelling population, including individuals with and without the risk factors that could be screened for. The prevalence of increased FII, FVIII or FIX is 20% (as we used the 80^{th} percentile in the control population as cut-off level), that of the FVL mutation is approximately 5% and of the prothrombin mutation 2% [23,24]. The proportion of individuals with at least one of these risk factors in the general population is therefore 0.52 (1-0.8*0.8*0.8*0.95*0.98). In our study, the odds ratio for travellers with one or more of these risk factors, as compared to those with none, was 4.7. When 4500 travellers make a flight longer than 4 hours, one develops VT. Of these 4500 travellers, 2355 (52%) have at least one of the risk factors. Of the cases, 83.6% has at least one risk factor (cases are 4.7*52/48 times more likely to have at least one risk factor than to have none). If a 'positive test' would lead to treatment with for example low molecular weight heparin (LMWH), which can prevent approximately 70% of the cases [25], 57.5% of the cases (70% of 82%) would be prevented. So to prevent one case of venous thrombosis, 7826 travellers need to be screened (4500 travellers to prevent 0.575 thrombosis), of whom 4096 (52% of 7826) would have to be treated with LMWH. The risk of a major haemorrhage for the use of LMWH is approximately 0.4% over a 14-day period [26], which is 0.09% per 3 days (assuming that each traveller would take LMWH for 3 days per journey). These numbers are derived from studies including only acutely ill patients. The bleeding risk in healthy travellers is probably much lower. If we would assume that the bleeding risk in healthy travellers is approximately 1/4th of that in acutely ill patients, 3 days of anticoagulation therapy would lead to 1 serious bleeding complication per 4667 travellers, meaning that prevention of 1 thrombotic event would cause almost 1 serious bleeding complication. This strategy can therefore not be recommended, being costly and with an unfavourable risk-benefit ratio. However, if screening and subsequent treatment with LMWH would be restricted to for example women using oral contraceptives, prevention of one event would require screening of 534 travellers using oral contraceptives, of whom 255 would have to be treated. Targeted screening and prophylaxis may therefore be justifiable. Similarly, it may be considered to treat everyone with a substantially increased relative risk without screening, such as women with the combination of a high BMI and oral contraceptive use. These issues need to be further explored in a randomized controlled trial.

From this case-control study, we conclude that high levels of FII and FVIII increase the risk of venous thrombosis in travellers and that the risk is further increased with the number of risk factors present per individual, as well as in travellers with specific combinations of risk factors. The effect of the risk factors we studied is not strong enough to promote screening and subsequent potentially harmful prophylaxis in all long distance travellers. However, targeted screening and prophylaxis may be justifiable.

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Chapter 7

The incidence of venous thrombosis in commercial airline pilots: a cohort study of 2630 pilots

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Abstract

Airline pilots may be at increased risk of venous thrombosis because air travel has recently been established as a risk factor for venous thrombosis. The aim of this study was to assess the risk of venous thrombosis in a cohort of Dutch airline pilots.

Methods: Airline pilots who had been active members of the Dutch Airline Pilots Association (ALPA), in Dutch called the Vereniging Nederlandse Verkeersvliegers (VNV), were questioned for the occurrence of venous thrombosis, presence of risk factors for venous thrombosis and number of flight hours per year and rank. Incidence rates among pilots were compared to that of the general Dutch population and to a population of frequently flying employees of multinational companies.

Results: 2630 male pilots were followed up for a total of 20 420 person-years. Six venous thromboses were reported, yielding an incidence rate of 0.3/1000 py. The standardized morbidity ratio, comparing these pilots to the general Dutch population adjusted for age, was 0.8. Compared to the employees, this standardized morbidity ratio was 0.7 when all employees were included and 0.6 when only the frequently travelling employees were included. The incidence rate did not increase with number of flight hours per year and did not clearly vary by rank.

Conclusions: the risk of venous thrombosis is not increased amongst airline pilots.

Introduction

Commercial airline pilots are occupationally exposed to factors that may have a negative impact on their health. Even though their overall mortality is lower than that in the general population[1-3], some diseases occur more often in airline pilots. Cohort studies have shown that the incidence rate of malignant diseases is increased in aviation crew members[3-11]. Especially skin-cancer (both melanoma and non-melanoma), leukaemia and breast-cancer occur more frequently in airline cabin crew than in the general population, possibly due to exposure to cosmic radiation, jet fuel, cabin air pollutants or constant changing of the circadian rhythm. Cosmic radiation may also be responsible for an increased risk of developing cataract later in life[12]. Furthermore, the incidence rates of HIV and AIDS, dermatitis and injuries have been shown to be increased in cabin crew members[3,13,14] as compared to the general population.

In recent years, it has become clear that long distance air travel increases the risk of venous thrombosis. Case-control and follow up studies have demonstrated that risk of venous thrombosis shortly after long haul travel is approximately 2-4 fold increased[15-19]. The absolute risk of a symptomatic venous thrombotic event within 8 weeks of flights longer than 4 hours is approximately 1 in 4500 flights[17]. The risk increases with duration of travel[17,20,21] and particularly when individuals are exposed to several flights within a short time period[17].

Because of their frequent exposure to air travel and because of the higher prevalence of conditions that increase the risk of venous thrombosis (malignant diseases, injuries), commercial airline pilots may be at increased risk of developing venous thrombosis. No large epidemiological studies have so far investigated the incidence of venous thrombotic disease in airline pilots. Knowledge of this incidence rate is needed to provide airline pilots with solid advice regarding the use of prophylactic measures such as exercises or elastic compression stockings. When the incidence rate is indeed increased, venous thrombosis may be a serious occupational health problem for airline pilots, since they are usually not allowed to fly while using anticoagulant drugs.

The aim of the current study was to assess the incidence rate of symptomatic venous thrombosis in commercial airline pilots and to compare this incidence rate to that of the general population as well as to that of a frequently travelling population of employees of international companies and organisations. The employees were used as a second control population in order to take the so-called healthy worker effect into account (meaning that the incidence rate of many diseases is lower in a working population than in the general population). Furthermore, we assessed the effect of number of flight-hours per year and type of most flown airplane on this incidence rate.

Methods

Study design

We performed a cohort study among commercial airline pilots. During a follow up period of 10 years, we assessed the occurrence of venous thrombotic events.

Participants: airline pilots

More than 95% of all commercial airline pilots in the Netherlands are member of the Dutch Airline Pilot Association (APLA), in Dutch called the Vereniging Nederlandse Verkeersvliegers (VNV). All pilots who were a member of the VNV at some point during the follow-up period and who were still alive in March 2003 were included in the study. Only the years that they were employed as a commercial airline pilot contributed to the total number of person years of follow up. The follow-up period started at January 1st 1993 or at start of employment as a commercial airline pilot if this was later. Follow-up ended at January 1st 2003, when venous thrombosis was diagnosed or when the employment as a commercial airline pilot ended, whichever occurred first. The VNV provided us with names and addresses of all possible participants. For the main analysis, only individuals who were still members of the VNV at the time the study was conducted were included. However, airline pilots may have ended their membership of the VNV because of occurrence of disease, such as venous thrombosis. Therefore, we also sent questionnaires to all pilots who had ended their membership of the VNV during the follow up period. Furthermore, the VNV provided us with data (names, birth dates and last known addresses) on pilots that had been a member after January 1993, but who had deceased at the time we performed the study, which made it possible to assess whether any of the deceased pilots had died due to venous thrombosis.

Control populations

The incidence rates of venous thrombosis in airline pilots were compared to two control populations. The first control group was the general Dutch population in 1994. Age-specific incidence rates of venous thrombosis were obtained through Prismant, a Dutch institution that keeps statistics on incidence rates according to ICD-9 codes (Prismant, Utrecht, the Netherlands).

As a so-called healthy worker effect (individuals who are employed are generally more healthy than those who are not) is likely to be present when comparing to the general population, we also included a second control group in our analysis. This control group consisted of a cohort of frequently flying employees of international companies and organisations. These employees had been enrolled in a study on the absolute risk of venous thrombosis after air travel, the results of which have recently been published[17]. All employees in this cohort received electronic questionnaires on the occurrence of venous thrombosis during a 5-year follow up period. From this cohort of 8755 employees, those who had made at least 5 long haul flights per year on average were selected. Their incidence rate of venous thrombosis during the time they were not exposed to air travel was compared to that of the airline pilots.

Questionnaires and flight data

All pilots were sent questionnaires with questions on general characteristics, such as age and sex, occurrence of venous thrombosis (at any time point during the follow up period), risk factors for venous thrombosis and flight data (number of flight hours per year, employing airline, types of airplanes flown and rank). Questionnaires were sent through regular mail and non-responding pilots received up to 2 reminders with 2-week intervals.

Outcomes

Participants who reported venous thrombosis were asked to fill in a consent form for medical chart review. Only symptomatic first venous thrombotic events that were diagnosed with objective methods were considered. Deep vein thrombosis had to be diagnosed by compression ultrasonography or venography. Pulmonary embolism had to be diagnosed by spiral-CT scanning, high probability ventilation-perfusion scanning or angiography. Superficial thrombophlebitis was not included.

Of the members who were deceased, we obtained causes of death from the central Bureau of Statistics (CBS), where all death certificates are registered.

Statistical analysis

Incidence rates were calculated by dividing the number of events by the total number of person-years the pilots were followed. We calculated both the overall incidence rate as well as incidence rates per category based on age and number of flight-hours per year. In the control-populations, age-specific incidence rates were calculated in the same way. Standardized overall incidence rates in these populations were calculated as the weighted average of the age-specific incidence rates, using the age-distribution of the airline pilots as weights. The ratio of these incidence rates is the standardized morbidity ratio (SMR), which may also be seen as the ratio of the observed over the expected number of cases. Standard errors were calculated based on a poisson distribution of the number of events. All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, Illinois, United States).

Protection of privacy

Since the diagnosis of venous thrombosis may have a significant impact on the career of a commercial airline pilot (they are not allowed to fly while they use anticoagulant therapy), we assured extra protection of their personal data: all questionnaires were coded; the key that linked these codes to the names and addresses of the pilots was deposited at a notary public. Only one administrative employee, who was sworn to secrecy, had access to this key, and only in the presence of the notary public.

Results

A total of 3525 airline pilots had been a member of the VNV at some point between January 1st 1993 and January 1st 2003. Of these airline pilots, 3237 were still a member of the VNV at the time they received the questionnaire (active members). A total of 288 pilots were no longer a member of the VNV when they received the questionnaire, but had been at some point during the follow up period (inactive members). Of the active members, 2474 pilots completed and returned the questionnaire, yielding a response of 76%. Of the 288 inactive members, 156 completed the questionnaire (response 54%). General characteristics of all participating active and in-active VNV-members are shown in Table 1.

Table 1: General characteristics of all participating airline pilots

	Active members	Archive members
Age, mean (range)	30.1 (18-63)	38.0 (19-60)
Sex, % male	96.1	97.3
Flight-hours/year, mean (range)	521 (0-1800)	516 (0-1500)
Rank		
Captain (% of py)	46.5	59.6
First officer (% of py)	46.0	36.1
Second officer (% of py)	7.5	4.4

The total follow-up time of the participating pilots who were still a member of the VNV at the time the study was performed added up to 20 420 person-years, with a mean follow up time per pilot of 8.3 years (range 0-10 years).

Since there were only very few female pilots (n=100, 3.8%) none of whom had experienced venous thrombosis, we decided to restrict all further analyses to male airline pilots only. The total follow up time of male airline pilots who were active members of the VNV when they received our questionnaire was 19 719 person-years.

Venous thrombosis

During the total follow up time, 6 objectively confirmed events of deep vein thrombosis or pulmonary embolism occurred. All patients were men and active members of the VNV. Three pilots had developed a deep vein thrombosis of the leg, two suffered from both deep vein thrombosis of the leg and pulmonary embolism and one airline pilot was diagnosed with a deep vein thrombosis of the arm. None of the inactive members of the VNV reported occurrence of venous thrombosis. During the follow-up period, 54 pilots or ex-pilots died, but in none of these pilots venous thrombosis was reported as the primary cause of death.

Incidence rates and standardized morbidity ratios

The overall incidence rate of venous thrombosis in the cohort of active members of the VNV was 0.3/1000 person-years (CI95 0.1-0.6 per 1000 person-years). Age-specific incidence rates of the airline pilots and both control populations are shown in Table 2. Although the incidence rate was highest in the oldest age category, the occurrence of venous thrombosis did not clearly increase gradually with age.

Table 2: Incidence rates in male airline pilots, the male general population and male frequently flying employees, stratified by age categories

Age	PY	Cases	IR* pilots (CI95)	IR population**	IR employees#	IR employees##
Overall	19 719	6	0.3 (0.1-0.6)	0.4	0.4 (0.2-1.8)	0.5
<20	41	0	0 (0-24.4)	0.1	0	0
20-25	1404	0	0 (0-0.7)	0.2	0	0
25-30	4025	1	0.2 (0-1.0)	0.2	0	0
30-35	4465	2	0.4 (0-1.3)	0.3	0	0.5 (0-2.1)
35-40	3486	0	0 (0-0.3)	0.4	0	0
40-45	2578	1	0.4 (0-1.6)	0.7	1.0 (0-4.2)	1.7 (0.4-3.8)
45-50	2006	0	0 (0-0.5)	0.9	1.0 (0-4.0)	0.4 (0-1.7)
50-55	1306	2	1.5 (0.1-4.5)	1.2	2.6 (0.7-7.7)	0.5 (0-2.2)
>55	408	0	0 (0-2.5)	0.4	0	3.3 (06-8.3)

Overall incidence rates in the general population and employees were standardized for the age of the airline pilots

* *IR: Incidence rate per 1000 person-years*

** *IR population: incidence rate per 1000 person-years in the general male Dutch population*

\# *IR employees1: incidence rate per 1000 person-years in male employees who made at least 5 long haul flights during the follow up period of 5 years, while they were unexposed to air travel*

\## *IR employees1: incidence rate per 1000 person-years in all male employees, while they were unexposed to air travel*

The age-standardized incidence rate in the general male Dutch population was 0.4 per 1000 person-years. In employees who made at least 5 long haul flights in their follow up period of approximately 5 years, the standardized incidence rate of venous thrombosis while they were unexposed to air travel was also 0.4/1000 person-years. When all employees were included, regardless of the

number of long haul flights made, the standardized incidence rate while they were unexposed to air travel was 0.5/1000 person-years.
The rate ratio (standardized morbidity ratio) comparing the airline pilots to the general Dutch population was 0.8 (CI95 0.7-1.0), i.e. the pilots experienced 0.8 times the number of events that would have occurred in the cohort if the morbidity rates of the population had applied. The standardized morbidity ratio comparing the airline pilots to the employees who travelled at least 5 times during the follow up period was 0.7 (CI95 0.6-0.9), and it was 0.6 (CI95 0.5-0.7) when we compared airline pilots to all male employees that were included in that study.

Effect of number of flight hours per year and rank
Table 3 shows the incidence rate of venous thrombosis per category of flight-hours per year. For the cases of venous thrombosis, the number of flight hours in the year preceding their thrombotic event was considered, since they probably flew less hours after their event in the year they developed venous thrombosis. There was no association between flight-hours per year and the incidence rate of venous thrombosis. In the same table, the effect of rank of the airline pilots is shown. The incidence rate of venous thrombosis was highest in second officers (0.7/1000 person-years, CI95 0-2.6/1000 person-years), but the numbers were too small to draw solid conclusions regarding the effect of rank on the occurrence of venous thrombosis.

Table 3: Incidence rates per number of flight-hours per year and for different ranks

	Person-years	Cases	IR* (CI95)
Flight-hours per year			
0-300	5856	1	0.2 (0-0.7)
300-600	6526	5	0.8 (0.2-1.6)
>600	3912	0	0 (0-0.3)
Rank			
Captain	9462	3	0.3 (0.1-0.8)
First officer	9306	2	0.2 (0.01-0.6)
Second officer	15723	1	0.7 (0-2.6)

* *IR: Incidence rate per 1000 person-years and corresponding 95% confidence intervals*

Discussion

In this follow up study among 2630 commercial airline pilots, with a total of 20 420 person years of follow up time, the incidence rate of venous thrombosis was 0.3/1000 py (CI95 0.1-0.6). This incidence rate was slightly lower than in the general population and also than in a population of frequently flying employees of international companies and organizations. Compared to the general Dutch population, the age-adjusted relative risk for venous thrombosis was 0.8 (CI95 0.7-1.0). Compared to healthy employees, it was 0.7 (CI95 0.6-0.9). The incidence rate of venous thrombosis in the airline pilots did not increase with number of flight-hours per year, nor was it associated with the rank of the pilots.

The low incidence rate of venous thrombosis in commercial airline pilots may be explained by the fact that pilots in general are healthier than the general population: the so-called healthy worker effect Several epidemiological studies have shown that overall mortality rates are lower in airline pilots than in the general population[1-3]. However, these epidemiological studies also showed that the incidence rate of cancer is increased in airline pilots. This may be caused by exposure to carcinogenic substances (jet fuel, cabin pollution, cosmic radiation). Despite exposure to these flight-related factors, or the higher prevalence of malignant diseases, no increased risk of venous thrombosis was found in this population. The healthy worker effect was countered by contrasting the pilots to another working population, but results were similar and not suggestive of an increased risk of thrombosis.

A surprising finding in this study was that the incidence rate did not clearly increase with age. This may be due to chance, since the number of cases was small. However, in a previous study amongst frequently travelling employees, the incidence rate of venous thrombosis was highest in the lowest age-category as well[17]. In the previous study, this was partly explained by a phenomenon called 'attrition of susceptibles', meaning that susceptible individuals are likely to develop a disease shortly after start of exposure to a risk factor. This may also be the case here, that airline pilots who develop venous thrombosis because of their profession are likely to develop thrombosis shortly after start of exposure (their employment), and subsequently seek different employment.

We may have underestimated the risk of venous thrombosis in airline pilots, because they may have been reluctant to confirm they suffered from venous thrombosis in the questionnaire, due to fear for possible consequences, i.e. losing their job. We tried to avoid non-respondence or misclassification by ensuring and communicating complete protection of privacy in our study. Our finding that the incidence rate of venous thrombosis in pilots is lower than in the general population is supported by the absence of any airline pilots who died of pulmonary embolism during the follow up period. If the risk of venous thrombosis amongst Dutch airline pilots would have been substantially higher than in the general Dutch population, one would also have expected fatal cases. Another finding that supports our conclusion that the risk of venous thrombosis is not increased in airline pilots is that we did not find an association between the number of flight hours per year and the risk of venous thrombosis, i.e. no 'dose-response relation'.

From this cohort study amongst Dutch airline pilots, we conclude that the risk of venous thrombosis is not increased in commercial airline pilots.

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Chapter 8

Summary

S. Kuipers

Summary

In venous thrombosis (VT), a blood clot develops in a vein, usually a deep vein of the leg, causing obstruction of the blood flow. This results in swelling, redness and pain of the affected limb. When part of this blood clot detaches, a potentially fatal condition, called pulmonary embolism (PE), may occur. A frequent complication of venous thrombosis is the post-thrombotic syndrome, a disabling condition with persistent swelling and pain of the affected extremity.

Individuals at older age and those with certain genetic risk factors, such as the factor V Leiden mutation, the prothrombin 20210A mutation, protein S or C deficiency and Antithrombin III deficiency, are at increased risk for developing venous thrombosis. However, this usually does not occur until environmental risk factors are present as well. Common environmental factors that are known to increase the risk of venous thrombosis are surgery (especially orthopedic surgery), trauma, immobilization, plaster cast, malignant diseases, pregnancy or delivery and use of oral contraceptive- or hormone replacement therapy. Another environmental risk factor that may increase the risk of venous thrombosis is long distance travel.

Long distance travel may lead to blood clot formation due to several pathophysiological mechanisms. Around 1850, the pathologist Virchow already posed three possible causes of thrombosis: venous stasis, damage of the vessel wall and changes in blood composition. Damage of the vessel wall seems to be more important in the development of arterial thrombosis (such as a myocardial infarction or ischemic stroke). In air travel, both venous stasis and changes in the blood composition may occur. Firstly, venous stasis may be the result of the prolonged immobility that occurs when passengers sit in a cramped position in an airplane seat. Dehydration due to the low air humidity in an airplane may lead to venous stasis as well. Furthermore, changes in the blood composition may arise due to the hypobaric hypoxia present in airplane cabins, exposure to jet fuel or other flight-related factors.

This thesis describes the results of several studies on epidemiological aspects of the association between long distance travel and venous thrombosis.

The first chapter serves as an introduction and provides an outline of the studies in this thesis.

Chapter 2 is a review that summarizes all literature available on the association between travel and venous thrombosis up to January 1st 2007. Both epidemiological research and studies on possible mechanisms responsible for venous thrombosis during and after travel are discussed. From this review article, we conclude that long distance travel increases the risk of venous thrombosis approximately 2-4 fold. Furthermore, a dose-response relationship between the risk of severe pulmonary embolism and duration of travel strongly suggests a causal association. The mechanism responsible for this increased risk of VT after air travel was not sufficiently studied to draw solid conclusions, but one controlled study showed evidence that not only immobilization but other air travel specific factors lead to coagulation activation.

In the 3rd chapter the use of prophylactic measures to prevent travel-related thrombosis by visitors of three international conferences in Australia was assessed through a survey that was sent to all overseas attendants of these conferences. We showed that a considerable number (over 80%) of them used some kind of preventive measure during travel. The type of preventive measures varied between conference, professional background, risk groups and nationality. Delegates of a haemostasis and thrombosis conference and especially medical doctors used more aggressive prophylaxis than delegates of the conferences that did not concern thrombosis.

The 4th chapter describes a study in a cohort of frequently flying employees of large international companies or organizations. In this cohort, the absolute risk of developing symptomatic venous thrombosis within 8 weeks of flights longer than 4 hours was 1 in 4656 flights. This risk increased with flight duration, up to 1 in 1264 after flights longer than 16 hours. Furthermore, the risk increased when employees were exposed to several flights in a short period of time (since exposure to air travel was defined as a period of 8 weeks after a flight, these 8-week time-windows were frequently overlapping) and it decreased with time after a long haul flight. The risk returned to baseline after approximately 8 weeks after the flight. Individuals that were most at risk for developing travel-related venous thrombosis in this cohort were young travellers, women – especially those taking oral contraceptives – , individuals who were particularly short or tall and those with a body mass index over 25kg/m^2.

In the 5th chapter, the effect of increased coagulation factors and that of interaction with other risk factors for venous thrombosis in long distance travellers is assessed. In a case-control study amongst 334 long distance travellers, we demonstrated an increased risk of venous thrombosis in individuals with high levels of coagulation factors II and VIII. The relative risk increased with the number of coagulation abnormalities (factor II, VIII and IX, prothrombin mutation and factor V Leiden mutation) and with the overall number of risk factors present per individual (coagulation factors, high body mass index and oral contraceptive use). The relative risk was highest in female travellers using oral contraceptives who also had high levels of FVIII (odds ratio 51.7, CI95 5.4-498). Combinations with the factor V Leiden mutation were associated with a particularly high relative risk as well. All these effects were superimposed on the relative risk of travel itself, which is about two in this population.

In the 6th chapter, the effect of other transient risk factors for venous thrombosis on the risk of air-travel related venous thrombosis was evaluated. Transient risk factors that had the most pronounced effect on the risk of travel-related venous thrombosis were recent surgery, oral contraceptive use and malignant diseases.

The 7th chapter describes the results of a study on occurrence of venous thrombosis amongst commercial airline pilots in the Netherlands. In this follow up study amongst 2630 pilots, the incidence rate of venous thrombosis was 0.3/1000 person years (CI95 0.1-0.6). This incidence rate was lower than in the general Dutch population and in a population of frequently flying employees of international companies or organisations. Compared to the general Dutch population, the age- and sex adjusted relative risk for venous thrombosis was 0.8 (CI95 0.7-1.0). The incidence rate of venous thrombosis in the airline pilots did not increase with number of flight-hours per year, nor was it associated with rank of the pilots.

From all studies described in this thesis, we conclude that the absolute risk of venous thrombosis after long distance travel in the general population is not high enough to promote widespread use of aggressive prophylaxis, such as anticoagulant therapy. The general advice that is now provided to air travellers (prevention of venous stasis by walking around, refraining from sleeping medication and drinking plenty non-alcoholic beverages) seems sufficient for most healthy air travellers although the effect of these measures has insufficiently been established. However, some subgroups of travellers are at increased risk for developing travel-related venous thrombosis, especially when several risk factors are combined in one traveller. For these subgroups of people with a highly increased risk, the risk-benefit ratio may favour the use of prophylactic measures. To date, it is not known which prophylactic measure is most suitable for prevention of travel-related thrombosis. Large randomized trials are required to assess who would benefit most from special exercises, elastic compression stockings, mechanical devices that promote venous blood flow or low molecular weight heparin.

Chapter 9
Samenvatting

S. Kuipers

Samenvatting

Veneuze trombose is een aandoening waarbij zich een bloedstolsel vormt op de verkeerde plaats, meestal in een van de venen van het been. Hierdoor wordt de terugvloed van het bloed richting het hart belemmerd, resulterend in zwelling, roodheid en pijn van het aangedane been. Wanneer een deel van een dergelijk bloedstolsel los raakt, kan dit door de bloedstroom naar de longen worden getransporteerd, waar het een levensgevaarlijke longembolie kan veroorzaken. Een frequent voorkomende, potentieel invaliderende complicatie van veneuze trombose is het zogenaamde post-trombotische syndroom, waarbij de zwelling en pijn van het aangedane been persisteert.

Ouderen en mensen met bepaalde genetische risicofactoren, zoals de factor V Leiden mutatie, de protëine 20210A mutatie, protëine S of C deficiëntie en Antithrombine deficiëntie hebben een verhoogd risico op het ontwikkelen van veneuze trombose. Een trombus ontwikkelt zich echter pas wanneer er eveneens bepaalde omgevingsfactoren aanwezig zijn die het risico extra verhogen. Bekende verworven risicofactoren zijn recente chirurgie (met name orthopaedische chirurgie), trauma, immobilisatie, gips, maligniteiten, zwangerschap, de kraamperiode en het gebruik van orale anticonceptie of hormoonvervangende therapie. Een andere omgevingsfactor die het risico op veneuze trombose verhoogt is reizen per vliegtuig.

Langdurig vliegen kan tot de vorming van bloedstolsels leiden op verschillende manieren. Rond 1850 postuleerde de patholoog Virchow drie factoren die pathofysiologisch een rol spelen bij het ontstaan van een thrombus: veneuze stase, beschadiging van de vaatwand en een veranderde samenstelling van het bloed. Beschadiging van de vaatwand lijkt een grotere rol te spelen bij het ontstaan van arteriele trombose (zoals een myocardinfarct of ischaemisch CVA). Reizen per vliegtuig zou zowel veneuze stase als een veranderende samenstelling van het bloed kunnen veroorzaken. Veneuze stase kan het gevolg zijn van langdurig stilzitten in de beperkte ruimte van een vliegtuigstoel. Uitdroging, ten gevolge van de verminderde luchtvochtigheid in een vliegtuig, zou eveneens tot veneuze stase kunnen leiden. Een veranderende samenstelling van het bloed zou een gevolg kunnen zijn van de hypobare hypoxie, brandstoffen of andere vliegtuig-gerelateerde factoren waaraan een vliegtuig passagier is blootgesteld.

Dit proefschrift beschrijft een aantal onderzoekingen naar epidemiologische aspecten van de relatie tussen reizen per vliegtuig en veneuze trombose.

Het eerste hoofdstuk dient als een inleiding, waarin het doel van de studies die zijn beschreven in dit proefschrift wordt uitgelegd.

Hoofdstuk 2 bestaat uit een overzichtsartikel, waarin alle reeds beschikbare literatuur op het gebied van veneuze trombose en reizen per vliegtuig op een systematische manier wordt samengevat. Zowel epidemiologische als meer pathofysiologische studies, waarin het mechanisme verantwoordelijk voor het verhoogde risico op veneuze trombose na vliegen wordt onderzocht, worden in dit hoofdstuk bediscussieerd. Uit dit artikel kon worden geconcludeerd dat het risico op veneuze trombose na een lange vlucht ongeveer 2-4 keer verhoogd is. Bovendien bestaat er een zogenaamde dosis-respons relatie tussen het risico op ernstige longembolieën en de duur van de vliegreis, hetgeen sterk pleit voor een causale relatie tussen vliegen en trombose. Het mechanisme verantwoordelijk voor dit verhoogde risico op veneuze trombose na vliegen werd nog niet voldoende bestudeerd voor het trekken van eenduidige conclusies, maar een gecontroleerde studie liet bewijs zien dat niet alleen immobilisatie, maar ook vliegtuig-specifieke factoren, zoals de lagere luchtdruk of het lagere zuurstofgehalte in een vliegtuig verantwoordelijk zouden kunnen zijn voor stollingsactivatie.

In het derde hoofdstuk wordt gekeken naar het gebruik van voorzorgsmaatregelen om vliegreis-gerelateerde veneuze trombose te voorkomen onder bezoekers van 3 grote internationale conferenties die gehouden werden in Australië. Dit werd gedaan door middel van een vragenlijst onderzoek onder deze bezoekers. In dit hoofdstuk lieten wij zien dat een groot deel (80%) van de bezoekers een of meerdere voorzorgsmaatregelen had genomen. Het soort preventieve maatregel wisselde sterk per conferentie, professionele achtergrond, risicoprofiel en nationaliteit van de bezoeker. Bezoekers van een congres over trombose en haemostase, vooral de artsen onder hen, gebruikten meer agressieve profylactische maatregelen dan deelnemers aan de congressen die niet over trombose gingen.

In het vierde hoofdstuk wordt een onderzoek beschreven dat werd gedaan in een cohort van frequent vliegende werknemers van grote internationale bedrijven en organisaties. In dit cohort was het absolute risico op het krijgen van een symptomatische veneuze trombose in de eerste 8 weken na een vlucht van minimaal 4 uur 1 op de 4656 vluchten. Dit risico nam toe met de duur van de vlucht, naar 1 op de 1264 vluchten na vluchten langer dan 16 uur. Bovendien was het risico hoger wanneer werknemers in korte tijd aan meerdere vluchten werden blootgesteld en nam het risico af met de duur na een vlucht. Het risico werd kleiner naarmate een vlucht langer geleden was en na ongeveer 8 weken was het risico op veneuze trombose niet langer verhoogd. In dit cohort hadden jongere mensen, vrouwen – vooral wanneer zij ook orale anticonceptie gebruikten – buitengewoon lange of korte werknemers en diegenen met een body mass index hoger dan 25 kg/m^2 een groter risico.

In hoofdstuk 5 wordt gekeken naar het effect van voorbijgaande risicofactoren voor veneuze trombose op het risico van reis-gerelateerde trombose, in hetzelfde cohort dat werd beschreven in hoofdstuk 4. Voorbijgaande risicofactoren die het risico op veneuze trombose het meest verhoogden waren recente operaties, het gebruik van orale anticonceptie en maligne aandoeningen.

In hoofdstuk 6 wordt het effect van verhoogde waarden of activiteit van stollingsfactoren en hun interactie met andere risicofactoren voor veneuze trombose onder reizigers beschreven. In een groot case-controle onderzoek onder 334 lange-afstands reizigers lieten wij een verhoogd risico op veneuze trombose zien onder personen met verhoogde waarden van de stollingsfactoren II en VIII. Bovendien nam het risico toe met het aantal procoagulante afwijkingen (verhoogde spiegels van de factoren II en VIII en/of de aanwezigheid van de factor V Leiden mutatie of de prothrombine 20210A mutatie) en met het totaal aantal aanwezige risicofactoren (de bovengenoemde procoagulante factoren, een hoge body mass index, gebruik van orale anticonceptie en het hebben van een positieve familieanamnese voor veneuze trombose). Het risico in dit onderzoek was het hoogst onder vrouwelijke reizigers die orale anticonceptie gebruikten en eveneens een verhoogde factor VIII waarde hadden. Combinaties met de factor V Leiden mutatie leidden eveneens tot een sterk verhoogd risico. Al deze effecten kwam bovenop het relatieve risico van reizen zelf, wat ongeveer 2 was in deze populatie.

In het zevende hoofdstuk worden de resultaten van een onderzoek onder Nederlandse verkeersvliegers gepresenteerd. In dit vervolgonderzoek onder 2630 piloten was het incidentiecijfer voor veneuze trombose 0.3 per 1000 persoonsjaren. Dit incidentiecijfer bleek lager dan dat in de algemene Nederlandse bevolking en dat in een cohort van frequent vliegende werknemers van internationale bedrijven en organisaties (beschreven in hoofdstuk 4 van dit proefschrift). Vergeleken bij de Nederlandse bevolking was het voor leeftijd en geslacht gecorrigeerde relatieve risico 0.8 (95% betrouwbaarheids interval 0.7-1.0). Het incidentiecijfer voor veneuze trombose onder deze verkeersvliegers nam niet toe met het aantal vluchten per jaar of de rang van de piloten.
Uit alle in dit proefschrift beschreven onderzoeken concluderen wij dat het

absolute risico op het ontwikkelen van veneuze trombose na een lange vliegreis in de algemene bevolking niet hoog genoeg is voor het ondersteunen van veelvuldig gebruik van potentieel gevaarlijke voorzorgsmaatregelen, zoals het gebruik van antistolling. Het algemene advies dat tot nu toe aan reizigers gegeven wordt (voorkomen van veneuze stase door genoeg te bewegen en veel niet-alcoholische dranken te gebruiken) lijkt afdoende voor de meeste gezonde vliegtuigpassagiers, ook al is het effect van deze maatregelen niet aangetoond. Er zijn echter subgroepen van reizigers die een verhoogd risico op veneuze trombose hebben, vooral wanneer er meerdere risico factoren voor trombose tegelijk aanwezig zijn. In deze groepen reizigers zou het voordeel van dergelijke voorzorgsmaatregelen wel op kunnen wegen tegen het risico ervan. Tot op heden is het echter niet bekend welke reizigers het meeste baat zouden kunnen hebben bij welke voorzorgsmaatregel. Grote gerandomiseerde onderzoeken onder hoog-risico reizigers zijn dan ook essentieel om te kunnen stellen welke reizigers in aanmerking komen voor het gebruik van bijvoorbeeld elastische steunkousen, speciale apparaatjes die de doorbloeding van de benen bevorderen of zelfs antistollende behandeling met bijvoorbeeld laag-moleculair gewichts heparine.

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