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Eur Respir J 2013; 42: 1156–1157 | DOI: 10.1183/09031936.00029913 | Copyright ©ERS 2013

Allergic burden and the risk of venous thromboembolism

To the Editor:

We read with keen interest a recent article by MAJOOR *et al.* [1], who studied the relationship between asthma and venous thromboembolism (VTE). They provided evidence for the increased risk of VTE, specifically pulmonary embolism (PE), among asthmatics. In final regression models, after adjustment for potential confounders, MAJOOR *et al.* [1] found that body mass index was the sole independent predictor of deep vein thrombosis (DVT) risk, while only severe asthma and oral corticosteroid use independently predicted PE.

Mechanisms underlying the intriguing association of asthma with VTE remain unclear. However, several previous papers published by us and other investigators [2–5] showed that allergic diseases are associated with a number of prothrombotic alterations involving enhanced platelet activation, formation of dense fibrin clots that are relatively resistant to lysis, increased plasminogen activator inhibitor-1 levels or a disturbed protein C anticoagulant pathway. In a case–control study of subjects between 20 and 45 years old, we demonstrated that atopic diseases are more prevalent in patients with distal DVT, but not those with PE, and allergy to timothy grass pollen was over-represented in the VTE group [2]. Discrepancies in the patient characteristics and methodology between the current study [1] and ours [2] are likely to explain differences in the reported results.

The results by MAJOOR *et al.* [1] might also suggest that there are links between thrombosis and atopic sensitisation and/or allergic inflammation. Although less prevalent than in children, the atopic phenotype of asthma is common in adults, and $\geq 50\%$ of adult asthmatics are positive for atopic sensitisation. The prevalence of other allergic diseases, such as atopic dermatitis and especially allergic rhinitis, which are quite common in the general adult population (about 2–10% and 20%, respectively), is increased in asthmatics in whom, when present, they further increase the allergic inflammation burden. One might speculate that the overall allergic inflammation burden could have also contributed to the increased risk of VTE which MAJOOR *et al.* [1] observed in severe asthma. Although they included atopy in the final regression models, showing lack of its effect, it would be interesting to evaluate VTE risk in the subgroups obtained by stratification of asthma based on accompanying allergic diseases and/or atopy, similar to those they had conducted according to asthma severity. It is also possible that the lack of any association of atopy in the regression analyses could have resulted from a rather limited number of VTE events ($n=35$) in the study by MAJOOR *et al.* [1].

Similarly, in this study, severe asthma showed the association with PE but not DVT and this observation might also be related to low numbers of PE ($n=19$) and DVT ($n=16$) events [1]. It cannot be excluded that DVT had been underestimated, which could have affected the results [1].

However, asthma has been independently reported to be associated with PE in a large retrospective primary care-based study by CAZZOLA *et al.* [6], although the DVT phenotype was not analysed in that study.

Moreover, PE has been reported to occur more frequently than DVT in patients suffering from chronic obstructive pulmonary disease, which is associated with a moderately increased risk of VTE [7].

It is possible that the association between severe asthma and PE, but not DVT, reported by MAJLOOR *et al.* [1] had a random component. However, if it is real, the differential effect of severe asthma on PE *versus* DVT occurrence might indicate that prolonged immobility and hospitalisation had no major impact on the VTE risk in this population, and allergic inflammation *per se* produces prothrombotic alterations, particularly if combined with the unfavourable effects of corticosteroids. Further investigations are needed to replicate the current findings by MAJLOOR *et al.* [1] and to elucidate their pathogenetic mechanisms, both genetic and environmental, including a potential influence of allergy on thrombosis.



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Recent epidemiological studies suggest that allergic diseases might increase the risk of venous thromboembolism <http://ow.ly/mK82P>

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Received: Jan 03 2013 | Accepted after revision: Jan 25 2013

Conflict of interest: None declared.

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Eur Respir J 2013; 42: 1157–1158 | DOI: 10.1183/09031936.00000913 | Copyright ©ERS 2013

From the authors:

We appreciate the suggestion by D.P. Potaczek and A. Undas that the overall allergic inflammation burden might have increased the risk of venous thromboembolism in our patients. Therefore, we performed a *post hoc* analysis in subgroups, after stratification for atopic and non-atopic asthma. But, again, we did not find any difference between the groups (table 1).

TABLE 1 Rate ratio (95% CI) of first pulmonary embolism and deep-venous thrombosis (asthma population *versus* general population)

| | Non-atopic asthma | Atopic asthma |
|---|-------------------|-------------------|
| Subjects n | 358 | 290 |
| All venous thromboembolism (definite and probable) | | |
| Deep-vein thrombosis | 1.60 (0.44–4.09) | 1.47 (0.30–4.29) |
| Pulmonary embolism | 6.74 (3.09–12.80) | 6.19 (2.48–12.74) |
| All definite venous thromboembolism | | |
| Deep-vein thrombosis | 1.20 (0.25–3.50) | 1.47 (0.30–4.30) |
| Pulmonary embolism | 6.75 (3.09–12.83) | 5.31 (1.95–11.57) |