Journal of Thrombosis and Haemostasis, **12**: 1580–1590 DOI: 10.1111/jth.12698

REVIEW ARTICLE

Thrombosis: a major contributor to the global disease burden

ISTH STEERING COMMITTEE FOR WORLD THROMBOSIS DAY[1]

To cite this article: ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. *J Thromb Haemost* 2014; **12**: 1580–90.

Summary. Thrombosis is a common pathology underlying ischemic heart disease, ischemic stroke, and venous thromboembolism (VTE). The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2010 documented that ischemic heart disease and stroke collectively caused one in four deaths worldwide. GBD 2010 did not report data for VTE as a cause of death and disability. We performed a systematic review of the literature on the global disease burden caused by VTE in low-income, middle-income and high-income countries. Studies from western Europe, North America, Australia and southern Latin America (Argentina) yielded consistent results, with annual incidence rates ranging from 0.75 to 2.69 per 1000 individuals in the population. The incidence increased to between 2 and 7 per 1000 among those aged $\geq$ 70 years. Although the incidence is lower in individuals of Chinese and Korean ethnicity, their disease burden is not low, because of population aging. VTE associated with hospitalization was the leading cause of disability-adjusted life-years (DALYs) lost in low-income and middle-income countries, and the second most common cause in high-income countries, being responsible for more DALYs lost than nosocomial pneumonia, catheter-related bloodstream infections, and adverse drug events. VTE causes a major burden of disease across low-income, middle-income and high-income countries. More detailed data on the global burden of VTE should be obtained to inform policy and resource allocation in health systems, and to evaluate whether improved utilization of preventive measures will reduce the burden.

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Received 7 July 2014
Manuscript handled by: F. R. Rosendaal
Final decision: F. R. Rosendaal, 9 August 2014

Keywords: cardiovascular diseases; deep vein thrombosis; public health; pulmonary embolism; thrombosis; venous thromboembolism.

Introduction

A doubling of life-expectancy and a quadrupling of the world population during the 20th century have been associated with a transition from infectious to non-communicable diseases as the major causes of death and disability worldwide [1–3]. Cardiovascular disease is a leading contributor to the burden caused by non-communicable diseases. Thrombosis is the most common underlying pathology of the three major cardiovascular disorders: ischemic heart disease (acute coronary syndrome), stroke, and venous thromboembolism (VTE).

The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study, which was initiated by the World Health Organization (WHO) and the World Bank, is a systematic scientific investigation aimed at quantifying the comparative magnitudes of health loss caused by diseases, injuries and risk factors by age, sex and geographic region throughout the world [3–5]. The most recent version of this effort, GBD 2010, documents the number of deaths from 235 causes from 1990 to 2010, using data from 187 countries and 21 regions; these regions are grouped further into seven super-regions [4,5]. The study also provides estimates of the years of life lost because of premature mortality (YLL), the years lived with disability (YLD), and the disability-adjusted life-years (DALYs) [4,5]. DALYs indicate how many years of healthy life are lost because of premature death or non-fatal illness or disability, and are calculated as the sum of YLL and YLD [6].

GBD 2010 documented 52.8 million deaths globally in 2010 [3]. Non-communicable disease accounted for 34.5 million deaths, or two of every three deaths [3]. Ischemic heart disease (7.0 million deaths) and stroke (5.9 million deaths) collectively caused one in four deaths worldwide [3]. The 7.0 million deaths resulting from ischemic heart disease represent a 35% increase since 1990. Approximately half of all stroke deaths resulted from ischemic stroke, which is caused by thrombosis. The 2.8 million deaths resulting from ischemic stroke

represent a 25% increase since 1990. Although there is substantial regional variation, ischemic heart disease ranks as the first or second most common cause of YLL in 13 of the 21 regions, and ranks in the top five causes of death in 17 regions [3]. Stroke ranks as the first or second most common cause of YLL in eight regions, and is in the top five most common causes in 14 regions [3]. Ischemic heart disease was the leading cause of DALYs lost worldwide in 2010 (up from fourth in 1990, an increase of 29%), and stroke was the third leading cause (up from fifth in 1990, an increase of 19%) [6]. More than 60% of new strokes, and 45% of deaths resulting from stroke, occur in individuals aged < 75 years [7].

GBD 2010 clearly documents the major impact of arterial thrombosis on the global disease burden, because it is the pathologic mechanism underlying most cases of ischemic heart disease and ischemic stroke. However, the study does not report data for VTE as a specific cause of death and disability. A cursory review of the literature from western Europe and North America suggests that VTE is a major contributor to the burden caused by non-communicable diseases. For example, Cohen *et al*. used an incidence-based epidemiology model to estimate the number of non-fatal symptomatic VTE events, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), and the number of VTE-related deaths across the European Union in 2004 (population of 454.4 million) [8]. The results yielded estimates of 684 019 DVT events, 434 723 PE events, and a total of 543 454 VTE-related deaths [8]. In the USA, investigators from the Centers for Disease Control and Prevention used data from the National Hospital Discharge Survey to estimate that there were an average of 547 596 adult hospitalizations with a diagnosis of VTE each year during 2007–2009 among the population of 301–307 million [9]. If VTE caused a proportionate burden of disease across the other global regions, it would be highly ranked in the causes of death and DALYs worldwide. Given that much of the mortality and morbidity resulting from VTE is potentially preventable [10–13], data on the disease burden are important for health systems and policy-makers for planning resource allocation, both for healthcare delivery and for setting research priorities.

We therefore performed a systematic review of the literature on the global burden of disease attributable to VTE. The objective was to review the evidence for disease burden in each of the geographic regions specified in GBD 2010, using the variables of annual incidence rate (number of new cases each year per 1000 population at risk), prevalence (proportion of the population with the condition at a point in time), annual number of deaths, and DALYs.

Methods: literature search and review

A computer search of the literature was performed with OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, and EMBASE, from inception of these databases to May 2014. We used the disease-related keywords venous thromboembolism, deep vein thrombosis, venous thrombosis, vein thrombosis, thrombophlebitis, pulmonary embolism, and lung embolism, together with the additional keywords incidence, prevalence, mortality, case fatality, morbidity, surveillance and epidemiology, years lived with disability (YLD), and disability-adjusted life-years (DALY), to search the titles and abstracts of articles in these databases. We also reviewed the bibliographies of published articles. We excluded non-human studies, case reports, and clinical trials, as well as non-relevant publication types, including reports of clinical conferences and editorials. We also excluded articles published in languages other than English; the current report is therefore confined to the literature published in English. The identified citations from each database were exported to an ENDNOTE library, where the citations were de-duplicated. The merged list of citations was exported to a Word document that included citation number, title, list of authors, the full abstract, and the journal citation.

The abstracts were reviewed independently by two reviewers (A.W. and G.R), who categorized them according to the level of evidence as either level A, level B, or other; disagreements were resolved through discussion and consensus. Level A evidence was defined as population-based estimates of the parameters of the disease burden (incidence, prevalence, number of deaths, and DALYs) in the general population (age $\geq$ 18 years) derived from either population-based cohort studies, or from analysis of national health system databases or private health insurance claims data within a defined population, or derived by using a combination of the former methods with appropriate epidemiologic modeling methods. Level B evidence was defined as estimates of the burden in specific subpopulations, such as the elderly and pregnant women, with the same methods as described for level A. The category of 'other' evidence included all other study designs without a defined population with which to derive the disease burden parameters, such as single hospital base cohort studies or record review, and autopsy studies. Population-based mortality studies based on hospital discharge or other databases, or health department death certificate data, were also assigned to the category of 'other.' This article focuses on the level A evidence for overall disease burden according to global region. Selected level B evidence on the relationship between age and disease burden was also included where relevant. The evidence categorized as 'other' was not systematically reviewed.

To simplify comparison of incidence results across studies and between global regions, all incidence rates were converted to a rate per 1000 individuals per year.

Results

Literature search

The computerized literature search identified a total of 9603 citations. Of these citations, 8817 (92%) were in the English language. After the de-duplication check, a total of 8702 citations remained for review.

The two independent reviewers were in agreement on the classified level of evidence for 8671 (99%) of the 8702 reviewed citations; the remaining 31 citations were classified after discussion and consensus between the reviewers. The final classification designated 29 citations as level A evidence [14–42], 29 as level B evidence [43–71], and the remainder as other. Most of the level A studies evaluated the incidence of VTE or its components, DVT and/or PE [14–40]; two studies evaluated the prevalence of VTE [41,42].

Incidence of VTE

The results of the studies classified as level A evidence of incidence are summarized in Table 1. This evidence comes from only two of the seven global super-regions designated by GBD 2010: those designated 'High Income', and 'Southeast Asia, East Asia, and Oceania'. Within the high-income super-region, 11 level A studies were from western Europe [8,14–23], 10 were from North America, two were from Australasia (both from Australia) [33,34], one was from the southern Latin America region (Argentina) [35], and one was from the Asia Pacific region (Korea) [36]. The three level A studies from the super-region of 'Southeast Asia, East Asia, and Oceania' all came from the region of East Asia [37–39] (two studies from Hong Kong and one from Taiwan).

The relationship between increasing age and the incidence of VTE was evaluated in several of the level A studies [9,19,21,22,24,30,32,35–38,40]. The results of these studies are summarized in Table 2.

The level B studies evaluated the incidence of VTE in various subpopulations, such as women during pregnancy or the postpartum period [43–54], males or females of selected age categories [55–64], subgroups with or without selected risk factors or comorbidities [65–70], or special categories of thrombosis [71]. All but one of the level B studies came from the high-income super-region; the exception was from Sub-Saharan Africa (South Africa) [51]. Within the high-income super-region, 14 of the level B studies were from western Europe [43,44,46,49,54,55,57–59,61–63,65,69], 11 were from North America [45,47,50,52,56,60,64,67,68,70,71], two were from Australasia (both from Australia) [48,53], and one was from the high-income Asia Pacific region (Japan) [66].

Prevalence of VTE

Two studies were identified that evaluated the prevalence of VTE; both were performed in the USA by the same investigators [41, 42]. The national prevalence of VTE was determined during the 5-year period from 2002 to 2006 from a health insurance claims database of 12.7 million enrollees that included both private insurance claims and Medicare claims. The prevalence of VTE was 3.2 per 1000 enrollees in 2002, and 4.2 per 1000 enrollees in 2006 [41]. Among patients aged $\geq$ 65 years, the prevalence in 2006 was 13.8 per 1000 enrollees, as compared with 2.3 per 1000 enrollees in those aged < 65 years [41]. The authors used the 2006 data to project the US national prevalence as 0.95 million cases, and to project the future prevalence in 2050 to be 1.82 million cases [41]. The second study found that the prevalence of VTE was highest in African American males, followed by Caucasian males, Caucasian females, and African American females [42]. Hispanic individuals of both sexes had lower prevalence rates [42].

DALYs

Our search identified two studies that evaluated disease burden in terms of DALYs [72,73]. The methodologically strongest was the study by Jha *et al*., as part of the WHO's Patient Safety Program [72]. This study used analytic modeling to estimate the incidence rates of VTE, annual number of cases, and DALYs resulting from VTE associated with hospitalization in high-income, middle-income and low-income countries [72]. The data for the modeling were generated from two sources: an extensive literature review, and epidemiologic studies commissioned by the WHO, which were conducted in 26 hospitals across eight low-income and middle-income countries in the Eastern Mediterranean and North Africa regions (Egypt, Jordan, Kenya, Morocco, South Africa, Sudan, Tunisia, Yemen) [74], and in 35 hospitals across five countries in Latin America (Argentina, Colombia, Costa Rica, Mexico, and Peru) [75]. This approach enabled the authors to estimate the number of VTE events associated with hospitalization during 2009 for 117.8 million hospitalizations among 1.1 billion citizens of high-income countries, and for 203.1 million hospitalizations among 5.5 billion citizens of low-income and middle-income countries [72,74,75].

The study reported incidence rates of VTE per 100 hospitalizations of 3.3 (95% confidence interval [CI] 1.9–4.8) in high-income countries, and 3.0 (95% CI 1.0–4.8) in low-income and middle-income countries [72]. The estimated annual numbers of cases of VTE were 3.9 million (95% CI 1.9–6.3) for high-income countries, and 6.0 million (95% CI 1.2–12.8) for low-income and middle-income countries. VTE was the leading cause of hospital-related DALYs lost overall, being responsible for a full one-third (7681) of the total of 22 644 DALYs, and VTE accounted for more DALYs lost than nosocomial pneumonia, catheter-related bloodstream infections, and adverse drug events [72]. VTE was the leading cause of DALYs lost in low-income and middle-income countries,

Table 1 Studies providing level A evidence for the burden of disease caused by venous thromboembolism (VTE): incidence per 1000 population per year

Author and year	Study design	Global super-region	Global region	Country	VTE incidence	DVT incidence	PE incidence
Hald *et al.* 2013 [14]	Population-based cohort combined with hospital-based discharge diagnosis, autopsy and procedure registries	High Income	Western Europe	Norway	1.48	NR	NR
Holst *et al.* 2010 [15]	Population-based cohort combined with national cause of death registry and national patient registry	High Income	Western Europe	Denmark	2.69	NR	NR
Moretti *et al.* 2010 [16]	Population-based hospital discharge database	High Income	Western Europe	Italy	NR	NR	0.189
Severinsen *et al.* 2010 [17]	Population-based cohort in men and women aged 50–64 years combined with the national patient registry	High Income	Western Europe	Denmark	1.15	0.65	0.51
Cohen *et al.* 2007 [8]	Incidence-based epidemiologic model of country-specific non-fatal VTE events and VTE-related deaths	High Income	Western Europe	France, Germany, Italy, Spain, Sweden, UK	NR	1.48	0.95
Heurta *et al.* 2007 [18]	Prospective population-based cohort identified from the general practice database. Nested case–control analysis also performed	High Income	Western Europe	UK	0.745	0.403	0.342
Naess *et al.* 2007 [19]	Population-based cohort identified from electronic hospital registries and case-finding search of tertiary-care center for discharge diagnoses of VTE	High Income	Western Europe	Norway	1.43	0.93	0.50
Guijarro *et al.* 2005 [20]	Hospital discharge database of the Andalusian healthcare service for 1998 to 2001	High Income	Western Europe	Spain	0.036*	NR	0.15*
Oger *et al.* 2000 [21]	Population-based cohort study of both hospitalized and outpatient cases within defined populations in 1998 and 1999 using standardized prospective data collection	High Income	Western Europe	France	1.83	1.24	0.60
Nordstrom *et al.* 1992 [22]	Population-based cohort study of hospital-based venography cases in 1987	High Income	Western Europe	Sweden	NR	1.55 male 1.62 female	NR
Kierkegarrd 1980 [23]	Population-based cohort study of hospital-based venography cases	High Income	Western Europe	Sweden	NR	0.85 male 0.68 female	NR
Tagalakis *et al.* 2013 [24]	Provincial healthcare databases linking hospital discharges and healthcare claims data for 2000–2009	High Income	North America	Canada (Quebec)	1.22	0.78	0.45
Yusuf *et al.* 2012 [9]	Search of the national hospital discharge database 2007–2009	High Income	North America	USA	2.39	1.52	1.15
Weiner *et al.* 2011 [25]	HCUP nationwide inpatient sample of hospital discharges and national cause of death file databases 1998–2006	High Income	North America	USA	NR	NR	1.12
Cushman *et al.* 2004 [26]	Population-based cohort study with prospective follow-up of patients combined with search of hospital discharge and Medicare records	High Income	North America	USA	1.61	1.17	0.45
Stein *et al.* 2004 [27]	Search of the national hospital discharge database	High Income	North America	USA	1.30†	1.04†	0.36†
Janke *et al.* 2000 [28]	Vital statistics data obtained from the Minnesota State Department of Health and hospital discharge data from a state uniform billing claims database 1980–1994	High Income	North America	USA	NR	NR	0.60–0.90 male 0.60 female
Klatsky *et al.* 2000 [29]	Population-based cohort study of a California pre-paid health plan for 1978–1985 combined with hospital record review	High Income	North America	USA	0.19‡	NR	NR
Silverstein *et al.* 1998 [30]	Population-based cohort study with medical record review and search of computerized databases of diagnoses and procedures, billing data, death certificates, and autopsy records	High Income	North America	USA	1.17	0.48	0.69
White *et al.* 1998 [31]	Database analysis of the linked California patient discharge dataset	High Income	North America	USA	NR	0.230§	NR

Table 1 (Continued)

Author and year	Study design	Global super-region	Global region	Country	VTE incidence	DVT incidence	PE incidence
Anderson *et al.* 1991 [32]	Population-based cohort study of hospital cases with hospital record review	High Income	North America	USA	1.07	0.48	0.23
Shiraev *et al.* 2013 [33]	National databases on hospitalization and deaths 2009–2010	High Income	Australasia	Australia	NR	NR	0.53
Ho *et al.* 2008 [34]	Population-based cohort study with cases identified prospectively and also retrospectively from the Western Australian Department of Health database	High Income	Australasia	Australia	0.83	0.52	0.31
Vazquez *et al.* 2013 [35]	Population-based cohort study within a health maintenance organization	High Income	Southern Latin America	Argentina	1.65	1.30	0.64
Jang *et al.* 2010 [36]	National health insurance database in 2008	High Income	High Income Asia Pacific	Korea	0.138	0.0531	0.0701
Lee *et al.* 2010 [37]	National health insurance claims database for Taiwan	Southeast Asia, East Asia, Oceania	East Asia	Taiwan	0.159	NR	NR
Cheuk *et al.* 2004 [38]	Database of Hong Kong Hospital Authority of all hospitalizations, diagnoses, procedures and outcomes 2000 to 2001	Southeast Asia, East Asia, Oceania	East Asia	Hong Kong	NR	0.171	0.039
Woo *et al.* 1988 [39]	National vital statistics analysis combined with hospital record review (rate is for 1985)	Southeast Asia, East Asia, Oceania	East Asia	Hong Kong	0.079	NR	NR

DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism. *This study evaluated cases for which VTE or PE was the primary reason for hospital admission. †The rates are for the Caucasian population. Corresponding incidence rates for African Americans were VTE 1.38, DVT 107, and PE 0.40, and those for Asian/Pacific Islanders were VTE 0.26, DVT 0.22, and PE 0.07. ‡The rate is for the overall population. Corresponding incidence rates by race were Caucasian 0.21, African American 0.22, Asian 0.02, and Hispanic 0.09. §The rate is for a first idiopathic DVT in a Caucasian population. Corresponding incidence rates by race were African American 0.293, Hispanic 0.139, and Asian/Pacific Islander 0.060.

Table 2 Incidence rates per 1000 population per year according to age category: studies providing level A evidence

Author and year	Global region	Country	Age 40–49 years	Age 50–59 years	Age 60–69 years	Age 70–79 years	Age ≥ 80 years
Kroger *et al.* 2010 [40]	Western Europe	Germany	0.30 male* 0.28 female	–	1.24 male 0.94 female	–	3.45 male 3.72 female
Naess *et al.* 2007 [19]	Western Europe	Norway	0.20 male†,‡ 0.17 female	0.72 male 0.72 female	1.14 male 0.93 female	1.85 male 1.45 female	3.73 male 3.84 female
Oger *et al.* 2000 [21]	Western Europe	France	1.52 male§ 1.05 female	–	5.33 male 4.53 female	–	10.81 male 12.04 female
Nordstrom *et al.* 1992 [22]	Western Europe	Sweden	0.69 male‡ 0.97 female	2.85 male 1.03 female	3.27 male 2.17 female	5.64 male 4.29 female	7.65 male 8.22 female
Tagalakis *et al.* 2013 [24]	North America	Canada (Quebec)	0.83	1.42	2.57	4.41	6.85
Yusuf *et al.* 2012 [9]	North America	USA	1.43	2.00	3.91	7.27	11.34
Silverstein *et al.* 1998 [30]	North America	USA	0.90 male† 0.45 female†	0.76 male 0.83 female	1.63 male 1.69 female	6.46 male 3.22 female	9.84 male 8.49 female
Anderson *et al.* 1991 [32]	North America	USA	0.17‡	0.43	1.19	2.32	2.91
Lee *et al.* 2010 [37]	East Asia	Taiwan	NR¶	NR¶	NR¶	NR¶	8.31 male 11.82 female
Cheuk *et al.* 2004 [38]	East Asia	Hong Kong	0.096**	–	–	0.81**	
Vazquez *et al.* 2013 [35]	Southern Latin America	Argentina (2006–2012)	NR¶	NR¶	NR¶	NR¶	5.93
Jang *et al.* 2011 [36]	High Income Asia Pacific	Korea (2008)	0.099 male 0.097 female	0.173 male 0.131 female	0.381 male 0.412 female	0.765 male 1.042 female	1.088 male 1.092 female

NR, not reported. *Age categories shown are 30–49 years, 50–69 years, and 70–90 years. †Age categories shown are 40–44 years, 50–54 years, 60–64 years, 70–74 years, and 80–84 years. ‡Incidence rates are for deep vein thrombosis (all venous thromboembolic events not reported). §Age categories shown are 40–59 years, 60–74 years, and ≥ 75 years. ¶Rates are shown in graphical form; actual numerical values not provided. **Age categories shown are 45–64 years and ≥ 65 years.

and ranked second in high-income countries [72]. Premature death was the source of 64% of the DALYs lost in high-income countries and of 66% of the DALYs lost in low-income and middle-income countries [72].

The second study was conducted by the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism [73]. This group used incidence data from Western Australia, together with mortality estimates and disability weighting derived from the literature, much of which comes from other countries, to estimate the DALYs associated with VTE in Australia for the year 2008. The estimated overall loss for Australia in 2008 was 78 408 DALYs [73]. Premature mortality (YLL) was 99.7% of the estimated total burden of disease [73].

Discussion

There are several inferences that can be drawn from our systematic review of the literature. First, there is substantial evidence that VTE is associated with a major global burden of disease. Second, most of the level A evidence of this burden comes from the super-region 'High Income' defined by GBD 2010, although some evidence also comes from the super-region of 'Southeast Asia, East Asia, and Oceania' (Table 1). Third, the evidence for disease burden is primarily based on the incidence of VTE events, and to a lesser extent on the estimated number of deaths for a region or country. Our review identified only one rigorous study estimating the DALYs associated with VTE [72]. Fourth, there is consistent and strong evidence that the global incidence of VTE increases with increasing age, and is especially high in the elderly (Table 2). This finding has major implications for global health, because life-expectancy continues to improve in low-income and middle-income countries, and in these countries the transition from infectious diseases to non-communicable diseases as the major causes of death and disability is continuing. Finally, the evidence and the above inferences lead us to recommend that VTE be measured as a specific cause of death in future efforts of the GBD project. We expand further on these themes in the paragraphs below.

Regarding the annual incidence of VTE, the studies from western Europe, North America, Australia, and southern Latin America (Argentina) yielded consistent findings. These studies reported overall annual incidence rates ranging from 0.75 to 2.69 per 1000 individuals in the population, with the incidence in most of the studies ranging between 1.07 and 1.83 (Table 1). The study by Oger *et al.* [21] reported that the incidence of VTE was similar to that of myocardial infarction in the same country during a similar time-frame. Furthermore, the study by Jha *et al.* [72] estimated that there were 3.9 million cases of hospital-associated VTE during 1 year among

1.1 billion citizens of high-income countries (3.5 per 1000 population), and 6.0 million cases among 5.5 billion citizens of low-income and middle-income countries (1.1 per 1000 population) [72]. Thus, the aggregate evidence from the literature indicates that VTE is a common condition globally across the spectrum of high-income, middle-income and low-income regions.

There was a strong and consistent association of increasing incidence of VTE with increasing age. The annual incidence increased to between 2 and 7 per 1000 population among those aged ≥ 70 years in most of the studies, and to between 3 and 12 per 1000 population among those aged ≥ 80 years (Table 2). This finding has major implications for healthcare systems and for the care of the elderly. For example, a study of the incidence of VTE among nursing home residents in Kansas reported an incidence of 13 per 1000 residents per year [70]. Reardon *et al*. analyzed nursing home records from 19 states in the USA, and found that one in 25 admissions had a diagnosis of VTE [56]. It is likely that the high incidence of VTE in the elderly reflects the high prevalence of comorbid acquired risk factors in these patients, especially malignancy, heart failure, and immobility associated with surgery or hospitalization for medical illness, which account for the majority of the population-attributable risk of VTE in older individuals. In contrast, genetic factors account for only 7–22% of the population-attributable risk in the elderly [76].

The significant burden of VTE is not confined to the elderly, and VTE should not be considered a disease of old age. The annual incidence among individuals in their 40s, 50s and 60s ranged from 0.2 to 5.3 per 1000 population (Table 2), with the incidence in the most contemporary studies ranging from 0.8 to 3.9 [9,24].

The level A studies from Taiwan, Hong Kong and Korea reported lower annual incidence rates of VTE and DVT (ranging from 0.079 to 0.171 per 1000 population; Table 1 [37–39]). These results are consistent with the findings of studies in the USA, which reported lower annual incidence rates of VTE in Asian Americans than in Caucasians and African Americans [31]. There was also a strong association between increasing age and increased incidence in the studies from Hong Kong, Taiwan, and Korea [36–38] (Table 2). So, although the overall incidence is lower in individuals of Chinese and Korean ethnicity, their disease burden is not low, because of population aging and increased life-expectancy. Recent studies undertaken in Asian countries have demonstrated rates of VTE after major surgery and in hospitalized medical patients approaching those observed in Western populations [77].

The literature review identified limited information on the number of deaths attributable to VTE. The strongest evidence comes from the study by Cohen *et al*., who used an incidence-based model in six European countries to estimate that there were 534 454 deaths related to VTE across the European Union in 2004 [8]. A similar approach applied to the data from the USA suggested that there were ~ 300 000 deaths resulting from VTE each year [78,79]. The direct ascertainment of deaths attributable to VTE is difficult, because of the low rate of autopsy in most countries, and because autopsy studies have consistently demonstrated that PE is often not diagnosed ante-mortem, and that deaths attributable to PE are frequently misclassified as cardiac deaths. Furthermore, PE may be the primary cause of death, such as in patients with unprovoked VTE, or a secondary (contributory) cause of death, e.g. in the cancer patient or the patient with multiple medical conditions. Secondary causes may not always be documented or measured in studies of causes of death. For these reasons, estimates of the number of deaths resulting from VTE based on death certificates or hospital discharge data will not reflect the actual death burden.

Our review found limited information on the DALYs associated with VTE. The study of Jha *et al*. [72] provides evidence that VTE causes a major burden of disease across low-income, middle-income and high-income countries. VTE was the highest ranked cause of DALYs overall among the seven causes of hospital-associated adverse events. However, because the study only evaluated DALYs related to inpatient adverse events, it underestimates the total contribution of VTE, as a substantial proportion of VTE events occur out of hospital [78]. Premature death accounts for approximately two-thirds of the DALYs lost because of VTE [72]. Thus, even among patients with underlying chronic or terminal illness (e.g. advanced heart failure or cancer), VTE causes earlier death for many of these patients.

Disability was responsible for 34% of the DALYs associated with VTE [72], indicating that VTE causes significant YLD because of the non-fatal consequences of DVT and PE. Despite treatment, approximately 10–20% of patients with DVT develop severe post-thrombotic syndrome, a chronic disorder that decreases quality of life and reduces the capacity to walk and to work [80,81]. In the most severe cases, patients with post-thrombotic syndrome can develop venous ulcers, which are slow to heal and costly for the healthcare system [80,81]. Heit *et al*. reported an incidence of venous ulcers of 1.8 per 1000 population per year [82]. PE is associated with chronic thromboembolic pulmonary hypertension in up to 4% of patients [83]. Patients with this disorder have varying degrees of respiratory and cardiac impairment. Therefore, the long-term consequences of VTE are associated with considerable disability, and are likely to produce significant YLD. Consequently, the disease burden of VTE occurs through both YLL and YLD. More recently, the long-term psychological consequences of PE have been shown to include emotional distress, worry and anxiety because of uncertainty about whether or when a recurrence might occur, and, in some cases, symptoms

characteristic of post-traumatic stress disorder [84]. Therefore, in addition to the physical burden, there is an emotional burden associated with VTE.

VTE may affect more people than those who suffer from it. First, current prevention strategies must be applied to large numbers of patients at risk. Most of these patients receive anticoagulant thromboprophylaxis, which is associated with major bleeding in 0.2–1.1% of patients [85–87]. Patients with thrombosis, particularly if they have a positive family history, are often tested for hereditary or acquired thrombophilic conditions. If abnormalities are found, this testing is sometimes extended to family members, which may lead to medical interventions, and have psychological consequences. The perceived risk of thrombosis affects many more people than those actually afflicted by it.

VTE was not assessed as a cause of death at the disaggregated level in GBD 2010 [3,5,6]. GBD 2010 used three criteria for including causes of death at the disaggregated level: potentially large burden, substantial health policy interest, and the feasibility of measurement [5]. We believe that VTE meets all of these criteria. The feasibility of evaluating VTE across the global regions is established by the results of the WHO Patient Safety Program [72,74,75]. The WHO is commended for including VTE among the adverse outcomes assessed in the Patient Safety Program. Future efforts of the GBD Study should include evaluation of VTE as a cause of death and the associated DALYs, both for hospital-associated events, which account for up to 60% of all VTEs [78], and for events that occur outside the hospital setting, such as unprovoked VTEs.

Prevention is the key to reducing death and disability resulting from VTE. This includes thromboprophylaxis in patients at risk (primary prevention), such as those undergoing surgery or those hospitalized with medical illnesses [10–12], and prevention of recurrent thromboembolic events in patients with established DVT or PE [88] (secondary prevention). Effective primary prevention is available for most high-risk patient groups [10–12]. However, a global audit of utilization of primary thromboprophylaxis showed widespread underuse in eligible patients [89]. There is evidence that a concerted effort by a health system to include VTE risk assessment at the time of hospital admission and the provision of appropriate primary thromboprophylaxis is effective in reducing the frequencies of VTE-related death and readmission with non-fatal VTE [90–91]. The increased implementation of proven, evidence-based primary prevention of VTE should be a global health priority. The safety and simplicity of extended anticoagulant therapy have improved significantly in recent years [88], and this approach to secondary prevention has the potential to markedly reduce the burden caused by recurrent VTE events if appropriately implemented on a global scale. Future research may further refine our ability to optimize the benefit-to-risk profile of anticoagulant treatment at the individual patient level, and minimize the side-effects of prevention. Strengthening the global effort to prevent VTE is consistent with the World Health Assembly's goal of significantly reducing the global burden caused by noncommunicable diseases by 2025 [92].

In conclusion, this literature review found substantial evidence of a major global disease burden caused by VTE. Although this burden has been less extensively evaluated than the burden caused by arterial thrombosis, which includes ischemic heart disease and ischemic stroke, the available evidence indicates a major burden of disease across low-income, middle-income and high-income countries. Because many of these events are potentially preventable, more detailed data on the burden caused by VTE should be obtained to inform public health policy and resource allocation in health systems, especially in regions where evidence is now limited or lacking, and to evaluate whether the broader and improved implementation of preventive measures will reduce the disease burden.

Disclosure of Conflict of Interests

No disclosures were requested by the editors.

Appendix

The members of the ISTH Steering Committee for World Thrombosis Day:

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