Graduated compression stockings as prophylaxis for flight-related venous thrombosis: systematic literature review

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Aim. This paper reports a systematic review whose objective was to evaluate the effectiveness of graduated compression stockings as prophylaxis for flight-related venous thrombosis, including deep vein thrombosis and superficial venous thrombosis, after air travel in the general population.

Background. Despite the extended history of the use of graduated compression stockings, their application to prevent flight-related thrombosis was not explored until flight-related thrombosis was perceived as a preventable illness. Even now, their effectiveness in preventing flight-related thrombosis remains unresolved.

Methods. Generic terms including stocking/s, sock/s, or hosiery/hosieries were used to search a variety of electronic databases. Based on the selection criteria, decisions regarding inclusion and exclusion of primary studies were made. Using a meta-analysis software program, relative risk for the incidence of deep vein thrombosis, superficial venous thrombosis, and intention-to-treat analysis was calculated.

Results. A total of nine randomized controlled trials were included. In the treatment group, two of 1237 participants developed deep vein thrombosis in comparison with 46 of 1245 in the control group. The weighted relative risk for deep vein thrombosis was 0·08, with fixed 95% confidence interval 0·03–0·23. In the treatment group, four of 826 participants developed superficial venous thrombosis in comparison with seven of 823 in the control group. The weighted relative risk for superficial venous thrombosis was 0·67. with fixed 95% confidence interval 0·24–1·87 (non-significant difference). Using intention-to-treat analysis, the risk for participants in the treatment group was 0·53 times as great as that for those in the control group.

Conclusions. This review demonstrates the effectiveness of medium compression pressure, below-knee graduated compression stockings in preventing flight-related deep vein thrombosis but not superficial venous thrombosis in low-medium- or high-risk participants.

Keywords: graduated compression stockings, meta-analyses, nurse/nursing, prophylaxis, systematic reviews, vascular disease

Background

The efficacy of the use of graduated compression stockings (GCS) as an efficient prophylaxis measure to prevent flight-related thrombosis still remains unresolved. In 2002, the World Health Organization initiated a comprehensive research programme to investigate the effectiveness of measures such as GCS in preventing venous thrombosis in air travellers (World Health Organization 2002). It is expected that there will be an increasing number of clinical studies in the area within the next couple years. A systematic review, especially a meta-analysis, in the area at this time could aggregate the effects of GCS from randomized controlled trials to provide an overall estimate of effect size. As a result, methodological bias or limitations and specifications of GCS in the existing primary studies could influence future clinical intervention studies.

Risk of venous thromboembolism

The risk of venous thromboembolism because of extended quiet sitting was first recognized during World War II (Simpson 1940). In 1940, 21 reported 'shelter deaths' from pulmonary embolism occurred after prolonged sitting in air raid shelters in London. Over a decade later, the possible association between deep vein thrombosis and long-haul air travel was reported in 1954 (Homans 1954). Since the 1960s, with increasing numbers of people travelling on long flights, studies started to investigate the incidence of flight-related (flight-associated) thrombosis, especially deep vein thrombosis (DVT) and superficial venous thrombosis (SVT). This problem has also been called 'economy class syndrome' (Symington & Stack 1977), 'coach class thrombosis' (Cruickshank *et al.* 1988a), 'flight-thrombosis', and 'traveller's thrombosis' (Giangrande 2001).

The link between air flight and thrombosis remains controversial. Estimations of odds ratios for DVT after long-haul flights are wide-ranging. Some case–control studies have found no association between air travel and DVT (Kraaijenhagen *et al.* 2000), while others have estimated that the odds ratio for venous thromboembolism could be up to 3·98 (95% CI 1·9–8·4) (Ferrari *et al.* 1999). Associations between flight and thrombosis are limited to high-risk individuals only (O'Keeffe & Baglin 2003). More than 80% of patients developing venous thromboembolism have one or more risk factors present before air travel (McQuillan *et al.* 2003). Therefore, it is not surprising that 2·7% of flight-related DVT was reported in high-risk subjects (Belcaro *et al.* 2001). The percentage of flight-related SVT reported ranges from 0·77% to 1·5% in high-risk subjects (Belcaro *et al.* 2001). DVT might progress to the development of pulmonary embolism and potential death. However, this is rare (O'Keeffe & Baglin 2003). After reviewing over 135 million flights during 1993–2000, it was concluded that the incidence of pulmonary embolism increased with a longer duration of flight (Lapostolle *et al.* 2001).

Thromboembolic process

In 1858, Rudolf Virchow proposed that the occurrence of one or more factors in the venous system often leads to a thromboembolic process. These factors were called Virchow's triad, and included changes in vessel wall (endothelial damage/lesion), changes in blood flow (venous stasis), and changes in properties of blood (hypercoagulability) (Nielsen 1991, Arfvidsson *et al.* 2000). Flight-related thrombosis is believed to be the result of the interaction or combination of these factors, caused by characteristics specific to air travel. Limited leg space on the flight often results in compression of veins, especially the popliteal vein (Belcaro *et al.* 2003). Changes in haemoconcentration are caused by decreased fluid intake and increased water loss in the dry atmosphere of airplane cabins (Carruthers *et al.* 1976, Sarvesvaran 1986, Cruickshank *et al.* 1988a, 1988b, Kraaijenhagen *et al.* 2000). Because of immobility, relative hypoxia, and the decreased air pressure in airplane cabins, fibrinolytic activity is reduced and vein wall factors are released, leading to venous stasis (Bendz *et al.* 2000). Hypobaric and hypoxic environment can cause activation of coagulation (Bendz *et al.* 2000). Biochemical changes on the flight include plasma viscosity, packed cell volume, and albumin concentrations (AMA Commission on Emergency Medical Services 1982, Landgraf *et al.* 1994). These air-travel characteristics distinguish air travel from other types of travel.

Recently, with the perception that flight-DVT might be a preventive illness, increasing attention has focused on intervention with preventive measures. GCS, also known as elastic compression stockings, travel stockings, or antiembolism stockings, is among the most commonly available and accepted method of external compression for the prophylaxis of flight-related thrombosis (Byrne 2001).

Graduated compression stockings

The origin of GCS used as a form of treatment can be traced back to the ancient Egyptians (Keachie 1995). The term GCS was used in this review to include all elastic socks and stockings/hosieries that could provide graduated compression

irrespective of length and pressure. The word graduated refers to the application of gradient compression pressures on sections of legs, with the pressure exerting at ankle is the greatest then the pressure gradually decreases up to calf or thigh level (Keachie 1995, Agu *et al.* 1999). Functions of GCS are contributed to this decreasing gradient from distal to proximal (Sigel *et al.* 1973, 1975). The greater the graduated pressure, the greater the reduction in venous pressure (Horner *et al.* 1980).

Using the Virchow's triad, Agu *et al.* (1999) suggested a multifactorial mechanism of GCS in preventing DVT. By providing external mechanical support, key functions of GCS include increasing venous blood velocity (Litter 1952, Meyerowitz & Nelson 1964, Spiro *et al.* 1970, Lawrence & Kakkar 1980, Ido *et al.* 1995), decreasing vein diameter (Sarin *et al.* 1992), counteracting the venous high pressure (Horner *et al.* 1980, Jones *et al.* 1980), controlling oedema (Myers *et al.* 1972), restoring valve function (McLachlin *et al.* 1960, Lewis *et al.* 1976, Sarin *et al.* 1992), and relieving symptoms (Somerville *et al.* 1974). The results are the reduction of the occurrence of one or more factors of Virchow's triad – decreased intimal tear, reduced stasis, and decreased coagulability (Agu *et al.* 1999).

For various groups of hospitalized patients, especially postsurgical patients, the effect of GCS for prevention of deep vein thrombosis was recognized by a Cochrane review (Amaragiri & Lees 2003). However, there has been no quantitative review of studies of the effectiveness of GCS for prevention of flight-related DVT in non-hospitalized participants or the general population. With the larger number of people involved in long-haul air travel and the appearance of various new primary studies in the field, such a meta-analysis at this time could aggregate the effects of GCS in primary studies to provide an overall estimate of effect size.

Objective

Following the instructions for reporting systematic reviews, especially meta-analyses (Moher *et al.* 1999), the objective of this systematic review was to evaluate the effectiveness of GCS as prophylaxis for flight-related thrombosis after air travel in the general population. Given other supportive evidence linking GCS and DVT, hypotheses rather than research questions were tested in this review. The hypotheses were:

- GCS are effective in preventing deep vein thrombosis (DVT) after flight in the general population; and
- GCS are effective in preventing SVT after flight in the general population.

Search methods

Selection criteria

Type of study

All randomized clinical trials (RCTs) with at least one intervention and one control group that evaluated the effectiveness of GCS for travelling were eligible for this review. Primary studies included were restricted on the basis of language. Because of the limitations of reviewers, only articles or results of primary studies in English or Chinese were included. Only completed research projects were included. Primary studies were not included if they used a model to simulate travelling, such as sitting with the torso and lower extremities restrained. Only primary studies conducted after actual flight travelling were included.

Type of participant

All air-flight, non-hospitalized participants, of either sex, including all age groups, irrespective of low- or high-risk for DVT and of any pre-existing illness, were included.

Type of intervention

Primary studies which evaluated any type of GCS for air travel in a healthy population were included. As there is no universal use of terms, each trial must refer to the use of elastic or GCS, socks, or hosiery. Primary studies were included if they compared GCS with either no prophylaxis or another method such as aspirin or low-molecular-weight heparin.

Type of outcome measure

Primary outcomes were objective measures of thrombosis, including DVT and SVT. Secondary outcomes were oedema, subjective feelings such as discomfort or pain, and acceptability/tolerability. Studies that only measured secondary outcome were not included. As methods of diagnosing travel-related thrombosis might be similar between primary studies, each study must refer to the use of ultrasound scan as a mean of diagnosing the DVT or SVT.

Databases searched

The search strategy included electronic searches of PubMed (MEDLINE), EMBASE: Drugs and Pharmacology, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Current Content, ISI Web of Science database (access to the Science Citation Index Expanded and Social Sciences Citation Index), and the most recent issue of the Cochrane Library (Issue 1, 2004). References or citations within obtained

reviews and articles were examined to identify additional studies. Other supplemental searching strategies included hand-searching of relevant journals and searches of trial registries such as the UK National Research Register. To identify unpublished trials, electronic databases such as Dissertation Abstracts (Bibliographic coverage of doctoral dissertations and master's theses from 1861 through the previous semester) and trial registries such as Current Controlled Trials (http://www.controlled-trials.com/) were also reviewed. Additional trials were sought from manufacturers of stockings. The final search date was in the end of March 2004.

In view of the lack of standard terminology, more generic terms such as stockings, socks, or hosiery were used in searching with the hope of locating studies that used the terms travel stockings, socks, or hosiery, elastic stockings, GCS, and elastic compression stockings.

Review methods

Studies that published in duplicate were included only once, but all published articles were obtained to supplement information. Based on the selection criteria specified above, decisions about inclusion or exclusion of primary studies were made after discussion between two investigators. Data extraction was performed and double-checked by both authors. Details of eligible studies were extracted and summarized using a data extraction form. Descriptive characteristics of the studies, including country, settings, participants, sample sizes, inclusion and exclusion criteria, description of any method other than GCS as flight-related thrombosis prophylaxis, outcome measures and outcome variables, were extracted on to a data collecting form. Other information extracted included characteristics of participants (including age, sex, and risk group for DVT) and details of intervention (types and length of GCS and duration of application of GCS).

A different form was designed to collect specific information on the statistical results of the studies, including numbers of DVT and/or SVT occurrences in each treatment and control group, and numbers of participants lost to follow-up tests for intention-to-treat analysis. Data extraction was performed and double-checked by both authors, and any disagreements were discussed and resolved.

Data synthesis was performed for the two primary outcome measures of incidence of DVT and SVT and intention-to-treat analysis. Analysis of intention-to-treat would consider participants lost to follow-up tests and incidences of DVT and/or SVT. This pooling of DVT and SVT events was based on the following two rationales. First, the occurrence of DVT coexistent in patients with SVT was high at about 20% (Prountjos *et al.* 1991). Second, SVT risk factors were close to those of DVT (Decousus *et al.* 2003).

Meta-analysis

There are two stages in the process of meta-analysis. The treatment effect (relative risk or odds ratio) of each individual study is calculated in the first stage. Relative risk (risk ratio or rate ratio) with 95% confidence intervals (CI) was calculated for each included study for incidence of DVT, as well as for analysis of the cumulative data. Relative risk is preferred for this analysis rather than odds ratio since: (1) the design of these included studies was a prospective cohort study (for a cohort study, relative effect of exposure (RR) can be measured); and (2) the values of relative risks are easier to interpret (relative risk is a ratio of disease probabilities). For rare disease, relative risk would make a good approximation to disease odds ratio. Because the probability of DVT or SVT in these included studies was small, such as smaller than 0·1 or P(DlE) = 0, the relative risk and odds ratio were not different or equivalent.

Instead of original (non-weighted) relative risk, the weighted (or pooled) relative risk is calculated in the second stage to reflect the amount of information that each study contains. A study with more precise results is given more weight. The mean treatment effect (non-weighted relative risk) is equal to the probability of events (DVT or SVT) in the treatment group divided by the probability of events in the control group. The pooled treatment effect estimate (weighted relative risk) is equal to the sum of treatment effect estimated in a study multiplied by the weight given to the study, then divided by the sum of weights across all studies.

Fixed effect models are advocated when the number of primary studies is small in order to draw meaningful inferences from the sample of primary studies to the universe (Hedges 1994). Given that the expected number of primary studies was small, fixed effect models were conceptually preferred for this meta-analysis. However, the chi-square test for heterogeneity was performed. Lack of heterogeneity among the effect sizes would indicate fixed effect models are preferred in this analysis than random effect models (Copper & Hedges 1994). The statistical analysis was performed using a meta-analysis software program (Cochrane Review Manager 4.1).

Description of studies

A total of nine primary studies that examined the effectiveness of GCS were included in this systematic review (Table 1).

Table 1 Description of included studies

	Scurr *et al.* (2001a, 2001b)	LONFLIT 2 (Belcaro *et al.* 2001)	LONFLIT 4-1 (Belcaro *et al.* 2002)		ONFLIT 4-2 (Cesarone *et al.* 2003b)		LONFLIT 4-3 (Cesarone *et al.* 2003a)		LONFLIT 5 (Belcaro *et al.* 2003)
			Part A	Part B	Part A	Part B	Part A	Part B	
Country (authors)	UK	Italy	Italy	Italy	Italy	Italy	Italy	Italy	Italy
Exclusions before randomization	248	Not reported	28	38	55			38 (Before randomization)	76
Statistical analysis	1. Contingency tables 2. Calculation of the differences in proportions 3. 95% CI 4. Intention-to-treat basis	Not stated	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis	1. Non-parametric tests 2. Analysis of variance 3. Intention-to-treat analysis
Setting	Before and after flights	Before and after flights	Before and after flights	Before and after flights	Before and after flights	Before and after flights	Before and after flights	Before and after flights	Before and after flights
Participants									
Total number of participants (randomized)	231	885	372	285	211	165 participants	150	134	224
Control	115	Not reported	188	143	108	82	76	68	114
Treatment	116	Not reported	184	142	103	83	74	66	110
Dropouts/lost (number of participants)	31	52	14	14	16	19	6	2	19
Control	16	Not reported	9	8	10	11	4	2	12
Treatment	15	Not reported	5	6	6	8	2	0	7
Total available for study (participants completed the study)	200 (not 231)	833	358	271	195	146	144	132	205
Participants in control group	116	422	179	135	98	71	72	66	102
Participants in treatment group	115	411	179	136	97	75	72	64	103
Sex	Both	Both	Both	Both	Both	Both	Both	Both	Both
Age: mean age ± SD (range)									
Control	62 (56–68)	44·8 ± 9 (20–80)	48·4 ± 7·3	47 ± 8	45 ± 9	46 ± 7	47 ± 5	46·9 ± 4	42·1 ± 10·3, (28–65)
Treatment	61 (56–66)		49 ± 7	48 ± 8	44·5 ± 9	45 ± 9	46 ± 8	47 ± 5	42·0 ± 9·0 (29–65)
Inclusive criteria*	Not related to DVT risk	High risk for DVT	Low-medium risk for DVT	Low-medium risk for DVT	Low-medium risk for DVT	Low-medium risk for DVT	Low-medium risk for DVT	Low-medium risk for DVT	High risk for DVT

Table 1 (*Continued*)

	Scurr *et al.* (2001a, 2001b)	LONFLIT 2 (Belcaro *et al.* 2001)	LONFLIT 4-1 (Belcaro *et al.* 2002)		ONFLIT 4-2 (Cesarone *et al.* 2003b)		LONFLIT 4-3 (Cesarone *et al.* 2003a)		LONFLIT 5 (Belcaro *et al.* 2003)
			Part A	Part B	Part A	Part B	Part A	Part B	
Exclusive criteria*	Five exclusive criteria identified	None reported	10 exclusive criteria identified	10 exclusive criteria identified	10 exclusive criteria identified	10 exclusive criteria identified	11 exclusive criteria identified	11 exclusive criteria identified	Eight exclusive criteria identified
Other method of DVT prophylaxis in both control and treatment group	None	Instructions: 1. Move often (3 minutes every hour) 2. Drink water (at least one glass every 2 hours) 3. Stretch limbs every hour for 2 minutes 4. Not keep baggage in the space under the seat 5. Avoid salty snacks 6. Wear comfortable cloths	Suggestions: 1. Mild exercise 2. Walking 3. Drinking water 4. Avoiding salty food 5. Avoiding excessive baggage restricting leg motion	Suggestions: 1. Mild exercise 2. Walking 3. Drinking water 4. Avoiding salty food 5. Avoiding excessive baggage restricting leg motion	Suggestions: 1. Mild exercise 2. Walking 3. Drinking water 4. Avoiding salty food 5. Avoiding excessive baggage restricting leg motion	Suggestions: 1. Mild exercise 2. Walking 3. Drinking water 4. Avoiding salty food 5. Avoiding excessive baggage restricting leg motion	Suggestions: 1. Mild exercise 2. Walking 3. Drinking water 4. Avoiding salty food 5. Avoiding excessive baggage restricting leg motion	Suggestions: 1. Mild exercise 2. Walking 3. Drinking water 4. Avoiding salty food 5. Avoiding excessive baggage restricting leg motion	Educational. video: 1. Mild exercise (standing and moving legs for 5–10 minutes every hour) 2. Drinking water regularly (100–150 cc/hour) 3. Avoiding baggage between seats
Interventions									
Type of treatment (GCS)	Mediven Travel, Medi UK Ltd, Hereford, UK Below-knee 18·4–21·1 mmHg at ankle (not 20–30 mmHg)	Commercially available (specification unavailable) Below-knee 25 mmHg at ankle	Scholl Flight Socks, UK Below-knee length 14–17 mmHg at ankle	Scholl Flight Socks, UK Below-knee length 14–17 mmHg at ankle	Sigvaris Traveno stockings (Ganzoni, Switzerland) Below-knee length 14–17 mmHg at ankle	Sigvaris Traveno stockings (Ganzoni, Switzerland) Below-knee length 14–17 mmHg at ankle	Kenkall Travel Socks, Tyco Healthcare, Mansfield, MA, USA Knee-length Ankle pressure 20–30 mmHg with decreasing pressure at the mid-calf and calf	Kenkall Travel Socks, Tyco Healthcare, Mansfield, MA, USA Knee-length Ankle pressure 20–30 mmHg with decreasing pressure at the mid-calf and calf	Scholl Flight Socks, UK Below-knee length 14–17 mmHg at ankle
Duration of treatment	Not reported	6–10 hours before the flight + 12·4-hour (10–15) flights	2–3 hours before the flight + 7–8 hours of flight	2–3 hours before the flight + 11–12 hours of flights	2–3 hours before the flight + 7–8 hours of flight	2–3 hours before the flight + 11–12 hours of flights	2–3 hours before the flight + 7–8 hours of flight	2–3 hours before the flight + 11–12 hours of flights	3–4 hours before the flight + 11·3- to 12-hour flights

Table 1 (*Continued*)

Outcomes									
Method of measure	Duplex ultrasound examination	Ultrasound scans	Ultrasound scans	Ultrasound scans	Ultrasound scans	Ultrasound scans	Ultrasound scans	Ultrasound scans	Ultrasound scans
Deep vein thrombosis (DVT)									
Control	12 (10% of 116)	22 limbs in 19 participants (4·5% of participants or 2·6% of limbs)	4	3	0	0	0	2	6
Treatment	0	1 limb (0·24% of participants or 0·12% of limbs)	0	0	0	0	0	0	1
P-value	< 0·001	< 0·02 (limbs) Treatment: 18·5 times lower DVT than control	< 0·05	< 0·05	Difference: non-significant	Difference: non-significant	Difference: non-significant	< 0·05	< 0·025
SVT									
Control	0	Eight limbs	2	3	0	0	0	2	0
Treatment	4 (3% of 115)	0 DVTs were reported only in participants sitting in window or central seats	0	0	0	0	0	0	0
P-value	0·04		< 0·05	< 0·05	Difference: non-significant	Difference: non-significant	Difference: non-significant	< 0·05	
Intention-to-treat analysis (lost to follow-up + DVT + SVT)									
Control	Not reported	Not reported	15	14	10	11	4	6	18/114 (15·6%)
Treatment			5	6	6	8	2	0	8/110 (7·3%)
P-value			< 0·05	< 0·05					< 0·05
Tolerability or discomfort	Not reported	Not reported	Very good No complaint or side effects	Very good No complaint or side effects	Very good No complaint or side effects	Not reported	Not reported	Not reported	Good No complaint or side effects
Others	None	None	Oedema (composite oedema score)	Oedema (composite oedema score)	Oedema (composite oedema score)	Oedema (composite oedema score)	Oedema (composite oedema score)	Oedema (composite oedema score)	Blood tests (D-dimer and fibrinogen)
Control			6·7	8·1	6·4	8·9	6·9	7·94	
Treatment			2·3	2·6	2·4	2·6	2·3	3·3	
P-value			< 0·05	< 0·005	< 0·05	< 0·05	< 0·05	Difference: non-significant	

*For a complete list of the inclusive or exclusive criteria, please refer to the individual study report.

All were published articles. Three of the reviewed articles (LONFLIT 4) reported the results of two trials with different clusters of participants. Hence, each was counted as two studies and reviewed independently. The studies included in the review were:
Scurr (Scurr *et al.* 2001a, 2001b, 2001c),
LONFLIT 2 (Belcaro *et al.* 2001),
LONFLIT 4-1-a (part I of the trial) (Belcaro *et al.* 2002),
LONFLIT 4-1-b (part II of the trial) (Belcaro *et al.* 2002),
LONFLIT 4-2-a (part I of the trial) (Cesarone *et al.* 2003b),
LONFLIT 4-2-b (part II of the trial) (Cesarone *et al.* 2003b),
LONFLIT 4-3-a (part I of the trial) (Cesarone *et al.* 2003a),
LONFLIT 4-3-b (part II of the trial) (Cesarone *et al.* 2003a), and
LONFLIT 5 (Belcaro *et al.* 2003).

Except for the Scurr study (Scurr *et al.* 2001a, 2001b), all were conducted by the same group of researchers in Italy in the past three years.

All of the included studies were RCTs. The number of participants completing the study ranged from 64 to 422 in the control or treatment group. Below-knee GCS were used in all the studies. All GCS were commercially produced by manufacturers in different countries. The pressure of GCS ranged from 17 to 30 mmHg at the ankle to 14–20 mmHg below the knee. In all the included studies, participants in the treatment group were advised to put on GCS before the start of the flight, 2–3 hours or 6–10 hours before the flight. The length of wearing GCS varied also depending on the duration of flights (7–15 hours).

Participants in two of the included studies were at high risk for DVT, six were at low to medium risk for DVT, while the other study did not specify the risk group for DVT of participants. Except for the Scurr study, all used additional methods of DVT prophylaxis in both the treatment and control groups, including instructions, suggestions, or educational videos, mild exercise (moving often and walking, stretching limbs), avoiding salty foods, drinking water regularly, avoiding baggage between seats, and wearing comfortable clothes.

The included studies all evaluated the occurrence of DVT and SVT as the outcome measure, and all used ultrasound scans to examine the occurrence of DVT or SVT before and after the flight. The LONFLIT 2 study reported that eight limbs were diagnosed with SVT, but information was not available on how many participants had SVT in both limbs. This study was excluded from the analysis of the occurrence of SVT. In this systematic review, statistical aggregation of all relevant studies on the occurrence of DVT or SVT is based on the number of participants (not the number of limbs) diagnosed with DVT or SVT after the flight. Follow-up of participants in the included studies occurred once within hours or days after the flight. Primary studies that were not RCTs, did not include DVT or SVT as an outcome measure, or used simulated model instead of actual flight were excluded (Table 2).

Table 2 Characteristics of excluded studies

Study	Reason for exclusion
Loew *et al.* (1998)	DVT or SVT not measured as an outcome
Weiss and Duffy (1999)	DVT not measured as an outcome Controlled clinical trial (CCT) – not RCT
Hollingsworth *et al.* (2001)	DVT not measured as an outcome Controlled clinical trial (CCT) – not RCT Simulated model – not on flights
Iwama *et al.* (2002)	DVT or SVT not measured as an outcome GCS + aspirin combined as treatment – confounding effect of DVT Simulated model – not on flights

DVT, deep vein thrombosis; SVT, superficial venous thrombosis; RCT, randomized controlled trial; GCS graduated compression stockings.

Methodological quality

The quality of primary studies was consistent, since the most were part of a series of LONFLIT trials (Table 3). All the included studies had one control and one treatment group, i.e. the number of arms was two. The number of participants included in the control and treatment groups was comparable. No statement in any of the studies indicated that the number of participants was based on sample size calculation. Exclusive criteria were specified, but inclusive criteria seemed to be unclear and contradictory in the LONFLIT trials. For example, there was no definition of obesity. Therefore, it is impossible to know whether this included participants who were taller than 190 cm and heavier than 90 kg, which was one of their exclusive criteria.

In addition, although the studies were self-identified as randomization controlled trials, methods of randomization were not specified. Blindness and contamination were not addressed by any of the included studies. It is impractical to use a blind approach with a physiological intervention study such as GCS, in which participants and researchers are aware of allocation.

Results

Results are presented as relative risks with 95% CI. Relative risk is the probability of DVT or SVT in the treatment group divided by the probability of DVT or SVT in the control

Table 3 Methodological quality of included studies

	Scurr *et al.* (2001a, 2001b)	LONFLIT 2 (Belcaro *et al.* 2001)	LONFLIT 4-1-a (Belcaro *et al.* 2002)	LONFLIT 4-1-b (Belcaro *et al.* 2002)	LONFLIT 4-2-a (Cesarone *et al.* 2003b)	LONFLIT 4-2-b (Cesarone *et al.* 2003b)	LONFLIT 4-3-a (Cesarone *et al.* 2003a)	LONFLIT 4-3-b (Cesarone *et al.* 2003a)	LONFLIT 5 (Belcaro *et al.* 2003)
Number of participants	132	833	358	271	195	146	144	130	205
Type of study design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Numbers of arms	2	2	2	2	2	2	2	2	2
Inclusive criteria	Listed	Listed	Not listed	Not listed	Not listed	Not listed	Not listed	Not listed	Listed
Exclusive criteria	Listed	Not listed	Listed	Listed	Listed	Listed	Listed	Listed	Listed
Sample size calculation	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Baseline comparable	Yes, except sex	Not reported	Stated	Stated	Stated	Stated	Stated	Stated	Stated
Masked/blinded outcome assessment	No	No	No	No	No	No	No	No	No
Analysis by intention-to-treat (lost to follow-up + deep vein thrombosis)	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes

group. As values of relative risk are smaller than one, this indicates that the probability of disease in the treatment group is much smaller than that in the control group. As noted earlier, relative risks approximately equate to the odds ratios, since the probability of DVT and SVT in the studies was small. Since the same groups of authors conducted all but one of the included studies and there were non-significant results from a chi-square test for heterogeneity, the values from a fixed effect model are presented.

All nine studies evaluated the incidence of DVT. Excluding three of these without any incidence of DVT in both groups, GCS were more effective than no GCS in preventing DVT (6/6 trials). Regardless of the levels of risks for DVT, a total of two of the 1237 participants were diagnosed with DVT by ultrasound scans in the treatment group (GCS), while 46 of the 1245 participants in the control group had DVT. There was a 0·16% DVT incidence in the treatment group in comparison with 3·69% in the control group. The relative risk (non-weighed) for DVT is 0·04 [non-weighted relative risk = the probability of DVT in the treatment group divided by the probability of DVT in the control groups = (2/1237)/(46/1245) = 0·16%/3·69% = 0·04]. The relative risk (weighted or pooled RR) for DVT is 0·08 (fixed 95% CI 0·03–0·23), *P*-value < 0·00001 (Figure 1) [the weighted relative risk = sum of (relative risk estimated in an individual study times the weighted give to the study), then divided by the sum of weights across all studies = (26·18 × 0·04 + 39·26 × 0·05 + 9·42 × 0·11 + 7·36 × 0·14 + 5·16 × 0·21 +12·63 × 0·17)/(26·18 + 39·26 + 9·42 + 7·36 + 5·16 + 12·63) = 8·25/99·68 = 0·08]. To reflect the amount of information that each study contributes to the average of the treatment effects, the weighted relative risk is chosen and reported here. Thus, a subject in the treatment group is 0·08 times as likely as one in the control group to have DVT.

Eight of the included studies evaluated the incidence of SVT. Excluding the four studies with zero incidences of SVT in both groups, GCS were more effective than no GCS in preventing SVT (3/4 trials). In general, regardless of levels of risks for DVT, a total of four of the 826 participants were diagnosed with SVT by ultrasound scans in the treatment group (GCS), while seven of the 823 participants in the control group were diagnosed. There was a 0·48% SVT incidence in the treatment group in comparison with 0·85% in the control group. The relative risk for SVT is 0·67 (fixed 95% CI 0·24–1·87) with a *P*-value of 0·4 (Figure 2). There is no statistical difference in SVT incidence between the treatment and control group.

One of the included studies (LONFLIT 2) was excluded from intention-to-treat analysis because of the number of participants who dropped out or were lost to follow-up.

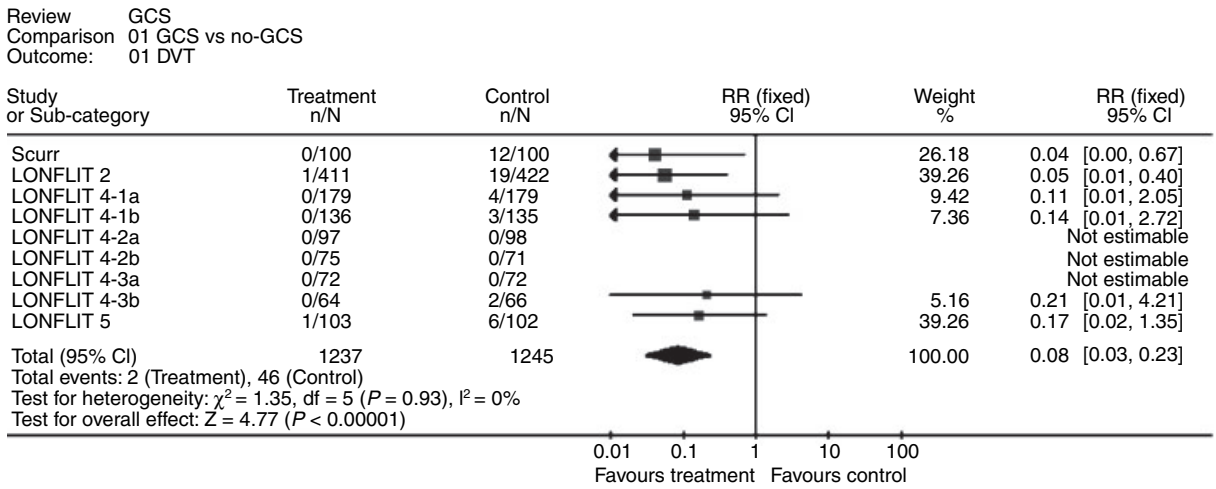

Figure 1 Relative risks and 95% confidence intervals of deep vein thrombosis, comparing graduated compression stockings with no graduated compression stockings.

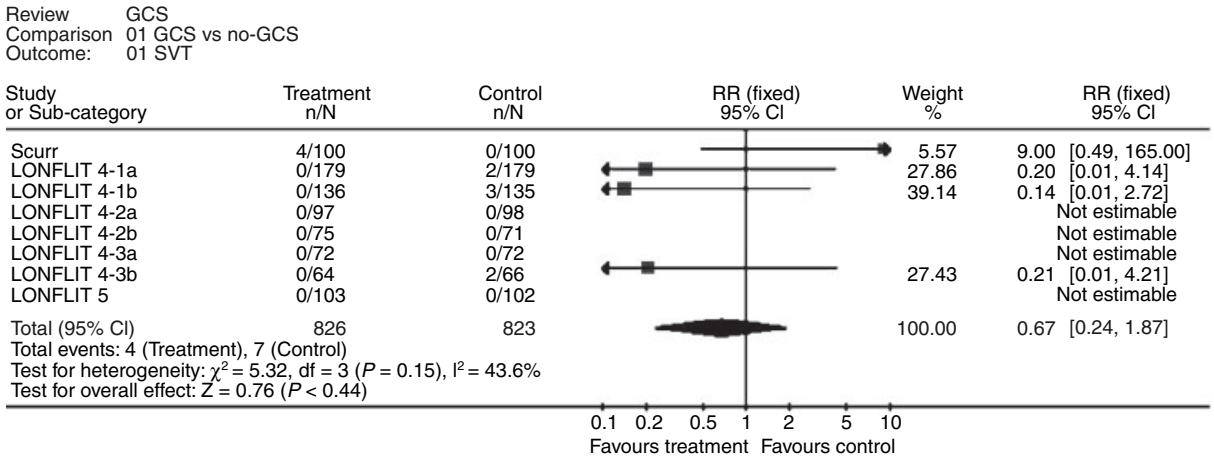

Figure 2 Relative risks and 95% confidence intervals for superficial venous thrombosis, comparing graduated compression stockings with no graduated compression stockings.

Using intention-to-treat analysis, a total of 55 of the 878 participants were lost to follow-up or diagnosed with DVT or SVT in the treatment group (GCS), while 105 of the 894 participants in the control group were lost. This is a 6·26% incidence of SVT in the treatment group in comparison with 11·74% in the control group. The relative risk is 0·53 (fixed 95% CI 0·39–0·72), *P*-value < 0·0001 (Figure 3).

Further analyses were performed on subject groups, including a high risk for DVT group and a low-medium risk for DVT group. For two of the included studies whose participants were at high risk of DVT, meta-analysis showed that GCS were more effective than no GCS in preventing DVT (2/2 trials). A total of two of the 514 participants were diagnosed with DVT by ultrasound scans in the treatment group (GCS), while 25 of the 524 participants in the control group had DVT. The relative risk for DVT is 0·08 (fixed 95% CI 0·02–0·34) with a *P*-value of 0·0006 (Figure 4). Because information on SVT was not available for the LONFLIT 2 study, no additional analysis on the incidence of SVT nor intention-to-treat analysis was performed.

For six of the included studies whose participants were identified as low-medium risk for DVT, three had zero incidences of DVT in both treatment and control groups. Meta-analysis showed that GCS were more effective than no GCS in preventing DVT (3/3 trials). A total of 0 of the 623 participants were diagnosed with DVT by ultrasound scans in the treatment group (GCS), while nine of the 621 participants

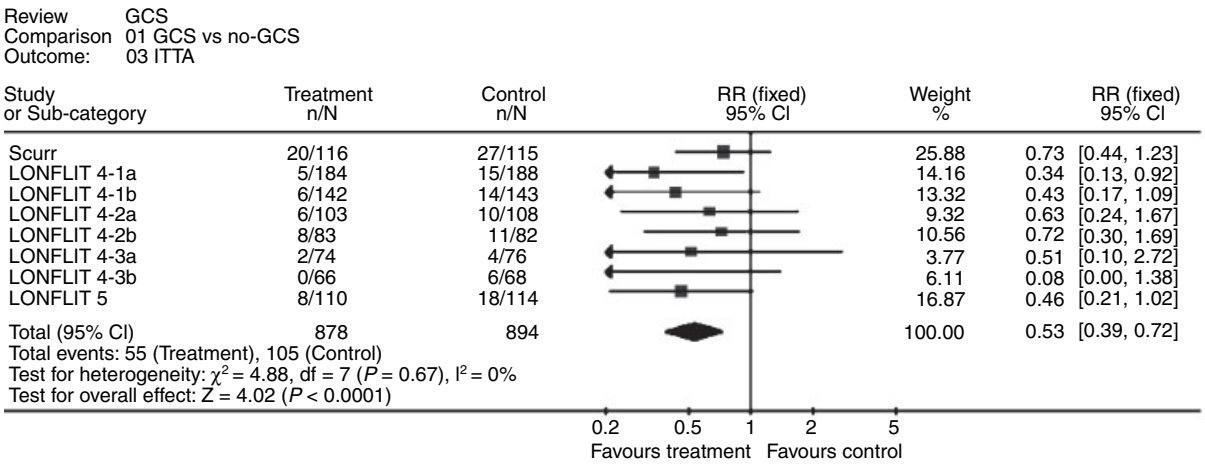

Figure 3 Relative risks and 95% confidence intervals comparing graduated compression stockings with no graduated compression stockings using intention-to-treat analysis (lost + deep vein thrombosis vs. superficial vein thrombosis).

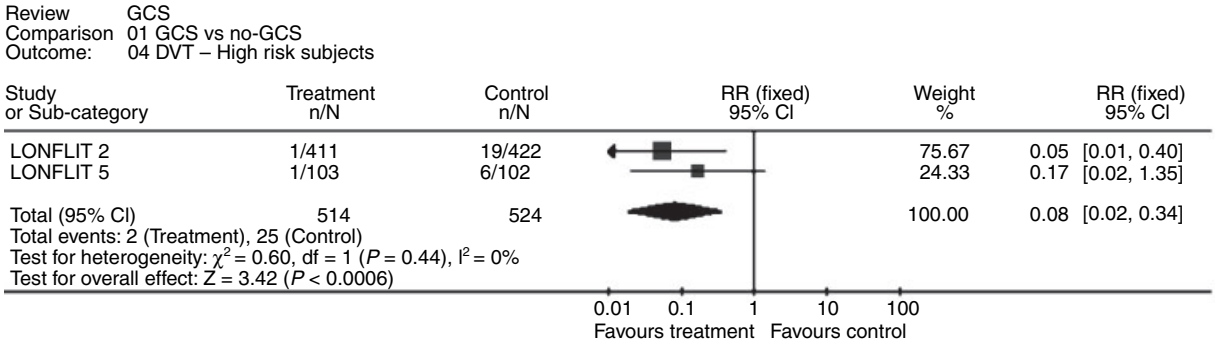

Figure 4 Relative risks and 95% confidence intervals of deep vein thrombosis, comparing graduated compression stockings with no graduated compression stockings (high risk participants only).

in the control group had DVT. The relative risk for DVT is 0·14 (fixed 95% CI 0·03–0·79) with a *P*-value of 0·03 (Figure 5).

Also, for the same group of participants from the three studies, GCS were more effective than no GCS in preventing SVT (3/3 trials). A total of 0 of the 623 participants were diagnosed with SVT by ultrasound scans in the treatment group, compared with seven of the 621 participants in the control group. The relative risk for SVT is 0·18 (fixed 95% CI 0·03–1·00) with a *P*-value of 0·5 (Figure 6). There is no statistically significant difference in SVT incidence between the treatment and control groups. An intention-to-treat analysis showed that a total of 27 of the 652 participants were lost to follow-up or diagnosed with DVT or SVT in the treatment group (GCS), while 60 of the 665 participants in the control group were lost to follow-up or diagnosed with DVT or SVT. The relative risk is 0·46 (fixed 95% CI 0·30–0·71) with a *P*-value of 0·0005 (Figure 7).

To evaluate oedema, a composite oedema score was calculated in six of the included studies. After the flight, the score in the treatment group was 2·4–3·5 times lower than that in the control group (6/6 trials). Except for five trials not reporting tolerability or discomfort, no participants in the rest of the trials reported any complaints or side effects from wearing GCS and had good tolerability.

Discussion

The results of this review indicate that the application of below-knee GCS statistically significantly decreased the occurrence of DVT but not SVT in long-haul air travellers. However, methodological bias may have an impact on the quality of these included studies, thus hindering inference from the results. Overall, the design of the included studies had two types of contamination. One is experimenter contamination. Observers such as technicians or researchers

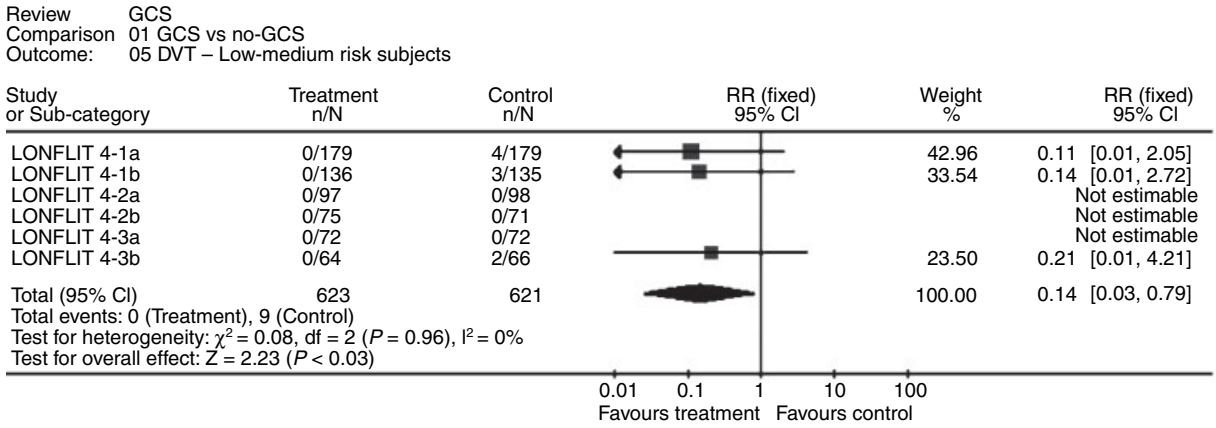

Figure 5 Relative risks and 95% confidence intervals of deep vein thrombosis, comparing graduated compression stockings with no graduated compression stockings (low-medium risk participants only).

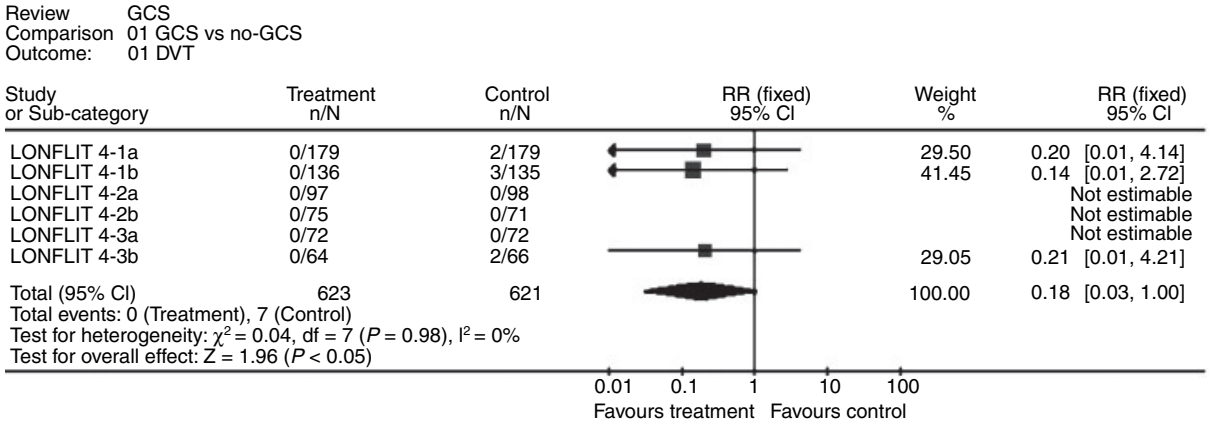

Figure 6 Relative risks and 95% confidence intervals of superficial vein thrombosis comparing graduated compression stockings with no graduated compression stockings (low-medium risk participants only).

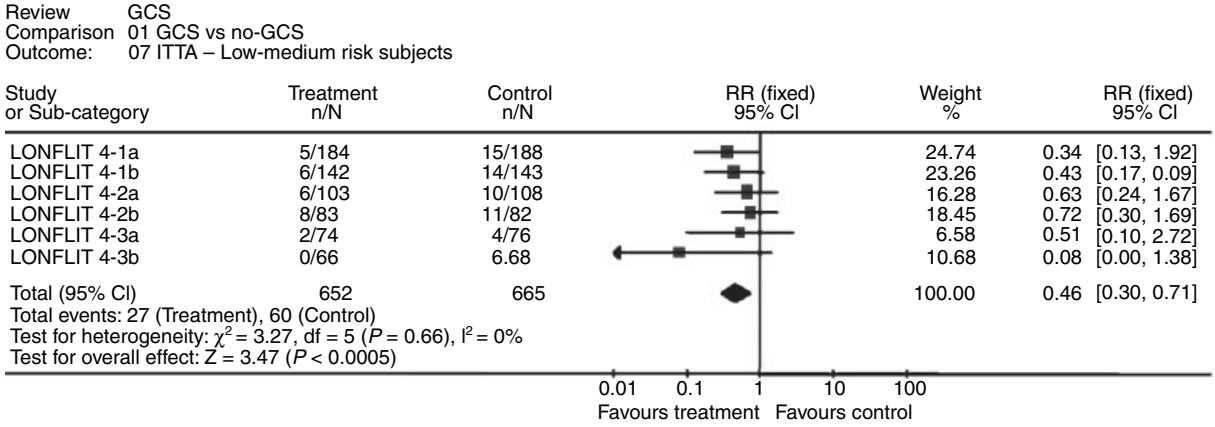

Figure 7 Relative risks and 95% confidence intervals comparing graduated compression stockings with no graduated compression stockings using intention-to-treat analysis (low-medium risk participants only).

who assessed the occurrence of DVT or SVT were not blind to group allocation. An ultrasound scan is the standard examination tool for leg thrombosis (Arfvidsson *et al.* 2000). Because of the strong subjectivity of ultrasound imaging diagnosis, it might be possible for observers to have a preconceived notion in favour a certain group of participants. The issue of potential observer bias was not addressed.

The other type of contamination is subject contamination. Since all the participants might have been on board the same flights, it is likely that there were some interactions between groups. This subject contamination may confound the therapeutic effect of GCS. Exercise, standing, stretching, drinking adequate water regularly, and avoiding constrictive clothes were suggested as another method of DVT prophylaxis in both treatment and control groups (Belcaro *et al.* 2001, 2002, 2003, Cesarone *et al.* 2003a, 2003b). Participants in the included studies were aware of the treatment. It is unclear if being in the treatment group also increased participants' use of other preventive measures suggested. The question then is if the effectiveness in preventing DVT was the result of GCS alone or GCS and other preventive measures. These preventive measures could be moderators or mediators that interact with GCS or confound their effect. Researchers need to monitor attentively the use of these preventive measures in both groups in their study.

The findings of the included studies were not consistent. The incidences of DVT reported in the control group (not wearing GCS) were wide-ranging from 0 to a surprising 12%, and from 0% to 1% in the treatment group. Interestingly, DVT was reported only by participants sitting in non-aisle (window or central) seats in LONFLIT 2 study. Given the lower incidence of DVT and SVT, it is impossible to differentiate characteristics of participants who developed these thrombotic events vs. those who did not in the included studies.

Most flight-related thrombosis is asymptomatic (Belcaro *et al.* 2003). Symptoms of flight-related DVT typically are not detected during the flight, but hours afterwards (Belcaro *et al.* 2001). Also, most pulmonary embolism occurs within hours after the flight (Belcaro *et al.* 2001). However, it is unclear how long the potential risk for flight-related thrombosis is sustained after flights (Bendz & Sandset 2002). None of the included studies attempted to track study participants after the single follow-up, which took place within hours or 2 days after flights. It is likely that these studies failed to identify any delayed occurrence of flight-related thrombosis.

Specifications of GCS also call for additional attention. Currently, the most common form of GCS used in travelling is below-knee in length. Compared with thigh- or full-length GCS, knee-length GCS is equally effective in preventing DVT, less expensive, less likely to wrinkle, easier to put on, and better tolerated (Williams & Palfrey 1988, Williams *et al.* 1996, Benko *et al.* 2001, Byrne 2001). Improper application of above-knee GCS can exert garter-like tourniquet effects, thus potentially increasing the risk of thrombosis (Whitley 1988). Thus, below-knee GCS is preferred over thigh-length or full-length GCS.

There is no international agreement on standards and classification for the pressure of GCS. The British standard for compression hosiery specifies three classes based on pressure exerted at the ankle. Class 1 GCS is 14–17 and 18–24 mmHg for class 2, and 25–35 mmHg for class 3 (British Standards Institution 1985). There are four grades in European standards. Grade 4 exerts pressures over 59 mmHg at the ankle (Keachie 1995). The 20–30 mmHg compression pressure seems to relate to the USA class I compression standard (Anderson 2001). The lack of agreement on GCS pressure classification causes problems and misunderstanding. In at least one of the included studies (Scurr *et al.* 2001a, 2001b) the authors reported that they used class I (20–30 mmHg) GCS based on the German Hohenstein compression standard, but they actually used 18·4–21·1 mmHg GCS as shown later in responds to questions raised by readers. Not only does the pressure needed to be effective in preventing flight-related thrombosis or oedema remains controversial. This issue is complicated by the fact that the pressures indicated by the manufacturers based on laboratory study hardly ever reflect the actual pressures exerted on a person's leg (Rukley 1992). Also, GCS fitting techniques have an influence on the amount of pressure applied to a leg (Cullum *et al.* 2001). It is commonly accepted that low pressure is better than no pressure, but high pressure is not necessarily better than low pressure. A risk of GCS is impairment of subcutaneous tissues oxygen. The greater the amount of compression GCS exert, the greater reduction in cutaneous blood flow (Halperin *et al.* 1948).

There are also questions about when to start wearing GCS. In the LONFLIT studies, participants were advised to wear them hours before the flight, but there was no attempt to check when they actually put them on. Common practice suggests GCS should be put on before getting out of bed in the morning. Even when good tolerability of GCS was reported, there was no information on how subjective tolerability was evaluated.

Conclusion

Implication for practice

The results of this review support the contribution of GCS in preventing flight-related thrombosis. Overall, below-knee,

What is already known about this topic

- Incidences of deep vein thrombosis and superficial venous thrombosis are assumed to be related to long air flights.
- Based on the mechanism of Virchow's triad, graduated compression stockings might be able to prevent flight-related venous thrombosis in non-hospitalized participants.

What this paper adds

- The application of medium compression pressure by below-knee graduated compression stockings decreased the occurrence of deep vein thrombosis but not superficial venous thrombosis in long-haul air travellers.
- Experimenter and subject contaminations may have affected the quality of the primary studies, thus hindering inference from the results.
- For graduated compression stockings to be a standard prophylaxis for flight-related thrombosis, more studies are needed.

medium compression pressure GCS seems to be effective in reducing the occurrence of flight-related DVT, regardless of DVT risks. The effectiveness of GCS in preventing SVT is questionable. Other than being effective in flight-related thrombosis prevention, advantages of GCS also include ease of use, relative safety, no side effects, being socially desirable (not inconveniencing other passengers on the same flight by regular exercise and constant movement). GCS is considered a viable, valuable and useful prophylaxis for DVT or SVT after flights and should be used to protect against flight-related thrombosis.

Awareness of the potential risks related to use of GCS cautions universal acceptance. No evidence was available to support for the application of other lengths of GCS. Higher compression pressure is only indicated for participants at high risk of DVT. It is also essential to have GCS that are sized and fitted correctly (Cowan 1997). Before more studies are available, high-risk participants for DVT should be advised to use GCS along with other preventive measures (Bagshaw 2001, Giangrande 2001).

Implication for research

For GCS to be a standard prophylaxis for flight-related thrombosis, more research is needed. Most of the existing studies have been conducted by the same group of researchers with participants travelling in Western countries. The designs of these studies are similar. Additional studies by other researchers are needed to increase diversity. Efforts should also focus on overcoming observer bias. Assessment of outcomes should be blind to treatment.

Given lower occurrences of DVT and SVT after flights, studies with larger numbers of participants are needed to detect the effect size. The decision on the number of participants should be based on a prior sample size calculation. Prolonged observation periods might be necessary to evaluate the occurrence of delayed DVT or SVT and pulmonary embolism (Belcaro *et al.* 2003). Repeated measurements may be valuable.

The optimal compression pressure of GCS to be used by airline passengers should be studied. Questions needing to be answered include what amount of compression pressure is most effective in preventing flight-related thrombosis in what groups of participants, and what risk group of patients can benefit from the application of GCS.

Some antithrombotic medications, such as aspirin or low-molecular-weight heparin (LMWH), were effective in preventing flight-related thrombosis in high-risk participants (Cesarone *et al.* 2002). Evidence is needed to support the superiority of GCS over other preventive measures on the basis of costs and other benefits. Further studies are needed to evaluate the prophylaxis of GCS in comparison of the prophylaxis of other measures such as antithrombotic mediations. Questions on whether the prophylactic effect of GCS can be enhanced when combined with other preventive measures also need to be answered.

Author contributions

HFH was responsible for the study conception and design; drafting of the paper; statistical expertise and supervision. HFH and FPL performed data collection; data analysis; critical revisions of the paper and provided administrative support.

References

Agu O., Hamilton G. & Baker D. (1999) Graduated compression stockings in the prevention of venous thromboembolism. *British Journal of Surgery* **86**, 992–1004.

AMA Commission on Emergency Medical Services (1982) Medical aspects of transportation aboard commercial aircraft. *JAMA Journal of American Medical Association* **247**, 1007–1011.

Amaragiri S.V. & Lees T.A. Elastic compression stockings for prevention of deep vein thrombosis. *The Cochrane Database of Systematic Reviews* 2000, Issue 1. Art. No.: CD001484. DOI: 10.1002/14651858.CD001484.

Anderson R. (2001) Deep-vein thrombosis in long-haul flights (Correspondence). *Lancet* **358**, 837–author reply 839.

Arfvidsson B., Eklof B., Kistner R.L., Masuda E.M. & Sato D.T. (2000) Risk factors for venous thromboembolism following prolonged air travel – Coach class thrombosis. *Hematology Oncology Clinics of North America* **14**, 391–400, IX.

Bagshaw M. (2001) Traveller's thrombosis: a review of deep vein thrombosis associated with travel. The Air Transport Medicine Committee, Aerospace Medical Association. *Aviation Space and Environmental Medicine* **72**, 848–851.

Belcaro G., Geroulakos G., Nicolaides A.N., Myers K.A. & Winford M. (2001) Venous thromboembolism from air travel – The LONFLIT study. *Angiology* **52**, 369–374.

Belcaro G., Cesarone M.R., Shah S.S.G., Nicolaides A.N., Geroulakos G., Ippolito E., Winford M., Lennox A., Pellegrini L., Brandolini R., Myers K.A., Simeone E., Bavera P., Dugall M., Di Renzo A. & Moia M. (2002) Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings. A Randomized trial: The LONFLIT 4 concorde Edema-SSL study. *Angiology* **53**, 635–645.

Belcaro G., Cesarone M.R., Nicolaides A.N., Ricci A., Geroulakos G., Shah S.S.G., Ippolito E., Myers K.A., Bavera P., Dugall M., Moia M., Di Renzo A., Errichi B.A., Brandolini R., Griffin A., Ruffini I. & Acerbi G. (2003) Prevention of venous thrombosis with elastic stockings during long-haul flights: The LONFLIT 5 JAP study. *Clinical and Applied Thrombosis Hemostasis* **9**, 197–201.

Bendz B. & Sandset P.M. (2002) Air travel and risk of venous thromboembolism. *Thrombosis Research* **108**, 15–17.

Bendz B., Rostrup M., Sevre K., Andersen T.O. & Sandset P.M. (2000) Association between acute hypobaric hypoxia and activation of coagulation in human beings. *Lancet* **356**, 1657–1658.

Benko T., Cooke E.A., McNally M.A. & Mollan R.A. (2001) Graduated compression stockings: knee length or thigh length. *Clinical Orthopaedics and Related Research* 197–203.

British Standards Institution (1985) *Specification for Graduated Compression Hosiery (BS 6612)*. British Standards Institution, London, UK.

Byrne B. (2001) Deep vein thrombosis prophylaxis: the effectiveness and implications of using below-knee or thigh-length graduated compression stockings. *Heart and Lung* **30**, 277–284.

Carruthers M., Arguelles A.E. & Mosovich A. (1976) Man in transit: Biochemical and physiological changes during intercontinental flights. *Lancet* **1**, 977–981.

Cesarone M.R., Belcaro G., Nicolaides A.N., Incandela L., De S., Geroulakos G., Lennox A., Myers K.A., Moia M., Ippolito E. & Winford M. (2002) 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* **53**, 1–6.

Cesarone M.R., Belcaro G., Errichi B.M., Nicolaides A.N., Geroulakos G., Ippolito E., Winford M., Lennox A., Pellegrini L., Myers K.A., Ricci A., Hans C., Simeone E., Bavera P., Dugall M., Moia M. & Stuard S. (2003a) The LONFLIT4-Concorde deep venous thrombosis and edema study: Prevention with travel stockings. *Angiology* **54**, 143–154.

Cesarone M.R., Belcaro G., Nicolaides A.N., Geroulakos G., Lennox A., Myers K.A., Moia M., Ricci A., Brandolini R., Ramaswami G., Bavera P., Dugall M., Ippolito E. & Winford M. (2003b) The LONFLIT4-Concorde – Sigvaris Traveno stockings in long flights (EcoTraS) study – a randomized trial. *Angiology* **54**, 1–9.

Cooper H. & Hedges L.V. (1994) Potentials and limitations of research synthesis. In *The Handbook of Research Synthesis* (Cooper H. & Hedges L.V., eds), Russell Sage Foundation, New York, pp. 521–529.

Cowan T. (1997) Compression hosiery. *Professional Nurse* **12**, 881–886.

Cruickshank J.M., Gorlin R. & Jennett B. (1988a) Air travel and thrombotic episodes: the economy class syndrome. *Lancet* **2**, 497–498.

Cruickshank J.M., Gorlin R. & Jennett B. (1988b) Thromboembolism and air travel. *Lancet* **2**, 1501.

Cullum N., Nelson E.A., Fletcher A.W. & Sheldon T.A. Compression for venous leg ulcers. *The Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD000265. DOI: 10.1002/14651858.CD000265.

Decousus H., Epinat M., Guillot K., Quenet S., Boissier C. & Tardy B. (2003) Superficial vein thrombosis: risk factors, diagnosis, and treatment. *Current Opinion in Pulmonary Medicine* **9**, 393–397.

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

Giangrande P.L.F. (2001) Air travel and thrombosis. *International Journal of Clinical Practice* **55**, 690–693.

Halperin M.H., Friedland C.K. & Wilkins R. (1948) The effect of local compression upon blood flow in the extremities of man. *American Heart Journal* **35**, 221–237.

Hedges L.V. (1994) Statistical considerations. In *The Handbook of Research Synthesis* (Cooper H. & Hedges L.V., eds), Russell Sage Foundation, New York, pp. 29–38.

Hollingsworth S.J., Dialysis M. & Barker S.G.E. (2001) "Long haul" flight and deep vein thrombosis: a model to help investigate the benefit of aspirin and below-knee compression stockings. *European Journal of Vascular and Endovascular Surgery* **22**, 456–462.

Homans J. (1954) Thrombosis of the deep leg veins due to prolonged sitting. *New England Journal of Medicine* **250**, 148–149.

Horner J., Fernandes J., Fernandes E. & Nicolaides A.N. (1980) Value of graduated compression stockings in deep venous insufficiency. *British Journal of Surgery* **280**, 820–821.

Ido K., Suzuki T., Taniguchi Y., Kawamoto C., Isoda N., Nagamine N., Ioka T., Kimura K., Kumagai M. & Hirayama Y. (1995) Femoral vein stasis during laparoscopic cholecystectomy: effects of graded elastic compression leg bandages in preventing thrombus formation. *Gastrointestinal Endoscopy* **42**, 151–155.

Iwama H., Furuta S. & Ohmizo H. (2002) Graduated compression stocking manages to prevent economy class syndrome. *American Journal of Emergency Medicine* **20**, 378–380.

Jones N.A., Webb P.J., Rees R.I. & Kakkar V.V. (1980) A physiological study of elastic compression stockings in venous disorders of the leg. *British Journal of Surgery* **67**, 569–572.

Keachie J. (1995) Prevention of re-ulceration. In *Leg Ulcers: Nursing Management – A Research- based Guide* (Cullum N. & Roe B., eds), Scutari Press, London, pp. 89–99.

Kraaijenhagen R.A., Haverkamp D., Koopman M.M., Prandoni P., Piovella F. & Buller H.R. (2000) Travel and risk of venous thrombosis. *Lancet* **356**, 1492–1493.

Landgraf H., Vanselow B., Schulte-Huermann D., Mulmann M.V. & Bergau L. (1994) Economy class syndrome: rheology, fluid balance, and lower leg edema during a simulated 12-hour long distance flight. *Aviation Space and Environmental Medicine* **65**, 930–935.

Lapostolle F., Surget V., Borron S.W., Desmaizieres M., Sordelet D., Lapandry C., Cupa M. & Adnet F. (2001) Severe pulmonary embolism associated with air travel. *New England Journal of Medicine* **345**, 779–783.

Lawrence D. & Kakkar V.V. (1980) Graduated, static, external compression of the lower limb: a physiological assessment. *British Journal of Surgery* **67**, 119–121.

Lewis C.E. Jr, Antoine J., Mueller C., Talbot W.A., Swaroop R. & Edwards W.S. (1976) Elastic compression in the prevention of venous stasis. A critical reevaluation. *American Journal of Surgery* **132**, 739–743.

Litter J. (1952) Thromboembolism; its prophylaxis and medical treatment; recent advances. *Medical Clinics of North America* **36**, 1309–1321.

Loew D., Gerlach H.E., Altenkamper K.H. & Schneider B. (1998) Effect of long-distance flights on oedema of the lower extremities. *Phlebology* **13**(2), 64–67.

McLachlin A.D., McLachlin J.A., Jory T.A. & Rawling E.G. (1960) Venous stasis in the lower extremities. *Annals of Surgery* **152**, 678–685.

McQuillan A.D., Eikelboom J.W. & Baker R.I. (2003) Venous thromboembolism in travellers: can we identify those at risk? *Blood Coagulation and Fibrinolysis* **14**, 671–675.

Meyerowitz B.R. & Nelson R. (1964) Measurement of the velocity of blood in lower limb veins with and without compression. *Surgery* **56**, 481–486.

Moher D., Cook D.J., Eastwood S., Olkin I., Rennie D. & Stroup D.F. (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* **354**, 1896–1900.

Myers M.B., Rightor M. & Cherry G. (1972) Relationship between edema and the healing rate of stasis ulcers of the leg. *American Journal of Surgery* **124**, 666–668.

Nielsen H.K. (1991) Pathophysiology of venous thromboembolism. *Seminars in Thrombosis and Hemostasis* **17**, 250–253.

O'Keeffe D.J. & Baglin T.P. (2003) Travellers' thrombosis and economy class syndrome: incidence, aetiology and prevention. *Clinical and Laboratory Haematology* **25**, 277–281.

Prountjos P., Bastounis E., Hadjinikolaou L., Felekuras E. & Balas P. (1991) Superficial venous thrombosis of the lower extremities co-existing with deep venous thrombosis. A phlebographic study on 57 cases. *International Angiology* **10**, 63–65.

Rukley C.V. (1992) Treatment of venous ulceration: compression therapy. *Phlebology* **1**, 22–26.

Sarin S., Scurr J.H. & Coleridge Smith P.D. (1992) Mechanism of action of external compression on venous function. *British Journal of Surgery* **79**, 499–502.

Sarvesvaran R. (1986) Sudden natural deaths associated with commercial air travel. *Medicine, Science and the Law* **26**, 35–38.

Scurr J.H., Machin S.J., Bailey, King S., Mackie I.J., McDonald S. & Smith P.D.C. (2001a) Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. *Lancet* **357**, 1485–1489.

Scurr J.H., Machin S.J. & Bailey-King S. (2001b) Wearing elastic compression stockings during long-haul flights prevented the development of deep venous thrombosis. *Evidence Based Medicine* **6**, 169.

Scurr J.H., Smith P.D.C. & Machin S. (2001c) Deep vein thrombosis in airline passengers – the incidence of deep vein thrombosis and the efficacy of elastic compression stockings. *Cardiovascular Surgery* **9**, 159–161.

Sigel B., Edelstein A.L., Felix W.R. J.r & Memhardt C.R. (1973) Compression of the deep venous system of the lower leg during inactive recumbency. *Archives of Surgery* **106**, 38–43.

Sigel B., Edelstein A.L., Savitch L., Hasty J.H. & Felix W.R. Jr (1975) Type of compression for reducing venous stasis. A study of lower extremities during inactive recumbency. *Archives of Surgery* **110**, 171–175.

Simpson K. (1940) Shelter deaths from pulmonary embolism. *Lancet* **236**, 744.

Somerville J.J., Brow G.O., Byrne P.J., Quill R.D. & Fegan W.G. (1974) The effect of elastic stockings on superficial venous pressures in patients with venous insufficiency. *British Journal of Surgery* **61**, 979–981.

Spiro M., Roberts V.C. & Richards J.B. (1970) Effect of externally applied pressure on femoral vein blood flow. *British Medical Journal* **1**, 719–723.

Symington I.S. & Stack B.H. (1977) Pulmonary thromboembolism after travel. *British Journal of Diseases of the Chest* **71**, 138–140.

Weiss R.A. & Duffy D. (1999) Clinical benefits of lightweight compression: reduction of venous-related symptoms by ready-to-wear lightweight gradient compression hosiery. *Dermatologic Surgery* **25**, 701–704.

Whitley A.J. (1988) Elastic stockings. *British Medical Journal (Clinical Research Ed.)* **296**, 413–414.

Williams J.T. & Palfrey S.M. (1988) Cost effectiveness and efficacy of below knee against above knee graduated compression stockings in the prevention of deep vein thrombosis. *Phlebologie* **41**, 809–811.

Williams A.M., Davies P.R., Sweetnam D.I., Harper G., Pusey R. & Lightowler C.D. (1996) Knee-length versus thigh-length graduated compression stockings in the prevention of deep vein thrombosis. *British Journal of Surgery* **83**, 1553.

World Health Organization (2002) *Who Launches Study of Venous Thrombosis and Air Travel*. Available at: http://www.who.int/mediacentre/news/releases/release40/en (last accessed 1 December 2003).