



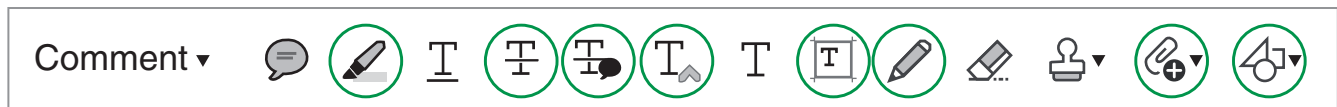
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Long-haul travel and venous thrombosis: What is the evidence?

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Travel is a booming business thanks to globalisation, the rise of commercial aviation and significant reductions in fare prices. In 2015, 3.5 billion passengers were carried on scheduled flights, a 6.8% increase on the previous year.¹

However, increased travel mobility is not entirely without risk. Venous thromboembolism (VTE), first linked to travel in the 1950s, is of particular concern. Growing public and media interest in this preventable and potentially fatal condition has prompted airlines, healthcare professionals and advisory bodies to offer advice on ‘traveller’s thrombosis’. The National Institute for Health and Care Excellence (NICE) advises compression stockings for all moderate or high-risk long-haul travellers, and consideration of low-molecular weight heparin (LMWH) in high-risk travellers. ‘General measures’ such as leg exercises and avoiding dehydration or excessive alcohol intake feature amongst advice given by patient websites and airline carriers. However, is this guidance evidence based?

This is debatable. Several issues exist regarding VTE, travel and available evidence, raising questions including: ‘*What travel-related factors determine an increased VTE risk?*’, ‘*Who is most likely to be affected by this risk?*’ and ‘*How should the risk be mitigated?*’ At a more fundamental level, ‘*How long is long-haul?*’ Studies addressing these questions are heterogeneous and therefore difficult to compare and draw conclusions from.

One area of consensus is that a travellers’ background VTE risk plays an important role in determining their travel-related risk. A 2008 international consensus statement grouped subjects into low, medium and high risk for traveller’s thrombosis; high-risk subjects included those with a personal history of VTE, malignant disease or recent major surgery.² Evidence indicates that subjects at low to medium risk of VTE have a 0–2% risk of developing thrombosis associated with long-haul air travel;^{3–5} this increases to 5% for individuals at high risk, such as those with a history of DVT or hypercoagulable states including factor V Leiden mutation and obesity.^{3,4}

Unfortunately, the inter-study consensus largely ends there. Studies employ various definitions of long-haul travel, ranging from journeys longer than 4 h to

7 h, up to 10–12 h. Furthermore, VTE assessment differs both in modality and timing. Two of the largest studies employed very different assessments. Researchers in the LONFLIT study performed systematic duplex ultrasound scanning (DUS) for all participants within 24 h of their flight.⁴ Conversely, the New Zealand Air Traveller’s Thrombosis Study considered subjects at risk for three months after travel and performed DUS only if they became D-dimer positive or symptomatic during this period.⁵ This may have led to an underestimation of DVT, as, although this assay is sensitive in suspected DVT, it may be less reliable in prediction of travel-related VTE. This is illustrated in the LONFLIT studies where there was no significant difference in the D-dimer level of those with ultrasound-detected VTE and those without.^{4,6} Lastly, many studies have significant dropout rates and insufficient subjects to accurately calculate risk. Due to the low incidence of DVT in the general population, studies require large numbers of travellers to confirm a significantly increased risk above controls.³

Evidence exists that VTE risk is not confined to air travel. Results from a large case-control study revealed a 2-fold increased VTE risk for all modes of travel including train, bus, car and plane, suggesting that immobility is an important contributing factor.⁷ However, in specific individuals, air travel increases VTE risk above simple immobility. One study compared participant’s blood results after an 8-h flight, an 8-h movie marathon and 8 h of normal activity. Markers of coagulation activation, specifically thrombin–antithrombin complexes, were raised in individuals after air travel but not in the other situations,⁸ particularly if using oral contraceptives or factor V Leiden mutation positive. This provides further evidence that specific patient risk factors convey an increased risk in travel.

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Another specific factor that may increase risk in travel is pregnancy. Pregnancy and the puerperium are recognised high-risk periods for VTE. Whilst no data are available on the exact risk of VTE in pregnant travellers, an estimated a risk of 0.03–0.1% has been suggested based upon the known separate risks for pregnant women and air travellers.⁹ No specific advice for pregnant travellers exists but, in many cases, pregnancy and the puerperium are grouped into ‘medium risk’ travellers.³

In addition to innate and travel-related factors, behavioural components have also been investigated. One study suggests selection of a window seat, sleeping or anxiety during a flight may slightly increase risk. Somewhat controversially, this same study reported that exercising, hydrating with non-alcoholic beverages and wearing stockings did not confer any protective effect, contradicting common advice from clinicians and airlines.¹⁰

Evidence suggests that risk rises with exposure. A large cohort study demonstrated that VTE risk rose with flight duration, particularly in high-risk groups.¹¹ Furthermore, a meta-analysis found an 18% increase in risk with every 2-h increase in travel duration by any mode, with an even greater increase of 26% associated with air travel.¹² Additionally, the more flights taken the greater the risk, raising concerns for the frequent flyer or business traveller. The risk tripled after five or more long-haul flights in one study and each extra flight increased the risk 1.4-fold.¹¹

So how can this risk be mitigated? Several trials have investigated methods of mechanical and pharmacological VTE risk reduction. LONFLIT-2 and five trials explored the use of compression stockings, demonstrating a statistically significant difference between the control group and those wearing stockings; 4.5% and 5.8% of controls developed DVT in LONFLIT-2 and 5 respectively, compared with 0.24% and 0.97% of those wearing stockings.^{4,6} Reviews synthesising current literature agree that there is evidence that compression stockings reduce travel-related VTE and can decrease leg oedema in low-risk individuals.³

Pharmacological VTE prophylaxis has been trialled including aspirin and LMWH. LONFLIT-3 found that aspirin did not significantly reduce VTE rates; however, the risk was essentially abolished in the LMWH-treated group.¹³ Another study examined the use of Flite Tabs (150mg Pinokinase), an oral fibrinolytic, in high-risk subjects. No thrombotic events occurred in the treatment group, compared to five DVTs (5.4%) and two superficial thromboses in the controls.¹⁴

The potential use of novel oral anticoagulant medications, such as apixaban, requires consideration. Their short half-life, rapid onset of action and oral administration make them an attractive option for VTE

prophylaxis in high-risk travellers. Their use in thromboprophylaxis after elective orthopaedic surgery is now well established with many trials demonstrating their comparable safety profile and improved VTE prevention when compared with LMWH.¹⁵ However, no trials examining their safety and efficacy in prevention of traveller’s thrombosis have been performed, and there is currently no licence for this specific indication. Potential drawbacks, such as the lack of reversal agents, should be considered and trials examining their use in travel-related prophylaxis are needed.

Here, a final question is raised – is the travel industry doing enough to raise awareness of the risk of VTE and encourage high-risk travellers to seek appropriate pre-travel advice? A recent study suggests not. Researchers found that one quarter of airlines warned of the risk of traveller’s thrombosis, and this was unchanged a year later after publication of the World Health Organisation’s Research into Global Hazards of Travel (WRIGHT) report.¹⁶

Significant heterogeneity exists in the available evidence on travel-related thrombosis, both in study methodology and with respect to basic definitions. Further high-quality studies should be performed in the context of an international consensus, conferring a standardised approach to obtain reliable evidence that can then be translated into much needed evidence-based guidance for both travellers and physicians.

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SC and SO researched literature and conceived the editorial. SC wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

References

1. The World of Air Transport in 2015, www.icao.int/annual-report-2015/Pages/the-world-of-air-transport-in-2015.aspx (accessed 18 February 2017).

2. Schobersberger W, Toff WD, Eklöf B, et al. Traveller's thrombosis: international consensus statement. *VASA Z Gefasskrankheiten* 2008; 37: 311–317.
3. Aryal KR and Al-Khaffaf H. Venous thromboembolic complications following air travel: what's the quantitative risk? A literature review. *Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg* 2006; 31: 187–199.
4. Belcaro G, Geroulakos G, Nicolaides AN, et al. Venous thromboembolism from air travel: the LONFLIT study. *Angiology* 2001; 52: 369–374.
5. Hughes RJ, Hopkins RJ, Hill S, et al. Frequency of venous thromboembolism in low to moderate risk long distance air travellers: the New Zealand Air Traveller's Thrombosis (NZATT) study. *Lancet Lond Engl* 2003; 362: 2039–2044.
6. Belcaro G, Cesarone MR, Nicolaides AN, et al. Prevention of venous thrombosis with elastic stockings during long-haul flights: the LONFLIT 5 JAP study. *Clin Appl Thromb Off J Int Acad Clin Appl Thromb* 2003; 9: 197–201.
7. Cannegieter SC, Doggen CJM, van Houwelingen HC, et al. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). *PLoS Med* 2006; 3: e307.
8. Schreijer AJM, Cannegieter SC, Meijers JCM, et al. Activation of coagulation system during air travel: a cross-over study. *Lancet Lond Engl* 2006; 367: 832–838.
9. Cannegieter SC and Rosendaal FR. Pregnancy and travel-related thromboembolism. *Thromb Res* 2013; 131(Suppl 1): S55–S58.
10. Schreijer AJM, Cannegieter SC, Doggen CJM, et al. The effect of flight-related behaviour on the risk of venous thrombosis after air travel. *Br J Haematol* 2009; 144: 425–429.
11. Kuipers S, Cannegieter SC, Middeldorp S, et al. The absolute risk of venous thrombosis after air travel: a cohort study of 8,755 employees of international organisations. *PLoS Med* 2007; 4: e290.
12. Chandra D, Parisini E and Mozaffarian D. Meta-analysis: travel and risk for venous thromboembolism. *Ann Intern Med* 2009; 151: 180–190.
13. Cesarone MR, Belcaro G, Nicolaides AN, et al. Venous thrombosis from air travel: the LONFLIT3 study – prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. *Angiology* 2002; 53: 1–6.
14. Cesarone MR, Belcaro G, Nicolaides AN, et al. Prevention of venous thrombosis in long-haul flights with Flite Tabs: the LONFLIT-FLITE randomized, controlled trial. *Angiology* 2003; 54: 531–539.
15. Rachidi S, Aldin ES, Greenberg C, et al. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. *Expert Rev Hematol* 2013; 6: 677–695.
16. Scurr JRH, Ahmad N, Thavarajan D, et al. Traveller's thrombosis: airlines still not giving passengers the WRIGHT advice! *Phlebology* 2010; 25: 257–260.