EVIDENCE SYNOPSIS

Title: Benefits of Measures to Prevent Venous Thromboembolism in People Undertaking Long-Haul Air Travel

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Clinical question: What are the benefits and harms of measures to prevent venous thromboembolism (VTE) in people undertaking long-haul air travel?

Author recommendations:

For healthy travelers who are planning a long-haul flight of more than 4 hours, in order to prevent VTE, clinicians should discuss with patients the low risk* of VTE associated with travel and suggest mobility exercises, hydration, and alcohol avoidance.

In order to prevent VTE in those travelers at moderate risk,* clinicians should suggest the above measures along with below-the-knee 20-30 mmHg compression hosiery used prior to and during travel.

For people who are planning to travel long distances in confined space and who are at high risk, clinicians may recommend the addition of pharmacoprophylaxis, such as low-molecular-weight heparin, after a comprehensive assessment of its potential benefits and risks.

Evidence and recommendations:

Quality of Evidence[a]	Strength of Recommendations[b]	Conclusion
Low	Weak	Favors risk stratification for VTE and prophylactic measures in long-haul air travelers with greater than minimal risk for VTE, including use of below-the-knee compression hosiery along with exercise and hydration during the flight

[a]Quality of evidence scale (GRADE): high, moderate, low, and very low.
[b]Strength of recommendations scale (GRADE): strong, weak, or no recommendation. For more information on the GRADE rating system, see http://www.gradeworkinggroup.org/index.htm.

*Risk levels are as described in the studies.

PICO:

Population	Healthy adults 18 years of age or older embarking on long-haul air flights or who have taken long-haul air flights in the previous 4 weeks
	Subgroups: overweight, pregnancy, use of oral contraceptives
Intervention	Lower-extremity compression stockings, type of stocking; calf exercises and mobilization; hydration; low-molecular-weight heparin, aspirin, combinations
	Frequency, dose, duration; time initiated before travel
Comparator	No prophylaxis; active comparators
Primary outcome(s)	Superficial phlebitis, acute deep venous thrombosis, or pulmonary embolism confirmed by ultrasonography or similar imaging
	Safety outcomes: all harms

What are the parameters of our evidence search?

Population: Long-haul jet travelers at low, medium, or high risk for VTE
Setting: Long-haul jet travel of 7 hours or more
Intervention: Compression hosiery (below the knee)
Comparator: No compression hosiery, with or without recommendations for exercise and/or hydration
Outcome: VTE after long-haul jet travel, diagnosed by ultrasonography

TABLE 1 Impact of Compression Stockings on VTE Rates for Long-Haul Jet Travelers

Outcome	ILLUSTRATIVE COMPARATIVE RISKS (95% CI)		Pooled Outcome Risk Difference (95% CI) N NT	Number of Participants (Studies)	Quality of Evidence (GRADE)	Comment
	Assumed Risk Rate of VTE in Control Groups	Corresponding Risk with Compression Hosiery				
VTE in all subjects[a]	**0.04 or 40/1000 events (0.02, 0.07)**	**0.004 or 4/1000 events (–0.003, 0.01)**	**–0.03 or a reduction of 30/1000**[b] **(–0.6, –0.01) 33**	**2513 (nine RCTs)**[1-7]	**Moderate**	For travelers at any VTE risk level, compression hosiery reduces the risk of VTE
Probability of VTE in low- and medium-risk subjects	0.02 (–0.005, 0.5)	0 events	–0.02 (–0.04, 0.004)	1244 (three RCTs)[1-3]	Moderate	
Probability of VTE in high-risk subjects	**0.07 (–0.007, 0.15)**	**0.004 (0, 0.010)**	**–0.06 (–0.09, –0.02) 17**	**1269 (three RCTs)**[4-6]	**Moderate**	

[a]Statistically significant findings are in bold font.
[b]The risk difference is calculated using a method different from the assumed and corresponding risks, hence the difference.
CI, Confidence interval; *GRADE,* Grading of Recommendations Assessment, Development and Evaluation; *NNT,* number needed to treat; *RCT,* randomized controlled trial.

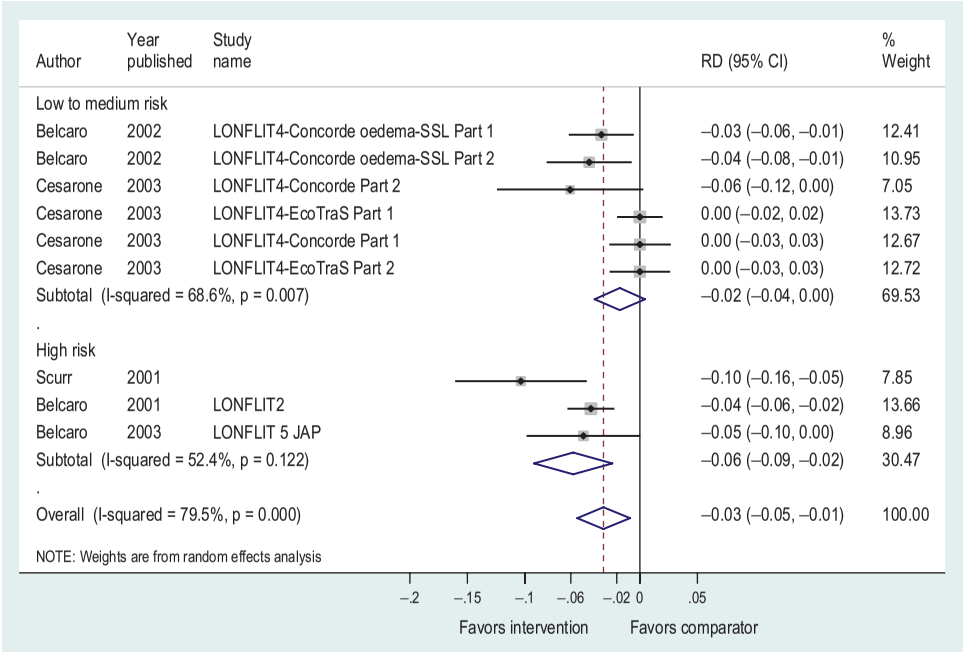

Fig. 1 **Effect of compression hosiery on VTE risk during long-haul flights**

Guidelines: Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines *Section 6.1; 2012. Kahn S, et al.*[8] *(AGREE II score: 71%) Strong recommendations are rated 1 and begin with "We recommend."* Weak recommendations are rated 2 and begin with "We suggest." The quality of evidence rating is high, A; moderate, B; or low, C.[9]

- For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C).
- For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee graduated compression stockings providing 15-30 mmHg of pressure at the ankle during travel (Grade 2C).
- For all other long-distance travelers, we suggest against the use of GCS (Grade 2C). For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C).

Guidelines on Travel-Related Venous Thrombosis. British Society of Haematology; 2011. Watson HG, et al. (AGREE II score: unavailable) Strong recommendations (Grade 1, "recommended") are made when there is confidence that the benefits either do or do not outweigh the harm and burden and costs of treatment. Where the magnitude of the benefit or lack of benefit is less certain, a weaker Grade 2 recommendation ("suggested") is made. Grade 1 recommendations can be applied uniformly to most patients, whereas Grade 2 recommendations require judicious application. The quality of evidence is graded as high, A (high-quality RCTs); moderate, B; or low, C.

- There is no evidence for an association between dehydration and travel-associated VTE, so while maintaining good hydration is unlikely to be harmful, it cannot be strongly recommended for prevention of thrombosis (Grade 2B). Maintaining mobility is a reasonable precaution for all travelers on journeys longer than 3 hours (Grade 2B).
- Assessment of risk should be made on an individual basis. Recent major surgery, active malignancy, previous VTE, or the presence of more than one risk factor identifies those travelers at highest thrombosis risk (Grade 1C).
- Travelers at the highest risk of travel-related thrombosis undertaking journeys of more than 3 hours should wear well-fitted below-knee compression hosiery (Grade 2B).
- When pharmacological prophylaxis is considered appropriate, anticoagulants, as opposed to antiplatelet drugs, are recommended. Usual contraindications to any form of thromboprophylaxis need to be borne in mind (Grade 2C).

Fitness to Fly for Passengers with Cardiovascular Disease; 2010. Smith D, et al. The Report of a Working Group of the British Cardiovascular Society (AGREE II Score: unavailable) No discussion of strength of recommendations or quality of evidence.

- Traveling for more than 4 hours doubles the risk of VTE compared with not traveling. The risk is highest in the first week following travel but persists for 2 months and is similar to that incurred by traveling by car, bus, or train over a similar period.
- For low-risk air travelers flying more than 6 hours, encourage mobility, exercising, and avoidance of dehydration. Also avoid alcohol and/or caffeine and hypnotics, particularly in a cramped environment.
- For those at moderate risk, in addition to the above, add compression stockings.
- For those at high risk, adoption of the low- and moderate-risk preventives. In addition, low-molecular-weight heparin may be considered (i.e., subcutaneous enoxaparin 40 mg on the morning of the flight and on the following day). Note the potential for bleeding and thrombocytopenia complications.
- Aspirin is not recommended in this context for prophylaxis of deep venous thrombosis or VTE.

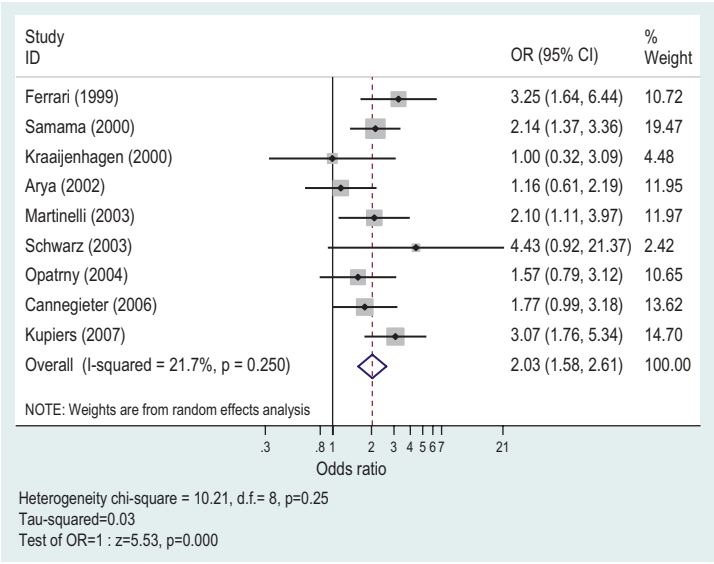

Fig. 1a Risk of VTE within 4 weeks of jet travel compared with no travel (>4 hours flight time)

Author commentary: We searched the literature on VTE and long-haul jet travel. The pooled odds of long-haul jet travelers developing VTE compared with those of matched persons who have not traveled is based on a meta-analysis of nine case-control studies (Appendix 1).[10-18] From this analysis, those persons exposed to long jet flights are twice as likely to be diagnosed with VTE than those without a recent history (4 weeks) of air travel. Despite the primary studies' design and being somewhat heterogeneous, they are of moderate quality. The results are consistent, relatively precise—with the exception of Schwarz and Kraaijenhagen—and not subject to detectable publication bias (Fig. 1a in the Appendix).[11,15] Of note, a well-conducted meta-analysis of 14 studies using similar primary studies found a statistically significant dose–response relationship with an 18% (95% CI 7%, 48%) higher risk of VTE for each 2-hour increase in travel time.[19] These results agree with other meta-analyses on the same topic.[20,21]

We searched the literature on the prophylactic effects of compression hosiery on air travel–related VTE. The results of six studies, three of which contained two sub-studies (flights of 7-8 hours and 11-12 hours) are included in our analysis (Table 1).[1-4,6,7] A stratified random-effects meta-analysis was performed, and the overall risk reduction when using any type of below-the-knee compression hosiery is 3.2%. The impact is more pronounced and statistically significant for high-risk travelers, with a risk reduction of 6%. The risk difference in the low- and medium-risk group is not significant (Fig. 1).

In travelers with more than baseline risk factors, one randomized controlled trial found that wearing graduated compression ankle stockings (20-30 mm Hg) before and during travel reduced the risk of VTE.[5] Other RCTs with similar populations and interventions found no statistically significant differences in VTE rates.[1-3] Nevertheless, the risk increases in persons who are older, pregnant, taking oral contraceptives or estrogen, immobile, or suffering from malignancies, obesity, surgery, recent trauma, thrombophilia, prior VTE, or family predisposition for VTE, so additional preventive measures may be indicated.[10-17,22,23-26]

TABLE 1a Pooled Odds of VTE after Long-Haul Jet Travel Compared with No Recent Long-Haul Jet Travel

OUTCOME: ODDS RATIO OF VTE IN AIR TRAVELERS COMPARED WITH THAT OF THOSE WHO HAVE NOT FLOWN						
Outcome	ILLUSTRATIVE COMPARATIVE RISKS (95% CI)		Pooled Outcome Odds Ratio (95% CI)	Number of Participants (Studies)	Quality of Evidence (GRADE)	Comment
	Assumed Risk in Controls (No Travel)	Corresponding Risk with Cases (>4 Hours Air Travel)				
Odds of VTE in travelers (cases) compared with nontravelers	Odds of VTE in control group 0.0067[a] (0.0065, 0.0068)	Odds of VTE in the cases group 0.01[a] (0.01, 0.015)	2.03 (1.6, 2.6)	43,826 (9)[10-17,22]	Very low	Across study results, there is consistency, moderate precision, and directness

[a]Weighted by sample size.
The comparative risks are reported as standardized mean differences with 97.5% one-sided confidence intervals.
Studies in bold font have statistically significant differences in outcome.
Because of rounding, the intervention and comparator numbers may not add up to the actual reported risk difference.
CI, Confidence interval; *GRADE,* Grading of Recommendations Assessment, Development and Evaluation; *RCT,* randomized controlled trial; *VTE,* venous thromboembolism.

For persons at high risk and traveling long distances, prophylactic anticoagulation using aspirin, low-molecular-weight heparin, or warfarin to reduce the VTE risk has been suggested and studied. The results indicate a risk reduction in the low-molecular-weight heparin group compared with the placebo and aspirin group; heparin reduced the incidence of VTE from 4.2% to 0. However, the study's strength is weakened by a 17% dropout rate.[7] Another RCT comparing pycnogenol, a profibrinolytic agent, with placebo resulted in the intervention group having no diagnosed VTE compared with 5.2% in the placebo group.[27] Note that all studies cited in this review have methodological weaknesses that may affect the evidentiary strength of the results, and most of these RCTs studying VTE and travel are from the same group of researchers.

Although the incidence of VTE associated with long-distance air travel is low, the effectiveness, safety, and low cost of compression hosiery make it an attractive preventive strategy for travelers.

The cited guidelines are generally consistent with the evidence in this synopsis.

Update alerts: Important new citations relevant to this topic are added here as they become available.

Glossary: AGREE II, Appraisal of Guidelines for Research and Evaluation; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; RCT, randomized controlled trial; VTE, venous thromboembolism.

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Appendix: Meta-analysis of case control studies of the relationship between long-haul jet travel and the incidence of VTE

Patients or population: Healthy adults 18 years of age or older

Exposure: Long-haul air flights in the previous 4 weeks

Comparison: No long-haul air travel

Outcome: VTE confirmed or diagnosed by ultrasonography or similar imaging

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