



OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE
Evidence-Based Practice Summary
VTE Risk and Prophylaxis in Long-distance Travelers

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BACKGROUND AND RATIONALE

Venous thromboembolism (VTE) is a common, lethal disease that affects hospitalized and non-hospitalized patients. VTE is frequently reoccurring and often overlooked. This condition can be asymptomatic and may result in long-term complications, which include both pulmonary hypertension and post-thrombotic syndrome. Deep vein thrombosis (DVT) and pulmonary embolism (PE) represent different types of VTE. Patients with VTE, typically have one or more associated risk factors referred to as a hypercoagulable state or thrombophilia. These risk factors are generally classified as either genetic (inherited) or acquired (environmental) and include immobilization or stasis (i.e. sitting for a long time while traveling).¹

Over the past decade, VTE associated with long-distance travel has emerged as an important public health concern. Numerous epidemiologic and case control studies have reported air travel as a risk factor for VTE. These studies set out to determine which populations are at risk and identify preventative measures, which may aid in reducing VTE as a potentially fatal event.¹

This evidence brief seeks to determine whether an increased risk of VTE is associated with longer travel times and whether the use of thromboprophylaxis is effective in decreasing the risk of VTE in travelers.

ASK THE QUESTION

In adults traveling by plane, train or automobile, does the risk of thrombosis increase with the length of travel?
In adults traveling by plane, train or automobile, does the use of thromboprophylaxis decrease the risk of VTE?

SEARCH FOR EVIDENCE

Databases: Ovid MEDLINE



Filters/limits: Comparative studies, controlled clinical trials, evaluation studies, guidelines, meta-analysis, RCTs, or systematic reviews in English language published since 2008.

See Appendix C for full search strategy.

CRITICALLY ANALYZE THE EVIDENCE

The literature search resulted in over 500 articles relating to VTE risk and prophylaxis in long distance travelers. Of the 500 studies, fifteen met the inclusion criteria for the brief. The analysis in this brief includes four systematic reviews and six non-randomized studies evaluating the association of VTE risk with travel length and two systematic reviews and three non-randomized studies evaluating thromboprophylaxis in long distance travelers.

LENGTH OF TRAVEL & INCREASED RISK OF VTE

Systematic Reviews:

The first systematic review (Chandra, 2009) aimed to estimate the risk for travel related VTE, determine whether a dose-response relationship exists, and identify reasons for the contradictory results of previous studies. The systematic review included 14 studies, these studies included over 4000 cases of VTE, 11 of these studies included patients traveling three or more hours. Three of the 11 studies had no travel length limitation or did not report travel time. Chandra (2009) found that the overall pooled relative risk for VTE in travelers was 2.0 (95% CI, 1.5 to 2.7). With regard to the dose-response, the authors found an 18% higher risk for VTE for each two-hour increase in duration of travel by any mode (P = 0.010) and a 26% higher risk for every two-hours of air travel (P = 0.005).

The second systematic review (Kuipers, 2007) analyzed 55 epidemiologic and pathophysiologic studies and found a correlational relationship between duration of travel time and VTE. Three of the case-controlled studies evaluated flight times over 8 hours; the resulting pooled OR was 3.9 (95% CI 1.4-10.7). There was high heterogeneity across the observational studies. However, two of the studies found the absolute risk for a symptomatic event within four weeks of flights greater than 4 hours as 1/4600 flights. The risk of severe PE occurring immediately after air travel increases with duration of travel, up to 4.8 per 1 million persons in flights greater than 12 hours.

The third systematic review (Philbrick, 2007) reviewed the methodologic strength of the literature, estimated the risk of travel-related VTE, evaluated the efficacy of preventive treatments, and developed evidence-based recommendations for practice. This review included 16 studies. For the outcome of risk of travel, the authors found that the 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.



The fourth systematic review (Trujillo-Santos, 2008) completed both a systematic review and meta-analysis of case-control studies to analyze the association between long travel times and the development of VTE; this review included nine different studies. Trujillo-Santos (2008) found the overall relationship between the antecedent of long travel time and subsequent VTE varied from OR = 1.1 to OR = 4.0 and was found to be significant in four studies. Of the two meta-analyses completed, one analysis focused on travel by plane, finding the relationship between long travel time was not significant (OR = 1.21; CI 95%, 0.95-1.55). The second meta-analysis focused on all types of transport, with a slightly higher clinical significance (OR = 1.46; CI 95%, 1.24-1.72).

Non-Randomized Studies

The first non-randomized study, (Beam, 2009) is a prospective cohort study that evaluated the overall risk of immobility in patients presenting to the ED who were evaluated for pulmonary embolism and included almost 8,000 patients. The authors found that the risk of VTE was substantially increased by presence of limb, whole-body, or neurologic immobility, but did not find risk associated by travel greater than eight hours (OR 1.19; 95% CI 0.85 to 1.67).

The second non-randomized study (Kuipers, 2014) was a prospective cohort study of 2,630 male pilots that assessed their risk of VTE. Kuipers (2014) reported six VTEs, yielding an incidence rate of 0.3 per 1000 person years and found that the incidence rate did not increase with number of flight hours per year or vary by pilot rank.

The third non-randomized study (MacCallum, 2011) was a case-controlled study including 550 cases with patients who were 18 and older, on anti-coagulants and had a confirmed VTE and 1,971 controls which aimed to quantify the risks of VTE associated with both long-haul air travel and cumulative flying time. The secondary aim was to compare the risks associated with air travel with those of other established risk factors for VTE. The authors found cumulative flying time greater than 12 hours in the previous 4 week period was associated with a threefold increased risk for VTE (OR 2.75, 95% CI, 1.44-5.28). Those who flew less than four hours in a single leg in the previous four week period had twice the risk of VTE (OR 2.20, 95% CI, 1.29-3.73).

The fourth non-randomized study (Pietrzyk, 2016) was a retrospective chart analysis that reported the occurrence of symptomatic DVT cases in cruise ship passengers after long haul flights. In the analyzed period, the study reported 0.15% of patients (three out of 2,007) were suspected of DVT after a flight time greater than 8 hours.

The fifth non-randomized study (Schreijer, 2009) was a case-control study with over 11,000 participants. This study evaluated the effect of flight-related behavior with the risk of venous thrombosis after air travel. The authors found that passengers sitting in window seats compared to



passengers sitting in aisle seats had a twofold increased risk of VTE (OR 2.2; 95% CI: 1.1-4.4), particularly in those who were obese (OR 6.1; 95% CI: 0.5-76.2). The studies show a slightly increased risk in passengers with anxiety (OR 2.5; 95% CI: 0.9-7.0) or who were sleeping (OR 1.5; 95% CI: 0.7-3.1). Alcohol consumption did not affect the risk (OR 1.1; 95% CI: 0.5-2.4). Passengers flying business class did have a lower risk (OR 0.7; 95% CI: 0.2-1.8).

The sixth non-randomized study (Lehmann, 2009) was a retrospective chart review of 257 patients that followed-up with all patients who were admitted between 1997 and 2006 at a hospital close to Frankfurt airport whom presented with economy class syndrome (ECS). The report concluded, in general, ECS was a rare event (one event per 5 million passengers), whereas long-haul flights over 5000 km., lead to a 17-fold risk increase compared when compared to shorter flights.

Overall, there is low quality evidence to indicate an increased risk of VTE when flying over 4 hours.

THROMBOPROPHYLAXIS & DECREASED RISK OF VTE:

Systematic Reviews:

The first systematic review (Clarke, 2006) included 10 studies and assessed the effects of wearing compression stockings versus not wearing compression stockings among people travelling on flights that were at minimum four hours long. Clarke (2006) found that studies which compared passengers wearing compression stockings on both legs vs. not wearing compression stockings (n=2821), 50 of the participants had a symptomless DVT; three wore compression stockings, 47 did not (OR 0.10, 95% CI 0.04 to 0.25, P < 0.00001). Due to a high risk of bias in the included studies, the second systematic review (Kuipers 2007) did not include an evaluation.

Non-Randomized Studies:

The first non-randomized study (Hitos, 2007) is a prospective cohort study examining factors affecting popliteal venous blood flow in 21 participants to determine the most effective exercise regimen for preventing venous stasis. The authors found that blood volume flow in the popliteal vein was reduced by almost 40% when participants were seated with no mobility and approximately twofold when participants sat motionless without feet touching the floor. "Foot exercises against increased resistance" positively enhanced volume flow (P < 0.0001).

The second non-randomized study (Ringwald 2014) is a cross sectional study that sought to identify complication predictors related to increased or decreased travel activity and complication rates during for patients on oral anticoagulation therapy (OAT). This study included 997 participants and the authors found that predictors for hemorrhages or thromboembolic complications while travelling were a result of former thromboembolic



complications (OR 2.77; 95%-CI 1.39-5.54, P = 0.004), former bleedings (OR 3.52; 95%-CI 2.02-6.11, P < 0.001) and Patient Self-Monitoring (PSM) (OR 3.60; 95%-CI 1.26-10.28, P = 0.017). A higher anticoagulation intensity (INR target value 2: 3) was not a significant predictor.

The third study (Tsoan 2010) is a prospective cohort study that included 26,172 consecutive patients with symptomatic, acute DVT PE, confirmed by objective clinical tests. This study analyzed the clinical characteristics and VTE risk factors in patients with VTE after long travel times, specifically, after long travel times by plane. Tsoan (2010) found that travelers with VTE used LMWH prophylaxis significantly less frequent than other patients in the registry (2.4% vs. 13%; OR 0.2; 95%CI: 0.1-0.3).

Overall, there is low quality evidence to indicate that thromboprophylaxis decreases the risk of VTE in travelers.

Appraisal Tables:

PICO Question: In adults traveling by plane, train or automobile, does the use of thromboprophylaxis decrease the risk of DVT/VTE?					
Outcome: Decreased risk of VTE					
Overall Quality Rating for Thromboprophylaxis and Decreased Risk of VTE					
Low Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome) <input type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)		Increase Quality Rating if: <input type="checkbox"/> Large effect <input type="checkbox"/> Dose-response gradient <input type="checkbox"/> Plausible confounders or other biases increase certainty of effect		Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very Low	
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Journal: <i>Cochrane Database of Systematic Reviews</i> Author: Clarke, M., et al. Year Published: 2006 Location: UK	Aim: To assess the effects of wearing compression stockings versus not wearing them among people travelling on flights lasting at least four hours.	Inclusion Criteria: Randomized trials of compression stockings versus no stockings in passengers on flights lasting at least four hours. Trials in which passengers wore a	Intervention: Ten randomized trials (n = 2856) were included; nine (n = 2821) compared wearing stockings on both legs versus not wearing them, and one (n = 35)	Results: Of the 9 trials, 7 included people judged to be at low or medium risk (n = 1548) and 2 included high risk participants (n = 1273). All flights lasted at least seven hours. 50 participants with follow-up data available in the trials of wearing stockings on both legs had a symptomless DVT; three wore stockings, 47 did not (odds ratio 0.10,	Study Limitations: <input checked="" type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive



	<p>Study Type: systematic review</p> <p>Size: 10 studies,</p>	<p>stocking on one leg but not the other, or those comparing stockings and another intervention were also eligible.</p>	<p>compared wearing a stocking on one leg for the outbound flight and on the other leg on the return flight.</p>	<p>95% confidence interval 0.04 to 0.25, P < 0.00001). There were no symptomless DVTs in three trials. No deaths, pulmonary emboli or symptomatic DVTs were reported. Wearing stockings had a significant impact in reducing edema (based on six trials). No significant adverse effects were reported.</p>	<p><input type="checkbox"/> Quality of the studies was not appraised or studies were of low quality</p> <p><input type="checkbox"/> Methods and/or results were inconsistent across studies</p>
<p>Journal: <i>Journal of Thrombosis & Haemostasis</i> Author: <i>Hitos, K., et al.</i> Year Published: 2007 Location: Australia</p>	<p>Aim: To examine factors affecting popliteal venous blood flow in order to determine the most effective exercise regimen to prevent venous stasis.</p> <p>Study Type: prospective cohort</p> <p>Size: 21</p>	<p>Inclusion Criteria: Study subjects included 21 healthy volunteers (21 limbs) from the Redeemer Baptist School, Sydney, Australia. Participants had no history of thrombosis, leg trauma, swelling, surgery, lymphedema, venous reflux or outflow obstruction.</p>	<p>Intervention: subjects were randomly assigned to various activities over a 9-week period. Subjects remained seated throughout the investigation and ultrasound examinations were performed. Baseline popliteal vein blood flow velocity, cross-sectional area and volume flow in subjects sitting motionless were assessed in the first 3 weeks. The remaining 6 weeks involved subjects performing airline-recommended activities, foot exercises, foot exercises against moderate resistance and foot exercises against increased resistance in order to determine the most beneficial method for enhancing popliteal venous flow. Sitting with feet not touching the floor and the effect of sleeping were also assessed.</p>	<p>Results: Blood volume flow in the popliteal vein was reduced by almost 40% with immobility of seated subjects and by almost 2-fold when sitting motionless with feet not touching the floor. Foot exercises against increased resistance positively enhanced volume flow (P < 0.0001).</p>	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Non-Randomized</p> <p><input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria</p> <p><input type="checkbox"/> Flawed measurement of both exposure and outcome</p> <p><input type="checkbox"/> Failure to adequately control confounding</p> <p><input checked="" type="checkbox"/> Incomplete or inadequately short follow-up</p> <p><input type="checkbox"/> Differences in important prognostic factors at baseline</p>



<p>Journal: <i>Journal of Internal Medicine</i> Author: Kuipers, S., et al Year Published: 2007 Location: Netherlands</p>	<p>Aim: To systematically review the epidemiologic and pathophysiologic studies about the association between travel and VTE.</p> <p>Study Type: Systematic Review</p> <p>Size: 11 RCTs</p>	<p>Inclusion Criteria: studies of air travel with VTE</p>	<p>Intervention: RCTs (n=11): assessed the effect of various prophylactic measures on the risk of VTE after air travel</p>	<p>Results: RCTs: Due to high risk of bias among studies the results were not discussed in the SR</p>	<p>Study Limitations: <input type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies</p>
<p>Journal: <i>Travel Medicine & Infectious Disease</i> Author: Ringwald, J., et al. Year Published: 2014 Location: Germany</p>	<p>Aim: To identify predictors for more or less travel activity and for complication rates during journeys for patients on oral anticoagulation therapy (OAT).</p> <p>Study Type: Cross Sectional Study</p> <p>Size: 997</p>	<p>Inclusion Criteria: patients between October 2009 and October 2010, who have been on long-term OAT for at least two years.</p> <p>Exclusion Criteria: transient OAT or severe underlying diseases (such as severe stroke, dementia) leading to a physical or mental disability to travel.</p>	<p>Intervention: A standardized questionnaire with 27 items was sent to patients. disability to travel. Demographic data (age, sex, education, current profession, marital status), indication for OAT, INR target range and type of monitoring (PSM or control by physician), travel habits before/after the onset of OAT, especially frequency, duration and destination of journeys were recorded. Thromboembolic complications and hemorrhagic episodes in the domestic environment and during travel were of special interest.</p>	<p>Results: 43.4% changed travel habits since onset of OAT with 24.9% and 18.5% reporting decreased or increased travel activity, respectively.</p> <p>Predictors for hemorrhages or thromboembolic complications while travelling were former thromboembolic complications (OR 2.77; 95%-CI 1.39-5.54, p = 0.004), former bleedings (OR 3.52; 95%-CI 2.02-6.11, p < 0.001) and PSM (OR 3.60; 95%-CI 1.26-10.28, p = 0.017). A higher anticoagulation intensity (INR target value 2: 3) was not a significant predictor.</p>	<p>Study Limitations: <input type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline</p>
<p>Journal: <i>Thrombosis Research</i> Author: Tsoran, I., et al. Year Published: 2010</p>	<p>Aim: To analyzed the clinical characteristics and VTE risk factors in patients with VTE</p>	<p>Inclusion Criteria: Consecutive patients with symptomatic, acute deep venous thrombosis</p>	<p>Intervention: The parameters recorded by the registry comprise details of each patient's baseline</p>	<p>Results: Travelers used LMWH prophylaxis significantly less frequently than other patients in the registry (2.4% vs. 13%; OR 0.2; 95%CI: 0.1-0.3)</p>	<p>Study Limitations: <input type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria</p>

<p>Location: Israel and Spain</p>	<p>after long traveling and particularly, after traveling by air.</p> <p>Study Type: Prospective cohort study. RIETE (Registro Informatizado de Enfermedad TromboEmbolica) study</p> <p>Size: 26172 consecutive patients with symptomatic, acute VTE were enrolled in the RIETE.</p>	<p>(DVT) or pulmonary embolism (PE), confirmed by objective tests</p> <p>Exclusion Criteria: If patients are currently participating in a therapeutic clinical trial or if they will not be available for a 3-month follow-up</p>	<p>characteristics; risk factors for VTE, including 6- hour and longer traveling during the last three weeks and the mode of traveling; hormone use; underlying diseases; clinical characteristics of the VTE event; usage of LMW prophylaxis. Patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention.</p>	<p>Table 3 Risk factors according to the mode of travel.</p> <table border="1"> <thead> <tr> <th></th> <th>Traveling by air</th> <th>Traveling by other means of transportation</th> <th>OR (95%CI)</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>Patient N</td> <td>111</td> <td>389</td> <td></td> <td></td> </tr> <tr> <td colspan="5">Clinical characteristics</td> </tr> <tr> <td>Mean age (y ± SD)</td> <td>51 ± 18</td> <td>56 ± 16</td> <td>-</td> <td>0.002</td> </tr> <tr> <td>Age >75 y</td> <td>12 (11%)</td> <td>48 (12%)</td> <td>0.7 (0.4-1.7)</td> <td>NS</td> </tr> <tr> <td>BMI</td> <td>27 ± 4.9</td> <td>29 ± 5.2</td> <td>-</td> <td>0.004</td> </tr> <tr> <td colspan="5">Risk Factors for VTE</td> </tr> <tr> <td>Previous VTE</td> <td>20 (18%)</td> <td>81 (21%)</td> <td>0.8 (0.5-1.4)</td> <td>NS</td> </tr> <tr> <td>Cancer</td> <td>10 (9.0%)</td> <td>38 (9.8%)</td> <td>0.9 (0.4-1.9)</td> <td>NS</td> </tr> <tr> <td>Immobilization due to neurologic disease</td> <td>0 (0%)</td> <td>0 (0%)</td> <td>-</td> <td>-</td> </tr> <tr> <td>Recent surgery</td> <td>2 (1.8%)</td> <td>13 (3.3%)</td> <td>0.5 (0.1-2.4)</td> <td>NS</td> </tr> <tr> <td>Hormone use</td> <td>14 (13%)</td> <td>29 (7.6%)</td> <td>1.8 (0.9-3.5)</td> <td>NS</td> </tr> <tr> <td>Pregnancy</td> <td>1 (3.0%)</td> <td>2 (2.9%)</td> <td>1.0 (0.1-12)</td> <td>NS</td> </tr> <tr> <td>Positive thrombophilia test</td> <td>21 (19%)</td> <td>65 (18%)</td> <td>1.2 (0.7-2.0)</td> <td>NS</td> </tr> <tr> <td colspan="5">Underlying diseases</td> </tr> <tr> <td>CHF</td> <td>4 (3.6%)</td> <td>4 (1.0%)</td> <td>3.6 (0.9-15)</td> <td>NS</td> </tr> <tr> <td>Chronic lung disease</td> <td>8 (7.2%)</td> <td>18 (4.6%)</td> <td>1.6 (0.7-3.8)</td> <td>NS</td> </tr> <tr> <td>Other underlying disease</td> <td>32 (29%)</td> <td>160 (41%)</td> <td>0.6 (0.4-0.9)</td> <td>0.019</td> </tr> <tr> <td>Abnormal creatinine level</td> <td>5 (4.5%)</td> <td>31 (8.0%)</td> <td>0.5 (0.2-1.4)</td> <td>NS</td> </tr> <tr> <td>Use of LMWH prophylaxis</td> <td>1 (0.9%)</td> <td>5 (1.3%)</td> <td>0.7 (0.1-6.0)</td> <td>NS</td> </tr> </tbody> </table>		Traveling by air	Traveling by other means of transportation	OR (95%CI)	P value	Patient N	111	389			Clinical characteristics					Mean age (y ± SD)	51 ± 18	56 ± 16	-	0.002	Age >75 y	12 (11%)	48 (12%)	0.7 (0.4-1.7)	NS	BMI	27 ± 4.9	29 ± 5.2	-	0.004	Risk Factors for VTE					Previous VTE	20 (18%)	81 (21%)	0.8 (0.5-1.4)	NS	Cancer	10 (9.0%)	38 (9.8%)	0.9 (0.4-1.9)	NS	Immobilization due to neurologic disease	0 (0%)	0 (0%)	-	-	Recent surgery	2 (1.8%)	13 (3.3%)	0.5 (0.1-2.4)	NS	Hormone use	14 (13%)	29 (7.6%)	1.8 (0.9-3.5)	NS	Pregnancy	1 (3.0%)	2 (2.9%)	1.0 (0.1-12)	NS	Positive thrombophilia test	21 (19%)	65 (18%)	1.2 (0.7-2.0)	NS	Underlying diseases					CHF	4 (3.6%)	4 (1.0%)	3.6 (0.9-15)	NS	Chronic lung disease	8 (7.2%)	18 (4.6%)	1.6 (0.7-3.8)	NS	Other underlying disease	32 (29%)	160 (41%)	0.6 (0.4-0.9)	0.019	Abnormal creatinine level	5 (4.5%)	31 (8.0%)	0.5 (0.2-1.4)	NS	Use of LMWH prophylaxis	1 (0.9%)	5 (1.3%)	0.7 (0.1-6.0)	NS	<p><input type="checkbox"/> Flawed measurement of both exposure and outcome</p> <p><input type="checkbox"/> Failure to adequately control confounding</p> <p><input type="checkbox"/> Incomplete or inadequately short follow-up</p> <p><input checked="" type="checkbox"/> Differences in important prognostic factors at baseline</p>
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<p>Journal: <i>Journal of General Internal Medicine</i> Author: Philbrick, J. T., et al</p> <p>Year Published: 2007 Location: University of Virginia</p>	<p>Aim: To review the methodologic strength of the literature, estimate the risk of travel-related VTE, evaluate the efficacy of preventive treatments, and de-velop evidence-based recommendations for practice.</p> <p>Study Type: Systematic Review</p> <p>Size: 25 studies</p>	<p>Inclusion Criteria: primary data concerning the risk of travel for VTE or tested preventive measures for travel-related VTE.</p>	<p>Intervention: Prevention (9 RCTs)</p>	<p>Results: <i>Prevention:</i> 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.</p>	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Systematic Review</p> <p><input type="checkbox"/> Review did not address focused clinical question</p> <p><input type="checkbox"/> Search was not detailed or exhaustive</p> <p><input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality</p> <p><input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies</p>																																																																																																				

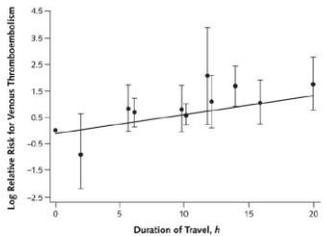
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1. Clarke, M., et al. (2006). "Compression stockings for preventing deep vein thrombosis in airline passengers." Cochrane Database of Systematic Reviews(2): CD004002.
2. Hitos, K., et al. (2007). "Effect of leg exercises on popliteal venous blood flow during prolonged immobility of seated subjects: implications for prevention of travel-related deep vein thrombosis." Journal of Thrombosis & Haemostasis 5(9): 1890-1895.
3. Kuipers, S., et al. (2007). "Travel and venous thrombosis: a systematic review." Journal of internal medicine 262(6): 615-634.
4. Ringwald, J., et al. (2014). "Travel habits and complications in patients treated with vitamin K antagonists: a cross sectional analysis." Travel Medicine & Infectious Disease 12(3): 258-263.



5. Tsoiran, I., et al. (2010). "Prolonged travel and venous thromboembolism findings from the RIETE registry." *Thrombosis Research* 126(4): 287-291.
6. Philbrick, J. T., et al. (2007). "Air travel and venous thromboembolism: a systematic review." *Journal of General Internal Medicine* 22(1): 107-114.

PICO Question: In adults traveling by plane, train or automobile, does the risk of thrombosis increase with the length of travel?					
Outcome: Increased risk of VTE					
Overall Quality Rating for Length of Travel and Increased Risk of VTE					
Low Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome) <input type="checkbox"/> Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) <input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)		Increase Quality Rating if: <input type="checkbox"/> Large effect <input type="checkbox"/> Dose-response gradient <input type="checkbox"/> Plausible confounders or other biases increase certainty of effect		Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very Low	
Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Journal: <i>Annals of Emergency Medicine</i> Author: Beam, D. M., et al. Year Published: 2009 Location: United States, 12 different medical centers	Aim: To evaluate the overall risk of immobility in patients presenting to the ED who are evaluated for pulmonary embolism. Study Type: Prospective cohort study Size: 7,940 patients	Inclusion Criteria: Patients presenting to the ED in 12 hospitals in the United States. Eligibility for enrollment required an order for an objective diagnostic test for pulmonary embolism, written by or under the supervision of a board-certified emergency physician.	Intervention/ Methods: In patients suspected of PE (n=7940), the clinicians recorded clinical features of each patient in the ED by using a Web-based data form. The form required one of 6 types of immobility: no immobility, general or whole-body immobility greater than 48 hours, limb (orthopedic) immobility, travel greater than 8 hours causing immobility within the previous 7 days, neurologic paralysis, or other immobility not listed above. Patients were followed for 45 days for outcome of venous thromboembolism, which required positive imaging results and clinical plan to treat.	Results: 545 of 7,940 (6.9%) were diagnosed with venous thromboembolism (354 pulmonary embolism, 72 deep venous thrombosis, 119 pulmonary embolism and deep venous thrombosis). Risk of venous thromboembolism varied, depending on immobility type: limb (OR=2.24; 95% confidence interval [CI] 1.40 to 3.60), general (OR=1.76; 95% CI 1.26 to 2.44), other (OR=1.97; 95% CI 1.25 to 3.09), neurologic (OR=2.23; 95% CI 1.01 to 4.92), and travel (OR=1.19; 95% CI 0.85 to 1.67). Risk of VTE was substantially increased by presence of limb, whole-body, or neurologic immobility but not by travel greater than 8 hours.	Study Limitations: <input checked="" type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline

				<p>Table 2. Breakdown of differing interventions associated with venous thromboembolism +/-</p> <table border="1"> <thead> <tr> <th>Category</th> <th>VTE (+)</th> <th>VTE (-)</th> <th>%</th> <th>PE (+)</th> <th>%</th> <th>DVT (+)</th> <th>%</th> <th>PE (+), DVT (-)</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>No intervention</td> <td>286</td> <td>6,127</td> <td>4.7</td> <td>228</td> <td>3.7</td> <td>49</td> <td>1.1</td> <td>72</td> <td>1.3</td> </tr> <tr> <td>Genital</td> <td>36</td> <td>223</td> <td>14</td> <td>20</td> <td>9</td> <td>2</td> <td>10</td> <td>4</td> <td>4</td> </tr> <tr> <td>Legs</td> <td>27</td> <td>122</td> <td>10</td> <td>11</td> <td>9</td> <td>2</td> <td>7</td> <td>4</td> <td>4</td> </tr> <tr> <td>Neck</td> <td>0</td> <td>580</td> <td>13</td> <td>20</td> <td>11</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Neurologic</td> <td>36</td> <td>150</td> <td>12</td> <td>15</td> <td>7</td> <td>0</td> <td>4</td> <td>2</td> <td>3</td> </tr> </tbody> </table> <p>VTE, Venous thromboembolism; PE, pulmonary embolism; DVT, deep-vein thrombosis.</p> <p>Table 3. Relative risk ratios* of the patients with different categories of mobility developing venous thromboembolism.</p> <table border="1"> <thead> <tr> <th>Category</th> <th>VTE (+)</th> <th>PE (+)</th> <th>DVT (+)</th> <th>PE (+), DVT (-)</th> </tr> </thead> <tbody> <tr> <td>Genital</td> <td>2.05 (1.39-3.20)</td> <td>1.87 (1.28-2.72)</td> <td>0.40 (0.24-0.68)</td> <td>0.70 (0.49-1.00)</td> </tr> <tr> <td>Legs</td> <td>3.07 (2.14-4.39)</td> <td>2.66 (1.85-3.92)</td> <td>0.40 (0.24-0.68)</td> <td>0.58 (0.44-0.80)</td> </tr> <tr> <td>Neck</td> <td>1.23 (0.83-1.84)</td> <td>0.29 (0.20-0.42)</td> <td>0.00 (0.00-0.23)</td> <td>0.26 (0.15-0.52)</td> </tr> <tr> <td>Neurologic</td> <td>2.50 (1.34-4.65)</td> <td>1.97 (0.99-4.25)</td> <td>0.00 (NA)</td> <td>0.72 (0.23-2.30)</td> </tr> <tr> <td>Other</td> <td>2.42 (1.68-3.50)</td> <td>1.28 (0.77-2.20)</td> <td>0.00 (0.00-0.64)</td> <td>0.62 (0.22-1.70)</td> </tr> </tbody> </table> <p>*Heterogeneity: I-squared=0.00; tau-squared=0.00; P=0.99; I-squared=0.00; tau-squared=0.00; P=0.99.</p>	Category	VTE (+)	VTE (-)	%	PE (+)	%	DVT (+)	%	PE (+), DVT (-)	%	No intervention	286	6,127	4.7	228	3.7	49	1.1	72	1.3	Genital	36	223	14	20	9	2	10	4	4	Legs	27	122	10	11	9	2	7	4	4	Neck	0	580	13	20	11	0	0	0	0	Neurologic	36	150	12	15	7	0	4	2	3	Category	VTE (+)	PE (+)	DVT (+)	PE (+), DVT (-)	Genital	2.05 (1.39-3.20)	1.87 (1.28-2.72)	0.40 (0.24-0.68)	0.70 (0.49-1.00)	Legs	3.07 (2.14-4.39)	2.66 (1.85-3.92)	0.40 (0.24-0.68)	0.58 (0.44-0.80)	Neck	1.23 (0.83-1.84)	0.29 (0.20-0.42)	0.00 (0.00-0.23)	0.26 (0.15-0.52)	Neurologic	2.50 (1.34-4.65)	1.97 (0.99-4.25)	0.00 (NA)	0.72 (0.23-2.30)	Other	2.42 (1.68-3.50)	1.28 (0.77-2.20)	0.00 (0.00-0.64)	0.62 (0.22-1.70)	
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<p>Journal: <i>Annals of Internal Medicine</i> Author: Chandra, D., et al Year Published: 2009 Location: Harvard School of Public Health</p>	<p>Aim: To estimate the risk for VTE in travelers, determine whether a dose-response relationship exists, and identify reasons for the contradictory results of previous studies.</p> <p>Study Type: Systematic Review with meta-analysis</p> <p>Size: 14 studies (11 case-control, 2 cohort, and 1 case-crossover) met inclusion criteria, including 4055 cases of VTE.</p>	<p>Inclusion Criteria: Reports were selected if they investigated the association between travel and VTE for persons who used any mode of transportation and if non-traveling persons were included for comparison.</p> <p>Exclusion Criteria: Studies were excluded if they only evaluated treatments for YTE, rather than travel as a risk factor for YTE; if YTE was diagnosed by less rigorous criteria (such as by using only administrative codes in outpatients); or if no comparison group of non-travelers was included (which would preclude estimation of relative risks [RRs] associated with travel).</p>	<p>Intervention: Patients traveling at least 3 hours (11 studies) with 3 studies with no limitation or not reporting travel time</p> <p>Comparator: non-travelers</p>	<p>Results: the overall pooled relative risk for VTE in travelers was 2.0 (95% CI, 1.5 to 2.7). Significant heterogeneity was present because of the method for selecting control participants (P = 0.008). When the studies that used referred control participants were excluded, the pooled relative risk for VTE in travelers was 2.8 (CI, 2.2 to 3.7), without significant heterogeneity. A dose-response relationship was identified, with an 18% higher risk for VTE for each 2-hour increase in duration of travel by any mode (P = 0.010) and a 26% higher risk for every 2 hours of air travel (P = 0.005).</p> <div data-bbox="1144 852 1470 1161"> <p>Figure 3. Relationship between duration of travel and relative risk for venous thromboembolism, as reported by 4 included studies.</p>  </div>	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies 																																																																																										
<p>Journal: <i>Journal of Internal Medicine</i> Author: Kuipers, S., et al Year Published: 2007 Location: Netherlands</p>	<p>Aim: To systematically review the epidemiologic and pathophysiologic studies about the association between travel and VTE.</p>	<p>Inclusion Criteria: studies of air travel with VTE</p>	<p>Intervention: <i>Case-control studies</i> (n=10): travel frequency of cases of symptomatic VTE compared to control population without</p> <p><i>Observational follow-up studies</i> (n=14): travelers who were screened for VTE most studies did not have a control population</p>	<p>Results: <i>Case-control studies:</i> The pooled OR of all studies together was 1.7 (95% CI 1.4-2.1) Three studies looked at flights longer than 8 hr and the pooled OR was 3.9 (95% CI 1.4-10.7)</p> <p><i>Observational follow-up study:</i> high heterogeneity amongst studies, However, two studies found the absolute risk of a symptomatic event within 4 weeks of</p>	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Systematic Review <input type="checkbox"/> Review did not address focused clinical question <input type="checkbox"/> Search was not detailed or exhaustive <input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality <input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies 																																																																																										

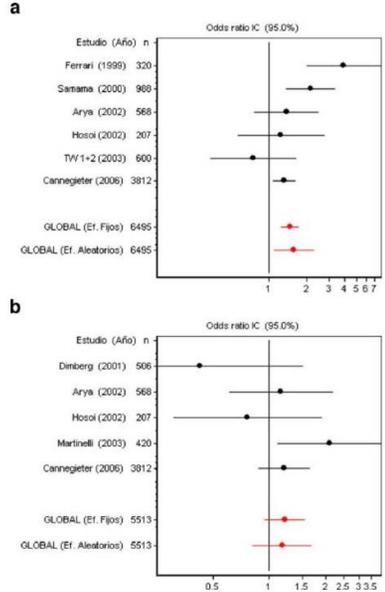
	<p>Study Type: Systematic Review</p> <p>Size: 55 studies</p>		<p>RCTs (n=11): assessed the effect of various prophylactic measures on the risk of VTE after air travel</p> <p>Pathophysiological studies (n=14): Studies looked at what factors and mechanisms increase the risk of VTE after air travel.</p>	<p>flights longer than 4 h as 1/4600 flights. The risk of severe PE occurring immediately after air travel increases with duration of travel, up to 4.8 per million in flights longer than 12 h.</p> <p>RCTs: Due to high risk of bias among studies the results were not discussed in the SR</p> <p>Pathophysiological studies: Variability among the included studies. The mechanism responsible for the increased risk of VT after (air) travel has insufficiently been studied to draw solid conclusions, but one controlled-study showed evidence for an additional mechanism to immobilization that could lead to coagulation activation after air travel.</p>																																					
<p>Journal: <i>Journal of Thrombosis & Haemostasis</i> Author: Kuipers, S., et al. Year Published: 2014 Location: Netherlands</p>	<p>Aim: To assess the risk of VTE in a cohort of Dutch airline pilots.</p> <p>Study Type: Prospective cohort study</p> <p>Size: 2630 male pilots</p>	<p>Inclusion Criteria: All pilots who were members of the Dutch pilot union between 1993-2003</p>	<p>Intervention: Airline pilots who had been active members of the Dutch aviation society (VNV) were questioned for the occurrence of VTE, presence of risk factors for VTE and number of flight hours per year and rank.</p> <p>Comparator: Incidence rates among pilots were compared with those of the general Dutch population and with a population of frequently flying employees of multinational organizations.</p>	<p>Results: Six VTEs were reported, yielding an incidence rate of 0.3 per 1000 py. The standardized morbidity ratio, comparing these pilots with the general Dutch population adjusted for age, was 0.8. Compared with the international employee cohort, the standardized morbidity ratio was 0.7 when all employees were included and 0.6 when only the frequently travelling employees were included. The incidence rate did not increase with number of flight hours per year and did not clearly vary by rank.</p> <p>Table 3 Incidence rates per number of flight-hours per year and for different ranks</p> <table border="1" data-bbox="1129 1166 1541 1344"> <thead> <tr> <th></th> <th>Person-years</th> <th>Cases</th> <th>IR* (CI95)</th> </tr> </thead> <tbody> <tr> <td>Flight-hours per year</td> <td></td> <td></td> <td></td> </tr> <tr> <td>0-300</td> <td>5856</td> <td>1</td> <td>0.2 (0-0.7)</td> </tr> <tr> <td>300-600</td> <td>6526</td> <td>5</td> <td>0.8 (0.2-1.6)</td> </tr> <tr> <td>> 600</td> <td>3912</td> <td>0</td> <td>0 (0-0.3)</td> </tr> <tr> <td>Rank</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Captain</td> <td>9462</td> <td>3</td> <td>0.3 (0.1-0.8)</td> </tr> <tr> <td>First officer</td> <td>9306</td> <td>2</td> <td>0.2 (0.01-0.6)</td> </tr> <tr> <td>Second officer</td> <td>15723</td> <td>1</td> <td>0.7 (0-2.6)</td> </tr> </tbody> </table> <p>*IR: incidence rate per 1000 person-years and corresponding 95% confidence intervals.</p>		Person-years	Cases	IR* (CI95)	Flight-hours per year				0-300	5856	1	0.2 (0-0.7)	300-600	6526	5	0.8 (0.2-1.6)	> 600	3912	0	0 (0-0.3)	Rank				Captain	9462	3	0.3 (0.1-0.8)	First officer	9306	2	0.2 (0.01-0.6)	Second officer	15723	1	0.7 (0-2.6)	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input checked="" type="checkbox"/> Differences in important prognostic factors at baseline
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<p>Journal: <i>British Journal of Haematology</i> Author: MacCallum, P. K., et al Year Published: 2011 Location: UK</p>	<p>Aim: Primary aim of quantifying the risks of VTE associated with both long-haul air travel and cumulative flying time. A secondary aim was to compare the risks associated with air travel with those of other established risk factors for VTE.</p> <p>Study Type: Case-control</p> <p>Size: 550 cases and 1971 controls</p>	<p>Inclusion Criteria: patients over 18 who were on anti-coagulants and a confirmed VTE. Controls were and a sexed matched</p>	<p>Intervention: A pack containing a letter from their general practitioner explaining the study and inviting them to participate, a consent form, a questionnaire and a stamped addressed envelope were sent at the same time to each case and their controls. The questionnaire was identical for cases and controls and requested information about basic demographic characteristics, past history of VTE, air travel within the past 2 years (including dates, departure from, destination, length of stay and return route) and surgery within the past 2 years (dates, type of operation, duration of inpatient stay).</p> <p>Surgery was included as a major risk factor for VTE that would probably be recalled in a similar manner to air travel by participants and be useful for comparison. It was categorized based on the questionnaire responses into low, moderate and high risk groups for VTE.</p>	<p>Results: Compared to not flying, cumulative flying time >12 h within the previous 4 weeks was associated with a threefold increase in the risk of VTE [odds ratio (OR) 2.75, 95% confidence interval (CI), 1.44-5.28]. Those who had flown >4 h in a single leg in the previous 4 weeks had twice the risk of VTE (OR 2.20, 95% CI, 1.29-3.73). These risks were no longer evident by 12 weeks and were similar to those of day-case or minor surgery (OR 5.35, 95% CI, 2.15-13.33).</p>	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Non-Randomized</p> <p><input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria</p> <p><input type="checkbox"/> Flawed measurement of both exposure and outcome</p> <p><input type="checkbox"/> Failure to adequately control confounding</p> <p><input type="checkbox"/> Incomplete or inadequately short follow-up</p> <p><input checked="" type="checkbox"/> Differences in important prognostic factors at baseline</p>
<p>Journal: <i>Journal of General Internal Medicine</i> Author: Philbrick, J. T., et al Year Published: 2007 Location: University of Virginia</p>	<p>Aim: 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.</p>	<p>Inclusion Criteria: primary data concerning the risk of travel for VTE or tested preventive measures for travel-related VTE.</p>	<p>Intervention: Risk of travel related VTE (6 case-control studies, 10 cohort studies)</p>	<p>Results: <i>Risk of Travel:</i> 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.</p>	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Systematic Review</p> <p><input type="checkbox"/> Review did not address focused clinical question</p> <p><input type="checkbox"/> Search was not detailed or exhaustive</p> <p><input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality</p> <p><input type="checkbox"/> Methods and/or results were inconsistent across studies</p>

	<p>Study Type: Systematic Review</p> <p>Size: 25 studies</p>			<p>Table 4. Logistic regression model evaluating association of clinical and study methodology factors with VTE</p> <table border="1"> <thead> <tr> <th>Variable</th> <th>OR</th> <th>95% CI</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Screening method</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Usual clinical care</td> <td>1.0*</td> <td></td> <td></td> </tr> <tr> <td>Screening ultrasound</td> <td>390</td> <td>200-761</td> <td><0.0001</td> </tr> <tr> <td>VTE outcomes reported</td> <td></td> <td></td> <td></td> </tr> <tr> <td>PE only</td> <td>1.0</td> <td></td> <td></td> </tr> <tr> <td>DVT only</td> <td>23</td> <td>10-52</td> <td><0.0001</td> </tr> <tr> <td>All VTE (PE and DVT)</td> <td>21</td> <td>16-27</td> <td><0.0001</td> </tr> <tr> <td>Mean travel duration</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Less than 6 h</td> <td>0.011</td> <td>0.0019-0.11</td> <td><0.0001</td> </tr> <tr> <td>6-8 h</td> <td>1.0</td> <td></td> <td></td> </tr> <tr> <td>More than 8 h</td> <td>2.3</td> <td>1.4-3.6</td> <td><0.0001</td> </tr> <tr> <td>Clinical VTE risk[†]</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Lower</td> <td>1.0</td> <td></td> <td></td> </tr> <tr> <td>Higher</td> <td>3.6</td> <td>2.2-5.8</td> <td><0.0001</td> </tr> </tbody> </table>	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	
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<p>Journal: <i>International Maritime Health</i> Author: Pietrzyk, W. S. Year Published: 2016 Location: Poland</p>	<p>Aim: To report the occurrence of symptomatic DVT cases in cruise ship passengers after long haul flights and to discuss applied diagnostic methods.</p> <p>Study Type: Retrospective chart analysis</p> <p>Size: 2,007 cruise ship passengers</p>	<p>Inclusion Criteria: adult patients treated at the Ship's Medical Centre (SMC) on a passenger vessel cruising in the sub-tropical and tropical regions, during the winter seasons of 2013 and 2014, was per-formed. The clinical data of patients who presented with a suspicion of DVT after an air flight which lasted more than 8 h were analyzed.</p> <p>Exclusion Criteria: ship crew members</p>	<p>Intervention: The working diagnosis of DVT was established on the basis of a patient's history and physical examination. The Wells score was used for risk stratification. Additionally an initial B-mode ultrasound examination of the lower extremity venous system, using a portable ultrasound device was performed by ship's doctor at the SMC. In order to assess the state of coagulation in the DVT suspected patients, an INR test using handheld device was performed in the SMC laboratory.</p> <p>Comparator: passengers without DVTs</p>	<p>Results: The study showed 3 (0.15%) patients suspected of DVT of a total number of 2,007 passengers who have completed a flight > 8 h in the analyzed period. The median time from the embarkation to the onset of symptoms was 68.7 h. Based on the Wells DVT score, in 2 (0.1%) patients the probability of DVT was determined to be likely. Both the ultrasound examinations and D-dimer tests were positive. Those patients were diagnosed by shore specialists as DVT. One (0.05%) patient determined as DVT unlikely according to the Wells scale, her INR indicated hypercoagulable state, but Duplex scan as well D-dimer test were negative and DVT suspicion was excluded.</p>	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input checked="" type="checkbox"/> Differences in important prognostic factors at baseline 																																																												
<p>Journal: <i>British Journal of Haematology</i> Author: Schreijer, A. J., et al. Year Published: 2009 Location: Netherlands, MEGA study</p>	<p>Aim: To study the effect of flight-related behavior on the risk of venous thrombosis after air travel.</p> <p>Study Type: Case-control</p> <p>Size: 11,033 participants</p>	<p>Inclusion Criteria: Between March 1999 and September 2004, all consecutive patients with a first episode of venous thrombosis were recruited at six anticoagulation clinics in the Netherlands and included patients aged between 18 and 70 years.</p>	<p>Intervention: All participants received a standardized questionnaire by mail. This questionnaire included, amongst others, questions relating to travel, weight, height, varicose veins and family history of venous thrombosis. The questionnaire was returned by 4637 patients (92%), 2821 partners (95%) and 2789 random control subjects (93%).</p>	<p>Results: From this population, 80 patients with VTE and 108 control subjects were selected who had recently (<8 weeks) travelled for more than 4 h by airplane. Window seating compared to aisle seating increased the risk twofold [odds ratio (OR) 2.2; 95% confidence interval (CI): 1.1-4.4], particularly in those who were obese (OR 6.1; 95% CI: 0.5-76.2). Anxiety (OR 2.5; 95% CI: 0.9-7.0) and sleeping (OR 1.5; 95% CI: 0.7-3.1) may increase the risk slightly. The risk was not affected by alcohol consumption (OR 1.1; 95% CI: 0.5-2.4).</p>	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline 																																																												

		<p>Exclusion Criteria: Patients who were unable to complete a questionnaire due to language or severe psychiatric problems were excluded</p>	<p>For the current analysis, participants who had travelled for more than 4 h by airplane (a long-distance flight) less than 8 weeks prior to the date of venous thrombosis (index date for cases) or the date of filling out the questionnaire (index date for controls) were included.</p> <p>Comparator: Partners of patients were asked to serve as control subjects. From January 2002 until December 2004, an additional control group was recruited using a random digit dialing method.</p>	<p>Flying business class may lower the risk (OR 0.7; 95% CI: 0.2-1.8).</p> <p>Behaviour and Air Travel Related Venous Thrombosis</p> <table border="1"> <thead> <tr> <th></th> <th>No. of patients (n = 80)</th> <th>No. of controls (n = 108)</th> <th>OR (95% CI)</th> <th>Adjusted OR (95% CI)*</th> </tr> </thead> <tbody> <tr> <td>Class</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Economy class (ref)</td> <td>72</td> <td>95</td> <td>1</td> <td>1</td> </tr> <tr> <td>Business/first class</td> <td>7</td> <td>13</td> <td>0.7 (0.3-1.9)</td> <td>0.7 (0.2-1.8)</td> </tr> <tr> <td>Seating</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Aisle seat (ref)</td> <td>34</td> <td>58</td> <td>1</td> <td>1</td> </tr> <tr> <td>Window seat</td> <td>33</td> <td>28</td> <td>2.0 (1.0-3.9)</td> <td>2.2 (1.1-4.4)</td> </tr> <tr> <td>Middle seat</td> <td>12</td> <td>21</td> <td>1.0 (0.4-2.2)</td> <td>1.1 (0.5-2.5)</td> </tr> <tr> <td>Use of alcohol</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No alcohol (ref)</td> <td>51</td> <td>65</td> <td>1</td> <td>1</td> </tr> <tr> <td>1 glass</td> <td>11</td> <td>24</td> <td>0.6 (0.3-1.3)</td> <td>0.5 (0.2-1.2)</td> </tr> <tr> <td>2 or more glasses</td> <td>18</td> <td>19</td> <td>1.2 (0.6-2.5)</td> <td>1.1 (0.5-2.4)</td> </tr> <tr> <td>Anxiety during flight</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No (ref)</td> <td>69</td> <td>101</td> <td>1</td> <td>1</td> </tr> <tr> <td>Yes</td> <td>11</td> <td>7</td> <td>2.3 (0.9-6.2)</td> <td>2.5 (0.9-7.0)</td> </tr> <tr> <td>Sleeping during flight (per hour of sleep)</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No (ref)</td> <td>21</td> <td>35</td> <td>1</td> <td>1</td> </tr> <tr> <td>Yes</td> <td>59</td> <td>73</td> <td>1.3 (0.7-2.6)</td> <td>1.5 (0.7-3.1)</td> </tr> <tr> <td>Sleep medication</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No (ref)</td> <td>71</td> <td>100</td> <td>1</td> <td>1</td> </tr> <tr> <td>Yes</td> <td>8</td> <td>8</td> <td>1.4 (0.5-3.9)</td> <td>1.2 (0.4-3.6)</td> </tr> </tbody> </table> <p>OR, odd ratio; CI, confidence interval; ref, reference group. *Adjusted for age and sex and duration of the flight. Due to missing data, the total amount of subjects do not add up to 188 for class (one missing) and seating (two missing).</p>		No. of patients (n = 80)	No. of controls (n = 108)	OR (95% CI)	Adjusted OR (95% CI)*	Class					Economy class (ref)	72	95	1	1	Business/first class	7	13	0.7 (0.3-1.9)	0.7 (0.2-1.8)	Seating					Aisle seat (ref)	34	58	1	1	Window seat	33	28	2.0 (1.0-3.9)	2.2 (1.1-4.4)	Middle seat	12	21	1.0 (0.4-2.2)	1.1 (0.5-2.5)	Use of alcohol					No alcohol (ref)	51	65	1	1	1 glass	11	24	0.6 (0.3-1.3)	0.5 (0.2-1.2)	2 or more glasses	18	19	1.2 (0.6-2.5)	1.1 (0.5-2.4)	Anxiety during flight					No (ref)	69	101	1	1	Yes	11	7	2.3 (0.9-6.2)	2.5 (0.9-7.0)	Sleeping during flight (per hour of sleep)					No (ref)	21	35	1	1	Yes	59	73	1.3 (0.7-2.6)	1.5 (0.7-3.1)	Sleep medication					No (ref)	71	100	1	1	Yes	8	8	1.4 (0.5-3.9)	1.2 (0.4-3.6)	
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<p>Journal: <i>Annals of Hematology</i> Author: Trujillo-Santos, A. J., et al. Year Published: 2008 Location: Spain</p>	<p>Aim: To carry out a systematic review and meta-analysis of case-control studies to analyze the association between long travels and the development of VTE.</p> <p>Study Type: Systematic Review</p> <p>Size: 9 studies</p>	<p>Inclusion Criteria: case-control studies, in any language, with no limit on the date of publication, and performed a cross search of the references cited in these studies.</p>	<p>Intervention: The estimated the risk ratio of deep-vein thrombosis (DVT) and of DVT and/or PE either after a travel (by any means of transport) or only after a travel by plane was calculated. The OR was used as a measure of association, with a confidence interval of 95%.</p>	<p>Results: The relation between the antecedent of a long travel and subsequent VTE varied from OR = 1.1 to OR = 4.0 and was found to be significant in four studies. The studies were highly heterogeneous in methodology. Two meta-analysis were carried out: only with travels by plane in which the relation was not significant (OR = 1.21; CI 95%, 0.95-1.55) and with all types of transport, with a slightly significant relation (OR = 1.46; CI 95%, 1.24-1.72).</p>	<p>Study Limitations:</p> <p><input type="checkbox"/> None</p> <p>Systematic Review</p> <p><input type="checkbox"/> Review did not address focused clinical question</p> <p><input type="checkbox"/> Search was not detailed or exhaustive</p> <p><input checked="" type="checkbox"/> Quality of the studies was not appraised or studies were of low quality</p> <p><input checked="" type="checkbox"/> Methods and/or results were inconsistent across studies</p>																																																																																																									

				 <p>a</p> <p>Odds ratio IC (95.0%)</p> <p>Estudio (Año) n</p> <p>Ferrari (1999) 320</p> <p>Santana (2000) 988</p> <p>Arya (2002) 568</p> <p>Hosoi (2002) 207</p> <p>TW1+2 (2003) 600</p> <p>Cannegieter (2006) 3812</p> <p>GLOBAL (Ef. Fijos) 6495</p> <p>GLOBAL (Ef. Aleatorios) 6495</p> <p>b</p> <p>Odds ratio IC (95.0%)</p> <p>Estudio (Año) n</p> <p>Dimberg (2001) 506</p> <p>Arya (2002) 568</p> <p>Hosoi (2002) 207</p> <p>Martinielli (2003) 420</p> <p>Cannegieter (2006) 3812</p> <p>GLOBAL (Ef. Fijos) 5513</p> <p>GLOBAL (Ef. Aleatorios) 5513</p> <p>Fig. 1 Forest plot for studies that evaluated the antecedent of any type of transport and only travels by plane. a Travels by any type of transport. b Travels by plane</p>	
<p>Journal: <i>European Heart Journal</i> Author: Lehmann, R., et al. Year Published: 2009 Location: Germany</p>	<p>Aim: to follow-up all patients with economy class syndrome, who were admitted to a hospital near the Frankfurt airport between 1997 and 2006.</p> <p>Study Type: Retrospective chart review</p> <p>Size: 257 patients</p>	<p>Inclusion Criteria: all patients presenting with acute PE to the emergency room or intensive care unit (ICU) of the University Hospital in Frankfurt between 1997 and 2006.</p> <p>Exclusion Criteria: Patients with secondary PE following hospitalization were excluded. After reviewing the medical charts patients where, in retrospect, admission was primarily based on a different diagnosis other than PE were excluded.</p>	<p>Intervention: all travel-associated PE cases, independent from the mode of transportation, were combined under ECS. This definition includes PE due to prolonged sitting in a plane, bus, train, or car, and one patient in a simulation. Furthermore, they distinguished between air-travel ECS and non-air-travel ECS.</p>	<p>Results: Out of the 257 patients with PE, 62 patients suffered from ECS (45 flight-associated PE and 17 from other travel-associated PE). ECS patients were prone to more hemodynamic relevant acute events, reflected by a higher rate of initial cardiopulmonary resuscitation (4.8% vs. 1.5%; P = 0.153) and higher percentage of massive PE (8% vs. 3%; P = 0.064). Intrahospital mortality was similar in both groups (ECS 4.8%, others 4.1%; P = 0.730). The long-term outcome of ECS patients was excellent (Kaplan-Meier analysis; P log-rank: 0.008 vs. other entities). In general, ECS was a rare event (one event/5 million passengers), where long-haul flights over 5000 km lead to a 17-fold risk increase compared with shorter flights.</p>	<p>Study Limitations:</p> <ul style="list-style-type: none"> <input type="checkbox"/> None Non-Randomized <input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria <input type="checkbox"/> Flawed measurement of both exposure and outcome <input checked="" type="checkbox"/> Failure to adequately control confounding <input type="checkbox"/> Incomplete or inadequately short follow-up <input type="checkbox"/> Differences in important prognostic factors at baseline



				<p>Table 3 Risk of pulmonary embolism in dependence on flight duration</p> <table border="1"> <thead> <tr> <th>Flight duration (h)</th> <th>Flight distance km</th> <th>No. of patients with PE</th> <th>No. (millions) of passengers 1997-2006</th> <th>Cases per million passengers</th> </tr> </thead> <tbody> <tr> <td>Unknown</td> <td>Unknown</td> <td>2</td> <td>-</td> <td>-</td> </tr> <tr> <td>0-6</td> <td>0-5000</td> <td>5</td> <td>165.7</td> <td>0.03</td> </tr> <tr> <td>6-9</td> <td>5000-7499</td> <td>22</td> <td>27.9</td> <td>0.8</td> </tr> <tr> <td>9-12</td> <td>7500-9999</td> <td>12</td> <td>39.1</td> <td>0.3</td> </tr> <tr> <td>>12</td> <td>>10 000</td> <td>4</td> <td>5.8</td> <td>0.7</td> </tr> <tr> <td>Total</td> <td></td> <td>45</td> <td>238.7 million</td> <td>0.2</td> </tr> </tbody> </table>	Flight duration (h)	Flight distance km	No. of patients with PE	No. (millions) of passengers 1997-2006	Cases per million passengers	Unknown	Unknown	2	-	-	0-6	0-5000	5	165.7	0.03	6-9	5000-7499	22	27.9	0.8	9-12	7500-9999	12	39.1	0.3	>12	>10 000	4	5.8	0.7	Total		45	238.7 million	0.2	
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References:

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2. Chandra, D., et al. (2009). "Meta-analysis: travel and risk for venous thromboembolism." *Annals of Internal Medicine* 151(3): 180-190.
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4. Kuipers, S., et al. (2014). "The incidence of venous thromboembolism in commercial airline pilots: a cohort study of 2630 pilots." *Journal of Thrombosis & Haemostasis* 12(8): 1260-1265.
5. MacCallum, P. K., et al. (2011). "Cumulative flying time and risk of venous thromboembolism." *British Journal of Haematology* 155(5): 613-619.
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10. Lehmann, R., et al. (2009). "Incidence, clinical characteristics, and long-term prognosis of travel-associated pulmonary embolism." *European Heart Journal* 30(2): 233-241.

The GRADE criterion used to evaluate the quality of evidence presented in research articles reviewed during the development of this brief. For more detailed information, see Appendix A.



External Guideline Recommendations:

In 2019, the **American Society of Hematology** will release their guideline for VTE in Non-Surgical Patients. Their draft, released in 2017 gave the following recommendations for VTE prophylaxis in long distance (>4 hours) travelers. –*These are NOT final*

- The ASH guideline panel suggests not using graduated compression stockings for long distance (> 4 hours) travel in people without known risk factors (*conditional recommendation, very low certainty in the evidence about effects*).
- The ASH guideline panel suggests against using LMWH in long-distance (>4 hours) travelers without known risk factors for VTE (*conditional recommendation, very low certainty of the evidence about effects*).
- The ASH guideline panel suggests against using Aspirin in long-distance (>4 hours) travelers without known risk factors for VTE (*conditional recommendation, very low certainty of the evidence about effects*).
- People without known risk factors who place a high value on prevention of VTE, may choose using GCS (also reduces edema). In people who are at substantially increased VTE risk (e.g. recent surgery, prior history of VTE, hormone replacement therapy, pregnant or postpartum women, active malignancy or two or more risk factors) the ASH guideline panel suggests using graduated compression stockings or prophylactic LMWH for long distance (> 4 hours) travel (*conditional recommendation, very low certainty in the evidence about effects*).
- In people who are at substantially increased VTE risk (e.g. recent surgery, prior history of VTE, hormone replacement therapy, pregnant or postpartum women, active malignancy or two or more risk factors) and where LMWH or GCS is not feasible (e.g. resource constrained



setting or aversion to other anticoagulants), the ASH VTE guideline committee suggests using aspirin rather than no treatment (*conditional recommendation, very low certainty in the evidence about effects*).

The 2017 **Saudi Arabia Ministry of Health** clinical practice guideline for the prophylaxis of VTE in long-distance travelers stated:

- In long distance (>8 hrs duration) high-risk travelers the panel suggests frequent ambulation for the prophylaxis of VTE (*conditional recommendation, very low quality evidence*).
- In long distance (>8 hrs duration) high-risk travelers the panel suggests calf muscle exercise for the prophylaxis of VTE. (*conditional recommendation, very low quality evidence*).
- In long-distance (>8 hrs duration) high-risk travelers the panel suggests sitting in an aisle seat for the prophylaxis of VTE. (*conditional recommendation, very low quality evidence*).
- In long-distance (>8 hrs duration) travelers at increased risk of VTE, the panel suggests using anticoagulants. (*conditional recommendation, very low quality evidence*).
- In long-distance (>8 hrs duration) high-risk travelers, the panel suggests not using gradual compression stockings for the prophylaxis of VTE. (*conditional recommendation, very low quality evidence*)

In 2012 the **American College of Chest Physicians** guideline on the prevention of VTE in nonsurgical patients recommended the following:

- 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 GCS providing 15 to 30 mm Hg 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*).

In 2011 the **British Society of Haematology** guideline on travel related VTE recommended the following:

- There is no evidence for an association between dehydration and travel-associated VTE and so whilst maintaining good hydration is unlikely to be harmful it cannot be strongly recommended for prevention of thrombosis (*recommendation grade 2, level of evidence, B*).
- There is indirect evidence that maintaining mobility may prevent VTE and, in view of the likely pathogenesis of travel-related VTE, maintaining mobility is a reasonable precaution for all travelers on journeys over 3h (*2B*).
- Global use of compression stockings and anticoagulants for long distance travel is not indicated (*1C*).
- Assessment of risk should be made on an individual basis but it is likely that recent major surgery (within 1 month), active malignancy, previous unprovoked VTE, previous travel-related VTE with no associated temporary risk factor or presence of more than one risk factor identifies those travelers at highest thrombosis risk (*1C*).
- Travelers at the highest risk of travel-related thrombosis undertaking journeys of >3 h should wear well fitted below knee compression hosiery (*2B*).
- Where pharmacological prophylaxis is considered appropriate, anticoagulants as opposed to anti-platelet drugs are recommended based on the observation that, in other clinical scenarios, they provide more effective thromboprophylaxis. Usual contraindications to any form of thromboprophylaxis need to be borne in mind (*2C*).

Guideline Ratings

Guideline Issuer and Date	ASH 2019	SA 2017	ACCP 2012	BSH 2011
1. Transparency	NA-DRAFT	A	A	A
2. Conflict of interest	NA-DRAFT	A	A	A
3. Development group	NA-DRAFT	A	A	B
4. Systematic Review	NA-DRAFT	A	A	A



5. Supporting evidence	A	A	A	A
6. Recommendations	A	A	A	A
7. External Review	A	NR	NR	A
8. Currency and updates	A	B	B	C

See Appendix B for full description of the Trustworthy Guideline grading system.



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Appendix A. GRADE criterion for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

- High: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high
Observational study–low
Any other evidence–very low

Criterion for increasing or decreasing level

Reductions

Study quality has serious (-1) or very serious (-2) problems
Important inconsistency in evidence (-1)
Directness is somewhat (-1) or seriously (-2) uncertain
Sparse or imprecise data (-1)
Reporting bias highly probable (-1)

Increases

Evidence of association† strong (+1) or very strong (+2)

†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.



Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania’s Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine’s “Standards for Developing Trustworthy Clinical Practice Guidelines” (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

- Who wrote the initial draft
- How the committee voted on or otherwise approved recommendations
- Evidence review, external review and methods used for updating are not addressed in this standard.



Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

Guideline development group

A	Guideline development group includes: 1) methodological experts and clinicians 2) representatives of multiple specialties
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.



Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review, which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

1. Describe itself as systematic or report search strategies using multiple databases
2. Define the scope of the review (including key questions and the applicable population)
3. Either include quantitative or qualitative synthesis of the data or explain why it is not indicated.

Notes:

- This element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
- A guideline may be rated “B” on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a “B” on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.



Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether



the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated

Appendix C. Search Strategy

Database: Ovid MEDLINE(R) <1946 to March Week 3 2018>

Search Strategy:

-
- 1 exp "embolism and thrombosis"/ci, ep, et, mo, pc, sn (103231)
 - 2 exp "embolism and thrombosis"/ (202337)
 - 3 exp Travel/ (23431)
 - 4 exp Aircraft/ (10561)
 - 5 3 or 4 (32919)
 - 6 1 and 5 (472)
 - 7 exp risk/ (1049172)
 - 8 exp vital statistics/ (824366)
 - 9 exp Preventive Health Services/ (537681)
 - 10 exp anticoagulants/ (201048)
 - 11 exp fibrinolytic agents/ (160458)
 - 12 7 or 8 or 9 or 10 or 11 (2342033)
 - 13 2 and 5 and 12 (363)
 - 14 ((etiol* or epidem* or risk* or caus* or suffer* or experienc* or incur* or occur* or frequen* or develop* or diagnos* or relat* or mortal* or death* or dead or die or dying or dies or died) adj10 ((embol* or thromb*) adj7 (travel* or flight* or flying or flew or flier* or flies or airplane* or aircraft* or airline* or jet or jets or passenger* or (long* adj3 distanc*))).mp. (336)
 - 15 ((prevent* or reduc* or stop* or inhibit* or interfer* or prophyla* or thromboprophyl*) adj10 ((embol* or thromb*) adj7 (travel* or flight* or flying or flew or flier* or flies or airplane* or aircraft* or airline* or jet or jets or passenger* or (long* adj3 distanc*))).mp. (93)
 - 16 ((warfarin* or coumarin* or heparin* or anticoagula* or anti-coagula* or rivaroxaban or apixaban or edoxaban or ((inhibit* or antagon* or block* or interfer*) adj3 (xa or vitamin k)) or hirudin or lepirudin or bivalirudin or argatroban or dabigatran or noac or noacs or doac or doacs) adj10 ((embol* or thromb*) adj7 (travel* or flight* or flying or flew or flier* or flies or airplane* or aircraft* or airline* or jet or jets or passenger* or (long* adj3 distanc*))).mp. (19)
 - 17 6 or 13 or 14 or 15 or 16 (610)



- 18 limit 17 to english language (507)
- 19 limit 17 to abstracts (349)
- 20 18 or 19 (572)
- 21 limit 20 to (clinical study or comparative study or controlled clinical trial or evaluation studies or guideline or meta-analysis or randomized controlled trial or systematic reviews or validation studies) (70)
- 22 exp Epidemiologic Studies/ (2128272)
- 23 20 and 22 (87)
- 24 21 or 23 (136)
- 25 20 not 24 (436)