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Risk of venous thromboembolism in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study

Low platelet counts in patients with primary immune thrombocytopenia (ITP) are associated with an increased risk for bleeding (Fogarty, 2009). Paradoxically, patients with chronic ITP (cITP) may also have an increased risk for venous thromboembolism (VTE) (Aledort *et al*, 2004; McMillan & Durette, 2004; Bussel *et al*, 2009). However, few, if any, formal epidemiological studies have examined the risk of VTE in cITP patients compared with the general population.

Therefore, to estimate the incidence rate (IR) of VTE for Danish cITP patients compared with a reference cohort from the general population, we conducted a nationwide population-based cohort study in Denmark (population of 5·3 million). Since 1968, all Danish residents are registered in the Civil Registration System (CRS) (Pedersen *et al*, 2006) and have received a 10-digit identification number, which allows unambiguous linkage between registries. Since 1977, the Danish National Patient Registry (DNPR) has covered all hospitalizations and, since 1995, all hospital outpatient and emergency room visits (Andersen *et al*, 1999). Registry data include dates of admission and discharge, a primary diagnosis reflecting the main reason for admission, and up to 20 secondary diagnoses. Through the DNPR we identified patients aged 18 years or older with a first-time registered diagnosis of ITP between 1996 and 2007. We then restricted the cohort to patients with adult cITP by including only those with two or more diagnoses of ITP over a period longer than 6 months. Further, we only excluded those with a cITP diagnosis which could not be verified through medical record review (Heden *et al*, 2009) and those with a registered VTE diagnosis preceding the date of cITP. To adjust for confounding by pre-existing morbidities we retrieved all previous diagnoses of the 19 chronic diseases included in the Charlson comorbidity index (Charlson *et al*, 1987). Comorbidity was classified as 'No' (none of the 19 diagnoses recorded) or 'Yes' (at least one of the 19 diagnoses recorded) as of the date of cITP diagnosis.

For each cITP patient, we randomly selected eight persons from the general population through the CRS as a reference cohort. The date of cITP diagnosis of the matched cITP patient was assigned as the index date for these persons. The reference cohort was matched on age, sex, and comorbidity and without any VTE diagnosis recorded in the DNPR prior to the index date.

We identified members of the two cohorts with a first-time diagnosis of VTE registered in hospital departments or outpatient clinics during follow-up. VTE was categorized as unprovoked in the absence of cancer diagnosed before or within 90 d after the VTE and in the absence of a diagnosed fracture, trauma, surgery, or pregnancy/delivery within 90 d before the date of VTE (Sørensen *et al*, 2007). Remaining VTEs were classified as provoked.

The patients were followed from date of cITP diagnosis or index date until date of VTE, death, emigration, or April 1, 2008, whichever occurred first. We computed the IR and corresponding 95% confidence interval (CI) as the number of VTEs per 1000 person-years at risk assuming that VTEs follow a Poisson distribution. We used Cox regression to estimate the incidence rate ratio (IRR) of VTE for cITP patients compared with the reference cohort controlling for age, sex, and presence of comorbidity. We stratified the analyses by sex, age (≤60 years, above 60 years), and comorbidity (yes/no). Furthermore, provoked and unprovoked VTEs were evaluated separately. The study was approved by the Danish Data Protection Agency (Record no. 2007-41-1101). The SAS statistical software package, version 9.2 (SAS Institute Inc., Cary, NC, USA), was used for statistical analyses.

We identified 391 patients with a diagnosis of cITP and no prior diagnosis of VTE. The reference cohort consisted of 3128 persons. The median (quartiles) age was 54 (37–72) years, 62%

Table I. Incidence rates (IR) and 95% confidence intervals (CI) of venous thromboembolism (VTE) in 391cITP patients and 3128 persons from the general population (reference cohort). Incidence rate ratios (IRR) for cITP cohort versus reference cohort, adjusted for the matching factors (age, sex, and comorbidity) using stratified Cox regression.

	Chronic ITP cohort			Reference cohort			
	Number of VTEs	Person-years	IR per 1000 person-years (95% CI)	Number of VTEs	Person-years	IR per 1000 person-years (95% CI)	Adjusted IRR (95% CI)
Total	10	1879	5·32 (CI: 2·86–9·89)	33	16 196	2·04 (CI: 1·45–2·87)	2·65 (CI: 1·27–5·50)
Unprovoked VTE	5	1879	2·66 (CI: 1·11–6·39)	18	16 195	1·11 (CI: 0·70–1·76)	2·26 (CI: 0·81–6·30)
Provoked VTE	5	1879	2·66 (CI: 1·11–6·39)	15	16 195	0·93 (CI: 0·56–1·54)	3·16 (CI: 1·11–8·98)
Female	3	1247	2·41 (CI: 0·78–7·46)	21	10 605	1·98 (CI: 1·29–3·04)	1·20 (CI: 0·35–4·14)
Male	7	632	11·07 (CI: 5·28–23·23)	12	5591	2·15 (CI: 1·22–3·78)	5·23 (CI: 1·99–13·75)
Age ≤ 60 years	4	1243	3·22 (CI: 1·21–8·57)	11	10 137	1·09 (CI: 0·60–1·96)	2·86 (CI: 0·91–8·97)
Age > 60 years	6	636	9·44 (CI: 4·24–21·01)	22	6059	3·63 (CI: 2·39–5·51)	2·51 (CI:0·97–6·50)
Charlson score = 0	5	1380	3·62 (CI: 1·51–8·70)	18	11 362	1·58 (CI: 1·00–2·51)	2·32 (CI: 0·85–6·35)
Charlson score ≥ 1	5	498	10·04 (CI: 4·18–24·12)	15	4833	3·10 (CI: 1·87–5·15)	3·10 (CI: 1·06–9·07)

Unprovoked VTE was defined as a primary VTE diagnosis (main reason for hospitalization should be VTE) in absence of a prior cancer diagnosis and in absence of surgery, trauma, pregnancy/delivery or fracture within 90 d before VT.

were women, and 62% had no comorbidity. In the cITP cohort, 10 incident VTEs occurred during 1879 person-years of follow-up [IR = 5·32 (95% CI: 2·86–9·89) per 1000 person-years], compared with 33 incident VTEs during 16 196 person-years of follow-up in the reference cohort [IR = 2·04 (95% CI: 1·45–2·87) per 1000 person-years] (Table I). This yielded an IRR of VTE of 2·65 (95% CI: 1·27–5·50) for cITP patients compared with the reference cohort. The IRR was high for both provoked and unprovoked VTE, and higher for men compared to women; however, our estimates were imprecise (Table I). Information on cITP-treatment and blood count at date of VTE was obtained from medical records in eight cITP patients; four were treated with corticosteroids, three received no treatment, and one splenectomized cITP patient who also had antiphospholipid antibodies was treated with rituximab. At date of VTE diagnosis six patients had normal platelet count, two had unknown platelet count and two of the cITP patients had low platelet count. One male cITP patient with an unprovoked VTE had a platelet count of 34×10^9/l and another male cITP patient, who was diagnosed with lung cancer <30 d after the VTE, had a platelet count of 30×10^9/l on the date of VTE. None of these two patients had antiphospholipid antibodies.

To our knowledge, this is the largest study to date of cITP and subsequent risk of VTE. Furthermore, we included a comparison cohort which enabled us to compare the IR of VTE in cITP patients with that of the general population. Data from the DNPR ensured a population-based design, avoiding selection bias due to loss to follow-up. Misclassification of cITP patients was minimized by verifying all cITP diagnoses through medical record review. We required two recorded ITP diagnoses for patients to be included. Therefore, our cITP patients may represent a selected group. While confounding from the matching factors is not likely, our measure of comorbidity was crude (i.e. yes/no). Thus we can not rule out residual confounding from comorbidity.

In conclusion, our study showed that cITP patients have a two-fold higher risk of VTE compared to the general population. It also showed that VTEs occur in cITP patients with low platelet count. Thus, increased risk of VTE should be considered in all cITP patients.

Conflicts of interest

M Severinsen, MC Engebjerg, DK Farkas, AØ Jensen, M Nørgaard, and HT Sørensen did not report receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study. S Zhao is employed by Amgen Inc.

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Marianne T. Severinsen[1,2]
Malene Cramer Engebjerg[1]
Dora Körmendiné Farkas[1]
Annette Østergaard Jensen[1]
Mette Nørgaard[1]
Sean Zhao[3]
Henrik Toft Sørensen[1]

[1]*Department of Clinical Epidemiology, Clinical Institute, Aarhus University Hospital, Aarhus,* [2]*Department of Clinical Biochemistry, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark, and* [3]*Global Epidemiology, Amgen Inc. One Amgen Center Drive, MS 24-2-A, Thousands Oaks CA, USA.*
E-mail: m.severinsen@rn.dk

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