

AIR TRAVEL AS A RISK FACTOR FOR VENOUS THROMBOEMBOLISM (VTE) AND THE EFFECTIVENESS OF PREVENTIVE MEASURES

A West Midland Health and Technology Assessment Collaboration report

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Report number: 39

ISBN No. 0-7044-2411-8

About West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from the West Midlands NHS or the NCCHTA programme. Reviews usually take 6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

About InterTASC

WMHTAC is a member of InterTASC which is a national collaboration of six academic units who do rapid reviews for the National Institute of Clinical Excellence. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports, advance methodological developments in this area of HTA and improve skills and capacity in the UK.

Contributions of authors

Y. Adi was the lead reviewer. He wrote the protocol, designed data abstraction and the form used in assessing the quality of the included studies. He contacted authors for further information and liaised with experts in the field to obtain background information. He also contributed to writing up the review and analysis of the data. R. Taylor and Y. Adi both carried out the inclusion & exclusion of the studies separately and both carried out double data extraction from the included studies. R. Taylor summarised the data, edited the review and contributed to the analysis and writing up the review. He also organised the peer-reviewers. S. Bayliss performed electronic database and internet searches. A. Rouse and G Lip both advised on the clinical aspects and commented on the review. All authors contributed to the final text.

Conflict of interest

This work has been undertaken by people funded by the NHS. The authors have received no funding from any sponsor in this work.

West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the recognition of air travel as a risk factor for venous thromboembolism (VTE) and the effectiveness of preventive measures report was:

Not supported

Current evidence did not demonstrate that the incidence of VTE was elevated by air travel and no intervention had been proven to be effective in reducing VTE in air travelers.

Anticipated expiry date:

- This report was completed in October 2002
- The searches were completed between 4th –7th June 2002. Additional searches for incidence of DVT and RCTs were carried out on 4th September 2002
- This report will expire in 2005.

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Abbreviations

CI	Confidence Interval
RCT	Randomised controlled trial
DVT	Deep vein thrombosis
LMWH	Low molecular weight heparin
NNT	Number needed to be treated
OR	Odds ratio
p	P Value
PE	Pulmonary embolism
SD	Standard deviation
VTE	Venous thromboembolism

1. Executive summary

Aim and objectives of the review

The aims of this review were to ascertain if air flight poses a serious risk to travellers in terms of the development of future venous thromboembolic disease (VTE) and, if so, provide advice on possible strategies for the prevention of VTE with air travel.

- 1) To determine the incidence of thromboembolic disease (VTE) in air travellers.
- 2) To assess the strength of evidence of air flight as a risk factor for VTE
- 3) To assess the efficacy of preventive interventions designed to reduce the risk of VTE in air travellers.

Background

Air flight in recent years has become a popular way of travelling; approximately 2 billion people worldwide travel on commercial airlines each year and the term ‘economy class syndrome’ or ‘traveller’s thrombosis’ has been widely used to describe a perceived link between air travel and VTE. The link between air flight and the development of deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE) – so called ‘thromboembolic disease’ - was first suggested in 1954 by a report describing DVT in a doctor after a 14-hour flight. Between 1954 and 1999 a number of anecdotal reports appeared reporting cases of VTE in people who had recently travelled by air. In recent years the link between air travel and VTE has received considerable mass media attention and there have been a number of notable cases reported in the press such as the death from pulmonary embolism of 28-year-old air stewardess following long distance flight from Sydney to London in September 2000. This incident was followed by a report from the House of Lord Select Committee on Science and Technology in November 2000.

Methods

A number of electronic databases and the internet were searched, (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register and National Research Register) up to September 2002. Hand searching of the reference lists of reviews and all included studies were undertaken. Contact was made with experts in the field to identify any studies that may have been missed, or any ongoing or unpublished research. There were no language exclusions.

The criteria for study inclusion were as follows:

i) **Incidence** of VTE during air flight:

Design: Any design other than case report

Population: Any individuals who have travelled by air regardless of sex, age or risk status

Exposure: Air travel (short or long haul flight)

Comparator: Indirect comparison with population incidence if available

Outcomes: Asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, or related mortality.

ii. Air flight as a **risk factor** for DVT

As incidence, except:

Design: Any comparative study design i.e. randomised controlled trial, prospective or retrospective cohort study or case-control study.

Comparator: No air travel

iii. **Effectiveness of interventions** to prevent VTE in air traveller

Design: Randomised controlled trials only

Population: Any individuals who have travelled by air regardless of sex, age or risk status

Intervention: Any intervention(s) used for prophylaxes of VTE. It was anticipated these would include both non-drug interventions (e.g. support stockings, in flight exercise, active hydration, restriction from alcohol) and drug intervention i.e. aspirin and heparin.

Comparator: either no intervention, placebo or any other form of comparative intervention.

Outcomes: Asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, pulmonary embolus (PE) or related mortality up to month after exposure

Studies excluded if they were experimental simulations of air flight conditions (e.g. hypobaric chambers).

Study selection was carried out independently by two reviewers using a standardised inclusion and exclusion form. The quality of risk factor and intervention studies were assessed in terms of the principle bias i.e. selection bias, detection bias, performance bias and attrition bias. Data abstraction was undertaken by a single reviewer using standardized extraction sheet and checked by a second reviewer. The detailed characteristics, quality, and results of all studies were tabulated. Where appropriate data were pooled using meta analyses. Where there was evidence of significant heterogeneity a random effects method was used.

The finding of this review

- We found relatively few studies that met the criteria for inclusion under the headings of each of the three aims of this systematic review; (i) Incidence of VTE in air travellers:- 6 studies; (ii) Air flight is a risk factor for VTE?:- 3 studies; and (iii) Intervention measures on the prevention of VTE?:- 2 studies.
- The comparison of findings across studies is made particularly difficult because of the variations in populations (i.e., proportion of high risk individuals) studied and the definitions of both outcome (i.e., asymptomatic v. symptomatic VTE) and exposure (i.e., differing durations of flight).
- Accepting these differences, there was little or no consistent evidence of an increased incidence of venous thromboembolic events (VTE) in air travellers. Moreover, we found no evidence to support the current belief that long haul (i.e., 2 hours or more) air flight is a risk factor for the development of VTE (OR 1.11 95% CI 0.64 to 1.94).

- The two case-control studies that have reported a statistically significant increase in the VTE with long haul travel (i.e. 3 hours or more) were not limited to air travel alone and included only high-risk individuals. The application of the findings of these studies specifically to air travel is uncertain.
- We identified 2 randomised controlled trials, these were not of high quality that may suggest prophylactic measures can significantly reduce the risk of VTE (primarily asymptomatic) in air travellers, for example, support stockings (OR 0.04, 0.01 to 0.23 95% CI), and low molecular weight heparin LMWH significantly reduces the risk $p=0.02$ but aspirin use was not associated with a reduced risk of DVT according to one RCT and there was a significant increase in the risk of bleeding events with both aspirin and heparin. No RCTs of other preventive measures, such as in-flight exercise or increased hydration, were identified
- The number of individuals identified in this review is only sufficient to detect a risk of developing DVT following air travel if the OR were to be 10 or over, based on current evidence.

Implications of findings for policy makers

Healthy people

The results of this review suggest that there is little or no evidence of increased risk of the development of VTE with air travel in otherwise healthy individuals. Therefore no special precautions are indicated or likely to reduce risk in this group.

People at risk

Given lack of evidence about effective interventions and contrary to current UK Department of Health guidance we would not recommend any additional clinical review or interventions for high risk individuals prior to air flight. There was little evidence to support any intervention as there were only 2 RCTs which were grossly under powered and the outcome reported were asymptomatic DVT only. Therefore, we do not recommend for patients to visit GPs unnecessarily.

Implications for findings for future research

- There remains a need to precisely quantify the potential added risk of air flight in high risk individuals (e.g. history of previous VTE, recent major surgery, malignancy, stroke) and particularly, the development of pulmonary embolism.

Rather than further case-control studies being undertaken we would recommend the combination of prospective controlled and epidemiological modelling studies. Careful consideration needs to be given to the power of such future studies.

2. Aim of the review

The aims of this review are to ascertain the degree of risk air flight poses to travellers in terms of the development of future venous thromboembolic disease (VTE) and, if so, provide advice on possible strategies for the prevention of VTE with air travel.

3. Objectives

- 1) To determine the incidence of venous thromboembolic disease (VTE) in air travellers.
- 2) To assess the strength of evidence of air flight as a risk factor for VTE and identify the potential factors that might influence the magnitude of such a risk.
- 3) To assess the efficacy of preventive interventions designed to reduce the risk of VTE in air travellers.

3. Background

3.1 Statement of Problem

The link between air flight and the development of deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE) – so called ‘thromboembolic disease’ - was first suggested in 1954 by a report describing DVT in a doctor after a 14-hour flight.¹ Between 1954 and 1999 a number of anecdotal reports appeared reporting cases of VTE in people who had recently travelled by air.^{2,3,4} In recent years the link between air travel and VTE has received considerable mass media attention and there have been a number of notable cases reported in the press such as the tragic death from pulmonary embolism of 28-year-old air stewardess following long distance flight from Sydney to London in September 2000. Air flight in recent years has become a popular way of travelling; approximately 2 billion people worldwide travel on commercial airlines each year.⁵ The terms ‘economy class syndrome’ or ‘traveller’s thrombosis’ have been widely used to describe the potential link between air travel and VTE.

3.2 Epidemiology of VTE

The term venous thromboembolism describes any thromboembolic events occurring within the venous system. This includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a radiologically confirmed partial or total thrombotic occlusion of the deep venous system of the legs sufficient to produce symptoms of pain or swelling.⁶ Proximal deep vein thrombosis affects the veins above the knee (popliteal, superficial femoral, common femoral, and iliac veins). Pulmonary embolism is a serious condition, which describes partial or total thromboembolic occlusion of pulmonary arteries.

3.2.1 The incidence of DVT

The incidence of DVT varies according to the sources and the age of the study population. The Department of Health state that the annual incidence of DVT is about 1 in 2000 people in the general population, ranging from less than 1 in 3000 in people under the age of 40 up to 1 in 500 in those over 80.⁷ Other sources stated the cumulative incidence of VTE in general population of Scandinavian men who were followed prospectively from age 50 to the age of 80 years to be 5/1000 by the age of 50 years and 107/1000 by the age of 80 years.⁸ A recent UK study that shows the annual incidence of symptomatic thrombosis presented to a hospital in a stable population of 650,000 is about 1/1000.⁹

The diagnosis of deep venous thrombosis of the calf is often difficult to make accurately on clinical grounds. This is because when only one of multiple veins is involved, the remaining patent vessels will allow an adequate venous return. DVT occurs less frequently in the upper limb than in the lower limb. 6.16 to 20% of the total population is thought to have some degree of increased clotting tendency. This indicates that there might be a "natural" underlying incidence of DVT in the general population associated with those factors alone.⁵

3.2.2 Incidence of pulmonary embolism

Pulmonary embolus occurs when a clot from a vein, originating in the venous sinuses of the calf or the femoral vein or the pelvis, detaches and becomes lodged in the pulmonary arterial tree. Rarely the right side of the heart is a source of a pulmonary embolus. Pulmonary embolism affects 1 per 1000 population per year and may contribute to 15-20% of all deaths in an acute general hospital.¹⁰ Pulmonary embolism incidence was estimated to be about 1 in 100 post-surgical patients who have suffered a DVT.

3.3 Natural history of VTE

Proximal extension develops in 40–50% of people with symptomatic calf vein thrombosis.¹¹ Many reported cases of isolated calf vein thrombosis are asymptomatic but detected radiologically for research purposes. Very limited evidence about the clinical significance of asymptomatic calf vein thrombosis exists. Similarly studies of the incidence of pulmonary embolism associated with isolated calf vein thrombosis detected asymptomatic embolism by ventilation–perfusion scanning, and it is not clear what the clinical significance of these findings are.¹² Data from both venogram and fibrinogen scans demonstrate that deep-vein thrombosis (DVT) usually originates in the deep-veins of the leg and pulmonary embolism originates in the deep veins of the legs in at least 90% of cases.¹³ If the thrombus extends above the knee, the patient is at risk for clinically detectable pulmonary embolism.

3.3.1 Diagnostic measures for VTE

There are a number of diagnostic tests that can be used to confirm the diagnosis of VTE¹⁴: Venography - the definitive investigation but it is invasive. A number of indirect diagnostic methods are available: Doppler ultrasound, impedance plethysmography, radio-iodine labelled fibrinogen uptake test and measurement of plasma D-dimer levels. Ventilation-perfusion scanning is a radiographic image technique which is often used to confirm or exclude the diagnosis of pulmonary embolism.

The need for objective diagnosis of VTE is illustrated by the following: Less than 50% of patients with clinically-suspected DVT or PE have the diagnosis confirmed when routine diagnostic imaging is performed.^{15,16}

A recent guideline suggests that in all patients with clinically-suspected DVT the diagnosis should be confirmed or excluded by the following diagnostic imaging¹⁷:

- non-invasive testing by ultrasound (compression or Duplex scanning), followed by contrast venography if negative to detect calf DVT and non-occlusive proximal DVT; or
- contrast venography (which detects both calf and proximal DVT); or
- serial (repeat after 7 days) non-invasive testing by ultrasound (compression or Duplex scanning) to detect proximal extension of calf DVT.

For Pulmonary embolism:

In all patients with clinically suspected PE, the diagnosis should be confirmed or excluded by an objective test. However in up to 25% of cases of PE, ventilation perfusion lung scans are diagnostic of PE and indicate anticoagulant therapy. In up to 25% of cases, lung scans are normal, and exclude PE. In the remaining 50% of cases, lung scans are non-diagnostic, and should be followed by venography or serial (repeat after 7 days) non-invasive testing by ultrasound and/or by spiral CT angiography or pulmonary angiography (if available).^{18,19,20}

3.3.2 Risk factors for VTE

Virchow (1858)²¹ first postulated that there were three factors (known medically as *Virchow's Triad*) that predispose to the formation of DVT:

- poor circulation or stagnation of the blood;
- excessive coagulability (thickening leading to increased tendency to clot) of the blood; and
- abnormalities in, or damage to, the walls of the blood vessels.

All individual and situational risk factors for DVT act via one or more of the above three possible factors. The risk of VTE has been shown to be increased in a number of specific population groups. Individuals with increased risk of VTE can be classified according to the likelihood of risk as high, moderate and low risk.

VTE can be fatal. One post mortem study extrapolated that 600 000 people develop PE each year in USA, of which 60 000 die as a result.²² Fatal pulmonary embolism occurs with the following frequency in patients who do not receive prophylaxis:

0.1 to 0.8 percent in patients undergoing elective general surgery.

2 to 3 percent in patients undergoing elective hip replacement.

4 to 7 percent in patients undergoing surgery for a fractured hip.

Factors increasing the risk of venous thrombosis include advanced age, malignancy, previous venous thromboembolism, obesity, heart failure, paralysis, or the presence of a haematological inhibitor deficiency state, hormonal therapy and oral contraceptive pills. The most common inhibitor deficiency state is activated protein C resistance, a defect usually caused by a mutation in the gene coding for coagulation factor V and known as factor V Leiden. This mutation is found in 3 to 7 percent of the white population.²³ The next most

common hereditary defect predisposing to thrombosis is the prothrombin G 20210A mutation which occurs in approximately 2 percent of the white population.²⁴

The risk is enhanced in patients with more than one predisposition to thrombosis. One study, for example, noted a 10-fold increase in risk of any venous thromboembolism and a 20 fold increase in risk of idiopathic thromboembolism among men who had both the Leiden mutation and hyperhomocysteinemia when compared to men with neither abnormality. The risk of VTE among individuals with both hyperhomocysteinemia and factor V Leiden was far greater than the sum of the individual risks associated with either abnormality alone. Medical patients who are immobilized (eg, with congestive heart failure, cancer, stroke, or following myocardial infarction) also present a significant risk for venous thromboembolism.

Pregnancy - The risk of VTE is increased in association with pregnancy. This phenomenon may relate in part to the progressive increase in resistance to activated protein C that is normally observed in the second and third trimesters.²⁵

The risk during both the intrapartum and the postpartum periods appears to be accentuated in those women who have an inherited deficiency of a naturally occurring anticoagulant, such as antithrombin III, protein C, or protein S. In one study, for example, the frequency of developing venous thrombosis during pregnancy or the postpartum period was approximately 8-fold greater in deficient compared with non-deficient women²⁶

Hospitalisation - There is a high risk of developing VTE while hospitalised for a reason other than DVT or pulmonary embolus. Based upon a review of residents of Olmsted County for the period from 1980 through 1990, the age- and sex-adjusted incidence of VTE was more than 130 times greater among hospitalised patients (960 per 10,000 person-years) than among community residents (7.1 per 10,000 person-years).²⁷ For both groups, the incidence of VTE increased with advancing age, and, with the exception of women <40 years of age, was higher in hospitalised men than women.

There is high risk associated with orthopaedic surgery resulting from a number of factors that contribute to venous stasis, including the supine position on the operating table, the anatomic positioning of the extremity, and, in patients undergoing total knee replacement, inflation of a thigh tourniquet to obtain a bloodless field [12]. In addition, intimal injury may result from positioning of the extremity, and compression of the femoral vein may occur due to flexion and adduction of the hip during surgery on this joint.

“A multiple hit” theory of the aetiology of VTE has been suggested.²⁸ i.e. VTE condition requires the presence of several risk factors simultaneously. The level of perceived risk has been categorised as low, moderate and high²⁹ Table 1.

Table 1 - Level of risk in VTE

Low risk	Age over 40 Obesity Active inflammation Polycythaemia Recent minor surgery (last three days)
Moderate risk	Varicose veins Heart failure (uncontrolled) Myocardial infarction (recent) Hormonal therapy Pregnancy/postnatal Lower limb paralysis Recent lower limb trauma (six weeks)
High risk	Previous VTE Thrombophilia Recent major surgery (six weeks) Previous cerebrovascular accident Malignancy Familial history of VTE

The risk of VTE increases with background factors such as age, obesity, immobility pregnancy, Puerperium or using a high dose oestrogen therapy (50 micrograms oestrogen per day). Particular acute conditions can be considered as precipitation factors e.g. surgery, malignancy, heart failure, and stroke.¹⁷ Hospital data can provide estimation of the risk associated with low, moderate and high risk group as shown in Table 2.

Table 2 - Percentage risk of developing venous thrombosis in hospital patients according to risk group³⁰

Level of risk	DVT	Fatal pulmonary embolism
Low risk	<10%	0.01%
Moderate risk	10-40%	0.1-1%
High risk	40-80%	1-10%

3.4 Potential link between air travel and VTE

A number of situational factors in aircraft cabins have been proposed to predispose to the development of VTE. These have included cramped seating positions, immobility, possible dehydration due to consumption of alcoholic drinks and other diuretics such as tea and coffee, and the low humidity of the aircraft cabin, relative hypoxia and reduced barometric pressure. These would apply to all passengers, whether or not they had individual risk factors for VTE. Detailed information linking DVT to the aircraft cabin environment has recently been reviewed with some details by the Building Research Establishment for the UK Department of Transport report³¹.

3.4.1 Dehydration

It is generally assumed that dehydration occurs on aircraft and that this increases the clotting tendency of the blood. Moyses (1988)³² describes an experiment in seated volunteers in which blood samples were drawn from foot veins. A rise in haematocrit and in plasma protein concentration after one hour of quiet sitting is noted, both of which, could predispose to thrombosis. This assumption has been challenged by others who propose that dehydration may be protective against DVT.³³ Landgraf et al (1994),³⁴ in their 12-hour simulated flight experiments designed to study pathological processes which might lead to DVT in long-distance air passengers, found a significant increase in plasma viscosity during daytime flights but not during night flights. Haematocrit and albumin concentrations showed only circadian

fluctuations. Blood samples were taken from arm veins and therefore do not reflect conditions in the deep leg veins in seated humans.

3.4.2 Seated posture

Simpson (1940)³⁵ found that 21 of 24 PE deaths in a two-month period occurred either in air raid shelters or as people were leaving them. He concluded that these deaths were caused by people sitting for long periods in deck chairs, with the front edge of the seat compressing the veins in the legs. This compression could have damaged the lining of the veins and also slowed the blood flow, affecting two out of three of Virchow's triad of risk factors. Cases of fatal PE decreased after the introduction of bunk beds for sleeping. Wright and Osborne (1951)³⁶ found that venous blood velocity in the seated position was two thirds of that in the supine position in normal volunteers. Crossing one leg over the other would compress the popliteal artery and result in decreased arterial flow, which may be an additional cause of venous stasis.

3.4.3 Lack of exercise

Landgraf et al (1994)³⁴ in their 12-hour simulated flight study examined oedema formation in seated volunteers, who were divided into two groups – exercising and non-exercising. The 'exercising group' had to leave the seats and walk around the cabin for 5 minutes every hour. They found an increase in lower leg volume in both groups, which was linear with respect to time. There were no significant differences in the leg volumes between the two groups.

3.4.4 Relative hypoxia

Two types of hypoxia may be important – 'global' due to decreased partial pressure of oxygen (pO₂) in inhaled cabin air and 'local', in the leg, due to decreased blood flow. Bendz et al (2000)³⁷ suddenly (within 10 minutes) exposed 20 male volunteers to a hypobaric environment similar to that of the aircraft cabin (76 kPa/2400 m). They found that markers of coagulation transiently increased by two- to eight-fold. They concluded that rapid exposure to hypobaric hypoxia may transiently activate coagulation. Others have criticised this study on the grounds that there were no controls, so it is difficult to know whether the changes were due to the pressure or hypoxic change, or to being placed in a hypobaric chamber for a week. Bartsch et al (2001)³⁸ suggested a control experiment in normoxia to rule out any artificial activation of coagulation due to blood sampling or handling methods.

Gunga et al (1996)³⁹ produced evidence that flying at 8000 ft (2438 m) creates hypoxic stress by measuring erythropoietin concentrations in seven men during an 8-hour flight. Erythropoietin production in the renal cortex is regulated by the amount of oxygen available to the tissues involved in its production. It was found that the erythropoietin concentrations increased significantly during the flight and returned to baseline values 8 hours after landing. Hypoxia also causes vasodilatation and increased capillary permeability thereby tending to worsen oedema (James 1996).⁴⁰ Recent data has challenged the assumption that hypoxia may cause thrombosis and suggested that in fact hypoxia may actually increase fibrinolysis.⁴¹

3.4.5 Reduced barometric pressure

One possible mechanism for an effect of reduced barometric pressure on blood clotting is via the formation of gas bubbles in the blood during decompression. Exposure of the blood to this gas surface may cause haematologic abnormalities. This phenomenon has been investigated in the context of decompression sickness after diving. For example, Tanoue et al (1987)⁴²

studied platelet behaviour during rabbit decompression sickness. Platelet counts significantly decreased after decompression, and platelet thrombi were found in the pulmonary arteries. They suggest that circulating air bubbles interact with platelets, causing the platelet release reaction, and these activated platelets participate in the formation of thrombi. Others⁴³ suggested that platelets recognise air bubbles in the blood as a foreign surface. Similar experiments in man during and after dives have produced conflicting results, leading some to suggest that activation of haemostatic mechanisms, platelet consumption and consumption of coagulation factors may be less significant in man than in animal models. For example, Goad et al (1976)⁴⁴ found that white cell count was the only haematological variable to correlate significantly with blood bubble count in decompression diving experiments. Returning to the possibility of sub-atmospheric decompression effects, Macmillan (1999)⁴⁵ points out that asymptomatic venous gas emboli have been detected by Doppler ultrasound at 10250 ft. It is possible, therefore, that gas emboli below the threshold size for ultrasound detection are present at lower altitudes. The rate of decompression would be particularly important in determining whether gas bubbles formed rather than the absolute pressure arrived at. This hypothesis may tie in with the Bendz *et al* (2000)³⁷ study where there was transient activation of coagulation in the first few hours after exposure to hypobaric hypoxia.

3.4.6 Humidity

Low humidity as a possible risk factor related to VTE is linked to causing dehydration through drying of the mucous membranes and skin. However, it was found that although low humidity of the cabin can lead to drying the mucous membranes, conjunctivae and skin. The drying of the pharynx may be interpreted as thirst, leading to a subjective feeling of dehydration. There is no evidence that exposure to low humidity environment can lead to dehydration. The maximum possible increase in body water loss over an 8-hour period in zero humidity environment, compared with a day-to-day environment, is around 100 ml. This may lead to minor increases in the secretion of antidiuretic hormone, but the normal range of plasma osmolarity is maintained.⁴⁶

In summary, there are a number of potential physiological factors that may explain the increased risk of VTE with air flight. However, it is important to highlight that the evidence to explicitly link these factors and VTE is extremely limited and therefore remains uncertain.

3.5 Current UK healthcare policy on advice/management of VTE and air travel

3.5.1 UK Department of Health (DoH) recommendations

In the UK, the current advice (May 2002) to individuals regarding air travel and VTE is as follows:⁴⁷

“Consult your doctor before the trip: if you have ever had a DVT or PE, a family history of clotting conditions, an inherited tendency to clot, cancer or had treatment for cancer in the past, undergone major surgery in the last three months, had hip or knee replacement within the last three months or ever suffered from a stroke.” “...You may also need to discuss treatment with blood-thinning drugs or use of elastic stockings if you are in a high risk group”.

The recommendation does not specify what advice GPs should give to their patients.

Although the advice is limited to high-risk groups these recommendations have a number of potentially profound resource implications on the NHS – increased primary care consultation, possible secondary care referral and commitment to clinical investigation, and drug tariff costs.

The recommendations for individuals during a flight were:⁴⁷

Be comfortable in your seat, bending and straightening your legs, feet and toes while seated every half-hour or so during the flight is advised. Pressing the balls of your feet down hard against the floor or foot-rest will also help increase the blood flow in your legs and reduce clotting. Upper body and breathing exercises can further improve circulation. Take occasional short walks, when in-flight advice suggests this is safe. Take advantage of refuelling stopovers where it may be possible to get off the plane and walk about. Drink plenty of water. Be sensible about alcohol, which in excess leads to dehydration and immobility. Avoid taking sleeping pills, which also cause immobility.

3.5.2 Advice from some commercial airlines

a) **British Airways** Health Service online document stated that: “Passengers with intrinsic risk factors such as history of DVT or pulmonary embolism, post thrombotic syndrome, chronic venous insufficiency, malignancy, coagulopathy, heart disease or pregnancy should in addition seek medical advice and take appropriate precautions. Prophylaxis with low molecular weight heparin or aspirin may be appropriate”⁴⁸

b) **Qantas**, an Australian airline recommends that “ if you feel you may be at risk from DVT, Qantas recommends that you consult with your doctor before you travel” Health information also provided on timetable and in flight magazine.⁴⁹

3.5.3 House of Lords Select Committee on Science & Technology

Some advice is given in a report from the House of Lords Select Committee on Science and Technology.⁵ This report criticised the government, regulators and the industry for “failing to give sufficient active attention to health”. The report also stated that the risk of DVT as a consequence of air travel in healthy individuals is exceedingly small. For those who are already at risk because of predisposing factors, there may be an additional risk from flying, but it is not currently quantifiable. Members of the committee also criticised the press for exaggerating the health risks from air travel and suggested changing the term of “economy class syndrome” to “travellers thrombosis”.

Recommendations by the House of Lords Select Committee on Science & Technology:

Those with no known predisposing factors:

- Move around in seat and in cabin as much as practicable
- Exercise calf muscles whilst seated by half-hourly flexing and rotating of ankles for a few minutes
- Avoid excess of alcohol and caffeine-containing drinks, both before and during flight
- Drink only water or non-caffeinated soft drinks or juices when thirsty or feeling dry

- Observe and act on advice given in in-flight media

Those at minor risk - i.e. meeting one or more of the following conditions

aged over 40
very tall, very short, or obese
previous or current leg swelling from any cause
recent minor leg injury or minor body surgery
extensive varicose veins

- As above plus the following:
- Avoid leg discomfort whilst seated
- Avoid alcohol and caffeine-containing drinks, both before and during flight
- Take only short periods of sleep, unless normal sleeping position can be attained
- Do not take sleeping pills
- Consider the need to wear support stockings

Those at moderate risk - i.e. meeting one or more of the following conditions

recent heart disease
pregnant or on any hormone medication - particularly the
contraceptive pill and Hormone Replacement Therapy (HRT)
recent major leg injury or leg surgery
family history of DVT

- All the above plus the following:
- Take professional medical advice about the risks involved
- Take pre-flight low dose aspirin as advised by doctor unless contra-indicated
- Take professional advice about the need to wear compression stockings

Those at substantial risk - i.e. meeting one or more of the following conditions

previous or current DVT
known clotting tendency
recent major surgery or stroke
current malignant disease or chemotherapy
paralysed lower limb(s)

- Consider avoiding or postponing flight, taking medical advice if unsure
- If travelling, all the above but have low molecular weight heparin prescribed instead of aspirin

It must be stated that the advice given above was based on evidence from experts in the field, individuals who suffered DVT and organisations rather than derived from empirical evidence based studies of the effect of air travel on the development of VTE cases in the general population or in certain population of high risk. The report admitted the paucity of data on DVT in relation to travel.

3.6 The evidence base for air travel and VTE

Since the early case reports linking air travel and VTE a number of epidemiological studies have been undertaken, including case-control studies. These were followed by studies that assessed the efficacy of various measures for the prevention of VTE in air travellers Table 3.

Table 3 - Landmark studies on finding the evidence of risk of air travel to VTE

First author (Year)	Type of studies
Homans (1954) ⁵⁰	First case report
Symington (1977) ⁵¹	First case series looking at travel histories if VTE cases
Kraaijenhagen (2000) ⁶⁴	First case-control study comparing air travel histories of DVT patients with those of control (non-VTE) individuals
Scurr (2001) ⁵⁹	First RCT of the prevention of VTE in air travellers (pilot study)
WHO study of VTE and air travel (2002) ⁵²	200 000 air travellers will be followed for a month to assess the incidence of thrombosis along other aspects which is planned to be presented in 2006

We have been unable to identify a systematic review that has undertaken a comprehensive search for studies on the risk of air travel on developing VTE; either incidence about the condition or the effectiveness of some measures currently available (stockings and LMWH) and assessment of the quality of included studies.

A recent review from the Building Research Establishment³¹ to the Department of Transport investigating the health in aircraft cabins including DVT stated that air flight seemed a plausible mechanism for developing DVT as air flight in theory affect all three fundamental predisposing factors: slow blood flow increased blood coagulability and damage or abnormality of the blood vessel wall. This review also stated that the effect of exercise has not been empirically shown to reduce the risk of DVT, and there are uncertainties over the effects of low humidity environment on water distribution in the body. The review added that the evidence is weak at present in linking reduced barometric pressure to increased blood coagulability. Local hypoxia although it has the potential to damage the venous valve linings and thus increased the risk of thrombosis, this has not been demonstrated on humans. There were a few reviews of case series of individuals who had suffered from VTE and the recent past history was examined to see the incidence of flight in those who developed VTE. Those studies were excluded, as they did not fulfil our included criteria particularly due to lack of a control group or the incidence of VTE among air travellers is not addressed. Those studies were listed in Appendix 11 among the excluded studies.

WHO recently announced the launch of a comprehensive research programme to investigate the unsolved issue regarding travellers' thrombosis⁵² The WHO study will include three principal areas:

Epidemiological studies to assess the incidence of travellers' thrombosis, to identify who is at great risk and the impact of pre-existing risk factors.

Pathophysiological studies will investigate the causal mechanisms particularly: immobility, cabin pressure, oxygen level.

Clinical studies will focus on the effectiveness of possible preventive strategies. It is hoped to give clear guidance to the travelling public regarding the risk and the most appropriate

preventive measures. However, the study will not be completed till 2006 subject to funding availability.

4. Methods

4.1 Search strategy

A number of electronic databases were searched, i.e., MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register and National Research Register. The internet sites of a number of health organisations (e.g. World Health Organisation) were also examined. Searches were undertaken between 4th –7th June 2002. Additional searches for incidence of DVT and RCTs were carried out on 4th September 2002. Hand searching of the reference lists of reviews and all included studies were undertaken. Contact was made with experts in the field to identify any studies that may have been missed, or any ongoing or unpublished research. References identified in non-English languages were eligible for inclusion.

The search strategy was designed in order to focus on air flight and VTE and thereby identify studies that addressed each of the three objectives of the report i.e. incidence studies, risk factor studies and studies assessing the efficacy of preventive measures (Appendix 1 to Appendix 5).

4.2 Inclusion & Exclusion criteria

To select studies to address each of the three objectives of the report differing inclusion criteria were applied:

i) **Incidence** of VTE during air flight

- Design: any design other than case report
- Population: any individuals who have travelled by air regardless of sex, age or risk status
- Exposure: air travel (short or long haul flight)
- Comparator: not required
- Outcomes: asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, or related mortality.

ii. Air flight as a **risk factor** for DVT

- Design: Any comparative study design i.e. randomised controlled trial, prospective or retrospective cohort study or case-control study.
- Population: Any individuals who have travelled by air regardless of sex, age or risk status.
- Exposure: Air travel (short or long haul flight)
- Comparator: No air travel
- Outcomes: Asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, pulmonary embolus (PE) or related mortality up to month after exposure

iii. **Effectiveness of interventions** to prevent VTE in air travellers

- Design: Randomised controlled trials only
- Population: Any individuals who have travelled by air regardless of sex, age or risk status
- Intervention: Any intervention(s) used for prophylaxes of VTE. It was anticipated these would include both non-drug interventions (e.g. support stockings, in flight exercise, active hydration, restriction from alcohol) and drug intervention i.e. aspirin and heparin.
- Comparator: either no intervention, placebo or any other form a comparative intervention.
- Outcomes: Asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, pulmonary embolus (PE) or related mortality up to month after exposure
- Studies excluded if they were experimental simulations of air flight conditions (e.g. hypobaric chambers).
- Study selection was carried out independently by two reviewers (YA and RT) using a standardised inclusion and exclusion form (see Appendix 6). A high level of agreement was obtained between reviewers (i.e. Weighted Kappa statistic: 0.92 95%CI: 0.81 to 1.00).

4.3 Quality assessment

The quality of risk factor and intervention studies were assessed in terms of the principle bias i.e. selection bias, detection bias, performance bias and attrition bias.⁵³ An adapted version of the *JAMA* checklist for harm was used to assess the quality of risk factor studies.⁵⁴ and a modified version of the Jadad scale used to assess the quality of effectiveness studies.⁵⁵

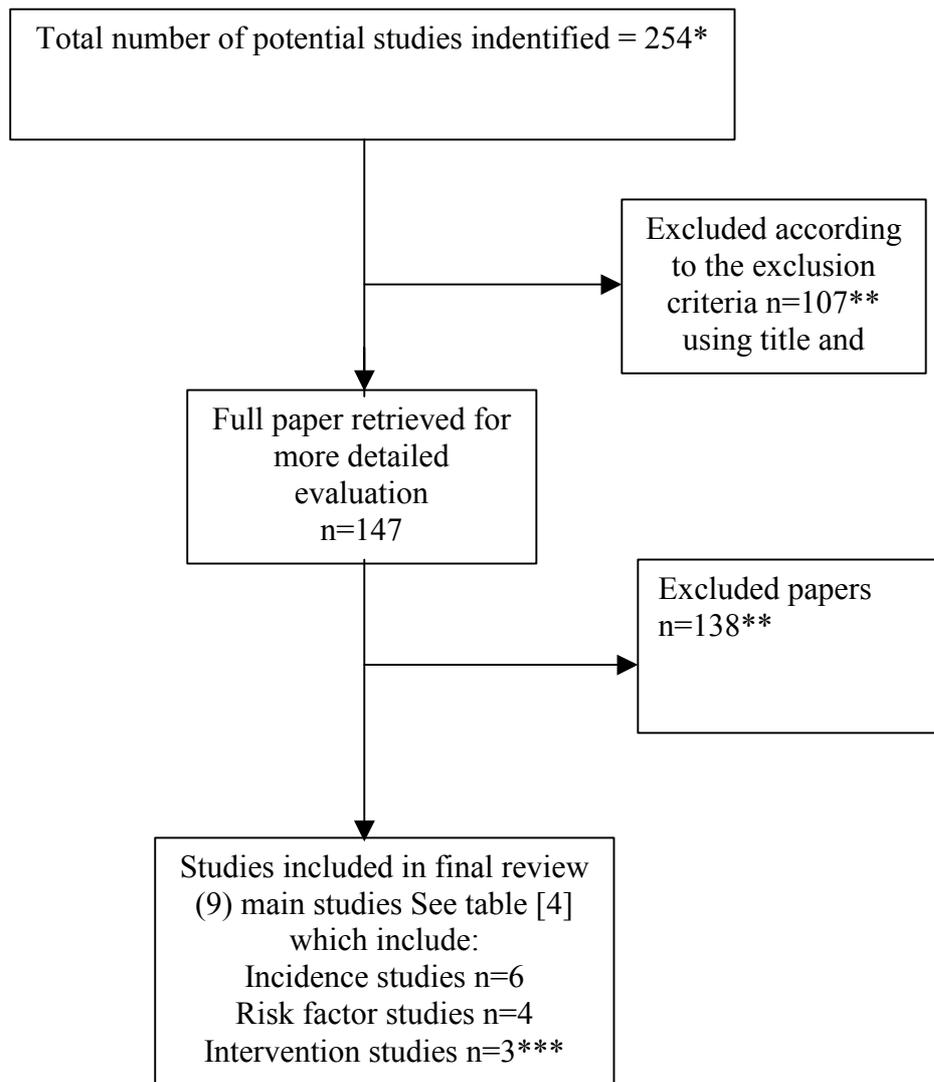
4.4 Data handling and synthesis

Data abstraction was undertaken by a single reviewer (YA) using standardized extraction sheet (see Appendix 10) and checked by a second reviewer (RT). The detailed characteristics, quality, and results of all studies were tabulated.

For incidence studies, data was extracted from individual studies as the proportion of air travellers who experienced the outcome of VTE. For risk factor studies, data was extracted from individual studies in the form of a 2x2 table i.e. VTE outcome by exposure (air travel) relative to control (no air travel), and the results expressed as a odds ratio. Although at the outset of the review it was intended to stratify the results according to particular factors (such as age, VTE risk status, duration and class of air travel) insufficient details were reported to allow this to be done. For intervention the outcome for both treatment and control groups were expressed as absolute risk reduction, relative risk reduction and number needed to treat. All results are expressed as means and 95% confidence intervals. Where appropriate data were pooled using meta analyses. Where there was evidence of significant heterogeneity a random effects method was used. Data analysis was undertaken using RevMan v.4.1 and Stata v.6.

5. Results & commentary

Figure 1 - Summary of included and excluded studies



*Removing duplicates

**See Appendix [11] for details

*** Three studies identified in 2 publications.

Table 4 - Summary of papers retrieved and reasons for exclusion

	Air travel as a <i>risk</i> factor in comparative studies	Incidence studies cohort studies	Interventions to reduce the risk of VTE in air travellers
Total number generated by search	254	33	60
Number of papers retrieved for detailed evaluation	147	33	12
Main reason for exclusion	<ul style="list-style-type: none"> • Reviews, editorial, comments, or news that present no original data • Studies that the data were obtained by simulation • Case series or individual reports stating VTE conditions and checking the previous history of air travel without a control group • Duplicate date of the same study 	<ul style="list-style-type: none"> • The papers are not answering the question what is the rate of people who do not apparently have VTE before travel, then travelled by air, then examined after return and found to be having VTE • Studies that reported the incidence of travel among those who have already developed VTE 	<ul style="list-style-type: none"> • Duplicate data
No of papers included in review	n=4	n=6 (4) of which are part of intervention studies; i.e. the non-intervention arm)	n=3

In total (363) studies were identified, 201 from MEDLINE, 144 from EMBASE, 12 from Cochrane Library, 2 from National Research Register, and 4 from reference lists of included studies. After exclusion of duplicate publications, the total number of studies identified was 259. Following application of the inclusion and exclusion criteria of the review, we included a total of six studies that allow examination of the incidence of VTE in air travellers (three studies were based on the data from the ‘no treatment’ arm of the VTE preventive intervention trials), four risk factor studies of VTE with air travel and three VTE preventive intervention studies (reported within two publications) in air travellers. The selection of the inclusion and exclusion process is summarised in Figure 1 and Table 4.

5.1 Incidence of VTE during air flight

Six studies were identified that contained data to allow the assessment of the incidence of VTE in air travellers. These included three studies designed specifically to assess incidence of VTE with air travel^{56,57,58} and the ‘non intervention’ of VTE preventive intervention arms of three trials in air travellers^{59,60,61}. We were not able to include case-control studies as the data was reported in terms of the incidence of travel in those who develop VTE. A summary of the study characteristics and incidence rates are summarised in Table 5. The details of these studies are provided in **Error! Reference source not found.**

Table 5 - Summary of studies of incidence of DVT in air travellers

	Johnston & Evans (2001)⁵⁶	Scurr (2001)⁵⁹	Arvidsson (2001)⁵⁷	Cesarone (2002)⁶⁰ LONFLIT 3	Belcaro (2001)⁵⁸ LONFLIT I	Belcaro (2001)⁵⁸ LONFLIT 2
Population	Healthy workers - Pilots	No history of VTE, apparently health individuals	Otherwise healthy-conference attendants	High risk group	Both low and high risk	High risk subjects
Outcome	VTE	DVT	DVT	DVT	DVT	DVT
Method of diagnosis	Not stated	Duplex examination and D-dimer assay	Duplex scan	Sonosite scanners	Ultrasound scanning	Ultrasound scanning
Nature of exposure	Population of pilots	≥ 8 hours flight	≥ 5 hours flight	Not stated	Average 12.4 hours flight	Average 12.5 hours
Reported rate of VTE n/N	27/9775 (0.30%)	12/116 (10.30%)	0/83 (0%)	4/100 (4.00%)	11/778 (1.4%)	19/422 (4.5%)
Period of follow up	Person-year data is not stated	Up to 6 weeks	4 weeks	Not stated	24 hours	24 hours

Commentary

- Johnston & Evans study – very different design to the other five and therefore not comparable. This is because the data was from Civil Aviation Authority for 1990-2000 of pilots, however the study is lacking vital details about the follow up. It is not clear how those were followed up and for how long during this 10 years study (person-year data is not available). It is not also clear how the VTE was diagnosed.
- The remaining 5 studies, all assess DVT only by diagnostic methods although the precise methods vary (see Table 5).
- Across the 5 studies there is wide variation in the incidence of VTE from 0% to 10%. Explanation for this might include the population characteristics or the nature of the exposure or both as well as the nature of the outcome. Also the quality of the studies in terms of case ascertainment may be variable.
- Because the details of exposure are not adequately reported (i.e not as an average exposure per person) it is not possible to comment on link between exposure and VTE
- Surprisingly the incidence of VTE in solely high risk groups was lower than the rate from Scurr⁵⁹ which was reported to be among an apparently healthy population.

5.2 Air flight as a risk factor for VTE

A total of four case-control studies presented data that allowed the quantification of air travel as risk factor for VTE. A narrative summary of each of these studies is provided below.

Ferrari et al (1999)⁶²:

160 patients hospitalised in a cardiology department presenting with DVT or PE. All journeys (by car, train, sea or air) lasting 4 hours or more in the preceding 4 weeks were investigated in a questionnaire comprised of >300 questions. The same questions were asked on the first few days and were repeated before hospital discharged. The same questions were put to age-matched control group. The control group was made up of consecutive patients admitted to

the same cardiology department, during the same period, for the same time. Patients with severe diseases that may have limited their mobility were excluded.

Of patients who had completed a journey, 9 had travelled by air. Long distance travel was statistically associated with increased risk of DVT/PE (odds ratio 3.98, 95 % CI 1.9 to 8.4)

Samama et al (2000)⁶³

494 cases of non-hospitalised confirmed DVT reported by GPs and 494 controls were also selected by the GPs as the next patient after the DVT case who had influenza or rhinopharyngeal syndrome, matched for age and sex. Long distance travel within the previous 3 weeks was enquired about regardless the mode of travel or how long the travel was not specified.

Long distance travel was associated with an increase in the risk of DVT. The odds ratio adjusted for age and sex was 2.35 (95% CI 1.45 to 3.80).

Kraaijenhagen et al (2000)⁶⁴

788 patients with suspected venous thrombosis, recent travel defined as any travel > three hours in the past 4 weeks. Cases were defined as those who were confirmed DVT by diagnostic tests (186) and for controls (602) individuals.

4 (2%) of cases had travelled by air, and 13 (2%) of controls had travelled by air. The odds ratio for the risk of VTE in relation to air travel was 1.0, 95% CI 0.3 to 1.6, which was not a significant finding.

Arya et al (2002)⁶⁵

568 consecutive patients with suspected DVT attending a London hospital either as referral from primary care or from attending A & E department were studied. 185 were in cases (confirmed DVT) and 383 in controls (No-DVT individuals). A full travel history was taken for air travel more than 3 hours duration in the preceding 4 weeks.

No significant link between DVT and air travel was demonstrated. However, a significant risk was only increased if travellers had at least one additional risk factor.

The characteristics, quality assessment and results of these studies are summarised in Table 6 and 7

Table 6 - Characteristics of case-control studies

	Ferrari et al (1999) France	Kraaijenhagen et al (2000) The Netherlands	Samama (2000) France	Ayra (2002) United Kingdom
Total sample Age (SD) Male (%)	N = 320 66 (16) yrs 188 (59%)	N = 788 62 (17.2) yrs 313 (40%)	N = 988 Pool age* 454 (36%)*	N = 568 54 (-) yrs 202 (36%)
Sources of cases	Consecutive patients hospitalised for DVT or PE	Consecutive individuals presenting to outpatients with confirmed DVT	Confirmed cases of DVT identified through general practices	Consecutive individuals with confirmed DVT presenting to an A&E Dept or primary care
Sources of control	No DVT or PE age-matched	Individuals where DVT not confirmed Age & sex matched	No DVT (494) Age/sex matched	Individuals where DVT not confirmed
Case definition	Ultrasound echo-Doppler examination)	Compression ultrasonography, D-dimer assay and clinical follow ups and venography, ventilation perfusion lung scan or angiogram)	Venography, duplex ultrasonography, B mode untrasonography, and /or impedance plethysmography	Duplex ultrasonography
Exposure	Any travel > 4 hrs in last 4 weeks (self report)	Air travel > 3hrs in last 4 weeks (Patient self report)	Any travel > 6 hrs in last 3 weeks (Patient self report – case notes)	Air travel > 3hrs* in last 4 weeks (Patient self report)

Table 6 - Characteristics of case-control studies - continued

	Ferrari et al (1999) France	Kraaijenhagen et al (2000) The Netherlands	Samama (2000) France	Ayra (2002) United Kingdom
Comments	<p>Of those cases with DVT only 9 out of 39 patients travel by air.</p> <p>The control group may be less likely to travel by air due to lower social class compared with cases.</p> <p>If control individual were ill in the last three weeks, they are less likely to have travelled compared with cases. This will increase the odds ratio of travel for DVT group.</p>	<p>Many flew less than 5 hours.</p> <p>People included in the study (cases or control) have several potential confounding factor they are not apparently healthy before the travel.</p> <p>There are limited numbers of patients with DVT who travel by air in cases (4) and control, (13).</p> <p>The number of hours in flight was 3 hours or over, a period seems shorter relative to other studies.</p> <p>Participants were asked about travel history before they knew the results of objective diagnosis to avoid recall bias.</p>	<p>Included patients in cases were individuals with surgery and plaster cast in previous 3 weeks. Flu or rhinopharygeal syndrome matched on sex and age+/- 10 years.</p> <p>Long –distance travel and not specifically air travel that was addressed as risk factor for DVT. The length of travel was not specified.</p> <p>GPs asked about the history of travel in the last 3 weeks, if control individual were ill in the last three weeks, they are less likely to have travelled compared with cases.</p> <p>The distribution of intrinsic and triggering risk factors are significantly different between case and control patients.</p>	<p>>8 hrs of air travel was not reported as a significant factor.</p> <p>The risk factor in relation to travel is only apparent if there was at least one risk factor</p>

Table 7 - Quality assessment for case-control studies about the risk of VTE

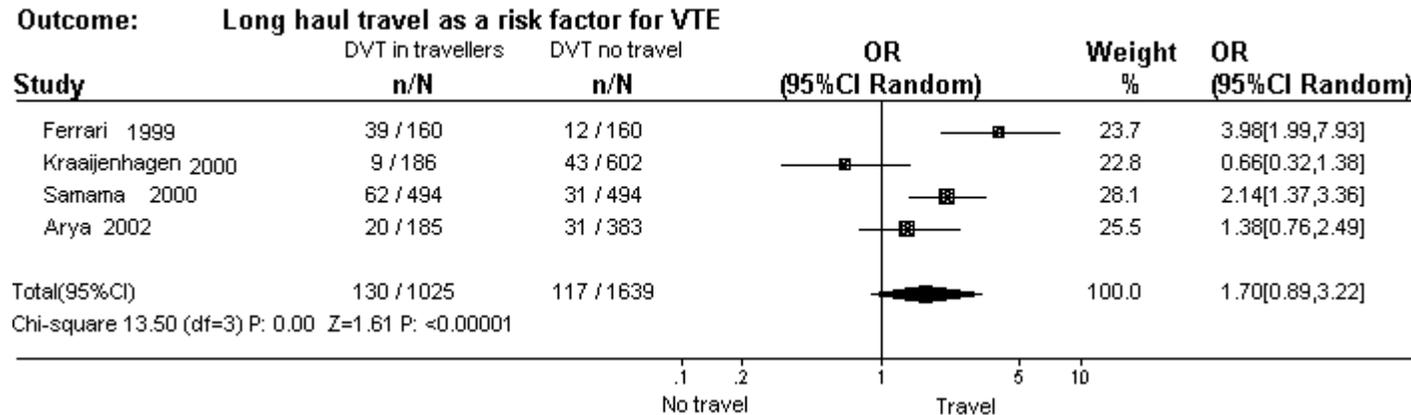
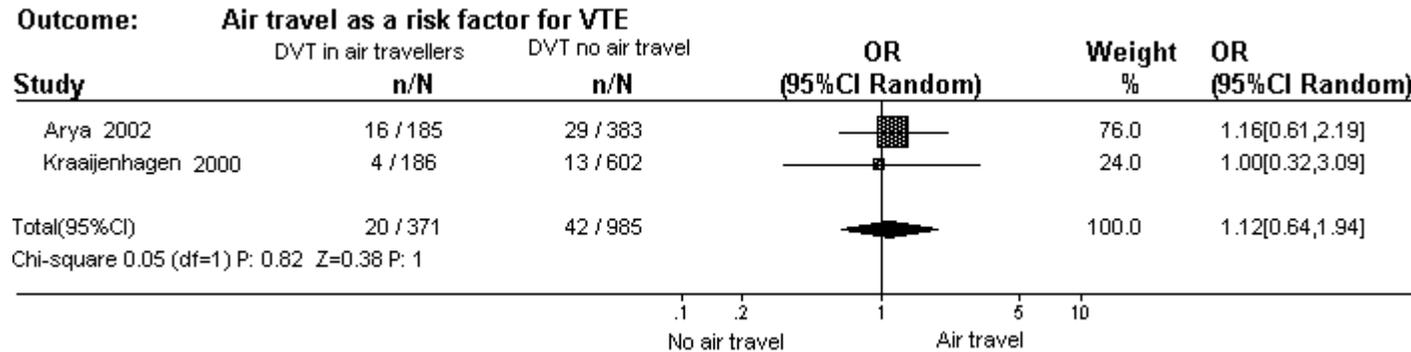
	Ferrari (1999)⁶²	Samama (2000)⁶³	Kraaijenhagen (2000)⁶⁴	Arya (2002)⁶⁵
1. Were the groups comparable? - Were the population characteristics the same? - If not, were other known prognostic factors adjusted for? - Apart from exposure were groups treated equally?	No Can't Tell Can't Tell	No Yes Can't Tell	No Yes Can't Tell	No No Can't Tell
2. Were exposures and outcomes measured in the same way? - Was there evidence of exposure application at an individual level (i.e. individual temp measurement)? - Was the outcome(s) measured at an individual level? - Was there no evidence of assessment bias (e.g. recall bias, interviewer bias)?	Yes Yes Can't Tell	Yes Yes Can't Tell	Yes Yes Can't Tell	Yes Yes Can't Tell
3. Was follow up sufficiently long and complete? - Was follow-up rate $\geq 80\%$? - If not, were reasons for incomplete follow up given? - If not, was there evidence that losses to follow up were similar to those who were followed up?	Yes - -	Yes - -	Yes - -	Yes - -
4. Is the temporal relationship correct? (i.e. exposure before outcome)	Can't tell	Can't tell	Can't tell	Can't tell
5. Is there a dose response? (i.e. risk of outcomes increases with increasing duration of air travel exposure)	Can't tell	Can't tell	Can't tell	No

Based on Levine et al, How to use an article about harm. User's Guides to Evidence-based Medicine. *JAMA* 1994;271:1615-9.

Table 8 - Summary of the findings of case-control studies – odds ratio (95% confidence intervals)

	Ferrari et al (1999)	Kraaijenhagen et al (2000)	Samama (2000)	Ayra (2002)
Any travel	3.98 (1.9-8.4) Travel ≥ 4h	0.7 (0.3-1.4)	2.35 (1.45-3.8)	1.4 (0.7-2.6) for any travel > 3h
Air travel >3 h	Not stated	1.0 (0.3-3.0)	Not stated	1.2 (0.6-2.3)
Air travel >8 h	Not stated	Not stated	Not stated	1.3 (0.6-2.8)
Any travel >3 h and ≥ 1 additional risk factor	Not stated	Not stated	Not stated	2.7 (1.2-6.4)
Plane travel >8 h and ≥ 1 additional risk factor	Not stated	Not stated	Not stated	3.0 (1.1-8.2)
Previous VTE	Not stated	Not stated	Not stated	1.7 (1.1-2.7)
Surgery	Not stated	Not stated	Not stated	6.7 (2.8-16.6)

Figure 2 - Air travel only



Commentary

The number of studies where it was possible to quantify the travel on the development of VTE was small and only 2 specific studies for air flight with a total sample size of only 62. All of the studies are case-control and therefore suffer from the problem of potential bias – particularly selection bias and in this case, detection/assessment bias. Thus the estimates of risk obtained may be unreliable.

Results indicate that for air travel alone there is no evidence that air flight increases (or decreases) the risk of developing VTE (pooled OR: 1.12 95%CI: 0.64 to 1.94). Pooling the results of the four studies in terms of exposure to all long haul travel (> 3 hours) there was a non-significant trend towards an increase in the risk in VTE (OR 1.70, 95% CI 0.80 to 3.22). The wide confidence intervals make it difficult to determine true risk, if any.

The two studies that individually showed a significant increase in VTE risk both considered all long haul travel exposure, only part of which would include air flight. Interestingly these two studies also only considered travel of 4 or more hours duration. Moreover the study by Ayra and colleagues demonstrated that travel only increases the risk of developing VTE in those with previous risk factors. This is supported by the study by Ferrari, the study with the highest risk of VTE with air flight and in which VTE cases were hospitalised.

5.3 Studies of interventions to prevent VTE with air travel

Three randomised controlled trials (RCTs) were identified that examined the impact of interventions designed to prevent VTE in air travellers. The interventions studied were compression stockings and LMWH and aspirin. The details of these trials are summarised below.

Scurr et al (2001)⁵⁹

Population

A total of 231 individuals (39% male) aged 56 to 68 years of age (mean age 62 yrs who intended to travel economy class with 2 sectors of 8 hours' duration within 6 weeks of enrolment (median flying time 24 hours for stocking group, 22 hours for control group) were recruited. Individuals were excluded if they had experienced previous episodes of venous thrombosis, use of anticoagulants, regular use of compression stockings, cardio-respiratory problems, or any other serious illness. A total of 87% of participants completed the study and were included in the analysis.

Intervention

Individuals were allocated to class-I (German Hohenstein compression standard; 20 to 30 mm Hg) below-knee elastic compression stockings (n = 115) or no stockings (n = 116). All were advised to put on the stockings before departure and to remove the stockings after arrival for every flight they took.

Main outcome measure

The presence of DVT confirmed by duplex ultrasonography.

Main results

Analysis was undertaken by intention to treat. At 48 hours after flight travel, no individuals in the stocking group sustained a symptomless DVT. Whereas 12 in the control group had ($P < 0.001$) (Table 9). Four subjects in the stocking group experienced superficial thrombophlebitis, whereas none in the control group did ($P = 0.04$).

Table 9 - Class-I elastic compression stockings vs no stockings during long-haul flights

Outcomes at 48 h	no of cases/N using no stockings	no of cases/N using stockings (%)	RRR (95% CI)	ARR	NNH (95% CI)
Deep venous thrombosis (asymptomatic)	12/116, (10%)	0/115, (0%)	100% (96 to 100)	10%	10 (6 to 17)
Other effects of stockings					
			RRI	ARI	NNH (95%CI)
Superficial thrombophlebitis	4/115, (3.5%)	0/116, (0%)	∞	3.5%	29 (12 to 493)

Conclusion

In passengers on long-haul flights, wearing class-I elastic compression stockings while flying prevented the development of symptomless deep venous thrombosis but increased the risk for superficial thrombophlebitis

Comments

An interesting finding in the study by Scurr and colleagues was the high incidence of asymptomatic thrombosis in the control group i.e. 10%. Given the low sensitivity of ultrasonography for calf-vein thrombosis, this finding may be an underestimate. This rate of thrombosis approaches that for general-surgery patients. However, all the thrombi were asymptomatic calf-vein thrombi. Also it is unknown whether thrombosis rates would be higher in at-risk patients who were excluded from the study. Although the study stated that the technician who undertook the duplex examination was unaware of which the group i.e. the intervention or control group, the possibility exist that the passengers were able to talk to the technician, and therefore this may cause bias.

The DVTs in all patients in the control group were asymptomatic, below the knee and associated with normal fibrin D-dimer level, raising the question that these thromboses were perhaps different from those found in clinical practice. Summary of the trial quality using the Jadad criteria shown in Appendix 8.

Lonflit study (2001)⁶¹**Population**

A total 833 individuals at high risk for venous thrombosis were randomised into 422 control and 411 in intervention group using below-knee stockings. The mean age was 44.8 years (range 20 to –80 yrs) and SD 12, and 57% were male. The average flight duration was 12.4 hours. Scans were made before and after the flights. The definition of high risk for DVT was based on having at least one of the followings: previous episodes of DVT, documented coagulation disorders, severe obesity, limitation of mobility, neoplastic disease in the last two years or large varicose veins.

Intervention

The use of below the knee graduated elastic stockings, providing a maximum compression of 25 mm Hg at the ankle.

Main outcomes

Deep vein thrombosis

Results

In the control group 4.5% experienced DVT in the leg but the rate in the group using the stockings was 0.24%.

Table 10 - Elastic stockings vs no stockings during long-haul flights

Outcomes within 24 hours after the flight	No of cases/N using no Stockings (%)	No of cases/N using stockings (%)	RRR (95% CI)	ARR	NNT (95% CI)
Deep venous thrombosis (symptomatic/asymptomatic)	19/422 (4.5%)	1/411 (0.24%)	95% (89 to 97)	4.26%	24 (15 to 41)

Comments

There were no details about how the randomisations was carried out and how the concealed allocation was maintained and whether masking was applied to the investigators. Summary of the trial quality using the Jadad criteria shown in Appendix 8.

LONFLIT 3 study (2002)⁶⁰**Population**

A total of 300 individuals of high risk group were randomised after informed consent into three groups: (i) no prophylactic therapy, (ii) aspirin treatment (400 mg orally of one dose daily for 3 days starting 12 hours before the beginning of the flight) and (iii) low –molecular-weight heparin (one dose injected 2-4 hours before the flight).

Intervention

Aspirin, LMWH

Main outcomes

The primary outcome was DVT and the superficial thrombosis was a secondary outcomes

Results

In the control group 4/83 (4.82) in the control had DVT compared with 3/84 (3.6%) in the aspirin arm and 0/82 (0%) in the LMWH group. LMWH significantly reduces the risk $p=0.02$.

Table 11 - Summary of findings of LONFLIT2 trial: the use of aspirin

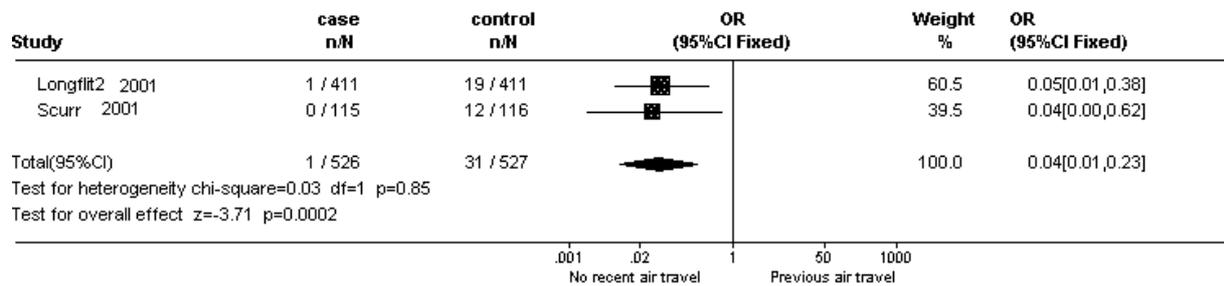
Outcomes within 24 hours after the flight	no of cases/N in the control (%)	no of cases/N using Aspirin (%)	no of cases/N using LMWH (%)
Deep venous thrombosis	4/83 (4.82%)	3/84 (3.6%)	0/82 (0%)
RRR	NA	25%	100%
ARR	NA	1.22%	4.82%
NNT (95% CI)	NA	81 benefit (18 harm to 12 benefit)	21 (9 to 476)

Conclusion

In high risk individuals some forms of drug prophylaxis appear to be effective in the prevention of VTE . LMWH is effective in reducing the DVT risk in long haul air travel. Aspirin found here to have limited efficacy and was associated with adverse side effects.

Comments

There were no details about how the randomisations were carried out and how the concealed allocation was maintained and whether masking was applied to the investigators. No consideration of cost effectiveness. Summary of the trial quality using the Jadad criteria shown in Appendix 8

Figure 3 - Stockings as an intervention to reduce VTE events

5. Discussion

5.1 Summary of findings

- We found relatively few studies under the headings of each of the three questions of this systematic review; (i) What is the incidence of VTE in air travellers?: 6 studies; (ii) What is the evidence that air flight is a risk factor for VTE?: 3 studies; and (iii) How effective are intervention measures on the prevention of VTE?: 2 studies.
- The comparison of findings across studies is made particularly difficult because of the variations in populations (i.e., proportion of high risk individuals) studied and the definitions of both outcome (i.e., asymptomatic v.s symptomatic VTE) and exposure (i.e., differing durations of flight).
- Accepting these differences, there was little or no consistent evidence of an increased incidence of venous thromboembolic events (VTE) in air travellers. Moreover, we found no evidence to support the current belief that long haul (i.e., 2 hours or more) air flight is a risk factor for the development of VTE (OR 1.11 95% CI .64 to 1.94).
- The two case-control studies that have reported a statistically significant increase in the VTE with long haul travel (i.e., 2 hours or more) were not limited to air travel alone and included only high risk individuals. The application of the findings of these studies specifically to air travel is uncertain.
- We did identify randomised controlled trial evidence that prophylactic measures can significantly reduce the risk of asymptomatic VTE in air travellers, for example, support stockings (OR 0.04, 0.01 to 0.23 95% CI), and low molecular weight heparin LMWH significantly reduces the risk p=0.02 but aspirin use was not associated with reduced risk of DVT and there was a significant increase in the risk of bleeding events with both aspirin and heparin. These RCTs were of moderate quality. No RCTs of other preventive measures, such as in-flight exercise or increased hydration, were identified.

5.2 Potential limitations of this report

- The major limitation of this report is the relatively small amount of controlled evidence that we were able to find. We were unable to identify any prospective control studies of air travel as a risk factor in the development of VTE. This review is seriously underpowered to detect a relatively small increase in the risk of VTE with air travel, should such an increase in risk truly exist.
- The potential number of individuals who would be required to demonstrate varying levels in the potential magnitude of risk of VTE with air flight are shown in Table 12.

Table 12 - Shows the sample size needed to show the risk of VTE in relation to air travel**

Background annual incident rate (event/passengers per unit time)	OR associated with travelling	No of air travellers	No of non air travellers	Events of exposed	Events of unexposed	Extra events in exposed	Total events
1/1000	1.5	82000	82000	123	82	41	205
1/1000	2	25500	25500	50	25	25	75
1/1000	3	8840	8840	27	9	18	36
1/1000	4	4370	4370	20	5	15	25
1/1000	6	2590	2590	18	3	15	21
1/1000	8	1720	1720	16	2	14	18
1/1000	10	1290	1290	10	1	9	11

**80% power and 5% significance

If the combined sample size from all the studies were approximately 8,600, (the maximum odds ratio reported with travel in any of the studies in this review⁶²) we would identify 15 extra cases of VTE that can be attributed to air travel. So far there has been no study that has achieved this sample size. On the bases of the total number of individuals in this review (i.e. n=1025 those with a history of travel and n=1636 of those without a history of a recent travel) this review would only detect an increased risk if only the OR associated with travel is approximately about 10 or greater.

- A criticism of any systematic review is its lack of comprehensiveness and therefore the potential for publication bias. Although we were unable to formally assess publication bias we believe this review can be considered the most comprehensive review of the literature to date.

5.3 Implications for policy makers

The results of this review suggest that there is little or no evidence of increased risk of the development of VTE with air travel in otherwise healthy individuals. Therefore no special precautions are indicated or likely to reduce risk in this group.

The evidence from this review appears to suggest that there is a potential benefit of drug and non-drug prophylactic interventions in high risk individuals (e.g. history of previous VTE, recent major surgery, malignancy, stroke). However, these interventions are not without their

negative effects. High risk individuals as part of their normal management are likely to be already receiving drug interventions and preventive advice. Given the results of this review and contrary to current UK Department of Health guidance it seems unnecessary to recommend any additional clinical review or interventions for high risk individuals prior to air flight. It must be stated that the evidence to support any intervention come from only two RCTs which are of moderate quality as well as the outcome reported was asymptomatic DVT.

Until the relationship between the progression of asymptomatic DVT and clinically significant DVT is established, information on the incidence of DVT can not be established. The data regarding incidence of DVT identified in this review was asymptomatic DVT. Recent clinical evidence states that very limited evidence exists on the clinical significance of DVT.⁶⁶

5.4 Implications for future research

There remains a need to precisely quantify the potential added risk of air flight in high risk individuals (e.g. history of previous VTE, recent major surgery, malignancy, stroke) and particularly, the development of pulmonary embolism. Rather than further case-control studies being undertaken we would recommend the combination of prospective controlled and epidemiological modelling studies. Careful consideration needs to be given to the power of such future studies.

APPENDICES

Appendix 1 – Search strategy for air travel as a **risk** factor for VTE.
MEDLINE database <1966 to Present>

-
- 1 (thrombophlebitis or venous thrombosis or pulmonary embolism).mp. (42363)
 - 2 (deep adj3 vein adj3 thrombosis).mp. (4733)
 - 3 dvt.mp. (2365)
 - 4 (venous adj3 thrombosis).mp. (10631)
 - 5 or/1-4 (43971)
 - 6 (air adj3 travel).mp. (402)
 - 7 flight.mp. (11603)
 - 8 flying.mp. (2441)
 - 9 aircraft.mp. (5506)
 - 10 aerospace medicine.mp. (8778)
 - 11 or/6-10 (22945)
 - 12 5 and 11 (206)
 - 13 limit 12 to human (201)
 - 14 from 13 keep 1-201 (201)

Appendix 2 – Search strategy for air travel as a **risk** factor for VTE.
EMBASE database <1980 to Present>

-
- 1 (vein thrombosis or deep vein thrombosis).mp. (18248)
 - 2 exp Lung Embolism/ or pulmonary embolism.mp. (13235)
 - 3 dvt.mp. (2182)
 - 4 venous thromboembolism.mp. (2267)
 - 5 thrombophlebitis.mp. (2917)
 - 6 or/1-5 (30252)
 - 7 flight.mp. (7350)
 - 8 flying.mp. (1639)
 - 9 aircraft.mp. (3005)
 - 10 aerospace medicine.mp. (1032)
 - 11 (air adj3 travel).mp. (274)
 - 12 or/7-11 (11325)
 - 13 6 and 12 (154)
 - 14 limit 13 to human (144)
 - 15 from 14 keep 1-144 (144)

Appendix 3 - Search strategy in Cochrane Collaboration, Cochrane Library 2002, Issue 2.

THROMBOEMBOLISM*:ME
PULMONARY-EMBOLISM*:ME
DVT
VTE
(VENOUS next THROMBO*)
(((#1 or #2) or #3) or #4) or #5)
(AIR near TRAVEL)
TRAVEL
FLYING
((#7 or #8) or #9)
(#6 and #10)

Appendix 4 – Search strategy for **incidence** of VTE in air travellers: MEDLINE database
<1966 to Present>

-
- 1 (thrombophlebitis or venous thrombosis or pulmonary embolism).mp. (42363)
 - 2 (deep adj3 vein adj3 thrombosis).mp. (4733)
 - 3 dvt.mp. (2365)
 - 4 (venous adj3 thrombosis).mp. (10631)
 - 5 vte.mp. (425)
 - 6 or/1-5 (44109)
 - 7 exp INCIDENCE/ or incidence.mp. (264796)
 - 8 (recorded adj case\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (867)
 - 9 occurrence.mp. (105607)
 - 10 frequen\$.mp. (498955)
 - 11 or/7-10 (797636)
 - 12 flight.mp. or exp aerospace medicine/ or exp aircraft/ (21473)
 - 13 flying.mp. (2441)
 - 14 or/12-13 (22641)
 - 15 6 and 11 (6248)
 - 16 15 and 14 (33)
 - 17 from 16 keep 1-33 (33)

Appendix 5 – Search strategy for **trials** on VTE in air travel: MEDLINE database <1966 to Present>

-
- 1 randomized controlled trial.pt. (164117)
 - 2 controlled clinical trial.pt. (61617)
 - 3 randomized controlled trials.sh. (24353)
 - 4 random allocation.sh. (45314)
 - 5 double blind method.sh. (69667)
 - 6 single-blind method.sh. (6607)
 - 7 or/1-6 (276789)
 - 8 (animal not human).sh. (2580370)
 - 9 7 not 8 (264012)
 - 10 clinical trial.pt. (334670)
 - 11 exp clinical trials/ (132751)
 - 12 (clin\$ adj25 trial\$).ti,ab. (82162)
 - 13 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (68781)
 - 14 placebos.sh. (21562)
 - 15 placebo\$.ti,ab. (73287)
 - 16 random\$.ti,ab. (239813)
 - 17 research design.sh. (31379)
 - 18 or/10-17 (572723)
 - 19 18 not 8 (532291)
 - 20 19 not 9 (279077)
 - 21 comparative study.sh. (993848)
 - 22 exp evaluation studies/ (421197)
 - 23 follow up studies.sh. (253534)
 - 24 prospective studies.sh. (147068)
 - 25 (control\$ or prospectiv\$ or volunteer\$).ti,ab. (1247310)
 - 26 or/21-25 (2529216)
 - 27 26 not 8 (1922464)
 - 28 27 not (9 or 20) (1550597)
 - 29 9 or 20 or 28 (2093686)
 - 30 (thrombophlebitis or venous thrombosis or pulmonary embolism).mp. (42363)
 - 31 (deep adj3 vein adj3 thrombosis).mp. (4733)
 - 32 dvt.mp. (2365)
 - 33 (venous adj3 thrombosis).mp. (10631)
 - 34 vte.mp. (425)
 - 35 or/30-34 (44109)
 - 36 exp TRAVEL/ or travel\$.mp. (18699)
 - 37 flight.mp. or exp Aerospace Medicine/ or exp Aircraft/ (21473)
 - 38 flying.mp. or exp Aviation/ (16024)
 - 39 (air adj travel\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (398)
 - 40 or/36-39 (45582)
 - 41 29 and 35 (10859)
 - 42 41 and 40 (55)
 - 43 from 42 keep 1-55 (55)

Appendix 7 - Further information about the incidence studies

	Johnston & Evans (2001)	Scurr (2001)	Arvidsson (2001)	Cesarone (2002) LONFLIT 3	Belcaro (2001) LONFLIT I	Belcaro (2001) LONFLIT 2
Age mean (range) yrs	39 (Not stated)	62 (56-68)	52 (25-80)	NS	44.8 (20-80)	46 Not stated
M:F ratio	Not stated	1:1	3:1	1:1	NS	NS
VTE n/N	27 / 9775* this (0.3/1,000) per year	12/116	0/83 (0/1000) up to 4 weeks after return	4/100 (40/1000)	11/778 (14/1000) 0/355 is the rate in low risk	19/422 (43/1000)
Associated risk factors	16 cases of VTE followed recent surgery/trauma		16 participants/83 with risk factors;6 with estrogen treatment, 3 malignancy, 2 previous DVT, 2 superficial DVT, 2 atrial fibrillation, 1 recent surgery.	High risk factors	Low or high risk factors	High risk
Other information	Healthy workers: Pilots.	The asymptomatic cases found only in the non-intervention group	Population: people attending a conference in Honolulu. One scan shows fresh thrombosis on return. No clinical symptoms reported.	All individuals are of high risk group Outcome: (60%) asymptomatic DVT		In the low risk group there was no single case of VTE reported. In the high risk group there were 19/389. who developed VTE
Comments	The finding do not support the argument that the environment of aircraft cabin may contribute to the risk of VTE in pilots	All cases were asymptomatic. The incidence calculated in the control group which did not use the intervention	Duplex scan after return home up to 4 weeks . the first scan was done for participants during the symposium. Only 49 had repeat duplex scan. One case of superficial femoral thrombosis reported.	It was stated that 60% of cases were asymptomatic	4 cases had proximal, 7 had distal venous system and 6 had superficial system. ITT used in the analysis 355 travellers with low risk factors i.e. had no cardiovascular disease Not stated if DVTs were symptomatic	19 DVT and 8 superficial thrombosis reported It was not stated if DVTs cases were symptomatic or asymptomatic

Appendix 8 - Quality assessment for RCTs

Criteria	Scurr (2001)	LONFLIT2 (2001)	LONFLIT3 (2002)
1. Is the allocation method really random? <ul style="list-style-type: none"> ▪ adequate (score 2) ▪ partial (score 1) ▪ inadequate (score 0) ▪ unknown/not reported (score 0) 	1	0	0
2. Was the treatment allocation concealed ? <ul style="list-style-type: none"> ▪ adequate (score 1) ▪ inadequate (score 0) ▪ unknown/not reported (score 0) 	0	0	0
3. Were baseline characteristics reported? <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) 	1	1	1
4. Were eligibility criteria specified? <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) 	1	1	1
5. Were assessors/research personnel blinded to outcomes? <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) ▪ unknown/not reported (score 0) 	1	0	0
6. Were the groups treated equally , except for the intervention? <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) ▪ unknown/not reported (score 0) 	0	0	0
7. Were losses to follow up reported? <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) ▪ unknown/not reported (score 0) ▪ 	1	1	1
8. Was ITT analysis carried out? <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) ▪ unknown/not reported (score 0) 	1	1	1
9. Was the unit of analysis appropriate? (i.e. individual/household etc.) <ul style="list-style-type: none"> ▪ yes (score 1) ▪ no (score 0) ▪ unknown/not reported (score 0) ▪ 	1	1	1
Total score	6/10	5/10	5/10

Appendix 9 - The included studies

- 1 Arfvidsson B, Eklof B, Kistner RL, Ogawa T, Parsi K. A prospective evaluation of the risk for venous leg thrombosis associated with prolonged air travel: A pilot study. *Cardiovascular Surgery* 2001; **9**:455-457.
- 2 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. *British Journal of Haematology* 2002; **116**:653-654.
- 3 Belcaro G, Geroulakos G, Nicolaidis AN, Myers KA, Winford M. Venous thromboembolism from air travel the LONFLIT study. *Angiology* 2001; **52**(6):369-374.
- 4 Cesarone MR, Belcaro G, Nicolaidis AN, Incandela L, De Sanctis MT, 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):1-6.
- 5 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.
- 6 Johnston RV, Evans ADB. Venous thromboembolic disease in pilots. *Lancet* 2001; **358**:1734.
- 7 Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Buller HR. Travel and risk of venous thrombosis. *Lancet* 2000;**356**: 1492-1493
- 8 Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Archives of Internal Medicine* 2000; **160**:3415-3420.
- 9 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.

Appendix 10 - Data abstraction form

Systematic review of air travel as a risk factor for VTE
Data Extraction Form

ID :

Reviewer: YA/RT

First author		Extraction date	
Title		Country	
Year, volume & page nos.		Date of study data collection	
Journal			

Study design

- RCT
- Non randomised trial
- Prospective cohort
- Retrospective cohort
- Case-control study

Other _____

Population characteristics

Exclusion criteria

Reported, details:

Not reported

Characteristics	Exposed	Not exposed
Crew	Yes/No/Not reported	Yes/No/Not reported
Passengers	Yes/No/Not reported	Yes/No/Not reported
Total number of individuals		
Age mean, SD (or range)		

PTO

Cont.

Characteristics	Exposed	Not exposed
Risk factor(s) reported before the flight:		
History of DVT or PE	Yes/No/Not reported	Yes/No/Not reported
Immobilisation for any reason	Yes/No/Not reported	Yes/No/Not reported
Family history of clotting	Yes/No/Not reported	Yes/No/Not reported
Cancer, or treatment for cancer	Yes/No/Not reported	Yes/No/Not reported
Major surgery in the last 3 months	Yes/No/Not reported	Yes/No/Not reported
Hip or knee replacement in the last 3 months	Yes/No/Not reported	Yes/No/Not reported
Heart failure		
Pregnancy	Yes/No/Not reported	Yes/No/Not reported
	Yes/No/Not reported	Yes/No/Not reported
Postpartum period		
Taking contraceptive pill	Yes/No/Not reported	Yes/No/Not reported
Hormone replacement therapy	Yes/No/Not reported	Yes/No/Not reported
Varicose veins	Yes/No/Not reported	Yes/No/Not reported
	Yes/No/Not reported	Yes/No/Not reported
Obesity		
Diabetes mellitus	Yes/No/Not reported	Yes/No/Not reported
Smoking history	Yes/No/Not reported	Yes/No/Not reported
Others	Yes/No/Not reported	Yes/No/Not reported

3. Nature of exposure

Characteristics of exposure*	
Flight class	First/business/economy/not stated
Length of flight (hours)	
Associated exposures*	
Physical activity during flight	
Alcohol intake	
Fluid intake	
Level of humidity	
Others	

*Comment if any differences in exposure between cases and controls

4. Outcomes

	How measured?	When measured?	Who assessed the outcome?
DVT Symptomatic Asymptomatic			
PE Symptomatic Asymptomatic			
Other outcomes* reported			

*Include only those as per protocol

Period of follow up

_____ days

Losses to follow up

	Not stated	n/N	Reason(s) if stated
Exposed			
Control			

Results

A. Clinical Outcomes

	Symptomatic DVT	No Symptomatic DVT
Exposed (n/N)		
Not exposed (n/N)		
	Asymptomatic DVT	No Asymptomatic DVT
Exposed (n/N)		
Not exposed (n/N)		
	Symptomatic PE	No Symptomatic PE
Exposed (n/N)		
Not exposed (n/N)		
	Asymptomatic DVT	No Asymptomatic DVT
Exposed (n/N)		
Not exposed (n/N)		

B. Other outcomes

Outcome		Mean (SD) or n/N	n/N
	Exposed Not exposed		

8. Analysis

	Comments:
Statistical techniques used:	

9. Other Comments

		Comments
1. Were the groups comparable? - Were the population characteristics the same? - If not, were other known prognostic factors adjusted for? - Apart from exposure were groups treated equally?	Yes/No/Can't Tell Yes/No/Can't Tell Yes/No/Can't Tell	
2. Were exposures and outcomes measured in the same way? - Was there evidence of exposure application at an individual level (i.e. individual temp measurement)? - Was the outcome(s) measured at an individual level? - Was there no evidence of assessment bias (e.g. recall bias, interviewer bias)?	Yes/No/Can't Tell Yes/No/Can't Tell Yes/No/Can't Tell	
3. Was follow up sufficiently long and complete? - Was follow-up rate $\geq 80\%$? - If not, were reasons for incomplete follow up given? - If not, was there evidence that losses to follow up were similar to those who were followed up?	Yes/No/Can't Tell Yes/No/Can't Tell Yes/No/Can't Tell	
4. Is the temporal relationship correct? (i.e. exposure before outcome)	Yes/No/Can't Tell	
5. Is there a dose response? (i.e. risk of outcomes increases with increasing duration of air travel exposure)	Yes/No/Can't Tell	

Based on Levine et al, How to use an article about harm. User's Guides to Evidence-based Medicine. *JAMA* 1994;271:1615-9.

Appendix 11 - The excluded studies (the studies that did not meet the inclusion criteria listed in page 14):

1. Advising patients about air travel. *Drug & Therapeutics Bulletin* 1996; **34**(4):30-32.
2. Air travel research at risk. *Pharmaceutical Journal* 26 JAN 2002 Vol 268(7182) (pp 86), 2002 2002;(7182):86.
3. Alberty-Ryoppy A, Juntunen J, Salmi T. Femoral neuropathy following anticoagulant therapy for "economy class syndrome" in a young woman. A case report. *Acta Chirurgica Scandinavica* 1985; **151**(7):643-645.
4. Allison JW, Glasier CM, Stark JE, James CA, Angtuaco EJ. Head and neck MR angiography in pediatric patients: a pictorial essay. *Radiographics* 1994; **14**(4):795-805.
5. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.
6. Anderson R. Deep-vein thrombosis in long-haul flights. *Lancet* 2001; **358**(9284):837.
7. Ansell JE. Air travel and venous thromboembolism--is the evidence in? *New England Journal of Medicine* 2001; **345**(11):828-829.
8. Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Sato D. Risk factors for venous thromboembolism following prolonged air travel: A 'prospective' study. *Vascular Surgery* 1999; **33**(5):537-544.
9. Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Sato DT. Risk factors for venous thromboembolism following prolonged air travel: Coach class thrombosis. *Hematology - Oncology Clinics of North America* 2000; **14**(2):391-400.
10. Arfvidsson B. Risk factors for venous thromboembolism following prolonged air travel: A prospective study. *Cardiovascular Surgery* 2001; **9**(2):158-159.
11. Auer J, Berent R, Punzengruber C, Eber B. Relapsing fever following a trip around the world. [German]. *Internistische Praxis* 2002; **42**(2):247-254.
12. Badrinath P. Air travel and venous thromboembolism - The jury is still out. *CMAJ: Canadian Medical Association Journal* 2002; **166**(7):885-886.
13. Bagshaw M, Simons R, Krol J. Jet leg, pulmonary embolism, and hypoxia. *Lancet* 1996; **348**(9024):415-416.
14. Bagshaw M. Traveller's thrombosis: A review of deep vein thrombosis associated with travel. *Aviation Space & Environmental Medicine* 2001; **72**(9):848-851.
15. Baumann H. Travelling, flying, mountaineering. *Archives of Gynecology & Obstetrics* 1991; **250**(1-4):1158-1160.
16. Beeton S. Pregnancy and travel. *Community Nurse* 1996; **2**(10):45-47.
17. Behnke AR. The Harry G. Armstrong Lecture. Decompression sickness: advances and interpretations. *Aerospace Medicine* 1971; **42**(3):255-267.
18. Bell DA, Davis WL, Osborn AG, Harnsberger HR. Bithalamic hyperintensity on T2-weighted MR: Vascular causes and evaluation with MR angiography. *American Journal of Neuroradiology* 1994; **15**(5):893-899.
19. Bendz B, Rostrup M, Sevre K, Andersen TO, Sandset PM. Association between acute hypobaric hypoxia and activation of coagulation in human beings. *Lancet* 11 NOV 2000 Vol 356(9242) (pp 1657-1658), 2000 2000;(9242):1657-1658.

20. Bendz B, Sevre K, Andersen TO, Sandset PM. Low molecular weight heparin prevents activation of coagulation in a hypobaric environment. *Blood Coagulation & Fibrinolysis* 2001; **12**(5):371-374.
21. Benigni J-P. Chronic venous insufficiency and the economy class syndrome. *Angeiologie* 2000; **52**(2):83-86.
22. Benoit R. [Traveller's thromboembolic disease. The economy-class syndrome]. *Journal des Maladies Vasculaires* 1992; **17**:Suppl-7.
23. Bergau L, Byrne NJ, Campbell MR, Davis JR, Deering JA, Gong H, Jr., et al. Medical guidelines for air travel. *Aviation Space & Environmental Medicine* 1996; **67**(10 SUPPL.):B1-B16.
24. Bettes TN, McKenas DK. Medical advice for commercial air travelers. *American Family Physician* 01 SEP 1999Vol 60(3) (pp 801-810), 1999 1999;(3):801-810.
25. Bierre AR, Koelmeyer TD. Pulmonary fat and bone marrow embolism in aircraft accident victims. *Pathology* 1983; **15**(2):131-135.
26. Bihari I, Sandor T. Thromboembolism in travelers. *Orvosi Hetilap* 2001; **142**(45):2469-2473.
27. Bischoff A. Economy class syndrome: Preventing thrombosis with foot exercises and supportive stockings. Travel Medicine Series no. 7: Thrombosis risk on long flights. *Fortschritte der Medizin* 1999; **117**(12):36.
28. Black J. Deep-vein thrombosis and pulmonary embolism. *Lancet* 1993; **342**(8867):352-353.
29. Booker JA. Pulmonary embolectomy by flying squad. *BMJ* 1972; **1**(796):355-356.
30. Borillo DJ. Pulmonary embolism in a pilot. *Aviation Space & Environmental Medicine* 1998; **69**(10):1011-1012.
31. Brown TP, Shuker LK, Rushton L, Warren F, Stevens J. The possible effects on health, comfort and safety of aircraft cabin environments. *Journal of the Royal Society for the Promotion of Health* 2001; **121**(3):177-184.
32. Brundrett G. Aircraft cabin environment. *Journal of the Royal Society for the Promotion of Health* 2000; **120**(2):82.
33. Brundrett G. Comfort and health in commercial aircraft: A literature review. *Journal of the Royal Society for the Promotion of Health* 2001; **121**(1):29-37.
34. Brundrett G. Who is responsible for specifying healthy travel conditions? *Journal of the Royal Society for the Promotion of Health* 2002; **122**(1):5.
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