Air Travel and Venous Thromboembolism: A Systematic Review

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CONTEXT: Despite multiple attempts to document and quantify the danger of venous thromboembolism (VTE) following prolonged travel, there is still uncertainty about the magnitude of risk and what can be done to lower it.

OBJECTIVES: To review the methodologic strength of the literature, estimate the risk of travel-related VTE, evaluate the efficacy of preventive treatments, and develop evidence-based recommendations for practice.

DATA SOURCES: Studies identified from MEDLINE from 1966 through December 2005, supplemented by a review of the Cochrane Central Registry of Controlled Trials, the Database of Abstracts of Reviews of Effects, and relevant bibliographies.

STUDY SELECTION: We included all clinical studies that either reported primary data concerning travel as a risk factor for VTE or tested preventive measures for travel-related VTE.

DATA EXTRACTION AND ANALYSIS: Two reviewers reviewed each study independently to assess inclusion criteria, classify research design, and rate methodologic features. The effect of methodologic differences, VTE risk, and travel duration on VTE rate was evaluated using a logistic regression model.

DATA SYNTHESIS: Twenty-four published reports, totaling 25 studies, met inclusion criteria (6 case-control studies, 10 cohort studies, and 9 randomized controlled trials). Method of screening for VTE [screening ultrasound compared to usual clinical care, odds ratio (OR) 390], outcome measure [all VTE compared to pulmonary embolism (PE) only, OR 21], duration of travel (<6 hours compared to 6–8 hours, OR 0.011), and clinical risk ("higher" risk travelers compared to "lower," OR 3.6) were significantly related to VTE rate. Clinical VTE after prolonged travel is rare [27 PE per million flights diagnosed through usual clinical care, 0.05% symptomatic deep venous thrombosis (DVT) diagnosed through screening ultrasounds], but asymptomatic thrombi of uncertain clinical significance are more common. Graduated compression stockings prevented travel-related VTE ($P<0.05$ in 4 of 6 studies), aspirin did not, and low-molecular-weight heparin (LMWH) showed a trend toward efficacy in one study.

CONCLUSIONS: All travelers, regardless of VTE risk, should avoid dehydration and frequently exercise leg muscles. Travelers on a flight of less than 6 hours and those with no known risk factors for VTE, regardless of the duration of the flight, do not need DVT prophylaxis. Travelers with 1 or more risk factors for VTE should consider graduated compression stockings and/or LMWH for flights longer than 6 hours.

KEY WORDS: venous thromboembolism; deep venous thrombosis; pulmonary embolism; air travel; transportation; systematic review.
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INTRODUCTION

In 2003, 104 million passengers flew into or out of the United States on transoceanic flights.[1] By 2015, this number will almost double. While in transit, some of these passengers will develop deep venous thrombosis (DVT) or pulmonary embolism (PE).[2–4] Despite multiple attempts to quantify the danger, there is still uncertainty about the risk of venous thromboembolism (VTE) from prolonged travel, which travelers should receive VTE prophylaxis, and what prophylactic measures should be used. We performed a systematic review of this literature to address the following questions: (1) What are the methodologic strengths and weaknesses in this literature? (2) What is the risk for travel-related VTE? (3) Are there effective preventive measures? Using our findings, we propose evidence-based recommendations for practice.

METHODS

Using the MEDLINE database from 1966 through December 2005, we searched for articles evaluating human subjects that either reported primary data concerning the risk of travel for VTE or tested preventive measures for travel-related VTE. Our search included the MESH headings *thromboembolism*, *thrombosis*, *venous thrombosis*, *thrombophlebitis*, and *pulmonary embolism*. We also searched under the MESH headings *travel*, *aerospace medicine*, *aviation*, and *transportation*, and the text words *flight* and *flying*. We then combined the 2 searches into an initial set of 465 articles. We sought additional articles by performing the same search strategy in the Cochrane Central Registry of

Controlled Trials and the Database of Abstracts of Reviews of Effects.[5] We then reviewed the references from relevant articles in the initial set for articles not already identified. We included case-control studies, cohort studies, and randomized controlled trials (RCTs), but excluded case reports, abstracts, and subgroup analyses of previously published studies.

Two of 3 authors (RS, DMB, and JTP) reviewed each study independently to determine whether it met inclusion criteria, classified it according to research design, and evaluated it for methodologic strength. The ratings of the 2 reviewers were compared and discrepancies were resolved by discussion to achieve consensus. To evaluate methodologic strength, we used 8 standards adapted from previous research on the natural history of disease.[6,7] These standards are described in the Appendix.

STATISTICAL ANALYSIS

For each cohort study group and RCT study arm, we recorded number of subjects, number of subjects with VTE, VTE outcome (PE, DVT, or both), travel duration (mean of less than 6 hours, mean of 6 to 8 hours, and mean greater than 8 hours), treatment (yes/no), method of screening for VTE (usual clinical care or screening ultrasound after travel) and clinical VTE risk of travelers (lower or higher). We then examined associations between these variables and VTE outcomes in untreated travelers using the 26 study arms where there was both travel and no intervention (treatment=no). Because the dependent variable was dichotomous (whether or not each participant had a VTE), we concluded that the natural distributional assumption was the binomial distribution. Because we only had summary data on groups rather than data on individual subjects, we used the total number of subjects in each group and the number of those with VTE to define a grouped binary data structure. We then fitted a logistic regression model to the data, where the coefficients of regression were log odds ratios (LOR). These coefficients were related to the dependent variable, VTE rate (r), by 2 transformations. The first was a transformation to an odds ratio (OR) and the second to a logarithm [$\text{LOR}=\log(r/(1-r)]$.[8,9] This method allows for a more realistic distributional assumption for the dependent variable than the normal distribution, accounts for different sample sizes of the studies, has more statistical power, allows independent variables to be incorporated into the model, estimates effect of those variables on the dependent variable, and decreases heterogeneity. We used SAS/STAT software, version 9.1, to fit the models and estimate the parameters (PROC GENMOD).

RESULTS

Descriptions of the Selected Studies

The search strategy identified 24 publications including 25 studies that met criteria for inclusion in this review.[10–33] There were 6 case-control studies, 10 cohort studies, and 9 RCTs, with 1 article including the results of both a cohort study and a RCT.[18]

The 6 case-control studies, described in Table 1, ranged in size from 207[14] to 988 subjects[12] and were from 4 different countries. Five of the 6 investigated risk from any form of travel,[11–15] while 1 limited its focus to air travel.[16] The 10 cohort studies, described in Table 2, ranged in size from 320[19] to more than 135 million subjects[17] and were performed in 9 countries. All investigated air travel risk only. The 9 RCTs, described in Table 3, ranged in size from 186[32] to 833[18] and were performed in 3 countries. All limited investigation to air travel. Eight of the 9 trials[18,27–33] came from the same group of investigators.

Methodologic Strengths of the Reviewed Studies

Compliance with the methodologic standards is noted in Tables 1 through 3. The reviewed studies used strong research methods to establish VTE diagnosis and to evaluate the efficacy of preventive interventions. Each of the included studies used objective diagnostic tests to confirm the VTE (standard 7, Appendix). Therefore, within the limits of the test operating characteristics, any reported episode of VTE was in fact VTE. Each of the preventive interventions was evaluated with RCTs so that conclusions about treatment efficacy are less prone to bias.

Methodologic Weaknesses the Reviewed Studies

There were 3 major methodologic weaknesses of the reviewed studies. Because none of the studies avoided all 3, it was impossible to precisely determine the risk of travel-related VTE.

First, the 4 largest cohort studies did not undertake routine VTE surveillance (standard 6, Appendix) but, rather, identified cases from retrospective reviews of medical records.[10,17,21,23] This strategy leads to a low count of VTE cases, particularly when PEs but not DVTs are counted and when cases are sought for a limited time period after travel in a limited number of medical settings.[10,17,21] As we expected, when cases are identified from medical records but without limits on time or setting, a higher count is reported.[23] When routine surveillance with lower extremity ultrasound is used, as occurred with most of the cohort studies and all of the controlled trials, there are many more VTE cases identified, mostly asymptomatic DVTs. Our multivariate analysis, controlling for travel duration and clinical risk, found that the OR for screening ultrasound–diagnosed VTE was 390 compared to VTE diagnosed through usual clinical care (Table 4).

Second, many of the studies were prone to volunteer bias. While 4 studies enrolled consecutive series or sampled the entire population,[10,17,21,23] most studies enrolled volunteers who tend to be healthier than nonvolunteers.[34] In addition, volunteer bias works to compound the "healthy traveler effect," providing an explanation for why the baseline risk of VTE in travelers is less than that of the general population.[23]

Third, outcome measures varied among studies. Some studies looked only for DVTs, others only for PEs, and others for all VTEs (i.e., both DVTs and PEs). As we expected, there were more frequently reported outcomes when DVT was included than when the outcome was PE alone [OR 23 and 21, respectively, for DVT and all VTE compared to PE alone (Table 4)].

Clinical Findings: Risk of Travel-Related VTEs

The cohort studies and the control groups of the RCTs provide information about the incidence of VTE after travel. These studies looked only at air travel and report a wide range of VTE

Table 1. Case-control studies

Author (ref) year subjects	Description of subjects		Travel type/duration	Exposure rate		Odds ratio (95% confidence interval)	Standards met*
	Cases	Controls		Cases	Controls		
Ferrari[11] 1999 320	Consecutive patients hospitalized for DVT or PE	Consecutive age-matched patients admitted to the same cardiology floor for the first time for a first event	Air, car, train within previous 4 wk/5.7 h mean duration)	39/160	12/160	Unadjusted: 3.98 (1.9–8.4)	2,4,6,7
Samama[12] 2000 988	Consecutive patients from general practitioner centers diagnosed with lower extremity DVT by objective tests	Sex and age matched (+/− 10 y) patients presenting with upper respiratory illness	"Long-distance travel"	62/494	31/494	Unadjusted: 2.35 (1.45–3.80)	1,4,6,7
Kraaijenhagen[13] 2000 788	Consecutive outpatients with clinically suspected lower extremity DVT who had VTE diagnosed by objective tests	Consecutive outpatients with clinically suspected lower extremity DVT with negative objective tests and uneventful 3-mo follow-up.	Air, boat, car, bus, train within prior 4 wk/At least 3 h	9/186	43/602	Overall: 0.7 (0.3–1.4) Subjects age <65: 1.0 (0.4–2.2) Travel >5 h: 0.4 (0.1–1.3) Air travel: 1.0 (0.3–1.4)	3,4,6,7,8
Hosoi[14] 2002 207	Consecutive patients referred to a vascular lab with clinically suspected DVT who had VTE diagnosed by duplex ultrasound	Consecutive patients referred to a vascular lab with clinically suspected DVT who had a negative duplex ultrasound	Air, boat, train, car, bus within prior 2 wk for least 3 h/5 h (median)	15/101	13/106	Overall: 1.3 (0.6–2.8) Air travel: 0.8 (0.3–1.9)	1,4,6,7,8
Arya[15] 2002 568	Consecutive outpatients referred to a DVT clinic with clinically suspected DVT who had VTE diagnosed by duplex ultrasound	Consecutive outpatients referred to a DVT clinic with clinically suspected DVT who had a negative duplex ultrasound		20/185	31/383	Any travel>3 h: 1.4 (0.7–2.6) Air travel>8 h: 1.3 (0.6–2.8) Any travel>3 h and additional risk factor: 2.7 (1.2–6.4)	1,2,4,6,7,8
Martinelli[16] 2003 420	Consecutive patients presenting to a thrombosis center for a thrombophilia screening with first episode of proximal DVT and/or PE in the preceding 24 mo	Sex-, age-, and education-matched subjects volunteering to be screened for thrombophilia in the same period as subjects	Air travel in preceding month	31/210	16/210	Overall: 2.1 (1.1–4.0) Air travel>8 h: 3.0 (0.9–9.5) Air travel and "thrombophilia": 16.1 (3.6–70.9) Air travel without "thrombophilia": 1.7 (0.7–3.7) Air travel and oral contraceptives: 13.9 (1.7–117.5)	1,2,3,4,7,8

DVT deep venous thrombosis, VTE venous thromboembolism, PE pulmonary embolism, V/Q scan ventilation perfusion lung scan.
**See Appendix for explanation of standards.*

Table 2. Cohort studies

Author (ref) year subjects	Description of subjects		Travel type, duration	Subjects with VTE/total	Incidence (95% CI)	Standards met*
	Travelers/controls	Cases				
Clerel[10] 1999 32,000,000	Travelers: all arriving air passengers	Passengers transported to hospital from airport with confirmed PE diagnoses	Air, mean 12.7 h	PE: 15/32,000,000	0.5 (0.3–0.8) per million	1,2,4,7
Lapostolle[17] 2001 135,290,000	Travelers: all arriving air passengers	Passengers transported to hospital from airport with confirmed PE diagnoses	Air, <3 h	PE: 0/88,490,000	0.00 (0.0–0.04) per million†	1,4,7,8
			Air, >=3 to <6 h	PE: 1/9,180,000	0.11 (0.01–0.71) per million	
			Air, >=6 to <9 h	PE: 9/22,530,000	0.40 (0.19–0.79) per million	
			Air, >=9 to <12 h	PE: 33/12,370,000	2.66 (1.83–3.79) per million	
			Air, >= 12 h	PE: 13/2,720,000	4.77 (2.66–8.41) per million	
Belcaro[18] 2001 778	Travelers: volunteer passengers planning long distance air travel	Travelers with diagnosis of DVT from screening ultrasound exam	Air, 10–15 h	Low-risk‡ DVT: 0/355 High-risk‡ DVT: 11/389	0.0% (0.0–1.0)† 2.8% (1.4–5.0)	2,6,7
Schwarz[19] 2002 320	Travelers: volunteers planning long distance air travel	Subjects with diagnosis of DVT from screening ultrasound exam	Air, >8 h	DVT: 0/160	0.0% (0.0–2.3)	2,3,4,6,7
	Controls: age, sex matched nontraveling volunteers		–	DVT: 0/160	0.0% (0.0–2.3%)	
Schwarz[20] 2003 2,311	Travelers: volunteers planning long-distance air travel	Subjects with diagnosis of DVT from screening ultrasound exam	Air, >8 h	DVT: 7/964	0.7% (0.3–1.5)	2,3,4,6,7
	Controls: nontraveling volunteers		–	DVT: 2/1,213	0.2% (0.02–0.6)	
Perez–Rodriguez[21] 2003 41,035,332	Travelers: all arriving air passengers on international flights	Passengers transported to hospital from airport with confirmed PE diagnoses	Air, <6 h	PE: 0/28,038,726	0.00 per million†	1,4,7,8
			Air, 6–8 h	PE: 1/3,926,208	0.25 (0.00–0.75) per million	
			Air, >8 h	PE: 15/9,070,398	1.65 (0.81–2.49) per million	
Hughes[22] 2003 878	Travelers: volunteers planning long-distance air travel	Passengers with elevated D-dimer or symptoms suggestive of VTE during 3-mo follow-up period and VTE diagnosis confirmed by objective test	Air, 39.4 h (mean)	VTE: 9/878 PE: 4; DVT: 5	1.03% (0.5–1.9)	2,4,6,7,8
			Air, <24 h	VTE: 0/123	0.0% (0.5–3.0)	
			Air, >24 h	VTE: 9/752	1.2% (0.6–2.3)	
Kelman[23] 2003 9,257,842	Travelers: all arriving passengers on international flights	All inpatients with the discharge diagnosis of DVT or PE who had arrived on an international flight within 14 d	Air	VTE: 246/9,257,842	26.6 per million (23–30)	1,4
Jacobson[24] 2003 899	Travelers: volunteers planning long-distance air travel	Subjects with diagnosis of DVT from screening ultrasound exam	Air, 11 h	DVT: 0/434	0.0% (0.0–0.9)	2,6
Gajic[25] 2005 8,860	Travelers: patients having elective surgery after long-distance air travel	Patients having new-onset VTE within 28 d of Surgery	Air, >5,000 km	VTE: 11/223	4.9% (2.5–8.7)†	4,7
	Controls: patients having elective surgery but no long-distance air travel		<5,000 km	VTE: 13/8,637	0.2% (0.08–0.3)	

CI confidence interval, DVT deep venous thrombosis, VTE venous thromboembolism, PE pulmonary embolism, CTPA computed tomographic pulmonary arteriography, V/Q scan ventilation perfusion scan.
**See Appendix for explanation of standards.*
†Differences between groups significant, P<0.001.
‡Low risk: no known VTE risk factors; high risk: previous DVT, known coagulation disorder, severe obesity, limited mobility, cancer, large varicose veins.

Table 3. Randomized controlled trials, stratified by risk of deep venous thrombosis

Author (ref) year subjects	Intervention	Mean duration air travel	Subjects with DVT*/total subjects						$P^{\dagger}$	Standards met‡
			Control			Intervention				
			Proximal	Distal	Total	Proximal	Distal	Total		
Air travelers without increased DVT risk§										
Scurr[26]	Graduated compression stockings 20–30 mmHg at ankle "put	16.5 h over	0/100	12/100	12/100	0/100	0/100	0/100	0.0003	2,4,5,6,7
2001 200	on before the start of travel"	13–32 d	0.0%	12%	12%	0.0%	0.0%	0.0%		
Belcaro[27] 2002 657	All subjects: mild leg exercises and hydration recommended	7–8 h	2/179	2/179	4/179	0/179	0/179	0/179	NS	2,3,4,5,6,7,8
			1.1%	1.1%	2.2%	0.0%	0.0%	0.0%		
	Intervention: graduated compression stockings 20–30 mmHg	11–12 h	3/135	0/135	3/135	0/136	0/136	0/136	NS	
	at ankle applied 2–3 h before flight		2.2%	2.2%	2.2%	0.0%	0.0%	0.0%		
Cesarone[28] 2003 282	All subjects: mild leg exercises and hydration recommended	7–8 h	0/72	0/72	0/72	0/72	0/72	0/72	NS	2,3,4,5,6,7,8
			0.0%	0.0%	0.0%	0.0%	0.0%	0.0%		
	Intervention: graduated compression stockings 14–17 mmHg	11–12 h	2/66	0/66	2/66	0/64	0/64	0/64	NS	
	at ankle applied 3–4 h before flight		3.0%	0.0%	3.0%	0.0%	0.0%	0.0%		
Cesarone[29] 2003 376	All subjects: mild leg exercises and hydration recommended	7–8 h	0/98	0/98	0/98	0/97	0/97	0/97	NS	2,3,4,5,6,7,8
			0.0%	0.0%	0.0%	0.0%	0.0%	0.0%		
	Intervention: graduated compression stockings 12–18 mmHg	11–12 h	0/71	0/71	0/71	0/75	0/75	0/75	NS	
	at ankle applied 3–4 h before flight		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%		
Air travelers with DVT risk factors‖										
Belcaro[18] 2001 833	All subjects: mild leg exercises and hydration recommended	12.4 h	–	–	19/422	–	–	1/411	<0.001	2,3,5,6,7
	Intervention: graduated compression stockings 25 mmHg				4.5%			0.2%		
	at ankle applied 6–10 h before flight									
Cesarone[30] 2002 249	All subjects: mild leg exercises and hydration recommended	"Long–haul"	–	–	4/82	–	–	3/84	NS	4,5,6,7
	Intervention: 400 mg ASA daily for 3 d, starting 12 h before flight				4.9%			3.6%		
	Intervention: enoxaparin 1 mg/kg injected 2–4 h before flight					–	–	0/82	NS	
								0.0%		
Belcaro[31] 2003 205	All subjects: educational video recommending mild leg exercises	11.8 h	5/102	1/102	6/102	0/103	1/103	1/103	NS	2,3,4,5,6,7
	and hydration		4.9%	1.0%	5.9%	0.0%	1.0%	1.0%		
	Intervention: graduated compression stockings 14–17 mmHg									
	at ankle applied 3–4 h before flight									
Cesarone[32] 2003 186	All subjects: educational video recommending mild leg exercises	7.7 h	–	–	5/92	–	–	0/94	<0.03	2,4,5,6,7
	and hydration				5.4%			0.0%		
	Intervention: Flite Tabs®¶									
Belcaro[33] 2004 211	All subjects: educational video recommending mild leg exercises	8.25 h	–	–	1/97	–	–	0/101	NS	4,5,6,7
	and hydration				1.0%			0.0%		
	Intervention: Pycnogenol®¶									

DVT deep venous thrombosis, ASA acetylsalicylic acid.

**All subjects had negative lower extremity ultrasounds prior to travel. All diagnoses of DVT were made by lower extremity ultrasonography performed routinely in all subjects after air travel.*

†*Fisher's exact test comparing total DVT rates.*

‡*See Appendix for explanation of standards.*

§*Generally, patients with history of DVT, obesity, cancer, coagulation disorders, or "serious" illness were excluded from these studies.*

‖*Inclusion criteria generally were history of venous thromboembolism (VTE), obesity, cancer, coagulation disorders, limitation of mobility, and varicose veins. Exclusion criteria generally were severe obesity (weight over 90 kg), clinical disorders requiring anticoagulation, and VTE within 6 months.*

¶*Flite Tabs® (Aidan, AZ, USA) contain pinokinase and nattokinase, given 2 capsules 2 hours before flight and 2 capsules 6 hours later, or placebo capsules: Pycnogenol® (Horphag Research Management, Geneva, Switzerland) given 100 mg, 2 capsules 2 hours before flight and 2 capsules 6 hours later and 1 capsule the next day, or placebo capsules.*

Table 4. Logistic regression model evaluating association of clinical and study methodology factors with VTE

Variable	OR	95% CI	*P*
Screening method			
Usual clinical care	1.0*		
Screening ultrasound	390	200–761	<0.0001
VTE outcomes reported			
PE only	1.0		
DVT only	23	10–52	<0.0001
All VTE (PE and DVT)	21	16–27	<0.0001
Mean travel duration			
Less than 6 h	0.011	0.0019–0.11	<0.0001
6–8 h	1.0		
More than 8 h	2.3	1.4–3.6	<0.0001
Clinical VTE risk†			
Lower	1.0		
Higher	3.6	2.2–5.8	<0.0001

P compared to reference category.
VTE venous thromboembolism, DVT deep venous thrombosis, PE pulmonary embolism, OR odds ratio, CI confidence interval.
**Reference category.*
†*See Table 2 for description of risk categories.*

risk, from none[19,24,29] to 12% of travelers.[26] As expected, studies of symptomatic VTE patients reported lower rates of VTE, about 0.5 PEs per million travelers presenting in the airport on the day of arrival[10,17,21] and 27 VTEs (both PE and DVT) per million travelers presenting within 14 days of travel.[23]

The studies performing ultrasound surveillance found much higher VTE rates in travelers, 1.2% DVT (44/3,820, ranging from 0 to 12%). Of note, all subjects were proven by ultrasound before embarkation to be DVT-free. One third of the reported DVTs were in proximal veins, and two thirds were in calf veins. However, only 2 of the 44 ultrasound-positive patients had symptoms. Therefore, the overall rate of symptomatic DVT was 0.05%, but with a wide 95% confidence interval (0.01% to 0.19%). One study screened travelers with the D-dimer test followed by 3 months of surveillance for VTE symptoms and reported a cumulative VTE rate of 1.0%, with 5 of 9 cases symptomatic.[22]

Two cohort studies included nontraveling control groups.[19,20] Although no statistically significant difference in VTE rates between travelers and nontravelers was found, in one of these studies there was a trend toward a higher DVT rate in the travelers (0.7% vs 0.2% in nontravelers, *P*=NS).[20]

A travel dose–response curve is demonstrated in individual studies[17,21] and confirmed by our multivariate model (Table 4). Symptomatic PE is almost unheard of for flights of less than 6 hours[17,21] [OR of 0.011 compared to flights of 6–8 hours (Table 4)], but flights of more than 8 hours have increased risks (OR for VTE of 2.3 compared to flights of 6–8 hours).

In addition to flight duration, our multivariate analysis found that a higher clinical VTE risk was associated with higher VTE rates (Table 4). Nine studies[17,20–22,26,27,30–32] reported the following risk factors in 126 VTE patients: age over 40, 45%; female hormone use, 31%; varicose veins, 19%; obesity, 17%; inherited clotting disorder, 6%; and other factors, 7%. None of these studies compared rates of DVT risk factors in VTE subjects with those of non-VTE subjects. Despite the publicity surrounding "economy class syndrome," no study compared the seating of VTE subjects (first class or not, aisle seating or not) with that of non-VTE subjects.

Only the case-control studies examined the risk of travel modes other than air, and only air travel was associated with VTE.[11–15]

Clinical Findings: Prevention

Table 3 lists the studies that evaluated preventive interventions, all RCTs. All subjects, whether in a control arm or an intervention arm, were encouraged to exercise and maintain good hydration during flight. The interventions tested were low-molecular-weight heparin (LMWH), aspirin, graduated compression stockings, and herbal remedies with putative antithrombotic properties. Only 1 study[30] evaluated LMWH (enoxaparin) and found a trend favoring effective DVT prevention that did not reach statistical significance. The same study found no effect from aspirin. No studies tested warfarin or unfractionated heparin. Graduated compression stockings, ranging from 12 mmHg to 30 mmHg at the ankle, were evaluated in 6 studies, and 4 of these studies reported a statistically significant benefit.[18,26,27,31] Of the 1,237 subjects using compression stockings, only 2 DVTs were found (0.2%), compared to 46 in the 1,245 controls (3.7%). Two studies[32,33] evaluated preparations containing pycnogenol, an extract of pine bark with antioxidant and possible antithrombotic effects,[35] with 1 study reporting fewer DVTs among treated passengers.[32]

DISCUSSION

We conclude that there is a risk of symptomatic VTE from prolonged air travel. Our estimate of the magnitude of this risk varies according to study methodology. If we depend on VTE rates identified through usual clinical care, the risk may be as low as 27 cases per million travelers [number needed to harm (NNH)=38,000].[23] This estimate, equivalent to 1.1 VTE per million person-days and incorporating the healthy traveler effect while avoiding volunteer bias, is close to but less than the baseline risk in general populations, estimated to be 1.9 to 5.2 VTE per million person-days.[23,36–40]

If we depend on ultrasound screening studies, the overall VTE risk may be as high as 1.2%. However, in contrast to symptomatic travel-related PE, little is known about the natural history of asymptomatic travel-related DVT. We believe that most asymptomatic thrombi resolve without treatment but that some progress to symptomatic DVTs and PEs during the several weeks after travel.[7,41,42] Therefore, the rate of clinically important travel-related VTEs must be less than the rate found by screening ultrasound studies. Counting only symptomatic DVTs, 0.05% is a more likely estimate of the incidence of clinically important DVTs from prolonged air travel. Assuming none of these travelers would have developed DVTs if they had stayed home, the NNH would be 2,000.

VTE risk is very low when flight time is less than 6 hours, but is progressively greater with longer-duration flights. However, the overall VTE risk is still much lower than what is considered the "low-risk" category in surgical patients (2% calf DVTs, 0.4% proximal DVTs, and 0.2% clinical PEs).[43] The odds of VTE after long flights (>8 hours) and for higher-risk travelers (Table 4) are slightly greater than those reported for "weak" VTE risk factors (e.g., bed rest more than 3 days, increasing age, laparoscopic surgery, obesity, antepartem pregnancy, and varicose veins) and similar to those reported for "moderate"

risk factors (e.g., arthroscopic knee surgery, congestive heart failure, hormone replacement therapy, stroke, postpartum pregnancy, previous thromboembolism, antithrombin deficiency, proteins C and S deficiencies, prothrombin G20210A, and heterozygous factor V Leiden).[44,45] They are much less than those reported for "strong" risk factors (e.g., hip fracture, joint replacement, major trauma, spinal cord injury, oral contraceptives plus factor V Leiden, and homozygous factor V Leiden).[44,45] Healthy travelers without VTE risk factors other than travel do not need to worry about VTE from prolonged air travel. However, travelers with VTE risk factors are at increased risk directly related to the importance of their risk factor(s) and the duration of their flight.

In addition to exercise and hydration for all travelers, compression stockings are helpful for long-haul travelers. LMWH does not have established efficacy, and none of the reviewed studies evaluated warfarin and unfractionated heparin. However, the efficacy of LMWH, unfractionated heparin, and warfarin for VTE prophylaxis has been established in other settings.[43] If compression stockings could not be used or if additional preventive measures were thought to be needed, we believe that various proven anticoagulant regimens (e.g., low-dose unfractionated heparin bid or tid; LMWH qd or bid) could be adapted to prolonged air travel, including the one used by Cesarone et al.[30] We favor the use of compression stockings over anticoagulants because the number needed to treat is likely more than 2,000 and there is some risk, although small, from anticoagulant use. Because aspirin is ineffective in other DVT prophylaxis settings, we were not surprised that the evidence available in this review did not suggest an aspirin benefit. We do not recommend pycnogenol preparations at this time, due to the limited data on its properties.

The decision regarding VTE prophylactic measures in long-distance air travelers should be made in a manner analogous to other decisions regarding VTE prophylaxis—according to the degree of risk. Unfortunately, in contrast to surgery, risk levels for air travel are not well defined for the clinical conditions associated with increased VTE risk. We make the following specific recommendations:

1. All air travelers should avoid dehydration and frequently exercise their leg muscles in their seats, as well as by walking in the aisle when possible.
2. Travelers with no known risk factors for VTE, regardless of the duration of the flight, have such a low risk of VTE that additional prophylactic measures are not necessary.
3. If, in a physician's judgment, prophylactic measures are warranted because a traveler has sufficiently increased VTE risk, knee-high graduated compression stockings, 15–30 mmHg at the ankle, have proven efficacy and should be recommended for flights longer than 6 hours.
4. LMWH, while neither proven nor disproved in this setting, can be used if graduated compression stockings are not an option or if VTE risk seems especially high.

As always, further research is needed; for example: evaluation of the VTE risk of travel (including the healthy traveler effect) using study methodology that avoids volunteer bias, screens for both PE and DVT, includes an assessment of VTE symptoms, and follows travelers for a sufficient time after arrival; evaluation of the clinical importance of asymptomatic DVT after prolonged travel; further investigation of the additional risk conferred by air travel on travelers with 1 or more VTE risk factors, including whether seating location is a risk factor; derivation and validation of a decision rule for VTE prophylaxis for air travel; further investigation of the VTE risk of other travel modalities; and further investigation of the effectiveness of other preventive measures including LMWH and unfractionated heparin.

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APPENDIX

Description of methodologic standards

Standard 1: Adequate description of the subject assembly process. (a) Methods for patient selection should be described in enough detail that the study could be replicated with a similar group of patients. (b) The number of eligible but not enrolled subjects, as well as any reasons for exclusion, should also be reported.

Standard 2: Adequate description of subjects. Summary demographic information (gender, age), as well as type and duration of travel, should be reported.

Standard 3: Equality of comparison groups. RCT should not only employ random allocation to treatment modality but also demonstrate that the treatment groups were similar in terms of demographics (age and sex) and duration of travel. In cohort studies with control groups, both demographic characteristics and VTE risk should be similar between groups; if not, statistical adjustment for differences should have been performed. In case-control studies, the cases and controls should be matched for age, sex, and at least 1 VTE risk factor; otherwise, statistical adjustment should take these variables into account. With the exception of travel history, cases and controls should be enrolled using the same selection criteria.

Standard 4: Adequate reporting of subject follow-up. The number of patients unavailable for outcome or exposure ascertainment should be reported, as well as the reasons why this information was not available.

Standard 5: Adequate description of treatment. Treatment should be described in enough detail so that other subjects could be treated in a similar fashion.

Standard 6: Unbiased surveillance for adverse outcomes and determination of exposure. For cohort and RCT studies, either objective VTE test results or systematic survey for travel-related VTE symptoms should be reported. For case-control studies, travel exposure should be ascertained in the same fashion for cases and controls, including use of measures that would limit recall bias.

Standard 7: Adequate VTE diagnostic evaluation. Any diagnoses of DVT or PE should be based on objective test results.

Standard 8: Analysis that takes type and duration of travel into account. VTE risk should be adjusted by travel type and duration.

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