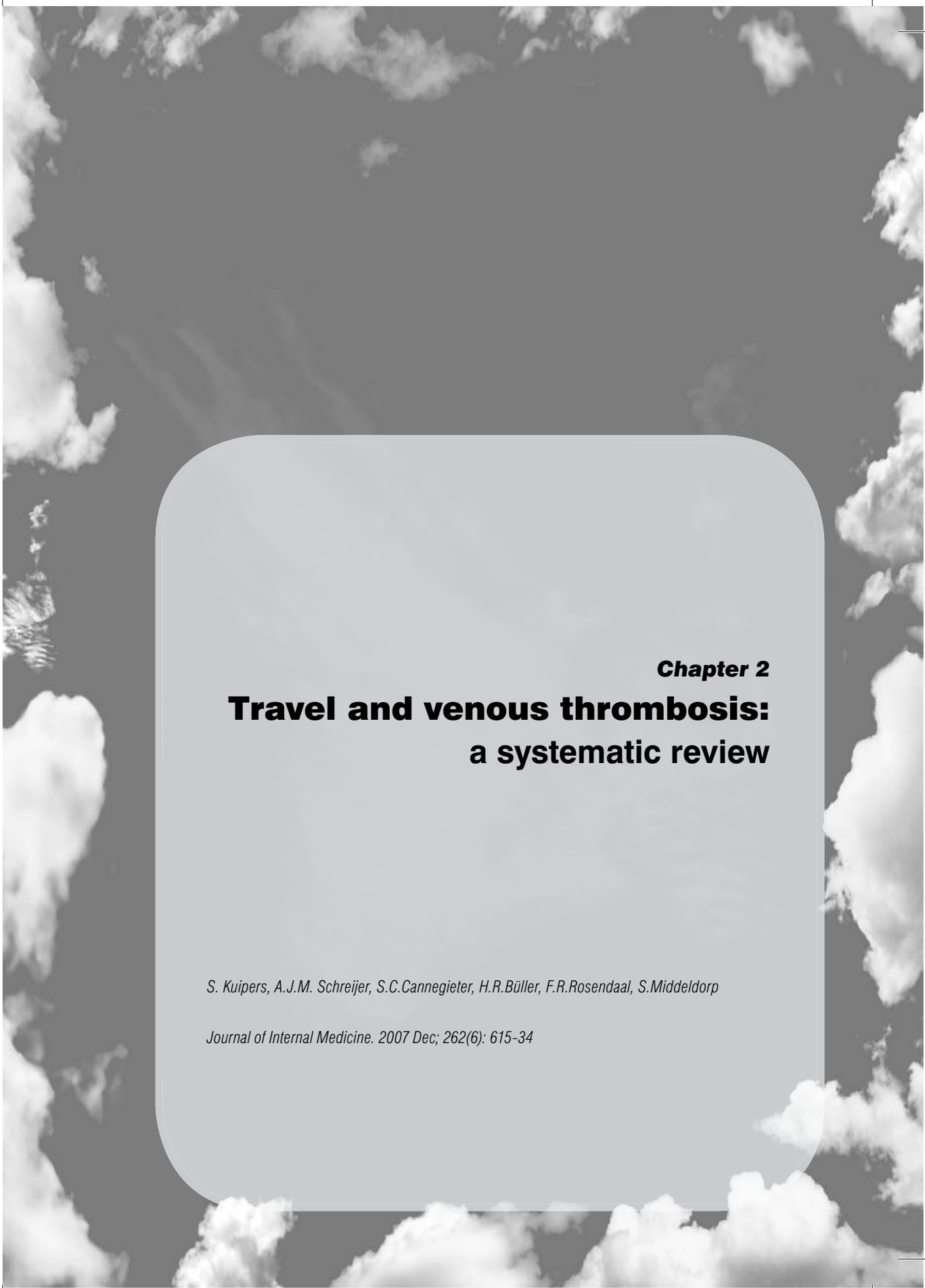
Air travel and venous thrombosis : results of the WRIGHT study : Part I: Epidemiology

Kuipers, S.



Chapter 2

Travel and venous thrombosis: a systematic review

S. Kuipers, A.J.M. Schreijer, S.C.Cannegieter, H.R.Büller, F.R.Rosendaal, S.Middeldorp

Journal of Internal Medicine. 2007 Dec; 262(6): 615-34

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%.

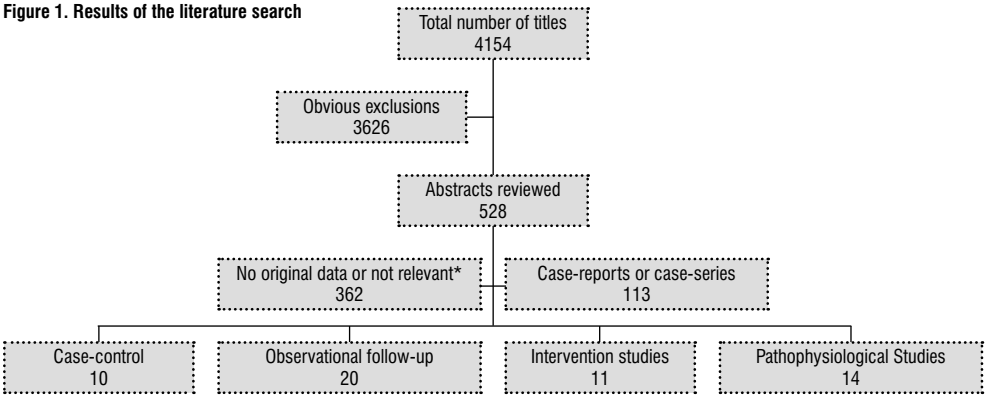
Due to the diversity of the study designs, no attempt to pool data for pathophysiological studies was made.

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-Johannesburg, 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 Imwh 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				

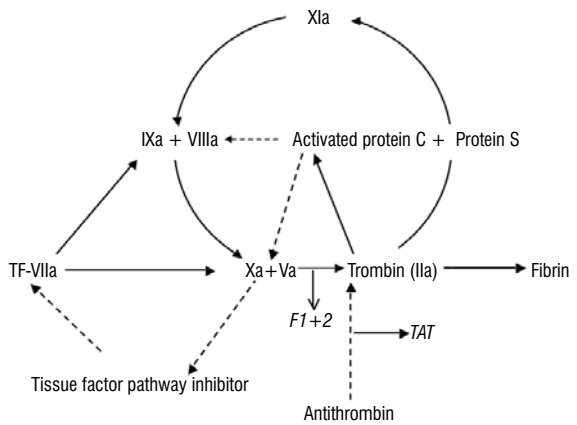
* *This table roughly indicates the changes in the most commonly used markers of coagulation activation and fibrinolyis during the several exposures. VT= venous thrombosis, FVL = Factor V Leiden mutation, OC=oral contraceptive/hormone use. When studies took blood from both arm and leg veins results from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

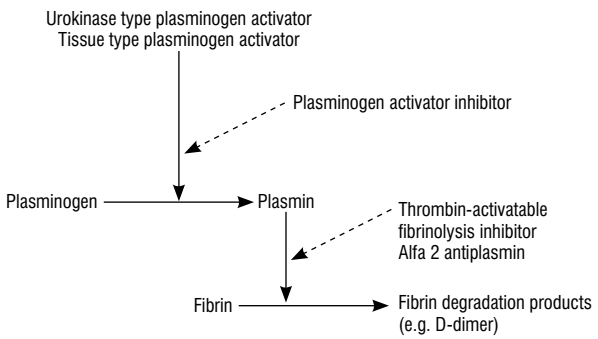
Increased levels of activated coagulation factors (such as FVIIa and FVIIIa) are also known to increase thrombin generation (50;51).

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.

Reference List

(1) Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000; 83:657-660.

(2) Naess IA, Christiansen SC, Cannegieter SC, Rosendaal FR, Hammerstroem J. A prospective study of anticardiolipin antibodies as a risk factor for venous thrombosis in a general population (the HUNT study). J Thromb Haemost 2006; 4:44-49.

(3) Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 1995; 346:1133-1134.

(4) Rosendaal FR, Vos HL, Poort SL, Bertina RM. Prothrombin 20210A variant and age at thrombosis. Thromb Haemost 1998; 79:444.

(5) Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353:1167-1173.

(6) Louvel J. Four cases of phlebitis due to air travel. Arch Mal Coeur Vaiss 1951; 44:748-749.

(7) Wiest GH. Look diagnosis. Economy class syndrome after tractor driving. MMW Fortschr Med 2005; 147:61.

(8) Symington IS, Stack BH. Pulmonary thromboembolism after travel. Br J Dis Chest 1977; 71:138-140.

(9) Sarvesvaran R. Sudden natural deaths associated with commercial air travel. Med Sci Law 1986; 26:35-38.

(10) Higgins J.P.T GS. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 Updated september 2006. 4. 2006. Internet Communication.

(11) Arya R, Barnes JA, Hossain U, Patel RK, Cohen AT. Long-haul flights and deep vein thrombosis: a significant risk only when additional factors are also present. Br J Haematol 2002; 116:653-654.

(12) Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR. Travel-Related Venous Thrombosis: Results from a Large Population-Based Case Control Study (MEGA Study). PLoS Med 2006;3:e307.

(13) Dimberg LA, Mundt KA, Sulsky SI, Liese BH. Deep venous thrombosis associated with corporate air travel. J Travel Med 2001; 8:127-132.

(14) Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: a case-control study. Chest 1999; 115:440-444.

(15) Hosoi Y, Geroulakos G, Belcaro G, Sutton S. Characteristics of deep vein thrombosis associated with prolonged travel. Eur J Vasc Endovasc Surg 2002; 24:235-238.

(16) Kraaijenhagen RA, Haverkamp D, Koopman MM, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. Lancet 2000; 356:1492-1493.

(17) Martinelli I, Taioli E, Battaglioli T, Podda GM, Passamonti SM, Pedotti P et al. Risk of venous thromboembolism after air travel: interaction with thrombophilia and oral contraceptives. Arch Intern Med 2003; 163:2771-2774.

(18) Parkin L, Bell ML, Herbison GP, Paul C, Skegg DC. Air travel and fatal pulmonary embolism. Thromb Haemost 2006; 95:807-814.

(19) Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med 2000; 160:3415-3420.

(20) ten Wolde M, Kraaijenhagen RA, Schiereck J, Hagen PJ, Mathijssen JJ, Mac Gillavry MR et al. Travel and the risk of symptomatic venous thromboembolism. Thromb Haemost 2003; 89:499-505.

(21) Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Sato DT. Risk factors for venous thromboembolism following prolonged air travel: a prospective study. Vascular surgery 1999; 33:537-544.

(22) Becker NG, Salim A, Kelman CW. Air travel and the risk of deep vein thrombosis. Aust N Z J Public Health 2006; 30:5-9.

(23) Belcaro G, Geroulakos G, Nicolaides AN, Myers KA, Winford M. Venous thromboembolism from air travel: the LONFLIT study. Angiology 2001; 52:369-374.
(24) Clerel M, Caillard G. Thromboembolic syndrome from prolonged sitting and flights of long duration: experience of the Emergency Medical Service of the Paris Airports. Bull Acad Natl Med 1999; 183:985-997.
(25) Gajic O, Warner DO, Decker PA, Rana R, Bourke DL, Sprung J. Long-haul air travel before major surgery: a prescription for thromboembolism? Mayo Clin Proc 2005; 80:728-731.
(26) Hertzberg SR, Roy S, Hollis G, Brieger D, Chan A, Walsh W. Acute symptomatic pulmonary embolism associated with long haul air travel to Sydney. Vasc Med 2003; 8:21-23.
(27) Hughes RJ, Hopkins RJ, Hill S, Weatherall M, Van de WN, Nowitz M et al. Frequency of venous thromboembolism in low to moderate risk long distance air travellers: the New Zealand Air Traveller's Thrombosis (NZATT) study. Lancet 2003; 362:2039-2044.
(28) Jacobson BF, Philippides M, Malherbe M, Becker P. Risk factors for deep vein thrombosis in short-haul cockpit crews: A prospective study. Aviation Space and Environmental Medicine 2002; 73:481-484.
(29) Jacobson BF, Munster M, Smith A, Burnand KG, Carter A, Abdool-Carrim AT et al. The BEST study--a prospective study to compare business class versus economy class air travel as a cause of thrombosis. S Afr Med J 2003; 93:522-528.
(30) Kelman CW, Kortt MA, Becker NG, Li Z, Mathews JD, Guest CS et al. Deep vein thrombosis and air travel: record linkage study. BMJ 2003; 327:1072.
(31) Kline JA, Putman M, Courtney DM. Fatal pulmonary embolism immediately after transatlantic air travel to the United States: less than one in a million. Thromb Haemost 2002; 87:342.
(32) Kuipers S, Cannegieter SC, Middeldorp S, Robyn L, Büller HR, Rosendaal FR. The absolute risk of venous thrombosis after air travel: a cohort study of 8,755 employees of international organisations. PLoS Med 2007; 4:e290.
(33) Lapostolle F, Surget V, Borron SW, Desmaizieres M, Sordelet D, Lapandry C et al. Severe pulmonary embolism associated with air travel. N Engl J Med 2001; 345:779-783.
(34) Paganin F. Risk of venous thromboembolism greatest within two weeks of long-haul flight. Evidence-Based Healthcare 2004: 8:133-135.
(35) Perez-Rodriguez E, Jimenez D, Diaz G, Perez-Walton I, Luque M, Guillen C et al. Incidence of air travel-related pulmonary embolism at the Madrid-Barajas airport. Arch Intern Med 2003; 163:2766-2770.
(36) Pheby DF, Codling BW. Pulmonary embolism at autopsy in a normal population: implications for air travel fatalities. Aviat Space Environ Med 2002; 73:1208-1214.
(37) Schwarz T, Langenberg K, Oettler W, Halbritter K, Beyer J, Siegert G et al. Deep vein and isolated calf muscle vein thrombosis following long-haul flights: pilot study. Blood Coagul Fibrinolysis 2002; 13:755-757.
(38) Schwarz T, Siegert G, Oettler W, Halbritter K, Beyer J, Frommhold R et al. Venous thrombosis after long-haul flights. Arch Intern Med 2003; 163:2759-2764.
(39) Belcaro G, Cesarone MR, Shah SS, Nicolaides AN, Geroulakos G, Ippolito E et al. Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings. A randomized trial: The LONFLIT 4 Concorde Edema-SSL Study. Angiology 2002; 53:635-645.
(40) Belcaro G, Cesarone MR, Nicolaides AN, Ricci A, Geroulakos G, Shah SS et al. Prevention of venous thrombosis with elastic stockings during long-haul flights: the LONFLIT 5 JAP study. Clin Appl Thromb Hemost 2003; 9:197-201.

(41) Belcaro G, Cesarone MR, Nicolaides AN, Geroulakos G, Acerbi G, Candiani C et al. The LONFLIT4-VENORUTON study: a randomized trial prophylaxis of flight-edema in normal subjects. Clin Appl Thromb Hemost 2003; 9:19-23.
(42) Belcaro G, Cesarone MR, Rohdewald P, Ricci A, Ippolito E, Dugall M et al. Prevention of venous thrombosis and thrombophlebitis in long-haul flights with pycnogenol. Clin Appl Thromb Hemost 2004; 10:373-377.
(43) Cesarone MR, Belcaro G, Nicolaides AN, Incandela L, De S, Geroulakos G et al. Venous thrombosis from air travel: the LONFLIT3 study--prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. Angiology 2002; 53:1-6.
(44) Cesarone MR, Belcaro G, Nicolaides AN, Geroulakos G, Lennox A, Myers KA et al. The LONFLIT4-Concorde--Sigvaris Traveno Stockings in Long Flights (EcoTraS) Study: a randomized trial. Angiology 2003; 54:1-9.
(45) Cesarone MR, Belcaro G, Brandolini R, Di Renzo A, Bavera P, Dugall M et al. The LONFLIT4-Venoruton Study: a randomized trial--prophylaxis of flight-edema in venous patients. Angiology 2003; 54:137-142.
(46) Cesarone MR, Belcaro G, Nicolaides AN, Ricci A, Geroulakos G, Ippolito E et al. Prevention of venous thrombosis in long-haul flights with Flite Tabs: the LONFLIT-FLITE randomized, controlled trial. Angiology 2003; 54:531-539.
(47) Cesarone MR, Belcaro G, Errichi BM, Nicolaides AN, Geroulakos G, Ippolito E et al. The LONFLIT4--Concorde Deep Venous Thrombosis and Edema Study: prevention with travel stockings. Angiology 2003; 54:143-154.
(48) Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 2001; 357:1485-1489.
(49) Report of the General Medical Counsil, Fitness to Practice Panel. 2007. Internet Communication.
(50) Bouma BN, Meijers JCM. Thrombin-activatable fibrinolysis inhibitor (TAFI, plasma procarboxypeptidase B, procarboxypeptidase R, procarboxypeptidase U). J Thromb Haemost 2003; 1:1566-1574.
(51) Dahlback B. Blood coagulation. Lancet 2000; 355:1627-1632.
(52) Ansari MT, Mahmood MT, Karlberg JP. The association between seated immobility and local lower-limb venous coagulability in healthy adult volunteers: a simulation of prolonged travel immobility. Blood Coagul Fibrinolysis 2006; 17:335-341.
(53) Bendz B, Rostrup M, Sevre K, Andersen TO, Sandset PM. Association between acute hypobaric hypoxia and activation of coagulation in human beings. Lancet 2000; 356:1657-1658.
(54) Boccalon H, Boneu B, Emmerich J, Thalamas C, Ruidavets JB. Long-haul flights do not activate hemostasis in young healthy men. J Thromb Haemost 2005; 3:1539-1541.
(55) Crosby A, Talbot NP, Harrison P, Keeling D, Robbins PA. Relation between acute hypoxia and activation of coagulation in human beings. Lancet 2003; 361:2207-2208.
(56) Hodkinson PD, Hunt BJ, Parmar K, Ernsting J. Is mild normobaric hypoxia a risk factor for venous thromboembolism? J Thromb Haemost 2003; 1:2131-2133.
(57) Schobersberger W, Fries D, Mittermayr M, Innerhofer P, Sumann G, Schobersberger B et al. Changes of biochemical markers and functional tests for clot formation during long-haul flights. Thromb Res 2002; 108:19-24.
(58) Schobersberger W, Mittermayr M, Innerhofer P, Sumann G, Schobersberger B, Klingler A et al. Coagulation changes and edema formation during long-distance bus travel. Blood Coagulation & Fibrinolysis 2004; 15:419-425.

(59) Schobersberger W, Schobersberger B, Mittermayr M, Fries D, Streif W. Air travel, hypobaric hypoxia, and prothrombotic changes. JAMA 2006; 296:2313-2314.
(60) Schreijer AJM, Cannegieter SC, Meijers JCM, Middeldorp S, Büller HR, Rosendaal FR. Activation of coagulation system during air travel: a crossover study. Lancet 2006; 367:832-838.
(61) Stricker H, Colucci G, Godio M, Mossi G, Mombelli G. The influence of a prolonged sitting position on the biochemical markers of coagulation activation in healthy subjects: evidence of reduced thrombin generation. J Thromb Haemost 2003; 1:380-381.
(62) Stricker H, Colucci G, Alberio L, Mombelli G. Variation in coagulation inhibitors during prolonged sitting: possible pathogenetic mechanisms for travel-associated thrombosis. J Thromb Haemost 2006; 4:900-902.
(63) Tardy B, Page Y, Zeni F, Decousus H, Comtet C, Cusey I et al. Phlebitis following travel. Presse Med 1993; 22:811-814.
(64) Tardy B, Tardy-Poncet B, Bara L, Laporte-Simitsidis S, Rascle F, Samama MM et al. Effects of long travels in sitting position in elderly volunteers on biological markers of coagulation activation and fibrinolysis. Thromb Res 1996; 83:153-160.
(65) Toff WD, Jones CI, Ford I, Pearse RJ, Watson HG, Watt SJ et al. Effect of hypobaric hypoxia, simulating conditions during long-haul air travel, on coagulation, fibrinolysis, platelet function, and endothelial activation. JAMA 2006; 295:2251-2261.
(66) Colucci G, Stricker H, Roggiani W, Haeberli A, Mombelli G. Venous stasis and thrombin generation. J Thromb Haemost 2004; 2:1008-1009.
(67) Simons R, Krol J. Jet leg, pulmonary embolism, and hypoxia. Lancet 1996; 348:416.
(68) Humphreys S, Deyermond R, Bali I, Stevenson M, Fee JP. The effect of high altitude commercial air travel on oxygen saturation. Anaesthesia 2005; 60:458-460.
(69) Maher JT, Levine PH, Cymerman A. Human coagulation abnormalities during acute exposure to hypobaric hypoxia. J Appl Physiol 1976; 41:702-707.
(70) Arfvidsson B. Risk factors for venous thromboembolism following prolonged air travel: a prospective study. Cardiovasc Surg 2001; 9:158-159.