A major contributor to global disease burden


**Background**—Thrombosis is the common pathology underlying ischemic heart disease, ischemic stroke, and venous thromboembolism (VTE). The Global Burden of Disease Study 2010 (GBD 2010) documented that ischemic heart disease and stroke collectively caused 1 in 4 deaths worldwide. GBD 2010 did not report data for VTE as a cause of death and disability.

**Objective**—To review the literature on the global burden of disease caused by VTE.

**Approach and Results**—We performed a systematic review of the literature on the global disease burden because of VTE in low-, middle-, and high-income countries. Studies from Western Europe, North America, Australia, and Southern Latin America (Argentina) yielded consistent results with annual incidences 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 ≥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 lost in low- and middle-income countries, and second in high-income countries, responsible for more disability-adjusted life-years lost than nosocomial pneumonia, catheter-related blood stream infections, and adverse drug events.

**Conclusions**—VTE causes a major burden of disease across low-, middle-, 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 use of preventive measures will reduce the burden. (Arterioscler Thromb Vasc Biol. 2014;34:2363-2371.)

**Key Words:** pulmonary embolism ■ thrombosis ■ venous thromboembolism ■ venous thrombosis

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

The Global Burden of Diseases, Injuries, and Risk Factors Study (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 magnitude of health loss because of diseases, injuries, and risk factors by age, sex, and geographic region throughout the world.4,5 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 7 super regions.4,5 The study also provides estimates of the years of life lost (YLL) because of premature mortality, the years lived with disability (YLD), and the disability-adjusted life-years (DALYs).4,5 DALYs estimate how many years of healthy life are lost because of premature death or nonfatal illness or disability and are calculated as the sum of YLL and YLD.5

GBD 2010 documented 52.8 million deaths globally in 2010.5 Noncommunicable disease accounted for 34.5 million deaths...
or 2 of every 3 deaths.\textsuperscript{3} Ischemic heart disease (7.0 million deaths) and stroke (5.9 million deaths) collectively caused 1 in 4 deaths worldwide.\textsuperscript{3} The 7.0 million deaths from ischemic heart disease represent a 35\% increase since 1990. About half of all stroke deaths were from ischemic stroke, which is caused by thrombosis. The 2.8-million deaths from ischemic stroke represent a 25\% increase since 1990. Although there is substantial regional variation, ischemic heart disease ranks as the number 1 or 2 causes of YLL in 13 of the 21 regions and ranks in the top 5 causes of death in 17 regions.\textsuperscript{3} Stroke ranks as the first or second cause of YLL in 8 regions and is in the top 5 causes in 14 regions.\textsuperscript{3}

Ischemic heart disease was the leading cause of DALYS lost worldwide in 2010 (up from fourth rank in 1990, an increase of 29\%), and stroke was the third leading cause (up from fifth rank in 1990, an increase of 19\%).\textsuperscript{3} More than 60\% of new strokes and 45\% of deaths from stroke occur in individuals <75 years of age.\textsuperscript{3}

GBD 2010 clearly documents the major impact of arterial thrombosis on global disease burden because it is the pathophysiological 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 from noncommunicable diseases. For example, Cohen et al\textsuperscript{4} used an incidence-based epidemiology model to estimate the number of nonfatal 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 454.4 million). The results yielded estimates of 684,019 DVT events, 434,723 PE events, and a total of 543,454 VTE-related deaths.\textsuperscript{4} In the United States, 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 to 2009 among the population of 301 to 307 million.\textsuperscript{5} If VTE causes 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 from VTE is potentially preventable,\textsuperscript{6,7} 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 because of VTE. The objective was to review the evidence for disease burden in each of the geographic regions specified in the GBD Study 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 using OVID Medline, OVID Medline In-Process and other nonindexed citations, and EMBASE, from inception of these databases to May 2014. We used the disease-related key words venous thromboembolism, deep-vein thrombosis, venous thrombosis, vein thrombosis, thrombophlebitis, pulmonary embolism, and lung embolism, together with the additional key words 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 nonhuman studies, case reports, and clinical trials, as well as nonrelevant publication types, including reports of clinical conferences and editorials. We also excluded articles published in languages other than English; and the current report is confined to the literature published in English. The identified citations from each database were exported to an ENDNOTE library where the citations were deduplicated. 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 2 reviewers (A.W., G.R.) who categorized them according to the level of evidence as 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 (aged ≥18 years) derived from population-based cohort studies or from analysis of national health system databases or private health insurance claims data within a defined population, or derived using a combination of the former methods with appropriate epidemiological modeling methods. Level B evidence was defined as estimates of the burden in specific subpopulations such as the elderly, pregnancy, etc, using the same methods described for level A. The category of other evidence included all other study designs without a defined population to derive the disease burden parameters, such as single hospital based 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 deduplication check, a total of 8702 citations remained for review.

The 2 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,\textsuperscript{14–42} 29 as level B evidence,\textsuperscript{43–71} and the remainder as other. Most of the level A studies evaluated the incidence of VTE or its components, DVT and PE\textsuperscript{44–46}, 2 studies evaluated the prevalence of VTE.\textsuperscript{51,52}

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 2 of the 7 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 the region of Western Europe,\textsuperscript{8,16–23} 10 were from North America, 2 were from Australasia (both from Australia),\textsuperscript{31,34} 1 was from the Southern Latin America region (Argentina),\textsuperscript{3} and 1 was from the Asia Pacific region (Korea).\textsuperscript{36} The 3 level A studies from the super region of Southeast Asia, East Asia, and Oceania all came from the region of East Asia\textsuperscript{57–59} (2 studies from Hong Kong and 1 from Taiwan).
Table 1. Studies Comprising Level A Evidence for Burden of Disease From VTE: Incidence per 1000 Population per Year

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Global Super Region</th>
<th>Global Region</th>
<th>Country</th>
<th>VTE Incidence</th>
<th>DVT Incidence</th>
<th>PE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hald et al</td>
<td>Population-based cohort combined with hospital-based discharge diagnosis, autopsy, and procedure registries</td>
<td>High income</td>
<td>Western Europe</td>
<td>Norway</td>
<td>1.48</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Holst et al</td>
<td>Population-based cohort combined with national cause of death registry and national patient registry</td>
<td>High income</td>
<td>Western Europe</td>
<td>Denmark</td>
<td>2.69</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Moretti et al</td>
<td>Population-based hospital discharge database</td>
<td>High income</td>
<td>Western Europe</td>
<td>Italy</td>
<td>NR</td>
<td>NR</td>
<td>0.189</td>
</tr>
<tr>
<td>Severinsen et al</td>
<td>Population-based cohort in men and women aged 50–64 years combined with the national patient registry</td>
<td>High income</td>
<td>Western Europe</td>
<td>Denmark</td>
<td>1.15</td>
<td>0.65</td>
<td>0.51</td>
</tr>
<tr>
<td>Cohen et al</td>
<td>Incidence-based epidemiological model of country-specific nonfatal VTE events and VTE-related deaths</td>
<td>High income</td>
<td>Western Europe</td>
<td>France, Germany, Italy, Spain, Sweden, and United Kingdom</td>
<td>NR</td>
<td>1.48</td>
<td>0.95</td>
</tr>
<tr>
<td>Huerta et al</td>
<td>Prospective population-based cohort identified using the General Practice database. Nested case–control analysis also done</td>
<td>High income</td>
<td>Western Europe</td>
<td>United Kingdom</td>
<td>0.745</td>
<td>0.403</td>
<td>0.342</td>
</tr>
<tr>
<td>Naess et al</td>
<td>Population-based cohort identified by electronic hospital registries and case-finding search of tertiary care center for discharge diagnoses of VTE</td>
<td>High income</td>
<td>Western Europe</td>
<td>Norway</td>
<td>1.43</td>
<td>0.93</td>
<td>0.50</td>
</tr>
<tr>
<td>Guijarro et al</td>
<td>Hospital discharge database of the Andalusian Healthcare Service for 1998–2001</td>
<td>High income</td>
<td>Western Europe</td>
<td>Spain</td>
<td>0.036*</td>
<td>NR</td>
<td>0.15*</td>
</tr>
<tr>
<td>Oger</td>
<td>Population-based cohort study of both hospitalized and outpatient cases within defined populations in 1998 and 1999 using standardized prospective data collection</td>
<td>High income</td>
<td>Western Europe</td>
<td>France</td>
<td>1.83</td>
<td>1.24</td>
<td>0.60</td>
</tr>
<tr>
<td>Nordström et al</td>
<td>Population-based cohort of hospital-based venography cases in 1987</td>
<td>High income</td>
<td>Western Europe</td>
<td>Sweden</td>
<td>NR</td>
<td>1.55 men and 1.62 women</td>
<td>NR</td>
</tr>
<tr>
<td>Kierkegaard</td>
<td>Population-based cohort of hospital-based venography cases</td>
<td>High income</td>
<td>Western Europe</td>
<td>Sweden</td>
<td>NR</td>
<td>0.85 men and 0.68 women</td>
<td>NR</td>
</tr>
<tr>
<td>Tagalakis et al</td>
<td>Provincial healthcare databases linking hospital discharges and healthcare claims data 2000–2009</td>
<td>High income</td>
<td>North America</td>
<td>Canada (Quebec)</td>
<td>1.22</td>
<td>0.78</td>
<td>0.45</td>
</tr>
<tr>
<td>Yusuf et al</td>
<td>Search of the National Hospital Discharge database 2007–2009</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>2.39</td>
<td>1.52</td>
<td>1.15</td>
</tr>
<tr>
<td>Cushman et al</td>
<td>Population-based cohort with prospective follow-up of patients combined with search of hospital discharge and Medicare records</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>1.61</td>
<td>1.17</td>
<td>0.45</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. Continued

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Global Super Region</th>
<th>Global Region</th>
<th>Country</th>
<th>VTE Incidence</th>
<th>DVT Incidence</th>
<th>PE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al27</td>
<td>Search of the National Hospital Discharge database</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>1.30†</td>
<td>1.04†</td>
<td>0.36†</td>
</tr>
<tr>
<td>Janke et al28</td>
<td>Vital statistics data obtained from the Minnesota State Department of Health and hospital discharge data from a State uniform billing claims database 1980–1994</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>NR</td>
<td>NR</td>
<td>0.60–0.90 men and 0.60 women</td>
</tr>
<tr>
<td>Klatsky et al29</td>
<td>Population-based cohort of a California prepaid health plan for 1978–1985 combined with hospital record review</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>0.19‡</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Silverstein et al30</td>
<td>Population-based cohort with medical record review and search of computerized databases of diagnoses and procedures, billing data, death certificates and autopsy records</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>1.17</td>
<td>0.48</td>
<td>0.69</td>
</tr>
<tr>
<td>White et al31</td>
<td>Database analysis of the linked California patient discharge data set</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>NR</td>
<td>0.230§</td>
<td>NR</td>
</tr>
<tr>
<td>Anderson et al32</td>
<td>Population-based cohort of hospital cases with hospital record review</td>
<td>High income</td>
<td>North America</td>
<td>United States</td>
<td>1.07</td>
<td>0.48</td>
<td>0.23</td>
</tr>
<tr>
<td>Shiraev et al33</td>
<td>National databases on hospitalization and deaths 2009–2010</td>
<td>High income</td>
<td>Australasia</td>
<td>Australia</td>
<td>NR</td>
<td>NR</td>
<td>0.53</td>
</tr>
<tr>
<td>Ho et al34</td>
<td>Population-based cohort study with cases identified prospectively and also retrospectively through Western Australian Department of Health database</td>
<td>High income</td>
<td>Australasia</td>
<td>Australia</td>
<td>0.83</td>
<td>0.52</td>
<td>0.31</td>
</tr>
<tr>
<td>Vázquez et al35</td>
<td>Population-based cohort within a health maintenance organization</td>
<td>High income</td>
<td>Southern Latin America</td>
<td>Argentina</td>
<td>1.65</td>
<td>1.30</td>
<td>0.64</td>
</tr>
<tr>
<td>Jang et al36</td>
<td>National Health Insurance database in 2008</td>
<td>High income</td>
<td>High income Asia Pacific</td>
<td>Korea</td>
<td>0.138</td>
<td>0.0531</td>
<td>0.0701</td>
</tr>
<tr>
<td>Lee et al37</td>
<td>National health insurance claims database for Taiwan</td>
<td>Southeast Asia, East Asia, Oceania</td>
<td>East Asia</td>
<td>Taiwan</td>
<td>0.159</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cheuk et al38</td>
<td>Database of Hong Kong Hospital Authority of all hospitalizations, diagnoses, procedures and outcomes 2000–2001</td>
<td>Southeast Asia, East Asia, Oceania</td>
<td>East Asia</td>
<td>Hong Kong</td>
<td>NR</td>
<td>0.171</td>
<td>0.039</td>
</tr>
<tr>
<td>Woo et al39</td>
<td>National vital statistics analysis combined with hospital record review (rate is for 1985)</td>
<td>Southeast Asia, East Asia, and Oceania</td>
<td>East Asia</td>
<td>Hong Kong</td>
<td>0.079</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

DVT indicates deep-vein thrombosis; HCUP, Healthcare Cost and Utilization Project; NR, not reported; PE, pulmonary embolism; and VTE, venous thromboembolism.

*This study evaluated cases where VTE or PE was the primary reason for hospital admission.
†The rates are for the white population. Corresponding incidence rates for blacks were VTE 1.38, DVT 1.07, PE 0.40, and for Asian/Pacific Islanders were VTE 0.26, DVT 0.22, and PE 0.07.
‡The rate is for the white population. Corresponding incidence rates by race were white 0.21, black 0.22, Asian 0.02, and Hispanic 0.09.
§The rate is for a first idiopathic DVT in white population. Corresponding incidence rates by race were black 0.293, Hispanic 0.139, and Asian/Pacific Islander 0.060.

Downloaded from http://atvb.ahajournals.org/ by guest on July 7, 2017
The relationship between increasing age and the incidence of VTE was evaluated in several of the level A studies.\textsuperscript{4,19,21,22,24,30,32,35–38,40} The results of these studies are summarized in Table 2.

The level B studies evaluated the incidence of VTE in various subpopulations, such as during pregnancy or the postpartum period,\textsuperscript{5,14,45–54} men or women of selected age categories,\textsuperscript{55–64} subgroups with or without selected risk factors or comorbidities,\textsuperscript{65–70} or special categories of thrombosis.\textsuperscript{71} All but one of the level B studies came from the super region designated high income; the exception was from Sub-Saharan Africa (South Africa).\textsuperscript{51}

Within the high-income super region, 14 of the level B studies were from the region of Western Europe,\textsuperscript{43,44,46,49,54,55,57–59,61–63,65,69} 11 were from North America,\textsuperscript{45,47,50,52,56,60,64,67,68,70,71} 2 were from the region of Asia Pacific (Japan).\textsuperscript{66}

Prevalence of VTE
Two studies were identified that evaluated the prevalence of VTE; both were done in the United States by the same investigators.\textsuperscript{9,19} The national prevalence of VTE was determined during the 5-year period from 2002 to 2006 using 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.\textsuperscript{41}

Among patients aged ≥65 years, the prevalence in 2006 was 13.8 per 1000 enrollees, compared with 2.3 per 1000 enrollees in those aged <65 years.\textsuperscript{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.\textsuperscript{41} The second study found that the prevalence of VTE was highest in black men, followed by white men, white women, and black women.\textsuperscript{42} Hispanic individuals of both sexes had lower prevalence.\textsuperscript{42}

Disability-Adjusted Life-Years
Our search identified 2 studies that evaluated disease burden in terms of DALYs.\textsuperscript{72,73} The methodologically strongest was the study by Jha et al,\textsuperscript{72} as part of the WHO’s Patient Safety Program. This study used analytic modeling to estimate the incidence rates of VTE, annual number of cases, and DALYs from VTE associated with hospitalization in high-, middle-, and low-income countries.\textsuperscript{72} The data for the modeling were generated from 2 sources: an extensive literature review and epidemiological studies commissioned by the WHO, which were conducted in 26 hospitals across 8 low- and middle-income countries in the Eastern Mediterranean and North Africa regions (Egypt, Jordan, Kenya, Morocco, South Africa, Sudan, Tunisia, and Yemen)\textsuperscript{72} and in 35 hospitals across 5 countries in Latin America (Argentina, Colombia, Costa Rica, Mexico, and Peru).\textsuperscript{73} 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- and middle-income countries.\textsuperscript{72,74,75}

The study reported incidences of VTE per 100 hospitalizations of 3.3 (95% confidence interval, 1.9–4.8) in high-income

### Table 2. Incidence Rates per 1000 Population per Year According to Age Category: Studies Comprising Level A Evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Global Region</th>
<th>Country</th>
<th>Age, 40–49 years</th>
<th>Age, 50–59 years</th>
<th>Age, 60–69 years</th>
<th>Age, 70–79 years</th>
<th>Age, ≥80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kröger et al\textsuperscript{41}</td>
<td>Western Europe</td>
<td>Germany</td>
<td>0.30 men* and</td>
<td>0.28 men</td>
<td>1.24 men and</td>
<td>0.94 men</td>
<td>3.45 men and</td>
</tr>
<tr>
<td>Naess et al\textsuperscript{19}</td>
<td>Western Europe</td>
<td>Norway</td>
<td>0.20 men †‡ and</td>
<td>0.17 women</td>
<td>0.72 men and</td>
<td>1.14 men and</td>
<td>1.85 men</td>
</tr>
<tr>
<td>Oger\textsuperscript{71}</td>
<td>Western Europe</td>
<td>France</td>
<td>1.52 men§ and</td>
<td>1.05 women</td>
<td>5.33 men and</td>
<td>4.53 women</td>
<td>10.81 men</td>
</tr>
<tr>
<td>Nordström et al\textsuperscript{17}</td>
<td>Western Europe</td>
<td>Sweden</td>
<td>0.69 men‡ and</td>
<td>0.97 women</td>
<td>2.85 men and</td>
<td>3.27 men and</td>
<td>6.54 men and</td>
</tr>
<tr>
<td>Tagalakis et al\textsuperscript{44}</td>
<td>North America</td>
<td>Canada (Quebec)</td>
<td>0.83</td>
<td>1.42</td>
<td>2.57</td>
<td>4.41</td>
<td>6.85</td>
</tr>
<tr>
<td>Yusuf et al\textsuperscript{40}</td>
<td>North America</td>
<td>United States</td>
<td>1.43</td>
<td>2.00</td>
<td>3.91</td>
<td>7.27</td>
<td>11.34</td>
</tr>
<tr>
<td>Silverstein et al\textsuperscript{30}</td>
<td>North America</td>
<td>United States</td>
<td>0.90 men† and</td>
<td>0.45 women‡</td>
<td>0.76 men and</td>
<td>1.63 men and</td>
<td>6.46 men and</td>
</tr>
<tr>
<td>Anderson et al\textsuperscript{22}</td>
<td>North America</td>
<td>United States</td>
<td>0.17†</td>
<td>0.43</td>
<td>1.19</td>
<td>2.32</td>
<td>2.91</td>
</tr>
<tr>
<td>Lee et al\textsuperscript{17}</td>
<td>East Asia</td>
<td>Taiwan</td>
<td>NR</td>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Cheuk et al\textsuperscript{16}</td>
<td>East Asia</td>
<td>Hong Kong</td>
<td>0.096¶</td>
<td>...</td>
<td>...</td>
<td>0.81¶</td>
<td>...</td>
</tr>
<tr>
<td>Vázquez et al\textsuperscript{20}</td>
<td>Southern Latin America</td>
<td>Argentina (2006–2012)</td>
<td>NR</td>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Jang et al. 2011\textsuperscript{18}</td>
<td>High income</td>
<td>Korea (2008)</td>
<td>0.099 men and</td>
<td>0.097 men</td>
<td>0.173 men and</td>
<td>0.381 men and</td>
<td>0.765 men and</td>
</tr>
<tr>
<td></td>
<td>Asia Pacific</td>
<td></td>
<td></td>
<td></td>
<td>0.131 women</td>
<td>0.412 women</td>
<td>1.042 women</td>
</tr>
</tbody>
</table>

NR indicates not reported.

*Age categories shown are 30 to 49, 50 to 69, and 70 to 90 years.
†Incidence rates are for deep-vein thrombosis (all venous thromboembolism not reported).
‡Age categories shown are 40 to 44, 50 to 54, 60 to 64, 70 to 74, and 80 to 84 years.
§Age categories shown are 40 to 59, 60 to 74, and ≥75 years.
||Rates are shown in graphical form; actual numeric values not provided.
¶Age categories shown are 45 to 64 and ≥65 years.
countries and 3.0 (95% confidence interval, 1.0–4.8) in low- and middle-income countries.\textsuperscript{72} The estimated annual number of cases of VTE was 3.9 million (95% confidence interval, 1.9–6.3) for the high-income countries and 6.0 million (95% confidence interval, 1.2–12.8) for the low- 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.\textsuperscript{72} VTE was the leading cause of DALY's lost in the low- and middle-income countries and ranked second in the high-income countries.\textsuperscript{72} Premature death was the source of 64% of the DALYs lost in high-income countries and for 66% of the DALYs lost in low- and middle-income countries.\textsuperscript{72}

The second study was conducted by the Australia and New Zealand Working Party on the Management and Prevention of VTE.\textsuperscript{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.\textsuperscript{73} The premature mortality (YLL) was 99.7% of the estimated total burden of disease.\textsuperscript{73}

**Discussion**

The results of our systematic review of the literature suggest several inferences. 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 of Southeast Asia, East Asia, and Oceania (Table 1). Third, the evidence of 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 1 rigorous study estimating the DALYs associated with VTE in Australia for the year 2008. The estimated overall loss for Australia in 2008 was 78 408 DALYs.\textsuperscript{73} The premature mortality (YLL) was 99.7% of the estimated total burden of disease.\textsuperscript{73}

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 contemporary studies ranging from 0.8 to 3.9.\textsuperscript{3,7,24} The level A studies from Taiwan, Hong Kong, and Korea reported lower annual incidences of VTE or DVT (ranging from 0.079 to 0.171 per 1000 population; Table 1),\textsuperscript{3,7,14} These results are consistent with the findings of studies in the United States, which reported lower annual incidences of VTE in Asian-Americans than in whites and blacks.\textsuperscript{31} There was also a strong association between increasing age and increased incidence in the studies from Hong Kong, Taiwan, and Korea\textsuperscript{a–c,26–38} (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.\textsuperscript{77}

The literature review identified limited information on the number of deaths because of VTE. The strongest evidence comes from the study by Cohen et al,\textsuperscript{5} who used an incidence-based model in 6 European countries to estimate that there were 534 454 deaths related to VTE across the European Union in 2004. A similar approach applied to the data from the United States suggested 300 000 deaths from VTE each year.\textsuperscript{78,79} The direct ascertainment of deaths due to VTE is difficult because of the low rate of autopsy in most countries and because autopsy studies have consistently demonstrated that pulmonary embolism is often not diagnosed antemortem and that deaths because of pulmonary embolism are frequently misclassified as cardiac deaths. Furthermore, pulmonary embolism may be the primary cause of death, such as in patients with unprovoked VTE, or a secondary (contributing) cause of death, for example, 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 from VTE based on death certificates or hospital discharge data will underestimate the death burden.

Our review found limited information on the DALY's associated with VTE. The study by Jha et al72 provides evidence that VTE causes a major burden of disease across low-, middle-, and high-income countries. VTE was the highest ranked cause of DALY's overall among the 7 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, because 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 in 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 DALY's associated with VTE,72 indicating that VTE causes significant YLD because of the nonfatal consequences of DVT and PE. Despite treatment, 10% to 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 al82 reported an incidence of venous ulcers of 1.8 per 1000 population per year. PE is associated with chronic thromboembolic pulmonary hypertension in approximately 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 documented 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 also an emotional burden associated with VTE.

VTE may affect more people than those who experience 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% to 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 2010.5,6 GBD 2010 used 3 criteria for including causes of death at the disaggregated level: potentially large burden, substantial health policy interest, and the feasibility of measurement.5 We think that VTE meets all of these criteria. The feasibility of evaluating VTE across the global regions is established by the results of the WHO’s 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 60% of all VTE79 and also for events that occur outside the hospital setting, such as unprovoked VTE.

Prevention is the key to reducing death and disability 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 PE38 (secondary prevention). Effective primary prevention is available for most high-risk patient groups.10-12 However, a global audit of the use of primary thromboprophylaxis documented widespread under-use in eligible patients.80 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 for reducing VTE-related death and readmission with nonfatal VTE.90,91 The increased implementation of proven, evidence-based primary prevention against VTE should be a global health priority. The safety and simplicity of extended anticoagulant therapy have improved significantly in recent years,89 and this approach to secondary prevention has the potential to markedly reduce the burden from recurrent venous thromboembolic 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 from noncommunicable diseases by 2025.92

In conclusion, this literature review found substantial evidence of a major global disease burden from VTE. Although this burden has been less extensively evaluated than the burden from arterial thrombosis, which includes ischemic heart disease and ischemic stroke, the available evidence indicates a major burden of disease across low-, middle-, and high-income countries. Because many of these events are potentially preventable, more detailed data on the burden because of 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.

Sources of Funding
We accepted no direct funding from government or corporate sources for the preparation of this article.

Disclosures
None.

References


Thrombosis: A Major Contributor to Global Disease Burden


ISTH Steering Committee for World Thrombosis Day

Arterioscler Thromb Vasc Biol. 2014;34:2363-2371; originally published online October 10, 2014;
doi: 10.1161/ATVBAHA.114.304488

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/34/11/2363