The 20th century saw life expectancy double and the world population quadruple because there was a global shift of morbidity and mortality from infectious to noninfectious causes. Cardiovascular diseases became the leading cause of death, of which 80% is borne by low- and middle-income countries. More specifically, thromboembolic conditions have been estimated to account for 1 in 4 deaths worldwide in 2010 and taken together, thrombosis, as the common underlying mechanism of myocardial infarction, ischemic stroke, and venous thromboembolism (VTE), is the leading global cause of mortality (up from 1 in 5 deaths in 1990). In addition, although the ranking of the top 4 causes of death and years of life lost (YLLs) have not changed, there has been a decrease in death and YLL from respiratory infections and an increase in death and YLLs from ischemic heart disease and ischemic stroke.

As a disease family, thrombosis comprises thromboses of the arteries and veins. The leading forms of arterial thromboses (as measured by morbidity and mortality) are ischemic heart disease and ischemic stroke. Ischemic heart disease and ischemic stroke comprise the major arterial thromboses and deep-vein thrombosis and pulmonary embolism comprise venous thromboembolism. Atrial fibrillation is a major risk factor for stroke and systemic arterial thromboembolism. Estimates of the global burden of disease were obtained from Global Burden of Disease Project reports, recent systematic reviews, and searching the published literature for recent studies reporting measures of incidence, burden, and disability-adjusted life-years. Estimates per 100,000 of the global incidence rate (IR) for each condition are ischemic heart disease, IR=1518.7; myocardial infarction, IR=139.3; ischemic stroke, IR=114.3; atrial fibrillation, IR=77.5 in males and 59.5 in females; and venous thromboembolism, IR=115 to 269. Mortality rates (MRs) for each condition are ischemic heart disease, MR=105.5; ischemic stroke, MR=42.3; atrial fibrillation, MR=1.7; and venous thromboembolism, MR=9.4 to 32.3. Global public awareness is substantially lower for pulmonary embolism (54%) and deep-vein thrombosis (44%) than heart attack (88%) and stroke (85%). Over time, the incidence and MRs of these conditions have improved in developed countries, but are increasing in developing countries. Public health efforts to measure disease burden and increase awareness of symptoms and risk factors need to improve, particularly in low- and middle-income regions to address this leading cause of morbidity and mortality.
heart disease and ischemic stroke. VTE comprises deep-vein thrombosis (DVT), most often involving the legs, and pulmonary embolism (PE).

Ischemic heart disease (also known as coronary artery disease, coronary heart disease, and atherosclerotic heart disease) is a group of diseases caused by atherothrombosis and the buildup of cholesterol plaques in the coronary circulation. Measuring ischemic heart disease can be challenging because there are different manifestations of disease and researchers use a variety of case definitions. For example, one of the major subclasses of ischemic heart disease is acute coronary syndrome. Acute coronary syndrome comprises 3 symptomatic manifestations of myocardial infarction: (1) ST-segment–elevation myocardial infarction, (2) non–ST-segment–elevation myocardial infarction, and (3) unstable angina. Epidemiological studies have aimed at measuring various levels of ischemic heart disease (including the broad grouping of ischemic heart disease, the finer grouping of acute coronary syndrome, and the stratified levels of ST-segment–elevation myocardial infarction, non–ST-segment–elevation myocardial infarction, and unstable angina) making consistent comparisons difficult across studies. As our understanding of these diseases has progressed over time, so have the terminology and case definitions used to study these diseases. An additional challenge assessing incidence trends over time is that detection of acute myocardial infarction events has likely improved with the use of biomarker and enzyme detection tests.

Stroke is a family of diseases often stratified into ischemic and hemorrhagic stroke. Ischemic stroke is a thrombotic condition similar to ischemic heart disease, but manifested as an obstruction in circulation to the brain. Atherosclerotic plaques in the cerebral or carotid arteries, and cardioembolism account for most of the underlying disease process. In developed countries, ≈85% of strokes are ischemic stroke because of thromboembolism, and 15% are hemorrhagic stroke, whereas in developing countries, ≈50% of ischemic strokes are hemorrhagic; this probably reflects differences in the detection and treatment of cardiovascular risk factors, especially hypertension.

Atrial fibrillation is a highly prevalent cardiac arrhythmia, which predisposes to thrombus formation and cardioembolism. Atrial fibrillation has been estimated to be responsible for ≤25% of ischemic strokes in Western countries. For further reading on atrial fibrillation, please refer to the recent compendium edited by Andrade et al.

Because the name implies, VTE entails the formation of blood clots in the veins, most commonly in the deep veins of the calf and thigh, though ≤10% of clots may form in the upper extremities. Pulmonary emboli are thrombi, which migrate to the lungs and can be the fatal manifestation of the disease.

In this first chapter of the Compendium, we aim to describe the epidemiology and global burden of disease for each of the above major thromboembolic conditions and the distribution and major determinants. Public awareness and interest among the medical and research communities vary across these thromboembolic conditions. For example, ischemic heart disease, ischemic stroke, and atrial fibrillation were all included in the Global Burden of Disease project, but VTE was not. Thus, data sources for summarizing the burden of these thrombotic conditions affected our ability to present comparable measures and estimates.

### Methods and Data Sources

The gold standard to measure the incidence of disease is through the use of population-based surveillance systems. Among surveillance systems, there is heterogeneity in design (eg, active versus passive), scope (eg, nationwide, regional, state, county, etc.), and duration over which the surveillance is conducted. In the absence of population-based surveillance, population-based cohorts also provide reliable estimates of disease incidence. Unfortunately, population-based estimates for thrombotic conditions are lacking for many countries, particularly those classified as developing.

One of the most common sources of existing data, which contribute to measuring disease burden is hospital discharge records. Given that most people experiencing a thrombotic condition (especially ischemic heart disease, ischemic stroke, and PE) have historically required hospitalization, hospital discharge records have proven to be useful. The primary limitations of hospital discharge data are (1) patients without access to a hospital are not captured in these data, (2) the databases of these records are often deidentified making it impossible to account for hospital transfers and readmissions, and (3) their positive predictive value is relatively low (74%) for venous thromboembolic diseases.

Another common approach to measuring global disease burden is through systematic reviews and meta-analyses of the published literature. This approach is dependent on the availability of published estimates of representative disease burden across countries, regions, and cultures. A prerequisite for pooling or comparing data across studies is implementing a standardized case definition to have the most reliable summary measures.

Burden of disease can be measured by both the number of events as well as the rate of events. In addition, cases of disease, death, and years lived with disability (YLD) are different approaches to measuring burden. Given continued population growth and aging of the population, disease burden typically grows when measured by the actual number of cases. This measure is useful when planning public health resources. However, rates of morbidity and mortality are generally better suited to understand the burden of disease while accounting for population growth. Adjusting (or standardizing) rates by age help measure disease burden while accounting for population aging. The disability-adjusted life-years (DALY) is a measure of burden, which is the sum of the YLL and the YLD.
because of a condition; the latter measure is a useful estimate of how disease affects physical, social, and mental health.

For this article, data sources for ischemic heart disease, ischemic stroke, and atrial fibrillation came from published reports from the Global Burden of Disease project as well as published articles as a means to incorporate the most recently published data potentially not yet incorporated into the Global Burden of Disease reports. Conducting a systematic review of the literature on each of these thrombotic conditions was beyond the scope of this article. Specific search terms used in our literature search included incidence, ischemic (and ischemic) heart disease, acute coronary syndrome, ischemic (and ischemic) stroke, and atrial fibrillation during 2010 to 2015.

The Global Burden of Disease project incorporated data from 188 countries between 1990 and 2013 and was the starting point for each of the arterial thrombotic conditions. A measure of the completeness and quality of data across geographic locations were calculated as the data representativeness index. The overall data representative index for ischemic heart disease was 50%, for ischemic stroke it was 73.9%, and for atrial fibrillation it was 13.3%.11

Quality studies on the incidence and mortality attributed to atrial fibrillation largely come from North America and Western Europe and are largely lacking from low- and middle-income countries.12,13

In contrast to the relatively large amount of data on arterial thromboses, there is much less data on VTE, even though they substantially contribute to the global burden of disease. For example, VTE was not included in the Global Burden of Disease project. Recently, a systematic review of the literature on the disease burden of VTE has been published.1 Data from this review served as the starting point for summary measures for VTE. The majority of the data on the incidence and mortality of VTE comes from high-income countries, especially North America, Western Europe, Australasia, and Southern Latin America. A literature search was conducted using the search terms incidence, venous thromboembolism, pulmonary embolism, and deep vein thrombosis to identify any new studies published after the aforementioned systematic review. We included data on mortality rates (MRs) for VTE, which used estimates from population-based cohort studies or those using International Classification of Diseases codes on death certificates to measure all-cause mortality.

In addition, in collaboration with Ipsos-Reid, a global social and media research firm, the World Thrombosis Day Steering Committee conducted an international internet-based survey of public awareness of thrombotic conditions.14 The 9 participating countries included: Argentina, Australia, Canada, Germany, Japan, Thailand, The Netherlands, the United Kingdom, and the United States. The participants were asked to indicate their awareness of the following health conditions: heart attack, thrombosis, stroke, DVT, AIDS, PE, high blood pressure, breast cancer, and prostate cancer.

### Measures of Disease Burden

Estimates for the IRs, MRs, YLDs, and DALYs for ischemic heart disease, ischemic stroke, atrial fibrillation, and VTE are shown in Table. Each estimate is reported per 100,000 population. The Global Burden of Disease projects reported age-standardized rates using the World Health Organization World Standard Population.20 When possible, the average estimate was reported for each stratum; however, ranges or sex-stratified estimates were reported when average estimates were not available.

### Ischemic Heart Disease

The Global Burden of Disease project reported that in 2013, there were 855,700 cases (95% confidence interval [CI], 819,900–8,919,000) of acute myocardial infarction and an age-standardized IR of 139.3 per 100,000 (95% CI, 133.2/100,000–145.4/100,000). When expanding the case definition to ischemic heart disease (including postmyocardial infarction, angina, or heart failure) in 2013, there were an estimated 92,521,000 cases (95% CI, 89,680,000–95,453,000) for an age-standardized IR of 1,518.7 per 100,000 (95% CI, 1,472.5/100,000–1,566.5/100,000). According to the 2015 statistical update from the American Heart Association, an estimated 635,000 people in the United States had a new acute myocardial infarction, ≈300,000 had a recurrent attack, and an additional 155,000 people had a silent first myocardial infarction each year.21

Over time, the global rate of acute myocardial infarction has been relatively stable though progress (as reflected in decreasing IRs) has been made in ischemic heart disease. From 1990 to 2013, there was only a 1.3% decrease in the age-standardized rate of acute myocardial infarction, whereas there was a 5.2% decrease in the age-standardized rate of ischemic heart disease.

The relatively constant reported rates of acute myocardial infarction may be affected by improved diagnostic methods in recent years. In the Framingham Heart Study in the United States, acute myocardial infarctions diagnosed by ECG (the traditional method) decreased by ≈50% from 1960 to 1999;

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<th>Table. Incidence, Mortality, YLD, and DALY Estimates of Thrombotic Conditions per 100,000 Population</th>
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DALY indicates disability-adjusted life-year; and YLD, years lived with disability.

*Estimates from the Global Burden of Disease project.3,11,12
†A single study estimated hospital-associated DALYs of pulmonary embolism to be 7.6.16
however, during that same time period rates of acute myocardial infarction diagnosed by biomarkers (a more sensitive method) increased 1.5×.5

Globally, the average age of first acute myocardial infarction was >70 years for high-income counties, whereas for many low- and middle-income regions (South Asia, North Africa, Middle East, and sub-Saharan Africa), the average age of acute myocardial infarction was <65 years.17 Males consistently have higher rates of ischemic heart disease (=1.5×) than females.22

Mortality from ischemic heart disease has decreased by an estimated 19.5% from 131.3 per 100,000 (95% CI, 126.4/100,000–142.2/100,000) in 1990 to 105.7 per 100,000 (95% CI, 98.8/100,000–111.9/100,000) in 2010. For example, in the United States, MRs from ischemic heart disease have decreased by 36.9% from 2000 to 2011.21 However, despite the decreasing MR, ischemic heart disease continues to be the leading cause of death worldwide and increased from the fourth leading cause of YLL in 1990 to the first leading cause of life lost in 2010.1 In 2011, 375,295 people died from ischemic heart disease in the United States for a death rate of 113.4 per 100,000.21

Global DALY estimates for ischemic heart disease ranged from 654 to 2,855 per 100,000. The majority of DALYs caused by ischemic heart disease is in middle-income regions where people <50 years of age frequently experience myocardial infarctions.23 By region, western South America, Central Africa, India and southeastern Asia, and Japan had the lowest rates of disability from ischemic heart disease (103/100,000–113/100,000), followed by Central America, northern South America, the rest of sub-Saharan Africa, and China (113/100,000–128/100,000), North America, southern South America, Western Europe, and Australia and New Zealand (128/100,000–148/100,000), Brazil, northern Africa, the Middle East, central Europe, and Papua New Guinea (148/100,000–173/100,000), and Eastern Europe and Central Asia had the highest rates of disability from ischemic heart disease (173/100,000–219/100,000).21 DALY rates tended to increase from 1990 to 2005 in most low- and middle-income regions, but they have been more stable in most regions since 2005.17

**Ischemic Stroke**

Stroke comprises ischemic stroke and hemorrhagic stroke, of which ischemic stroke is a thrombotic condition and accounts for ≈67% of strokes11 (in developed countries ≤85% of strokes are ischemic) and roughly half of stroke-related deaths,3 both in developing and developed countries. The Global Burden of Disease project estimated that in 2013, there were 6,893,000 cases (95% CI, 6,550,000–7,352,000) of ischemic stroke for an age-standardized rate of 114.3 per 100,000 population (95% CI, 108.5/100,000–122.3/100,000). This represents an 11.13% decrease in IR from 1990, largely driven by improvements in developed countries.11 Because developing countries continue to improve control of hypertension and other risk factors, the same shift toward a relative increase in ischemic strokes is also likely to be observed.

Reported rates of ischemic stroke vary widely across countries, sex and age strata, and high-risk populations. Feigin et al24 reported IRs for regional areas across the globe. Australia, Central America, and northwestern South America had the lowest IRs of ischemic stroke, <134.9 per 100,000, Western Europe, Argentina, and Chile had IRs ranging from 134.9 per 100,000 to 179.7 per 100,000, the United States, Canada, Western Africa, India, South Korea, and Japan had rates ranging from 179.8 per 100,000 to 216.1 per 100,000, Brazil, much of sub-Saharan Africa (excluding South Africa), and southeast Asia had rates ranging from 216.2 per 100,000 to 251.8 per 100,000. North Africa, South Africa, Eastern Europe, and the Middle East had rates ranging from 251.9 per 100,000 to 336.3 per 100,000, and the rest of Asia (eg, Russia, China, Mongolia, and Kazakhstan) had rates >336.3 per 100,000.25 Incidence estimates of ischemic stroke also vary widely regionally within countries. For example, in the US estimates ranged from 74 per 100,000 in California23 to 329 per 100,000 in participants of the Atherosclerosis Risk in Communities (ARIC) cohort.26 In China, incidence of ischemic stroke ranged from 47.0 per 100,000 in males in Shanghai27 to 507.6 per 100,000 in northern China among Mongolian men.28

Age is a strong risk factor for ischemic stroke with the rate ratio for each increasing decade more than doubling (IRR, 2.15; 95% CI, 1.93–2.39).26 Selected IRs include 545 per 100,000 in the United States Medicare population (those aged ≥65 years) in 200826 and between 497 per 100,000 and 524 per 100,000 among Texans aged ≥75 years.26 Even though the highest rates are associated with increasing age, incidence of stroke is increasing in people <50 years of age,24 whereas, since 2000, rates of ischemic stroke have been decreasing by about 40% in the Medicare population.29 Females tend to have lower rates of ischemic stroke, but estimated risk rates have a huge range from 0.7 per 100,000 to 115.3 per 100,000.29 In the United States, the IRR among males is 1.22 (95% CI, 1.08–1.39) compared with females.26

In the United States, the incidence of ischemic stroke varies by race. Those of black race have a reported rate ratio of between 1.35 and 1.89 compared with whites.26 In Texas, Mexican Americans had rates between 1.05× and 2.0× greater than non-Hispanic whites.30

The major risk factors for ischemic stroke are shared with ischemic heart disease. Specifically, hypertension (IRR, 2.39; 95% CI, 2.02–2.84), diabetes mellitus (IRR, 1.73; 95% CI, 1.52–1.97), coronary heart disease (IRR, 1.93; 95% CI, 1.65–2.26), and current smoking (IRR, 1.95; 95% CI, 1.64–2.31)26 all increase the risk of ischemic stroke.

According to the Global Burden of Disease project, in 2010, ischemic stroke accounted for 2,835,400 deaths (95% CI, 2,657,000–3,262,800) for an age-standardized death rate of 42.3 per 100,000 population (39.6/100,000–48.7/100,000). Mortality after stroke in the ARIC communities declined over time by 10% to 20%, particularly among those aged <65 years. Similar trends have been observed in men (but not women) in the Framingham study22 in Minneapolis-St. Paul12; in Tromsø, Norway23; and in Auckland, New Zealand,30 but not observed in Oxfordshire, United Kingdom30 or Perth, Australia.31 Even greater decreases in mortality because of stroke were observed in Denmark (45% reduction from 1994–1998 to 2009–2011).
Atrial Fibrillation
The estimated global number of prevalent cases of atrial fibrillation in 2010 was 33.5 million with 5 million new cases occurring each year. The 2010 age-adjusted IR of atrial fibrillation in men was 77.5 per 100,000 (95% CI, 65.2/100,000–95.4/100,000) and 59.5 per 100,000 (95% CI, 49.9/100,000–74.9/100,000) in women. In contrast to ischemic heart disease and ischemic stroke that have experienced decreases in the age-standardized rate change, there was actually a 9.7% increase in YLDs between 1990 and 2013. When assessing the number of atrial fibrillation–related ischemic strokes tripled in the United Kingdom.

The increasing prevalence of atrial fibrillation and its population impact (DALYs) likely reflects the convergence of 3 major factors: (1) global population increase and population aging, with increased life expectancies (especially >75 years of age), (2) the impact of obesity on increasing prevalence of diabetes mellitus (a key risk factor), and (3) success in reducing the mortality from ischemic heart disease, with a larger population surviving with key risk factors for atrial fibrillation, including coronary artery disease, congestive heart failure, and hypertension.

Venous Thromboembolism
As an aggregate condition comprising DVT, PE, or both, estimates of the incidence of VTE ranged from 79 per 100,000 (in Hong Kong) to 269 per 100,000 population (in Denmark). When stratified by disease presentation, incidence estimates for PE ranged from 39 per 100,000 (in Hong Kong) to 115 per 100,000 population (in the United States) and incidence estimates for DVT ranged from 53.1 per 100,000 (in Korea) to 162 per 100,000 population (in Sweden). Reported VTE incidence estimates are higher among black populations and lower among Asian, Asian American, and Native American populations.

The incidence of VTE increases with increasing age. For example, in the United States, 1 study estimated the following age-stratified incidences: 143 per 100,000 among ages 40 to 49 years, 200 per 100,000 among ages 50 to 59 years, 391 per 100,000 among ages 60 to 69 years, 727 per 100,000 among ages 70 to 79 years, and 1134 per 100,000 among ages ≥80 years.

There is a complex relationship between the incidence of VTE and sex, as it is modified by age. Women have higher rates of VTE than men in those aged <55 years, which corresponds to being premenopausal and the effect of estrogen as a risk factor for VTE. Men have higher incidence of VTE among those aged 60 to 80 years, and then among those aged 80+ years, women again have a higher incidence than men.

The explanation for the observed increased rate among women aged 80+ years is attributed to the longer life expectancy of women.

The major risk factors for VTE include recent hospitalization, recent surgery, cancer, and immobilization. In addition, there are specific genetic conditions that predispose primarily to VTE, such as the Factor V Leiden gene mutation, the prothrombin gene mutation 20210, deficiencies of antithrombin deficiency, protein C or protein S, and the antiphospholipid antibody syndrome. However, these genetic factors account for only 7% to 22% of the population attributable risk in the elderly. Conditions such as inflammatory bowel disease, systemic lupus erythematosus, and disseminated intravascular coagulation are also risk factors for VTE. Medications, such as those containing estrogen and progesterone, Tamoxifen, Raloxifene, also increase the risk of a venous thromboembolic event. Approximately 50% to 60% of the disease burden from VTE is associated with recent hospitalization, either for surgery or for acute medical illness. Cancer-associated VTE accounts for 20% of the total VTE burden. The remaining 20% to 30% of the burden consists mainly of unprovoked VTE, which occurs in the absence of identifiable risk factors or in association with only minor risk factors. Patients with unprovoked VTE are predominantly younger (<50 years of age).
than those with hospital-associated VTE, and this is consistent with the estimates of a higher attributable risk for genetic factors in patients of younger age.

Methodologically firm global estimates of mortality caused by VTE are not available. In the United States, using vital records, Horlander et al15 estimated the age-adjusted (standardized to the 2000 US population and using US census data to calculate the denominator) MR related to PE to be 9.4 per 100,000. However, using a combination of surveillance data and modeling methods, the Centers for Disease Control and Prevention estimated the MR to range between 19.4 per 100,000 and 32.3 per 100,000.16,51

In the United States, surveillance data indicate that ≈60,000 to 100,000 people die from VTE each year. However, using modeling methods, Heit et al15 estimated the annual number of venous thromboembolic deaths may reach 300,000. Using a similar modeling-based method in 6 European countries, Cohen et al52 estimated 370,012 VTE-related deaths in a population of 310.4 million.

A hospital-based study estimated the global burden of DALYs from VTE to be 7.6 per 100,000. Given that hospital-associated VTE accounts for only 60% of the disease burden, the above DALY estimate is an underestimate of the true burden. The reported DALYs were 2.4x greater in low- and middle-income countries and in high-income countries.19

**Public Awareness**

Public awareness is higher for myocardial infarction and stroke than VTE. In order of awareness, participants were aware of blood pressure (90%), heart attack (88%), AIDS (87%), stroke (85%), breast cancer (85%), prostate cancer (82%), thrombosis (68%), PE (54%), and DVT (44%). When stratified by country, awareness varied greatly depending on the condition. However, the United Kingdom consistently ranked high in the awareness of heart attack, stroke, and VTE. Lower awareness was associated with younger age and being male. Public awareness that blood clots are preventable was low (45%). In addition, awareness of symptoms of DVT and PE were 28% and 19%, respectively. The most recognizable risk factor was immobility (63%), though awareness of recent hospitalization (25%), recent surgery (36%), and cancer (16%) was poor.14

**Summary and Conclusions**

The incidence of arterial thrombotic conditions is high and has been relatively well-studied. The incidence of VTE is comparable with ischemic stroke, yet data on its worldwide burden of disease is limited, particularly when measured by MRs and DALYs. Furthermore, the ability to compare rates across studies and countries is difficult because of different methods (such as age standardization) and differing age and sex distributions within each population. Public awareness is lower for VTE than the arterial thrombotic conditions.

Although the Table was designed to efficiently compare the worldwide burden of disease by thrombotic condition, the data quality and representativeness are limited and thus should be interpreted with caution. For example, time trends in incidence of VTE have been poorly studied and to get regional estimates for incidence, some studies date as far back as the 1980s. Similarly, measuring death attributable to VTE (PE) is challenging for many reasons, including the multifactorial nature of death and the low rates of autopsy in most countries. Without a standard method to measure VTE-associated mortality, it is difficult to provide reliable representative and comparable estimates across geographic locations and over time.

Given the interconnectedness of these thrombotic conditions, parsing out the DALYs attributed to each condition can be challenging. From a public health perspective, in the context of limited resources and challenges in motivating people to change their lifestyle, prevention messages and interventions that contribute to reducing the global burden of all thrombotic conditions will likely have the biggest impact regardless of the measure used.

An important aspect of each of these thrombotic conditions is their risk of recurrence. Patients who have had a first-time event need medical treatment to reduce the risk of recurrence. Increasing the public’s awareness of these conditions and their risk factors is an equally important public health goal to reduce mortality associated with each condition. Increasing public health surveillance for these conditions, particularly VTE, will foster improved understanding of the burden of disease. In addition, as biomedical advances are made to improve the treatment of arterial and venous thrombotic conditions (as described in more detail in later chapters of the *Compendium*), our ability to consistently make reliable estimates of disease burden is critical in measuring the impact of these advances in the population.

**Disclosures**

G.E. Raskob has received consultant fees for clinical research from Bayer Healthcare, BMS, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, Isis Pharmaceuticals, Janssen, Pfizer, and Portola. A.M. Wendelboe has no disclosures.

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Global Burden of Thrombosis: Epidemiologic Aspects
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Circ Res. 2016;118:1340-1347
doi: 10.1161/CIRCRESAHA.115.306841
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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