The LONFLIT4–Concorde — Sigvaris Traveno Stockings in Long Flights (EcoTraS) Study

A Randomized Trial

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The LONFLIT1/2 studies have established that in high-risk subjects after long (> 10 hours) flights the incidence of deep venous thrombosis (DVT) may be between 4% and 6%. The LONFLIT4 study was aimed at evaluating the control of edema and DVT prevention in low-medium-risk subjects. In this study prophylaxis of edema with specific travel stockings was evaluated in 2 separate studies involving flights lasting 7 hours and 10–12 hours. Part I. Subjects at low-medium risk for DVT were contacted; 55 subjects were excluded for several nonmedical, travel-related problems or inconvenient evaluation time; the remaining 211 were randomized into 2 groups to evaluate prophylaxis with elastic stockings in 7–8-hour, long-haul flights. The control group had no prophylaxis; the treatment group used below-knee, Sigvaris Traveno elastic stockings (Ganzoni, Switzerland, producing 12–18 mm Hg of pressure at the ankle). Color duplex scanning was used to evaluate the possible presence of DVT; edema/swelling were evaluated with a composite score including the presence of edema (with an edema tester), variations in ankle circumference and leg volumetry, subjective swelling, and discomfort (scale ranging from 0 to 10). Results: Of the 103 included subjects in the stockings group and 108 in the control group (total 211), 195 subjects completed the study. Dropouts (16) were due to low compliance or traveling and connection problems. Age, sex distribution, and risk factors distributions were comparable in the 2 groups. Stockings Group: Of 97 subjects none had DVT or superficial thromboses. Control Group: Of 98 subjects none had thrombosis. The level of edema at inclusion was comparable in the 2 groups of subjects. After flights there was an average score of 6.4 (1.3) in the control group, while in the stockings group the score was on average 2.4 (SD 1), 2.6 times lower than in the control group ($p < 0.05$). In the control group 83% of the subjects had an evident increase in ankle circumference and volume that was visible at inspection and associated with discomfort. The control of edema with stockings was clear, considering both parametric data (circumference and volume) and

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nonparametric (analogue scale lines) measurements. Part II. In this part of the study 200 subjects at low-medium risk for DVT were contacted; 35 subjects were excluded for several nonmedical, travel-related problems or inconvenient evaluation time; the remaining 165 were randomized into 2 groups to evaluate prevention in flights lasting between 11 and 12 hours. The control group had no prophylaxis; the treatment group used Traveno stockings. Of the 83 included subjects in the stockings group and 82 in the control group (total 165), 146 subjects completed the study. Dropouts were due to low compliance or connection problems. Age/sex distribution were comparable. Of 75 subjects completing the study in the stockings group and 71 in the control group, none had thrombosis. The average level of edema at inclusion was comparable in the 2 groups (1.1). After the flight there was a score of 8.9 (2) in controls; in the stockings group the score was 2.56 (1.3) ($p < 0.05$). The control of edema and swelling with stockings even after 11 hours of flight was clear, considering both parametric (circumference, volume) and nonparametric (analogue scale lines) measurements. The tolerability of the stockings was very good and there were no complaints or side effects. In conclusion Sigvaris Traveno stockings are very effective in controlling edema in long-haul flights.

Introduction

Recently much attention has been generated about the risk of venous thrombosis after prolonged flights.[1] Initially, the attention was caused by the death of a young woman from pulmonary embolism after a flight from Australia to the U.K.[2] Homans[3] first reported venous thrombosis after air travel in the 1950s, presenting the case of a physician who developed deep venous thrombosis (DVT) after a 14-hour flight.[3] The condition was termed "economy class syndrome."[4] Venous stasis, possibly caused by prolonged sitting in a limited space, was considered to be an important causal factor. Similar circumstances such as sitting for hours in shelters in London during the Second World War had been shown to be associated with up to a sixfold increase in sudden death from pulmonary embolism.[5] Prolonged travel has also been reported to be associated with DVT and pulmonary embolism.[6] In a recent case-control study including 788 patients, no increased risk of DVT among travellers was found and only 17 had a history of previous air travel.[7] However, another case-control study reported that a history of recent travel was found almost 4 times more often in patients with DVT than in controls.[6] Compression of veins such as the popliteal vein on the edge of the seat could be a contributing factor to venous stasis and DVT. Hemoconcentration, due to decreased fluid intake and water loss in the dry atmosphere of airplane cabins, has been implicated,[8] together with the diuretic effect of alcohol. Another study reported that a history of recent travel was found almost 4 times more often in patients with DVT than in controls.[6] In another study the coroner for the area including Heathrow airport in London reported 61 deaths in arriving passengers over 3 years, 11 due to pulmonary embolism. In the same period venous thromboembolism was attributable to only 1 of 28 deaths in passengers waiting to embark.[9]

Biochemical changes have been reported in healthy volunteers during simulated long flights.[10] Plasma viscosity, packed cell volume, albumin concentrations, fluid balance, and lower limb size were measured. No dehydration was shown, but there was retention of fluid corresponding to an approximate 1 kg increase in body weight. This study did not, however, consider the changes in cabin-related factors such as decreased air pressure, mild hypoxia, and low humidity,[11] which are difficult to reproduce in laboratory conditions. These factors clearly distinguish the effects of long-haul air travel from other types of travel. The decreased air pressure and relative hypoxia may reduce fibrinolytic activity and cause release of vein wall factors that lead to venous stasis.[12] The hypobaric environment may increase activated coagulation.[13]

Further prospective epidemiologic studies are required to identify the incidence of this condi-

tion and to define subjects at higher risk. The ideal prospective study should screen many passengers before and after prolonged flights. Current evidence suggests that any association between symptomatic DVT and long-distance flights is weak and that its incidence is probably lower than the impression given by recent publicity. However, the prevalence of DVT may be particularly high in high-risk subjects. Many airlines claim that thromboembolism usually develops after the flight when the passenger had left the airplane or that a thrombus might have been present at the beginning of the flight so that they are not involved with the problem. In the past no advice has been given to passengers, but based on recent evidence,[14,15] airlines have now started to give advice[16] suggesting methods to avoid "stasis," without mentioning thrombosis. From past experience of prophylaxis, appropriate measures to prevent DVT might include general advice to passengers to stand up, stretch, exercise, drink water, avoid putting baggage under the seat to have more leg space, and avoid constrictive clothes. Subjects with risk factors for DVT such as a past history of DVT, hormonal treatment, malignancy, or recent surgery, should carefully discuss additional protective measures with their physicians including postponing the flight. Further preventive measures might include elastic stockings and antithrombotic prophylaxis with low-molecular-weight heparin. At the moment there is no evidence that antiplatelet agents may be effective in this condition.

The LONFLIT1 study[14,17] has evaluated the incidence of DVT in low-risk subjects after long-haul flights in the high-risk group. 2.7% of subjects had a DVT. In total there was a thrombotic event in 4.8% of subjects. The LONFLIT2 study was a prospective, randomized evaluation of DVT prevention with elastic stockings.[14] Among subjects with stockings, DVT incidence was significantly decreased (stockings decreased 18.75 times the incidence of DVT in long-haul flights in high-risk subjects). The Lonflit3 study has shown a significant difference in DVT reduction, in high-risk subjects with 1 dose of low-molecular-weight heparin LMWH (Clexane®/enoxaparin).[15-18]

The aim of this new, independent study was to evaluate the protective effects of specific antithrombotic stockings on the development of edema and its control. These stockings (Traveno, Ganzoni) have been developed for use in flights; in this study only low- and medium-risk subjects traveling in economy in long-haul flights (7–11 hours) were included.

Patients and Methods: Part I

London–New York

Subjects at low-medium risk for DVT were contacted and preincluded; 55 subjects were excluded for several nonmedical, travel-related problems or inconvenient evaluation time; the remaining 211 were randomized into 2 groups to evaluate prophylaxis with elastic stockings in 7–8-hour, long-haul flights: the control group had no prophylaxis; the treatment group used specifically designed elastic stockings (below-knee, Traveno stockings producing 12–18 mm Hg of pressure at the ankle). Subjects were advised to wear the stockings before going to the airport (2–3 hours before the flight). High-risk criteria for DVT are those previously indicated in LONFLIT studies 1, 2, and 3[14,17,18] such as previous episodes of DVT or superficial vein thrombosis, coagulation disorders, severe obesity, limitation of mobility due to bone or joint problems, neoplastic disease within the previous 2 years, clinical cardiovascular disease, or large varicose veins. Also subjects taller than 190 cm and heavier than 90 kg were excluded. Ultrasound scanning protocol (before-after flights): Sonosite scanners with a 7.5–13 MHz, high-resolution, linear probe (Sonosite, Bothell, WA, USA) were used to evaluate the venous system by compressing of the major veins (femorals, popliteals, and tibials).[13-21] Exclusion criteria were cardiovascular diseases or any clinical disease requiring medical treatment, bone or joint problems, problems limiting mobility, diabetes, hypertension, severe obesity, recent thrombosis, or the presence of thrombi at the preflight examination. Suggestions to passengers (ie, mild exercise, walking, drinking water, avoiding salty food, avoiding excessive baggage, restricting leg motion) were given to both groups.

The edema score (Table I) was based on the edema tester, ankle circumference, volume measurements, subjective swelling, and discomfort score. Items 1, 4, and 5 were based on an analogue scale line (1 to 10) directly defined by the subjects before and after the flights.

The edema tester is applied under a sphygmomanometer applied at the ankle level for 3 minutes at a constant pressure of 50 mm Hg. The pressure and the tester produce skin marks that are related to the presence and quantity of edema at the perimalleolar region. Ankle circumference was measured with a tape at the smallest ankle diameter. This method can measure with accuracy differences in variations > 1 cm. Volume vari-

Table I. Parameters and items considered in the evaluation of edema.

	Scale	0	1	2
1. Edema test	1–10	1–2	3–6	7–10
2. Ankle circumference	cm	0–1	>1 <3	>4
3. Volume	mL	0–2	>2 <6	>6
4. Subjective swelling	1–10	1–2	3–6	7–10
5. Discomfort	1–10	1–2	3–6	7–10
Max score		0	5	10

Worst case 10. No edema 0.

ations were measured with water displacement (a plexiglas leg-shaped chamber with a parallel 2 mm diameter tube connected with the main water chamber). This method (Thulesius) can measure water displacement (and its variations due to increased leg volume) with a range of accuracy of < 2 mL.

Evaluation of Edema

Some degree of edema is present in almost all (> 90%) passengers traveling for more than 5 hours.[14] The combined edema score (Table I) was developed in the San Valentino Vascular Project and in the Irvine Labs to assess in a quantifiable and reproducible way the edema/swelling observed in both normal subjects and patients (ie, those with diabetic microangiopathy and chronic venous insufficiency). The edema score is based on combined evaluation of parametric data such as the edema tester, the variations in ankle circumference (in cm), and volume measurements (in mL or in percent variation of the baseline volume) combined with the subjective assessments of swelling and discomfort (measured on an analogue scale line). Items 4 and 5 are based on a scale line (ranging from 0 to 10) directly defined by the subjects before and after the flights. The edema tester (Aci-Medical, CA, USA) is a plastic device developed to assess edema in a semiquantitative way. The device is applied at the internal perimalleolar region underneath a standard sphygmomanometer, with its distal edge 2–3 cm proximal to the medial malleolus; pressure is applied for 3 minutes (maintaining the sphygmomanometer at a constant pressure of 50 mm Hg). Pressure on the tester produces skin marks that are related to the presence and quantity of edema at the perimalleolar region. The edema tester had been studied and validated, and previous studies indicate good reproducibility in standardized conditions.

Ankle circumference is measured with a tape at the smallest ankle diameter. This method can measure with accuracy differences in variations of size > 1 cm.

Volume variations are measured with water displacement (a plexiglas leg-shaped chamber with a parallel 2 mm diameter tube connected with the main water chamber). This method (originally developed by Thulesius[22]) can accurately measure water displacement (and its variations due to increased leg volume) with a range of accuracy of < 2 mL.[22-26] The maximum calf size is carefully detected before volume measurements and marked onto the skin. The leg is immersed in water and the water level and its displacement are measured at the maximum calf circumference. The leg volume before the flight is arbitrarily considered to be 100% and any increase in volume is therefore measured as a percentage.

Patients and Methods: Part II

Extension. London-Phoenix

The same procedures and criteria were used in this part of the study, which included subjects flying for a longer period (11–12 hours). In this

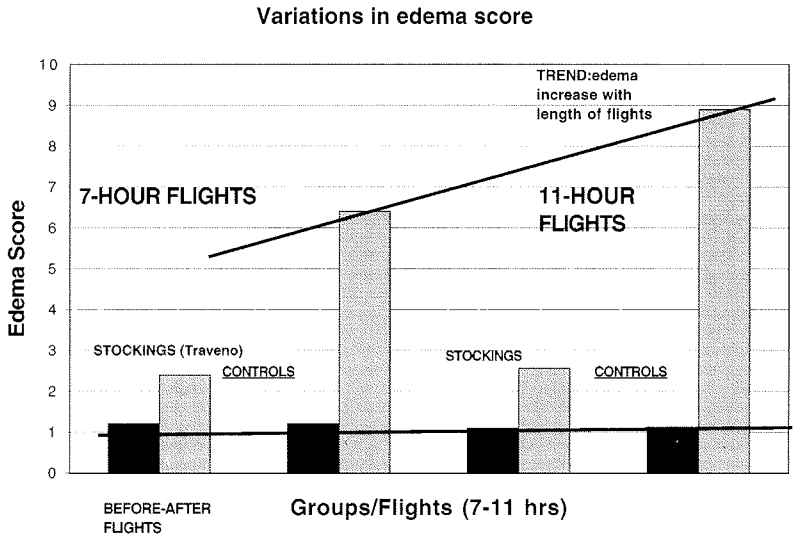

Figure 1. Edema score before and after flights in the stocking groups (black columns) and in the control groups (gray). The treatment and control group observed in a 7-hour flight are on the left of the graph and the groups observed in more prolonged flight (11–12 hours) are on the right of the graph. The trend in increasing the edema level with the length of the flight can be extrapolated (higher, gray columns relative to untreated controls). There is a very limited increase in edema level with stockings, with increasing flight length. The difference between trend increases is significant ($p < 0.05$).

part of the study, 200 subjects at low-medium risk for DVT were contacted; 35 subjects were excluded for several nonmedical, travel-related problems or inconvenient evaluation time; the remaining 165 were randomized into 2 groups to evaluate prophylaxis in flights lasting between 11 and 12 hours. The control group had no prophylaxis; the treatment group used below-knee, Traveno stockings.

Statistical analysis was conducted using nonparametric tests and the analysis of variance considering the event-free subjects completing the protocol and calculating both the incidence of events (DVT, superficial thrombosis) considering individuals and limbs and using intention-to-treat analysis.

Results: Part I

Of the 103 included subjects in the stockings group and 108 in the control group (total 211), 195 (92%) subjects completed the study (Table II). Dropouts (16) were due to compliance, traveling, and/or connection problems (10 in the control group, 6 in the stockings group). Age and sex

Table II. Part I of the study. Patients and events.

	Stockings	Controls	Total	Difference
Included	103	108	211	ns
Lost	6	10	16	ns
Completed	97	98	195	ns
DVT, number (%)	0 (0%)	0 (0%)	0 (0%)	ns
SVT, number (%)	0 (0%)	0 (0%)	0 (0%)	ns
Thrombotic events total	0 (0%)	0 (0%)	0 (0%)	ns

DVT = deep vein thrombosis, SVT = superficial vein thrombosis.

Table III. Results: Variation in edema (mean and SD) before and after the flight.

	Before the Flight	After the Flight
Subjects with stockings	1.2 (0.3)	2.4 (1)
Subjects without stockings	1.2 (0.2)	6.4 (1.3)
p Value	ns	0.05*

*Mann Whitney U-test.

Table IV. Part II of the study. Patients and events.

	Stockings	Controls	Total	Difference
Included	83	82	165	ns
Lost	8	11	19	ns
Completed	75	71	146	ns

Table V. Results: Variation in edema (mean and SD) before and after the flight.

	Before the Flight	After the Flight
Subjects with stockings	1.1 (0.2)	2.56 (1.3)
Subjects without stockings	1.1 (0.1)	8.9 (2)
p Value	ns	0.05*

*Mann Whitney U-test.

distribution were comparable in the 2 groups as were risk factors distributions.

Ultrasound Evaluation

Of 97 subjects completing the study (mean age 44.5; SD 9; M:F = 53:44), none had DVT or superficial thromboses in the stockings group. Also, of 98 subjects (mean age 45; SD 9; M:F = 54:44) none had a DVT or superficial thromboses among controls.

Tolerability

The tolerability of the stockings was very good and there were no complaints or side effects.

Edema Evaluation

The level of edema at inclusion was comparable in the 2 groups of subjects (Table III). After the flight there was an average score of 6.4 (SD 1.3) in the control group, while in the stockings group

the score was on average 2.4 (SD 1) ($p < 0.05$), 2.6 times lower than in the control group ($p < 0.05$). In the control group 83% of the subjects had an evident increase in ankle circumference and volume that was clearly visible at inspection and associated with discomfort. Therefore, the control of flight edema with stockings was clear considering both parametric data (circumference and volume) and nonparametric (analogue scale lines) measurements.

Results: Part II

Of the 83 included subjects in the stockings group and 82 in the control group (total 165), 146 subjects completed the study. Dropouts (19) were due to low compliance or connection problems. Age/sex distributions were comparable in the groups.

Ultrasound Evaluation

In the stockings group, of 75 subjects completing the study (mean age 45; SD 9; M:F = 44:31), none had deep or superficial thromboses. In the control group, of 71 subjects completing the study, no thrombotic event was observed (mean age 46; SD 7; M:F = 39:32) (Table IV).

Edema Evaluation

The average level of edema at inclusion was comparable in the 2 groups (1.1). After the flight there was a score of 8.9 (SD 2) in controls while in the stockings group the score was 2.56 (SD 1.3) ($p < 0.05$) (Table V). The control of edema and swelling with stockings even after 11 hours of flight was clear considering both parametric (circumference, volume) and nonparametric (analogue scale lines) measurements. At the end of the flight a limited amount of edema and swelling was observed in all subjects wearing stockings. Significant edema and swelling were observed in all subjects not wearing stockings. The amount of edema/swelling—expressed both by nonparametric and parametric tests—indicates a progressive increase of edema with the length of duration of the flight (Figure 1). The effect of stockings appears to be progressively more relevant with the length of the flight.

Discussion

Flight (and any travel-related) thrombosis and embolism has received an increasing attention, and it is a completely preventable disease.[14,17,27-32] British Airways specifically mentions in its educational programs DVT and methods of prevention.[28] Airlines are under more pressure to provide medical care in flights.[29,30] Limited in-flight data are available concerning DVT or pulmonary embolism,[30-32] which occur, if detected, mostly in the hours after the flight. It is possible that most of the signs and symptoms of swelling observed in our study would have been completely neglected by the study subjects (who considered some form of swelling almost normal after sitting for so long). A report[33] suggests than in prolonged flights (24 hours) some 10% of passengers may be affected by symptomless DVT, but this study was based on a very limited sample and subjects were not assessed just after the flight. Further studies are required to evaluate better the incidence of DVT, the cost and benefits of prophylaxis with stockings or drugs for subjects at higher risk, and the efficacy of other measures (ie, educational programs). The evaluation of the occurrence of pulmonary embolism requires larger numbers of subjects and more prolonged observations. However, it is clear that the main cause of the problem, namely, swelling and DVT, arises from limited space available in flights in airplanes. If DVT is a very significant clinical problem, edema and swelling, which are observed in almost all subjects traveling for more than 2–4 hours, are a very frequent complaint and cause a series of problems, symptoms, and signs that are potentially also linked to stasis and may be involved in the genesis of DVT. Edema and swelling are largely the results of immobility in association with the decreased air pressure in the cabin environment. They may be aggravated by the presence of venous disease, diabetic microangiopathy, and other conditions causing edema (ie, cardiac and renal insufficiency and antihypertensive treatment). Motion can be helpful but not sufficient.[34-36] In some cases, edema compressing minor veins may be an important initial cause of DVT (classified, unpublished data from the LONFLIT studies),[36] and therefore, controlling edema with stockings could be, at least theoretically, important to decrease the incidence of DVT.

The observations resulting from this large, randomized study indicate that prevention of edema and swelling with specific flight stockings is very effective. A more specific study should

evaluate the effect of these stockings both in edema control and in DVT prevention in higher risk subjects.

Conclusion

DVT in long-haul flights is an important safety issue.[1,17,21,22] The WHO has recently organized a meeting to discuss the problem and potential strategies of evaluating the rate of DVT in a large passengers sample and the effects of prevention.[31] The incidence of DVT, particularly in high-risk subjects, may be high, and therefore, prophylaxis is advisable. On the basis of initial data, elastic compression stockings are the easiest and least problematic (no side effects) solution for prophylaxis. In very high-risk subjects 1 dose of enoxaparin is effective in decreasing DVT risks. Exercise during flights—if and when possible in economy, diet suggestions, less baggage on board to keep free leg space, and larger empty spaces on planes may help, as well as suggestions from physicians not to travel (or travel differently) in conditions of particularly high risk. Patients with a history of thrombosis and chronic venous insufficiency are at particularly higher risk[37] to develop new episodes (56% of patients in the LONFLIT3 study, with a documented DVT, had a possible, previous episode of thrombosis). This study indicates that edema, which is common and observed in almost all subjects, even those with healthy circulation, could be an important prevention issue.[38,39] Specific stockings prevent the development of edema in almost subjects at low-moderate risk for DVT.

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