Journal of Thrombosis and Haemostasis, **3**: 1432–1436

ORIGINAL ARTICLE

The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS-13 deficiency

D. R. TERRELL,*† L. A. WILLIAMS,*† S. K. VESELY,† B. LÄMMLE,‡ J. A. K. HOVINGA‡ and J. N. GEORGE*†

**Hematology-Oncology Section, Department of Medicine, College of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; †Department of Biostatistics and Epidemiology, College of Public Health, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; and ‡Central Hematology Laboratory, University Hospital, Inselspital, University of Bern, Bern, Switzerland*

To cite this article: Terrell DR, Williams LA, Vesely SK, Lämmle B, Hovinga JAK, George JN. The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS-13 deficiency. *J Thromb Haemost* 2005; **3**: 1432–6.

Summary. *Background:* Accurate estimates of the incidence of thrombotic thrombocytopenic purpura (TTP) are important to assess the resources required for current treatments as well as to anticipate the need to develop new treatments. Previous estimates have been indirect and have not reported data on patients with ADAMTS-13 deficiency. *Objective:* To determine the incidence of patients with TTP-hemolytic uremic syndrome (HUS) in three categories: all patients with clinically suspected TTP-HUS, patients with idiopathic TTP-HUS, and patients with severe ADAMTS-13 deficiency. *Methods:* Incidence rates were estimated from the Oklahoma TTP-HUS Registry, analyzing all 206 consecutive patients from January 1, 1996 to June 30, 2004 who were treated with plasma exchange for their initial episode of clinically suspected TTP-HUS. ADAMTS-13 activity was measured in 186 (90%) of the 206 patients. *Results:* The age–sex–race standardized annual incidence rates were 11.29×10^6 (95% CI: 9.70–12.88) for all patients with clinically suspected TTP-HUS; 4.46×10^6 (95% CI: 3.43–5.50) for patients with idiopathic TTP-HUS; and 1.74×10^6 (95% CI: 1.06–2.41) for patients with severe ADAMTS-13 deficiency ($< 5\%$ activity). In all three categories, the incidence rates were greater for women and for blacks. For patients with severe ADAMTS-13 deficiency, the age–sex standardized incidence rate ratio of blacks to non-blacks was 9.29 (95% CI: 4.33–19.93). *Conclusions:* Accurate incidence rate estimates for all patients with clinically suspected TTP-HUS, idiopathic TTP-HUS, and TTP associated with severe ADAMTS-13 deficiency have been determined. The greater incidence among women and blacks is comparable with their increased risk for other autoimmune disorders.

Keywords: hemolytic uremic syndrome, incidence, racial disparity, thrombotic thrombocytopenic purpura.

Correspondence: James N. George, The University of Oklahoma Health Sciences Center, Hematology-Oncology Section, P.O. Box 26901, Oklahoma City, OK 73190, USA.
Tel.: (405) 271-4222; fax: (405) 271-6444; e-mail: james-george@ouhsc.edu

Received 7 January 2005, accepted 8 March 2005

Introduction

Accurate estimates of the incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) are important in order to assess the resources required for current standard treatments and also to anticipate the number of patients who may benefit from potential new treatments, such as replacement therapy with recombinant ADAMTS-13 [1].

Previous estimates of the incidence of TTP have been indirect. Török *et al*. estimated the annual incidence of TTP to be 3.7×10^6, based on analysis of the USA death certificates from 1968 to 1991 [2]. However, death certificate data may be inaccurate. A recent autopsy study documented that the sensitivity and the positive predictive value of death certificates for predicting the cause of death were only 47% and 54%, respectively [3]. Furthermore, the method of Török *et al*. [2] required an estimate of the TTP mortality rate in order to calculate the total number of patients from the number of recorded deaths. For this calculation, they estimated the mortality rate to be 30% [2], but during the years of this analysis plasma exchange treatment was introduced and the mortality rate dramatically decreased, from 90% [4] to approximately 20% [5]. Therefore, the use of a single mortality rate estimate may have caused additional inaccuracy.

Miller *et al*. estimated the USA incidence of TTP from claims submitted to a health insurer covering 18 states [6]. Their annual incidence rate estimate of 3.8×10^6 [6] was nearly identical to the estimate of Török *et al*. [2]. However, their data

may have been biased by the selection of patients with health insurance and the inconsistency of insurance claims reports. Neither study [2,6] reported data on patients with ADAMTS-13 deficiency.

In contrast to these indirect estimates [2,6], we have directly determined the incidence rates for TTP-HUS from the data of The Oklahoma TTP-HUS Registry. We have estimated the incidence rate for all patients with clinically suspected TTP-HUS, patients with idiopathic TTP-HUS, and patients with severe ADAMTS-13 deficiency. We have standardized our incidence rates to the USA census data to make our data generalizable to the USA population.

Methods

The Oklahoma TTP-HUS registry

The Registry includes all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide plasma exchange treatment for clinically suspected TTP or HUS [7,8], based on the presence of microangiopathic hemolytic anemia and thrombocytopenia without an apparent etiology [5,9]. Because the OBI is the sole provider of plasma exchange services for all hospitals in central, western, and southeastern Oklahoma, the Registry is an inception cohort of all consecutive patients in a defined geographic region. The standard practice in our region is to treat all adult patients who have clinically suspected TTP or HUS, as well as children with TTP and atypical HUS, with plasma exchange. Therefore, we use the comprehensive term, TTP-HUS, to describe all patients. The only patients systematically excluded from the Registry are those not treated with plasma exchange, such as children with typical (diarrhea-associated) HUS who are managed with supportive care. Adults who present with a prodrome of bloody diarrhea are treated with plasma exchange and are therefore included in the Registry. The Registry region includes 58 of the 77 Oklahoma counties with a population in 2000, the midpoint for the 8.5 years of this analysis, of 2.31×10^6 [10]. The Oklahoma City Metropolitan Statistical Area, a region including six counties with a population of 1.08×10^6, was considered to be urban; the other 52 counties were considered to be rural [10]. The Oklahoma TTP-HUS Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Incidence rates

Our incidence rate estimates were determined from patients who had their initial episode of TTP or HUS between January 1, 1996 and June 30, 2004. Patients enrolled prior to 1996 were excluded for two reasons: (i) the number of patients enrolled in The Oklahoma TTP-HUS Registry increased each year from 1989, the year the Registry began, to 1995, similar to other experience [11]. Since 1995, there have been no consistent trends in the number of patients enrolled each year. (ii) Serum samples for measurement of ADAMTS-13 activity have only been routinely collected since November 13, 1995 [7].

From January 1, 1996 to June 30, 2004, 206 consecutive patients were enrolled who were permanently or temporarily living within the Registry region at the time of their initial episode; three additional patients were excluded from this analysis because they were referred from outside the Registry region. No patients for whom the OBI was requested to provide plasma exchange treatment for clinically suspected TTP or HUS declined to be enrolled. Follow-up is complete on all 206 patients to the present time.

Each patient was classified by age, sex, race, and urban or rural residence. Patients' race was defined by the investigators. Census data for race were defined as black (black alone or in combination with one or more other races, including both Hispanic and non-Hispanic blacks) or non-black (all other racial designations). Patients were assigned to counties according to their residence at the time of their initial episode. Standard methodologies were used to calculate standardized incidence rates (number of new cases divided by person-years of observation) and incidence rate ratios [12]. Age-, sex-, and race-specific incidence rates were calculated using the population data of the Registry region. To make these incidence rates generalizable to the USA population, they were standardized for age, sex, and race using the age, sex, and race distribution of the USA population. Both Oklahoma and the USA population data were obtained from the USA Census 2000, the midpoint for the 8.5 years of this analysis [10].

We calculated incidence rates using three different criteria to define TTP-HUS: (i) all patients who had an initial episode of clinically suspected TTP-HUS in whom the decision to initiate plasma exchange treatment was made; (ii) patients with idiopathic TTP-HUS, excluding TTP-HUS associated with hematopoietic stem cell transplantation, pregnancy, drugs, bloody diarrhea, or patients with an additional or alternative diagnosis; [7] and (iii) patients with severe ADAMTS-13 deficiency ($< 5\%$ activity; Table 1). No patients had a family history of TTP or HUS or had a history of recurrent episodes since childhood; therefore these data reflect the incidence of acquired TTP-HUS.

ADAMTS-13 measurements

ADAMTS-13 activity was measured as previously described [13,14] on serum samples collected immediately prior to the first plasma exchange treatment in 186 (90%) of the 206 patients. The clinical categories of these 186 patients are presented in Table 1. This assay method is reproducible, effectively discriminating among different ADAMTS-13 levels when compared with other current assays [15], and is used as the standard to validate new assay methods for ADAMTS-13 [16]. Patients were defined as having severe ADAMTS-13 deficiency if they had $< 5\%$ activity [14], either at the time of their initial presentation or at the time of a subsequent relapse. Among the 20 patients for whom we had no samples for ADAMTS-13 measurements, six died immediately after plasma exchange was

Table 1 Number of patients enrolled in the Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) Registry, January 1, 1996–June 30, 2004 according to clinical categories and ADAMTS-13 measurement

Diagnostic categories	All patients with suspected TTP-HUS ($n = 206$)	Patients with ADAMTS-13 measurements ($n = 186$)	Patients with ADAMTS-13 activity $< 5\%$ ($n = 27$)
Hematopoietic stem cell transplantation	9	8	0
Pregnancy/postpartum	14	13	2
Drug-associated	26	21	0
Bloody diarrhea prodrome	12	12	0
Additional/alternative diagnosis	68	62	1
Autoimmune disease	26	23	0
Sepsis	18	16	0
Systemic malignancy	8	7	0
HIV infection	4	4	1
Malignant hypertension	3	3	0
Multiorgan failure	9	9	0
Idiopathic	77	70	24

Criteria for defining the diagnostic categories have been previously described [7].

requested, before treatment could be begun and a sample collected; in the 14 other patients, the samples were either not obtained or misplaced by error.

Results

Using any of the three criteria to define TTP-HUS, most patients were women (Table 2); the relative frequency of women increased as the defining criteria became more specific: all patients with suspected TTP-HUS, 67%; idiopathic TTP-HUS, 73%; severe ADAMTS-13 deficiency, 74%. The relative frequency of black patients also increased as the defining criteria became more specific: all patients with suspected TTP-HUS, 19%; idiopathic TTP-HUS, 27%; severe ADAMTS-13 deficiency, 44% (Table 2). TTP-HUS was less common in people ≤19 years old (Fig. 1), even though the percentage of the USA population is similar in the three younger age groups in Table 2 (≤19 years, 29%; 20–39 years, 29%; 40–59 years, 26%) [10]. The age range among all patients with suspected TTP-HUS reflects the heterogeneity of these syndromes (Fig. 1). For example, the 13 women with pregnancy or postpartum-associated TTP-HUS were all young (17–37 years old) and the 11 patients with quinine-associated TTP-HUS were all older (42–79 years old). Most patients (24 of 27, 89%) with severe ADAMTS-13 deficiency were between 20 and 59 years old. Most patients (24 of 27, 89%) with severe ADAMTS-13 deficiency had idiopathic TTP-HUS [7]; two were postpartum and one had HIV infection (Table 1).

Table 2 Number of patients enrolled in the Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) Registry, January 1, 1996–June 30, 2004 according to age, sex, race, and criteria for disease definition

	Suspected TTP-HUS ($n = 206$)		Idiopathic TTP-HUS ($n = 77$)		ADAMTS-13 deficient ($n = 27$)	
Sex	Non-black	Black	Non-black	Black	Non-black	Black
Men, age (years)						
≤19	2	1	2	1	1	0
20–39	9	7	2	2	0	2
40–59	22	7	4	3	2	2
60–79	15	0	4	0	0	0
≥80	5	0	3	0	0	0
Women, age (years)						
≤19	7	0	3	0	1	0
20–39	29	10	10	5	7	4
40–59	37	11	16	7	3	4
60–79	34	2	8	2	1	0
≥80	6	2	4	1	0	0

Criteria for defining the three categories for TTP-HUS and the racial categories are described in Methods.

The standardized incidence rate of all patients with clinically suspected TTP-HUS in the Oklahoma Registry was 11.29×10^6 (Table 3). The standardized incidence rate of patients with idiopathic TTP-HUS was 4.46×10^6 and the standardized incidence rate of patients with severe ADAMTS-13 deficiency was 1.74×10^6. The standardized incidence rate ratio comparing blacks with non-blacks was significantly > 1 using any of the three criteria to define TTP-HUS (Table 3). Among patients who had TTP associated with severe ADAMTS-13 deficiency, the incidence rate ratio indicates that the incidence rate of TTP associated with severe ADAMTS-13 deficiency is more than ninefold higher in blacks than non-blacks. The standardized incidence rate ratio of TTP-HUS comparing women with men was also significantly > 1 for any of the three criteria. There may have been an increased incidence of TTP-HUS among patients who live in urban counties compared with rural counties (Table 3).

Discussion

Estimates of the incidence rates for TTP-HUS from The Oklahoma TTP-HUS Registry should be more accurate than previous estimates, because all patients within a defined geographic area for whom plasma exchange treatment was requested for clinically suspected TTP-HUS were identified and enrolled. Previous estimates of the incidence of TTP were indirect, requiring extrapolation of data from death certificates [2] or from insurance claims records [6].

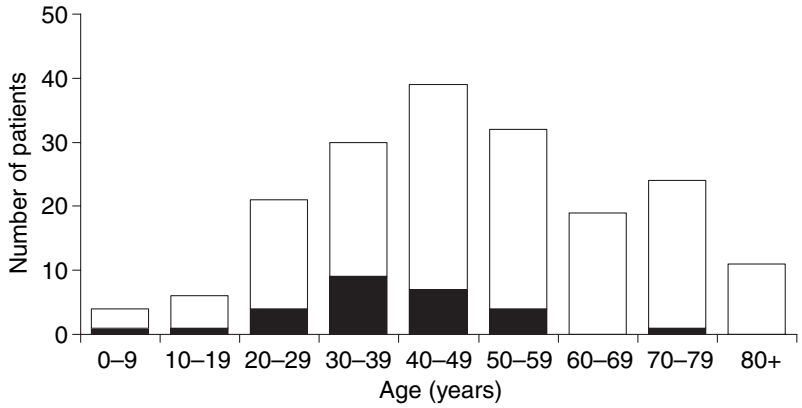

Fig. 1. Age distribution of patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS). The open bars represent all 186 patients for whom ADAMTS-13 activity was measured. The subset of 27 patients with severe ADAMTS-13 deficiency (< 5% activity) is represented by the lower black sections of these bars.

Table 3 Annual incidence per 10^6 population of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) in the Oklahoma TTP-HUS Registry

		Incidence rate ratios		
Criteria for definition	Incidence rates (all patients)	Women/men	Black/non-black	Urban/rural
Suspected TTP-HUS	11.29 (9.70–12.88)	1.85 (1.37–2.49)	3.07 (2.16–4.37)	1.41 (1.05–1.88)
Idiopathic TTP-HUS	4.46 (3.43–5.50)	2.44 (1.45–4.09)	4.92 (2.95–8.19)	1.38 (0.84–2.27)
ADAMTS-13-deficient	1.74 (1.06–2.41)	2.68 (1.11–6.51)	9.29 (4.33–19.93)	2.14 (0.84–5.24)

For calculation of the incidence rates for all patients and of the urban/rural incidence rate ratios, incidence data were standardized for age, sex, and race. For calculations of incidence by race, data were standardized for age and sex. For calculations of incidence by sex, data were standardized for age and race.
Data in parentheses are 95% confidence intervals.

Our estimate of the incidence of all patients with clinically suspected TTP-HUS who were treated with plasma exchange, 11.29×10^6, is threefold greater than the two previous reports on the incidence of TTP [2,6]. This may be due to the heterogeneity of these patients (Table 1). Some patients subsequently had an alternative diagnosis made after plasma exchange was begun, such as unsuspected sepsis or disseminated malignancy [7]. Although these 206 patients were heterogeneous, with multiple different etiologies and associated clinical conditions and some may not have had TTP-HUS, this estimate is important to anticipate the resources required for plasma exchange services, as the request for plasma exchange treatment was the defining criterion for these patients.

Our estimate of the incidence of patients defined as having idiopathic TTP-HUS, excluding TTP-HUS associated with hematopoietic stem cell transplantation, pregnancy, drugs, bloody diarrhea, or patients with an additional or alternative diagnosis [7,17], was similar to the previous estimates of the incidence of TTP [2,6]. This may indicate that patients currently described as idiopathic TTP-HUS, a subset of all patients with clinically suspected TTP-HUS, resemble patients whose death certificates [2] or insurance claims [6] were coded as TTP. However, patients with non-idiopathic TTP-HUS also have the characteristic clinical features of TTP and may also have severe ADAMTS-13 deficiency [7].

Our estimate of the incidence of patients who had severe ADAMTS-13 deficiency is important to anticipate the need to develop new therapies. The standardized incidence rate for patients with severe ADAMTS-13 deficiency is lower than for all patients with clinically suspected TTP-HUS or patients with idiopathic TTP-HUS. TTP associated with severe ADAMTS-13 deficiency was rare in children and older adults, consistent with previous observations [18]. Also the incidence of women and blacks among patients with severe ADAMTS-13 deficiency was greater than among all patients with clinically suspected TTP-HUS (Table 3).

The greater incidence rate of TTP-HUS among women is consistent with many previous observations [19]. The increased relative frequency of blacks among patients with TTP has been suggested in previous case series [2,7,17,20,21]. There may also be an increased incidence of TTP-HUS among patients who live in urban counties compared with rural counties, perhaps due to a higher index of suspicion in the urban hospitals related to awareness of The Oklahoma TTP-HUS Registry. Increased recognition of TTP associated with publicity about a clinical trial was previously documented in Canada [11].

As acquired severe ADAMTS-13 deficiency may be an autoimmune disorder [1,13], the increased incidence among women and blacks may be comparable with their increased risk

for developing other autoimmune disorders, such as systemic lupus erythematosus [22]. The increased incidence among blacks could also be related to their higher plasma levels of von Willebrand factor (VWF) [23], which may increase their risk for VWF-mediated platelet thrombus formation in the absence of ADAMTS-13.

Limitations of this analysis are that some patients may have died before the diagnosis of TTP-HUS was considered and some patients residing within the Registry region may have received treatment elsewhere. Also the incidence rate for patients with severe ADAMTS-13 deficiency may be underestimated because ADAMTS-13 activity was not measured in 20 patients. The strength of these data is the direct analysis of consecutive patients within a defined geographic region over 8.5 years.

Acknowledgement

This study was supported by grant no. 32-66756.01 from the Swiss National Science Foundation.

References

1 Moake JL. Thrombotic microangiopathies. *New Engl J Med* 2002; **347**: 589–600.
2 Török TJ, Holman RC, Chorba TL. Increasing mortality from thrombotic thrombocytopenic purpura in the United States – analysis of national mortality data, 1968–1991. *Am J Hematol* 1995; **50**: 84–90.
3 Sington JD, Cottrell BJ. Analysis of the sensitivity of death certificates in 440 hospital deaths: a comparison with necropsy findings. *J Clin Pathol* 2002; **55**: 499–502.
4 Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine (Baltimore)* 1966; **45**: 139–59.
5 Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *New Engl J Med* 1991; **325**: 393–7.
6 Miller DP, Kaye JA, Shea K, Ziyadeh N, Cali C, Black C, Walker AM. Incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. *Epidemiology* 2004; **15**: 208–15.
7 Vesely SK, George JN, Lammle B, Studt J-D, Alberio L, El-Harake MA, Raskob GE. ADAMTS-13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood* 2003; **101**: 60–8.
8 George JN, Vesely SK, Terrell DR. The Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) registry: a community perspective of patients with clinically diagnosed TTP-HUS. *Semin Hematol* 2004; **41**: 60–7.
9 George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Blood* 2000; **96**: 1223–9.
10 US Census Bureau. *Census 2000 Summary File 2; using American Fact Finder*. Available at: http://factfinder.census.gov, accessed on August 27, 2004.
11 Clark WF, Garg AX, Blake PG, Rock GA, Heidenhwim AP, Sackett DL. Effect of awareness of a randomized controlled trial on use of experimental therapy. *JAMA* 2003; **290**: 1351–5.
12 Greenland S, Rothman KJ. Introduction to stratified analysis. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology*, 2nd edn. Philadelphia, USA: Lippincott, Williams, and Wilkins, 1998.
13 Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, Krause M, Scharrer I, Aumann V, Mittler U, Solenthaler M, Lammle B. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *New Engl J Med* 1998; **339**: 1578–84.
14 Bianchi V, Robles R, Alberio L, Furlan M, Lammle B. von Willebrand factor-cleaving protease (ADAMTS-13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura. *Blood* 2002; **100**: 710–3.
15 Tripodi A, Chantarangkul V, Bohm M, Budde U, Dong JF, Friedman KD, Galbusera M, Girma J-P, Moake J, Rick ME, Studt J-D, Turecek PL, Mannucci PM. Measurement of von Willebrand factor cleaving protease (ADAMTS-13): results of an international collaborative study involving 11 methods testing the same set of coded plasmas. *J Thromb Haemost* 2004; **2**: 1601–9.
16 Whitelock JL, Nolasco L, Bernardo A, Moake J, Dong JF, Cruz MA. ADAMTS-13 activity in plasma is rapidly measured by a new ELISA method that uses recombinant VWF-A2 domain as substrate. *J Thromb Haemost* 2004; **2**: 485–91.
17 Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS-13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and non-idiopathic thrombotic thrombocytopenic purpura. *Blood* 2004; **103**: 4043–9.
18 Furlan M, Lammle B. Aetiology and pathogenesis of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. *Best Pract Res Clin Haematol* 2001; **14**: 437–54.
19 George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Curr Opin Hematol* 2003; **10**: 339–44.
20 Conlon PJ, Howell DN, Macik G, Kovalik EC, Smith SR. The renal manifestations and outcome of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in adults. *Nephrol Dial Transplant* 1995; **10**: 1189–93.
21 Elkins SL, Wilson PP, Files JC, Morrison FS. Thrombotic thrombocytopenic purpura: evolution across 15 years. *J Clin Apheresis* 1996; **11**: 173–5.
22 McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, Kwoh CK. Incidence of systemic lupus erythematosus: race and gender differences. *Arthritis Rheum* 1995; **38**: 1260–76.
23 Miller CH, Haff E, Platt SJ, Rawlins P, Drews CD, Dilley AB, Evatt B. Measurement of von Willebrand factor activity: relative effects of ABO blood type and race. *J Thromb Haemost* 2003; **1**: 2191–7.