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The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs

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Abstract

Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is an important cause of preventable mortality and morbidity. In this study, we summarize estimates of per-patient and aggregate medical costs or expenditures attributable to incident VTE in the United States. Per-patient estimates of incremental costs can be calculated as the difference in costs between patients with and without an event after controlling for differences in underlying health status. We identified estimates of the incremental per-patient costs of acute VTEs and VTE-related complications, including recurrent VTE, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and anticoagulation-related adverse drug events. Based on the studies identified, treatment of an acute VTE on average appears to be associated with incremental direct medical costs of $12,000 to $15,000 (2014 US dollars) among first-year survivors, controlling for risk factors. Subsequent complications are conservatively estimated to increase cumulative costs to $18,000–23,000 per incident case. Annual incident VTE events conservatively cost the US healthcare system $7–10 billion each year for 375,000 to 425,000 newly diagnosed, medically treated incident VTE cases. Future studies should track long-term costs for cohorts of people with incident VTE, control for comorbid conditions that have been shown to be associated with VTE, and estimate incremental medical costs for people with VTE who do not survive. The costs associated with treating VTE can be used to assess the potential

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economic benefit and cost-savings from prevention efforts, although costs will vary among different patient groups.

1. Introduction

Estimates of costs of disease can be used to project the benefit of prevention [1,2]. Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with more than one-half million hospitalizations in the United States (US) each year [3], and is a contributing cause in 100,000 or more deaths [4,5]. It causes long-term morbidity, notably post-thrombotic syndrome (PTS) following DVT and chronic thromboembolic pulmonary hypertension (CTEPH) following PE. Medical costs for VTE in the US have been estimated to total $5–10 billion per year [6]. Published estimates of the total economic impact of VTE, including the value of lost economic output due to premature mortality, are as high as $69 billion per year [7,8]. This paper reviews published estimates of the burden of VTE on the US healthcare system in terms of per-patient and aggregate incremental direct medical costs.

Estimates of the incidence of clinically validated VTE diagnoses fall in the range of 1.0–1.5 per 1000 persons per year, excluding studies of adults over 45 years. Two US studies reported all-age annual incidence of 1.18 per 1000 population in Rochester County, MN, during 1991–1997 [9] and 1.33 per 1000 population in Worcester, MA, during 2009 [10]. Applied to the US population of approximately 320 million people those incidence rates suggest 375,000–425,000 recognized incident VTE cases per year, not including cases that remain undiagnosed and untreated. Two population-based studies from Canada and France reported incident (first) VTE diagnoses in 1.22–1.36 per 1000 people [11,12]. Two prospective Norwegian cohort studies of adults of all ages reported incidence rates of 1.43–1.48 per 1000 person-years [13,14], which applied to 245 million US adults implies 350,000–365,000 incident cases per year in adults. Because VTE is a chronic condition, prevalence exceeds incidence; 1 million Americans may have prevalent treated VTE [15].

2. Methods

Following publication of a critique [6] of published estimates of the economic burden of VTE in the US [7], the author of that critique (SDG) conducted a non-structured literature review in late 2013. To maximize comparability, only studies based on US data published since 2002 were included for the primary search for estimates of first-year treatment costs for patients with an incident VTE. A subsequent structured search of PubMed was conducted in July 2014 to identify US studies that mentioned cost or economics in connection with “deep vein thrombosis”.

Among 259 studies identified in the 2014 search, 59 English-language articles were examined for potential relevance on the basis of titles. Three of the 59 articles met the inclusion criteria of reporting estimates of per-patient incremental medical costs or expenditures for both inpatient and outpatient care for US patients with acute incident DVT or PE that were not restricted to narrowly defined patient groups, such as those undergoing surgery or treatment for cancer. Studies that presented data on charges alone were not included because hospital charges are typically a multiple of both resource costs and payments [16]. Similarly, studies that reported just treatment costs for patients with VTE rather than net costs relative to matched patients without VTE were not included. Studies that assessed only inpatient costs were excluded due to incomplete ascertainment of treatment costs. In addition, we reviewed studies that provided estimates of downstream costs of recurrence of VTE, complications of acute VTE, and complications of treatment as well as studies that modeled aggregate costs of incident VTE in the US.

We summarize estimates of incremental costs of medical treatment for incident cases of VTE and complications in the adult US population calculated from either the payer or the healthcare sector perspectives. Costs are calculated as the value of the resources needed to provide care or using average payments as a proxy for average costs.

We estimated the incremental or net medical costs of treating VTE and complications using an incidence-based approach that models the present value of medical costs for incident cases of VTE occurring in a given year, including costs in future years, relative to similar individuals who do not develop VTE. It differs from a treatment cost approach which focuses on affected patients and seeks to determine which services and costs were condition-specific [17]. The incidence-based approach, unlike the prevalence-based approach that estimates costs during a given year for all individuals with a prevalent condition, allows analysts to calculate the avoidable average cost of a new case, which can inform economic analyses of the value of prevention [17,18].

The healthcare costs of treating a patient with an incident VTE include the costs of treating the acute event as well as the costs of complications of VTE, including recurrent VTE, and complications of treatment. Aggregate treatment costs in a year are the product of annualized treatment costs for each incident event times the probability that the incident event occurs in a year. It is crucial that the same case definition and ascertainment be used for both incidence and treatment costs, since using a looser definition for incidence than for costs can overstate aggregate costs [6].

The per-person incremental or net cost of incident VTE is the difference in mean annualized costs between patients with and without VTE controlling for confounding by conditions that predispose people to VTE. One study of postoperative VTE in surgical inpatients found that the difference in expenditures controlling for confounding was less than one-fourth of the gross difference [19]. About one-fifth of patients who develop a VTE have active cancer [20], which increases medical costs independently of VTE [21]. One controls for confounding by pre-event health status through multivariable regression analysis, propensity score matching, and adjusting for differences in average treatment costs during the year prior to the index event. One of the best predictors of healthcare costs is healthcare costs in the preceding year [22].

We report average (mean) medical costs or expenditures per-person in 2014 US dollars using the Personal Consumption Expenditures (PCE) price index for health by function [23]. All costs in the text have been rounded to the nearest 100 dollars; the sum of rounded numbers may differ. The mean cost for an incident case is multiplied by the number of incident cases to calculate aggregate cost.

3. Results

3.1. Person-level empirical estimates of incremental costs of care

3.1.1. Acute VTE and first-year costs—MacDougall et al. used claims data to calculate annualized costs of care for patients who had a first acute VTE event compared with similar patients, all of whom had 360 pre-index days free of claims associated with DVT or PE. The authors used regression analysis to control for age, sex, duration of follow-up, and pre-index comorbidities; 85% of VTE patients had a predisposing medical condition (Table 1) [24]. Monthly costs for individuals with less than 12 months of post-VTE claims data were annualized using regression to adjust monthly costs, based on data for patients with 12 months of data. Average adjusted annualized post-index medical costs for the VTE group were 12 times higher than for matched control patients controlling for post-index covariates, $42,100 vs. $3500, a difference of $38,600. However, medical expenditures for the year preceding the index event were also higher for the VTE group, $29,200, vs. $4600 for the control group. Subtracting the difference in pre-index costs from the adjusted post-index mean expenditures, the VTE-attributable per-patient cost during the year following the VTE event in the MacDougall et al. study was approximately $13,900 [24]. A previous review of VTE cost estimates cited the cost estimate that did not adjust for the elevated medical costs experienced during the year before the VTE event [25].

Lefebvre et al. also used nationwide claims data restricted to adults with 12 months of insurance coverage prior to the index date, thereby identifying newly diagnosed and presumed incident cases of VTE. They used propensity score matching in an analysis of private insurance claims data; they matched 16,969 adults with a VTE during the period 2004–2008, who had no VTE during the preceding 12 months, with controls. The propensity score was generated using factors such as pre-index healthcare costs and comorbidity index [26]. The average length of follow-up was 260–270 days, with payments calculated on an annualized basis by dividing total costs per person by the number of months of data for that individual and multiplying by 12 [26]. The data were weighted by number of months, e.g., a person with 6 months of data is weighted by 0.5 relative to someone with 12 months of data (personal communication, Patrick Lefebvre, January 26, 2015). Mean annual all-cause payer per-patient expenditures were calculated to be $37,800 and $19,800 for the VTE and non-VTE groups, respectively, a difference of $18,000 (95% confidence interval $16,700–$19,200) per person-year [26].

The estimates reported by Lefebvre et al. would be valid if monthly treatment costs were constant over time. However, monthly treatment costs diminish following an acute VTE event as use of anticoagulants diminishes [24]; 3–6 months of treatment is standard [27]. According to a methods reference cited by Lefebvre et al., analysts should include length of follow-up as a regression covariate to avoid biased estimation of annualized treatment costs if monthly costs are suspected to vary by duration of treatment [28].

Spyropoulos and Lin reported health plan expenditures during 12 months following a hospitalization with DVT or PE for roughly 5700 persons during 1998 to 2004 with a secondary inpatient diagnosis of DVT or PE who had continuous enrollment for the following 365 days [29]. They matched patients who had a secondary hospital diagnosis of VTE with patients without any VTE diagnosis who had the same principal hospital diagnosis and subtracted the average cost of the latter from that of the former to estimate costs attributable to DVT/PE. The annual net cost of a VTE secondary diagnosis was approximately $12,400. In addition, the authors reported average gross payments of $18,100 for patients with a primary VTE diagnosis, which includes costs associated with conditions that may have provoked the VTE event. A limitation of the study design is that the exclusion of patients censored due to death or disenrollment can lead to biased estimates [30].

3.1.2. Long-term complications — overall and VTE recurrence—Costs associated with complications of acute VTE contribute to the economic burden of VTE (Table 2). Complications of acute VTE include both VTE recurrence and specific complications (e.g., PTS and CTEPH). Costs of treating complications during the first 12 months are included in the previous section. In one study recurrent VTE, PTS, and other complications (thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency) accounted for 18.3% of the all-cause difference in first-year treatment costs [26].

Between 10% and 30% of survivors of acute VTE develop a recurrent VTE within 5 years, with a peak following discontinuation of anticoagulation treatment [31]. The risk is higher for patients with unprovoked VTE, [32] and the long-term cost of an incident VTE event is likely to vary with the clinical context. The average cost for patients with recurrent VTE may also be higher because of comorbid conditions. In one study patients who had a recurrence within 12 months had average annualized expenditure $55,100 higher, but just one-fifth of the difference in expenditures, $11,000, was attributable to the treatment of VTE and complications [33].

Little information is available on VTE-associated costs beyond the first year. A Swedish study by Bergqvist et al. at one hospital recorded complications during 10–15 years of follow-up among 257 patients with acute DVT and 241 matched patients who did not have an initial thrombosis [34]. The total incremental cost of treating complications between post-DVT patients and controls, excluding seven who developed an incident DVT, was equivalent to 73% of the first-year cost of treating incident DVT among those seven controls.

PTS can result in chronic limb heaviness, swelling, pain, paresthesia, and, in severe cases, venous leg ulcers, which occur in 4–6% of survivors of proximal lower-extremity DVT [35–38]. Overall, PTS develops in 30–50% of patients with a proximal leg DVT [39–41]. Among 355 hospital patients in Quebec with acute DVT who developed PTS adjusted medical costs over the average for other patients with DVT after adjustment for confounders [42].

Caprini et al. used Medicare fee schedules to predict first-year treatment of roughly $1100 for patients with mild-moderate PTS (without leg ulcers) and $5000 for severe PTS with open ulcers [43]. MacDougall et al. used billing codes to identify PTS in 25.9% of patients with a recent DVT or PE [24]. They calculated annualized medical costs for those with 2 to 11 months of follow-up by applying an adjustment factor based on those with 12 months of follow-up. Mean annualized medical cost for patients with PTS, $60,500, was higher by $14,800 relative to the cost for patients who did not have PTS, $45,700. After subtracting pre-index treatment costs, the incremental cost of treating PTS was roughly $7800.

CTEPH, a condition requiring lifelong anticoagulation [44–46], develops in roughly 1% [47–51], or 4% [52,53] of survivors of PE. Patients who develop CTEPH are much more expensive to treat than other PE patients, with average monthly expenditures of $5500 and $600, respectively [54]. However, CTEPH patients are far more likely to have congestive heart failure or chronic pulmonary disease [54]. Also, patients with a massive PE are more likely to develop CTEPH [55]. No risk-adjusted treatment cost estimates were identified.

3.1.3. Treatment complications—Adverse drug events from anticoagulation—primarily bleeding—also contribute to VTE treatment costs, although most costs occur during the first year. Cost estimates per bleed event vary widely (Table 2). Lefebvre et al. projected average direct treatment costs of $9900 for a major extra-cranial bleed and $120 for a clinically relevant non-major bleed [56]. O'Brien and Caro reported that major and minor bleeds occurred in 1.0% and 1.4% of treated patients, respectively, with estimated costs per bleeding event of $11,000 and $3500, respectively [57]. The per-patient cost of post-DVT bleeds on an annualized basis was approximately $300, with minor bleeds accounting for 31% of the total, or $100 per patient. Bullano et al. reported that the average cost of a bleed that required hospitalization was $22,800, and one managed on an outpatient basis cost $400 [58]. The average annualized costs of major and minor bleeds were approximately $1200 and $100 per patient with VTE.

The cost of heparin-induced thrombocytopenia (HIT) is not well established, with average costs of possibly $5000–7000 [57,59]. HIT is unlikely to be a major cost of VTE treatment going forward because of decreased use of heparin.

3.2. Aggregate estimates of VTE treatment costs

Two US studies reviewed in this paper reported adjusted incremental medical costs of approximately $12,400–$13,900 per patient during the first 12 months, including first-year costs of complications [24,29]. A third study that assumed constant monthly costs of VTE treatment throughout the first 12 months reported a higher estimate, but that study also reported a 95% confidence interval bracketing the point estimate by plus or minus 7% [26]. Applying that range to the other two cost estimates implies a range of $11,500 to $14,900 in first-year cost per adult with incident VTE.

If one subtracts the 18% added cost of complications during the first 12 months in a US study [26] from the 73% cumulative cost from a Swedish study [34], complications beyond the first year conservatively add 55% to first-year costs. The total cost per patient with presumed incident VTE, assuming that complications over several years raise total cost by 55%, is therefore approximately $17,900 to $23,100. With a likely range of 375,000 to 425,000 incident cases diagnosed each year among US adults, our incidence-based estimate of aggregate medical costs of treating VTE and its complications is $6.7 to $9.8 billion per year.

Mahan and colleagues presented estimates of both total and “indirect” (mortality) costs for two estimates of incident VTE cases in the US, 480,000 and 960,000 per year [8]. The difference between total and indirect costs is direct medical costs, which for the lower incidence rate was $9.3 billion in 2014 US dollars in the “base” model and $10.2 billion in the “long-term attack rate” version [8]. Those estimates imply an average cost per incident case of $19,400–$21,200. Despite the overall similarity to our per-person treatment cost estimates, their estimates of the costs for outpatient DVT events, PE events and hospital readmissions due to recurrent VTE were gross costs and did not net out medical costs for similar patients. Also, Mahan et al. adjusted costs for inflation using the medical care component of the Consumer Price Index (CPI), which excludes payments by Medicaid, Medicare Part A, and employers and whose growth has historically exceeded changes in all-payer healthcare prices [23,60]. For example, their estimate of the average gross treatment cost for outpatient DVT events of $14,963 in 2010 dollars [7] adjusted from 1997 to 1998 cost data [61] compares with a cost in 2010 dollars of $13,138 using the PCE deflator that uses data for all healthcare payers.

Mahan et al. [7] may have overstated treatment costs for complications. The estimated cost of treating PTS was based on a study of patients with open leg ulcers [43], who are the most severely affected patients with PTS, and are higher than other estimates [24]. Their estimated treatment cost for HIT was based on a study that used charges [62], and the incremental cost of treating HIT may be less than $10,000 [58, 59].

4. Discussion

These cost estimates are subject to caveats. First, use of administrative data could bias the average estimated cost of treatment through misclassification of who has an incident condition [16]. Although ICD-9 codes for DVT or PE have fairly high reliability in inpatient records, a fraction of inpatients with those codes do not have acute VTE [63]. Many outpatients classified as having VTE on the basis of an ICD-9 code for DVT and a prescription for an anticoagulant may not have acute DVT confirmed by medical records [64]. Second, cost estimates reflect the therapies available at the time studies were conducted; for example, novel oral anticoagulant agents used to treat VTE may be associated with fewer bleeding complications but higher medication costs [56].

An incidence-based cost approach requires estimates of numbers of newly diagnosed patients with VTE, excluding recurrent events or diagnoses. Some published VTE incidence estimates that exceed the range used in this analysis were based on administrative data without clinical validation [3,65], or included recurrent VTE events. For example, two recent expert reviews [66,67] cited a French study that reported a VTE incidence rate of 1.83 per 1000 [11], but the incidence of *first* VTE events in that study was 1.36 per 1000. New US population-based surveillance studies with clinical validation of suspected cases [68] do not appear likely to alter the range of estimates.

4.1. Future VTE treatment cost studies

Additional studies of medical costs attributable to VTE treatment are needed in order to incorporate newer treatment patterns, in particular novel oral anticoagulants, and control for potential confounding factors. In addition to chronic conditions, future studies might explore the impact of short-term or transient VTE risk factors such as acute infections, hospitalization or surgery on the estimates of VTE treatment costs [69, 70].

Another challenge is to adjust VTE cost estimates for mortality. Medical costs rise sharply in the period just before death, which can be modeled using phase-of-care cost analyses in which costs vary nonlinearly with duration [71]. Short-term mortality is high among patients with incident VTE, but many deaths are due to life-threatening conditions such as active cancer, heart failure or severe respiratory disease [12]. Among hospitalized patients in one study diagnosed with acute PE, 15.3% subsequently died with 90 days, one-third of whom died from the PE [72]. One in 4 patients with an incident VTE die within 12 months, including 1 in 2 patients with cancer-associated VTE [12].

More work is needed on costs of treating complications. For example, no risk-adjusted estimates of treating CTEPH are available; Mahan et al. [8] projected an annual cost of CTEPH treatment of roughly $15,000 in 2014 dollars based on an expert consensus document [73]. US studies have relied on private insurance claims data which are subject to attrition due to turnover in health plan enrollments. For example, one study of treatment patterns reported that fewer than 40% of subjects were continuously enrolled in a managed care plan for 1.5 years [74]. To assess long-term cost implications of complications, researchers should consider use of Medicare claims data or data from state all-payer claims databases.

Researchers could model the net cost of anticoagulation strategies taking into account costs associated with complications and bleeding or other treatment complications. Such analyses could include assessments of the impact of non-adherence to recommended anticoagulation therapy, the choice of anticoagulant agents, and extended VTE therapy using either oral anticoagulants or antiplatelets, i.e., aspirin. For example, Amin et al. recently analyzed the direct cost of VTE treatment using four new oral anticoagulants compared with warfarin [75].

More studies are needed of the costs of treating VTE in specific patient groups such as major orthopedic surgical patients [76] and pediatric patients [77]. One study reported that the total cost of care during the first 6 months post-discharge from orthopedic surgery was $3500 [78], whereas another study reported that the *monthly* cost during the first 3 months was $3300 higher than for matched controls [79]. One study reported that gross healthcare expenditures for pediatric patients with apparently unprovoked VTE averaged approximately $20,000, but no attempt was made to calculate incremental or attributable costs due to VTE [77].

The net cost of incident VTE among patients with active cancer also requires clarification using data with clinical information. Average 12-month adjusted expenditures for privately insured US cancer patients who developed VTE have been found to be approximately

$30,000 higher [80–82]. However, VTE-related treatment costs accounted for less than one-third of the overall cost difference [81], and much of the cost difference may be due to differences in the distribution of factors that increase VTE risk, e.g., site and stage of cancers. VTE is a marker of aggressive tumors [83]; patients with metastases have a 2 to 19-fold greater risk of VTE [21] and also a higher risk of VTE recurrence [84].

5. Conclusion

We conclude that the best currently available estimates of the aggregate economic impact of incident or prevalent VTE cases on the US healthcare system are in the range of $7 billion to $10 billion per year, consistent with the majority of previous estimates [6]. Gross per-person treatment costs yield higher estimates, but people with VTE often have higher treatment costs for reasons unrelated to the VTE. It is essential to calculate risk-adjusted costs through use of adjustments for comorbidities or differences in pre-index treatment costs. Additional studies are needed to improve estimates of VTE-associated medical costs controlling for risk factors for VTE and assessing long-term costs associated with complications such as VTE recurrence, PTS, and CTEPH.

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References

1. Rice DP. Cost of illness studies: what is good about them? Injury Prevention. 2000; 6:177–179. [PubMed: 11003181]
2. Gold, M.; Siegel, J.; Russell, L.; Weinstein, M. Cost-effectiveness in Health and Medicine. Oxford University Press; New York: 1996.
3. CDC. Morbidity and Mortality Weekly Report. Centers for Disease Control and Prevention; 2012. Venous thromboembolism in adult hospitalizations — United States, 2007–2009; p. 401-404.
4. HHS. The Surgeon General’s Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Office of the Surgeon General; 2008.
5. Thromboembolism: an under appreciated cause of death. Lancet Haematology. 2015; 2:e393. [PubMed: 26686033]
6. Grosse SD. Incidence-based cost estimates require population-based incidence data. A critique of Mahan et al. Thromb Haemost. 2012; 107:192–193. [PubMed: 22159589]
7. Mahan CE, Holdsworth MT, Welch SM, Borrego M, Spyropoulos AC. Deep-vein thrombosis: a United States cost model for a preventable and costly adverse event. Thromb Haemost. 2011; 106:405–415. [PubMed: 21833446]
8. Mahan CE, Borrego ME, Woersching AL, Federici R, Downey R, Tiongson J, et al. Venous thromboembolism: annualised United States models for total, hospital-acquired and preventable costs utilising long-term attack rates. Thromb Haemost. 2012; 108:291–302. [PubMed: 22739656]
9. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost. 2005; 3:1611–1617. [PubMed: 16102026]
10. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). Am J Med. 2014; 127:829–839 e5. [PubMed: 24813864]
11. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d’Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost. 2000; 83:657–660. [PubMed: 10823257]

12. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study cohort. The American Journal of Medicine. 2013; 126(832):e13–e21. [PubMed: 23830539]
13. Braekkan S, Mathiesen E, Njølstad I, Wilsgaard T, Størmer J, Hansen J. Family history of myocardial infarction is an independent risk factor for venous thromboem-bolism: the Tromsø study. J Thromb Haemost. 2008; 6:1851–1857. [PubMed: 18665924]
14. Naess I, Christiansen S, Romundstad P, Cannegieter S, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007; 5:692–699. [PubMed: 17367492]
15. Deitelzweig S, Johnson B, Lin J, Schulman K. Prevalence of clinical venous throm-boembolism in the USA: current trends and future projections. Am J Hematol. 2011; 86:217–220. [PubMed: 21264912]
16. Riley GF. Administrative and claims records as sources of health care cost data. Med Care. 2009; 47:S51–S55. [PubMed: 19536019]
17. Barlow WE. Overview of methods to estimate the medical costs of cancer. Med Care. 2009; 47:S33–S36. [PubMed: 19536013]
18. Lipscomb J, Barnett PG, Brown ML, Lawrence W, Yabroff KR. Advancing the science of health care costing. Med Care. 2009; 47:S120–S126. [PubMed: 19536003]
19. Encinosa WE, Hellinger FJ. The impact of medical errors on ninety-day costs and outcomes: an examination of surgical patients. Health Serv Res. 2008; 43:2067–2085. [PubMed: 18662169]
20. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case–control study. Arch Intern Med. 2000; 160:809–815. [PubMed: 10737280]
21. Kourlaba G, Relakis J, Mylonas C, Kapaki V, Kontodimas S, Holm MV, et al. The humanistic and economic burden of venous thromboembolism in cancer patients: a systematic review. Blood Coagul Fibrinolysis. 2015; 26:13–31. [PubMed: 25202884]
22. Boscardin CK, Gonzales R, Bradley KL, Raven MC. Predicting cost of care using self-reported health status data. BMC Health Serv Res. 2015; 15:406. [PubMed: 26399319]
23. Bureau of Economic Analysis (BEA). What Accounts for the Differences in the PCE Price Index and the Consumer Price Index?. Washington, D.C: 2010.
24. MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm. 2006; 63:S5–S15. [PubMed: 17032933]
25. Ruppert A, Steinle T, Lees M. Economic burden of venous thromboembolism: a systematic review. J Med Econ. 2011; 14:65–74. [PubMed: 21222564]
26. Lefebvre P, Laliberte F, Nutescu EA, Duh MS, LaMori J, Bookhart BK, et al. All-cause and potentially disease-related health care costs associated with venous thromboembolism in commercial, Medicare, and Medicaid beneficiaries. J Manag Care Pharm. 2012; 18:363–374. [PubMed: 22663169]
27. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood. 2014; 123:1794–1801. [PubMed: 24497538]
28. Diehr P, Yanez D, Ash A, Hornbrook M, Lin D. Methods for analyzing health care utilization and costs. Annu Rev Public Health. 1999; 20:125–144. [PubMed: 10352853]
29. Spyropoulos A, Lin J. Direct medical costs of venous thromboembolism and subsequent hospital readmission rates: an administrative claims analysis from 30 managed care organizations. J Manag Care Pharm. 2007; 13:475. [PubMed: 17672809]
30. Huang Y. Cost analysis with censored data. Med Care. 2009; 47:S115–S119. [PubMed: 19536024]
31. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. Lancet. 2010; 376:2032–2039. [PubMed: 21131039]
32. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thrombo-embolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003; 362:523–526. [PubMed: 12932383]

33. Lefebvre P, Laliberté F, Nutescu EA, Duh MS, LaMori J, Bookhart BK, et al. All-cause and disease-related health care costs associated with recurrent venous thromboembolism. Thromb Haemost. 2013; 110:1288–1297. [PubMed: 24085327]

34. Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. Ann Intern Med. 1997; 126:454–457. [PubMed: 9072931]

35. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron M-J, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med. 2008; 149:698–707. [PubMed: 19017588]

36. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet. 2014; 383:880–888. [PubMed: 24315521]

37. Schulman S, Lindmarker P, Holmström M, Lärfars G, Carlsson A, Nicol P, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. J Thromb Haemost. 2006; 4:734–742. [PubMed: 16634738]

38. Mohr, DN.; Silverstein, MD.; Heit, JA.; Petterson, TM.; O'fallon, WM.; Melton, LJ. Mayo Clinic Proceedings. Elsevier; 2000. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study; p. 1249-1256.

39. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis. 2009; 28:465–476. [PubMed: 19224134]

40. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol. 2009; 145:286–295. [PubMed: 19222476]

41. Kreidy R. Contribution of recurrent venous thrombosis and inherited thrombophilia to the pathogenesis of postthrombotic syndrome. Clin Appl Thromb Hemost. 2015; 21:87–90. [PubMed: 23892685]

42. Guanella R, Ducruet T, Johri M, MIRON MJ, Roussin A, Desmarais S, et al. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost. 2011; 9:2397–2405. [PubMed: 21951970]

43. Caprini JA, Botteman MF, Stephens JM, Nadipelli V, Ewing MM, Brandt S, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. Value Health. 2003; 6:59–74. [PubMed: 12535239]

44. Copher R, Cerulli A, Watkins A, Laura MM. Treatment patterns and healthcare system burden of managed care patients with suspected pulmonary arterial hypertension in the United States. J Med Econ. 2012; 15:947–955. [PubMed: 22554140]

45. Johnson S, Delate T, Boka A, Shaw P, Zager C. Characterizing the financial burden of pulmonary arterial hypertension within an integrated healthcare delivery system. J Med Econ. 2013; 16:1414–1422. [PubMed: 24074226]

46. Ozsu S, Cinarka H. Chronic thromboembolic pulmonary hypertension: medical treatment. Pulmonary Circulation. 2013; 3:341. [PubMed: 24015333]

47. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Haematologica. 2010; 95:970–975. [PubMed: 20053871]

48. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006; 130:172–175. [PubMed: 16840398]

49. Poli D, Miniati M. The incidence of recurrent venous thromboembolism and chronic thromboembolic pulmonary hypertension following a first episode of pulmonary embolism. Current Opinion in Pulmonary Medicine. 2011; 17:392–397. [PubMed: 21743331]

50. Otero R, Oribe M, Ballaz A, Jimenez D, Uresandi F, Nauffal D, et al. Echocardio-graphic assessment of pulmonary arterial pressure in the follow-up of patients with pulmonary embolism. Thromb Res. 2011; 127:303–308. [PubMed: 21247617]

51. Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L, et al. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. Medicine. 2006; 85:253–262. [PubMed: 16974210]
52. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004; 350:2257–2264. [PubMed: 15163775]
53. Dentali F, Donadini M, Gianni M, Bertolini A, Squizzato A, Venco A, et al. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. Thromb Res. 2009; 124:256–258. [PubMed: 19193397]
54. Kirson NY, Birnbaum HG, Ivanova JI, Waldman T, Joish V, Williamson T. Excess costs associated with patients with chronic thromboembolic pulmonary hypertension in a US privately insured population. Applied Health Economics and Health Policy. 2011; 9:377–387. [PubMed: 21888449]
55. Barros A, Baptista R, Nogueira A, Jorge E, Teixeira R, Castro G, et al. Predictors of pulmonary hypertension after intermediate-to-high risk pulmonary embolism. Revista Portuguesa de Cardiologia (English Edition). 2013; 32:857–864.
56. Lefebvre P, Coleman C, Bookhart B, Wang S, Mody S, Tran K, et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. J Med Econ. 2014; 17:52. [PubMed: 24156243]
57. O'Brien JA, Caro JJ. Direct medical cost of managing deep vein thrombosis according to the occurrence of complications. PharmacoEconomics. 2002; 20:603–615. [PubMed: 12141888]
58. Bullano MF, Willey V, Hauch O, Wygant G, Spyropoulos AC, Hoffman L. Longitudinal evaluation of health plan cost per venous thromboembolism or bleed event in patients with a prior venous thromboembolism event during hospitalization. J Manag Care Pharm. 2005; 11:663–673. [PubMed: 16194130]
59. McGarry LJ, Thompson D, Weinstein MC, Goldhaber SZ. Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients. Am J Manag Care. 2004; 10:632–642. [PubMed: 15515996]
60. Bureau of Labor Statistics (BLS). The Consumer Price Index (updated 6/2015). Washington, D.C: 2015.
61. Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G. Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin. Chest. 2002; 122:108–114. [PubMed: 12114345]
62. Creekmore FM, Oderda GM, Pendleton RC, Brixner DI. Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. Pharmacotherapy. 2006; 26:1438–1445. [PubMed: 16999654]
63. Kaafarani HM, Borzecki AM, Itani KM, Loveland S, Mull HJ, Hickson K, et al. Validity of selected patient safety indicators: opportunities and concerns. J Am Coll Surg. 2011; 212:924–934. [PubMed: 20869268]
64. Nelson RE, Grosse SD, Waitzman NJ, Lin J, DuVall SL, Patterson O, et al. Using multiple sources of data for surveillance of postoperative venous thromboembolism among surgical patients treated in Department of Veterans Affairs hospitals, 2005–2010. Thromb Res. 2015; 135:636–642. [PubMed: 25666908]
65. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010; 121:1896–1903. [PubMed: 20404252]
66. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015; 12:464–474. [PubMed: 26076949]
67. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost. 2014; 12:1580–1590. [PubMed: 25302663]
68. Wendelboe AM, Campbell J, McCumber M, Bratzler D, Ding K, Beckman M, et al. The design and implementation of a new surveillance system for venous thrombo-embolism using combined active and passive methods. Am Heart J. 2015; 170:447–454 e18. [PubMed: 26385027]

69. Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of hospitalization for venous thromboembolism. Circulation. 2012; 125:2092–2099. [PubMed: 22474264]
70. White RH. Identifying risk factors for venous thromboembolism. Circulation. 2012; 125:2051–2053. [PubMed: 22474263]
71. Yabroff KR, Warren JL, Schrag D, Mariotto A, Meekins A, Topor M, et al. Comparison of approaches for estimating incidence costs of care for colorectal cancer patients. Med Care. 2009; 47:S56–S63. [PubMed: 19536010]
72. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999; 353:1386–1389. [PubMed: 10227218]
73. McLaughlin V, Archer S, Badesch D. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. Circulation. 2009; 119:2250–2294. [PubMed: 19332472]
74. Christensen L, Sasane R, Hodgkins P, Harley C, Tetali S. Pharmacological treatment patterns among patients with attention-deficit/hyperactivity disorder: retrospective claims-based analysis of a managed care population. Curr Med Res Opin. 2010; 26:977–989. [PubMed: 20178404]
75. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Comparison of differences in medical costs when new oral anticoagulants are used for the treatment of patients with non-valvular atrial fibrillation and venous thromboembolism versus warfarin or placebo in the US. J Med Econ. 2015:1–34. [PubMed: 26705579]
76. Baser O, Supina D, Sengupta N, Wang L, Kwong L. Impact of postoperative venous thromboembolism on Medicare recipients undergoing total hip replacement or total knee replacement surgery. Am J Health Syst Pharm. 2010; 67:1438–1445. [PubMed: 20720243]
77. Boulet SL, Amendah D, Grosse SD, Hooper WC. Health care expenditures associated with venous thromboembolism among children. Thromb Res. 2012; 129:583–587. [PubMed: 21872297]
78. Nutescu EA, Shorr AF, Farrelly E, Ruslan H, Happe LE, Franklin M. Burden of deep vein thrombosis in the outpatient setting following major orthopedic surgery. Ann Pharmacother. 2008; 42:1216–1221. [PubMed: 18611992]
79. Vekeman F, LaMori JC, Laliberté F, Nutescu E, Duh MS, Bookhart BK, et al. Risks and cost burden of venous thromboembolism and bleeding for patients undergoing total hip or knee replacement in a managed-care population. J Med Econ. 2011; 14:324–334. [PubMed: 21506632]
80. Connolly G, Dalal M, Lin J, Khorana A. Incidence and predictors of venous throm-boembolism (VTE) among ambulatory patients with lung cancer. Lung Cancer. 2012; 78:253–258. [PubMed: 23026639]
81. Khorana AA, Dalal MR, Lin J, Connolly GC. Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumors undergoing chemotherapy in the United States. ClinicoEconomics and Outcomes Research. 2013; 5:101. [PubMed: 23430767]
82. Lyman GH, Eckert L, Wang Y, Wang H, Cohen A. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. Oncologist. 2013; 18:1321–1329. [PubMed: 24212499]
83. Wun T, White RH. Venous thromboembolism (VTE) in patients with cancer: epidemiology and risk factors. Cancer Invest. 2009; 27:63–74. [PubMed: 19291526]
84. Louzada ML, Majeed H, Dao V, Wells PS. Risk of recurrent venous thromboembolism according to malignancy characteristics in patients with cancer-associated thrombosis: a systematic review of observational and intervention studies. Blood Coagul Fibrinolysis. 2011; 22:86–91. [PubMed: 21245746]

Table 1

Published estimates of per-patient acute venous thromboembolism costs.

Category	Citation	Patient characteristics: VTE	Patient characteristics: Non-VTE	When diagnosed	How diagnosed	Data	Types of costs	Time period	Cost estimates (2014 US dollars)	Estimation method	How controls selected
Medical inpatients	Spyropoulos and Lin [29]	Secondary diagnosis of VTE, N = 5,712; age, mean = 57.6	3 matched controls per case	Discharge diagnosis	ICD-9-CM codes	Integrated Health Care Information Services National Managed Care Database (1998–2004)	Hospitalization (facility and professional) and outpatient (visit, procedure, and prescription)	Initial hospitalization and 12 months following discharge	$12,421 for VTE as secondary diagnosis	Average	Matched on primary diagnosis to patients with VTE as secondary diagnosis
All insured persons	MacDougall et al. [24]	N = 26,264; 56.0% female; age, mean = 54.3	N = 78,263; 56.1% female; age, mean = 53	Any point during data availability	ICD-9-CM codes	PharMetrics Patient-Centric Database Jan 1, 1997–Mar 31, 2004	Inpatient, outpatient, pharmacy reimbursed payments by plans	Annualized costs	Average annualized adjusted cost for VTE cases = $42,108 Excess total costs after subtracting difference in pre-index costs = $13,908	GLM regression adjusting for demographic and clinical characteristics	Matched 3:1 on gender, age, and duration of follow-up
	Lefebvre et al. (2012) [26]	N = 16,969; 56.9% female; age, mean 54.6	N = 16,969; 57.0% female; age, mean = 56.5	Any point during data availability	ICD-9-CM codes	Ingenix IMPACT National Managed Care Database 2004–2008	Inpatient, outpatient, pharmacy	1-year following VTE event	Excess total cost = $17,981	Non-parametric estimations of annualized cost differences	Propensity score matching

Note: VTE = venous thromboembolism; ICD-9-CM = international classification of disease, ninth revision, clinical modification; GLM = generalized linear model; NA = not applicable.

Table 2

Published estimates of per-patient venous thromboembolism-related complications costs.

Category	Citation	Patient characteristics: Complications	Patient characteristics: No complications	When diagnosed	How diagnosed	Data	Types of costs	Time period	Cost estimates (2014 US dollars)	Estimation method	How controls selected
All complications	Lefebvre et al. [26]	N = 16,969; 56.9% female; age, mean = 54.6	N = 16,969; 57.0% female; age, mean = 56.5	Any point during data availability	ICD-9 codes	Ingenix IMPACT National Managed Care Database 2004–2008	Inpatient, outpatient, pharmacy	1-year following VTE event	Excess total cost = $3286	Non-parametric estimations of annualized cost differences	Propensity score matching
Recurrent VTE	Lefebvre [33]	N = 8001; 52.4% female; age, mean = 56.7	N = 8001; 51.8% female; age, mean = 57.1	Diagnosed with recurrent VTE at any point following initial VTE	ICD-9-CM codes	Ingenix National Managed Care Database	Outpatient, hospitalization, and pharmacy	1-year following recurrent VTE	Mean all-cause cost difference = $55,518 Mean disease-related cost difference = $11,120	Comparison of means	Propensity score matching
PTS	Caprini et al. [43]	(Overall) 65% female; age, mean = 72	NA	Surgical hospital stay	NA	Parameter values taken from the published literature	Office visits, vascular lab tests, medical supplies, medications, vein ligation and stripping, SEPS procedure, comprehensive ulcer treatment, other hospitalizations/procedures	Lifetime	Mild/moderate PTS = $1104, severe PTS = $5022	Simulation model	NA
	MacDougall et al. [24]	N = 1781; 65.8% female	N = 624; 66.3% female	90 days or more after the DVT/PE diagnosis	Syndromal definition: pain and swelling persisting 6 months or longer and evidence of venous valvular incompetence	PharMetrics Patient-Centric Database Jan 1, 1997–Mar 31, 2004	Inpatient, outpatient, pharmacy	Annualized costs	Incremental mean cost = $7790; excess total mean cost = $14,829 Incremental median cost = $3001; excess total median cost = $6007	GLM regression for mean cost Pre-index and post-index comparison for median cost	Matched on gender, age, and duration of follow-up
CTEPH	Kirson et al. [54]	N = 289; 57.1% female; age, mean = 52.2	NA	At any point during observation window	ICD-9-CM, CPT, and HCPCS codes	Private insurance claims database	Inpatient, outpatient, pharmacy	Per-patient month costs estimated over variable follow-up times (mean follow-up = 21.5 months)	Excess cost = $4942	Wilcoxon rank-sum tests	Matched based on demographic characteristics
HIT	O'Brien and Caro [57]	N = 840; age, mean = 68	N = 27,321; age, mean = 64	At any point during 1997	ICD-9-CM codes	All-payer discharge data from 1997 from 6 US states	Inpatient, outpatient	6 months following DVT	$5498	Comparison of means	Patients in dataset with DVT without complications
	Creekmore et al. [62]	N = 44; 45.5% female; age, mean = 57.3	N = 212; 53.8% female; age, mean = 57.1	At any point between 2000 and 2004	Assessment of treatment and ELISA test result	University of Utah	Inpatient physician, laboratory, pharmacy, and other	During initial hospitalization	Unadjusted = $52,280;	Comparison of means	Matched based on age, hospital service, and admitting ICD-9 code

Category	Citation	Patient characteristics: Complications	Patient characteristics: No complications	When diagnosed	How diagnosed	Data	Types of costs	Time period	Cost estimates (2014 US dollars)	Estimation method	How controls selected
						Hospital data Hospital data			adjusted = $42,853		
Bleeding	O'Brien and Caro [57]	N = 697 (287 with major bleed, 410 with minor bleed); age, mean = 68	N = 27,321; age, mean = 64	Admitted with DVT as principal diagnosis during 1997	ICD-9-CM codes	Hospital discharge data from 6 US states	Inpatient, outpatient	6 months following DVT	$11,018 for patients with major bleed; $3518 for patients with minor bleed	Comparison of means	Patients in dataset with DVT without complications
	Bullano et al. [58]	N = 781 (169 with major bleeds, 612 with minor bleeds)	N = 1001; mean age for study sample = 61.6	Following a hospital admission with VTE during 1998–2000	ICD-9, CPT, UB-92 and GPI codes	Medical and pharmacy data from 2 health plans in the Southeast and Western US	Inpatient, outpatient, and pharmacy	Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months)	$22,885 for bleed event requiring hospitalization; $357 for bleed event with no hospitalization	GLM regression for mean post-index bleed event comparisons	Patients in dataset with VTE without complications
	Lefebvre et al. [56]	(Overall) age, mean = 57	NA	On-treatment for acute DVT or PE	NA	Transition probabilities obtained from EINSTEIN Trails and published literature	Unit costs of resources from CPT and ICD-9 codes	Per-event cost	Base case treatment of bleeds = $9935; clinically-relevant non-major bleeds = $116	Simulation model	NA

Note: VTE = venous thromboembolism; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; PE = pulmonary embolism; PTS = post-thrombotic syndrome; HIT = heparin-induced thrombocytopenia; ICD-9-CM = international classification of disease, ninth revision, clinical modification; CPT = current procedural terminology; HCPCS = health care common procedure coding system; UB = universal billing; GPI = generic product identifier; GLM = generalized linear model; NA = not applicable.