Guidelines on travel-related venous thrombosis

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Summary

- **Long duration travel is a weak risk factor for the development of VTE. The incidence of VTE after flights of greater than 4 hours is 1 in 4656 and for flights of more than 8 hours in low and intermediate risk flyers is around 0.5%.**
- **Severe symptomatic pulmonary embolism in the period immediately after travel is extremely rare after flights of less than 8 hours. In flights over 12 hours the rate is 5 per million**
- **VTE may be attributable to travel if it occurs up to 8 weeks following the journey**
- **The risk of travel-related thrombosis is higher in individuals with pre-existing risk factors for the development of VTE.**
- **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 (2B)**
- **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 travellers on journeys over 3 hours (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 travellers at highest thrombosis risk (1C)**
- **Travellers at the highest risk of travel-related thrombosis undertaking journeys of greater than 3 hours 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).**

1. Objective

The guideline was drawn up to inform practitioners in the UK who are involved in counselling patients regarding travel-associated venous thromboembolism. It aims to provide information on the incidence of thrombosis, risk factors for thrombosis and strategies for the prevention of thrombosis.

2. Methods

The writing group was made up of two members of the BCSH taskforce in haemostasis and thrombosis from the UK. Medline was systematically searched for English language publications up to June 2008. Relevant references generated from initial papers and published guidelines/reviews were also examined. Meeting abstracts were not included. *Key terms*: venous thrombosis, deep vein thrombosis, venous thromboembolism, pulmonary embolism, travel, traveler's thrombosis *Critical appraisal*: Criteria used to quote levels of evidence and strength of recommendations are according to the GRADE system (Guyatt *et al* 2006).Strong recommendations (grade 1 "recommended") are made when there is confidence that the benefits either do or do not outweigh the harm and burden and costs of treatment. Where the magnitude of the benefit or not is less certain a weaker grade 2 recommendation ("suggested") is made. Grade 1 recommendations can be applied uniformly to most patients whereas grade 2 recommendations require judicious application. The quality of evidence is graded as A (high quality randomised clinical trials), moderate B or low C (Guyatt *et al* 2006) A draft guideline was produced by the writing group, revised and agreed by consensus. Further comment was made by the members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was reviewed by a sounding board of approximately 40 UK haematologists, the BCSH and the Committee of the British Society for Haematology and comments were incorporated where appropriate.

3. Introduction

This guideline aims to provide a brief synopsis of the data supporting an association between travel and venous thrombosis and the data on interventions to prevent travel-associated thrombosis. Finally, recommendations are given for travel based on the available data.

There is evidence that long distance travel is a risk factor for the development of venous thromboembolism (VTE). The available data suggest that the risk is not confined to air travel, increases with the duration of travel and results in clinical thrombosis more often in travellers with pre-existing risk factors. The most common finding in studies of air travellers is asymptomatic calf vein thrombosis. Life threatening pulmonary embolism is extremely rare.

Studies assessing mechanical thromboprophylaxis suggest that compression stockings are effective at preventing travel-associated thrombosis. There are few studies on the prevention of travel-associated thrombosis by pharmacological methods and the findings of most of these studies cannot now be accepted in view of the serious concerns about research activities of the lead author (http://webcache.gmc-uk.org/minutesfiles/3313.HTML). While it is clear that there is no indication for routine thromboprophylaxis some groups of travellers, who can be identified by the presence of risk factors for VTE and proposed duration of travel, may benefit.

4. Evidence for an association between travel and thrombosis

Five prospective studies have investigated the incidence of development of deep vein thrombosis following travel. In these studies the subjects were evaluated before travelling using objective methods to exclude deep vein thrombosis (DVT) and were investigated after travel using objective methods to diagnose DVT (Hughes *et al*, 2003;Jacobson *et al*, 2003;Schwarz *et al*, 2002;Schwarz *et al*, 2003;Scurr *et al*, 2001). The travellers in these studies were deemed by the authors to be of low to intermediate risk for development of VTE. Four excluded individuals with a history of previous VTE (Hughes *et al*, 2003;Jacobson *et al*, 2003;Schwarz *et al*, 2003;Scurr *et al*, 2001). All excluded travellers on oral anticoagulants for any reason. In all five studies individuals who had worn compression stockings could be identified so that the incidence of thrombosis in non-stocking wearers could be calculated. In all

five studies the duration of travel was over 8 hours. The incidence of DVT ranged from 0-12%. Overall, if the studies were combined the rate of development of all venous thrombosis including isolated calf muscle vein thrombosis (ICMVT) and DVT and pulmonary embolus (PE) was 52/3001 (1.7%). The study by Scurr and colleagues is a statistical outlier with a reported rate of isolated calf vein thrombosis of 12% in low risk flyers not wearing compression hosiery (Scurr *et al*, 2001). None of the events were symptomatic and half were associated with the finding of a negative D-dimer test which has been shown consistently to be associated with a high negative predictive value for exclusion of DVT in low risk individuals. The incidence of all venous thrombosis in the remaining studies was 40/2901 (1.4%). When ICMVT were excluded the incidence of deep vein thrombosis or PE was 16/2901 (0.5%) and the incidence of symptomatic VTE was 10/2901 (0.3%). In the study by Hughes et al 146 flyers wore stockings and amongst these were 4 individuals who sustained events. In non-stocking wearers the rate of DVT/PE in these 4 studies was therefore 12/2755 (0.4%).

In two of the studies the incidence of thrombosis in travellers was compared with matched controls using the same methods for detection of DVT (Schwarz *et al*, 2002;Schwarz *et al*, 2003). Thromboses were classified as isolated calf muscle vein thromboses (ICMVT) or DVT depending on the ultrasound findings. ICMVT was observed in 24/1124 (2.1%) flyers compared with 11/1373 (0.8%) controls, while DVT was seen in 7/1124 (0.6%) flyers compared with 2/1373 (0.15%) controls. Symptomatic DVT occurred in 2/1124 (0.18%) of flyers versus 1/1373 (0.07%) of controls. In summary the data from these studies suggest an incidence of symptomatic DVT in travellers flying for over eight hours of 1 in 560 or alternatively an excess of 1 symptomatic DVT in 950 eight hour flights compared with controls. These data may however be subject to ascertainment bias related to the nature and design of the studies included.

In a study of 8775 employees of international companies who flew regularly the rate of development of VTE was 1 in 4656 flights of greater than 4 hours (Kuipers *et al* 2007).

Four retrospective studies have assessed the associations between long distance flying and the early onset of significant pulmonary embolism (PE) (Clerel & Caillard, 1999;Kline *et al*, 2002;Lapostolle *et al*, 2001;Perez-Rodriguez *et al*, 2003) These studies include data on more than 300 million flights and provide evidence for three main associations. Firstly early symptomatic PE is rare with an incidence of less than 0.5 per million for all flyers and 1 in 115 million for individuals flying for less than 6 hours. (Clerel & Caillard, 1999;Lapostolle *et al*, 2001;Perez-Rodriguez *et al*, 2003;Philbrick *et al*, 2007). There is compelling evidence for an association between duration of travel and early onset PE. In the two largest studies the rate of early PE was very similar at around 5 per 10^6 for flights of over 12 hours (Clerel & Caillard, 1999;Lapostolle *et al*, 2001) and pulmonary embolism was seen predominantly in passengers who had flown for a long time (93% > 8 hours, 82% > 9 hours and 76.5% >12 hours). Thirdly, most travellers who developed PE had pre-existing risk factors for the development of VTE.

. A population based descriptive study estimated that the risk of fatal PE is 0.5 per million and 1.3 per million for air flights of greater than 3 hours and 8 hours respectively. For flights of greater than 8 hours the odds ratio for fatal pulmonary embolism was 7.9 (95% CI 1.1-55.1) (Parkin *et al*, 2006).

Case-control studies also support an association between travel and thrombosis (Arya *et al*, 2002;Cannegieter *et al*, 2006;Ferrari *et al*, 1999;Martinelli *et al*, 2003;Parkin *et al*, 2006;Samama, 2000;ten *et al*, 2003). In some of these studies episodes of travel of as little as “over-3 hours” were linked to an increased thrombosis risk, while in others an effect was only seen when periods of travel of 10-15 hours were considered (ten Wolde *et al*, 2003). Case control studies suggest that travel is associated with around a 3-fold relative risk for DVT. Against a background rate of DVT of 1 in 1000 per annum and accepting a risk period for DVT of 1 month this suggests that an episode of prolonged travel would be expected to be followed by a symptomatic DVT in the following month once in 4,000 journeys.

The period of risk for developing VTE following long distance air travel has been reported at between 2 and 8 weeks (Kelman *et al* 2003, Kuipers *et al* 2007)

Key summary points

- **Long duration travel is a weak risk factor for the development of VTE. The incidence of VTE after flights of greater than 4 hours is 1 in 4656 and for flights of more than 8 hours in low and intermediate risk flyers is around 0.5%.**
- **Severe symptomatic pulmonary embolism in the period immediately after travel is extremely rare after flights of less than 8 hours. In flights over 12 hours the rate is 5 per million**
- **VTE may be attributable to travel if it occurs up to 8 weeks following the journey**

5. Role of risk factors in the development of thrombosis

VTE is a multicausal disorder and the accumulation of risk factors added to an individual's inherent thrombotic risk determines whether or not thrombosis develops. In clinical practice decisions about thromboprophylaxis are made by considering the patient's thrombosis risk and the illness or proposed surgical intervention. A similar approach should be taken to travel-related thrombosis where risk is related to pre-existing factors and duration of travel. The data suggest that duration of travel of 3 hours upward is associated with a thrombotic risk. The incidence of symptomatic VTE, most of which are confined to the calf, in low risk travellers after 8 hour flights is around 0.5% and the incidence of early symptomatic pulmonary embolism in all flyers is around 1 in 2 million. In studies where the role of risk factors in travel-associated VTE have been assessed, recent trauma or surgery, previous VTE or varicose veins, active cancer, hormone therapy and obesity are mentioned. Determining the level of risk associated with these factors is difficult because their prevalence in all travellers is not known and interpreting the data on hormone use particularly may be misleading in view of the widespread use of the combined oral contraceptive pill and hormone replacement therapy. Data suggesting that there is an increased risk of travel-related thrombosis in patients who are heterozygous for factor V Leiden do not indicate that this

abnormality should be routinely sought in prospective travellers (Cannegieter *et al*, 2006).

- **The risk of travel-related thrombosis is higher in individuals with pre-existing risk factors for the development of VTE.**

6. Strategies for prevention of travel-associated VTE

Mechanical and pharmacological methods of prophylaxis have been assessed in randomised clinical trials. In most of the studies the endpoint was asymptomatic calf vein DVT. Because of the concern about the research output of the group involved in all but one of these studies we have considered only the data from the remaining randomised controlled trial (Scurr *et al*, 2001). In this study of low risk flyers asymptomatic deep vein thrombosis was observed in 12 of 100 compared with none of 100 wearing compression hosiery.

It is notable that of the nine travellers who developed VTE in the NZATT study, 6 adopted some form of thromboprophylaxis. Four wore compression stockings, 3 in combination with aspirin, and a further 2 took aspirin alone. The rate of development of DVT was 4/146 (2.7%) in passengers wearing compression stockings, 5/275 (1.8%) in those taking aspirin and 3/466 (0.6%) in those using neither (Hughes *et al*, 2003). Although there may be confounding factors contributing to this observation it does indicate that the benefit of these interventions is likely to be limited

There are no good data on the effect of pharmacological prophylaxis in this setting and any recommendations must therefore be based on extrapolation from other situations where this approach has been used.

Despite the commonly given advice that travellers should maintain good hydration there is no evidence to support an association between dehydration and the development of VTE (Schreijer *et al*, 2008).

Recommendations (Also see appendix 1)

- **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 (2B)

- **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 travellers on journeys over 3 hours (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 travellers at highest thrombosis risk (1C)**
- **Travellers at the highest risk of travel-related thrombosis undertaking journeys of greater than 3 hours 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).**

Conflict of interest: TPB and HGW have no conflict of interest to declare

Appendix 1

Duration of travel **Risk Group**	**< 3 hours**	**3-8 hours**	**> 8 hours**
Low	Nil	Nil	Nil
Intermediate	Nil	Nil or stockings	Stockings
High	Nil	Stockings	Stockings+/- Anticoagulant

Risk Group	**Examples of risk factors for VTE**
Low	None
Intermediate	All others e.g. Up to 6 weeks post partum. Previous unprovoked VTE no longer on anticoagulants. Previous travel-related VTE Combinations of risk factors.
High	Major surgery in previous 4 weeks Active cancer undergoing chemo-radiotherapy in the previous 6 months, awaiting surgery or chemo-radiotherapy or in palliative phase

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