Venous thromboembolism: racial and ethnic influences

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The epidemiology and risk factors for venous thromboembolism are well described in European populations, but such data is scarce in other ethnic groups. Venous thrombosis has traditionally been perceived as affecting only Europeans; this erroneous belief is reinforced by the low incidence of the common hereditary thrombophilias outside Europe, together with the lack of general perception and poor availability of diagnostic services in developing countries. It is now evident that venous thrombosis is prevalent across a number of different racial groups. Furthermore, conventional thrombophilia testing has been shown to be uninformative in most non-Europeans and laboratory reference ranges for these tests may be inappropriate for some non-European populations. Further research is needed to characterize the nature of venous thromboembolism in non-Europeans.

Keywords: deep-vein thrombosis, ethnicity, pulmonary embolism, race, thrombophilia, thromboprophylaxis

Influence of race & ethnicity on disease

Whether race and ethnicity influences the pathophysiology of disease remains a matter of controversy. A variety of classifications for race have been proposed, but there is no agreement on a universal categorization system [1]. A classification system employed by the USA Census includes five broad ethnic/racial groupings (African–American, White, Asian, Pacific Islander and American Indian or Alaskan native) [2]. Alternative classifications have been used in the UK (e.g., White, Black, Asian, Chinese and Mixed). Racial groupings are based on the geographic origin of our ancestors [3] and are determined by patterns of mating in geographically isolated populations, where physical barriers of sea, desert and mountains have separated populations. Within these racial groups, selective mating between those of similar ethnicity provides genetic subgroups based on ethnic influences. Ethnic origin is a broader concept than race and reflects religion, culture, skin color, language, tradition and common genetic ancestry (e.g., Romany, Arab, Tutsi and Ashkenazi). Studies of population genetics indicate the presence of significant genetic variation between different racial groups, with discrete ethnic subsets within major racial groups [4].

There is abundant evidence for an effect of race and ethnicity on the risks, outcomes and treatments for common diseases [5]. A number of race-specific genetic variants have been characterized that predispose to/protect against disease [6–8] and modify the effects of drugs in racial and ethnic subgroups [9–11]. In addition to genetic influences, a variety of sociocultural factors contribute to the widespread inequality in disease outcomes in these groups [5].

Venous thrombosis: the 'European burden'?

Our understanding of the epidemiology and risk factors for venous thrombosis in non-Europeans remains limited. Venous thrombosis has historically been perceived as a disease restricted to European populations [12,13], an erroneous belief reinforced by the low incidence of hereditary thrombophilia in non-Europeans together with the lack of diagnostic services in underdeveloped countries. Early studies had pointed to a lower incidence of deep-vein thrombosis (DVT) and pulmonary embolism (PE) in Asian, African and African–American populations than in those of European origin. In an autopsy-based study of 1200 cases of PE, higher rates of thrombosis were reported in North Americans (15%) than in Japanese subjects (0.7%) [14]. Venous thrombosis rates in California (USA) had been shown to be lower in Hispanics and Pacific Islanders than in Caucasians [15], and similar findings were reported by another group in the same region of America [16]. Other studies reported a very low incidence of postoperative DVT in Alaskan natives [17], and reduced incidence and mortality rates for PE in Asians/Pacific Islanders [18]. Low incidence rates for DVT were found in a black Caribbean population (11–17/100,000) [19], and lower rates of PE were found at autopsy in Uganda than in St Louis (MO, USA) [20]. Interestingly, a low incidence of postoperative DVT was previously reported in Sudanese patients [21] and in Malaysians [22].

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Recent data have confirmed that, rather than being a disease restricted to Europeans, venous thromboembolism (VTE) has a worldwide prevalence [23]. The absence of common prothrombotic risk factors for VTE in non-European subjects, many of whom have a family history of thrombosis, suggested that they possess as yet uncharacterized coagulation disturbances.

Venous thrombosis in Europeans

Epidemiology, gender & acquired risk factors

The epidemiology of venous thrombosis in Europeans and US whites has been extensively documented, with annual incidence rates for first symptomatic VTE ranging between 71 and 117 cases per 100,000, with a marked increase over the age of 60 years [24]. Although VTE was previously assumed to occur predominantly in surgical patients or those with malignancy, it is now evident that it is as common in the acute medical setting [24]. Despite the consistent association between VTE and pregnancy, hormone replacement and oral contraceptives, there is no strong evidence for a difference in incidence rate for a first episode of venous thrombosis between Caucasian men and women, but rates of recurrent VTE rates are substantially higher in Caucasian men [25].

Hereditary thrombophilia in Europeans

Inherited thrombophilic mutations can be found in 30–70% of Europeans with idiopathic or recurrent VTE [26]. The Factor V (FV) Leiden mutation is the most prevalent of these, occurring in 2–15% in the general population of Europe and in 20–50% of subjects with VTE [27,28]. Prothrombin (PT) G20210A is a common gene polymorphism occurring in 6% of Europeans with venous thrombosis and in 2% of healthy controls [12]. These mutations have a similar worldwide distribution, and are both rare outside Europe. Coinheritance of these mutations (or homozygosity for a single mutation) has a synergistic effect on the increased risk of VTE, as well as being associated with thrombosis at a younger age [29]. The prevalence of FV Leiden within Europe varies between countries [12,13], with a mean allele frequency of 2.7%. The peak frequency occurs in Greeks (15%) with lower frequencies in Italy, Finland and Holland (1.4–1.5%). It is thought that FV Leiden is a founder mutation and was spread throughout Europe by Neolithic farmers 10,000 years ago. The population distribution of the rarer hereditary thrombophilias (antithrombin, protein C and protein S deficiencies) is poorly defined.

Venous thrombosis in non-European populations

Recent reports suggest that VTE is common across a variety of racial groups, including Japanese, African–Americans, Afro–Caribbeans and West Africans [23,24,30,31].

Ethnic groups in America

A number of studies have investigated the incidence of VTE in the major ethnic groups of California, a US state with a racially diverse population [32–34]. In one of the studies, the authors found an significantly higher incidence of VTE in African–Americans compared with Caucasians, Hispanics and Pacific-Islanders [32]. A study of acute PE in a North American general hospital found similar rates of PE in African–Americans compared with US whites [35], and a recent study of PE diagnosis in the USA showed no difference in diagnostic rates between African–Americans and white Americans [36]. Other studies have reported an increased incidence of PE and increased mortality following PE in African–Americans compared with Caucasians [37,38]. A study in New Jersey (USA) [39] reported a 62% higher rate of PE in black women and a 47% higher rate of PE in black men compared with white patients, but no difference in mortality rates. Finally, African–Americans are reported to have higher complication rates (death, bleeding or recurrent VTE) than white Americans, which was not explained by access to healthcare [40].

The Genetic Attributes and Thrombosis Epidemiology (GATE) is a large case–control study examining racial differences in the pathogenesis of VTE [41]. This study found similar rates of VTE in African–Americans compared with white Americans (125/174 vs 130/196; $p > 0.2$). The prevalence of a family history of VTE was found to be similar in both racial groups (28 vs 29%).

Asia

A small number of reports pointed to a low incidence of VTE in Asians when compared with Caucasians [42–44]. In a study of autopsy data, Hirst *et al.* found a far higher PE prevalence in North America than in Japan [45]. The belief that post-operative DVT was rare in Asians was in part owing to underdiagnosis, and led to thromboprophylaxis being infrequently prescribed for surgical patients in these populations. Thromboprophylaxis policy should now be reconsidered in light of several studies that show similar rates of postoperative VTE in this group

(including Malaysian, Thai, Chinese, Korean, Japanese and Singaporean patients) compared with Europeans [46–50]. In a study of SE Asian patients undergoing major joint surgery in the absence of pharmacological thromboprophylaxis, 41% (121/295) of subjects developed venographically proven postoperative DVT (proximal DVT in 30/295 and PE in 2/407 of subjects) [47]. In a prospective study in Japanese patients undergoing major abdominal surgery [50], 20.8% (36/173) had objectively confirmed distal DVT, 2.9% (5/173) had proximal DVT and one patient had asymptomatic PE. Venous thrombosis is known to occur in Chinese women during pregnancy [51] and following gynecological surgery [52]. Symptomatic VTE also occurs in Chinese children (0.74/100,000) at a rate comparable with Caucasian children [53]. DVT is common among Asian patients following ischemic stroke (45% by day 25–30) [54]. Preliminary data suggest differences in thrombosis site, with a lower incidence of proximal DVT and symptomatic PE in Asians compared with Europeans, but the reasons for this remain unclear [49,50,52]. As in European populations, low-molecular-weight heparin appears to be effective in postoperative DVT prophylaxis in Asians [55,56].

UK black population

Similar VTE rates have been reported in the UK black population compared with UK whites [23]. Of those with DVT, black subjects were younger than white subjects, with a trend towards black subjects experiencing more proximal DVTs. Identifiable acquired risk factors for VTE in black patients were: surgery (23%), malignancy (3%), recent travel of more than 4-h duration (10%), obesity (53%), pregnancy (6%), hormone-replacement therapy (3%) and combined oral contraceptive pill (3%); 23% were 'idiopathic'. There was no significant difference between the two groups for the following risk factors: malignancy, surgery, immobility, trauma, previous VTE, estrogen use and intravenous drug abuse. Travel was more frequently a risk factor in whites with DVT; in blacks with DVT, obesity and pregnancy were more frequent risk factors than in white subjects.

Race, gender & recurrent VTE

It is now recognized that men have a higher recurrent VTE rate than women [57–59], with the reported increase in risk ranging from 40 to 400%. White *et al.* studied the influence of gender and race on VTE recurrence in the racially diverse population of California, USA, and found that overall, women had a 40% lower VTE recurrence rate compared with men [25]. Although similar recurrence rated were found in men of different races, recurrence rates in Hispanic women were far higher than women of other races, and were similar to those in men. It is well known that recurrent VTE rates vary depending on the trigger for the initial event and the persistent risk factors for VTE. Clearly, the effect of gender on VTE recurrence varies between racial groups and therefore cannot be generalized.

Hereditary thrombophilia in non-Europeans

Inherited thrombophilia

FV Leiden is not restricted to mainland Europe, but is predictably seen in Caucasian Australian (2%) and North American (3%) populations owing to known emigration patterns. In population surveys, FV Leiden was not detected in any African, South-East Asian, Chinese or indigenous Australasian populations [12,60]. Prevalence of FV Leiden in north Indian patients with DVT is 12% [61]. FV Leiden is thought to have arisen as a founder mutation and spread throughout Europe from the Middle East by Neolithic farmers 10,000 years ago [13]. The low prevalence of the FV Leiden mutation in US blacks (0.4%) [41] and UK blacks (1.8%) [23] has presumably occurred as a result of interbreeding in multiracial communities. Low prevalence rates for FV Leiden have also been reported in other US racial groups, including Hispanics, Asian–Americans and Native Americans [62]. Pepe *et al.* reported an absence of FV Leiden in non-European groups, including sub-Saharan Africans, south-east Asians, Native Americans and Ethiopians [60]. Similarly, the PT20210 polymorphism occurs in 2.3% of healthy Caucasians [12] compared with 0.2% in US blacks [41] and 0% in UK blacks [23]. This polymorphism was not detected in Australasia, Africa, south-east Asia or the Middle East in one large survey [32], and Franco *et al.* reported its absence in Brazilian blacks, Asians and Native Americans [63]. A relatively high prevalence of hereditary protein C and protein S deficiency has been reported to occur in Chinese populations, possibly as a result of consanguinity. An elevated FVIII:C level has been reported to be a common, dose-dependent risk factor for DVT in a UK black population [23].

Fibrinogen

The limited studies of fibrinogen level and VTE in non-Europeans provide evidence of a weak association. Fibrinogen levels are reported to be higher in African–American populations than in US whites [64,65], and have been weakly associated with VTE in this group [66]. Recent reports suggest that UK blacks have lower fibrinogen concentrations when compared with UK whites [67], but the relationship between fibrinogen and VTE has not been studied in this group.

Several studies indicate that fibrinogen level is independently associated with the β-fibrinogen -455G/A polymorphism in white subjects, but this polymorphism has not consistently been associated with either arterial or venous disease. Reports suggest that β-455A allele frequency is lower in healthy US and UK black populations when compared with white populations [66,67].

African–Americans have been reported to have significantly higher fibrinogen levels than white Americans [64,65], which may partly explain their substantially higher rates of stroke and ischemic heart disease [68]. In a small study, Austin *et al.* reported a trend towards increased risk of VTE in African–Americans with fibrinogen concentrations greater than 4g/l, but this finding was not statistically significant [66].

African and Caribbean populations in the UK have higher mortality from stroke, but lower rates of ischemic heart disease than UK whites [69]. This mortality from stroke is likely to be owing to the high prevalence of hypertension in UK blacks [70]. Lower rates of coronary disease in UK blacks compared with UK whites may be owing to the favorable lipid profile in this group [71], although similarly favorable lipid profiles in US blacks [72] have not been associated with a similar protective effect. Cook *et al.* reported significantly lower fibrinogen levels in UK blacks compared with UK whites, and hypothesized that this may explain the lower risk of coronary disease in this population [67]. It is not known whether elevated fibrinogen level is a risk factor for VTE in the UK black population. The *Bcl* I B2 and -455A alleles are under-represented in both UK and US black populations [66–67], and have not been associated with fibrinogen level or thrombotic disease in these populations.

Executive summary

Influence of race & ethnicity on disease

- Whether race influences the pathophysiology of disease remains controversial.
- There is no universal classification for race or ethnicity.

Venous thrombosis: the 'European burden'?

- Venous thrombosis was previously erroneously perceived as a disease restricted to Europeans.
- It is now established that venous thromboembolism (VTE) has a worldwide prevalence.

Venous thrombosis in Europeans

- The epidemiology of VTE in Europeans has been well characterized.
- Inherited thrombophilic mutations can be found in 30–70% of Europeans with idiopathic or recurrent VTE.
- Men have a higher rate of recurrent VTE than women.

Venous thrombosis in non-Europeans

- The absence of common hereditary prothrombotic risk factors for VTE in most non-Europeans, many of whom have a family history of thrombosis, suggests that they possess uncharacterized coagulation disturbances.
- Elevated FVIII, D-dimer and fibrinogen concentrations are prothrombotic risk factors in the UK black population.
- Recurrent venous thrombosis is overall more common in men, but this is not true in all racial groups.

Conventional thrombophilia testing

- Reference ranges for thrombophilia tests in European populations are inappropriate for a UK black population.
- Conventional thrombophilia testing is uninformative in most non-Europeans patients with VTE, and negative results should be interpreted with caution in these populations.

Future perspective

- Research into the inherited and acquired risk factors for VTE in non-European populations is needed.
- Promoting an awareness of the risk of VTE and the efficacy of thromboprophylaxis in non-European medical establishments is also required.
- Evaluating the outcome following venous thrombosis in non-Europeans (recurrent venous thrombosis, post-thrombotic syndrome and pulmonary hypertension) is necessary.
- It is also of importance to establish the causes of differences in the site of venous thrombosis between racial groups.

Conventional thrombophilia testing

Reference ranges for thrombophilia tests in European populations are inappropriate for a black population, leading to a significant proportion of healthy black subjects being misdiagnosed as having protein C, protein S and possibly antithrombin deficiency using reference ranges derived from white populations [73]. Healthy black Africans were found to have significantly lower protein S and protein C levels, with a trend towards lower antithrombin levels compared with healthy white Europeans. Negative results have been reported in over 90% (130/142) of UK black patients with VTE undergoing thrombophilia testing and may lead to a false reassurance of normality, and positive results using inappropriate reference ranges may now be viewed as unreliable [74].

Conclusion & future perspective

Rather than being limited to Europeans, VTE is clearly a disease affecting a broad range of ethnic groups, and efforts need to be focused on raising awareness of the disease in health professionals treating these communities. Given the low incidence of hereditary thrombophilia in non-Europeans, the significant rates of VTE in these populations suggest they possess as yet uncharacterized prothrombotic risk factors. Data on race are vital to enable us to understand the reasons for differences in disease prevalence and outcome across racial groups, but biomedical research in racial minority groups is sparse. More important, perhaps, is the target of reducing the health inequality prevalent in ethnic minority groups. This will be achievable only if evidence-based research into the causes of inequality becomes a priority, particularly in the developed world.

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- **Reported that the prevalence of hereditary thrombophilia in a UK black population with VTE (9.1%) was significantly lower than the UK white population with VTE (30%).**