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DEBATE

Interventions to prevent venous thrombosis after air travel: are they necessary? No

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Travel was first associated with venous thrombosis in the 1930s, when cases were reported after long trips by car. From the mid-1950s on, there has been a steady stream of reports associating long-haul air travel with venous thrombosis [1]. The phrase 'economy class syndrome' was coined in 1977 [2], and the first controlled study stems from 1986 [3]. Seen in that light, the recent clamor for aggressive therapy may be slightly surprising. Has anything changed? Has the mass travel that followed the postwar industrial boom led to an epidemic of venous thrombosis in front of our very eyes which we have completely missed?

We recently showed that the risk of venous thrombosis is mildly elevated after travel (of more than 4 h) not only by air, but also by bus, train or car, and is of the same magnitude as the risk conferred by the use of oral contraception [4]. One may wonder whether those who advocate medicinal thromboprophylaxis for air travel also take the logical step of prescribing this for all women who use oral contraceptives, and all holiday-makers who travel by car or bus. The relevance of the risk increase lies not in the risk for the individual traveler, which is low, but in the overall burden of thrombosis caused by traveling, which is high because of the enormous number of travelers. This should lead not to unfounded advice to travelers, but to large randomized trials into interventions that can safely be used by large numbers of travelers.

The survey that we carried out among attendants of the ISTH Congress in Sydney in 2005, which is published in this issue, shows that a substantial proportion (80%) of them felt that, for themselves, preventive measures were in order. Whereas a large proportion only did exercise during the flight, no less than 17% wore elastic stockings, and 28% used some form of chemoprophylaxis (aspirin, heparin, vitamin K antagonists). A lack of consensus is apparent from the wide variation in use of thromboprophylaxis by nationality and professional background. Although there may be a difference between what doctors prescribe to themselves and what they prescribe to their patients, it seems likely that this variation reflects differences in how experts advise air travelers.

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These different policies stem from the absence of evidence showing a beneficial, or detrimental, effect of any form of preventive action. The old adage in the absence of clear proof of benefit is not to intervene: *in dubio abstine*. In modern medicine, this is usually interpreted as meaning that we need evidence from randomized trials on clinical endpoints before we succumb to our drive for action. Obviously, there are exceptions; few would insist on randomized trial evidence that parachute use may be helpful to prevent 'death related to gravitational challenge' [5].

The behavior of the attendants of the ISTH Congress, whom we may qualify as a group of experts voting with their feet, shows that clearly this is not such an obvious case. As none of the preventive measures, except in all likelihood exercising in the seat, is without risk, the guiding principle of *in dubio abstine* applies, and my contribution to this debate could end here. Nevertheless, let us look at the numbers that are known and try to imagine what randomized data, if available, would look like.

For this imaginary approach, I will only use data from studies with clinical endpoints, i.e. deep vein thrombosis and pulmonary embolism, and dismiss studies that have investigated the occurrence of asymptomatic clots after travel, as detected by imaging techniques, even those that investigated the effect of elastic stockings, aspirin or heparin in reducing the incidence of asymptomatic clots. Studies with surrogate endpoints may have a use in showing whether a certain intervention is likely to have an effect, but not whether the potential benefits outweigh the risks of complications. We already know that exercise, elastic stockings, heparin and even aspirin reduce the occurrence of venous thrombosis. So does streptokinase, but that does not imply that it would be a good idea to administer this to all air travelers.

The question that a randomized trial would address is how many cases of clinical thrombosis would be prevented by prophylactic measures, and at the cost of how many complications. Because of several recent studies, the risk of thrombosis after air travel is reasonably well known [4,6–8]. Travel of more than 4 h in duration leads to a doubling of the risk of venous thrombosis in the subsequent 8 weeks. As the overall baseline incidence of venous thrombosis is one per 1000 per year, these

findings predict an absolute risk of one per 6500 passengers. This is in line with a recent large study among employees of international organizations and multinational companies, where we found one thrombotic event per 6000 flights in 10 000 employees [9]. So, if an intervention was 100% effective, the numbers-needed-to-treat (NNT, number of individuals to be treated to prevent one case of disease) would be 6000. As no intervention is so perfect as to prevent all cases of disease, the true benefit will be smaller: if we assume that heparin has a relative risk (RR) of 0.30 (preventing 70% of events) [10], elastic stockings an RR of 0.40 [11,12] and aspirin an RR of 0.75 [13], the NNT to prevent one case of thrombosis are 8500 for heparin, 10 000 for elastic stockings and 24 000 for aspirin use.

When so many people need to be treated to prevent one thrombosis, a small risk of side effects could offset the balance. For exercise, we have no evidence at all that it does any good, but it is unlikely to pose a risk, especially when performed while the person is seated. For elastic stockings, there are only studies suggesting a reduction in asymptomatic thrombosis. In one of these studies, grade I elastic stockings also caused symptomatic superficial vein thrombosis in 3% of patients, demonstrating that elastic stockings do carry a risk of side effects [14]. This may particularly be the case when stockings are not fitted individually. Tight stockings may pose a serious risk in patients with limb ischemia.

Aspirin, heparin and other antithrombotic drugs all carry a risk of hemorrhage. These risks are small, but so is the risk of thrombosis. The risk of major hemorrhage for the use of low molecular weight heparin was reported in two large series of medical patients to be about 0.4% over a 14-day period [15]. Prophylaxis for travel-related thrombosis would probably be administered for 1–3 days, which would lead to absolute risks of major hemorrhage ranging from 0.024% to 0.107%, or 1 in 1000 to 1 in 3500 individuals (whereas we needed to treat 8500 individuals to prevent one thrombosis). For aspirin, the Physicians' Health Study reported an excess incidence of major hemorrhage of 31 per 10 000 person-years [16]. Assuming an elevated risk for 1 week after taking aspirin, this translates to an excess incidence of 0.60 per 10 000 person-weeks, or 1 in 17 000 travelers (whereas we needed to treat 24 000 individuals to prevent one thrombosis). Vitamin K antagonists carry an additional risk because of the unpredictable dose–response relationship, and are clearly inappropriate. From these calculations, it appears that the number of major hemorrhages that these antithrombotic drugs will cause is greater than the number of cases of air-travel related thrombosis that they will prevent; that is, they will do more harm than good.

So, indiscriminate use of prophylaxis is clearly inadvisable. But what about risk groups? The risk of thrombosis after air travel is particularly elevated in those with prothrombotic mutations or obesity, those who use oral contraceptives and who travel a very long distance, and, in all likelihood, those with a personal history of thrombosis. For some of these risk groups, the risk/benefit ratio based on the numbers I used above may become positive. However, this will still be a marginal benefit, which may in reality well be absent, for we have no information on whether the environment of an airplane, with reduced air pressure, stress and anxiety, distorted circadian rhythm and unusual food and fluid intake, affects the risk and severity of hemorrhage. We may safely assume, however, that treatment possibilities for a bleeding patient at 10 000 m are somewhat limited. Therefore, in those who are perceived to be at increased risk, advice to exercise regularly is the only rational and safe approach.

Disclosure of Conflict of Interests

The author states that he has no conflict of interest.

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