ERJ Express. Published on December 20, 2012 as doi: 10.1183/09031936.00150312

Risk of deep-vein thrombosis and pulmonary embolism in asthma

Christof J. Majoor[1], Pieter W. Kamphuisen[4], Aeilko H. Zwinderman[3], Anneke ten Brinke[5], Marijke Amelink[1], Lucia Rijssenbeek-Nouwens[6], Peter J. Sterk[1], Harry R. Büller[2], Elisabeth H. Bel[1]

Department of [1]Respiratory Medicine, [2]Vascular Medicine, and [3]Clinical Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam, The Netherlands.

[4] Department of Vascular Medicine, University Medical Centre Groningen, Groningen, The Netherlands.

[5] Department of Respiratory Medicine, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands.

[6] Dutch Asthma Centre, Davos Dorf, Switzerland.

Corresponding author:

C.J. Majoor

Dept. of Respiratory Medicine

Academic Medical Center

P.O. Box 22660

1100 DE Amsterdam, The Netherlands

Telephone: +31-20-5664356

Fax number: +31-20-5669001

Email: c.j.majoor@amc.uva.nl

Abstract

Increasing evidence suggests that patients with asthma have activated coagulation within the airways. Whether this leads to an increase in venous thromboembolic events (VTE) is unknown. We therefore assessed the incidence of VTE in patients with mild-moderate and severe asthma as compared to an age- and gender-matched reference population.

648 patients with asthma (283 with severe and 365 patients with mild-moderate asthma) visiting 3 Dutch outpatient asthma clinics were studied. All patients completed a questionnaire about a diagnosis of deep-vein thrombosis (DVT) and pulmonary embolism (PE) in the past, their risk factors, history of asthma and medication use. All VTE were objectively verified.

In total, 35 VTE events (16 DVT and 19 PE) occurred at a median age of 39 (range 20-63) years. The incidence of PE in patients with severe asthma was 0.93 (95% Confidence Interval (CI): 0.42-1.44) per 1000 person-years, 0.33 (95%CI: 0.07-0.60) in mild-moderate asthma, and 0.18 (95%CI: 0.03-0.33) in the general population, respectively. Severe asthma and oral corticosteroid use were independent risk factors of PE (hazard ratios: 3.33 (1.16-9.93) and 2.82 (1.09-7.30), respectively). Asthma was not associated with DVT.

Severe asthma greatly enhances the risk of pulmonary embolism, particularly if chronic corticosteroids are used.

Keywords:

asthma, corticosteroids, pulmonary embolism, venous thromboembolism.

INTRODUCTION

Chronic inflammatory diseases have been associated with activation of coagulation(1;2) and an increased risk of venous thromboembolic events (VTE), in particular during active disease. This has been shown for inflammatory bowel disease,(3) rheumatoid arthritis,(4) diabetes mellitus(5) and chronic obstructive pulmonary disease (COPD).(6) Also asthma has been associated with a procoagulant and antifibrinolytic activity in the airways.(7;8) However, whether this procoagulant shift translates into a higher risk of symptomatic VTE is unknown. Therefore, we hypothesized that asthma, in particular severe, refractory asthma,(9) predisposes to an increased risk of thromboembolic complications. The present study was designed to determine the incidence of deep-vein thrombosis (DVT) and pulmonary embolism (PE) in outpatients with mild-moderate and severe asthma, and to compare the incidence rates to an age-, and gender-matched reference population.

METHODS

Study population:

Adult patients with mild-moderate or severe asthma according to international criteria,(10;11) who visited the outpatient pulmonary clinic of 3 Dutch tertiary asthma clinics (1 academic, 1 non-academic, 1 asthma centre) were consecutively recruited between December 1st 2010 and May 1st 2011. The reference population was retrieved from a publication by Naess and colleagues representing a sample from the general population in Norway as this population is the best match to the Dutch population.(12) This population of 94.194 individuals of 20 years and older (mean age 46 yr (range 20-103 yr) participated in a large scale general health study (HUNT2 study) and were followed from 1995-2001.(13)

Questionnaire

To assess the prevalence of VTE, subjects completed a questionnaire during their routine follow-up visit to the outpatient clinic. The questionnaire contained a set of questions about a history of DVT and PE, anticoagulant therapy, risk factors for VTE as well as asthma specific questions, including inhaled or oral corticosteroid treatment at the time of the thromboembolic event. The complete questionnaire is given in the online supplement as figure E1.

Diagnosis of venous thromboembolism

In the study population all VTE events were objectively verified. In all identified events medical records of the patients were reviewed and adjudicated blindly, using international criteria for DVT and PE.(14-16) In the reference population Naess et al verified venous

thromboembolic events by using the same criteria.(12) Additional details on the method for verifying the diagnosis of PE and DVT are provided in the online data supplement.

VTE was categorised as first event or recurrent event, as well as provoked or idiopathic event. Provoked VTE was defined as VTE occurring under oral contraceptive use, recent surgery, confinement to bed, positive family history of VTE, and pregnancy. Other VTE events were considered idiopathic.

Statistical analysis:

The primary study outcome was the incidence of first episode of DVT and PE in asthma patients. Secondary outcomes were covariables associated with the incidence of first DVT and PE. Cumulative incidences of VTE, PE and DVT were estimated using Kaplan Meier survival probabilities. In order to match the incidences of the present population with that of the reference population we performed an indirect standardization procedure using age and gender specific VTE-incidence numbers from Naess et al.(12) Using these numbers, the expected cumulative PE-hazard at the age of the first episode of PE (or at the age of censoring if a patient did not have PE), was calculated for every patient by summing the age-gender specific incidences of Naess et al. The expected cumulative PE-hazards after asthma-onset were calculated as the differences between the total cumulative hazards minus the cumulative hazards until the age of asthma-onset.

The incidence of PE in the age and gender-matched general population was calculated as the expected number of PE according to Naess divided by the total number of personyears for our study population. Rate ratio's were computed by dividing the number of PE in our sample by the sum of the expected cumulative PE-hazards. Exact 95% confidence intervals

were calculated assuming that the number of PE followed a Poisson distribution. The same procedure was performed to calculate the incidences and rate ratio's of DVT.

Multivariate regression of the PE- or DVT-risk on cofactors was performed using the Cox proportional hazards regression model. Age-gender specific population hazards (according to Naess et al)(12) were used as time-dependent offset-variables as described by Anderson et al.(17) Asthma severity was the time-dependent covariate. Potential cofactors were atopy, gender, BMI, smoking status, inhaled corticosteroid use, oral corticosteroid use, and forced expiratory volume in one second (FEV1) relative to forced vital capacity (FVC). Data were processed in SPSS for windows version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 762 adults with asthma fulfilled the criteria for inclusion. Thirteen patients were irretrievable, 91 did not return the questionnaire, six patients were excluded for psychological reasons, three had language problems and in one patient there was incomplete demographic data (Figure 1). Thus, a total of 648 patients, 365 patients with mild-moderate asthma and 283 patients with severe asthma, were analysed. Patients were aged between 18 and 88 years old. Other patient characteristics are summarized in Table 1 for the two groups separately. Characteristics of non-participating patients did not differ from those participating (data not shown).

VTE events in patients with asthma

Thirty-five (5.4%) first episodes of VTE occurred in patients with asthma (17 with mild-moderate asthma, and 18 with severe asthma) during 31889 person-years (Table 2). Sixteen (46%) patients suffered from DVT and 19 (54%) from PE (with or without DVT). Definite DVT was confirmed in 12 patients, and 4 patients had a probable DVT (clinical suspicion without objective diagnostic imaging). Definite PE was diagnosed in 16 patients (11 by CT-scan, 5 by high probability V/Q scan) and 3 patients had a probable PE (1 with typical symptoms and intermediate probability V/Q scan, and 2 with typical symptoms and proven DVT). All patients (definite and probable DVT and PE) were treated with 6 months of anticoagulation. Therefore, probable cases were included in the analysis.

VTE occurred in 10 (3.8%) men and 25 (6.5%) women (p=0.04). Provoked VTE occurred in 24 (68.6%) patients. (oral contraceptive use (n=11), recent surgery (n=9), positive family history of VTE (n=6), and pregnancy (n=3)). Seven patients had more than one risk factor. Although

not significant, idiopathic VTE was noted more often in patients with severe asthma (39% versus 24%)(p=0.31).

Median age at first event was 39 years (range 20-57) in patients with severe asthma and 39 years (range 22-63) in patients with mild-moderate asthma. In patients with severe asthma the majority of VTE (89%) occurred after the onset of asthma, as compared to 41% in patients with mild-moderate asthma (Chi-square: p=0.003). Seven patients with severe asthma (39%) and 3 patients (18%) with mild-moderate asthma had recurrent thromboembolic events, (p=0.16). Twelve patients with severe asthma (67%) and none with mild-moderate asthma used chronic oral corticosteroids at the time of the first VTE.

Comparison between patients with severe asthma, mild-moderate asthma and the general population

The cumulative incidences for VTE, PE and DVT for patients with severe and mild-moderate asthma, and the general population are shown in Figure 2 A-C. The incidence of VTE in patients with severe asthma was 1.29 per 1000 person-years (95% confidence interval (95% CI): 0.69-1.88) as compared to 0.95 (95% CI: 0.50-1.40) in patients with mild-moderate asthma and to 0.46 (95% CI: 0.23-0.70) in the general population, respectively. The incidence of PE in patients with severe asthma was 0.93 (95% CI: 0.42-1.44) per 1000 person-years, 0.33 (95%CI: 0.07-0.60) in patients with mild-moderate asthma and 0.18 (95%CI: 0.03-0.33) in the general population, respectively. The incidence of DVT in patients with severe asthma was 0.36 (95% CI: 0.04-0.67) per 1000 person-years, 0.61 (95%CI: 0.25-0.98) in patients with mild-moderate asthma and 0.28 (95%CI: 0.10-0.47) in the general population, respectively.

Standardized rate ratio's for first PE and DVT in patients with severe and mild-moderate asthma were 8.93 (95% CI 4.62-15.63) and 3.97 (95% CI 0.97-9.12), respectively, while the rate ratio's for DVT were not significantly increased (1.62 (95% CI 0.44-4.14) and 1.45 (95% CI 0.30-4.23), respectively). Excluding the probable cases of DVT and PE the rate ratios did not markedly change the results: the rate ratio for PE was 8.93 (95% CI 4.62-15.63) and 2.67 (95% CI: 0.55-7.80), respectively. (Table 3.)

Risk factors of DVT and PE

Univariate Cox regression showed that severe asthma and the use of oral corticosteroids were associated with PE. Mild-moderate asthma, severe asthma and BMI were associated with DVT. Other factors, such as ICS dose (for both as a continuous variable and a dichotomous variable (with a cutoff dose of fluticasone (or equivalent drug) of 1000 ug/day)), atopy, current and ex- smoking, gender, and FEV1/FVC were not associated with PE or DVT. In multivariate Cox regression model only severe asthma (Hazard ratio (HR) 3.33, 95%CI: 1.16-9.93) and oral corticosteroid use (HR: 2.82, 95% CI: 1.09-7.30) were associated with PE, and BMI with DVT (HR: 1.09, 95% CI: 1.01-1.16).

DISCUSSION

Our results show an almost nine-fold increased risk of pulmonary embolism in patients with severe asthma as compared to the general population. In addition, a trend towards a 3.5-fold increased risk of PE was found in patients with mild-moderate asthma. Severe asthma and the use of oral corticosteroids were risk factors of pulmonary embolism in multivariate analysis. Interestingly, asthma was not associated with DVT. These results suggest that the incidence of pulmonary embolism is increased in patients with severe asthma, particularly in patients using oral corticosteroids.

To our knowledge this is the first study investigating the relation between asthma of different severities and venous thromboembolic events. Two studies in the primary care setting found an association between VTE and asthma.(18;19) In the first study a slightly increased risk of PE was found in patients with asthma,(18) whereas in the second study the prevalence of asthma in women using oral contraceptives who were diagnosed with VTE was somewhat higher as compared to those without VTE.(19) In both studies the severity and treatment of asthma were not explored. Another study evaluated the incidence of VTE in patients with atopic diseases and found a higher risk of DVT and PE in patients with allergic rhinitis or elevated specific IgE to a panel of common aero-allergens. No increased risk was found in patients with asthma probably because the sample size was too small.(20) Yet another study found an association between Churg-Strauss syndrome and DVT, which is interesting since Churg-Strauss syndrome is often associated with severe asthma.(21) Also other airway diseases such as COPD, have been associated with increased risk of pulmonary embolism, in particular amongst hospitalized patients during an exacerbation.(6;22). Our results show that patients with asthma are at increased risk of PE, in particular those with

severe disease. Together these studies suggest that disease severity is an important risk factor for pulmonary embolism in patients with airways disease.

The strength of our study is the high number of 283 patients with well characterized severe asthma,(10) which is comparable to the number of patients included in the NIH sponsored multicentre Severe Asthma Research Programme (SARP) studies.(23;24) Nevertheless, the number of patients with PE and DVT in our study was modest, hence some of the subanalyses should be interpreted with caution. This could also explain the lack of association between PE and mild-moderate asthma. Furthermore, our study was based on self-reported VTE, which might have caused missclassification . Overestimation was, however, ruled out since all self-reported thromboembolic events were confirmed by objective measurements including compression ultrasound for DVT and CT-scanning or high probability ventilation-perfusion scanning for PE.

Finally, the Norwegian population was used as control group for Dutch asthma patients. Observed incidence rates of VTE in the Norwegian population were similar to rates for first events in other western European countries including France and Sweden.(25;26) Therefore, we believe that the Norwegian population could be used as an adequate reference population in our study.

The mechanism by which severe asthma may predispose to pulmonary embolism is complex. First, there is extensive evidence that inflammation alters the balance between procoagulant and fibrinolytic activity and that inflammation and coagulation stimulate each other.(8;27) This has been observed in animal models and lung tissue of humans with acute lung injury,(28) and pneumonia.(29) Also in the asthmatic airway there is evidence of activation

of the extrinsic coagulation cascade, with involvement of both plasma and locally derived factors.(7;8) This is supported by a recent finding showing local vascular inflammation in asthma and COPD (30), as well as the observation of higher incidence of PE than DVT in COPD patients (22), and evidence that in other chronic inflammatory disorders such as diabetes, rheumatoid arthritis and ulcerative colitis, a higher incidence of pulmonary embolism has not been observed.(3-5) Taken together, the results of the present study suggest that in particular in severe asthma the balance between coagulation and fibrinolysis is seriously disturbed.

Second, inactivity of the patients with severe asthma might have been a potential trigger for VTE. However, this would have led to a higher incidence of DVT than PE, which was not the case in our study.

Finally, patients with severe asthma continuously use (ultra)high doses of inhaled corticosteroids, receive bursts of systemic corticosteroid during exacerbations, and often need chronic oral corticosteroid treatment for control of their asthma. Corticosteroid-induced hypercoagulability has been described for many years,(31) but is still controversial whether the use of corticosteroids itself or the underlying (severe) disease contributes to the hypercoagulable state.(32)

The findings of the present study may have important clinical implications. Pulmonary embolism is a potentially life threatening complication that may occur in relatively young patients with severe asthma. Doctors should therefore increase their awareness and lower the threshold for the evaluation of patients with severe asthma for possible pulmonary embolism. In addition, we believe that strategies to reduce the risk of pulmonary embolism,

such as thromboprophylaxis, may be considered in patients with prednisone-dependent asthma.

In conclusion, our study suggests that patients with asthma, in particular those with severe, refractory disease, have a high risk of pulmonary embolism, which may be further increased by asthma severity and oral corticosteroids.

Acknowledgements:

We thank J.C. de Groot and S.B. de Nijs for their help with the recruitment of the patients.

Authors'contributions:

Conception and design: P.W.K., A.H.Z., P.J.S., C.J.M., H.R.B., and E.H.B. Data collection: C.J.M., A.M., A.tB., and L.R. Analysis and interpretation: C.J.M., P.W.K., A.H.Z., E.H.B. Drafting and editing manuscript: all authors.

Funding: The study was funded by a grand from Dutch Asthma Foundation. (Grant nr. AF 3.2.11.021) The study sponsor had no involvement in the study design; the collection, analysis and interpretation of data nor in the writing of the report; and in the decision to submit the paper for publication.

Figure legends:

Figure 1. Flow diagram of study patients

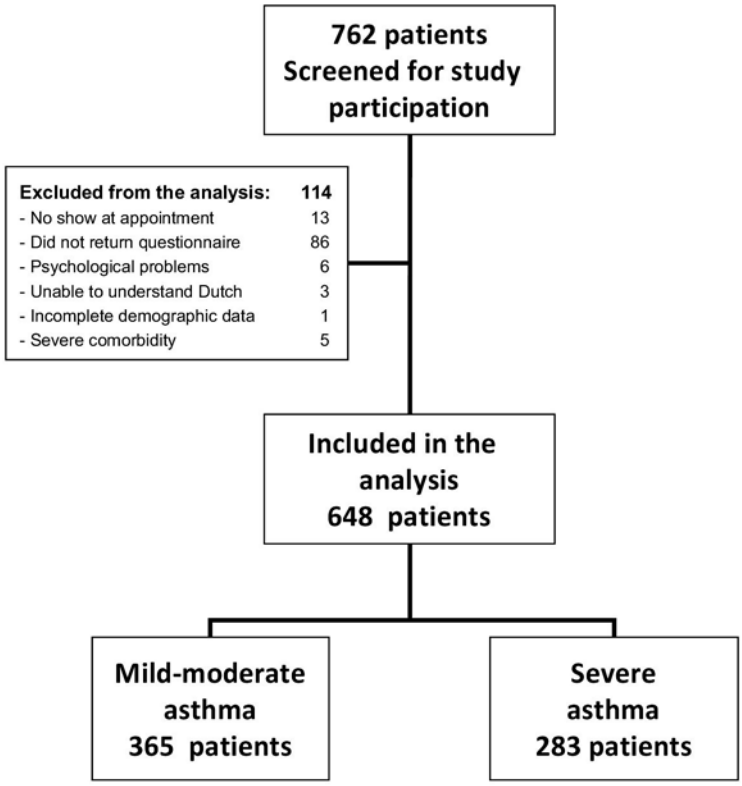
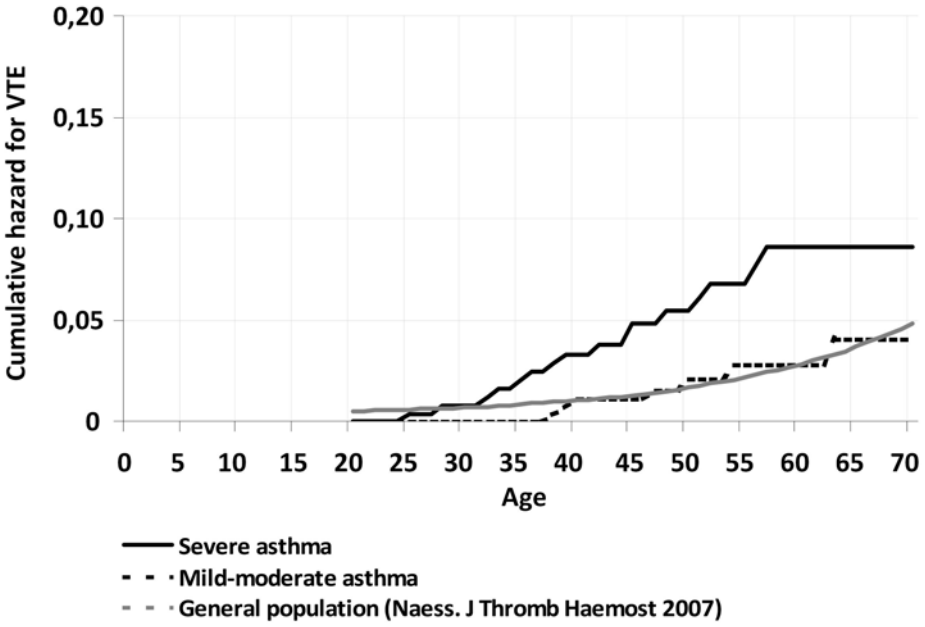
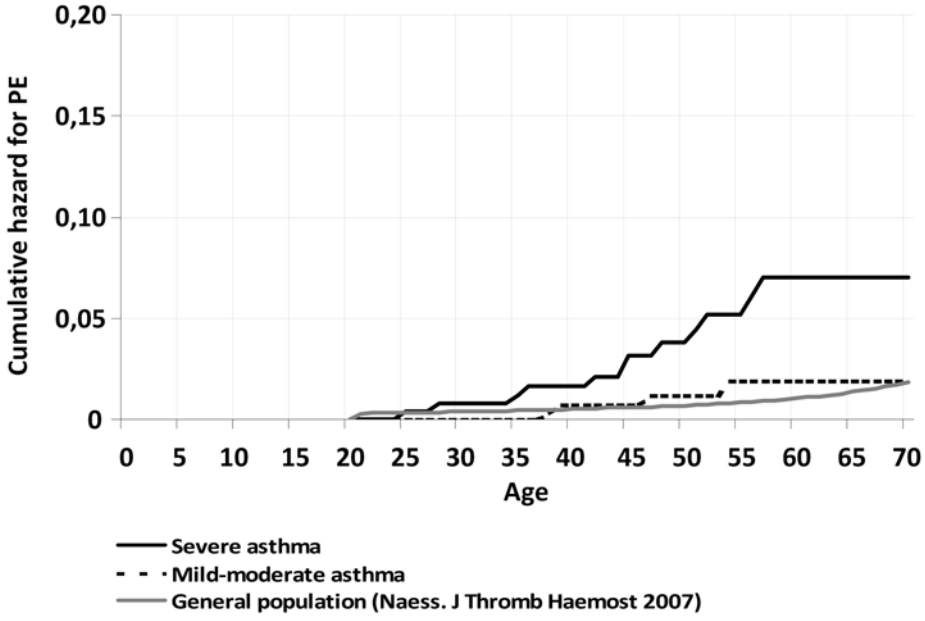


Figure 2. Cumulative hazards for VTE, PE, and DVT in asthma of different severities and the general population.

A: Venous thromboembolism



B: Pulmonary embolism



C: Deep-vein thrombosis

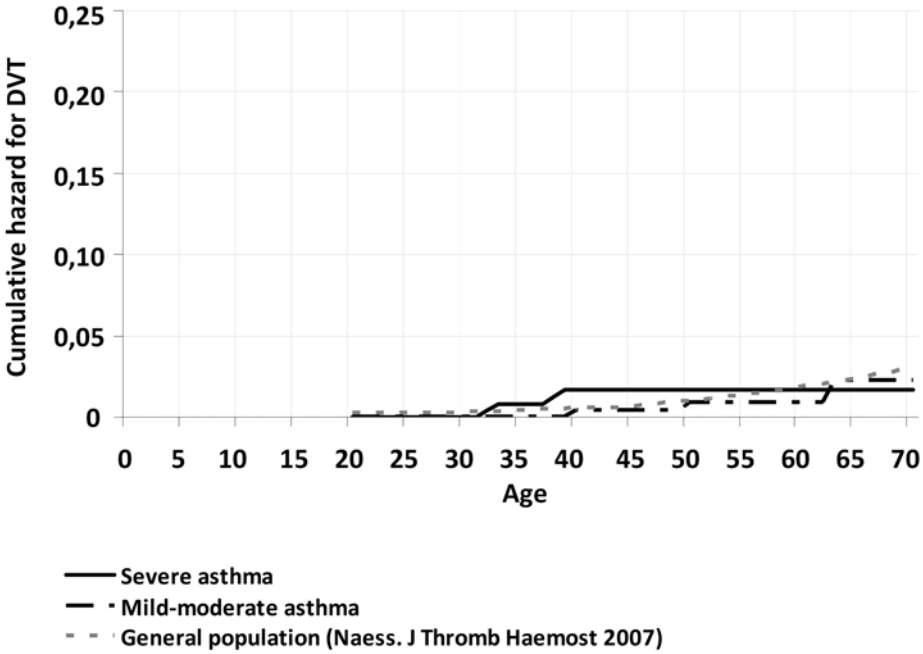


Table 1. Baseline characteristics.

	Mild-moderate asthma (n=365)	Severe asthma (n=283)
Age (years)	50 (18-88)	51 (17-77)
Female sex (%)	58	61
BMI (kg/m2)	28 (17-45)	27 (18-59)
Age of asthma onset (years)*	39 (0-78)	27 (0-70)
Duration of asthma (years)*	5.0 (0.1-78)	20 (0.1-76)
Atopy (%)	42	49
Smoking history*		
Never smoker (%)	52	64
Ex smoker (%)	40	33
Current smoker (%)	8	3
Severe exacerbations in previous year		
<1/year (%)	73	28
1-2/year (%)	20	31
>2/year (%)	8	41
FEV1 post bronchodilator (% pred.)	97.0 (22 -146)	84.9 (23.1-133)
ICS dose ≥1000 µg/day (%)	0	85
Chronic oral corticosteroid (%)	0	38
Omalizumab (%)	0	7

BMI Body mass index; FEV1 Forced Expiratory Volume in 1 second; ICS inhalational corticosteroid; pred. predicted

* data derived from questionnaires; not objectively confirmed in 26 patients

Values are presented as median (range) or % of total.

Table 2. Venous thromboembolic events in study population.

	Mild-Moderate asthma (n=365)	Severe asthma (n=283)
Total number of personyears	**17914**	**13975**
Before and after asthma onset		
All VTE (n)	17	18
Deep venous thrombosis (only DVT) (n)	11	5
Pulmonary embolism (+/- DVT) (n)	6	13
Before asthma onset		
All VTE (n)	10	2
Deep venous thrombosis (only DVT) (n)	8	1
Pulmonary embolism (+/- DVT) (n)	2	1
After onset of asthma		
All VTE (n)	7	16
Deep venous thrombosis (only DVT) (n)	3	4
Pulmonary embolism (+/- DVT) (n)	4	12

VTE venous thromboembolic event

DVT deep venous thrombosis

Table 3. Rate ratio (95% CI) of first PE and DVT (asthma population versus general population).

	Mild-moderate asthma N=365	Severe asthma N=283
All VTE (Definite and probable)		
Deep-vein thrombosis	1.45 (0.30-4.23)	1.62 (0.44-4.14)
Pulmonary embolism	3.56 (0.97-9.12)	8.93 (4.62-15.63)
All definite VTE		
Deep-vein thrombosis	1.45 (0.30-4.23)	1.21 (0.25-3.55)
Pulmonary embolism	2.67 (0.55-7.80)	8.93 (4.62-15.63)

REFERENCES

Reference List

(1) Del Rosso M., Fibbi G, Matucci CM. The urokinase-type plasminogen activator system and inflammatory joint diseases. Clin Exp Rheumatol 1999 July;17(4):485-98.

(2) Saibeni S, Saladino V, Chantarangkul V, Villa F, Bruno S, Vecchi M, de FR, Sei C, Tripodi A. Increased thrombin generation in inflammatory bowel diseases. Thromb Res 2010 March;125(3):278-82.

(3) Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010 February 20;375(9715):657-63.

(4) Matta F, Singala R, Yaekoub AY, Najjar R, Stein PD. Risk of venous thromboembolism with rheumatoid arthritis. Thromb Haemost 2009 January;101(1):134-8.

(5) Stein PD, Goldman J, Matta F, Yaekoub AY. Diabetes mellitus and risk of venous thromboembolism. Am J Med Sci 2009 April;337(4):259-64.

(6) Rizkallah J, Man SF, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2009 March;135(3):786-93.

(7) Brims FJ, Chauhan AJ, Higgins B, Shute JK. Coagulation factors in the airways in moderate and severe asthma and the effect of inhaled steroids. Thorax 2009 December;64(12):1037-43.

(8) de Boer JD, Majoor CJ, van 't Veer C, Bel EH, van der Poll T. Asthma and coagulation. Blood 2012 January 18.

(9) ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. Am J Respir Crit Care Med 2004 September 15;170(6):601-5.

(10) Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, Wagener AH, Wagers SS, Sterk PJ, Compton CH. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2010 November 23.

(11) National Institutes of Health,National Heart,Lung,and Blood Institute. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO Workshop Report. 2010. Available from: http://www.ginasthma.org

(12) Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007 April;5(4):692-9.

(13) Holmen J, Midthjell K, Kruger Ø, Langhammer A. The Nord-Trøndelag Health Study 1995-1997 (HUNT2). Norsk Epidemiologi 2003;13[1], 19-32. 2003.

(14) Gottschalk A, Sostman HD, Coleman RE, Juni JE, Thrall J, McKusick KA, Froelich JW, Alavi A. Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. J Nucl Med 1993 July;34(7):1119-26.

(15) Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004 July 1;117(1):19-25.

(16) van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, Kruip MJ, Kwakkel-van Erp JM, Leebeek FW, Nijkeuter M, Prins MH, Sohne M, Tick LW. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006 January 11;295(2):172-9.

(17) Andersen PK, Borch-Johnsen K, DeckertT, Green A, Hougaard P, Keiding N, Kreiner S. A Cox regression model for the relative mortality and its application to diabetes mellitus survival data. Biometrics 1985 41[4], 921-932.

(18) Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 2007 May 14;167(9):935-43.

(19) Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae K. Oral contraceptives and venous thromboembolic disease. Analyses of the UK General Practice Research Database and the UK Mediplus database. Hum Reprod Update 1999 November;5(6):688-706.

(20) Undas A, Ciesla-Dul M, Drazkiewicz T, Potaczek DP, Sadowski J. Association between atopic diseases and venous thromboembolism: a case-control study in patients aged 45 years or less. J Thromb Haemost 2011 April;9(4):870-3.

(21) Allenbach Y, Seror R, Pagnoux C, Teixeira L, Guilpain P, Guillevin L. High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: a systematic retrospective study on 1130 patients. Ann Rheum Dis 2009 April;68(4):564-7.

(22) Bertoletti L, Quenet S, Mismetti P, Hernandez L, Martin-Villasclaras JJ, Tolosa C, Valdes M, Barron M, Todoli JA, Monreal M. Clinical presentation and outcome of venous thromboembolism in chronic obstructive pulmonary disease. Eur Respir J 2011 September 1.

(23) Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R, Jr., Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 2010 February 15;181(4):315-23.

(24) Wenzel SE, Busse WW. Severe asthma: lessons from the Severe Asthma Research Program. J Allergy Clin Immunol 2007 January;119(1):14-21.

(25) Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000 May;83(5):657-60.

(26) Zoller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation 2011 August 30;124(9):1012-20.

(27) Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med 2010 February;38(2 Suppl):S26-S34.

(28) Hofstra JJ, Schouten M, Levi M. Thrombophilia and outcome in severe infection and sepsis. Semin Thromb Hemost 2007 September;33(6):604-9.

(29) Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006 April 1;367(9516):1075-9.

(30) Wanner A, Mendes ES. Airway endothelial dysfunction in asthma and chronic obstructive pulmonary disease: a challenge for future research. Am J Respir Crit Care Med 2010 December 1;182(11):1344-51

(31) Cosgriff SW, Diefenbach AF, Vogt W, Jr. Hypercoagulability of the blood associated with ACTH and cortisone therapy. Am J Med 1950 December;9(6):752-6.

(32) Van Zaane B, Nur E, Squizzato A, Gerdes VE, Buller HR, Dekkers OM, Brandjes DP. Systematic review on the effect of glucocorticoid use on procoagulant, anticoagulant and fibrinolytic factors. J Thromb Haemost 2010 August 23.