Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial

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Summary

Background The true frequency of deep-vein thrombosis (DVT) during long-haul air travel is unknown. We sought to determine the frequency of DVT in the lower limb during long-haul economy-class air travel and the efficacy of graduated elastic compression stockings in its prevention.

Methods We recruited 89 male and 142 female passengers over 50 years of age with no history of thromboembolic problems. Passengers were randomly allocated to one of two groups: one group wore class-I below-knee graduated elastic compression stockings, the other group did not. All the passengers made journeys lasting more than 8 h per flight (median total duration 24 h), returning to the UK within 6 weeks. Duplex ultrasonography was used to assess the deep veins before and after travel. Blood samples were analysed for two specific common gene mutations, factor V Leiden (FVL) and prothrombin G20210A (PGM), which predispose to venous thromboembolism. A sensitive D-dimer assay was used to screen for the development of recent thrombosis.

Findings 12/116 passengers (10%; 95% CI 4·8–16·0%) developed symptomless DVT in the calf (five men, seven women). None of these passengers wore elastic compression stockings, and two were heterozygous for FVL. Four further patients who wore elastic compression stockings, had varicose veins and developed superficial thrombophlebitis. One of these passengers was heterozygous for both FVL and PGM. None of the passengers who wore class-I compression stockings developed DVT (95% CI 0–3·2%).

Interpretation We conclude that symptomless DVT might occur in up to 10% of long-haul airline travellers. Wearing of elastic compression stockings during long-haul air travel is associated with a reduction in symptomless DVT.

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Introduction

Every year the number of passengers travelling over long distances by air increases. Physicians working close to major airports have seen individual cases presenting with thromboembolic problems after air travel.[1–3] Results of retrospective clinical series[4–6] suggest that up to 20% of patients presenting with thromboembolism have undertaken recent air travel. Ferrari et al[7] reported a strong association between deep-vein thrombosis (DVT) and long travel (>4 h) in a case-control study, although only a quarter of his patients with DVT travelled by air. Kraaijenhagen and colleagues[8] looked at travel in the previous 4 weeks in patients presenting with DVT. They concluded that travelling times of more than 5 h were not associated with increased risk of DVT. The true frequency of this problem remains unknown and controversial. Episodes of DVT can arise without any symptom. Less than half the patients with symptomless DVT will develop symptoms, and only a few of those go on to have a clinically detectable pulmonary embolism.[9,10] In surgical series, a link between symptomless DVT, symptomatic DVT, and pulmonary embolism has been established.[11,12] Patients undergoing surgical procedures are assessed for risk, and appropriate prophylaxis is implemented.[13] We undertook a randomised controlled trial to assess the overall frequency of DVT in long-haul airline passengers and the efficacy of a class-I elastic compression stocking for the duration of the flight.

Volunteers and methods

Participants

Volunteers were recruited by placing advertisements in local newspapers and travel shops, and by press releases. The Aviation Health Institute referred many of the volunteers initially screened for this study, which took place in the Vascular Institute at the Stamford Hospital, London, UK. Passengers were included if they were over 50 years of age and intended to travel economy class with two sectors of at least 8 h duration within 6 weeks. Passengers were invited to undergo preliminary screening, which included an examination and completion of a medical questionnaire about previous illnesses and medication. Volunteers were excluded from the study if they had had episodes of venous thrombosis, were taking anticoagulants, regularly wore compression stockings, had cardiorespiratory problems, or had any other serious illness, including malignant disease. The study was approved by Stamford Hospital ethics committee. Volunteers who gave informal written consent were included in the study.

Investigators

Volunteers who were eligible for inclusion were investigated by duplex ultrasonography (General Electric LOGIQ 700, GE Medical Systems, Waukesha, USA) to detect evidence of previous venous thrombosis. The lower limbs were assessed by two technicians skilled in assessment of venous problems. Examinations were done with volunteers standing. To assess the competence of deep and superficial veins the technicians manually

compressed the calf and measured the duration of reverse flow by colour or pulsed doppler sonography. Venous reflux was defined as duration of reverse flow exceeding 0·5 s. The presence of current or previous venous thrombosis was assessed from the B-mode image, colour flow mapping, and compression assessment of veins during B-mode imaging. Passengers who had evidence of previous thrombosis were excluded.

In the first 30 volunteers, ultrasound examination was undertaken 2 weeks before air travel and again within 2 days of the start of the first flight to provide a control interval in which occurrence of spontaneous DVT could be assessed in this population. No acute DVT was detected during this period. The logistics of the study made it difficult for passengers to attend Stamford Hospital on two occasions before travel and this part of the investigation was abandoned in the remaining volunteers. All subsequent volunteers were screened once before they travelled.

Blood was taken from all participants before travel for a series of haemostatic tests. Full blood and platelet counts were done on a routine cell counter. We used the Dimertest Gold EIA assay (Agen Biomedical Ltd, Acacia Ridge, Australia) to measure D-dimer. We took the upper 95% confidence limit of normal value as 120 pg/L. We used routine PCR techniques for identification of the factor V Leiden and prothrombin G20210A gene mutations.

Randomisation
Volunteers were randomised by sealed envelope to one of two groups. The control group received no specific additional treatment; the other group was given class-I (German Hohenstein compression standard; 20–30 mm Hg) below-knee elastic compression stockings (Mediven Travel; Medi UK Ltd, Hereford, UK). Participants were advised to put on the stockings before the start of travel and to remove the stockings after arrival for every flight by which they travelled. Although the stockings were allocated randomly, the passengers were aware of the treatment. Passengers arranged their own air travel. There was no collaboration with the airlines, although two passengers were upgraded from economy to business class.

Evaluation
Passengers reattended the Stamford Hospital within 48 h of their return flight. They were interviewed by a research nurse and completed a questionnaire inquiring about: duration of air travel, wearing of stockings, symptoms in the lower limbs, and illnesses and medication taken during their trip. Most passengers removed their stockings on completion of their journey. The nurse removed the stockings from those passengers who had continued to wear them. A further duplex examination was then undertaken with the technician unaware of the group to which the volunteer had been randomised. Another blood sample was taken for repeat D-dimer assay. In passengers for whom clinically significant abnormalities of the lower limb veins were detected on duplex ultrasonography, including calf vein thrombosis, the volunteers' general practitioners were notified in writing so that treatment could be arranged.

Statistics
Because of insufficient published data we could not pre-calculate sample size. Since the investigation was intended as a pilot study, we chose a total of 200 passengers. Recruitment was continued until 100 volunteers had been investigated in each group. A finding
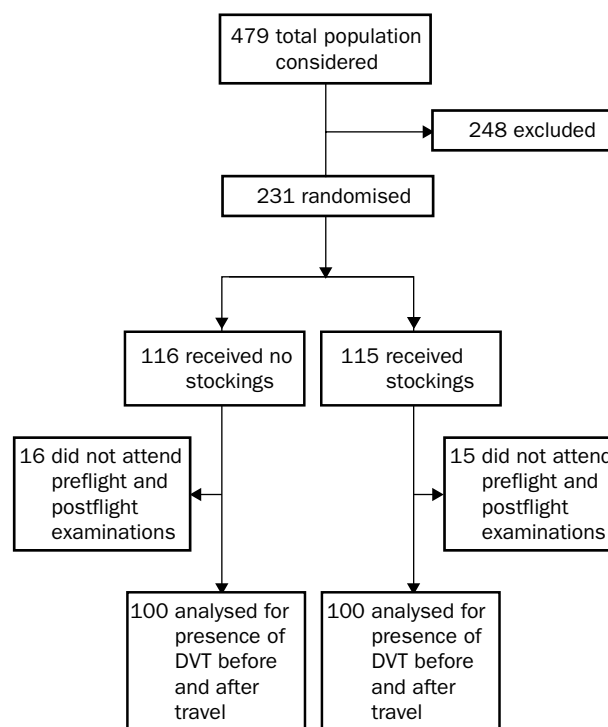
Trial profile

of no case of venous thrombosis in this number of passengers would have resulted in a 95% CI for the rate of DVT of 0–2%. To measure a thrombotic event occurring in 2% or fewer passengers would require a very large study, and the low frequency would have limited implications for air travellers. Data were analysed by contingency tables and calculation of the differences in proportions, and 95% CIs by a computer program (CIA version 1.1, 1989, BMA Publishers, London, UK). We used median and interquartile range for haematological data since data were not normally distributed. Haematological data were included in the analysis only when volunteers were examined before and after travel. All other analyses were done on an intention-to-treat basis, which included all randomised participants.

Results
Volunteers were excluded before randomisation if they did not fulfil the entry requirements or could not attend hospital for investigation both before and after travel (figure). Thus, 231 of 479 volunteers were randomised. 27 passengers were unable to attend for subsequent ultrasound investigation because of ill-health (three), change of travel plans, or inability to keep appointments (24). Two who

	No stockings	Stockings
Number	116	115
Age (years)	62 (56–68)	61 (56–66)
Number of women (%)	61 (53%)	81 (70%)
Number with varicose veins	41	45
Days of stay	17 (13–32)	16 (13–27)
Hours flying time	22 (18–36)	24 (19–35)
Haemoglobin (g/L)	142 (133–149)	140 (133–147)
WBC (×10⁹/L)	5·9 (5·0–7·3)	6·0 (5·0–6·9)
Packed cell volume	0·44 (0·42–0·47)	0·44 (0·41–0·46)
Platelets (×10⁹/L)	240 (206–272)	242 (219–290)
Number FVL positive	7	4
Number PGM positive	1	3

Median (interquartile range) shown, unless otherwise indicated. WBC=white blood cells. FVL=factor V Leiden. PGM=prothrombin gene mutation.

Table 1: **Characteristics of study groups**

	DVT	No DVT	SVT	No SVT
Number	12	188	4	196
Number of women	7	117	4	120
Age (years)	67 (58–68)	62 (55–68)	67 (64–70)	62 (55–68)
Days of stay	18 (8–21)	16 (13–27)	18 (16–21)	16 (13–26)
Hours flying time	21 (17–25)	24 (18–27)	28 (25–33)	24 (18–35)
Haemoglobin (g/L)	142 (132–146)	140 (133–148)	130 (125–133)	140 (133–148)
WBC ($\times 10^9$/L)	6·1 (5·7–7·0)	6·0 (5·0–7·1)	6·3 (5·6–6·8)	6·0 (5·0–7·2)
Packed cell volume	0·44 (0·42–0·47)	0·44 (0·42–0·47)	0·40 (0·39–0·40)	0·44 (0·42–0·47)
Platelets ($\times 10^9$/L)	240 (206–272)	244 (216–285)	264 (237–236)	241 (214–286)
Number FVL positive	2	9	1	10
Number PGM positive	0	4	1	3
Preflight D-dimer (pg/L)*	44,45,54,66	ND	33,58	ND
Postflight D-dimer (pg/L)	33,41,54,59,63,91	ND	36,93	ND
Stockings	0	100	4	96

Volunteers grouped according to presence of symptomless deep vein thrombosis (DVT) and superficial thrombophlebitis (SVT). Median (interquartile range) shown, unless otherwise indicated. WBC=white blood cells. FVL=factor V Leiden. PGM=prothrombin gene mutation. ND=not detectable (below the limit of sensitivity of the assay, 32 pg/L). *D-dimer values are those individual values greater than 32 pg/L, all other passengers had concentrations less than 32 pg/L.

Table 2: **Age and haematological data in 200 passengers examined before and after air travel**

were upgraded to business class and two taking anticoagulants were also excluded. A similar number of men and women were excluded in the two groups: six and nine in the stocking group and seven and nine in the no stocking group, respectively. The remaining 200 passengers were invesigated before and after long-haul economy air travel. None of the 31 volunteers who were excluded after randomsiation underwent follow-up duplex ultrasound examination.

The characteristics of the two groups were closely matched, but by chance a greater proportion of women were included in the stocking group (table 1). Table 2 shows results of haematological investigations. After air travel, 12 (10%; 95% CI 4·8–16·0%) passengers not wearing elastic stockings had developed symptomless DVT in the calf that were detected on duplex ultrasound examination. None of the 115 passengers (CI 0–3·2%) wearing compression stockings had DVT. A further four people all of whom were wearing compression stockings, developed superficial thrombophlebitis in varicose veins (3%; 1·0–8·7%). None of the no-stockings-group developed superficial thrombophelbitis (0–3·1%). Four of the patients with symptomless DVT were given low-molecular-weight heparin subcutaneosuly for 5 days and were referred to their general practitioner for further treatment. The remaining eight were asked to take aspirin, referred to their general practitioner, and advised to undergo a further scan and receive treatment if appropriate. General practitioners were kept informed of these developments. The four passengers with superficial thrombophlebitis received treatment, one with aspirin and three with a non-steroidal anti-inflammatory drug (diclofenac).

14 (7%) of the 200 participants examined both before and after travel, were heterozygous for either factor V Leiden (11) or prothrombin gene mutation (four). One person had both gene mutations and had an episode of thrombophlebitis. Two passengers with symptomless DVT were factor V Leiden positive. The full blood count, platelet count, and D-dimer assays provided no prognostic

	Number of participants	
	No stockings	Stockings
Aspirin	9	11
Hormone replacement therapy	8	16
Thyroxine	6	6
Antihypertensives, including diuretics	10	12
Antipeptic ulcer drugs	8	3

*Includes additions to usual drugs.

Table 3: **All drugs taken by volunteers who attended for examination before and after air travel***

information.

The before and after travel questionnaires were examined to identify concomitant medication, including that begun during air travel (table 3). Only two passengers took drugs in addition to their usual medication. Most drugs were evenly distributed in the two groups, although there was a trend towards more patients taking hormone replacement therapy in the stocking than in the non-stocking group (percentage difference 8%,CI −1 to 17%). Several volunteers took aspirin as part of their regular medication.

Discussion

About one in ten passengers not wearing elastic compression stockings developed symptomless DVT after airline travel, which is a surprisingly large proportion of the study group. The passengers were all aged more than 50 years and undertook long journeys by air (median 24 h), both of which are factors that could increase the risk of thrombosis. As far as we are aware no other workers have undertaken such a prospective study.

Other investigators[14] have shown postoperative symptomless DVT (detected by radio-fibrinogen scanning) in about 30% of general surgical patients in whom no prophylactic measure was applied. We accept that symptomless calf vein thrombosis is probably not a major risk to health, but the approach might be useful in future interventional studies. Published clinical series have recorded DVTs detected after investigation of calf symptoms. They showed that 10–20% of isolated calf vein thromboses extend to more proximal veins.[15,16] Pulmonary embolism can arise in about 10% of patients presenting with isolated calf vein thrombosis.[15,17] However, patients presenting with symptomatic calf vein thrombosis often have recognised predisposing factors such as malignant disease or thrombophilia.[15,16] We excluded patients with a history of serious illness or previous thrombotic episodes and all those with post-thrombotic vein damage on duplex ultrasonography. We believe that the thrombi detected in our study were attributable to long-haul air travel. Environmental changes that take place during long-haul air travel may provoke calf vein thrombosis. Once the journey has been completed these factors no longer apply, allowing spontaneous resolution of calf vein thromboses without complication in most cases.

In our study no symptomless DVT was detected in the stocking group. In hospital practice there is evidence that graduated compression stockings are effective at reducing the risk of DVT after surgical treatment.[18] Our findings strongly suggest that stockings also protect against

symptomless DVT after air travel. However, four passengers with varicose veins developed superficial thrombophlebitis while wearing stockings. In all four, thrombophlebitis occurred in varicose veins in the knee region which were compressed by the upper edge of the stocking.

The prothrombotic gene mutations that we investigated are together present in about 10% of European populations. The combined prevalence of these abnormalities was 7% in our volunteers, but 19% in those developing superficial or deep venous thrombosis. These data should be regarded with caution, in view of the small number of people we studied.

D-dimer, a specific degradation product of cross-linked fibrin, measured by a sensitive EIA procedure, is a useful diagnostic aid in detection of venous thromboembolism.[19] Failure to detect raised concentrations of D-dimer in passengers with positive ultrasound scans might be related to the short half-life of D-dimer (about 6 h), combined with the long (up to 48 h) time of blood sampling on return from travel. This interval between completion of the final leg of air travel and testing may have affected the usefulness of the test. Additionally, in all volunteers who developed symptomless DVT, the thrombus arose only in calf veins which would also result in a modest rise in plasma D-dimer.

Ferrari and co-workers[7] have also shown an association between travel and developments of DVT, but only a quarter of their patients with DVT had travelled by air. Although Kraaijenhagen and colleagues[8] recorded no association of DVT with travel, many of their airline passengers have flown for less than 5 h. These case-control studies also indicate that DVT related to air travel is not a major healthcare problem, perhaps because only a small proportion of the population undertakes long-haul journeys at any time. These investigators included people with several potential confounding factors such as previous venous thrombosis, malignant disease, and recent surgery, whereas we excluded such individuals. Bendz et al[20] simulated long-haul flights in a hypobaric chamber and noted substantially increased plasma markers of thrombosis in volunteers exposed to reduced ambient pressure. A major drawback was that they did not have a control group. However, their findings suggest a possible additional mechanism for thrombosis after air travel. We measured D-dimer values but, because of the study design, we could not show an association with the development of symptomless DVT.

We accept that our method of recruitment was not ideal, although we did exclude individuals at highest risk. We were concerned that because of their interest in the problem some of the volunteers may have taken steps to reduce the occurrence of venous thrombosis—ie, by being active during the flight and drinking more fluids. We could not assess the effect that participation in the study had on the behaviour of volunteers while aboard the aircraft. These factors would have applied equally to both our study groups. Whether leg exercises, walking, or drinking water prevent thrombotic events after airline travel remains to be established.

The randomisation procedure was not stratified or miminised for any factor, since we regarded this study as a pilot investigation, which resulted in even distribution between the study groups for most factors. Volunteers with the most important predisposition to DVT—a previous history of evidence of DVT—were excluded, ensuring that no bias resulted from this factor.[21] However, the stocking group contained more women than men (table 1). There is little evidence that women are more or less susceptible than men to venous thrombosis in the age group we investigated.[22] After airline travel, symptomless DVT was more-or-less evenly distributed between men and women (five of 55 men and seven of 61 women, table 3) in the non-stocking group.

We used duplex ultrasonography to detect symptomless DVT. Venography was judged unethical in symptomless volunteers. Others have shown[23,24] that duplex ultrasonography is a reliable method of detecting calf vein thrombosis, as well as proximal vein thrombosis, in symptom-free patients. In a series of studies the reliability of duplex ultrasonography in the diagnosis of calf vein thrombosis has been compared with venography.[25–29] The main failing of duplex ultrasonography is that it may underestimate the true frequency of calf vein thrombosis, but it has a specificity of 79–99%. Our data may have underestimated the true rate of calf vein thrombosis by as much as 30%. The fact that some individuals wore compression stockings until shortly before the post-travel examination is unlikely to have affected the sensitivity of the test. The most important factors determining the reliability of this examination are whether it is technically possible to image the deep veins and the presence of post-thrombotic vein damage.[28] All volunteers with post-thrombotic appearance on ultrasonography were excluded from this investigation and none of our participants had severe calf swelling, which would have prevented adequate images of the calf veins being obtained. We believe that the frequency of symptomless DVT that we recorded is reliable.

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